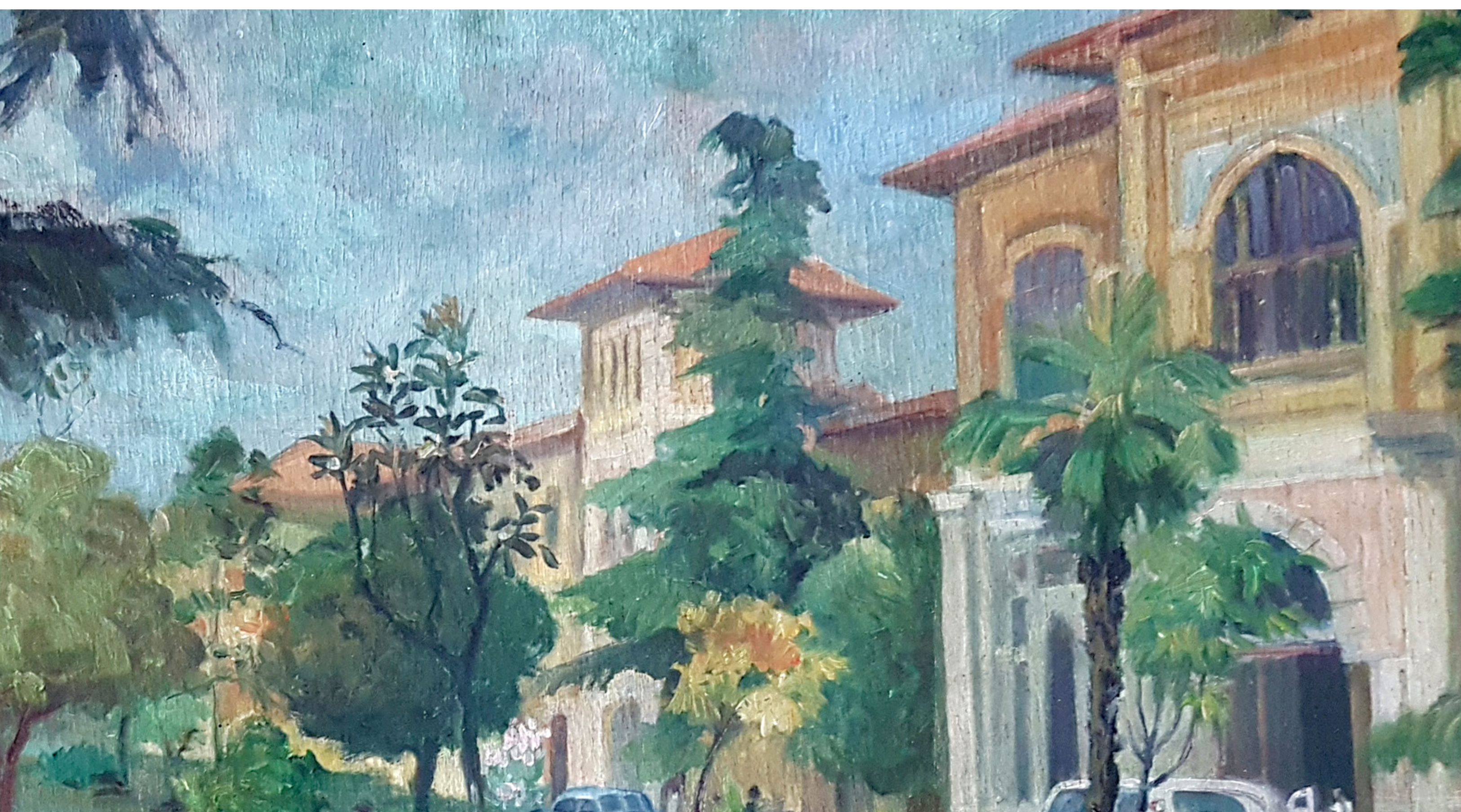
ISSN 2630-5720

HNH
HAYDARPAŞA NUMUNE EDUCATION HOSPITAL
1936

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

Volume 65 Issue 4 Year 2025



KARE

www.hnhtipdergisi.com

ISSN 2630-5720

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

SCIENTIFIC EDITORIAL BOARD

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

Volume 65 Issue 4 Year 2025

October - November - December

PUBLICATION MANAGER

Assoc. Prof. Ali Sürmelioğlu, M.D.

Owner on Behalf of
Haydarpaşa Numune Training and Research Hospital

Address: Tıbbiye Cad. No: 23 34668 Üsküdar 34668 Istanbul
Phone: +90 (216) 542 32 32 / 0 (216) 542 32 00
Fax: +90 (216) 336 05 65

MANAGING EDITOR

Prof. Seniha Şenbayrak, MD.

CONTACT EDITOR

Prof. Seniha Şenbayrak, MD.

Address: Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları Kliniği
Tıbbiye Cad No: 23 Selimiye Üsküdar, 34668 Istanbul
Phone: +90 216 542 32 32 / 1952
Web: www.hnhtipdergisi.com
E-mail: editor@hnhjournal.com

PUBLISHER

Kare Publishing

Address: Göztepe Mah. Fahrettin Kerim Gökay Cad. No: 200 Da: 2, Göztepe, Kadıköy-Istanbul, Turkiye
Phone: +90 216 550 61 11
Web: www.karepb.com
E-mail: kare@karepb.com

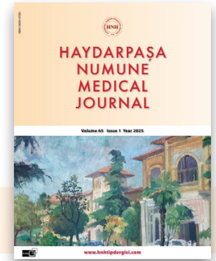
Publications Coordinator: Zehra Suğra Türksavaş **Graphic Design:** Beste Kurtcu Ay

Cover Image: İbrahim Çallı (1882-1960)

Indexed in TUBITAK ULAKBIM TR, EBSCO, CINAHL, Turkish Medline, ProQuest, CABI and GALE Cengage.
Published four times a year.

Issue date: December 2025 • International publication

Additional author information is available from the journal's web site: hnhtipdergisi.com



INSTRUCTIONS FOR AUTHORS

Haydarpaşa Numune Medical Journal - Haydarpasa Numune Med J (formerly: Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Tıp Dergisi) is a double-blind peer-reviewed, and open-access journal. The journal aims rapid publication of papers in all fields of the medical sciences on a regular basis. Haydarpaşa Numune Med J publishes original papers of experimental and clinical research, reviews, case reports, and articles on the current issues of medicine.

Four issues are released every year in March, June, September, and December. The language of publication is English. Only manuscripts prepared in English are accepted for publication in our journal. Free full-text articles are available at www.hnhtipdergisi.com.

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 the National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Submission is a representation that neither the manuscript nor its data have been previously published (except abstracts and press reports published in connection with scientific meetings) or are currently under consideration for publication.

Materials copied from other sources must be accompanied by a written statement from both author and publisher giving permission to Haydarpaşa Numune Med J for reproduction. It is the author's responsibility to ensure that permissions are obtained. The differences between the papers should be explained in detail.

Ethics committee approval of research protocols in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies, and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included indicating that the written, informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they might undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. If there is a chance that a patient may be identified from a photograph or other image, or any accompanying text, releases signed by the patient or their legal representative should be enclosed. Identifying images should also be anonymized.

All submissions are screened with similarity detection software (iThenticate by Turnitin).

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

AUTHORSHIP CRITERIA

Haydarpaşa Numune Med J follows the authorship criteria developed by the International Committee of Medical Journal Editors. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article.

Authorship credit should be based only on; (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship. All others who contributed to the work who are not listed as authors should be named in the acknowledgments, and their contribution should be described. Authorship of multicenter trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the acknowledgments. Financial and material support should also be acknowledged.

All statements and opinions expressed in the manuscripts published in Haydarpaşa Numune Med J reflect the views of the author(s). All liability for the advertisements rests with the appropriate organization(s). The Editor-in-Chief, and Kare Media do not accept any responsibility for claims made in articles or advertisements.

ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

At submission, the journal should require authors to disclose whether they used artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work. Authors who use such technology should describe, in both the cover letter and the submitted work, how they used it. Chatbots (such as ChatGPT) should not be listed as authors because they cannot be responsible for the accuracy, integrity, and originality of the work, and these responsibilities are required for authorship. Therefore, humans are responsible for any submitted material that included the use of AI-assisted technologies. Authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased. Authors should not list AI and AIassisted technologies as an author or co-author, nor cite AI as an author. Authors should be able to assert that there is no plagiarism in their paper, including in text and images produced by the AI. Humans must ensure there is appropriate attribution of all quoted material, including full citations.

COPYRIGHT STATEMENT

The authors transfer all copyright to the manuscript to the Haydarpaşa Numune Med J according to the framework of national and international regulations at the start of the evaluation process. A Copyright Transfer Form signed by the corresponding author must be submitted to the journal with the manuscript. A separate form should be submitted for each manuscript. Manuscripts submitted without a Copyright Transfer Form will not be accepted. After acceptance of the manuscript, all of the authors must complete and sign a Copyright Transfer Form. The authors must affirm that they will not submit the work to another journal, publish it in the original or another language, or allow a third party to use the manuscript without the written permission of the Haydarpaşa Numune Med J. In the event that the manuscript is rejected, all copyrights transfer back to the authors. Manuscripts that are declined will not be returned, with the exception of artwork.

Authors retain copyright and grant the journal right of first publication with the work simultaneously licensed under a Creative Commons 4.0 License. When distributing or re-publishing the Work, the Author agrees to credit the Journal as the place of first publication.

All content is the authors' responsibility. All financial liability and legal responsibility associated with the copyright of submitted tables, figures, and other visual materials protected by national and international laws rest with the authors. The authors take responsibility for any legal proceedings issued against the journal.

To clarify scientific contributions and responsibilities and any conflict of interest issues relevant to the manuscript, all parts of the Authors' Contribution Form must be completed by the corresponding author and the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest must be completed online by all authors. Both forms should be included with the manuscript at the time of original submission.

Author names will be published as they are listed on the Copyright Transfer Form. Requests for changes in affiliation or the order of names at a later date cannot be granted to protect all parties involved.

FEES

There is no fee for our standard article submission and publication process. Articles are reviewed and accepted articles are scheduled for publication.

POLICY OF SCREENING FOR PLAGIARISM

The manuscripts are scanned by the Publisher's Office using the iThenticate program for determination of plagiarism and non-ethical situations.

OPEN ACCESS

Haydarpaşa Numune Medical Journal is an open access journal which means that all content is freely available without charge to the user or his/her institution. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles, or use them for any other lawful purpose, without asking prior permission from the publisher or the author. This is in accordance with the BOAI definition of open access.

COMMONS USER LICENSES

Creative Commons Attribution-NonCommercial (CC BY-NC) For non-commercial purposes, lets others distribute and copy the article, and to include in a collective work, as long as they credit the author(s) and provided they do not alter or modify the article.

REVIEW PROCESS

The journal aims at rapid publication of the submitted manuscripts. Haydarpaşa Numune Med J promotes expert refereeing by peers as a tried and true method for the maintenance of standards of excellency in the scientific community. All papers are double blind peer-reviewed to determine the originality, validity and importance of content and conclusions. Manuscripts will be reviewed by two external reviewers for content, originality, importance to the field, appropriateness of statistical analysis, and derivation of conclusions. In the case of discrepancies between peer reviewers, the manuscript would be sent to a third reviewer. All reviewers remain anonymous. Final decision regarding the acceptance of the submitted articles belong to editor-in-chief.

All reviews will be completed within one month of submission to the journal. Authors will be sent reviewers comments that are judged to be useful to them. In principle, the instructions, objections and requests made by the reviewers should be strictly followed. With revised form of manuscript, the authors should state clearly and precisely every step taken in accordance with the reviewers' requests. The description should be listed on a numbered basis, in the order of reviewers' comments. Altered paragraphs in the new version of the manuscript should be specified using page and paragraph numbers. Paragraph on top of a page is considered no 1, even if it does not begin on that page.

All manuscript submissions are encouraged to be submitted electronically to www.hnhtipdergisi.com. Along with revised form, the accepted paper in its final form also should be sent to www.hnhtipdergisi.com.

SUBMISSION OF THE MANUSCRIPTS

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be
- completed by all contributing authors) at the time of the initial submission. These forms are available for download at www.hnhtipdergisi.com.

All correspondence will be sent to the first-named author unless otherwise specified. Corresponding author is expected to provide an e-mail address for all further correspondence. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the Journal it is being submitted (i.e., original article, review article, or case report etc). Authors will be notified of the receipt of their paper and the number assigned to it. The number should be included in all further correspondence.

Authors should note, however, that manuscripts may be returned after initial review by the editorial office if the paper is deemed unlikely to be reviewed favorably by virtue of size restrictions and/or general interest for the readership. This rapid rejection process enables the author to promptly submit for publication elsewhere.

Preparation of the Manuscript

General Format: All manuscripts should be typed using the standard A4-size format document with 2.5 cm-wide margins on all sides. The references should be numbered consecutively in the order of their first mention in the text. All text material, including references, footnotes, and table and figure legends, should be typed using double-spacing in an 11 point font with left alignment and without hyphenated line breaks. The fonts Times New Roman or Arial should be used in the text, for symbols, and all other special characters. Please use the editing features of your word processing program to type bold or italic letters, mathematical symbols, Greek letters, subscript and superscript characters. Please take care not to confuse the letters O and I with the numerals 0 and 1. To set a left indent for a paragraph, click the TAB button once. Only the International System of Units (SI) should be used for units of measurement. Please review the final version of the manuscript very carefully, especially for formatting and editing errors. Please note that American English spelling and terminology should be used in the manuscripts.

All pages of the manuscript should be consecutively numbered starting from the title page (page 1, title page; page 2, Turkish abstract (Turkish authors only); page 3, English abstract, etc.). Page numbers should be indicated on the upper right-hand corner of each page. The final electronic version of the manuscript should be in ".doc", "docx" or ".rtf" format.

Title page: A separate title page should be submitted with all manuscripts and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name, affiliation(s), ORCID ID, and highest academic degree(s) of the author(s),
- Details of any grant or other sources of support,
- Name, address, telephone (including mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill authorship criteria.

Abstract: An abstract should be submitted with all manuscripts with the exception of Letters to the Editor. The abstract of an Original Article should be structured with subheadings (Objective, Methods, Results, and Conclusion). All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

Please refer to Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords at the end of the abstract to be used for subject indexing. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Introduction: State the specific purpose and available data relevant to the study.

Methods: All methods used to select participants and conduct the study should be described in detail. Known methods should be cited. Novel or modified methods used should be described in detail. Doses, concentrations, routes, and duration of administration of drugs and chemical agents should be indicated. A concise report of all statistical methods used for summarizing available data and for testing the proposed hypothesis should be provided under a subtitle, including the p value criteria determined for statistically significant difference. Statistical evaluation conducted should be explained in detail. Standard statistical methods should be used as much as possible. If rarely employed or novel statistical methods were used, then the relevant references should be cited. When necessary, more detailed explanations about unusual, complex, or new statistical methods can be provided in separate files for readers as online supplementary data. When a trademarked drug, product, hardware, or software program is mentioned within the main text, product information, include the name of the product, the manufacturer of the product, and the city and the country of the company headquarters (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA). The recommendations in the statistics section of the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" (http://www.ICMJE.org) should be taken into consideration.

Results: The study results should be presented in logical sequence and in detail. The findings should be supported by figures and tables. Information given in figures and tables should not be repeated in the text unless absolutely required.

Discussion: Data relevant to the study subject matter should be examined, evaluated, and substantiated with references from domestic and international sources. General information irrelevant or superfluous to the report should not be included.

Acknowledgement: The names of individuals who contributed to the study but who fail to meet the criteria of authorship should be mentioned in this section. The written consent of all individuals mentioned should be obtained.

Manuscript Types

Haydarpaşa Numune Med J publishes the types of articles briefly described below.

Research Articles: This is the most important type of article, since it provides new information based on original research. The main text of original articles should be structured with an Introduction, Methods, Results, Discussion, Conclusion, and References subheadings. Please see Table 1 for limitations for Research Articles.

Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489–93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Review Articles: Reviews prepared by authors who have extensive knowledge of a particular field and whose scientific background has been translated into a large volume of publications with a high citation potential are welcomed. Submissions from such authors may also be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should include an Introduction, Clinical and Research Consequences, and Conclusion sections. Please refer to Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include an Introduction, Case Presentation, and Discussion subheadings. Interesting and unusual images are an advantage in the evaluation process. Please see Table 1 for the limitations for Case Reports.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
Review Article	5000	350	50	6	10
Case Report	1500	200	15	No tables	5

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above each table. Abbreviations used in the table should be defined below the table by footnotes (even if they are defined within the main text). Tables should be created using the word processing software "insert table" command and they should be arranged clearly to provide easy reading. Data presented in tables should not be a repetition of the data presented within the main text but should support the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks may be used on the images to support the figure legends. Like the rest of the submission, the figures should also be blind. Any information within the images that may identify an individual or institution should be anonymized. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. References should be restricted to closely pertinent material. Accuracy of citation is the author's responsibility. References should conform exactly to the original spelling, accents, punctuation, etc. All references should be cited inside the text.

The reference styles for different types of publications are presented in the following examples.

Journal Article:

Marshall RD, Stein DJ, Liebowitz MR, Yehuda R.; A pharmacotherapy algorithm in the treatment of PTSD. Psychiatric Annuals 1996;26:217–26.

Book Section:

Author. Title. In: Editor, `editor`.^`editors`. Book Title. Edition ed. Place Published: Publisher; Year. p. Pages.

Philips SJ, Whisnant JP. Hypertension and Stroke. In: Laragh JH, Brenner BM (editors). Hypertension pathophisiology, diagnosis, and management. 2nd ed. New York: Raven Press, 1995: 465–78.

Books with a Single Author:

Author. Title. Edition ed. Place Published: Publisher; Year.

Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Conference Proceedings:

Author. Title. In: Editor, `editor`.^`editors`. Conference Name; Year of Conference Date; Conference Location: Publisher; Year of Conference|. p. Pages.

Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:

Author. Title. Type. Place Published: Institution; Year Date. Report No.: Report Number.

Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis:

Author. Title. Type. Place Published: Institution; Year Date. Report No.: Report Number.

Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Epub Ahead of Print Articles:

Author. Title. Alternate Title Year Date Accessed.doi: DOI. [Epub ahead of print].

Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Webpage:

Author. Title. Available at: URL. Accessed Access Date, Access Year.

Disclaimer

Haydarpaşa Numune Med J is an independent scientific journal, and published quarterly. It is distributed free of charge.

Views expressed in the journal do not necessarily reflect sponsoring pharmaceutical companies' own published literature. A mention of a company in the journal is neither an offer nor solicitation.

WITHDRAWAL POLICY

Withdrawal of a manuscript will be permitted only for the most compelling and unavoidable reasons. For withdrawal of a manuscript authors need to submit an "Article withdrawal Form", signed by all authors mentioning the reason for withdrawal to the Editorial Office. The form is available from the web page of the journal. Authors must not assume that their manuscript has been withdrawn until they have received appropriate notification to this effect from the editorial office.

In a case where a manuscript has taken more than six months' time for review process, that allows the author to withdraw manuscript.

After receiving the Article withdrawal Form, Haydarpaşa Numune Medical Journal Editorial Board will investigate the reason of withdrawal.

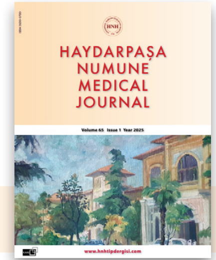
If the reason finds to be acceptable, the author is allowed to withdraw the manuscript. If not Haydarpaşa Numune Medical Journal will not accept any manuscripts from the same author for one year.

Important notes: Manuscripts may be withdrawn at any stage of review and publication process by submitting a request to the editorial office. Manuscript withdrawal will be permitted after submission only for the most compelling and unavoidable reasons.

If the author wants to withdraw a manuscript, the author needs to submit a completed "Article withdrawal Form", signed by all authors of the manuscript stating the reasons for manuscript withdrawal. The form is available from the web page of the journal.

The manuscript will not be withdrawn from publication process until a completed, signed form is received by the editorial office. Authors must not assume that their manuscript has been withdrawn until they have received appropriate notification to this effect from the Haydarpaşa Numune Medical Journal editorial office.

Commons User Licenses

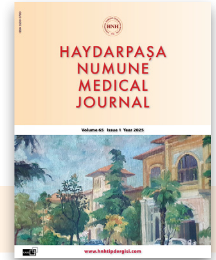


hnhtipdergisi.com

CONTENTS

Volume 65 **Issue** 4 **Year** 2025

ORIGINAL ARTICLES



hnhtipdergisi.com

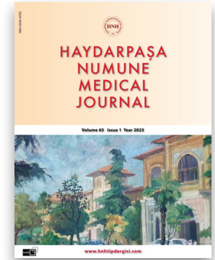
CONTENTS

Volume 65 **Issue** 4 **Year** 2025

SYSTEMATIC META-ANALYSIS

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.54289
Haydarpasa Numune Med J 2025;65(4):297–301



hnhtipdergisi.com

ORIGINAL ARTICLE

Regaining the Rhythm: Early Outcomes After Reinstating Coronary Artery Bypass Surgery in a Previously Suspended Center

Anıl Akbaş, Kübra Gözaçık Karakaş, Tamer Cebe

Department of Cardiovascular Surgery, Batman Training and Research Hospital, Batman, Türkiye

Abstract

Introduction: This study aims to evaluate the early outcomes of isolated coronary artery bypass grafting (CABG) procedures performed at a center that had temporarily suspended surgical services due to a shortage of surgical staff and later resumed operations.

Methods: A total of 42 patients who underwent isolated on-pump CABG between January 2023 and February 2025 were retrospectively analyzed. Demographic characteristics, preoperative risk factors, intraoperative variables, and early postoperative outcomes were evaluated using descriptive statistical methods.

Results: The mean age of the patients was 61.9±10.3 years, and 71.4% were male. The most common comorbidities were hypertension (31.0%), diabetes mellitus (38.1%), and chronic kidney disease (7.1%). The mean ejection fraction was 52.7%, and the mean body mass index was 26.3 kg/m^2. All patients underwent surgery with cardiopulmonary bypass. The mean CPB time was 67.9 minutes, and the cross-clamp time was 39.4 minutes. The average hospital stay was 8.2±3.9 days. Early postoperative complications included acute kidney injury (11.9%), new-onset atrial fibrillation (14.3%), respiratory failure (7.1%), stroke or transient ischemic attack (9.5%), wound infection (4.8%), and reoperation (11.9%). The early mortality rate was 7.1%.

Discussion and Conclusion: The early outcomes of CABG surgeries performed in our reactivated center are within acceptable limits regarding complication rates. The findings suggest that the surgical program was successfully restructured and patient safety was maintained. However, further prospective studies with larger patient series are required for more robust evaluation of outcomes.

Keywords: Coronary artery bypass; health care quality; mortality; postoperative complications.

Coronary artery disease (CAD) is one of the leading causes of cardiovascular mortality worldwide and remains a major public health concern in both developed and developing countries [1]. CABG, a surgical treatment for CAD, has been shown to be superior to medical and percutaneous interventions in terms of symptom control, improved quality of life, and long-term survival—particularly in patients with multivessel disease, left main coronary artery involvement, and diabetes mellitus [2].

CABG not only involves surgical intervention but also requires a multi-step and sensitive management process, from preoperative risk assessment to postoperative

Correspondence: Anıl Akbaş, M.D. Department of Cardiovascular Surgery, Batman Training and Research Hospital, Batman, Türkiye
Phone: +90 488 221 30 66 **E-mail:** dr.anilakbas@gmail.com
Submitted Date: 28.05.2025 **Revised Date:** 07.06.2025 **Accepted Date:** 10.06.2025
Haydarpaşa Numune Medical Journal

intensive care. This complex structure necessitates coordinated collaboration across various disciplines such as cardiovascular surgery, cardiology, anesthesiology, intensive care, nursing, and support units. Therefore, CABG is a true team effort that demands a high level of coordination to achieve clinical success [3].

In our center, the previously initiated CABG program had to be suspended for a period due to a shortage of cardiovascular surgeons. However, in the recent period, the program has been reactivated with the reinforcement of the surgical team and the provision of adequate infrastructure and equipment support. During this process, the multidisciplinary team structure has also been reorganized, and surgical case management has been systematized.

In this study, we retrospectively analyzed the early-term outcomes of operations performed within the reinitiated CABG program in our center. Mortality, morbidity, and complication rates were examined, along with clinical variables that may influence these outcomes. Our aim is to assess our current situation in light of these data and to contribute to the development of future treatment approaches.

Materials and Methods

Study Design and Patient Selection

This retrospective study includes patients who underwent isolated CABG surgery for coronary artery disease at our center between January 2023 and February 2025. Patients who underwent concomitant valve surgery, aortic surgery, or any other cardiac surgical intervention during the same session were excluded from the study. Ethical approval was obtained from the Ethics Committee of Batman Training and Research Hospital (decision no: 420, date: 20.03.2025), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

All patient data were obtained by reviewing the hospital information system and surgical records. Demographic characteristics (age, sex, body mass index) and comorbidities (such as hypertension, diabetes mellitus, and chronic kidney disease) were recorded. In the preoperative evaluation, variables such as left ventricular ejection fraction (EF), coronary anatomy, whether the surgery was performed under emergency or elective conditions, as well as biochemical parameters, were analyzed.

Preoperative biochemical evaluation included HbA1c (%) and creatinine (mg/dL) levels as indicators of glycemic control and renal function; hemoglobin, hematocrit, leukocyte ($\times 10^3$/mm^3), and platelet ($\times 10^3$/mm^3) counts as indicators of systemic inflammation and hematologic status; international normalized ratio (INR) values for coagulation status; and total cholesterol, LDL cholesterol, and triglyceride levels for lipid profile assessment.

Regarding the surgical procedure, all patients were operated using cardiopulmonary bypass (on-pump technique). Intraoperative variables such as the number and type of grafts used (arterial or venous), cross-clamp time, and cardiopulmonary bypass duration were analyzed. In the postoperative follow-up, data were collected on the length of hospital stay, erythrocyte suspension (ES) use, early-term mortality (within the first 30 days after surgery), need for reoperation, infections, postoperative arrhythmias, respiratory distress, neurological complications, and acute kidney injury.

Statistical Analysis

Measures of central tendency (mean and median) and measures of dispersion (standard deviation and interquartile range) were calculated. Absolute and relative frequencies were determined for categorical variables. Descriptive statistics were used to summarize the clinical characteristics of the patient group and to support clinical decision-making processes.

Surgical Technique

In all patients, access to the pericardial cavity was achieved via standard median sternotomy. Following systemic heparinization, cardiopulmonary bypass (CPB) was initiated using cannulas placed in the aorta and right atrium. Aortic cross-clamping was applied to arrest the heart, and cold blood cardioplegia solution was administered to achieve cardiac arrest. All procedures were performed using the on-pump technique.

Target coronary arteries were identified according to the revascularization plan. In all patients, the left internal mammary artery (LIMA) and great saphenous vein (SVG) grafts were used. Following the completion of distal anastomoses, proximal anastomoses were performed on the aorta under side-clamping. After achieving hemostasis, a drain was placed in the mediastinum, and the sternum was closed using steel wires. Intraoperative transfusion of ES was administered when needed, in accordance with national and international consensus guidelines on patient blood management.

Table 1. Preoperative parameters

Parameter	Value (mean±SD or %)
Male gender	71.4%
Age (years)	61.9±10.7
Body mass index (kg/m^2)	26.3±3.8
Ejection fraction (%)	52.7±10.2
Hemoglobin (g/dL)	14.2±1.9
Hematocrit (%)	43.1±5.5
HbA1c (%)	6.8±1.5
Creatinine (mg/dL)	1.02±0.21
White blood cell count (x10^3)	9.6±3.4
Platelet count (x10^3)	238.5±46.7
INR	1.08±0.11
Total cholesterol (mg/dL)	180.9±43.5
LDL cholesterol (mg/dL)	107.2±31.8
Triglycerides (mg/dL)	151.4±83.6

SD: Standard deviation; INR: International normalized ratio; LDL: Low-density lipoprotein.

Table 2. Intraoperative parameters

Parameter	Value (mean±SD or %)
Number of bypasses	3.4±0.7
Cardiopulmonary bypass time (min)	67.9±21.5
Cross-clamp time (min)	39.4±15.2

Table 3. Postoperative complications

Complication	Number of patients (n)	Rate (%)
Acute kidney injury	5	11.9
New-onset atrial fibrillation	6	14.3
Respiratory failure	3	7.1
Stroke/TIA	4	9.5
Wound infection	2	4.8
Early mortality	3	7.1
Reoperation	5	11.9

TIA:Transient ischemic attack.

Postoperative Monitoring and Follow-up

Postoperatively, all patients were transferred to the intensive care unit (ICU) while intubated. Within the framework of routine postoperative monitoring parameters, hemodynamic stability, rhythm monitoring, and bleeding control were ensured. Once clinical stability was achieved, patients were extubated and transferred to the ward.

Results

The mean age of the patients included in the study was 61.9 years. Of the patients, 71.4% were male and 28.6% were female. The mean body mass index (BMI) was 26.3 kg/m^2, and the mean EF was calculated as 52.7% (Table 1).

Evaluation of preoperative biochemical parameters revealed a mean hemoglobin (Hgb) level of 14.2 g/dL, Hct level of 43.1%, HbA1c level of 6.8%, creatinine level of 1.02 mg/dL, and leukocyte count of 9.6×10^3/mm^3. The average INR was 1.08. In the lipid profile assessment, total cholesterol was 180.9 mg/dL, LDL cholesterol was 107.2 mg/dL, and triglyceride level was 151.4 mg/dL (Table 1).

Intraoperative data showed that the mean number of coronary artery bypasses per patient was 3.4 (Table 2). The most frequently used graft combination was LIMA and SVG. All patients received cardiopulmonary bypass support.

The mean cardiopulmonary bypass time was 67.9 minutes, and the mean aortic cross-clamp time was 39.4 minutes (Table 2).

During the postoperative follow-up period, the average length of hospital stay was 8.2 days.

Among postoperative complications, acute kidney injury occurred in 11.9% of patients. New-onset atrial fibrillation was observed in 14.3% of cases. Respiratory failure was noted in 7.1% of patients, while neurological complications—such as stroke or transient ischemic attack (TIA)—were recorded in 9.5%. Surgical site infection occurred in 4.8% of patients (Table 3).

The early-term (within 30 days) mortality rate was calculated at 7.1%. During the same period, 11.9% of patients required reoperation due to bleeding disorders, cardiac tamponade, or other surgical causes (Table 3).

Discussion

In this study, we evaluated the early clinical outcomes of patients who underwent CABG following the re-establishment of the surgical program in our center. The data obtained indicate that the procedure was performed with generally acceptable rates of mortality and morbidity.

The preoperative demographic and biochemical characteristics of the patients in our study were largely consistent with those reported in similar studies from other centers. In particular, our findings related to mean age, EF, BMI, and biochemical parameters were in line with the patient profiles documented by various international centers [4]. This consistency supports the notion that our study population reflects the general CABG population and that the outcomes may be considered broadly applicable.

In our cohort, the mean age was 61.9 years, the mean BMI was 26.3 kg/m^2, and the mean EF was 52.7%. Additionally, 71.4% of the patients were male and 28.6% were female. In the study by Dassanayake et al. [5], which examined 12,736 patients who underwent isolated CABG, 75.2% were male (n=9.573) and 24.8% were female (n=3.163). This distribution is comparable to the gender ratios in our study. That same study reported that female patients were generally older than males (mean age: 65 vs. 66 years) and had a higher burden of comorbidities. Although our study did not include a gender-based subgroup analysis, the demographic structure of our population appears to be consistent with international data.

In our study, the mean cardiopulmonary bypass (CPB) time was 67.9 minutes, and the mean aortic cross-clamp time (XCT) was 39.4 minutes in patients undergoing isolated on-pump CABG. In contrast, the multicenter prospective E-CABG study by Ruggieri et al. [6] reported an average CPB time of 84±34 minutes and XCT time of 58±25 minutes.

In this context, both the CPB and XCT durations in our study were shorter than those reported by Ruggieri et al. [6] The notably shorter XCT time may reflect reduced myocardial ischemia duration and effective myocardial protection. The shorter CPB time, on the other hand, may be attributed to surgical team efficiency, grafting strategies, and optimized operative protocols.

Compared to international data, these relatively shorter operative times suggest that our surgical process is both safe and efficient. Nevertheless, to better understand their impact on early outcomes, these parameters should be further analyzed in relation to postoperative complications and mortality.

In our series, the incidence of postoperative new-onset atrial fibrillation (AF) was 14.3%. In the literature, the incidence of AF after CABG is generally reported to range between 20–40%. Thus, our results lie at the lower end of this spectrum. In the prospective study by Omar et al. [7], which included 366 patients, the incidence of postoperative AF was 26.8%. That study found advanced age, preoperative anemia, and low EF to be significantly associated with AF. Although our patient cohort also had a relatively high mean age and moderately reduced EF, the lower observed AF rate may be explained by patient selection, perioperative care protocols, and effective use of pharmacological prophylaxis. However, it is important to interpret this lower rate with caution due to the limited sample size.

In the study published by Apaydın et al. [8], the relationship between AF following CABG and the insertion site of the drainage tube was investigated. The study demonstrated that intercostal drain placement was associated with significantly higher levels of pain and an increased incidence of AF compared to subxiphoid placement. These findings suggest that the drain insertion site may be an independent predisposing factor for postoperative AF. However, since drain placement sites were not evaluated in our study, further analysis is needed to explore this relationship.

Surgical site infection (SSI) was observed in 4.8% of patients in our study. This rate is lower than the 7.3% reported by Alghamdi et al. [9] in their evaluation of infections following cardiac surgery. Risk factors for SSI identified in that study included diabetes, advanced age, obesity, and prolonged operative times. In our cohort, the incidence of these risk factors may have been relatively limited. Additionally, differences in institutional protocols, patient selection, and preoperative preparation may contribute to the observed variation.

The 30-day mortality rate following isolated CABG in our study was 7.1%. This is notably higher than the 3.2% reported in a large-scale national registry study from Denmark by Adelborg et al. [10], and the 2.61% reported in a multicenter cohort of 34.310 patients from the Italian National Health System [10,11]. However, the Italian study revealed considerable variation in mortality across institutions, ranging from 0.33% to 7.63%, highlighting the influence of institutional experience. The relatively high mortality rate observed in our center may be explained by the recent reinitiation of our CABG program, the limited number of cases, and the high-risk nature of the patient population. Furthermore, the lower mortality rates reported in the aforementioned studies likely reflect many years of accumulated experience, meticulous patient selection, and robust quality assurance processes. In this regard, it is reasonable to expect that outcomes will improve over time in newly restructured centers, especially with systematic performance monitoring and quality improvement initiatives.

During the reactivation process of our center, several challenges were encountered. Due to the suspension of surgical services, the local population had turned to alternative centers in neighboring cities, making it initially difficult to regain patient trust. Additionally, the surgical team faced some adaptation issues in re-establishing operational routines after a long hiatus. Nevertheless, with prior experience, strong team cohesion, and determination, these difficulties were successfully overcome, and the system was restored to full functionality in a short period.

Despite our center's recent reintroduction of CABG surgery, the rapid progress and promising outcomes observed suggest that the program has been re-established through a well-structured and disciplined approach. The emphasis on team cohesion, operational discipline, and patient safety has enabled our center to steadily move toward surgical excellence. The experience gained during this period is promising for the sustainability of clinical performance in the future.

Limitations

This study was conducted retrospectively and at a single center, and the limited sample size restricts the generalizability of the findings. As data were obtained from hospital records, the level of detail for some clinical parameters was limited. Furthermore, the follow-up period was confined to the early postoperative phase, and long-term outcomes could not be evaluated. Since only the on-pump surgical technique was used, comparisons with alternative surgical approaches were not possible. Therefore, multicenter prospective studies are needed to support and expand upon our findings.

Conclusion

In conclusion, the re-establishment of our CABG program yielded safe and efficient early outcomes, characterized by short operative times and low complication rates. Although the mortality rate reflects the initial adaptation phase, these findings validate the feasibility of restoring surgical services through a disciplined team approach. Continued quality monitoring and increased case experience are expected to further improve survival and long-term results.

Ethics Committee Approval: The study was approved by Batman Training and Research Hospital Ethics Committee (No: 420, Date: 20.03.2025).

Use of AI for Writing Assistance: No artificial intelligence tools were used in the preparation or analysis of this manuscript.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – A.A.; Design – A.A.; Supervision – T.C.; Data collection and/or processing – A.A., K.G.K.; Analysis and/or interpretation – K.G.K.; Literature search – A.A., T.C.; Writing – A.A., K.G.K., T.C.; Critical review – A.A., K.G.K., T.C.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research received no financial support from any funding agency in the public, commercial, or not-for-profit sectors.

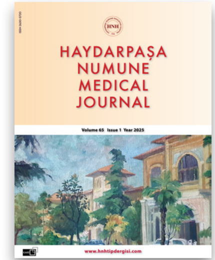
References

1. Onat A. TEKHARF taramalarının yöntemi, kohortları ve takibi. In: Onat A, Can G, Yüksel H, Ademoğlu E, Erginel Ünaltuna N, Kaya A editors. TEKHARF 2015: yetişkinlerimizin sağlığı ve kronik hastalıklara tıbbın yaklaşımına öncülük. İstanbul: Logos Yayıncılık; 2015. p.15. [In Turkish]
2. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022. Available at: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001038. Accessed Sep 11, 2025.
3. Bonzel T, Schächinger V, Dörge H. Description of a Heart Team approach to coronary revascularization and its beneficial long-term effect on clinical events after PCI. Clin Res Cardiol 2016;105:388–400. [CrossRef]
4. D'Agostino RS, Jacobs JP, Badhwar V, Fernandez FG, Paone G, Wormuth DW, et al. The society of thoracic surgeons adult cardiac surgery database: 2018 update on outcomes and quality. Ann Thorac Surg 2018;105:15–23. [CrossRef]
5. Dassanayake MT, Norton EL, Ward AF, Wenger NK. Sex-specific disparities in patients undergoing isolated CABG. Am Heart J Plus 2023;35:100334. [CrossRef]
6. Ruggieri VG, Bounader K, Verhoye JP, Onorati F, Rubino AS, Gatti G, et al. Prognostic impact of prolonged cross-clamp time in coronary artery bypass grafting. Heart Lung Circ 2018;27:1476–82. [CrossRef]
7. Omar A, Ehab M Elshihy, Singer M, Zarif D, Dawoud O. Perioperative risk factors predisposing to atrial fibrillation after CABG surgery. Heart Surg Forum 2021;24:E402–6. [CrossRef]
8. Apaydın Z, Timur B, Yazıcı B, Gözaçık K, Akbaş A, Aksu T, et al. A new predisposing factor for postoperative atrial fibrillation: Tube insertion site. Thorac Cardiovasc Surg 2024. [CrossRef]
9. Alghamdi BA, Alharthi RA, AlShaikh BA, Alosaimi MA, Alghamdi AY, Yusnoraini N, et al. Risk factors for post-cardiac surgery infections. Cureus 2022;14:e31198. [CrossRef]
10. Adelborg K, Horváth-Puhó E, Schmidt M, Munch T, Pedersen L, Nielsen PH, et al. Thirty-year mortality after coronary artery bypass graft surgery: A Danish nationwide population-based cohort study. Circ Cardiovasc Qual Outcomes 2017;10:e002708. [CrossRef]
11. Seccareccia F, Perucci CA, D'Errigo P, Arcà M, Fusco D, Rosato S, et al. The Italian CABG outcome study: Short-term outcomes in patients with coronary artery bypass graft surgery. Eur J Cardiothorac Surg 2006;29:56–64. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.67864
Haydarpasa Numune Med J 2025;65(4):302–312

ORIGINAL ARTICLE



hnhtipdergisi.com

The Effects of SGLT-2 Inhibitors on Biochemical Parameters, Kidney Function, and Adverse Events in Elderly Patients with Diabetes Mellitus and Chronic Kidney Disease: A Retrospective Single-Center Study

Bülent Demirelli

Department of Nephrology, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye

Abstract

Introduction: SGLT2 inhibitors (SGLT2i) have multiple metabolic benefits, including reducing glycated hemoglobin, weight, and blood pressure. Additionally, there are strong renoprotective effects in selected populations. The aim of our study was to investigate changes in biochemical parameters, incidence of complications, and associated factors following SGLT2i use in elderly patients.

Methods: The study population comprised patients aged 60 years and older who were treated with SGLT2i. The clinical and biochemical data were subjected to analysis at the baseline, six-month, and twelve-month marks following the commencement of treatment. The incidence of complications was evaluated.

Results: A total of 64 patients were included in the analysis, with 54.7% of them being female and an average age of 66.8±5.6 years. Significant reductions in blood pressure, HbA1c, estimated glomerular filtration rate (eGFR), and proteinuria were observed after treatment. Conversely, there was a notable increase in serum magnesium and phosphorus levels. The eGFR exhibited a decline of 3.7 mL/min at the six-month mark, which subsequently slowed to a decrease of 2.4 mL/min at the twelve-month interval. Four patients developed acute kidney injury (AKI), and seven patients experienced urinary tract infections (UTIs) after treatment. The most significant factor associated with the occurrence of side effects was identified as high CRP levels (OR: 1.261; p=0.024).

Discussion and Conclusion: The findings of our study indicate that SGLT2i are effective in improving glycemic control, blood pressure, and proteinuria in elderly patients. It is noteworthy that patients with elevated CRP levels prior to treatment experienced a higher incidence of side effects, indicating that such patients may require closer monitoring.

Keywords: Acute kidney injury; C-reactive protein; chronic kidney disease; diabetes mellitus; sodium-glucose co-transporter 2 inhibitors; urinary tract infections.

Diabetic kidney disease is a serious complication of Type 2 Diabetes mellitus (T2DM). It is the leading cause of end-stage kidney disease (ESRD) and therefore represents a major challenge in clinical practice and public health [1]. In order to overcome this problem, studies published in the last 5 years have been groundbreaking for the nephrology community, which has been waiting for a new and effective treatment for about 20–25 years

Correspondence: Bülent Demirelli, M.D. Department of Nephrology, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye
Phone: +90 536 235 32 42 **E-mail:** demirellibulent@gmail.com
Submitted Date: 20.04.2025 **Revised Date:** 28.04.2025 **Accepted Date:** 02.07.2025
Haydarpaşa Numune Medical Journal

after the understanding of the nephroprotective effects of renin-angiotensin blockers and the start of their clinical use [2]. Sodium glucose transporter-2 inhibitors (SGLT2i), Glucagon-like peptide-1 (GLP-1) agonists, and nonsteroidal mineralocorticoid receptor antagonists (nMRA) have shown promise for patients with diabetic nephropathy, with studies supporting their renoprotective effects [3]. SGLT2i, which is more commonly used among these drugs, shows its effect by inhibiting glucose reabsorption in the proximal tubules where 90% of glucose is reabsorbed. Thus, sodium excretion increases along with urinary glucose excretion. By changing tubuloglomerular feedback, it has been found to have positive effects such as decreasing intra-glomerular pressure and preventing hyperfiltration, as well as improving tubular oxygenation and reducing fibrosis [4]. There are six Food and Drug Administration (FDA) approved SGLT2i; empagliflozin and dapagliflozin are available for use in Türkiye.

In patients with T2DM enrolled in the EMPA-REG OUTCOME study, empagliflozin was associated with a reduced incidence of new-onset overt albuminuria, new-onset or worsening nephropathy, kidney replacement therapy initiation, and kidney disease-related mortality (HR: 0.61, 95% CI: 0.53–0.70; p<0.0001) [5]. In the DECLARE-TIMI 58 study (dapagliflozin vs. placebo) in patients with T2DM, a 1.3% absolute and 24% relative risk reduction (HR: 0.76; 95% CI: 0.67–0.87) was observed in secondary kidney outcomes (eGFR decline of 40% or more below 60 ml/min, new-onset ESRD, and death from kidney/cardiovascular causes) [6]. In accordance with the evidence of cardiorenal protection, the Kidney Disease Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends the use of SGLT2i for all patients with Type 2 DM and CKD (eGFR 20 mL/min/1.73 m^2 or higher), irrespective of glycemic level. The treatment may be continued until the point at which kidney replacement therapy is required, provided that the patient is able to tolerate this [7]. Although SGLT2i is an effective method of managing blood glucose levels and providing cardiovascular and kidney benefits, it is associated with a number of side effects. Such adverse effects include an elevated risk of diabetic ketoacidosis, genital and urinary tract infections (UTIs), and acute kidney injury (AKI). Further research is being conducted with the aim of enhancing our understanding of these risks and of reducing them while simultaneously optimizing the therapeutic benefits of SGLT2i [8].

The prevalence of Type 2 diabetes mellitus (T2DM) in older patients is increasing as the population ages and life expectancy increases. In 2021, 25% of the 530 million people with diabetes worldwide were older adults. By 2045, the number of older adults with diabetes is expected to double [9]. The older adult population is characterized by considerable heterogeneity, with notable variability in self-care, sarcopenia, and mobility [10]. It remains unclear whether diabetes contributes to the development of frailty or whether it is a consequence of the presence of multiple chronic conditions. The provision of diabetes care to frail older adults is a challenging endeavor, compounded by the presence of multiple comorbidities, polypharmacy, hypoglycemia, and the increasing detrimental effects of other adverse events [11]. Previous studies have highlighted potential concerns regarding the use of SGLT2i in elderly populations, particularly in light of the known side effects associated with this medication, including candidiasis and UTIs. However, SGLT2i have been demonstrated to confer a range of clinical benefits beyond their glucose-lowering effect, including a reduced risk of cardiovascular death, all-cause mortality, heart failure, kidney disease, and improvements in weight and blood pressure [12,13]. In light of these multiple beneficial effects, ease of administration, good tolerability, and negligible hypoglycemia, SGLT2i appear to be an ideal therapeutic option for older adults. Post hoc analyses of drug trials also demonstrate the clinical value of SGLT2i in this population. The study of dapagliflozin in patients over the age of 65 demonstrated that the drug was efficacious in this age group and that it was safe in terms of side effects [14]. A similar outcome was observed with empagliflozin [15]. Nevertheless, a meta-analysis of data from elderly patients revealed an increased incidence of acute kidney injury, genital mycotic infections, and diabetic ketoacidosis, while the renoprotective effects observed in patients with eGFR below 60 ml/min were found to be diminished in comparison to those observed in the placebo group [16]. In light of the existing literature, it is unclear whether SGLT2i has beneficial or adverse effects on elderly patients. In practice, clinicians are often reluctant to prescribe SGLT2 inhibitors to older people with diabetes because of safety concerns. This is because the expected cardiovascular and kidney benefits are likely to occur in the distant future, while dehydration and genital infections can cause immediate discomfort [17]. Consequently, our study aimed to investigate the impact of SGLT2i on biochemical parameters, the incidence of complications, and the potential associated factors in elderly patients with diabetes and CKD at 6 and 12 months following drug administration.

Materials and Methods

Data Management

The study included patients over 60 years of age with DM who were followed up in the nephrology outpatient clinic between 2022 and 2024 and who were started on SGLT2i for the purpose of treating DM and providing cardiorenal protection. The clinical and biochemical findings of the patients were subjected to retrospective analysis, resulting in the preparation of a data set. The clinical findings, comorbidities, medications, and current blood and urine tests (urea, creatinine, C-reactive protein (CRP), albumin, hemogram, lipid levels, parathormone, HbA1c, CRP, proteinuria, and albuminuria) were recorded, as were the demographic characteristics of the patients. The creatinine values of all patients at the 6th and 12th month after the commencement of treatment were analyzed and recorded. Furthermore, all hospital admissions within one year from the start of treatment were analyzed retrospectively.

The exclusion criteria comprised the following: age below 60 years, receiving kidney replacement therapy, eGFR < 25 ml/min/1.73 m^2, previous use of SGLT-2i treatment, diagnosis of type 1 DM, presence of active urinary tract infection, dehydration, hypovolemia, sepsis, or urinary catheterization, complication-free interruption of SGLT-2i treatment after initiation, insufficient data available.

Complication Definition

In accordance with the existing literature, acute kidney injury (AKI) was defined as an increase in creatinine levels of 0.5 mg/dL [18]. In addition to the symptoms of cystitis, a urinalysis with ≥10 WBC/µL and positive results for leukocyte esterase and nitrite on the dipstick test were interpreted as indicative of acute cystitis and an uncomplicated urinary tract infection (UTI). The occurrence of two or more UTIs within a month or three or more UTIs within a year was defined as recurrent UTI [19].

Statistical Analysis

The statistical analyses were conducted using the SPSS (version 23.0, SPSS, Chicago, IL, USA) software. Descriptive statistical methods were employed to analyze the data, with mean±standard deviation used for continuous numerical variables with and without normal distribution, and number and percentage used for categorical variables. The blood pressure measurements and results of patients who were initiated on SGLT-2 inhibitors were analyzed according to three categories: baseline, six months, and 12 months. A repeated measures analysis of variance (Greenhouse-Geisser) was conducted on the repeated measurements of normally distributed parameters to facilitate a comparison of the three time periods. In the case of non-normally distributed parameters, a Friedman analysis was conducted when three parameters were compared, while a Wilcoxon analysis was employed when two parameters were compared (non-parametric tests). Finally, a Bonferroni correction was applied. A two-group comparison was conducted between patients with and without side effects of SGLT2i. For normally distributed numerical variables, an Independent Sample T-test was employed; for non-normally distributed variables, a Mann-Whitney U-test was used; and for categorical variables, a chi-square test was applied. The parameters that were significant in the univariate analysis and did not show multicollinearity were included in the binary logistic regression analysis. The backward LR strategy was applied in the multivariate analysis. The risk estimates were presented as unadjusted (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI). The Hosmer-Lemeshow statistic was used to determine the fit of the model in the logistic regression analysis. A p-value of less than 0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

All procedures performed in the study were conducted in accordance with the ethical standards set forth by the Clinical Research Ethics Committee of Kırklareli University Faculty of Medicine. The protocols in this study (Protocol No. P202300036/02) were approved by the aforementioned committee and are in alignment with the ethical principles set forth in the 1964 Declaration of Helsinki.

Written informed consent was obtained from all patients/authors participating in the study.

Results

A total of 64 patients were included in the study, of whom 35 were female (54.7%) and the mean age was 66.8±5.9 years. A total of 53 patients (83.8%) had an estimated glomerular filtration rate (eGFR) below 60 ml/min, while 44 patients (68.8%) exhibited proteinuria. The mean duration of diabetes diagnosis was 13.5±9 years. In the group of 44 patients with proteinuria, the mean duration of diagnosis was 2±1.8 years. Hypertension was present in 58 patients (90.6%), coronary artery disease (CAD) in 27 (42.5%), heart failure in 12 (18.8%), and diabetic retinopathy/neuropathy in 24 (37.5%). Of the patients, 33 (51.6%) were administered dapagliflozin, while 31

Table 1. Patient demographics and data analysis

Parameters	Results n=64		Parameters	Results n=64	
	n	%		n	%
Categorical variables			Diuretic	36	56.3
Female	35	54.7	ACEi /ARB	46	71.4
Dapagliflozin	33	51.6	Statin	31	48.4
Empagliflozin	31	48.4	Adverse effects after SGLT-2	11	17.2
eGFR <60 ml/ min	53	82.8	AKI	4	6.3
Proteinuria	44	68.8	UTIs	7	10.9
Coronary artery disease	27	42.5		Mean±SD	
Heart failure	12	18.8	Numerical variables		
Hypertension	58	90.6	Age	66.8±5.9	
Diabetic Retinupathy/Neuropathy	24	37.5	Duration of CKD diagnosis (years)	3.1±2.3	
Metformin	34	53.1	CAD, duration of diagnosis (years)	2.4±2	
Sulfanilurea	2	3.1	HF, duration of diagnosis (years)	1.9±0.9	
DPP-4i	20	31.3	Proteinuria, duration of diagnosis (years)	2±1.8	
Insulin	28	43.8	Duration of diabetes diagnosis (years)	13.5±9	
GLP-1 Agonist	3	4.7	Duration of hypertension diagnosis (years)	13.1±10.1	
Acetylsalicylic acid	37	57.8			

CKD: Chronic kidney disease; CAD: Coronary artery disease; HF: Heart failure; eGFR: Estimated glomerular filtration rate; SD: Standard deviation; AKI: Acute kidney injury; UTIs: Urinary tract infection; SGLT-2i: Sodium glucose transporter 2 inhibitor; DPP-4i: Dipeptidyl peptidase-4 inhibitor; ACEi : Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; GLP -1: Glucagon -like peptide-1.

(48.4%) were administered empagliflozin. The remaining parameters are presented in Table 1.

A comparison of blood pressure measurements, urine, and blood tests of the patients before and 6–12 months after treatment revealed a statistically significant reduction in systolic (p = 0.0001) and diastolic blood pressure (p=0.001), fasting blood glucose (p=0.015), HbA1c value (p=0.0001), eGFR level (p=0.001), proteinuria (p=0.013), and albuminuria (p=0.0001) values compared to the pretreatment period. Significant increases were observed in serum creatinine (p=0.001), urea (p=0.039), magnesium (p=0.005), and phosphorus (p=0.048) values between the groups. No significant differences were observed in serum albumin, potassium, sodium, calcium, bicarbonate, hemoglobin, lipid levels, vitamin D, parathormone, ferritin, uric acid, and CRP values between the groups. The results are presented in Table 2.

When patients were divided into two groups according to eGFR values, stage 1–2 and stage 3–4, there was no significant difference in the change in eGFR between the two groups at 0 and 12 months (p=0.075) (Fig. 1).

A total of 11 patients (17.1%) experienced side effects potentially associated with SGLT2i. Of the aforementioned patients, four developed acute kidney injury (AKI) and seven developed urinary tract infection (UTI). Of the patients diagnosed with UTI, six presented with acute cystitis/uncomplicated UTI, while one presented with recurrent cystitis. A urine culture was requested from patients presenting with symptoms of urinary tract infection. Systemic antibiotic therapy was initiated in patients exhibiting both clinical and laboratory findings (positive urine culture) indicative of infection. No patients developed a UTI that necessitated hospitalization or a complicated UTI, such as pyelonephritis. In six of the seven patients diagnosed with UTI, SGLT2i treatment was reinitiated following treatment, and UTI did not recur. Consequently, the treatment could be continued. However, as a single patient developed recurrent UTIs (more than three in a twelve-month period) and no other identifiable cause was identified, SGLT2i treatment was discontinued at the thirteenth month of treatment. All patients diagnosed with a UTI were female, and no underlying facilitating factor was identified.

Kidney dysfunction was identified in three of the four patients with AKI during the initial month of treatment. Given that prerenal causes were postulated to be the etiology in two of these patients, SGLT2i was discontinued, and they were monitored with regard to oral hydration. At the outpatient clinic follow-up, the creatinine values of

Table 2. Presentation of the parameters measured before and 6 and 12 months after the start of SGLT-2i and the results of the analysis between months

Parameter (mean±SD), n=64	Pretreatment	Month 6	Month 12	p
Systolic blood pressure (mm Hg)	133.9±17.9	125±14.7***	122±13.5***,X	**0.0001**
Diastolic blood pressure (mm Hg)	78.1±9.4	73.7±8.6*	72.5±10.3*	**0.001**
Glucose (mg/dl)	177±93.3	140±54.9*	147.6±57.2	**0.015**
Creatinine (mg/dl)	1.27±0.4	1.36±0.46**	1.32±0.44*	**0.001**
eGFR (CKD-EPI 2021) (ml/min/1.72 m^2)	58.4±18.9	54.7±19.8*	56±19.3	**0.001**
Urea (mg/dl)	50.9±21	56.4±23.8*	53.8±19.1	**0.039**
Sodium (mEq /L)	139.5±2.8	140.3±3.2	139.8±2.6	0.124
Potassium (mEq /L)	4.7±0.4	4.7±0.5	4.7±0.4	0.77
Calcium (mg/dl)	9.7±0.4	9.7±0.5	9.5±1	0.25
Magnesium (mg/dl) n=55	1.9±0.3	N/A	2.1±0.3	**0.005**
Phosphorus (mg/dl) n=61	3.6±0.5	3.8±0.5	3.8±0.5	**0.048**
Albumin (g/dl) n=62	4.4±0.3	4.3±0.3	4.3±0.3	0.07
Bicarbonate (mEq /L) n=37	24.6±3	N/A	25.6±3	0.132
Hemoglobin (g/dl)	12.9±1.8	12.9±1.8	13±1.9	0.35
Cholesterol (mg/dl)	186±42	179±44	175±38	0.22
LDL (mg/dl)	105±36	99.4±35.3	99.5±32	0.36
HDL (mg/dl)	46±13	46.6±13.1	44.8±13.2	0.46
Triglyceride (mg/dl)	183±89	163±75	158±90	0.09
Vitamin D (ng/mL) n=49	22.8±12.8	N/A	25.7±9.2	0.43
Parathyroid hormone (pg/mL) n=40	71±40	N/A	64.2±36.6	0.91
Ferritin (ml/ng)	76±76	69±66	80±79.8	0.55
Uric acid (mg/dl) n=51	6.1±2	N/A	5.6±1.5	0.83
Proteinuria (gr/day) n=44	894±956	418±631,*n=30	477±657	**0.013**
Albuminuria (gr/day) n=33	615±817	N/A	250±485	**0.0001**
HbA1c (%)	8.6±2.3	7.6±1.6*	7.4±1.2***	**0.0001**
CRP (mg/L)	4.7±4	5.3±6.4	4.3±3.8	0.51

*: $p<0.05$ vs 0.month; **: $p<0.001$ vs 0.month; ***: $p<0.0001$ vs 0.month, X: $p<0.05$ vs 6th month. SD: Standard deviation; LDL: Low density lipoprotein; HDL: High density lipoprotein; CRP: C reactive protein; HbA1c: glycosylated hemoglobin; eGFR: Estimated glomerular filtration rate.

these two patients were found to have decreased to the basal level, and SGLT2i was restarted. Examination of the emergency department applications of the remaining two patients revealed elevated creatinine levels. They were admitted to the hospital and monitored for AKI. One patient developed AKI in the third month of treatment, which was attributed to gastroenteritis-related prerenal causes and was managed with intravenous hydration. The final patient was diagnosed with cardiorenal syndrome type 2 and was undergoing treatment with diuretics. Despite a reduction in the diuretic dose following the initiation of SGLT2i treatment, the patient was hospitalized with AKI secondary to diuretic excess and decreased oral intake. However, kidney functions and the patient's condition improved with hydration and a reduction in the diuretic treatment. SGLT2i was restarted in both patients at the outpatient clinic control. There were no cases of AKI following the restart of SGLT2i.

A comparison of the two groups, defined as those with and without side effects within a one-year period, revealed that female gender ($p=0.047$) and high pre-treatment CRP level

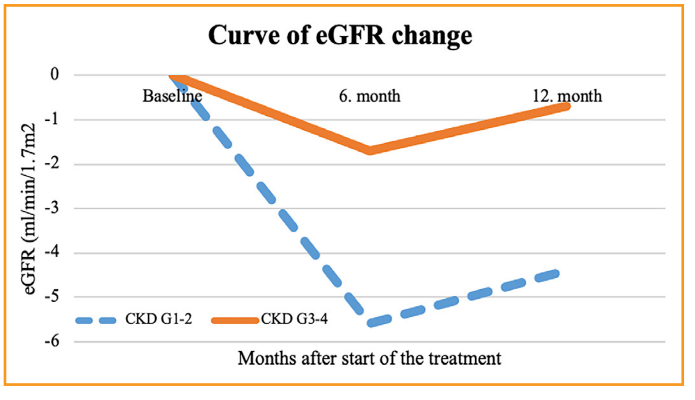


Figure 1. Change in eGFR by stage of chronic kidney disease after treatment initiation.

CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate.

Table 3. Parameters that were found to differ between the two groups when patients were grouped according to Sglt2 inhibitor-related side effects (univariate analysis)

Parameter	No side effects (n=53)		Side effects (n=11)		p
	n	%	n	%	
Gender					
Female	26	74.3	9	25.7	0.047
Male	27	93.1	2	6.9	
CRP (mg/L)	4±3.9		7.9±3		0.001

CRP: C reactive protein.

Table 4. Parameter found to be associated in multivariate analysis when patients were grouped according to SGLT-2 inhibitor-related side effects (binary logistic regression-forward LR)

Parameter	p	Exp (B)	95% CI (low-high)
CRP (mg/L)	0.024	1.261	1.032–1.573

CI: Confidence interval.

(p=0.001) were significantly more prevalent in the group with side effects (Table 3). No statistical significance was found in the comparison of the type of SGLT-2 inhibitor and the frequency of side effects.

The results of the multivariate analysis indicated that the only factor associated with the occurrence of side effects was the pretreatment CRP level (OR 1.261; 95% CI 1.032–1.573; p=0.024) (Table 4).

Discussion

The global prevalence of diabetes mellitus is increasing, with the condition continuing to cause chronic health problems. Diabetes mellitus is a significant contributor to CKD, with kidney replacement therapy and cardiovascular mortality. Intensive glucose control and blood pressure management are key strategies for slowing the progression of CKD in diabetic patients [20]. Furthermore, due to the complex pathophysiology of DM, it is necessary to implement targeted prevention and treatment strategies to reduce organ damage. In this search for treatments, following the astonishing results shown in randomized controlled trials in terms of prevention of cardiovascular events, the drug group SGLT2i, which has also demonstrated significant efficacy in preventing the progression of CKD regardless of diabetes status, has initiated a paradigm shift in the treatment of patients with kidney disease as well as DM [21,22]. The treatment of diabetes in the elderly presents a number of challenges, including potential drug interactions and the paucity of data from randomized controlled trials. Moreover, the specific guidelines for the treatment of DM in the elderly address the use of the most recently approved therapies, such as SGLT2i, only to a limited extent [23]. Although a post-hoc analysis of the pivotal studies of empagliflozin and dapagliflozin revealed that efficacy and safety in elderly patients were comparable to other populations, the most recent meta-analysis yielded conflicting results [13,15,16]. Accordingly, the objective of this study was to make a contribution to the existing literature by determining the effects of SGLT2i in elderly patients. The objective was to investigate the effects and safety of these drugs in clinical practice in diabetic patients over 60 years of age, as well as the parameters affecting the incidence of side effects over a one-year period. Significant reductions in glycemic parameters, blood pressure, and proteinuria/albuminuria were observed following the administration of SGLT2i, while there was a notable increase in blood magnesium, phosphorus, and urea levels. Although a significant decline in kidney function was observed during the initial six-month period, the eGFR demonstrated a tendency towards improvement over the longer term (one year). With regard to adverse effects, UTI and AKI were moderate and did not necessitate the discontinuation of treatment, except in one patient. The independent parameter in terms of adverse effects was the level of CRP prior to the initiation of treatment.

In individuals with no underlying pathology, all tubular glucose is reabsorbed, and there is no urinary excretion of glucose. SGLT1 and 2 play a role in the renal reabsorption of glucose. SGLT2 is responsible for 90% of glucose reuptake in segment 1 of the proximal tubule, while SGLT1 accounts for the remaining 10% [24]. The selective inhibition of SGLT channels by SGLT2i or phlorizin derivatives, collectively known as gliflozins, has been demonstrated to exert profound metabolic and hemodynamic effects [25]. They function by blocking SGLT2 in the proximal tubule of the kidney, thereby preventing glucose reabsorption, increasing glucose excretion, and osmotic diuresis [26]. In contrast to other antidiabetic drugs, which act by increasing insulin secretion or enhancing insulin sensitivity to receptors, these agents prevent the reuptake of glucose into the bloodstream, thereby improving HbA1c levels and glucose parameters. In addition to reducing glycemia, these agents have been observed to exert additional beneficial effects, including modest reductions in systemic blood pressure (4–6 mmHg) and weight loss [27,28]. The results of our study demonstrated a significant improvement in glycemic parameters in our patients, which is in accordance with the findings reported in the literature. Furthermore, a notable reduction in both systolic and diastolic blood pressure was observed.

The mechanism underlying diabetic kidney disease is the elevation of intraglomerular pressure and hyperfiltration resulting from the overstimulation of the renin-angiotensin-aldosterone system (RAAS), in addition to the direct effects of hyperglycemia. An increase in angiotensin-2 and SGLT1/2 receptor levels has been observed in patients with diabetic CKD [2]. SGLT2i exerts its renoprotective effects by suppressing the RAAS through the stimulation of tubuloglomerular feedback (TGF) and increased transmission to the macula densa, which is a consequence of decreased reabsorption of sodium and glucose. This results in the constriction of the afferent arterioles and a reduction in glomerular hydrostatic pressure. It is hypothesized that this provides kidney protection by reducing hyperfiltration injury [29]. In the study conducted by Kohan et al. [30], it was observed that the mean eGFR change in patients undergoing treatment with SGLT2i (dapagliflozin) exhibited a decrease of 4.8 and 4.4 ml/min, respectively, in the sixth and twelfth months of treatment when compared to the pretreatment period. In another study, the eGFR decreased by 4 mL/min at week 12 in patients with stage 3 CKD who were treated with empagliflozin. However, there was a slight improvement at week 52. It is noteworthy that the eGFR returned to its original baseline values following the cessation of the drug treatment [31]. The longer-term effects of SGLT2i on kidney functions have been investigated in placebo-controlled studies with extended follow-up periods. The results of these clinical trials indicated that SGLT2i typically resulted in an initial reduction in eGFR. In the longer term, evidence indicates that it preserves kidney function and slows the progression of CKD [32–34]. The data indicate that the initial reduction in eGFR in response to SGLT2 inhibition is reversible and thus reflects functional rather than structural changes [32]. It is anticipated that an annual decline in eGFR will occur in patients with CKD. While there is no clear limit to this decline, it is recommended that individuals exhibiting an eGFR decline of more than 3 ml/min/1.73 m^2/year undergo further investigation [35]. In our study, a decrease of 3.7 and 2.4 ml/min was observed at 6 and 12 months, respectively. As observed in previous literature, our study similarly demonstrated that hemodynamic decline in the early phase tended to improve over a longer period of time. In a meta-analysis conducted by Liu et al. [16] on elderly patients, it was reported that the renoprotective effects decreased in patients with eGFR below 60 ml/min, and early-stage eGFR decline did not reach the baseline level. Although our study did not include a longer follow-up period, the mean eGFR of the patient population was 58 ml/min, and GFR changes consistent with the aforementioned study were detected.

SGLT2i has been demonstrated to diminish proteinuria, with multiple proposed mechanisms of action. Firstly, proteinuria is reduced as a consequence of increased TGF and decreased intraglomerular pressure and hyperfiltration [36]. Furthermore, SGLT2 inhibition elevates the concentration of ketones, which suppress mTORC1 hyperactivation. Consequently, podocyte injury and proteinuria are diminished [37]. Additionally, SGLT2i has been demonstrated to contribute to a reduction in both systolic and diastolic blood pressure, which has an indirect effect on the reduction of proteinuria [38]. These effects collectively contribute to a reduction in proteinuria and a slowing of the progression of chronic kidney disease. The results of our study demonstrated a statistically significant reduction in proteinuria levels among the patient cohort. The observed increase in proteinuria at month 12 compared to month 6 appears to be associated with the recovery of the eGFR to its baseline level. Nevertheless, the considerable reduction in proteinuria compared to the baseline continues at month 12.

SGLT2i is a class of drugs that has been demonstrated to exert an influence on serum electrolyte levels, including magnesium and phosphate. A meta-analysis demonstrated an increase in mean magnesium levels of 0.04 to 0.1 mmol/L following treatment [39]. The potential mechanisms underlying this phenomenon include volume depletion and augmented magnesium reabsorption, which may occur in the proximal tubule or thick ascending limb [40]. A study conducted on three patients with refractory hypomagnesemia demonstrated that canagliflozin, empagliflozin, and dapagliflozin were capable of reducing fractional excretion of magnesium and elevating serum magnesium levels. This suggests that SGLT2i may represent a novel therapeutic avenue for conditions characterized by hypomagnesemia [41]. It is possible that SGLT2i may increase tubular reabsorption of phosphate, which could result in elevated serum phosphate levels [42]. In our study, the administration of SGLT2i was found to result in a notable elevation in magnesium and phosphorus levels.

Although SGLT2i has numerous beneficial effects, it has been linked to a number of adverse events, including diabetic ketoacidosis, genital infection, decreased intravascular volume, and an elevated risk of AKI, fractures, amputations, pancreatitis, and UTIs [43,44]. In elderly patients, it was reported that 23.5% of patients discontinued the drug due to adverse effects, with the most common being genitourinary tract infection [34]. This rate was 17.1% in our study. As demonstrated in the aforementioned study, age was identified as a contributing factor to the incidence of side effects. The younger age of the patients in our study may have contributed to a reduction in the incidence of side effects (mean age 75.4±3.9 vs. 66.8±5.9 years).

SGLT2i may contribute to volume depletion and predispose to AKI through its natriuretic properties, effects on TGF, and various other mechanisms. In addition, the volume and intrarenal hemodynamic effects of SGLT2i may be synergistic when combined with RAAS antagonists and conventional diuretics, which are commonly prescribed in this patient population with T2DM [45]. It has also been suggested that it may cause AKI due to its uricosuric effect and medullary hypoxia [46]. The FDA has expressed concerns regarding the potential risk of AKI associated with SGLT2i. In December 2015 and June 2016, the FDA issued two warnings pertaining to the safety of SGLT2i. The aforementioned warnings were issued due to the reporting of 101 confirmed cases of AKI with canagliflozin or dapagliflozin to the FDA adverse event reporting system since 2013 [47]. Nevertheless, a recent randomized, placebo-controlled trial demonstrated that there is no elevated risk of AKI during SGLT2 inhibition [6]. Moreover, meta-analyses have shown that the incidence of AKI is reduced rather than increased compared with the control group [48,49]. In contrast to case reports, placebo-controlled studies and meta-analyses have been more effective in demonstrating the safety of SGLT2i with respect to kidney function [48]. It is important to note that the risk of AKI due to other causes in elderly patients with CKD and DM is not lower than in the general population. The reversible AKI observed in five patients in our study can be interpreted within this framework.

The presence of T2DM has been demonstrated to elevate the risk of developing UTIs and non-sexually transmitted genital infections, a phenomenon that can be attributed to elevated levels of glucose in the urine [50]. The pharmacologically induced urine glucose with SGLT2i may result in an increased growth rate of commensal genital microorganisms. It can be reasonably deduced that the risk of genital infections and UTIs is likely to be further increased in patients treated with SGLT2i [51]. In December 2015, the FDA issued a warning that SGLT2i may cause serious urinary tract infections [52]. A number of systematic reviews and meta-analyses have been conducted to examine this issue, but the findings are inconsistent [28,53]. It has been estimated that between 10 and 15 percent of women taking SGLT2i will develop urinary tract infections and vulvovaginitis [51]. In a study conducted by Lunati and colleagues, the two most common reasons for drug discontinuation in elderly patients were found to be UTI and worsening kidney function [34]. In our study, the prevalence of UTI was 10.9%, with all patients with UTI being female. The findings are consistent with those of previous studies and indicate that, particularly in women with recurrent vulvovaginitis and urinary tract infections, the underlying condition should be addressed before initiating treatment and the drug should be started with greater caution.

Factors that may predict drug side effects have been previously investigated in the literature. In a study investigating the side effect of AKI in patients started on SGLT2i, the frequency was found to be 1.8%. It was shown that the frequency of AKI increased in elderly patients, patients with higher serum potassium, glucose, creatinine, and albuminuria [54]. In another study, a higher incidence of AKI was found in elderly patients, high drug dosages, loop diuretic users, and patients with impaired kidney function [55]. Banerjee et al. [56] showed that duration of DM was the factor that increased the risk of SGLT2i-related genital mycotic infection in men. In our study, elevated CRP was found to be a determinant of adverse events. One explanation for this may be the exacerbation of subclinical inflammation, such as unrecognized genital or asymptomatic urinary tract infections, especially in older patients, after SGLT2i initiation. Moderate elevations in CRP can often be detected, especially in lower urinary tract infections [57]. When the relationship between CRP and AKI, another adverse effect, was reviewed in the literature, it was reported that elevated CRP was identified as a risk factor for AKI [58]. In addition, patients with elevated CRP may be more susceptible to AKI of prerenal origin. It is therefore plausible that elevated CRP is associated with adverse effects. Although SGLT2i is generally well tolerated by most patients, clinicians should consider potential adverse effects and warn patients when prescribing these agents. In older patients with a high potential for adverse effects, such as those with frequent urinary tract infections or predisposing factors for urinary tract infections, patients with inadequate volume status and signs of infection, it may be more rational to delay treatment or to start treatment with close follow-up. The detection of infectious diseases in elderly patients can be difficult because of weak clinical findings. Therefore, patients with elevated CRP should be questioned in detail, and caution should be exercised when starting drugs such as SGLT2i, which have good long-term effects but interfere with compliance in the event of illness.

It should be noted that the present study was not without limitations. As the study was based on data extracted from electronic medical records, we encountered missing data and difficulties in accessing the results of some previous laboratory tests, which are common limitations of retrospective studies. It would be beneficial to corroborate our findings with a longer follow-up period. The sample size was necessarily limited by the fact that the study was conducted in a single center and included a group of elderly patients with chronic kidney disease. A randomized study with a similar group, including patients not using SGLT2i, may provide a more accurate answer to the questions that were the aim of our study. Finally, although comorbidity and polypharmacy are confounding factors in terms of the etiology of AKI, we attempted to avoid overestimating SGLT2i-related side effects by minimizing the impact of these factors as much as possible.

Conclusion

SGLT2i confer substantial benefits with regard to cardiovascular and kidney health in elderly patients with T2DM, thereby representing a highly valuable therapeutic option. The findings of our study demonstrate that treatment with SGLT2i is associated with notable improvements in glycemic parameters, blood pressure, and proteinuria/albuminuria in elderly patients with T2DM. SGLT2i represents an efficacious alternative for the enhancement of metabolic parameters, the conservation of kidney functionality, and the stabilization of electrolytes, including magnesium. In particular, despite a decline in eGFR observed during the initial six-month treatment period, eGFR tends to improve after one year. However, the use of SGLT2i has been linked to a number of adverse effects. These include an increased risk of urinary tract infections, genital mycotic infections, and volume depletion. It is therefore recommended that adverse events such as AKI and UTI be monitored carefully during treatment. The adverse effects observed during the course of this study were mild and infrequent, and in no case did they necessitate the complete cessation of the drug. An elevated CRP level prior to treatment was found to be associated with the occurrence of adverse events. In order to optimize the established beneficial effects of this pharmacological category, which is generally considered safe in this patient population, it is crucial to be aware of the potential adverse effects and their management, and to advocate for the continued use of the drug.

Ethics Committee Approval: The study was approved by Kırklareli University Clinical Research thics Committee (Protocol No. P202300036/02, Date: 15.06.2023).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declare that there is no conflict of interest.

Financial Disclosure: The author declared that this study has received no financial support.

References

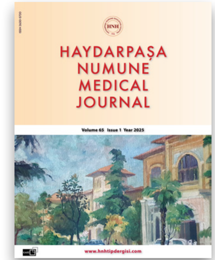
1. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: A 21st century challenge. Lancet Diabetes Endocrinol 2014;2:56–64. [CrossRef]
2. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompór T. Inflammation and oxidative stress in diabetic kidney disease: The targets for SGLT2 inhibitors and GLP-1 receptor agonists. Int J Mol Sci 2021;22:10822. [CrossRef]
3. Mazzieri A, Porcellati F, Timio F, Reboldi G. Molecular targets of novel therapeutics for diabetic kidney disease: A new era of nephroprotection. Int J Mol Sci 2024;25:3969. [CrossRef]
4. Sinha SK, Nicholas SB. Pathomechanisms of diabetic kidney disease. J Clin Med 2023;12:7349. [CrossRef]
5. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–34. [CrossRef]
6. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57. [CrossRef]
7. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 2022;102:S1–127. [CrossRef]
8. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. Diabetes Metab 2018;44:457–64. [CrossRef]
9. Ogurtsova K, Guariguata L, Barengo NC, Ruiz PL, Sacre JW, Karuranga S, et al. IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. Diabetes Res Clin Pract 2022;183:109118. [CrossRef]
10. Mitnitski A, Howlett SE, Rockwood K. Heterogeneity of human aging and its assessment. J Gerontol A Biol Sci Med Sci 2017;72:877–84.
11. Evans M, Morgan AR, Davies S, Beba H, Strain WD. The role of sodium-glucose co-transporter-2 inhibitors in frail older adults with or without type 2 diabetes mellitus. Age Ageing 2022;51:afac201. [CrossRef]
12. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular

outcome trials. Lancet 2019;393:31–9. Erratum in: Lancet 2019;393:30. [CrossRef]
13. Brown E, Wilding JPH, Alam U, Barber TM, Karalliedde J, Cuthbertson DJ. The expanding role of SGLT2 inhibitors beyond glucose-lowering to cardiorenal protection. Ann Med 2021;53:2072–89. [CrossRef]
14. Cahn A, Mosenzon O, Wiviott SD, Rozenberg A, Yanuv I, Goodrich EL, et al. Efficacy and safety of dapagliflozin in the elderly: Analysis from the DECLARE-TIMI 58 study. Diabetes Care 2020;43:468–75. [CrossRef]
15. Monteiro P, Bergenstal RM, Toural E, Inzucchi SE, Zinman B, Hantel S, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. Age Ageing 2019;48:859–66. [CrossRef]
16. Liu Y, An C, Liu P, Yang F, Zhao Q. Comparative safety of sodium-glucose co-transporter 2 inhibitors in elderly patients with type 2 diabetes mellitus and diabetic kidney disease: A systematic review and meta-analysis. Ren Fail 2023;45:2217287. [CrossRef]
17. Jeon JY, Kim DJ. Benefit and safety of sodium-glucose co-transporter 2 inhibitors in older patients with type 2 diabetes mellitus. Diabetes Metab J 2024;48:837–46. [CrossRef]
18. Zhuo M, Paik JM, Wexler DJ, Bonventre JV, Kim SC, Patorno E. SGLT2 inhibitors and the risk of acute kidney injury in older adults with type 2 diabetes. Am J Kidney Dis 2022;79:858–67.e1. [CrossRef]
19. Al Lawati H, Blair BM, Larnard J. Urinary tract infections: Core curriculum 2024. Am J Kidney Dis 2024;83:90–100. [CrossRef]
20. Bahjat M, Ahmed MH, saad Hassan M. Diabetes And chronic renal failure: A relationship. J Adv Sci Nanotechnol 2022;1:141–6. [CrossRef]
21. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. JAMA Cardiol 2021;6:148–58. [CrossRef]
22. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: Collaborative meta-analysis of large placebo-controlled trials. Lancet 2022;400:1788–801.
23. American Diabetes Association. 12. Older adults: Standards of medical care in diabetes-2019. Diabetes Care 2019;42(Suppl 1):S139–47. [CrossRef]
24. Malhotra A, Kudyar S, Gupta AK, Kudyar RP, Malhotra P. Sodium glucose co-transporter inhibitors - A new class of old drugs. Int J Appl Basic Med Res 2015;5:161–3. [CrossRef]
25. Podestà MA, Sabiu G, Galassi A, Ciceri P, Cozzolino M. SGLT2 inhibitors in diabetic and non-diabetic chronic kidney disease. Biomedicines 2023;11:279. [CrossRef]
26. Garg V, Verma S, Connelly K. Mechanistic insights regarding the role of SGLT2 inhibitors and GLP1 agonist drugs on cardiovascular disease in diabetes. Prog Cardiovasc Dis 2019;62:349–57. [CrossRef]
27. Lee PC, Ganguly S, Goh SY. Weight loss associated with sodium-glucose cotransporter-2 inhibition: A review of evidence and underlying mechanisms. Obes Rev 2018;19:1630–41. [CrossRef]
28. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab 2016;18:783–94. [CrossRef]
29. Skrtić M, Yang GK, Perkins BA, Soleymanlou N, Lytvyn Y, von Eynatten M, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. Diabetologia 2014;57:2599–602. [CrossRef]
30. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014;85:962–71. [CrossRef]
31. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369–84. [CrossRef]
32. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. Clin Sci (Lond) 2018;132:1329–39. [CrossRef]
33. Thomson SC, Vallon V. Renal effects of sodium-glucose co-transporter inhibitors. Am J Cardiol 2019;124(Suppl 1):S28–S35. [CrossRef]
34. Lunati ME, Cimino V, Gandolfi A, Trevisan M, Montefusco L, Pastore I, et al. SGLT2-inhibitors are effective and safe in the elderly: The SOLD study. Pharmacol Res 2022;183:106396. [CrossRef]
35. Tsai CW, Ting IW, Yeh HC, Kuo CC. Longitudinal change in estimated GFR among CKD patients: A 10-year follow-up study of an integrated kidney disease care program in Taiwan. PLoS One 2017;12:e0173843. [CrossRef]
36. Clemmer JS, Yen TE, Obi Y. Modeling the renoprotective mechanisms of SGLT2 inhibition in hypertensive chronic kidney disease. Physiol Rep 2023;11:e15836. [CrossRef]
37. Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, Yasuda-Yamahara M, et al. SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mTORC1 inhibition. Cell Metab 2020;32:404–19.e6. [CrossRef]
38. Afrooghe A, Nematollahi N, Hakemi MS, Nassiri A. MO157: Evaluating the effect of SGLT2 inhibitors on proteinuria and glomerular filtration rate in non-diabetic patients with proteinuria. Nephrol Dial Transplant 2022;37(Suppl 3):gfac066.059. [CrossRef]
39. Tang H, Zhang X, Zhang J, Li Y, Del Gobbo LC, Zhai S, et al. Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia 2016;59:2546–51. [CrossRef]

40. Dominguez Rieg JA, Xue J, Rieg T. Tubular effects of sodium-glucose cotransporter 2 inhibitors: intended and unintended consequences. Curr Opin Nephrol Hypertens 2020;29:523–30. [CrossRef]
41. Ray EC, Boyd-Shiwarski CR, Liu P, Novacic D, Cassiman D. SGLT2 inhibitors for treatment of refractory hypomagnesemia: a case report of 3 patients. Kidney Med 2020;2:359–64. [CrossRef]
42. Filippatos TD, Tsimihodimos V, Liamis G, Elisaf MS. SGLT2 inhibitors-induced electrolyte abnormalities: An analysis of the associated mechanisms. Diabetes Metab Syndr 2018;12:59–63. [CrossRef]
43. Qiu M, Ding LL, Zhang M, Zhou HR. Safety of four SGLT2 inhibitors in three chronic diseases: A meta-analysis of large randomized trials of SGLT2 inhibitors. Diab Vasc Dis Res 2021;18:14791641211011016. [CrossRef]
44. Andreea MM, Surabhi S, Razvan-Ionut P, Lucia C, Camelia N, Emil T, et al. Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors: harms or unexpected benefits? Medicina (Kaunas) 2023;59:742. [CrossRef]
45. Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 2017;40:1479–85. [CrossRef]
46. Hahn K, Ejaz AA, Kanbay M, Lanaspa MA, Johnson RJ. Acute kidney injury from SGLT2 inhibitors: potential mechanisms. Nat Rev Nephrol 2016;12:711–2. [CrossRef]
47. Perlman A, Heyman SN, Matok I, Stokar J, Muszkat M, Szalat A. Acute renal failure with sodium-glucose-cotransporter-2 inhibitors: Analysis of the FDA adverse event report system database. Nutr Metab Cardiovasc Dis 2017;27:1108–13. [CrossRef]
48. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7:845–54. [CrossRef]
49. Menne J, Dumann E, Haller H, Schmidt BMW. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: A systematic review and meta-analysis. PLoS Med 2019;16:e1002983. [CrossRef]
50. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. Diabetologia 2007;50:549–54. [CrossRef]
51. Liu J, Li L, Li S, Jia P, Deng K, Chen W, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. Sci Rep 2017;7:2824. [CrossRef]
52. U.S. Food & Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious. Accessed Dec 11, 2025.
53. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2016;4:411–9. [CrossRef]
54. Schumacher C, Chorpash A, Bolch C, Eagan K, Nimer S, Van Dril E. Identification of risk factors associated with acute kidney injury in patients taking sodium-glucose cotransporter-2 inhibitors. Pharmacotherapy 2024;44:249–57. [CrossRef]
55. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 2015;38:403–11. [CrossRef]
56. Banerjee M, Mukherjee A, Hazra A, Mukhopadhyay S. Baseline predictors of genital mycotic infections following sodium-glucose cotransporter-2 inhibitors initiation in men with type 2 diabetes. Indian J Pharmacol 2023;55:338–9. [CrossRef]
57. Narayan Swamy SN, Jakanur RK, Sangeetha SR. Significance of C-reactive protein levels in categorizing upper and lower urinary tract infection in adult patients. Cureus 2022;14:e26432. [CrossRef]
58. Li J, Chen J, Lan HY, Tang Y. Role of C-reactive protein in kidney diseases. Kidney Dis (Basel) 2022;9:73–81. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.67778
Haydarpasa Numune Med J 2025;65(4):313–319



hnhtipdergisi.com

ORIGINAL ARTICLE

Evaluation of the Impact of Maternal Feeding Attitudes on Anthropometric Measurements in Aged 2–6 Years

Mehmet Çavuşoğlu[1], Seda Özmen Sever[2], Güzin Zeren Öztürk[2]

[1]Department of Family Medicine, Yağlıdere District State Hospital, Giresun, Türkiye
[2]Department of Family Medicine, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye

Abstract

Introduction: This study aimed to assess the influence of maternal feeding attitudes on the anthropometric measurements of children aged 2–6 years.

Methods: Mothers of children aged 2–6 years who applied to the outpatient clinics of the Family Medicine Clinic at Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital were included in this study. The children's weight and height measurements were recorded, and the Sociodemographic Data Form was completed by the mothers. The Mother's Attitudes Towards the Feeding Process Scale (MATFPS) was used to evaluate maternal feeding attitudes. A p value of <0.05 was considered statistically significant.

Results: The study included 159 participants. The mean age of the children was 44.93 months. The mean weight was 16.67 kg, and the mean height was 102.06 cm. There were 29 children (18.2%) whose weight percentile and 44 children (27.7%) whose height percentile were outside the normal range (<25^{th} percentile or ≥97^{th} percentile). When the relationship between children's height and weight percentiles and the total MATFPS score was evaluated, a negative correlation was found between children's height and weight and the total MATFPS score (r=-0.236, p=0.003; r=-0.299, p<0.001, respectively). Children with height and weight percentiles <25p had the highest scores in the total and subscales of the MATFPS, whereas children with height and weight percentiles ≥97p had the lowest scores in the total and subscales.

Discussion and Conclusion: This study demonstrated that maternal feeding attitudes have an impact on children's weight percentiles. Specifically, as negative maternal feeding attitudes increased, a decrease in children's weight was observed. Therefore, maternal feeding practices should always be assessed during primary care follow-up visits.

Keywords: Child; feeding behavior; growth; maternal behavior.

Feeding practices are a critical concern for parents, particularly mothers, due to their significant influence on a child's early developmental trajectory. It is known that during the period from the cessation of breastfeeding at the age of 2 years until the age of 6 years, a child's nutrition is largely influenced by the attitudes and behaviors of the caregiver [1]. During early childhood, maternal feeding behaviors are essential for ensuring optimal growth and developmental outcomes. Moreover, this phase critically shapes the development of lifelong dietary patterns in children [2]. While the influence of the caregiver can direct the child toward healthy foods, coercive and inappropriate attitudes may lead to nutritional problems in the child [1–3]. Authoritarian and coercive feeding practices, such as forcing children to eat, are

Correspondence: Seda Özmen Sever, M.D. Department of Family Medicine, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye
Phone: +90 505 817 86 99 **E-mail:** sedaaozmen@gmail.com
Submitted Date: 28.02.2025 **Revised Date:** 03.07.2025 **Accepted Date:** 22.07.2025
Haydarpaşa Numune Medical Journal

associated with increased eating difficulties, including food neophobia and pickiness [4]. Conversely, positive feeding strategies, such as modeling and repeated taste exposure, are associated with healthier eating habits [5].

For some parents, having an overweight child reinforces the belief that their child is healthy and that their parenting is sufficient. However, this perception contributes to an increased prevalence of overweight and obesity in children [6]. In contrast, the negative impact of maternal restrictive and coercive attitudes on children's weight has been demonstrated [7,8].

In the evaluation of nutritional status, monitoring children's growth is essential [9]. A key component of routine child health follow-up in primary care is the performance of anthropometric measurements to monitor physical development and growth. Plotting these measurements on standardized growth charts allows the child's individual growth trajectory to be compared with peers of the same sex, thereby facilitating the identification of potential growth-related problems [10].

The objective of this study is to assess the influence of maternal feeding attitudes on anthropometric measurements of children aged 2–6 years, a period marked by post-breastfeeding transitions during which caregiver behavior has a critical impact on growth and development.

Materials and Methods

This was a single-center, descriptive study.

Population and Sample of the Study

Mothers of children aged 2–6 years who applied to the outpatient clinics of the Family Medicine Clinic at Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital for any reason between 24.05.2022 and 24.07.2022 were included in the study. The study was conducted in accordance with the Declaration of Helsinki. The sample size was calculated using the Centers for Disease Control and Prevention (CDC) Epi Info software. The number of mothers with children in this age group who applied for any reason within a one-month period was 90, and over a three-month period, the sample size was calculated as 159 out of 270 with a 95% confidence interval. Parents of children with congenital or acquired diseases affecting growth and development, as well as those who declined to participate, were excluded.

Data Collection

After obtaining informed consent, a data collection form consisting of 17 questions was administered face-to-face by the researcher. In the first part of the form, questions addressed the mothers' age, education level, occupation, weight, height, and the fathers' height. In the second part, the Mother's Attitudes Towards the Feeding Process Scale (MATFPS) was used to assess maternal feeding attitudes. The scale was developed by Habibe Dilsiz and İhsan Dağ, and its validity and reliability analyses have been conducted. MATFPS consists of five subscales: Negative Affect During Meal (NADM), Attitudes towards Insufficient/Unbalanced Feeding (AIF), Negative Feeding Strategies (NFS), Forced Feeding (FF), and Reaction to the Viewpoints of Others (RVO). The scale includes a total of 27 items rated on a five-point Likert scale ranging from "Never" to "Always." The minimum possible score is 27, and the maximum possible score is 135. Higher scores on both the subscales and the total scale indicate an increase in problems related to maternal feeding attitudes [11].

Anthropometric measurements of the children at the time of application were obtained using an electronic scale with a sensitivity of 0.1 kg and a DESIS-ELW model stadiometer with a sensitivity of 0.1 cm. Percentile calculations were performed using reference values for body weight, height, head circumference, and body mass index (BMI) in Turkish children adapted by Neyzi et al. [12] BMI was calculated using the standard formula kg/m^2. The target height of the children was calculated using Tanner's formula based on midparental height, and the percentile value on the growth curve at age 18 years was used. For weight and height percentiles, values below the 25^{th} percentile were considered low, values between the 25^{th} and 97^{th} percentiles were considered normal, and values $\geq 97^{th}$ percentile were considered high. For BMI percentiles, values below the 25^{th} percentile were considered low, values between the 25^{th} and 95^{th} percentiles were considered normal, and values $\geq 95^{th}$ percentile were considered high.

Statistical Analysis

Descriptive statistics are presented as mean±standard deviation for normally distributed continuous variables and as median (interquartile range: Q1–Q3) for non-normally distributed variables, whereas categorical variables are presented as numbers and percentages. Categorical variables were examined using Pearson's chi-square test. The Kolmogorov–Smirnov test was employed to assess the normal distribution of continuous variables. For continuous variables that did not meet the assumption of normality, the Kruskal–Wallis H test was used to compare differences among the three groups. In cases where the Kruskal–Wallis test revealed a statistically significant difference, pairwise comparisons were conducted using the Mann–Whitney U test. To control for type I error due to multiple comparisons, the Bonferroni correction was applied, and the adjusted significance threshold was set at $p<0.0167$ for the three pairwise comparisons. The Spearman correlation test was used to examine relationships between continuous variables. The level of statistical significance was accepted as $p<0.05$. The SPSS 25.0 software package was used for data analysis.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital on 24/05/2022 (Approval No: 3563).

Results

The study included 159 participants. The mean age of the participating mothers was 34.01±5.09 years (min=25, max=50). Of the mothers, 53.5% (n=85) were employed, and 84.9% (n=135) had a high school education or higher. The mean height of the mothers was 161.75±5.51 cm (min=147, max=178), and the mean height of the fathers was 176.06±6.72 cm (min=160, max=192). The mean BMI of the mothers was 25.45±4.98 kg/m^2 (min=17.30, max=42.68). Each participant had at least one and at most five children. Among the children, 54.1% (n=86) were girls. The mean age of the children was 44.93 months (min=24, max=72), with a mean weight of 16.67±3.73 kg (min=10.7, max=34) and a mean height of 102.06±10.31 cm (min=80, max=133). The mean BMI was 15.93±2.08 kg/m^2 (min=10.2, max=27.10).

The weight, height, and BMI percentile distributions of the children are shown in Table 1. A total of 29 children (18.2%) had a weight percentile outside the normal range (<25th or ≥97th percentile), 44 children (27.7%) had a height percentile outside the normal range, and 50 children (31.4%) had a BMI percentile outside the normal range (<25th or ≥95th percentile). The mean midparental height of the children was 168.37±7.94 cm (min=151, max=186). Thirteen children (8.2%) were below the target height percentile, whereas 146 children (91.8%) were at or above it.

The mean breastfeeding duration reported by mothers was 18.92±7.67 months (min=2, max=36). The responses of mothers to questions regarding the nutrition and follow-up process of their children are presented in Table 2.

As maternal age increased, there was a statistically significant increase in children's weight and BMI percentile values (p=0.048 and p=0.047, respectively). However, no statistically significant differences were found between mothers' education level or employment status and children's height, weight, or BMI percentiles (p>0.05).

A positive and statistically significant relationship was observed between mothers' weight and children's weight (r=0.205, p=0.024). Similarly, a positive and statistically significant relationship was found between mothers' BMI values and children's BMI values (r=0.197, p=0.030).

Table 1. The weight, height and BMI percentile distributions of the children

Anthropometric measure	<25p		25-97p (25-95p*)		≥97p (≥95p*)	
	n	%	n	%	n	%
Weight (<25p / ≥97p)	23	14.5	130	85.5	6	3.8
Height (<25p / ≥97p)	34	21.4	115	78.6	10	6.3
BMI (<25p / ≥95p)	38	23.9	109	68.6	12	7.5

*: For BMI, ≥95th percentile was used as the upper cutoff; for weight and height, ≥97th percentile was used. BMI: Body mass index.

Table 2. The responses of mothers to the questions about the nutrition and follow-up process of their children

	Response	n	%
Did you exclusively breastfeed your child for the first six months?	Yes	125	78.6
	No	34	21.4
Do you regularly take your child to infant-child follow-ups at the family health center?	Yes	153	96.2
	No	6	3.8
Did you use the vitamin D and iron supplements given during your child's follow-ups regularly and in the recommended amounts?	Yes	124	78.0
	No	35	22.0
Have you ever asked your doctor to prescribe food supplements - multivitamins - to increase your child's appetite or to support growth and development?	Yes	50	31.5
	No	109	68.5

The mean total MATFPS score was 65.82±17.19 (min=29, max=107). The mean subgroup scores were as follows: NADM, 14.94±5.8 (min=6, max=30); AIF, 24.74±7.12 (min=9, max=40); NFS, 10.24±3.95 (min=5, max=23); FF, 5.48±2.02 (min=4, max=12); and RVO, 10.42±3.7 (min=4, max=19).

When maternal age was compared with the total and subgroup MATFPS scores, a statistically significant negative correlation was observed only with the FF subgroup score (r=-0.194, p=0.014). No statistically significant differences were found between mothers' education level, employment status, or children's sex and the total MATFPS score (p>0.05). When MATFPS total and subgroup scores were compared according to whether mothers had one child or more, both the total MATFPS score and the FF subgroup score were significantly higher among mothers with one child (p=0.029 and p=0.007, respectively).

Analysis of the relationship between children's anthropometric percentiles and MATFPS scores revealed negative correlations between both children's height and weight and the total MATFPS score (r=-0.236, p=0.003 and r=-0.299, p<0.001, respectively). Children's weight was also negatively correlated with all MATFPS subgroups (r=-0.291, p<0.001 for NADM; r=-0.207, p=0.009 for AIF; r=-0.287, p=0.003 for NFS; r=-0.178, p=0.025 for FF; and r=-0.181, p=0.023 for RVO). Similarly, children's height was negatively correlated with all subgroups except AIF (r=-0.258, p=0.001 for NADM; r=-0.170, p=0.032 for NFS; r=-0.157, p=0.048 for FF; and r=-0.197, p=0.013 for RVO).

As shown in Table 3, children with height and weight percentiles <25p had the highest scores in the total and subgroup MATFPS scores, whereas children with height and weight percentiles ≥97p had the lowest scores in the total and subgroup scores. In addition, the NADM and NFS

Table 3. The distribution of participants' MATFPS subgroup scores according to their children's height, weight, and BMI percentiles

MATFPS subscale and total scores	Percentile	<25p[1] Median (Q1-Q3)	25-97p[2] Median (Q1-Q3)	≥97p[3] Median (Q1-Q3)	p*	Post-hoc comparisons**
Negative affect during meal	Weight	19 (13-24)	14 (10-18.25)	12.5 (10.25-14.25)	**0.041**	1-2: 0.021 1-3: 0.036 2-3: 0.477
	Height	16.5 (12.5-21)	14 (11-19)	10 (8-13.5)	**0.007**	1-2: 0.045 1-3: 0.004[a] 2-3: 0.026
	BMI	15.5 (11.75-19.75)	14 (10-18.5)	16.5 (13.75-19)	0.169	
Attitudes towards insufficient/ unbalanced feeding	Weight	24 (31-31)	25 (19-29.25)	19.5 (15.25-25)	0.195	
	Height	24 (17.75-32.25)	25 (19-29)	26.5 (17.75-30.25)	0.979	
	BMI	27 (22-32)	22 (19-29)	24 (20.5-29)	0.134	
Negative feeding strategies	Weight	13 (9-15)	9 (7-12)	8 (6.75-10.25)	**0.027**	1-2: 0.015[b] 1-3: 0.031 2-3: 0.383
	Height	11 (7.75-15)	9 (7-12)	9 (7.25-11)	0.181	
	BMI	9.5 (7-15)	9 (7-12)	12 (8.5-14.75)	0.180	
Forced feeding	Weight	5 (4-8)	4 (4-7)	4 (4-4.75)	0.283	
	Height	4 (4-8.25)	5 (4-7)	4 (4-4)	0.068	
	BMI	5 (4-7)	4 (4-6)	6 (4-8.75)	0.095	
Reaction to the viewpoints of others	Weight	10 (8-14)	11 (8-13)	7 (6-9.75)	0.180	
	Height	11.25 (8-14.25)	10 (8-13)	10 (6-12.25)	0.361	
	BMI	10 (8-13.25)	11 (7.5-13)	12 (8.25-14)	0.676	
Total	Weight	70 (58-84)	62 (52-79)	48.5 (45.75-61.75)	**0.022**	1-2: 0.069 1-3: 0.016[c] 2-3: 0.044
	Height	69 (56-85.25)	62 (52-79)	59 (45.75-70.25)	0.179	
	BMI	70 (57.75-83)	61 (51.5-78)	73.5 (50-83.25)	0.135	

*: Kruskal–Wallis test was used. P<0.05 was considered statistically significant; **: Post-hoc analysis was performed using the Mann–Whitney U test with Bonferroni correction. For pairwise comparisons, p<0.0167 was considered statistically significant. [a,b,c]: Statistically significant after Bonferroni correction (p<0.0167). MATFPS: Mother's Attitudes Towards the Feeding Process Scale; BMI: Body mass index.

subgroups were associated with weight, whereas height was associated with NADM. BMI was not associated with any of the MATFPS subgroups.

Discussion

This study aimed to evaluate the effect of mothers' attitudes toward nutrition on their children's anthropometric measurements. Although most children had weight, height, and BMI values within the expected range for their age, a trend was observed in which children's height, weight, and BMI decreased as mothers' MATFPS scores increased. This finding suggests that as negative maternal feeding attitudes intensified, children's physical growth indicators declined.

Proper nutrition remains a central concern for parents in facilitating optimal child development. Parental approaches to early childhood nutrition have significant long-term implications for children's future eating habits, either fostering or hindering healthy dietary patterns [13]. At the same time, childhood nutrition also plays an important role in health outcomes during adulthood [14].

In the decision-making process regarding infant nutrition, many factors influence mothers, including infants' nutritional needs and perceived benefits, cultural factors, maternal health status, habits, level of knowledge, and the challenges and conveniences associated with breastfeeding [15].

In the literature, a study examining the relationship between maternal age and feeding practices reported that parents younger than 30 years tend to use more controlling feeding practices with their children [16]. As parental pressure-feeding practices increase, children are more likely to develop eating-related problems, such as picky eating, reduced enjoyment of food, and decreased food intake, leading to negative food-related outcomes and lower BMI values [17–19].

In our study, the finding that children's weight and height percentile values decreased as mothers' forced-feeding subscale scores increased is consistent with these reports. Similarly, the decrease in children's weight and BMI percentile values alongside increasing forced-feeding subscale scores as maternal age decreased further supports this association.

An important finding of our study was that as children's weight and height percentile values increased, decreases were observed in all maternal subscale scores and the total MATFPS score, except for the Attitudes towards Insufficient/Unbalanced Feeding subscale. However, the Attitudes towards Insufficient/Unbalanced Feeding subscale score was found to decrease with increasing BMI. In a similar study conducted in Türkiye using the MATFPS, a negative correlation was also observed between the total MATFPS score and BMI values [20].

This may be due to the fact that, during childhood, weight is perceived by mothers as an indicator of health [21]. In one study, nearly one-third of parents were unable to correctly assess their children's weight, while more than half of the parents of obese children made incorrect evaluations [21]. In another study examining how mothers perceive their children's appetite and appearance, it was reported that mothers' perceptions of their children's appearance often did not reflect the children's actual appearance, highlighting unrealistic maternal approaches [22]. It has been shown that mothers of underweight children tend to perceive their children as having higher weight, whereas mothers of overweight children tend to perceive their children as having lower weight [22].

In our study, a significant relationship was also identified between mothers' weight and BMI values and children's weight and BMI values [23]. In a study evaluating the impact of maternal feeding behaviors on early childhood obesity, mothers were followed during pregnancy and their children were monitored until the age of three, revealing a correlation between maternal overweight or obesity and the likelihood of children becoming overweight or obese [23]. In a review evaluating 11 studies from different countries, although childhood obesity was acknowledged as multifactorial, maternal overweight or obesity was found to have a significant impact on childhood obesity [24]. Similarly, in our study, supporting these findings, a correlation was identified between maternal weight and child weight [24].

When examining the relationship between the main focus of the study, MATFPS, and anthropometric measurements, it was observed that mothers of children with lower percentile values had higher mean MATFPS scores, whereas mean scores decreased as percentile values increased. This finding indicates that increasing problematic maternal feeding attitudes are likely to be associated with a decrease in children's anthropometric percentiles.

Numerous studies in the literature have demonstrated the impact of maternal feeding practices and eating habits on children's nutrition and development [25–27]. It is well known that one of the most common problems in early childhood that may lead to developmental issues is picky eating behavior, and that parent-related factors constitute the most significant cause of this behavior [28]. In a study evaluating the effects of maternal feeding practices at one year of age on children's nutrition at two years of age, the use of pressure to eat at one year was associated with lower fruit consumption at two years, whereas healthy eating modeling at one year was associated with higher vegetable consumption at two years [29].

The effect of differences in maternal feeding practices on children's weight was also demonstrated in a study evaluating Vietnamese mothers with children aged 2–5 years, which showed that a persuasive feeding style negatively affected children's weight-for-height ratio [30]. In our study, it was observed that as mothers' negative feeding attitudes increased, children's weight decreased, suggesting that maternal attitudes constitute a crucial component of child nutrition and emphasizing the central role of mothers in their children's feeding practices. Therefore, families should be informed about the components of a healthy eating model for children and ways to ensure dietary variety [31]. At the same time, it should be acknowledged that feeding is also an emotional process for mothers, and appropriate support should be provided.

Balanced and healthy nutrition in children is closely related to maternal feeding attitudes. As motherhood represents a new phase in a woman's life beginning with pregnancy, it is essential that mothers receive adequate support and education on all relevant issues, including child nutrition, to ensure the upbringing of healthy future generations.

Conclusion

In this study, the effects of mothers' feeding attitudes on the anthropometric measurements of children aged 2–6 years were examined. Evaluation of the feeding process and maternal attitudes revealed that maternal feeding attitudes had a significant impact on children's weight percentiles. Specifically, as negative maternal feeding attitudes increased, a decrease in children's weight was observed. In particular, the Negative Affect During Meal subscale was found to affect both height and weight. These findings indicate that increasing negative maternal attitudes toward feeding are associated with adverse effects on children's anthropometric measurements. Therefore, mothers' feeding practices should be routinely assessed during primary care follow-up visits. When necessary, nutrition education and guidance should be provided to support the development of healthy feeding behaviors and promote optimal growth in children. Educational programs for mothers are believed to have a positive impact on children's long-term health outcomes.

Ethics Committee Approval: The study was approved by Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (No: 3563, Date: 24.05.2022).

Use of AI for Writing Assistance: All content, including the text, tables, and figures, was created by the authors.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – G.Z.Ö., M.Ç.; Design – G.Z.Ö., M.Ç.; Supervision – G.Z.Ö., M.Ç., S.Ö.S.; Fundings – G.Z.Ö., M.Ç., S.Ö.S.; Materials – G.Z.Ö., M.Ç., S.Ö.S.; Data collection and/or processing – M.Ç.; Analysis and/or interpretation – G.Z.Ö., M.Ç., S.Ö.S.; Literature search – M.Ç., S.Ö.S.; Writing – M.Ç., S.Ö.S.; Critical review – G.Z.Ö., M.Ç., S.Ö.S.

Conflict of Interest: The authors declare that there is no conflict of interest.

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

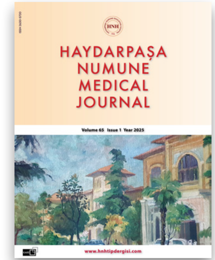
References

1. Savage JS, Fisher JO, Birch LL. Parental influence on eating behavior: conception to adolescence. J Law Med Ethics 2007;35:22–34. [CrossRef]
2. Berti C, Socha P. Infant and young child feeding practices and health. Nutrients 2023;15:1184. [CrossRef]
3. Klesges RC, Stein RJ, Eck LH, Isbell TR, Klesges LM. Parental influence on food selection in young children and its relationships to childhood obesity. Am J Clin Nutr 1991;53:859–64. Erratum in: Am J Clin Nutr 1991;54:iv. [CrossRef]
4. Rigal N, Chabanet C, Issanchou S, Monnery-Patris S. Links between maternal feeding practices and children's eating difficulties. Validation of French tools. Appetite 2012;58:629–37. [CrossRef]
5. Moore SN, Tapper K, Murphy S. Feeding strategies used by mothers of 3-5-year-old children. Appetite 2007;49:704–7. [CrossRef]
6. Baughcum AE, Burklow KA, Deeks CM, Powers SW, Whitaker RC. Maternal feeding practices and childhood obesity: a focus group study of low-income mothers. Arch Pediatr Adolesc Med 1998;152:1010–4. [CrossRef]
7. Scaglioni S, Arrizza C, Vecchi F, Tedeschi S. Determinants of children's eating behavior. Am J Clin Nutr 2011;94(6 Suppl):2006S–11S. [CrossRef]
8. Johannsen DL, Johannsen NM, Specker BL. Influence of parents' eating behaviors and child feeding practices on children's weight status. Obesity (Silver Spring) 2006;14:431–9. [CrossRef]
9. Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. World Health Organ Tech Rep Ser 1995;854:1–452.
10. İnce OT, Kondolot M, Yalçın SS. Büyümenin izlenmesi ve büyüme duraklaması. Turk J Pediatr 2011;5:181–92. [Article in Turkish]
11. Dilsiz H, Dağ İ. Mother's attitudes towards the feeding process scale: development, validity and reliability study. Turk J Pediatr Dis 2020;14:7–15. [Article in Turkish] [CrossRef]

12. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Weight, height, head circumference, and body mass index references for Turkish children. Çocuk Sağlığı Hastalıkları Derg 2008;51:1–14. [Article in Turkish]
13. Arlı M, Şanlıer N, Küçükkömürler S, Yaman M. Anne ve çocuk beslenmesi. 10th ed. Ankara: Pegem Akademi; 2017. p.1–233. [In Turkish] [CrossRef]
14. Brown R, Ogden J. Children's eating attitudes and behaviour: a study of the modelling and control theories of parental influence. Health Educ Res 2004;19:261–71. [CrossRef]
15. Radzyminski S, Callister LC. Mother's beliefs, attitudes, and decision making related to infant feeding choices. J Perinat Educ 2016;25:18–28. [CrossRef]
16. Klerks M, Roman S, Bernal MJ, Haro-Vicente JF, Sanchez-Siles LM. Complementary feeding practices and parental pressure to eat among spanish infants and toddlers: a cross-sectional study. Int J Environ Res Public Health 2021;18:1982. [CrossRef]
17. McPhie S, Skouteris H, McCabe M, Ricciardelli LA, Milgrom J, Baur LA, et al. Maternal correlates of preschool child eating behaviours and body mass index: a cross-sectional study. Int J Pediatr Obes 2011;6:476–80. [CrossRef]
18. Westen SC, Mitchell TB, Mayer-Brown S, Resmini Rawlinson A, Ding K, Janicke DM. Mother and father controlling feeding behaviors and associations with observed mealtime family functioning. J Pediatr Psychol 2019;44:1174–83. [CrossRef]
19. Galloway AT, Fiorito LM, Francis LA, Birch LL. 'Finish your soup': counterproductive effects of pressuring children to eat on intake and affect. Appetite 2006;46:318–23. [CrossRef]
20. Bayindir-Gümüş A, Yardimci H, Koç N, Sezer E, Kara-Uzun A. Relationships between maternal feeding attitudes and child nutritional problems. Nurs Health Sci 2024;26:e70015. [CrossRef]
21. Suligowska K, Buczny J. Obesity in polish children and parents' perception of their children's weight status: the results of the SOPKARD-junior study. Int J Environ Res Public Health 2022;19:4433. [CrossRef]
22. Aksu SB, Zeren Öztürk G. Evaluation of mothers' opinions on appetite and body shape perception of their children. Public Health 2021;195:126–31. [CrossRef]
23. Ardic C, Usta O, Omar E, Yıldız C, Memis E. Effects of infant feeding practices and maternal characteristics on early childhood obesity. Arch Argent Pediatr 2019;117:26–33. [Article in English, Spanish] [CrossRef]
24. Mannino A, Sarapis K, Moschonis G. The effect of maternal overweight and obesity pre-pregnancy and during childhood in the development of obesity in children and adolescents: a systematic literature review. Nutrients 2022;14:5125. [CrossRef]
25. Shloim N, Edelson LR, Martin N, Hetherington MM. Parenting styles, feeding styles, feeding practices, and weight status in 4-12 year-old children: a systematic review of the literature. Front Psychol 2015;6:1849. [CrossRef]
26. Goodman LC, Roberts LT, Musher-Eizenman DR. Mindful feeding: A pathway between parenting style and child eating behaviors. Eat Behav 2020;36:101335. [CrossRef]
27. Lowe KD, Lott MA, Jensen CD. Associations between parent-child communication and connectedness, parent feeding behavior, and child body mass in pre-adolescent children. J Pediatr Psychol 2021;46:59–68. [CrossRef]
28. Taylor CM, Emmett PM. Picky eating in children: causes and consequences. Proc Nutr Soc 2019;78:161–9. [CrossRef]
29. Gregory JE, Paxton SJ, Brozovic AM. Maternal feeding practices predict fruit and vegetable consumption in young children. Results of a 12-month longitudinal study. Appetite 2011;57:167–72. [CrossRef]
30. Ayre SK, Jansen E, Gallegos D, Tran CQ, Do DN, Nambiar S. Initial investigation of associations between feeding practices, eating behaviours, and weight status in Vietnamese children using modified questionnaires. Obes Res Clin Pract 2022;16:301–6. [CrossRef]
31. Ramos M, Stein LM. Development children's eating behavior. J Pediatr (Rio J) 2000;76(Suppl 3):S229–37. [Article in Portuguese] [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.44538
Haydarpasa Numune Med J 2025;65(4):320–326



hnhtipdergisi.com

ORIGINAL ARTICLE

Medial Scar Fish-Tail Brachioplasty with Ultrasound and Power-Assisted Liposuction in Arm Ptosis

Alpay Duran[1], Hasan Büyükdoğan[2]

[1]Department of Plastic, Reconstructive and Aesthetic Surgery, İstanbul Aydın University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Plastic, Reconstructive and Aesthetic Surgery, Private Practice, İstanbul, Türkiye

Abstract

Introduction: This paper discusses the surgical outcomes and complications of the medial scar fish-tail brachioplasty technique used with UAL (LIPOSAVER, LHbiomed Co., Korea) and PAL (Microaire, USA) in treating Teimourian grade III to IV arm ptosis.

Methods: A retrospective study was conducted using patient data and chart reviews from the authors' private cosmetic practice. It focused on patients who underwent fish-tail (FT) brachioplasty combined with UAL/PAL from October 2020 to April 2023. The study comprised 31 healthy participants. A comprehensive review of all patients' demographic data, surgical records, complications, lipoaspirate volumes, and patient satisfaction was undertaken.

Results: From October 2020 to April 2023, a total of 31 fish-tail brachioplasty procedures using UAL/PAL were carried out. The mean age was 36.3±15.2 years, the body mass index (BMI) was 27.3±4.3 kg/m^2, and all patients were female. Of the patients, 9 (29%) underwent isolated fish-tail brachioplasty with UAL/PAL, while 22 patients (71%) opted for additional procedures. Regarding complications, 7 patients (22.5%) experienced issues. The most common complications seen with fish-tail brachioplasty with UAL/PAL were minor wound dehiscence at the T-junction in 3 patients (9.6%), hypertrophic scar in 2 patients (6.4%), seroma in 1 patient (3.2%), and surgical site infection in 1 patient (3.2%). The overall complication rate was 22.5%.

Discussion and Conclusion: Medial scar fish-tail brachioplasty, combined with UAL/PAL, is a safe and efficient method. This combination provides a viewpoint on defining the aesthetic components of the arm.

Keywords: Arm lift; brachioplasty; liposuction; PAL; UAL.

Ancient sculptors viewed the arms of a sculpture as more than just a physical component, recognizing them as essential for conveying movement, emotion, and the overall narrative of the piece. They meticulously considered how the arms interacted with the rest of the body and the surrounding space, ensuring consistency in perspective and proportions from every angle. The gestures of the arms could convey various states and emotions, such as power, grace, or aggression. Every person has a unique physique, and achieving the perfect arm shape requires a keen artistic eye. Contemporary brachioplasty approaches aim not just to remove excess skin but also to create a harmonious aesthetic balance with the rest of the body.

Brachioplasty, originally coined as brachial dermolipectomy by Itturaspe and Fernandez in 1954, has observed numerous alterations over the years [1]. Despite these changes, the final scar placement and appearance, as well as the precise amount of tissue removal, continue

Correspondence: Alpay Duran, M.D. Department of Plastic, Reconstructive and Aesthetic Surgery, İstanbul Aydın University Faculty of Medicine, İstanbul, Türkiye
Phone: +90 536 625 35 89 **E-mail:** dr.alpayduran@hotmail.com
Submitted Date: 29.04.2025 **Revised Date:** 30.07.2025 **Accepted Date:** 07.08.2025
Haydarpaşa Numune Medical Journal

to present challenges for plastic surgeons. Past research has incorporated the use of energy-based tools like ultrasound-assisted liposuction (UAL), laser-assisted liposuction (LAL), power-assisted liposuction (PAL), and radiofrequency-based devices in cases of Teimourian grade I, IIa, IIb, and III arm ptosis [2–4]. However, surgical removal of excessive skin and fat deposits remains the go-to method for treating Teimourian grade IIb, III and IV arm ptosis. Better cosmetic results for arm contouring can be achieved through the use of various energy-based liposuction techniques in conjunction with the brachioplasty procedure. However, there is no consensus on the most effective approach, scar placement, and the appropriate length of incisions [5]. Teimourian and Malekzadeh published a comprehensive classification of arm ptosis in 1998 [6]. Many patients seeking upper arm contouring fall into the categories of stage IIb, III, or IV, and for these patients, brachioplasty is typically recommended [7,8]. This paper discusses the surgical outcomes and complications of the medial scar fish-tail brachioplasty technique used with UAL (LIPOSAVER, LHbiomed Co., Korea) and PAL (Microaire, USA) in treating Teimourian grade III to IV arm ptosis.

Materials and Methods

A retrospective study was conducted using patient data and chart reviews from the authors' private cosmetic practice. The study was conducted in accordance with the principles of the Helsinki Declaration, and informed consent was obtained from the subjects. Ethical approval was obtained from the Clinical Research Ethical Board of Medipol University. The study focused on patients who underwent fish-tail (FT) combined with UAL/PAL from October 2020 to April 2023. The study comprised 31 healthy participants (Fig. 1). Patients were excluded if they had conditions impacting microcirculation, such as diabetes mellitus, cardiopulmonary diseases, hereditary bleeding, or thrombotic disorders. Those using herbal products and patients who had previously undergone revision brachioplasty were also ruled out. A comprehensive review of all patients' demographic data, surgical records, complications, lipoaspirate volumes, and patient satisfaction was undertaken. Surgeries were performed under general anesthesia, with a mean follow-up period of 12 months (Figs 2–5). The evaluation of outcomes was conducted through an online patient satisfaction survey 1 year post-operation. Satisfaction was gauged at the one-year mark to assess the results of medial scar FT brachioplasty combined with UAL/PAL, using a simple Likert scale. The scale ranged from 1 (very satisfied), 2 (satisfied), 3 (dissatisfied), to 4 (very unsatisfied), and was administered by an independent observer.

Surgical Technique

All procedures were completed under general anesthesia while patients were in a supine position with their arms outstretched at a 90-degree angle on the table. The arms were sterilized and draped, and a small incision was made above the medial epicondyle at the front of the arm to administer the tumescent fluid. This fluid, a super-wet solution, was made up of one liter of Ringer's lactate, 10 cc of 2% lidocaine, and 1 cc of 1:1000 epinephrine.

Following this, UAL was implemented, focusing on the deep and superficial planes of the fish-tail excision area beneath the bicipital groove, the posterior aspect of the arm, and the anterolateral arm. Ultrasound energy, set on the superficial mode at 60% power with a 3-grooved tip probe, was applied. The duration was determined by the amount of tumescent fluid used, one minute for every 100 cc.

Next, PAL was carried out with a 4 mm blunt aspiration cannula. This was focused on the areas for brachioplasty excision, the posterior aspect of the arm, and the anterolateral arm. In the operating room, all patients were given antibiotic prophylaxis, which continued for ten days after the operation. Drains were removed 24 hours later. Lastly, patients were instructed to wear a compression arm garment for at least 4 weeks.

Figure 1. Preoperative drawing of the medial scar fish tail brachioplasty technique.

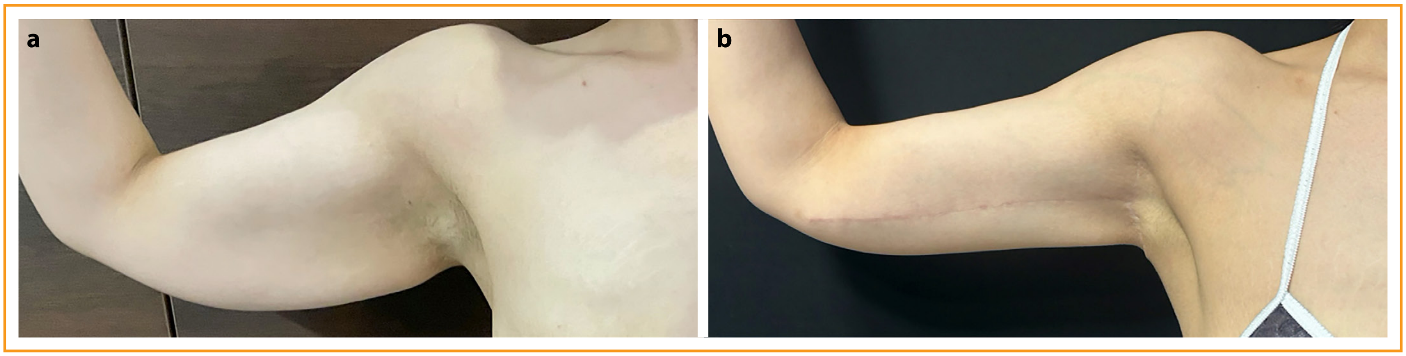


Figure 2. Preoperetive anterior view of the case **(a)** and postoperative anterior view of the case after one year **(b)**.

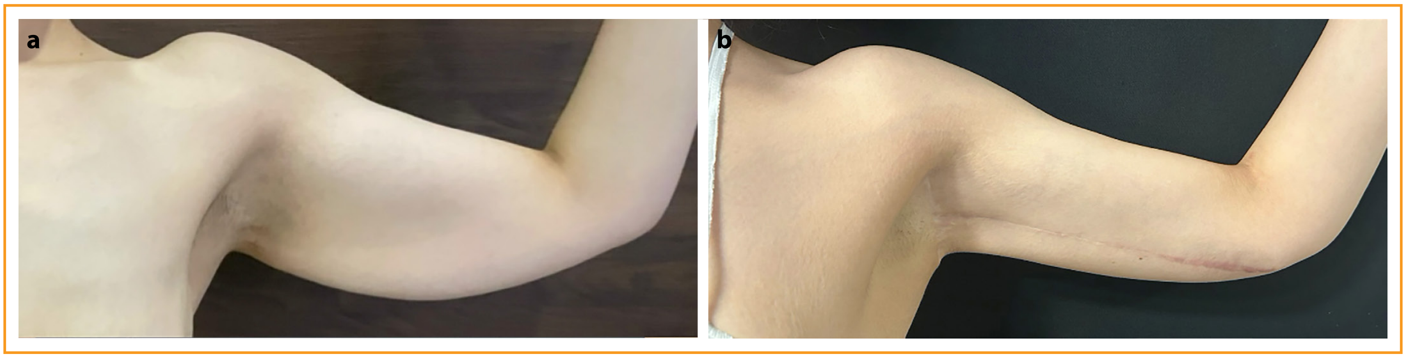


Figure 3. Preoperetive anterior view of the case **(a)** and postoperative anterior view of the case after one year **(b)**.

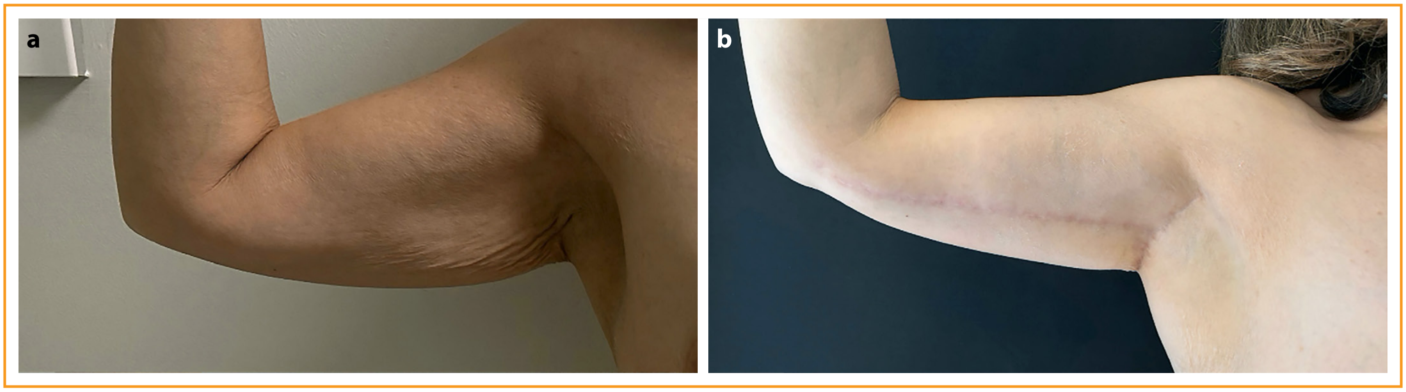


Figure 4. Preoperetive anterior view of the case **(a)** and postoperative anterior view of the case after one year **(b)**.

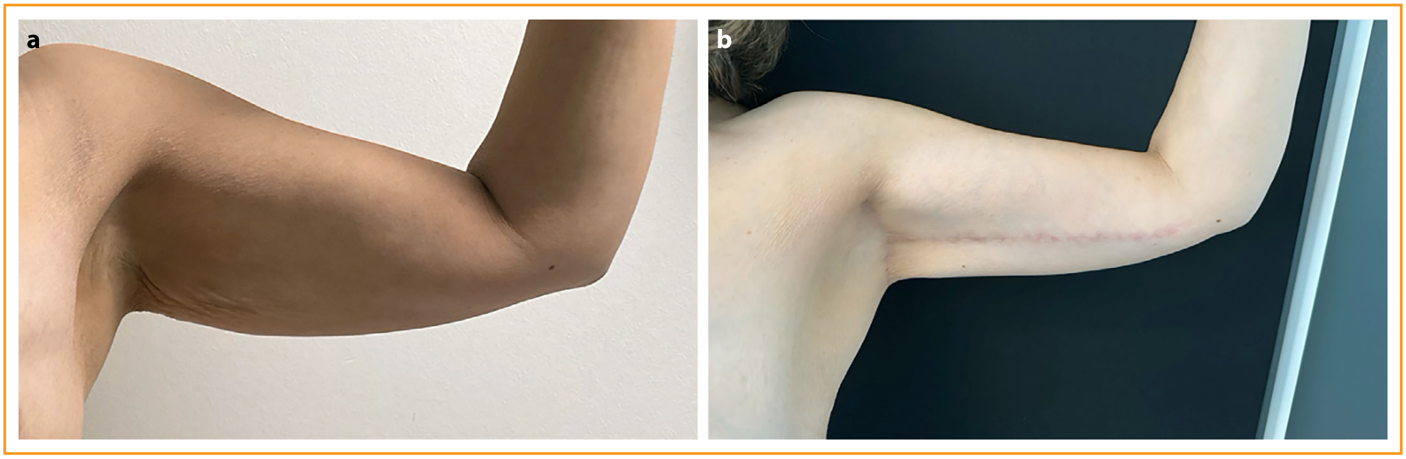


Figure 5. Preoperetive anterior view of the case **(a)** and postoperative anterior view of the case after one year **(b)**.

Table 1. Patient demographics

Total number of cases	31
Mean age (±SD)	36.3±15.2 years
Mean BMI (±SD)	27.3±4.3 kg/m^2
Sex	31 Female
Isolated fishtail brachioplasty	9 pts (29%)
Brachioplasty with additional procedures	22 pts (71%)
Patients with complications	7 pts (22.5%)

SD: Standard deviation; BMI: Body mass index.

Results

From October 2020 to April 2023, a total of 31 fish-tail brachioplasty procedures using UAL/PAL were carried out. The mean age was 36.3±15.2 years, the body mass index (BMI) was 27.3±4.3 kg/m^2, and all patients were female. Of the patients, 9 (29%) underwent isolated fish-tail brachioplasty with UAL/PAL, while 22 patients (71%) opted for additional procedures. Regarding complications, 7 patients (22.5%) experienced issues (Table 1).

The most common complications seen with fish-tail brachioplasty with UAL/PAL were minor wound dehiscence at the T-junction in 3 patients (9.6%), hypertrophic scar in 2 patients (6.4%), seroma in 1 patient (3.2%), and surgical site infection in 1 patient (3.2%). The overall complication rate was 22.5%. The patients were followed up for an average of 12 months (9–24 months). Generally, the surgery duration for a UAL/PAL brachioplasty was 140 minutes (ranging from 98 to 155 minutes), and the average amount of aspirated fluid was 380 cc (ranging from 250 to 650 cc). Most of the patients (87.1%) were satisfied with their overall surgical outcome from the fish-tail brachioplasty with a combination of UAL/PAL. The patient with seroma, the patient with wound dehiscence, and the 2 patients with hypertrophic scar were the only patients who did not report a satisfactory surgical outcome (12.9%).

Discussion

The rise in popularity of bariatric surgery has significantly altered the reasons why patients seek arm lift procedures. In the past, most of these procedures were primarily related to lipodystrophy in the arm area from weight loss caused by diet and exercise or senile elastosis. Today, however, a considerable patient group comprises those who have undergone bariatric surgery. Roughly 63% of all arm lifts are conducted on patients who have experienced massive weight loss [9]. In particular, cases related to senile elastosis or bariatric surgery, especially severe ones (Grade III and IV), show that despite reduced skin elasticity and postoperative scarring, arm lifts continue to play a critical role in aesthetic surgery.

Lockwood is recognized for popularizing the modern method of brachioplasty. This method focuses on eliminating excess skin through a T-shaped incision across the arm and axilla. According to the author of the study, adjustments were made to the brachioplasty procedure to ensure the arm flap is firmly attached to the axillary fascia and to reinforce incision repairs in the superficial fascial system. This adjustment is aimed at reducing the chances of scar widening or shifting and preventing the creation of unnatural contours [10]. Modern brachioplasty techniques and their adaptations have inspired many surgeons to devise new methods, particularly in the pursuit of the perfect brachioplasty. The goal of these techniques is to minimize scar length, enhance concealment, and aim for low complication rates. Some of these techniques include the sinusoidal pattern scar, a posterior scar accompanied by a Z-plasty, a fish-like design, L-brachioplasty, the short-scar method, and S-shaped incisions [8,11–14].

In a meta-analysis by Albraa and colleagues, 29 brachioplasty studies involving 1,578 patients were analyzed. The authors highlighted that all these studies were observational. Complication rates identified were 9.9% for abnormal scarring, 7.79% for sagging or recurrence, 6.81% for wound separation, 5.91% for seroma, 3.64% for infection, 2.47% for nerve-related issues, 2.46% for lymphedema or lymphocele formation, 2.27% for skin necrosis or delayed healing, and 2.06% for hematoma [15].

Commonly seen complications in our study, such as seroma, wound healing problems, and hypertrophic scar, aligned with the findings from the meta-analysis. We did not identify any cases of hematoma, nerve damage, or thromboembolism.

Rohrich and colleagues used the short-scar brachioplasty technique on 165 patients, ranging from 3 to 58 months. Complications included two cases of superficial wound separation (managed with wound care within 7 to 10 days), one lymphocele, and three instances of scar widening, with two needing revision. The study noted a 3.6% complication rate for short-scar medial brachioplasty cases. The authors emphasized that this procedure is specifically for type IIa and IIb patients and is not a substitute for traditional brachioplasty. Candidates for this procedure should have moderate skin excess and limited lipodystrophy in the upper third to half of the arm [16].

There are varying views on the ideal scar placement following brachioplasty procedures [1,6,17,18]. Some surgeons prefer the posterior scar method, some the posteromedial approach, and others the medial scar approach. However, according to a study by Samra et al. [19], it is widely agreed that the straight medial scar is the preferred choice among the general population, plastic surgeons, and brachioplasty patients. This scar placement ranks highest among both males and females across all ages.

Arm liposuction has been elaborately discussed in scientific literature. Some have identified it as the main technique for arm reduction, while others have proposed it as an initial step before undertaking excision surgery [14,20–22]. Although diverse liposuction techniques have been widely reported with satisfactory outcomes, eliminating the requirement for brachioplasty in arm ptosis of grade I, IIa/b, and III, it is crucial to acknowledge gaps in objective data concerning long-term results for grade IIb, III, or IV arm ptosis. It is also important to note that postoperative scars are a serious concern for some patients, while others deal with sagging arm skin and soft tissue [2,23,24].

Elderly patients dealing with senile elastosis or those with diminished skin quality post-bariatric surgery, particularly those in grade III and IV arm ptosis categories, present significant challenges to plastic surgeons. Energy-assisted liposuction is frequently used in these patients, though modern brachioplasty methods remain the primary surgical consideration.

In their research on arm contouring using PAL and fat transfers, Abboud and colleagues elucidate their approach for grade I, II, and III arm ptosis. This involves expanding the recipient site through vibration and creating layered tunnels. By introducing the cannula into the arm's superficial subcutaneous spaces, tethered tissues are released, hence facilitating skin retraction post-surgery [23]. They argue that liposuction and fat transfers may provide sound results for patients with mild to moderate brachial ptosis while stating that further investigations are needed to confirm the effectiveness of this technique for grade IV brachial ptosis cases.

Bossert et al. [25] used traditional liposuction techniques for brachioplasty to treat arm deformities resulting from significant weight loss. Their method involved excising tissue from the medial part of the upper arm and lateral chest wall, using liposuction to reduce the remaining fat on the back of the arm. Their research demonstrates that this combination of arm liposuction and excision is a safe and effective strategy for treating upper arm deformities following significant weight loss. In their study, the complication rate for brachioplasty was approximately 46%. They found no notable difference in complication rates between patients who only underwent excisional brachioplasty and those who had both excisional brachioplasty and arm liposuction. The rates were 43.6% and 49.2%, respectively. The most common complication they observed was seroma [25].

In our study, apart from the excision areas, deep plane UAL/PAL was applied to the posterior arm and anterolateral arm for FT brachioplasty. Our current study found a complication rate of 22.5% for FT brachioplasty. Comparatively, De Ruz et al.'s [26] study found a 41.7% total complication rate among patients who underwent traditional suction-assisted liposuction with medial brachioplasty (single ellipse). Nguyen's study of 21 UAL-assisted posterior brachioplasty procedures reported complications in only two cases, indicating liposuction-assisted posterior brachioplasty as an effective and consistent method for patients with extenuated arm skin and fat redundancy [8]. A review by Sisti et al. [27] showed an overall 28.9% complication rate with a varying range of 0–21% for surgical revisions in brachioplasty, though no major complications such as thromboembolic events or sepsis were reported.

In their article, Di Pietro et al. [28] compared the outcomes of traditional brachioplasty with liposuction-assisted brachioplasty. They noted an early surgical complication in one of the 11 patients (9%) from the liposuction-assisted brachioplasty group. Despite this, they found a significantly lower complication rate in this group ($p<0.01$). Nevertheless, the study pointed out cosmetic complications in two instances.

In a different study, Zomerlei et al. [29] evaluated the experiences of 96 patients who underwent brachioplasty. They aimed to identify factors that might influence positive or negative results. According to their findings, 53.7% of patients (n=51) had simultaneous circumferential arm liposuction. No correlation was found between this procedure, incision type, pre-surgery changes in BMI, postoperative use of closed suction drains, and complication or revision rates. Through logistic regression analysis, the study found no statistically significant increase in complications when additional procedures were concomitantly performed with brachioplasty.

This study has several limitations. First, the relatively low mean BMI and younger average age of the cohort may have contributed to more favorable aesthetic outcomes and lower complication rates. Second, the absence of a control group limits the ability to draw direct comparisons with other techniques. The high rate of concomitant procedures may confound the interpretation of outcomes specifically attributable to the brachioplasty technique. The current study did not explore the application of posterior or posteromedial scar patterns. A more exhaustive examination involving various excision patterns and brachioplasty techniques could reveal contrasting findings. Additionally, evaluating different liposuction techniques alongside medial scar brachioplasty might yield diverse outcomes.

Conclusion

Despite the growing demand for lipobrachioplasty after massive weight loss or senile elastosis, no universally accepted brachioplasty technique has been established to significantly enhance surgical outcomes. However, medial scar fish-tail brachioplasty combined with UAL/PAL is a safe and efficient method. This combination provides a viewpoint on defining the aesthetic components of the arm. The study shows that using UAL/PAL on areas outside of the excision area is a safe and effective way to address upper arm deformities.

Ethics Committee Approval: The study was approved by Medipol University Ethics Committee (No: 367, Date: 28.03.2024).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – A.D.; Design – A.D.; Supervision – A.D.; Materials – A.D.; Data collection and/or processing – A.D., H.B.; Analysis and/or interpretation – A.D., H.B.; Literature search – A.D., H.B.; Writing – A.D., H.B.; Critical review – A.D.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors received no financial support for the research, authorship, and publication of this article.

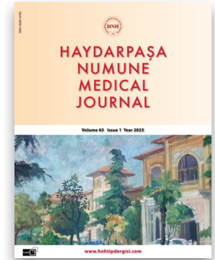
References

1. CORREA ITURRASPE M, FERNANDEZ JC. Brachial dermolipectomy. Prensa Med Argent 1954;41:2432–6.
2. El-Fahar MH, El-Gharbawi AH. Ultrasound-Assisted Liposuction (UAL) Arm contouring in non-post-bariatric patients: no rush for brachioplasty. Aesthetic Plast Surg 2023;47:260–8. [CrossRef]
3. Leclère FM, Alcolea JM, Vogt P, Moreno-Moraga J, Mordon S, Casoli V, et al. Laser-assisted lipolysis for arm contouring in Teimourian grades I and II: a prospective study of 45 patients. Lasers Med Sci 2015;30:1053–9. [CrossRef]
4. Theodorou S, Chia C. Radiofrequency-assisted liposuction for arm contouring: technique under local anesthesia. Plast Reconstr Surg Glob Open 2013;1:e37. [CrossRef]
5. Reed LS. Brachioplasty with limited scar. Clin Plast Surg 2014;41:753–63. [CrossRef]
6. Teimourian B, Malekzadeh S. Rejuvenation of the upper arm. Plast Reconstr Surg 1998;102:545–53. [CrossRef]
7. Ahmad MSI. Circumferential lipobrachioplasty is a safe procedure. Plast Reconstr Surg 2021;147:337–44. [CrossRef]
8. Nguyen AT, Rohrich RJ. Liposuction-assisted posterior brachioplasty: technical refinements in upper arm contouring. Plast Reconstr Surg 2010;126:1365–9. [CrossRef]
9. American Society of Plastic Surgeons. 2006 National plastic surgery statistics: Cosmetic and reconstructive procedure trends. Available at: https://www.plasticsurgery.org/%20media/statistics/loader.cfm?url_/commonspot/security/getfile.cfm&PageID_23628. Accessed Sep 19, 2023.
10. Lockwood T. Brachioplasty with superficial fascial system suspension. Plast Reconstr Surg 1995;96:912–20. [CrossRef]
11. Pascal JF, Le Louarn C. Brachioplasty. Aesthetic Plast Surg 2005;29:423–30. [CrossRef]
12. Strauch B, Greenspun D, Levine J, Baum T. A technique of brachioplasty. Plast Reconstr Surg 2004;113:1044–9. [CrossRef]
13. Chandawarkar RY, Lewis JM. 'Fish-incision' brachioplasty. J Plast Reconstr Aesthet Surg 2006;59:521–5. [CrossRef]
14. Hurwitz DJ, Holland SW. The L brachioplasty: an innovative approach to correct excess tissue of the upper arm, axilla, and lateral chest. Plast Reconstr Surg 2006;117:403–13. [CrossRef]
15. Aljerian A, Abi-Rafeh J, Ramirez-GarciaLuna J, Hemmerling T, Gilardino MS. Complications in brachioplasty: a systematic review and meta-analysis. Plast Reconstr Surg 2022;149:83–95. [CrossRef]
16. Hill S, Small KH, Pezeshk RA, Rohrich RJ. Liposuction-assisted short-scar brachioplasty: technical highlights. Plast Reconstr Surg 2016;138:447e–50e. [CrossRef]
17. Richards ME. Minimal-incision brachioplasty: a first-choice option in arm reduction surgery. Aesthet Surg J 2001;21:301–10. [CrossRef]
18. Guerrero-Santos J. Brachioplasty. Aesthetic Plast Surg 1979;3:1–14. [CrossRef]
19. Samra S, Samra F, Liu YJ, Sawh-Martinez R, Persing J. Optimal placement of a brachioplasty scar: a survey evaluation. Ann Plast Surg 2013;71:329–32. [CrossRef]
20. Gilliland MD, Lyos AT. CAST liposuction of the arm improves aesthetic results. Aesthetic Plast Surg 1997;21:225–9. [CrossRef]
21. Vogt PA. Brachial suction-assisted lipoplasty and brachioplasty. Aesthet Surg J 2001;21:164–7. [CrossRef]
22. Lillis PJ. Liposuction of the arms. Dermatol Clin 1999;17:783–97. [CrossRef]
23. Abboud MH, Abboud NM, Dibo SA. Brachioplasty by power-assisted liposuction and fat transfer: a novel approach that obviates skin excision. Aesthet Surg J 2016;36:908–17. [CrossRef]
24. Eaves FF 3rd. Commentary on: brachioplasty by power-assisted liposuction and fat transfer: a novel approach that obviates skin excision. Aesthet Surg J 2016;36:918–9. [CrossRef]
25. Bossert RP, Dreifuss S, Coon D, Wollstein A, Clavijo-Alvarez J, Gusenoff JA, et al. Liposuction of the arm concurrent with

brachioplasty in the massive weight loss patient: is it safe? Plast Reconstr Surg 2013;131:357–65. [CrossRef]
26. de Runz A, Brix M, Gisquet H, Pujo J, Minetti C, Colson T, et al. Satisfaction and complications after lower body lift with autologous gluteal augmentation by island fat flap: 55 case series over 3 years. J Plast Reconstr Aesthet Surg 2015;68:410–8. [CrossRef]
27. Sisti A, Cuomo R, Milonia L, Tassinari J, Castagna A, Brandi C, et al. Complications associated with brachioplasty: a literature review. Acta Biomed 2018;88:393–402.
28. Di Pietro V, Colicchia GM, Cervelli V, Gentile P. Arm contouring after massive weight loss: liposuction-assisted brachioplasty versus standard technique. J Cutan Aesthet Surg 2018;11:73–8. [CrossRef]
29. Zomerlei TA, Neaman KC, Armstrong SD, Aitken ME, Cullen WT, Ford RD, et al. Brachioplasty outcomes: a review of a multipractice cohort. Plast Reconstr Surg 2013;131:883–9. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.57442
Haydarpasa Numune Med J 2025;65(4):327–332



hnhtipdergisi.com

ORIGINAL ARTICLE

Socio-Demographic Evaluation of Patients Admitted to the Pediatric Emergency Department and Outpatient Clinic With A Diagnosis of Intoxication

Halil Alkaya[1], Tamay Gürbüz[1], Tuğba Altıntaş[2], Çağatay Nuhoğlu[1]

[1]Department of Pediatrics, Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye
[2]Department of Health Management, Üsküdar University, İstanbul, Türkiye

Abstract

Introduction: This study aims to retrospectively analyze the demographic, sociocultural, and clinical characteristics of childhood poisoning cases. The study evaluates the types of substances causing poisoning, their distribution by age group, hospital admission times, and treatment approaches.

Methods: Poisoning cases in individuals under 18 years of age who presented to the Pediatric Emergency Department of Haydarpaşa Numune Training and Research Hospital in 2017 were retrospectively examined. Patients' age, gender, cause of poisoning, treatment methods, and clinical data were recorded. The NCSS 2007 program was used for statistical analyses.

Results: The study included 112 children. Poisoning occurred at home in 94.6% of cases; 58.0% were suicide attempts, and 42.0% were accidental. The most common toxic substances were antidepressants (18.8%) and analgesics (17.9%). Poisoning involved self-administration in 41.1% of cases and others' medications in 53.5%. Depression was the most common comorbid condition (27.4%).

Discussion and Conclusion: Poisoning is a significant health issue, particularly in children under five years of age and those over twelve. Education for families, psychological support, and early intervention are essential. Teaching young children not to taste unknown substances, encouraging adolescents through confidence-building and problem-solving strategies, increasing adolescent health centers, and restricting over-the-counter drug sales could reduce poisoning incidents.

Keywords: Childhood poisoning; suicide attempts; toxic substances.

The concepts of poison, poisoning, and treatment have existed throughout human history. Hippocrates (460–377 BC), who is generally considered the father of medicine, described many poisons and their treatments and was the first to mention the principles of clinical toxicology. However, the term "poison" was first used in English literature around the 1230s to describe air or drugs with deadly contents [1].

Mid-20th-century analyses by the American Academy of Pediatrics highlighted that poisoning was one of the most common medical emergencies in children, emphasizing the seriousness of the issue and leading to the implementation of necessary preventive measures [2]. Worldwide, poisoning cases constitute a significant proportion of emergency department admissions, particularly among children [3,4]. In developed countries, the annual incidence of poisoning

Correspondence: Halil Alkaya, M.D. Department of Pediatrics, Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye
Phone: +90 532 174 13 96 **E-mail:** halilalkaya2910@gmail.com
Submitted Date: 04.12.2024 **Revised Date:** 02.08.2025 **Accepted Date:** 16.08.2025
Haydarpaşa Numune Medical Journal

ranges between 0.02% and 0.93%, while in our country, this rate is between 0.46% and 1.57% [5,6].

In our country, the most common causes of poisoning are medications, household chemicals, toxic gases, foods, plants, and poisonous animals [7]. According to the 2008 National Poisoning Center report, products used for human health (such as medications) rank first among poisoning agents, with a rate of 69.74% [8]. According to 2016 data from the AAPCC (American Association of Poison Control Centers), the number of reported poisoning cases was 2,159,032, of which 62.82% were in individuals under the age of 18 and 31.79% were in children under 5 years old [9].

Altered consciousness, sudden arrhythmias without known heart disease, the sudden onset of symptoms and signs, or similar symptoms observed in multiple individuals not associated with any diagnosed illness should raise suspicion of poisoning [3]. The time between the poisoning incident and hospital admission, the type and amount of poison, and the child's age are important for diagnosis and treatment [10]. For this reason, each country should take its own precautions and develop a poisoning management approach based on regional risks [11]. Especially in developing countries like Türkiye, considering that poisoning in children is associated with high mortality, this is a significant issue and needs to be addressed. Poisoning is a global problem affecting children worldwide and is one of the most common reasons for emergency room visits [12].

The regional distribution of poisoning cases, the causes of poisoning, and their clinical reflections by age group provide important information for public health and form the basis for shaping health policies.

In our study, we aimed to retrospectively examine the demographic, socio-cultural, and clinical findings of pediatric poisoning cases who applied to and were hospitalized at Haydarpaşa Numune Training and Research Hospital throughout 2017. Additionally, we aimed to contribute to the poisoning database in our country.

Materials and Methods

This study was designed as a retrospective analysis of the medical records of all patients under the age of 18 who were diagnosed with poisoning and admitted to the Pediatric Emergency Department of Haydarpaşa Numune Training and Research Hospital, University of Health Sciences, between January 1 and December 31, 2017. Data obtained from the patients' archived files included age, gender, presenting symptoms, Glasgow Coma Score, complications, treatments applied, whether gastric lavage or activated charcoal was administered, location of the poisoning, time elapsed before hospital presentation, type and classification of the toxic substance, whether the substance belonged to the patient or another individual, the cause of poisoning (suicide or accident), treatment method, need for intensive care, presence of comorbidities, and length of hospital stay. These data were analyzed statistically.

Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 software (Kaysville, Utah, USA). Descriptive statistics, including mean, standard deviation, median, frequency, percentage, minimum, and maximum values, were used to summarize the data. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Since most of the data did not conform to a normal distribution, nonparametric tests were applied. The Mann–Whitney U test was used for comparisons between two independent groups, as it does not require normally distributed data. For comparisons involving three or more groups, the Kruskal–Wallis test was applied, and if significant differences were found, Bonferroni–Dunn post hoc analysis was conducted to determine which groups differed. Relationships between categorical variables were assessed using the Pearson chi-square test when appropriate, while Fisher's exact test and Fisher–Freeman–Halton test were used in cases of small sample sizes or low expected frequencies. A p-value of <0.05 was considered statistically significant. The application of these statistical methods ensured accurate interpretation of the data and enhanced the reliability of the study findings.

Ethical approval for the study was granted by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital, University of Health Sciences, on February 6, 2018 (Decision No: 127). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

The study was conducted with 112 children diagnosed with intoxication who were admitted to the Pediatric Health and Diseases Clinic of Haydarpaşa Numune Training and Research Hospital between January 1, 2017, and December 31, 2017. Of the patients, 67.9% (n=76) were female and 32.1% (n=36) were male. The age range of the children was 0.8 to 17.4 years, with a mean age of 10.64±6.40 years. In terms of age distribution, 34.8% (n=39) were 5 years old or younger, 6.3% (n=7) were between 6 and 11 years old, and 58.9% (n=66) were 12 years or older. Comorbid conditions were present in 19.6% (n=22) of the patients, with depression being the most common, observed in 27.4% (n=6) of these cases (Table 1).

The duration of observation and hospitalization ranged from 6 to 130 hours, with a mean of 33.34±23.68 hours. Poisonings occurred at home in 94.6% (n=106) of the cases and outside the home in 5.4% (n=6). Regarding the cause, 58.0% (n=65) of the children were cases of intentional poisoning (suicide attempt), while 42.0% (n=47) were accidental.

The most frequently ingested toxic substances were antidepressants (18.8%, n=21), analgesics (17.9%, n=20), non-steroidal anti-inflammatory drugs (8.9%, n=10), antipsychotics (8.0%, n=9), antibiotics (6.3%, n=7), antihistamines (5.4%, n=6), antidiabetics (5.4%, n=6), and ACE inhibitors (4.5%, n=5). Other substances (42.9%, n=48) included antispasmodics, anticoagulants, ethanol, mushrooms, corrosive agents, herbal products, leukotriene antagonists, antiemetics, and carbon monoxide.

In terms of substance ownership, 41.1% (n=46) of children used their own medications, 53.5% (n=60) used medications belonging to others, and 5.4% (n=6) ingested non-medicinal substances. The time from poisoning to hospital admission ranged from 0.2 to 61 hours (Table 2).

Table 1. Distribution of demographic characteristics

Demographic characteristics	n	%
Age (years)		
Min-max (median)	0.8-17.4 (14)	
Mean±SD	10.64±6.40	
≤5 years	39	34.8
6-11 years	7	6.3
≥12 years	66	58.9
Gender		
Female	76	67.9
Male	36	32.1
Comorbid disease		
None	90	80.4
Present	22	19.6
Depression	6	27.4
ADHD	3	13.6
Epilepsy	2	9
Bipolar disorder	2	9
Anxiety	2	9
Anorexia nervosa	1	4.5
Other (asthma, acute bronchitis, atopic dermatitis, upper respiratory tract infection)	6	27.4

SD: Standard deviation; ADHD: Attention deficit hyperactivity disorder.

Symptoms developed in 15.2% (n=17) of the children, with nausea and vomiting being the most common (23.6%, n=4). Glasgow Coma Scale (GCS) scores were 13 in 2.7% (n=3), 14 in 2.7% (n=3), and 15 in 94.6% (n=106) of the cases. Complications were observed in 1.8% (n=2) of patients and included hypoglycemia and QT prolongation.

Regarding treatment, 0.9% (n=1) of the children received akineton, 92.8% (n=104) received hydration therapy, 1.8% (n=2) received hydration with N-acetylcysteine, 0.9% (n=1) received hydration with bicarbonate, 2.7% (n=3) received hydration with ranitidine, and 0.9% (n=1) received hyperbaric oxygen therapy. Gastric lavage was performed in 43.7% (n=49), and activated charcoal was administered in 69.6% (n=78) of the cases. Intensive care unit (ICU) indication was present in 2.7% (n=3) of the children (Table 3).

Table 2. Distribution of characteristics related to intoxication incidents

Intoxication characteristics	n	%
Location of intoxication incident		
Home	106	94.6
Outside the home	6	5.4
Mode of intoxication		
Suicide	65	58.0
Accident	47	42.0
Toxic substances ingested		
Antidepressant	21	18.8
Analgesic	20	17.9
NSAIDs	10	8.9
Antipsychotic	9	8.0
Antibiotic	7	6.3
Antihistamine	6	5.4
Antidiabetic	6	5.4
ACE Inhibitor	5	4.5
Other (vitamin, beta agonist, decongestant, gastroprotective agent, antihypertensive, leukotriene antagonist, antiemetic, carbon monoxide (co), antispasmodic, ethanol, antihyperlipidemic, anticoagulant, mushroom, corrosive substance, plant extract)	48	42.9
Ownership of the drug used		
Own medication	46	41.1
Non-own medication	60	53.5
Non- drug (Ethanol, CO, Mushroom, Plant extract, Drain cleaner)	6	5.4
Time to arrival at hospital (hours)		
Min-max (median)	0.2-61 (2)	

CO: Carbon monoxide; ACE: Angiotensin-converting enzyme; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 3. Distribution of in-hospital characteristics

In-Hospital characteristics	n	%
Symptoms		
None	95	84.8
Present	17	15.2
Dizziness	2	11.7
Altered Consciousness	2	11.7
Nausea-Vomiting	4	23.6
Other (fainting, jaw clenching, toothache, fatigue, hallucination, diarrhea, speech difficulty)	9	53
Vital Signs		
GCS 13	3	2.7
GCS 14	3	2.7
GCS 15	106	94.6

GCS: Glasgow coma scale.

When data were analyzed by age group, the presence of comorbid conditions differed significantly across age categories (Fisher–Freeman–Halton test, p=0.003). Comorbidities were more common in children aged ≥12 years (30.3%) than in those aged ≤5 years (5.1%) and 6–11 years (0%).

Antidepressant use also varied significantly by age (p=0.03). Post hoc analysis showed that children aged 6–11 years (42.9%) and ≥12 years (22.7%) had higher rates of antidepressant use than those aged ≤5 years (7.7%).

The rate of using one's own medication was significantly higher in the ≥12 years group (59.1%) compared to the ≤5 years (17.9%) and 6–11 years (0%) groups (p<0.001).

Table 4. Evaluation of comorbid conditions and intoxication characteristics by age group

Variable	≤5 years (n=39)		6–11 years (n=7)		≥12 years (n=66)		p
	n	%	n	%	n	%	
Comorbid conditions	2	5.1	0	0	20	30.3	0.003[a]
Location of intoxication							
Home	38	97.4	7	100	61	92.4	0.598[a]
Outside	1	2.6	0	0	5	7.6	
Mode of intoxication							
Suicide	6	15.4	4	57.1	55	83.3	<0.001[a]
Accident	33	84.6	3	42.9	11	16.7	
Antidepressant use	3	7.7	3	42.9	15	22.7	0.03[a]
Ownership of medication							
Own	7	17.9	0	0	39	59.1	<0.001[a]
Not own	31	79.5	6	85.7	23	34.8	
Non-drug	1	2.6	1	14.3	4	6.1	
Hospital arrival time (hours), median (min–max)	24 (6–72)		33 (24–130)		24 (8–130)		0.002[d]

[a]: Fisher-Freeman-Halton test; [d]: Kruskal-Wallis test. *: p<0.05; **: p<0.01.

Table 5. Evaluation of hospital characteristics by age group

Variable	≤5 years (n=39)		6–11 years (n=7)		≥12 years (n=66)		p
	n	%	n	%	n	%	
Symptoms							
None	36	92.3	7	100	52	78.8	0.122[a]
Present	3	7.7	0	0	14	21.2	
Complications							
None	39	100	7	100	64	97	0.586[a]
Present	0	0	0	0	2	3	
Gastric lavage							
Not done	19	48.7	5	71.4	39	59.1	0.427[a]
Done	20	51.3	2	28.6	27	40.9	
Activated charcoal							
Not done	12	30.8	1	14.3	21	31.8	0.842[a]
Done	27	69.2	6	85.7	45	68.2	
ICU indication							
None	39	100	6	85.7	64	97	0.137[a]
Present	0	0	1	14.3	2	3	
Observation and admission duration (hours), median (min–max)	24 (6–72)		33 (24–130)		24 (8–130)		0.002[d]

[a]: Fisher-Freeman-Halton test; [d]: Kruskal-Wallis test. *: p<0.05; **: p<0.01. ICU: Intensive care unit.

Hospital arrival times also differed significantly by age group (Kruskal–Wallis test, p=0.002). Post hoc comparisons revealed that children aged 6–11 years had the longest delay in reaching the hospital, followed by those aged ≥12 years (Table 4). However, there were no statistically significant differences between age groups in terms of poisoning location, symptoms, complications, gastric lavage, or activated charcoal administration (all p>0.05).

Finally, the duration of hospital stay differed significantly across age groups (Kruskal–Wallis test, p=0.002). Post hoc analysis indicated that children aged 6–11 years had a longer median hospital stay (33 hours) than children in the other groups (median 24 hours) (Table 5).

Discussion

In our study, 34.8% of the cases (n=39) were children aged ≤5 years, 6.3% (n=7) were children aged 6–11 years, and 58.9% (n=66) were children aged ≥12 years. In another study, poisoning incidents were most commonly observed in children under 5 years of age, with 39.4% of cases occurring in children aged 13 months to 4 years and 21.7% in children aged 0–12 months [13]. In the study by Sümer et al. [14] conducted between 2003 and 2009, 73.8% of the 233 cases presenting to the Pediatric Emergency Department of Kahramanmaraş Sütçü İmam University Medical Faculty were children aged 7 months to 4 years. The predominance of cases in children aged ≥12 years in our study differs from many previous reports in which poisoning is more frequent among younger children. This difference may be explained by the higher risk of household accidents in younger children, whereas adolescents more frequently tend to experiment with substances or medications. This pattern may be associated with increasing curiosity and risk-taking behaviors with age. Although direct evidence in the literature is limited, observational findings support this interpretation.

Comorbidities were observed in 19.6% of the children (n=22), with depression being the most common comorbidity, present in 27.4% (n=6) of these cases. This finding suggests that children with psychological problems may be at a higher risk for poisoning. Psychiatric disorders, particularly depression, are known to be associated with suicide attempts and self-harming behaviors in children and adolescents. However, studies directly examining the relationship between psychiatric conditions and poisoning in pediatric populations remain limited. Therefore, further research is needed to clarify the impact of psychological factors on childhood poisoning.

The duration of observation and hospitalization ranged from 6 to 130 hours, with a mean of 33.34±23.68 hours. In a previous study, hospitalization durations for poisoned patients ranged from 8 hours to 10 days, with a mean of 43.8±29 hours. Differences in hospitalization duration may be attributed to variations in patient characteristics, poisoning severity, and treatment approaches. In our study, 94.6% of poisonings (n=106) occurred at home, whereas 5.4% (n=6) occurred outside the home. The predominance of home-based poisonings indicates that access to harmful substances in the domestic environment poses a significant risk, underscoring the importance of preventive measures and increased awareness among families.

When examining toxic substances, the most frequently encountered substances were antidepressants (18.8%, n=21), analgesics (17.9%, n=20), nonsteroidal anti-inflammatory drugs (8.9%, n=10), antipsychotics (8.0%, n=9), antibiotics (6.3%, n=7), antihistamines (5.4%, n=6), antidiabetic drugs (5.4%, n=6), ACE inhibitors (4.5%, n=5), and other substances (42.9%, n=48). In the study by Bükülmez et al. [8], the most common cause of poisoning was corrosive substances, accounting for 51.4% of cases (148 cases), while 21.9% (63 cases) were related to drug poisoning. This difference may be attributed to variations in poisoning types and population characteristics.

Symptoms developed in 15.2% of the children (n=17), with nausea and vomiting being the most common symptoms, observed in 23.6% of cases (n=4). Another study reported that the most common symptoms included nausea and vomiting (14.1%), dizziness (13.3%), oropharyngeal hyperemia (9%), and loss of consciousness (8.5%) [14]. Our findings suggest that gastrointestinal symptoms are more common in children and provide an important clinical clue. The evaluation and management of symptoms such as nausea and vomiting may play a critical role in the recognition of this patient group.

Statistically significant differences in the presence of comorbidities were found across age groups. The prevalence of comorbidities was higher in children aged ≥12 years. This may be explained by longer exposure to stressors, environmental allergens, or infections in older children, which may facilitate the development of certain comorbidities over time. However, given the limited number of studies addressing this issue, long-term follow-up studies are needed to evaluate comorbidity rates across different age groups.

Antidepressant use was significantly higher in children aged 6–11 years and ≥12 years compared with children aged ≤5 years. The more frequent use of antidepressants in older children may be explained by higher diagnosis rates of psychiatric disorders such as depression and anxiety in these age groups and the increased use of antidepressants in their treatment. In addition, emotional and psychological fluctuations during adolescence may also contribute to this finding.

Gender differences were associated with the type of poisoning, with suicide rates being significantly higher in girls than in boys. Another study also reported that most suicide attempts were made by girls (73.8%) [15]. This finding may be related to the tendency of adolescent girls to internalize emotional and social problems more than boys. Such internalization may lead to difficulties in emotion regulation and increase engagement in risky behaviors. However, due to the limited literature on this topic, further studies are needed to investigate gender-based differences in emotional coping strategies.

Conclusion

Poisoning is an important public health issue because of its preventable morbidity and mortality. Although it can occur in all age groups, it is more frequently observed in children under the age of 5 years and those older than 12 years. Therefore, it is crucial for families with children in these age groups to receive preventive education on poisoning. In our study, the notably high rate of suicide attempts during adolescence highlights the need for targeted poisoning prevention education for this age group. Timely access to healthcare services and the quality of these services are critical during the treatment process. In addition, families and communities should be educated about poisoning, medications must be stored safely, children should be prevented from tasting unknown substances, and adolescents should be supported in developing self-confidence and problem-solving skills. The establishment of more adolescent health centers, restriction of over-the-counter medication sales, and the organization of nationwide awareness campaigns may help reduce poisoning incidents.

Ethics Committee Approval: The study was approved by University of Health Sciences, Haydarpaşa Numune Training and Research Hospital Ethics Committee (No: 127, Date: 06.02.2018).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – H.A., T.G., Ç.N.; Design – H.A., T.G., Ç.N.; Supervision – T.G., Ç.N.; Materials – H.A., T.G.; Data collection &/or processing – H.A., T.G.; Analysis and/or interpretation – H.A., T.G., T.A., Ç.N.; Literature search – H.A., T.G.; Writing – H.A.; Critical review – T.G., Ç.N.

Conflict of Interest: The authors declare that there is no conflict of interest.

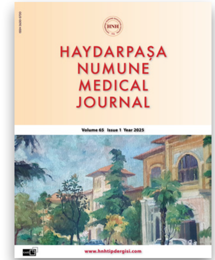
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hoffman RS, Goldfrank LR. Historical Principles and Perspectives. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. Goldfrank's Toxicologic Emergencies. Available at: https://aneskey.com/historical-principles-and-perspectives/. Accessed Dec 22, 2025.
2. Arena JM. The pediatrician's role in the poison control movement and poison prevention. Am J Dis Child 1983;137:870–3. [CrossRef]
3. Öner N, İnan M, Vatansever Ü, Turan Ç, Çeltik C, Küçükuğurluoğlu Y, et al. Trakya bölgesinde çocuklarda görülen zehirlenmeler. Türk Pediatri Arşivi 2004;39:25–30. [Article in Turkish]
4. Karaarslan B, Turla A, Aydın B. Ondokuz Mayıs üniversitesi tıp fakültesi acil servisine başvuran koroziv madde zehirlenmeleri. Van Tıp Derg 2007;14:109–13. [Article in Turkish]
5. Çanakçı E, Kaya Y, Karataş A. Retrospective analysis of intoxication cases admitted to our intensive care unit. Kocatepe Med J 2017;18:100–5.
6. Hakkoymaz H, Kilci Aİ, Güler Ö, Yaman FN, Okyay RA. Evaluation of the patients admitted to the emergency room due to poisoning in terms of clinical characteristics and costs. Sakarya Med J 2019;9:470–8. [CrossRef]
7. Tunçok Y, Kalyoncu Nİ. T.C. sağlık bakanlığı birinci basamağa yönelik zehirlenmeler tanı ve tedavi rehberi. 2. Baskı. Ankara: Yücel Ofset Matbaacılık Tic. Ltd. Şti. 2007. [In Turkish]
8. Özcan N, İkincioğulları D. Ulusal zehir danışma merkezi 2008 yılı çalışma raporu özeti. Turk Hij Den Biyol Derg 2009;66:29–58. [Article in Turkish]
9. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th annual report. Clin Toxicol (Phila) 2017;55:1072–252. [CrossRef]
10. Sinanoğlu MS, Berk E. Clinical spectrum of acute poisoning cases admitted to the pediatric emergency department. Haydarpasa Numune Med J 2023;63:316–22. [CrossRef]
11. World Health Organization. Poisoning prevention and management. Geneva: WHO Press; 2012.
12. Araz C, Toklucu MÖ, Güven Ş, Pala E, Okur T. Retrospective analysis of childhood poisoning in Ümraniye. Haydarpaşa Numune Med J 2016;56:147–60. [Article in Turkish]
13. Sümer V, Güler E, Karanfil R, Dalkıran T, Gürsoy H, Garipardıç M, et al. Retrospective evaluation of poisoning cases who presented to the Pediatric Emergency Unit. Turk Arch Pediatr 2011;46:226–32. [CrossRef]
14. Bükülmez A, Gürhan Tahta E, Şen TA, Alpay F. Evaluation of patients with intoxication admitted to the pediatric emergency service. Kocatepe Med J 2013;14:11–6.
15. Ünlü G, Aksoy Z, Ersan EE. Evaluation of children and adolescents whit attempted suicide. Pamukkale Med J 2014;7:176–83. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.47048
Haydarpasa Numune Med J 2025;65(4):333–339



hnhtipdergisi.com

ORIGINAL ARTICLE

The Effectiveness of Biofeedback Therapy in Treating Dysfunctional Voiding and Enuresis in Children: A Retrospective Study

Arzu Canmemiş[1], Berfin Özgenur Aydın[2], Çigdem Ulukaya Durakbaşa[2]

[1]**Division of Pediatric Urology, Department of Pediatric Surgery, İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye**

[2]**Department of Pediatric Surgery, İstanbul Medeniyet University, İstanbul, Türkiye**

Abstract

Introduction: Biofeedback therapy is a non-invasive approach used to treat children with dysfunctional voiding (DV) and daytime enuresis (DE). It improves voluntary relaxation of the pelvic floor muscles and normalizes voiding patterns. This study aimed to evaluate clinical indications, treatment responses, and changes in uroflowmetry parameters and voiding curve patterns in children receiving biofeedback therapy.

Methods: This retrospective study included children aged 5–18 years with DV or DE who underwent at least two pre-treatment uroflowmetry (UFM) and electromyography (EMG) evaluations between April 2023 and March 2024. A standardized biofeedback protocol was administered weekly by a trained nurse under the supervision of a pediatric urologist. Voiding symptoms, EMG activity, and uroflowmetry parameters were assessed. McNemar and Wilcoxon signed-rank tests were used for statistical analysis.

Results: A total of 42 female patients (mean age: 12±3.2 years) were evaluated. Non-monosymptomatic enuresis (31%) and DV-related urinary tract infections (24%) were the most common indications. Daytime incontinence was present in 33% of patients, and 62% had a history of urinary tract infections. Although complete response rates were low, improvements were observed in EMG relaxation (83%) and bell-shaped voiding curves, which increased markedly from 26.3% to 84% by the 8th session. Voided volume and Qmax increased significantly ($p<0.05$). Children with ≥5 voids per day showed a significantly higher treatment response ($p=0.031$).

Discussion and Conclusion: Biofeedback therapy effectively improves voiding parameters and pelvic floor muscle relaxation; however, complete dryness remains limited, particularly in patients with nocturnal enuresis.

Keywords: Biofeedback; dysfunctional voiding; EMG activity; enuresis; urinary patterns.

Enuresis is a frequent presenting complaint in pediatric urology clinic visits. The International Children's Continence Society (ICCS) defines monosymptomatic enuresis (MSE) as nocturnal urinary incontinence in children aged over five years without accompanying lower urinary tract symptoms [1]. Approximately 10% of 7-year-old children and 5% of 10-year-old children experience this condition, with a persistence rate of 0.5–1% into adulthood [2,3].

Non-monosymptomatic enuresis (NMSE) is defined as nocturnal enuresis accompanied by lower urinary tract

Correspondence: Arzu Canmemiş, M.D. Division of Pediatric Urology, Department of Pediatric Surgery, İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye
Phone: +90 216 606 52 00 **E-mail:** arzuc2023@gmail.com
Submitted Date: 26.05.2025 **Revised Date:** 16.07.2025 **Accepted Date:** 18.08.2025
Haydarpaşa Numune Medical Journal

symptoms such as daytime urinary incontinence, urgency, or increased voiding frequency. NMSE accounts for approximately 30% of all enuresis cases [4,5]. Dysfunctional voiding is a prevalent lower urinary tract symptom affecting 3.8% of boys and 6% of girls aged 7 years [6]. These conditions highlight the importance of targeted therapeutic strategies.

Urotherapy serves as the cornerstone of non-invasive treatment for pediatric urinary incontinence and voiding dysfunction. Standard urotherapy integrates lifestyle modifications, regular voiding habits, adequate fluid intake, prevention of constipation, and pelvic floor muscle training. Biofeedback therapy can be an effective intervention for children with dysfunctional voiding and non-monosymptomatic enuresis (NMSE) with urgency and incontinence symptoms. It facilitates awareness and control of pelvic floor muscle activity through auditory or visual feedback, aiming to normalize voiding patterns. It is particularly beneficial for children with dysfunctional voiding characterized by overactive pelvic floor muscles [7]. The International Children's Continence Society (ICCS) has outlined the definitions, indications, and practice of urotherapy in children and adolescents with dysfunctional voiding or NMSE [1,8,9].

Our study focuses on evaluating the indications, treatment response rates, and changes in uroflowmetry parameters and voiding curve patterns in children undergoing biofeedback therapy. Additionally, it aims to identify the critical number of sessions necessary to predict clinical response, providing insights into optimizing treatment protocols for pediatric patients with voiding dysfunction.

Materials and Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee (Approval No:17.04.2025-495), and informed consent was obtained from all patients or their legal guardians before participation. Medical records of patients receiving biofeedback therapy between April 2023 and March 2024 were reviewed. Children aged 5–18 years with dysfunctional voiding or enuresis who had undergone at least two pre-treatment uroflowmetry and electromyography (EMG) evaluations constituted the study group. A retrospective analysis was conducted of the outcomes of our biofeedback training program administered to patients who were unresponsive to initial management between April 2023 and March 2024. Children under 5 years of age and those with anatomical or neurogenic bladder conditions were excluded.

At our center, all patients with lower urinary tract symptoms and enuresis initially undergo a 1-month behavioral therapy program. Behavioral therapy includes encouraging adequate fluid intake during the day, scheduled voiding, management of constipation, and avoidance of tea, coffee, and carbonated drinks. For children with MSE, fluid intake is restricted for two hours before bedtime. Following behavioral therapy, patients with persistent symptoms receive either medical treatment or biofeedback therapy, depending on the treating physician's preference.

A urinary tract infection (UTI) was defined as ≥100,000 CFU/mL of bacteria in a midstream urine sample. Bladder capacity was determined as the maximum voided volume recorded in voiding diaries. UFM-EMG was performed at least twice, and patients with abnormal voiding curves and increased EMG activity were diagnosed with dysfunctional voiding. UFM-EMG curves were classified as normal, staccato, tower, intermittent, or plateau based on ICCS recommendations [4]. Patients were assessed at the 4th and 8th weeks. For patients who were noncompliant with therapy by the 4th week, treatment was discontinued. The remaining patients received biofeedback therapy for up to 8 weeks, with reevaluation at the end of this period. Therapy was extended to 12 weeks for patients showing improvement without achieving full recovery. For patients without progress by the 8th week, therapy was terminated.

Surface EMG electrodes were placed at the 2 o'clock and 10 o'clock positions of the anal sphincter to detect pelvic floor muscle activity. Biofeedback training involved the use of a computer animation that allowed children to manipulate on-screen objects by contracting or relaxing the pelvic floor muscles. Each session lasted 20 minutes and consisted of 10-second contraction and relaxation cycles. All UFM measurements and biofeedback sessions were conducted by the same nurse. Children attended weekly biofeedback sessions and were instructed to perform pelvic floor exercises at home three times per week for 20 minutes. Symptoms and incontinence were reassessed using bladder diaries before each session.

Parents and children were instructed to record voiding frequency, fluid intake, episodes of incontinence, and the number of wet nights before the subsequent session. Regular voiding every 3 hours with adequate fluid intake was encouraged. Proper toilet positioning and adherence to home exercises were repeatedly emphasized.

The evaluated outcomes in this study included treatment results according to indication, reduction in urinary tract infection (UTI) frequency, normalization of voiding curves, normalization of EMG activity, maximum voiding flow rate (Qmax), and voiding time.

Treatment success was defined according to ICCS criteria as clinical response assessed by the percentage reduction in wet nights: no response (<50% reduction), partial response (50–99% reduction), or full response (100% reduction with no wet nights) [4].

Statistical Analysis

Statistical analyses were conducted using SPSS 26.0, with a confidence level of 95%. Pre- and post-treatment changes in categorical variables were analyzed using the McNemar test. Changes in numerical variables were assessed using the Wilcoxon test. Age-related treatment response was analyzed using the t-test, and associations between treatment response and categorical variables were examined using the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the participants was 12±3.26 years (min–max: 5–18). All patients were female. The most common indication was NMSE (n=13, 31%), followed by dysfunctional voiding–associated UTI (n=10, 23.8%). Demographic characteristics are presented in Table 1.

Table 1. Demographic characteristics of patients

	n	%
Age (year)	12±3.26	
Indication		
Non-monosymptomatic enuresis	13	31
UTI	10	23.8
Monosymptomatic enuresis	7	16.7
Daytime incontinence	6	14.3
Dysfunctional voiding	2	4.8
Pollakiuria	2	4.8
Dysfunctional voiding	2	4.8
Post-void residual urine	1	2.4
Form of onset		
Primary	14	43.8
Secondary	18	56.3
Referring clinic		
Pediatric nephrology	24	57.1
Pediatric urology	17	40.5
Pediatric surgery	1	2.4
Parental status		
Together	41	97.6
Mother deceased	1	2.4

UTI: Urinary tract infection.

The most common daytime symptom was incontinence (n=14, 33.3%) (Table 2). A history of UTIs was present in 26 patients (61.9%). Among the medications used, prophylactic antibiotics were the most prevalent, prescribed to 17 patients (70.8%), followed by anticholinergics in 8 patients (33.3%).

Biofeedback therapy did not demonstrate an effect on constipation, fecal incontinence, or voiding frequency. Data on constipation and voiding frequency before and after treatment are presented in Table 3.

Biofeedback therapy was effective in reducing daytime and nighttime incontinence and the frequency of UTIs. Complete response rates were 22.2% for UTIs, 16.7% for daytime incontinence, 0% for nocturnal enuresis, and 7.7% for NMSE (p>0.05). Patients with a voiding frequency of ≥5 times per day showed a significantly higher treatment response compared with those with a voiding frequency of <5 times per day (p=0.031) (Table 4, 5).

Table 2. The patients' symptoms and medications.

	n	%
Daytime symptom		
Incontinence	14	33.3
Retention	8	19
Urge	9	21.4
No	11	26.2
History of urinary tract infections		
No	16	38.1
Yes	26	61.9
Medications used		
Anticholinergics	8	33.3
Prophylaxis	17	70.8
Laxatives	6	25
Other medications	4	16.7

Table 3. Effect of biofeedback therapy on constipation and voiding frequency

	Before treatment		After treatment		p
	n	%	n	%	
Constipation					
No	34	81	37	88.1	0.453
Yes	8	19	5	11.9	
Fecal incontinence					
No	41	97.6	41	97.6	1.000
Yes	1	2.4	1	2.4	
Voiding frequency					
Less than 5/day	16	38.1	17	42.5	0.727
5 or more/day	26	61.9	23	57.5	

Table 4. Changes in incontinence and UTI frequency following treatment

	n	Mean rank	p
Frequency of daytime urinary incontinence after treatment (days)<Frequency of daytime urinary incontinence before treatment (days)	11	7.05	0.025
Frequency of daytime urinary incontinence after treatment (days)>Frequency of daytime urinary incontinence before treatment (days)	2	6.75	
Frequency of daytime urinary incontinence after treatment (days)=Frequency of daytime urinary incontinence before treatment (days)	28		
Frequency of nighttime urinary incontinence after treatment (hours)<Frequency of nighttime urinary incontinence before treatment (hours)	12	8.88	0.008
Frequency of nighttime urinary incontinence after treatment (week)>Frequency of nighttime urinary incontinence before treatment (week)	3	4.50	
Frequency of nighttime urinary incontinence after treatment (week)=Frequency of nighttime urinary incontinence before treatment (week)	26		
Frequency of UTI after treatment (years)<Frequency of I UTI before treatment (years)	14	9.21	0.012
Frequency of UTI after treatment (years)>Frequency of UTI before treatment (years)	3	8.00	
Frequency of UTI after treatment (years)=Frequency of UTI before treatment (years)	18		

Wilcoxon test. UTI: Urinary tract infection.

Table 5. Response rates to treatment

	Response to treatment				p
	Yes		No		
	n	%	n	%	
Age (mean±SD)[a]	12±294		12.12±3.34		0.932
Comorbidities[b]					
No	2	11.1	16	88.9	0.438
Yes	5	21.7	18	78.3	
Constipation[b]					
No	5	15.2	28	84.8	0.606
Yes	2	25	6	75	
Fekal incontinence[b]					
No	7	17.5	33	82.5	1.000
Yes	0	0	1	100	
History of UTI[b]					
No	3	18.8	13	81.3	1.000
Yes	4	16	21	84	
Voiding frequency[b]					
Less than 5	0	0	16	100	0.031
5 or more	7	28	18	72	
Medications used[b]					
Anticholinergics	1	14.3	6	85.7	1.000
Prophylaxis	4	25	12	75	0.273
Laxatives	2	33.3	4	66.7	0.270
Other medications	1	25	3	75	1.000
Indication[b]					
UTI	2	22.2	7	77.8	0.130
Daytime incontinence	1	16.7	5	83.3	
Monosymptomatic enuresis	0	0	7	100	
Non-monosymptomatic enuresis	1	7.7	12	92.3	
Other	3	50	3	50	

[a]: t-test; [b]: Chi-square test. UTI: Urinary tract infection.

Initially, increased EMG activity was common; however, by the 12th session, most patients demonstrated significant relaxation (83.3%), while only 16.7% continued to show increased activity (Table 6).

At the first session, 26.3% of patients exhibited a bell-shaped voiding pattern, which increased to 84% by the eighth session. This rate plateaued at the eighth session and persisted through the twelfth session (Table 6, Fig. 1).

Table 6 and Figure 1 present changes in three parameters—voided volume (mL), Qmax (mL/s), and voiding time (seconds)—over eight sessions. A statistically significant increase in voided urine volume and Qmax values was observed when these parameters were compared successively from the 1st to the 8th session ($p<0.05$). No significant change was observed in voiding duration (Figs. 1, 2).

Table 6. Changes in electromyographic activity, voiding patterns, and uroflow parameters during biofeedback therapy

Session	EMG relaxation		EMG increase		Bell-shaped voiding pattern		Voided volume (mL)	Qmax (mL/s)	Voiding time (sec)
	n	%	n	%	n	%			
1st	11	26.3	31	73.7	11	26.3	193.47±156.99	13.7±11.8	77±136
8th	24	56.0	7	16.7	35	84.0	247.48±168.43	17.6±14.9	40±55
12th	24	56.0	7	16.7	35	84.0	202±111	15.5±6.8	20±9.9

EMG: Electromyography.

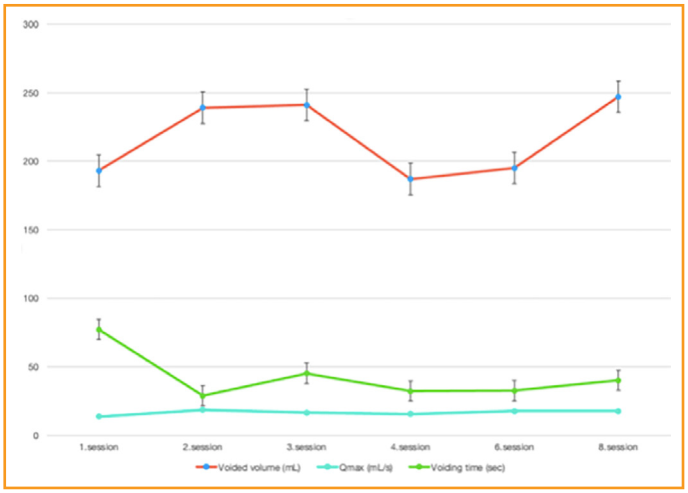


Figure 1. Changes in parameters.

Discussion

Biofeedback therapy has been reported as a non-invasive and potentially effective approach for the treatment of dysfunctional voiding and daytime enuresis in children [7–9]. It helps children become aware of normal voiding cycles and teaches them to consciously relax their pelvic floor muscles during urination [10,11]. The success of biofeedback largely depends on the motivation of children and their families, adherence to the program, and compliance with standard behavioral therapy. Additionally, the presence of a trained urotherapy nurse is crucial. In this study, treatment sessions were conducted by a single experienced nurse, and indications were mainly determined by a single pediatric urologist or nephrologist, which likely contributed to the consistency of our results.

Numerous studies have reported varying outcomes regarding the efficacy of biofeedback. Some have demonstrated significant improvements in dysfunctional voiding and NMSE, whereas others have reported limited or no benefit [4,12–15]. Reported success rates for the treatment of daytime symptoms and NMSE range from 28% to 64%. For example, in a prospective controlled study evaluating intra-anal biofeedback for resistant MSE, 60% of patients achieved a partial response by the third month, while none achieved complete dryness [16]. According to the International Children's Continence Society (ICCS), desmopressin and alarm therapy are recommended as first-line treatments for MSE, whereas biofeedback is considered appropriate

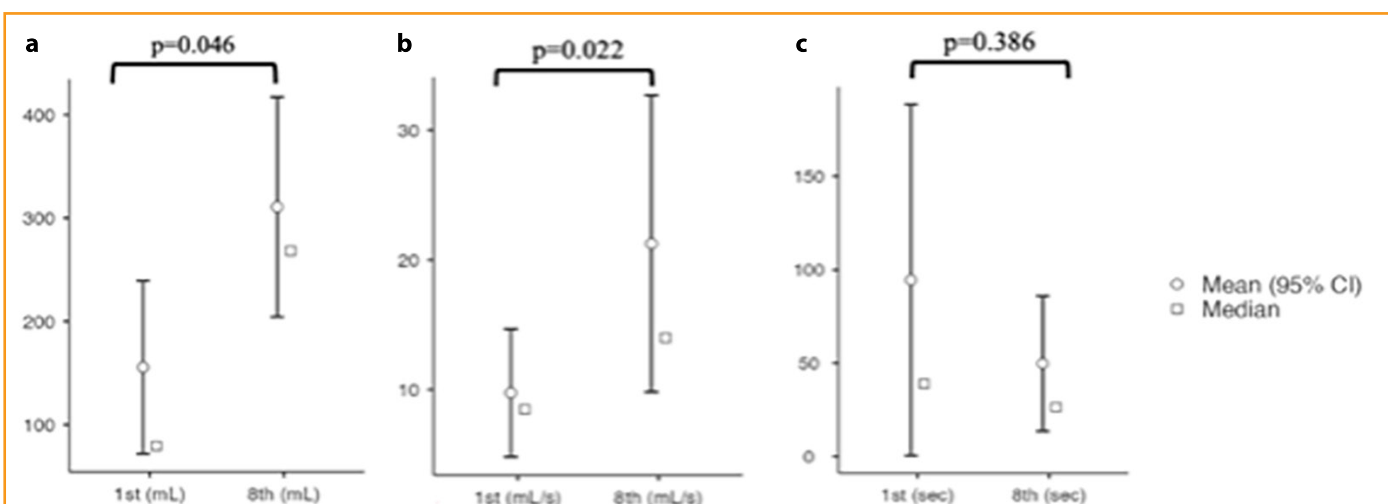


Figure 2. Comparison variables before and after sessions. (a) Voided volume, (b) Qmax, (c) Voiding duration.

for children with dysfunctional voiding. In NMSE, correction of voiding posture and prioritization of daytime symptom treatment are essential, as emphasized in the updated ICCS standardization document on the management and treatment of nocturnal enuresis [17]. Our findings are consistent with ICCS recommendations; although biofeedback reduced the frequency of wet episodes, it did not result in complete dryness.

Improvements in uroflow patterns and EMG relaxation are consistent with the expected effects of biofeedback therapy. In our study, bell-shaped voiding curves increased to 84% by the eighth session and remained stable thereafter [9,18–20]. However, despite these improvements, complete dryness was not consistently achieved. These results further support ICCS recommendations, which endorse biofeedback for dysfunctional voiding while emphasizing the prioritization of daytime symptom management in NMSE [17].

Patients who voided five or more times per day showed better responses to biofeedback therapy compared with those with lower voiding frequency. This finding is consistent with previous studies suggesting that voiding frequency and bladder capacity may guide treatment strategies [21]. Interestingly, the use of anticholinergic medications, which was common in our cohort, appeared to be a negative predictor of treatment success, although this association did not reach statistical significance in our study.

Constipation remains a challenging comorbidity. Although some studies suggest that biofeedback may improve functional constipation, meta-analyses report limited efficacy in this context [22–24]. Similarly, our findings showed no significant change in constipation symptoms, indicating a need for more targeted interventions.

Significant improvements in uroflowmetry (UFM) parameters following biofeedback therapy have been previously documented, including increased voided volume and maximum flow rate (Qmax), along with reduced voiding time [25,26]. These findings are consistent with our results, in which voided volumes increased significantly by the eighth session. However, variability in Qmax and voiding time may reflect external factors such as stress or urgency during testing.

Regarding treatment duration, one study reported improvements after a mean of 2.2 sessions, with peak improvement in voiding patterns observed by the eighth session and sustained through the twelfth session [27]. In our cohort, bell-shaped voiding patterns were observed in 43.5% of patients by the third session, increasing to 84% by the eighth session and remaining stable thereafter. These findings support an 8–12-week treatment period to optimize outcomes, maintain motivation, and avoid unnecessary prolongation of therapy.

This study has several limitations. As the cohort included only female patients, the generalizability of the findings is limited. The relatively short follow-up period precluded assessment of long-term treatment efficacy. Moreover, the absence of a control group limited the ability to evaluate the effectiveness of biofeedback therapy in a comparative context. Most participants were children with refractory symptoms who had not responded to prior medical and behavioral therapies; therefore, leaving them untreated was considered ethically inappropriate, making a randomized controlled design unfeasible. Another limitation was the inability to systematically monitor adherence to the recommended home exercise program. Despite these limitations, our study demonstrates the effectiveness of biofeedback therapy, particularly in refractory dysfunctional voiding, and highlights the importance of identifying patient profiles most likely to benefit, as well as the need to develop standardized clinical protocols.

Conclusion

In this study, biofeedback therapy was found to be effective in the treatment of dysfunctional voiding and in reducing the frequency of urinary tract infections (UTIs). Episodes of incontinence in children with daytime incontinence were reduced by this non-invasive treatment modality. However, biofeedback was not successful in achieving complete dryness or in the treatment of MSE. Overall, the results support the effectiveness of biofeedback therapy in normalizing voiding patterns and facilitating conscious relaxation of the pelvic floor muscles.

Ethics Committee Approval: The study was approved by İstanbul Medipol University Ethics Committee (No: 495, Date: 17.04.2025).

Use of AI for Writing Assistance: No artificial intelligence tools were used in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – A.C.; Design – A.C.; Supervision – Ç.U.D.; Fundings – A.C.; Materials – B.Ö.A., A.C.; Data collection and/or processing – A.C., B.Ö.A.; Analysis and/or interpretation – A.C., Ç.U.D.; Literature search – A.C.; Writing – A.C.; Critical review – Ç.U.D.

Conflict of Interest: The authors declare that there is no conflict of interest.

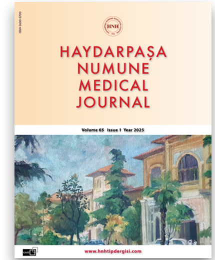
Financial Disclosure: This study was conducted without any institutional or financial support.

References

1. Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgül S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010;183:441–7. [CrossRef]
2. Sarici H, Telli O, Ozgur BC, Demirbas A, Ozgur S, Karagoz MA. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. J Pediatr Urol 2016;12:159.e1–6. [CrossRef]
3. Franco I, von Gontard A, De Gennaro M; International Childrens's Continence Society. Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: a standardization document from the International Children's Continence Society. J Pediatr Urol 2013;9:234–43. [CrossRef]
4. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471–81. [CrossRef]
5. Butler R, Heron J; Alspac Study Team. Exploring the differences between mono- and polysymptomatic nocturnal enuresis. Scand J Urol Nephrol 2006;40:313–9. [CrossRef]
6. Soygür T. Alt üriner sistem disfonksiyonlu hastanın evalüasyonu. Turkiye Klinikleri J Urology-Special Topics 2010;3:55–8. [Article in Turkish]
7. Feldman AS, Bauer SB. Diagnosis and management of dysfunctional voiding. Curr Opin Pediatr 2006;18:139–47. [CrossRef]
8. Nieuwhof-Leppink AJ, Hussong J, Chase J, Larsson J, Renson C, Hoebeke P, et al. Definitions, indications and practice of urotherapy in children and adolescents: - A standardization document of the International Children's Continence Society (ICCS). J Pediatr Urol 2021;17:172–81. [CrossRef]
9. Ebiloglu T, Ergin G, Irkilata HC, Kibar Y. The biofeedback treatment for non-monosymptomatic enuresis nocturna. Neurourol Urodyn 2016;35:58–61. [CrossRef]
10. Koenig JF, McKenna PH. Biofeedback therapy for dysfunctional voiding in children. Curr Urol Rep 2011;12:144–52. [CrossRef]
11. Combs AJ, Glassberg AD, Gerdes D, Horowitz M. Biofeedback therapy for children with dysfunctional voiding. Urology 1998;52:312–5. [CrossRef]
12. Alyami F, Ewida T, Alhazmi H, Trbay M, Arafa M, Tahir M, et al. Biofeedback as single first-line treatment for non-neuropathic dysfunctional voiding children with diurnal enuresis. Can Urol Assoc J 2019;13:E7–E9. [CrossRef]
13. Dos Reis JN, Mello MF, Cabral BH, Mello LF, Saiovici S, Rocha FET. EMG biofeedback or parasacral transcutaneous electrical nerve stimulation in children with lower urinary tract dysfunction: A prospective and randomized trial. Neurourol Urodyn 2019;38:1588–94. [CrossRef]
14. Vasconcelos M, Lima E, Caiafa L, Noronha A, Cangussu R, Gomes S, et al. Voiding dysfunction in children. Pelvic-floor exercises or biofeedback therapy: a randomized study. Pediatr Nephrol 2006;21:1858–64. [CrossRef]
15. Jacobsen LV, Jørgensen CS, Kaas Sørensen KM, Enemark L, Rittig S, Kamperis K. The efficacy of physiotherapeutic intervention with biofeedback assisted pelvic floor muscle training in children with dysfunctional voiding. J Pediatr Urol 2021;17:793.e1–e6. [CrossRef]
16. Abd El-Moghny SM, El-Din MS, El Shemy SA. Effectiveness of intra-anal biofeedback and electrical stimulation in the treatment of children with refractory monosymptomatic nocturnal enuresis: a comparative randomized controlled trial. Int Neurourol J 2018;22:295–304. [CrossRef]
17. Nevéus T, Fonseca E, Franco I, Kawauchi A, Kovacevic L, Nieuwhof-Leppink A, et al. Management and treatment of nocturnal enuresis-an updated standardization document from the International Children's Continence Society. J Pediatr Urol 2020;16:10–9. [CrossRef]
18. Hoekx L, Vermandel A, Wyndaele JJ. Functional bladder capacity after bladder biofeedback predicts long-term outcome in children with nocturnal enuresis. Scand J Urol Nephrol 2003;37:120–3. [CrossRef]
19. Sancak EB, Akbaş A, Kurt Ö, Alan C, Ersay AR. The effectiveness of biofeedback therapy in children with monosymptomatic enuresis resistant to desmopressin treatment. Turk J Urol 2016;42:278–84. [CrossRef]
20. Berry A, Rudick K, Richter M, Zderic S. Objective versus subjective outcome measures of biofeedback: what really matters? J Pediatr Urol 2014;10:620–6. [CrossRef]
21. Haid B, Tekgül S. Primary and secondary enuresis: pathophysiology, diagnosis, and treatment. Eur Urol Focus 2017;3:198–206. [CrossRef]
22. Jarzebicka D, Sieczkowska J, Dadalski M, Kierkus J, Ryzko J, Oracz G. Evaluation of the effectiveness of biofeedback therapy for functional constipation in children. Turk J Gastroenterol 2016;27:433–8. [CrossRef]
23. Qi W, Zhou Y, Zhong M, Lv G, Li R, Wang W, et al. The effect of biofeedback treatment for children with non-neurogenic voiding dysfunction: A systematic review and meta-analysis. Neurourol Urodyn 2022;41:868–83. [CrossRef]
24. Li F, Feng L, Yang Y, Ma X, Kang T, Huang W. The effect of biofeedback on nonneurological dysfunctional voiding in children: A meta-analysis and systematic review. J Pediatr Urol 2024;20:565–80. [CrossRef]
25. Nelson JD, Cooper CS, Boyt MA, Hawtrey CE, Austin JC. Improved uroflow parameters and post-void residual following biofeedback therapy in pediatric patients with dysfunctional voiding does not correspond to outcome. J Urol 2004;172:1653–6. [CrossRef]
26. Desantis DJ, Leonard MP, Preston MA, Barrowman NJ, Guerra LA. Effectiveness of biofeedback for dysfunctional elimination syndrome in pediatrics: a systematic review. J Pediatr Urol 2011;7:342–8. [CrossRef]
27. Shei Dei Yang S, Wang CC. Outpatient biofeedback relaxation of the pelvic floor in treating pediatric dysfunctional voiding: a short-course program is effective. Urol Int 2005;74:118–22. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI:10.14744/hnhj.2025.90592
Haydarpasa Numune Med J 2025;65(4):340–345



hnhtipdergisi.com

ORIGINAL ARTICLE

Neuropsychometric Differences in Posterior Cortical Atrophy and Alzheimer's Disease

Hakan Nasırlı[1], Özden Erkan Oğul[2], Lütfü Hanoğlu[3]

[1]Department of Cognitive Rehabilitation, İstanbul Medipol University Faculty of Health Sciences, İstanbul, Türkiye
[2]Department of Ergotherapy, İstanbul Medipol University Faculty of Health Sciences, İstanbul, Türkiye
[3]Department of Neurology, İstanbul Medipol University Faculty of Medicine, İstanbul, Türkiye

Abstract

Introduction: Posterior cortical atrophy (PCA), a rare syndrome also known as the visual variant of Alzheimer's disease, has been the subject of limited neuropsychological research. This study aimed to examine neuropsychometric deterioration patterns in PCA and compare them with those in typical Alzheimer's disease (AD).

Methods: The study included 19 patients diagnosed with AD (n=12) or PCA (n=7) who were treated at a private hospital. Neuropsychometric data assessing cognitive domains including attention, memory, executive functions, visuospatial skills, and language were collected.

Results: Statistical analysis revealed that the PCA group had significantly higher long-term spontaneous recall scores on the Öktem Verbal Memory Processes Test (p=0.021) compared with the AD group. Additionally, Benton Face Recognition Test scores were significantly lower in the PCA group (p=0.032). Although not statistically significant, immediate visual memory scores were lower in the PCA group (p=0.092) compared with AD patients.

Discussion and Conclusion: This study aimed to facilitate differential diagnosis through neuropsychological tests. Although this aim was not fully achieved, the results are valuable. Larger studies with more comprehensive test batteries may provide further insight into differential diagnosis and support cognitive rehabilitation approaches.

Keywords: Alzheimer's disease; neurodegenerative diseases; neuropsychologic tests; posterior cortical atrophy.

Typical Alzheimer's disease (AD) is primarily characterized by an amnestic syndrome associated with hippocampal and temporoparietal atrophy, typically emerging around the age of 65 [1]. The initial pathology in the medial temporal lobes leads to memory impairment and functional deficits in learning new information [2,3]. However, early-stage variant phenotypes of Alzheimer's disease that exhibit focal atrophy can manifest as frontal variants, language variants (left parietal), and visual–perceptual variants (right parietal) [1,4].

Posterior cortical atrophy (PCA), also known as the visual variant of Alzheimer's disease, is a rare syndrome resulting from neurodegeneration in the parietal, occipital, and occipitotemporal cortices [5]. In this syndrome, impairments in the ventral pathway (occipitotemporal pathway) may manifest as components of Gerstmann syndrome (acalculia, finger agnosia, and right-left disorientation), while dysfunctions in the dorsal pathway (occipitoparietal pathway) may lead to components of Balint's syndrome (simultanagnosia, optic ataxia, and oculomotor apraxia)

Correspondence: Özden Erkan Oğul, M.D. Department of Ergotherapy, İstanbul Medipol University Faculty of Health Sciences, İstanbul, Türkiye
Phone: +90 532 476 79 13 **E-mail:** oogul@medipol.edu.tr
Submitted Date: 07.01.2025 **Revised Date:** 28.07.2025 **Accepted Date:** 24.08.2025
Haydarpaşa Numune Medical Journal

[6,7]. Additionally, symptoms such as alexia, visual agnosia, and transcortical sensory aphasia [6], as well as dressing apraxia, ideomotor apraxia, or constructional apraxia, can also be observed [7]. Homonymous hemianopia is an early indicator of PCA. Moreover, structural and functional impairments in the temporoparietal cortex can lead to issues such as a decline in verbal fluency, anomia, and working memory problems [8]. While episodic memory, executive functions, and language skills appear to be preserved in the early stages of PCA, as the disease progresses to dementia, a comprehensive deterioration of nearly all cognitive functions can occur [5].

Posterior cortical atrophy is considered a challenging condition to diagnose. Patients are often examined by several ophthalmology specialists before the neurological nature of the disease is recognized [6]. PCA causes impairments across multiple cognitive domains, although not all of these impairments are observed in every patient. As suggested by studies in the literature, each PCA patient presents with unique features and cognitive deficits. Some of these impairments, such as simultanagnosia, may be overlooked during neuropsychometric assessments unless specifically addressed.

The aim of this study was to compare the neuropsychometric profiles of patients with PCA with those of patients with typical Alzheimer's disease and, through this comparison, to identify characteristic patterns of cognitive impairment in PCA as assessed by neuropsychometric evaluation in dementia clinics.

Materials and Methods

This retrospective study was conducted between 2017 and 2020 at the Neurology Clinic of Medipol University Hospital. Data were collected from patients diagnosed with PCA and AD. Seven patients with PCA and twelve patients with AD were included in the study. Due to the rarity of PCA [9], only 10 cases were collected over a 3-year period, with three suspected cases excluded. The diagnoses were made based on the clinical criteria for Alzheimer's disease revised in 2011 by the NINCDS (National Institute of Neurological and Communicative Disorders and Stroke) and ADRDA (Alzheimer's Disease and Related Disorders Association), as well as the diagnostic criteria for PCA revised by the Posterior Cortical Atrophy Study Group in 2015 [10,11]. Patients diagnosed with other diseases that could cause cognitive impairment and illiterate patients were excluded from the study. Patients with primary eye diseases were excluded from the PCA group. Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Medipol University Non-Interventional Clinical Research Ethics Committee (approval number 10840098-604.01.01-E.20637).

Study Design

Neuropsychometric data routinely administered at the Medipol University Hospital Dementia Clinic were used for both PCA and AD patients. The following tests were administered to assess cognitive domains:

- Attention: Forward and backward digit span tests from the Wechsler Memory Scale–Revised (WMS-R) battery [12].
- Executive Functioning: Category fluency test, phonemic fluency test, fruit-name pairing test [13], proverb interpretation test [14], similarity test [15], Stroop test [16], clock drawing test [17].
- Memory Assessment: Öktem Verbal Memory Test (ÖSBST) [18], WMS-R logical memory test, WMS-R visual reproduction test [12].
- Visual Perceptual Functioning: Benton Face Recognition Test [19].
- Language Skills: Boston Naming Test [20].

Additionally, the Standardized Mini Mental Status Examination (MMSE) [21] and the Clinical Dementia Rating (CDR) scale [22] were also used. The data obtained from these assessments were statistically analyzed.

Statistical Analysis

The data obtained in the present study were analyzed using the SPSS 17 for Windows package program. Patient characteristics were reviewed using descriptive statistics. Discrete variables are presented as count (%) and continuous variables as mean (SD), as appropriate. For comparisons of demographic characteristics and neuropsychological features between patients with PCA and those with AD, the independent-samples Mann–Whitney U test was applied to non-normally distributed continuous variables, and the Pearson chi-square test was applied to categorical variables. The limit for statistical significance was set at $p<0.05$.

Results

The mean age of patients with PCA was 62.42±9.48 years, whereas the mean age of patients with AD was 73.41±8.75 years. Patients with PCA were significantly younger than those with AD. Demographic characteristics and general cognitive features of the participants are shown in Table 1. Apart from age, no significant differences were found

Table 1. Demographic and global cognitive features of patients

	PCA		AD		
	Min-max	**Mean±SD**	**Min-max**	**Mean±SD**	**p**
Age (year)	55–82	62.42±9.48	61–85	73.41±8.75	0.011*[a]
Education (year)	5–15	7.71±4.11	0–11	4.83±.3.45	0.107[b]
MMSE	13–22	17±0.74	10–22	16.75±4.02	0.276[a]
CDR	1–2	1.4±0.44	1–2	1.33±0.44	0.837[a]
	n	**%**	**n**	**%**	
Gender					
Female	4	57.1	7	58.3	0.96[b]
Male	3	42.9	5	41.7	

[a]: Mann-Whitney test; [b]: Chi-square test. *: p<.05. PCA: Posterior cortical atrophy; AD: Alzheimer disease; SD: Standard deviation; MMSE: Standardize mini mental test; CDR: Clinical dementia rating scale.

Table 2. Neuropsychometric profile in PCA and AD

	PCA		AD		
	Min-max	**Mean±SD**	**Min-max**	**Mean±SD**	**p**
Attention					
Digit Span-F	3–6	4.57±1.27	3–5	4±0.95	0.284
Digit Span-B	0–6	2.14±2.03	0–4	1.58±1.16	0.548
Memory					
I-Visual memory	0–7	1.57±2.63	0–6	3.25±1.86	0.092
L-Visual memory	0–7	0.85±1.21	0–6	1±2.33	0.383
I-Story memory	0–16	8.42±5.65	0–18	8.35.19	0.899
L-Story memory	0–20	8.28±7.76	0–17	5.83±5.89	0.470
ÖVMPT-I	0–5	2.85±1.95	0–4	1.91±1.50	0.259
ÖVMPT-L	15–126	58.57±37.99	15–68	44.41±14.85	0.612
ÖVMPT-S	0–15	5±5.29	0–4	0.75±1.42	0.021*
ÖVMPT-R	0–13	4.14±4.87	0–10	4.75±3.19	0.491
ÖVMPT-DR	0–15	9.42±5.79	1–12	7.41±3.50	0.330
Executive f.					
Fruit-name fluency	0–9	4.57±3.04	0–9	4.58±2.96	1
Phonemic fluency	0–35	17.85±13.49	0–28	10.75±9.94	0.252
Categorical fluency	3–14	9.57±4.15	4–14	9.83±3.27	0.966
Abstract Thinking	0–4	2±1.52	0–5	2.75±1.42	0.319
Similarity	1–10	5.71±2.87	2–10	5.08±2.15	0.521
Clock drawing	0–3	1.14±1.34	0–4	2.16±1.80	0.175
Stroop-TD	46–243	96.28±72.14	8–286	129.16±67.84	0.271
Stroop error	0–40	13.42±14.85	2–46	15.33±12.61	0.524
Visuoper. skills					
BFRT	25–37	31.57±4.96	30–42	37.08±3.67	0.032*
Language skills					
BNT	11–27	19.57±5.82	9–24	16.33±3.98	0.204

*: p<.05. PCA: Posterior cortical atrophy; AD: Alzheimer disease; SD: Standard deviation; Digit Span-F: Digit span forward; Digit Span-B: Digit span backward; I-Visual memory: Immediate visual memory; L-Visual memory: long-term visual memory; I-Story memory: Immediate story memory; L-Story memory: Long-term story memory; ÖVMPT: Öktem verbal memory process test; I: Immediate; L: Learning; S: Spontaneous; R: Recognition; DR: Delayed recall; executive func.: Executive function; Stroop-TD: Stroop time difference; Visuoper. Skills: Visuoperceptual skills; BFRT: Benton facial recognition test; BNT: Boston naming test; Global Cog. Skill: Global cognitive skills; MMSE: Mini mental state examination; CDR: Clinical dementia rating scale.

between the two groups in terms of other demographic data and general cognitive characteristics (p>0.05). Both groups demonstrated similar cognitive features.

No significant differences were found in attention scores, as measured by the forward and backward digit span tests of the WMS, between patients with PCA and AD (p>0.05). WMS immediate visual memory scores were lower in patients with PCA compared with those with AD, although the difference approached statistical significance (p=0.092). WMS long-term visual memory scores were also relatively lower in patients with PCA, whereas WMS story memory and verbal memory scores were lower in patients with AD. Among these measures, only the verbal memory spontaneous recall score reached statistical significance (p=0.021), while the other parameters did not (p>0.05).

When executive function performance was examined, phonemic fluency scores were higher in the PCA group; however, no statistically significant differences were observed in the other fluency tests (p>0.05). Similarly, no significant differences were found in abstract reasoning or similarity tests. The clock drawing test, which assesses both executive function and visual perception, revealed slightly lower scores in patients with PCA, but this difference was not statistically significant (p>0.05). Likewise, no significant difference was observed in Stroop test scores (p>0.05) (Table 2).

Evaluation of visual–perceptual skills using the Benton Face Recognition Test showed that patients with PCA had significantly lower scores than patients with AD (p=0.032). In the Boston Naming Test, patients with PCA scored higher than those with AD; however, this difference was not statistically significant (p>0.05).

Discussion

In our study comparing the neuropsychological profiles of patients with PCA and AD, patients with PCA had statistically higher spontaneous recall scores in verbal memory than patients with AD, but significantly lower Benton Face Recognition Test scores. Immediate visual memory scores were lower in patients with PCA than in those with AD, although this difference approached statistical significance.

PCA is a dementia subtype that occurs at a younger age than AD [9]. This explains the significant age difference between the two groups and does not pose a disadvantage for the interpretation of the results. Moreover, the similarity of the two groups in terms of education level, MMSE scores, and dementia stage provides a solid baseline for the discussion of the findings.

When visual memory performance, one of the distinctive cognitive impairments in PCA, was compared, patients with PCA were found to have lower immediate visual memory scores than patients with AD, with the difference approaching statistical significance. This finding is consistent with the literature [23–25].

In Alzheimer's disease, the first lesions typically appear in areas associated with memory and learning, such as the hippocampus and the association cortex, and the most common complaint in patients with AD is forgetfulness [26]. Studies comparing the clinical presentations of AD and PCA report relatively small differences; however, memory impairment is generally more pronounced in AD than in PCA. Kas et al. [27] reported that episodic memory is more severely affected in typical AD, and Peng et al. [28] showed that short-term memory and spontaneous retrieval skills are more impaired in patients with AD than in those with PCA in neuroimaging-based studies. In the present study, spontaneous recall was statistically more impaired in patients diagnosed with AD than in those diagnosed with PCA, in line with the literature.

PCA is a neurodegenerative disease characterized clinically by severe visual–perceptual problems. Visual–perceptual disorders arise from dysfunction of the dorsal (occipitoparietal) and ventral (occipitotemporal) visual pathways. These higher-order visual–perceptual deficits represent the core clinical and cognitive features that define the PCA syndrome [29]. In our study, the mean BRFT scores of patients in the PCA group indicated severe impairment relative to age- and education-adjusted norms. When compared with the AD group, patients with PCA demonstrated significantly worse visual–perceptual abilities. Valenti et al. [30], in a neuroimaging study of patients with amyloid deposition in posterior brain regions without dementia, suggested that posterior amyloid accumulation, as observed in PCA, leads to visual–perceptual impairments. They examined the relationship between amyloid pathology and neurocognitive performance and reported impairments in the BRFT in 23% of participants and in the Benton Judgment of Line Orientation Test in 13.6%, findings associated with parietal lobe pathology. Previous studies consistently indicate that patients with PCA exhibit more severe visual–perceptual disturbances than patients with AD, and the results of our study confirm this observation [23,26,31–33].

Studies comparing PCA and AD emphasize that visual–perceptual deficits predominate in PCA, whereas memory impairment is more prominent in AD. The findings of the present study support this distinction, indicating that visual–perceptual dysfunction is a hallmark of PCA, while memory disturbances are more characteristic of AD [23,24].

Identifying the distinctive neuropsychological features of PCA, known as the visual variant of AD, may reduce misdiagnosis and improve recognition of PCA in clinical practice. However, studies on PCA, an atypical form of Alzheimer's disease, remain limited both in the international literature and in our country, which underscores the value of the present study.

Limitation

The small sample size is a limitation of this study. Given the rarity of PCA, this limitation is understandable. Nonetheless, the results support findings from previous studies.

Conclusion

The data from this study suggest that, compared with patients with AD, patients with PCA experience more prominent visual–perceptual deficits and relatively better memory performance. Future studies with larger sample sizes, more comprehensive neuropsychometric test batteries, and advanced imaging techniques may provide further insight into the relationships between cognitive impairments and contribute to improved differential diagnosis and rehabilitation strategies.

Ethics Committee Approval: The study was approved by Medipol University Non-Interventional Clinical Research Ethics Committee (No: 10840098-604.01.01-E.20637, Date: 28.06.2018).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – L.H., Ö.E.O.; Design – L.H., Ö.E.O.; Supervision – Ö.E.O., L.H.; Fundings – H.N.; Materials – H.N.; Data collection and/or processing – H.N.; Analysis and/or interpretation – Ö.E.O., L.H.; Literature search – H.N.; Writing – H.N., Ö.E.O.; Critical review – L.H.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

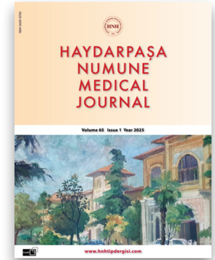
References

1. Lam B, Masellis M, Freedman M, Stuss DT, Black SE. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimers Res Ther 2013;5:1. [CrossRef]
2. Mavioğlu H. Alzheimer Hastalığı In: Tanrıdağ O, editör. Davranış Nörolojisi - Beyin Davranış İlişkilerinin Organizasyon Prensipleri, Sendromları ve Hastalıkları. İstanbul; Nobel Tıp Kitabevleri: 2015. p.146–52. [In Turkish]
3. Castro M, Smith GE. Mild cognitive impairment and Alzheimer's disease. In Lichtenberg PA, Mast BT, Carpenter BD, Loebach Wetherell J, editors. APA handbook of clinical geropsychology, Vol. 2. Assessment, treatment, and issues of later life. American Psychological Association: USA; 2015. p.173–207.
4. Mendez MF. Early-onset alzheimer disease. Neurol Clin 2017;35:263–81. [CrossRef]
5. Crutch SJ. Elizabeth Warrington Prize Lecture. Seeing why they cannot see: understanding the syndrome and causes of posterior cortical atrophy. J Neuropsychol 2014;8:157–70. [CrossRef]
6. Maia da Silva MN, Millington RS, Bridge H, James-Galton M, Plant GT. Visual dysfunction in posterior cortical atrophy. Front Neurol 2017;8:389. [CrossRef]
7. Weill-Chounlamountry A, Poncet F, Crop S, Hesly N, Mouton A, Samri D, et al. Physical medicine and rehabilitation multidisciplinary approach in a case of posterior cortical atrophy. Ann Phys Rehabil Med 2012;55:430–9. [CrossRef]
8. Weill-Chounlamountry A, Alves J, Pradat-Diehl P. Non-pharmacological intervention for posterior cortical atrophy. World J Clin Cases 2016;4:195–201. [CrossRef]
9. Schott JM, Crutch SJ. Posterior Cortical Atrophy. Continuum (Minneap Minn) 2019;25:52–75. [CrossRef]
10. Crutch SJ, Schott JM, Rabinovici GD, Murray M, Snowden JS, van der Flier WM, et al. Consensus classification of posterior cortical atrophy. Alzheimers Dement 2017;13:870–84.
11. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9. [CrossRef]
12. Wechsler D. WMS-R: Wechsler memory scale-revised manual. San Antonio, TX: Psychological Corporation; 1987.
13. Parker DM, Crawford J, McKinlay WA. Assessment of frontal lobe dysfunction. A handbook of neuropsychological assessment. London: Routledge; 1992.
14. Kumral E. Klinik Nöropsikoloji ve Nöropsikiyatrik Hastalıklar. İstanbul: Güneş Tıp Kitabevleri; 2014. [In Turkish]
15. Davies G, Piovesana A. Adult verbal abstract reasoning assessment instruments and their clinimetric properties. Clin Neuropsychol 2015;29:1010–33. [CrossRef]
16. Karakaş S, Erdoğan E, Soysal Ş, Ulusoy T, Yüceyurt Ulusoy İ, Alkan S. Stroop testi TBAG formu: türk kültürüne standardizasyon çalışmaları, güvenirlik ve geçerlik. Klinik Psikiyatri 1999;2:75–88.
17. Brodaty H, Moore CM. The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. Int J Geriatr Psychiatry 1997;12:619–27. [CrossRef]
18. Öktem Ö. Öktem Sözel Bellek Süreçleri Testi (ÖSBST) El kitabı. Ankara: Türk Psikologlar Derneği Yayınları; 2011. [In Turkish]
19. Karakaş S. Handbook of BILNOT battery: Research and

development studies for neuropsychological tests. Ankara: Türk Psikologlar Derneği Yayınları; 2004. [In Turkish]
20. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. 2nd Ed. Philledelphia: Lea& Febiger; 1983.
21. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Reliability and validity of the standardized mini mental state examination in the diagnosis of mild dementia in Turkish population. Turk Psikiyatri Derg 2002;13:273–81. [Article in Turkish]
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4. [CrossRef]
23. Li J, Wu L, Tang Y, Zhou A, Wang F, Xing Y, et al. Differentiation of neuropsychological features between posterior cortical atrophy and early onset Alzheimer's disease. BMC Neurol 2018;18:65. [CrossRef]
24. Aresi A, Giovagnoli AR. The role of neuropsychology in distinguishing the posterior cortical atrophy syndrome and Alzheimer's disease. J Alzheimers Dis 2009;18:65–70. [CrossRef]
25. Trotta L, Lamoureux D, Bartolomeo P, Migliaccio R. Working memory in posterior cortical atrophy. Neurol Sci 2019;40:1713–6. [CrossRef]
26. Braak H, Del Tredici K, Schultz C, Braak E. Vulnerability of select neuronal types to Alzheimer's disease. Ann N Y Acad Sci 2000;924:53–61. [CrossRef]
27. Kas A, de Souza LC, Samri D, Bartolomeo P, Lacomblez L, Kalafat M, et al. Neural correlates of cognitive impairment in posterior cortical atrophy. Brain 2011;134:1464–78. [CrossRef]
28. Peng G, Wang J, Feng Z, Liu P, Zhang Y, He F, et al. Clinical and neuroimaging differences between posterior cortical atrophy and typical amnestic Alzheimer's disease patients at an early disease stage. Sci Rep 2016;6:29372. [CrossRef]
29. Migliaccio R, Gallea C, Kas A, Perlbarg V, Samri D, Trotta L, et al. Functional connectivity of ventral and dorsal visual streams in posterior cortical atrophy. J Alzheimers Dis 2016;51:1119–30. [CrossRef]
30. Valenti R, Charidimou A, Xiong L, Boulouis G, Fotiadis P, Ayres A, et al. Visuospatial functioning in cerebral amyloid angiopathy: a pilot study. J Alzheimers Dis 2017;56:1223–27. [CrossRef]
31. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012;11:170–8. [CrossRef]
32. Firth NC, Primativo S, Marinescu RV, Shakespeare TJ, Suarez-Gonzalez A, Lehmann M, et al. Longitudinal neuroanatomical and cognitive progression of posterior cortical atrophy. Brain 2019;142:2082–95. [CrossRef]
33. Firth NC, Primativo S, Brotherhood E, Young AL, Yong KXX, Crutch SJ, et al. Sequences of cognitive decline in typical Alzheimer's disease and posterior cortical atrophy estimated using a novel event-based model of disease progression. Alzheimers Dement 2020;16:965–73. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.38159
Haydarpasa Numune Med J 2025;65(4):346–350



hnhtipdergisi.com

ORIGINAL ARTICLE

The Relationship between Obstructive Sleep Apnea Syndrome and Neutrophil–Lymphocyte and Platelet–Lymphocyte Ratios

Tayfun Çalışkan[1], Kadir Canoğlu[2]

[1]Department of Pulmonology, İstanbul Aydın University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Pulmonology, University of Health Sciences, Sultan Abdulhamid Han Training and Research Hospital, İstanbul, Türkiye

Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) is a condition characterized by hypoxemia or arousal associated with apnea or hypopnea due to partial or complete collapse of the upper airway. This study aimed to assess the correlation between the diagnosis and severity of OSAS and the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

Methods: This retrospective analysis included 65 patients who underwent polysomnography at Sultan II. Abdulhamid Han Training and Research Hospital. Patients with simple snoring and controls had an apnea–hypopnea index (AHI) of <5, patients with mild OSAS had an AHI of 5–14.9, those with moderate OSAS had an AHI of 15–29.9, and those with severe OSAS had an AHI of ≥30. Lymphocyte, neutrophil, and platelet counts were obtained from complete blood count parameters measured before polysomnography. NLR and PLR were calculated accordingly.

Results: A total of 65 patients were included in the study. Eighteen patients (28%) with AHI<5 constituted the control group, and 47 patients (72%) with AHI≥5 constituted the OSAS group. Among the 47 patients with OSAS, 17 (36%) had mild OSAS, 15 (32%) had moderate OSAS, and 15 (32%) had severe OSAS. The mean NLR was 2.39±1.59 in patients with OSAS and 1.96±1.21 in patients without OSAS, with no statistically significant difference (p=0.68). The mean PLR was 141.56±139.97 in patients with OSAS and 98.66±27.91 in patients without OSAS, also showing no statistically significant difference (p=0.95). NLR and PLR did not differ significantly among patients with mild, moderate, and severe OSAS (p=0.185 and p=0.149, respectively).

Discussion and Conclusion: In this study, NLR and PLR were not associated with either the diagnosis or the severity of OSAS.

Keywords: Neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; sleep apnea.

Apneas and hypopneas in ventilation are hallmarks of the relatively common sleep-related condition known as obstructive sleep apnea syndrome (OSAS). Its prevalence varies between 6% and 17% in the general population and can reach 50% in older age groups. Its incidence has been reported as 24% in adult males and 9% in females aged 30–60 years. It has also been reported that, in some countries, the prevalence has reached 50%, affecting approximately 1 billion individuals globally [1–3].

OSAS is a condition in which the upper airways recurrently collapse, resulting in either a significant reduction in airflow (hypopnea) or a complete cessation of airflow

This article was presented as an oral presentation (SS-243) at the 23rd annual congress of the Turkish Thoracic Society.

Correspondence: Tayfun Çalışkan, M.D. Department of Pulmonology, İstanbul Aydın University Faculty of Medicine, İstanbul, Türkiye
Phone: +90 212 444 1 428 **E-mail:** drtcaliskan@yahoo.com
Submitted Date: 31.07.2025 **Accepted Date:** 03.09.2025
Haydarpaşa Numune Medical Journal

(apnea) [4]. Obesity, increased neck circumference, advanced age, and male sex are established risk factors [5]. OSAS is a significant risk factor for cardiovascular diseases, particularly hypertension, coronary artery disease, heart failure, and stroke, as endothelial dysfunction represents a key pathophysiological mechanism [6]. Polysomnography (PSG) demonstrating an apnea–hypopnea index (AHI) of 5 events per hour is considered diagnostic [2].

OSAS, independent of obesity, leads to increased levels of proinflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], and interleukin-8 [IL-8]) and chemokines. In addition, continuous positive airway pressure (CPAP) treatment has been shown to significantly reduce these inflammatory markers [2]. In particular, IL-8 plays a crucial role in neutrophil and monocyte migration to the vascular endothelium [7].

OSAS can also directly affect the cardiovascular system by increasing coagulation factors and platelet activation and may affect the central nervous system by increasing blood–brain barrier permeability [8]. Two important indicators of systemic inflammatory response are the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), which have been widely studied in conditions such as sepsis, malignancy, rheumatological diseases, and trauma [9]. OSAS also induces endothelial dysfunction through hypoxic stress and enhances systemic inflammation. Therefore, the aim of this study was to evaluate the relationship between NLR and PLR and the diagnosis and severity of OSAS.

Materials and Methods

A total of 65 patients who were evaluated at the Chest Diseases outpatient clinic of Sultan II. Abdulhamid Han Training and Research Hospital and underwent polysomnography at the sleep center between November 2018 and November 2019 were retrospectively included in the study. Patients with a history of malignancy, rheumatological or hematological diseases, or chronic liver disease that could affect neutrophil, platelet, or lymphocyte counts were excluded. Ethical approval for the study was obtained from the Ümraniye Training and Research Hospital Ethics Committee (Decision No: 238).

A ≥90% reduction in airflow from baseline lasting at least 10 seconds was defined as apnea. Hypopnea was defined as a ≥30% reduction in airflow from baseline lasting at least 10 seconds, accompanied by ≥3% oxygen desaturation or arousal on electroencephalography (EEG).

Based on AHI values, the study population was divided into four groups. Patients with AHI<5 were defined as the simple snoring and control group, whereas those with AHI≥5 were defined as the OSAS group. For OSAS severity classification, patients with AHI values of 5–14.9 were classified as mild OSAS, those with 15–29.9 as moderate OSAS, and those with ≥30 as severe OSAS.

Neutrophil, lymphocyte, and platelet counts were obtained from complete blood count parameters measured before PSG. The neutrophil count was divided by the lymphocyte count to calculate the NLR, and the platelet count was divided by the lymphocyte count to calculate the PLR.

Statistical Analysis

Descriptive analyses, including frequency distributions, percentages, mean values, interquartile range (IQR), and median values, were used to summarize the data. The Kolmogorov–Smirnov test was used to assess normality of distribution. For continuous variables, the Mann–Whitney U test was applied for non-normally distributed data, and the t-test was used for normally distributed variables. Comparisons of NLR and PLR among mild, moderate, and severe OSAS groups were performed using ANOVA. A 95% confidence interval was applied, and a $p<0.05$ was considered statistically significant.

Results

A total of 65 patients participated in the study. Eighteen patients (28%) were in the control group with AHI<5, and 47 patients (72%) were in the OSAS group with AHI≥5. When OSAS severity among the 47 patients was evaluated according to AHI values, 17 patients (36%) were classified as mild OSAS, 15 patients (32%) as moderate OSAS, and 15 patients (32%) as severe OSAS.

The mean NLR in patients with and without OSAS was 2.39±1.59 and 1.96±1.21, respectively, with no statistically significant difference ($p=0.68$). The mean PLR in patients with and without OSAS was 141.56±139.97 and 98.66±27.91, respectively, and this difference was also not statistically significant ($p=0.95$) (Table 1). Comparisons among patients with mild, moderate, and severe OSAS showed no statistically significant differences in NLR or PLR according to disease severity ($p=0.185$ and $p=0.149$, respectively) (Table 2).

Table 1. Comparison of NLR and PLR in patients with and without OSA diagnosis

	AHI score								
	<5				≥5				
	Mean	SD	Median	Min-max	Mean	SD	Median	Min-max	p
NLR	2.39	1.59	1.73	0.95-6.11	1.96	1.21	1.55	0.76-7.49	0.68
PLR	141.56	139.97	88.88	54.05-567.54	98.66	27.91	92.72	49.70-173.86	0.95

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; OSA: Obstructive sleep apnea; AHI; Apnea hypopnea score; Min: Minimum; Max: Maximum; SD: Standard deviation.

Table 2. The relationship between NLR and PLR and the severity of OSA according to AHI

	AHI score												
	<15				15-30				≥30				
	Mean	SD	Median	Min-max	Mean	SD	Median	Min-max	Mean	SD	Median	Min-max	p
NLR	1.86	0.83	1.65	1.17-4.18	2.04	1.83	1.35	0.76-7.49	2.02	1.01	1.76	1.19-5.20	0.185
PLR	106.58	35.41	97.23	57.47-173.86	87.24	24.50	85.71	49.70-143.51	99.03	17.30	94.51	69.60-139.04	0.149

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; OSA: Obstructive sleep apnea; AHI: Apnea hypopnea score; Min: Minimum, Max: Maximum; SD: Standard deviation.

Discussion

Recurrent episodes of partial or complete upper airway collapse are a hallmark of OSAS, accompanied by apnea or hypopnea lasting longer than 10 seconds, resulting in hypoxemia or electroencephalographic arousals [10]. Increased rates of hypertension, type 2 diabetes mellitus, arrhythmia, heart failure, stroke, atherosclerotic heart disease, pulmonary hypertension, and dementia have all been associated with OSAS [10]. OSAS, similar to obesity, stimulates white adipose tissue and leads to the release of systemic inflammatory mediators. In addition, intermittent hypoxia related to OSAS is a key contributor to the release of inflammatory markers. Among these markers, adipokines and tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) play important roles in chronic systemic inflammatory processes. As a consequence, cardiovascular diseases related to endothelial dysfunction may develop [11]. Accordingly, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are used as indices reflecting inflammatory reactions and immune responses in various chronic diseases, including cancer, infections, and chronic obstructive pulmonary disease [12]. Therefore, this study evaluated the association between OSAS and NLR and PLR.

In 2015, Koseoğlu et al. [13] published a retrospective analysis including 284 patients. OSAS and control groups were defined using an apnea–hypopnea index (AHI) cut-off of 5, and mild, moderate, and severe OSAS groups were also established. While no relationship was found between NLR and OSAS, the OSAS group had lower PLR values than the control group. Additionally, PLR was observed to decrease as OSAS severity increased, and NLR was associated with nocturnal hypoxemia. In our study, although PLR was also lower in patients with OSAS than in the control group, this difference was not statistically significant. Furthermore, the relationship between hypoxemia and NLR and PLR was not evaluated in our study.

Erdim et al. [14] analyzed 180 patients in a study involving obese children, of whom 83 met the inclusion criteria. Obese patients had significantly higher NLR and PLR values than non-obese patients. In that study, the AHI cut-off for OSAS diagnosis in children was defined as 1. In contrast, in our study, patients with OSAS exhibited lower NLR and PLR values. Differences in study populations, including the inclusion of adults in our study versus pediatric patients in the other study, as well as differing diagnostic criteria for OSAS, may explain this discrepancy.

In a study conducted by Hizli et al. [15], 98 patients with OSAS and 28 controls were included, and OSAS severity was classified as mild, moderate, and severe, similar to our study. NLR and PLR were found to be ineffective in assessing both the diagnosis and severity of OSAS.

Although PLR values tended to decrease with increasing OSAS severity, this trend was not statistically significant. The findings of our study are consistent with these results. In that study, fibrinogen-to-albumin and C-reactive protein-to-albumin ratios were significantly higher in patients with moderate and severe OSAS compared with controls; however, these inflammatory markers were not evaluated in our study [15].

A total of 4518 cases from 17 studies were evaluated in the meta-analysis by Wu et al. [16] published in 2018; 1013 controls, 896 patients with mild OSAS, 832 with moderate OSAS, and 1588 with severe OSAS were included. In that study, a correlation was identified between OSAS and elevated NLR and PLR. In addition, increases in NLR and PLR were associated with worsening OSAS severity [16]. These findings contradict the results of our study. However, significant heterogeneity was reported for NLR, whereas heterogeneity was low in the moderate OSAS subgroup.

In a more recent meta-analysis by Attia et al. [17], 26 studies were evaluated. In that analysis, patients with OSAS had higher NLR and PLR values than control subjects. Similarly, heterogeneity was high for both inflammatory markers. In contrast to the findings by Wu et al. [16], OSAS severity was not correlated with either NLR or PLR in this meta-analysis [17]. The association of NLR and PLR with OSAS in that study represents another difference from our findings.

Conclusion

In the present study, NLR and PLR were not found to be associated with either the diagnosis or the severity of OSAS. This finding may be related to the limited sample size of the study. Conflicting results regarding this issue have also been reported in the literature. Although substantial evidence suggests that OSAS is associated with systemic inflammation, further studies are needed to clarify the role of systemic inflammatory markers in the diagnosis and assessment of OSAS severity.

Ethics Committee Approval: The study was approved by Ümraniye Training and Research Hospital Ethics Committee (No: 238, Date: 18.12.2019).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – T.Ç., K.C.; Design – T.Ç.; Supervision – T. Ç.; Materials – T.Ç., K.C.; Data collection and/or processing – T.Ç., K.C.; Analysis and/or interpretation – K.C.; Literature search – T.Ç.; Writing – T.Ç., K.C.; Critical review – T.Ç.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This study was conducted without any institutional or financial support.

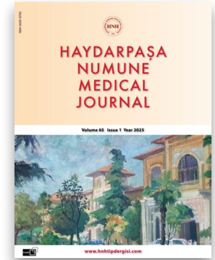
References

1. Lv R, Liu X, Zhang Y, Dong N, Wang X, He Y, et al. Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome. Signal Transduct Target Ther 2023;8:218. [CrossRef]
2. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev 2017;34:7081. [CrossRef]
3. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019;7:687–98. [CrossRef]
4. Antonaglia C, Passuti G. Obstructive sleep apnea syndrome in non-obese patients. Sleep Breath 2022;26:513–8. [CrossRef]
5. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. Rev Endocr Metab Disord 2015;16:25–34. [CrossRef]
6. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009;64:631–6.
7. Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T, Ouchi Y. Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol (1985) 2003;94:179–84. [CrossRef]
8. Zolotoff C, Bertoletti L, Gozal D, Mismetti V, Flandrin P, Roche F, et al. Obstructive sleep apnea, hypercoagulability, and the blood-brain barrier. J Clin Med 2021;10:3099. [CrossRef]
9. Islam MM, Satici MO, Eroglu SE. Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, and delta neutrophil index: An extensive literature review. Turk J Emerg Med 2024;24:8–19. [CrossRef]
10. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. JAMA 2020;323:1389–400. [CrossRef]
11. Abbasi A, Gupta SS, Sabharwal N, Meghrajani V, Sharma S, Kamholz S, et al. A comprehensive review of obstructive sleep apnea. Sleep Sci 2021;14:142–54.
12. Zhou Y, Tian N, Li P, He Y, Tong L, Xie W. The correlation between neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with nonalcoholic fatty liver disease: a cross-sectional study. Eur J Gastroenterol Hepatol 2022;34:1158–64. [CrossRef]
13. Koseoglu S, Ozcan KM, Ikinciogullari A, Cetin MA, Yildirim E, Dere H. Relationship between neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and obstructive sleep apnea syndrome. Adv Clin Exp Med 2015;24:623–7. [CrossRef]

14. Erdim I, Erdur O, Oghan F, Mete F, Celik M. Blood count values and ratios for predicting sleep apnea in obese children. Int J Pediatr Otorhinolaryngol 2017;98:85–90. [CrossRef]
15. Hizli O, Cayir S, Coluk Y, Kayabasi S, Yildirim G. The novel indicators of moderate to severe sleep apnea: fibrinogen to albumin ratio vs. CRP to albumin ratio. Eur Arch Otorhinolaryngol 2021;278:851–5. [CrossRef]
16. Wu M, Zhou L, Zhu D, Lai T, Chen Z, Shen H. Hematological indices as simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome: a meta-analysis. J Thorac Dis 2018;10:6509–21. [CrossRef]
17. Attia MM, Qasim MA, Alhamwi HS, Ali M, Alsharief EA, Ali JS, et al. Using the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic markers for obstructive sleep apnea: a systematic review and meta-analysis of observational studies. Cureus 2024;16:e72539. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.09471
Haydarpasa Numune Med J 2025;65(4):351–356



hnhtipdergisi.com

ORIGINAL ARTICLE

The Effects of Intraarticular Ozone Injection on Pain, Functional Status and Activities of Daily Living in Patients with Knee Osteoarthritis

Zeynep Candan, Selin Aksungur, Emre Ata, Figen Yılmaz

Department of Physical Medicine and Rehabilitation, University of Health Sciences, Sultan II. Abdulhamid Han Training and Research Hospital, Istanbul, Türkiye

Abstract

Introduction: Knee osteoarthritis (KOA) is a common painful joint disease. Although many pharmacological and non-pharmacological treatment methods are available, the use of traditional and complementary medicine approaches has increased in recent years. Intra-articular ozone injection is considered an effective and cost-effective method among these approaches and has been shown to be beneficial in painful musculoskeletal conditions in various studies. The aim of this study was to evaluate the short- and medium-term effects of intra-articular ozone injection on pain, functional status, and activities of daily living in patients with knee osteoarthritis.

Methods: Data were obtained retrospectively from the medical records of patients diagnosed with KOA between January 1, 2019, and September 1, 2019. Patients who received intra-articular ozone injections (n=27) according to a routine protocol (two sessions per week for a total of four sessions, with doses of 25–20–10–10 gamma, respectively) were included. Evaluations were recorded at baseline, at the second week post-treatment (PT), and at 1 month and 3 months PT using the VAS, WOMAC, Lequesne Knee Index, and Nottingham Health Profile.

Results: The mean age of the patients (n=27) was 64.81±11.41 years (range: 44–82). Of the patients, 85.2% (n=23) were female and 14.8% (n=4) were male. All parameters showed significant improvement at 2 weeks PT compared with baseline, and the observed improvement persisted at the 1st and 3rd month PT evaluations ($p<0.05$). No significant differences were found between the second week, 1st month, and 3rd month evaluations ($p>0.05$).

Discussion and Conclusion: Intra-articular ozone injection in patients with knee osteoarthritis may have positive effects on pain, functional status, and activities of daily living in the short and medium term. Larger-scale controlled clinical trials with longer follow-up periods are needed.

Keywords: Injection; knee osteoarthritis; ozone.

Osteoarthritis affects more than 240 million people worldwide, and the most common type is knee osteoarthritis. The knee is most frequently affected in up to 10% of males and 13% of females aged over 60 years. Knee osteoarthritis (KOA) is a common cause of pain and functional impairment and is frequently encountered in clinical practice within the spectrum of musculoskeletal disorders. As the global population continues to age, it remains a growing health concern of increasing significance. Risk factors include age, female sex, overweight and obesity, repetitive joint use, muscle weakness, and genetic factors [1].

Correspondence: Zeynep Candan, M.D. Department of Physical Medicine and Rehabilitation, University of Health Sciences, Sultan II. Abdulhamid Han Training and Research Hospital, Istanbul, Türkiye
Phone: +90 539 595 50 90 **E-mail:** drzeynepcandan@gmail.com
Submitted Date: 24.03.2025 **Revised Date:** 22.04.2025 **Accepted Date:** 10.09.2025
Haydarpaşa Numune Medical Journal

KOA is a complex disease that leads to disturbances in tissue homeostasis of the articular cartilage and changes in the subchondral bone [1]. While the pathogenesis of osteoarthritis has historically focused primarily on cartilage degeneration, recent research has underscored the inflammatory nature of KOA, characterized by inflammation in both the cartilage and synovium that progresses alongside degenerative processes. Proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-18, along with increased oxidative stress and metalloproteinase activity, are implicated in cartilage degeneration [2,3].

Various treatment modalities for KOA are available and are categorized as pharmacological and non-pharmacological approaches. Among non-pharmacological treatments, patient education, exercise, weight management, modification of daily life activities, and various physical therapy modalities are included. Within pharmacological treatments, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) may be the initial agents of choice. Narcotic analgesics can be considered for refractory cases. Additionally, interventional therapies such as intra-articular (IA) administration of corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and ozone injections are used [4,5]. IA treatments may be preferred in patients who do not respond to systemic medical treatment or who have contraindications to systemic medications [6].

Ozone is a colorless gas with a distinct odor and has been used as a therapeutic agent for various diseases since its discovery [7]. Ozone therapy is considered an effective treatment method for damaged articular cartilage in KOA. Ozone mitigates the inflammatory environment that damages the cartilage matrix and induces chondrocyte apoptosis in KOA. TNF-α is strongly associated with joint and bone damage, and ozone therapy reduces TNF-α concentrations, thereby decreasing other proinflammatory cytokines that perpetuate the chronic inflammatory process. By increasing the activity of the superoxide dismutase enzyme, ozone therapy accelerates the breakdown of free oxygen radicals, thus slowing the degenerative process. It also exerts analgesic and anti-inflammatory effects through the inhibition of phospholipase A2 [8].

As a result, when traditional treatments are compared with ozone therapy for knee osteoarthritis, traditional approaches mainly focus on symptom relief and slowing disease progression, whereas ozone therapy aims to utilize its anti-inflammatory and regenerative properties. Comparisons of ozone therapy with other treatment methods for knee osteoarthritis have been reported. The effect of ozone appears more rapidly; however, its duration of efficacy has been observed to be shorter than that of hyaluronic acid and PRP injections [9,10]. It has been emphasized that combining ozone therapy with physical therapy modalities and exercise enhances overall treatment efficacy [11].

Although the efficacy of ozone therapy in the treatment of KOA has been demonstrated, its use as a therapeutic agent remains controversial [12]. In recent years, ozone therapy has been used in the treatment of acute and chronic knee osteoarthritis in Europe, with studies reporting rapid pain relief, reduced swelling, and improved mobility. However, the exact mechanisms, optimal application frequency, and dosage of ozone in KOA treatment remain unclear [13]. In various studies, the most effective dose for reducing superoxide dismutase and IL-6 levels has been reported as 40 mcg. Accordingly, it has been emphasized that the optimal anti-inflammatory dose is 40 mcg, while the anti-inflammatory effect decreases as the dose is reduced to 20 mcg. When the dose exceeds 40 mcg, a reduction in anti-inflammatory efficacy has been observed [14]. In another study conducted in patients with rheumatoid arthritis, TNF-α concentrations in synovial fluid were evaluated, and TNF-α levels were found to decrease most effectively at a dose of 40 mcg, followed by a decrease at a dose of 20 mcg [15].

In the present study, patients were treated with an initial dose of 25 mcg for anti-inflammatory effect, followed by 20 mcg, and received an induction dose of 10 mcg in the final two injections. The aim of this study was to evaluate the short- and medium-term effects of intra-articular ozone injection on pain, functional status, and activities of daily living in patients with knee osteoarthritis.

Materials and Methods

Data for this study were retrospectively collected by reviewing the medical records of patients diagnosed with KOA who underwent IA ozone injection between January 1 and September 1, 2019. The study included patients with KOA stages 2–4 according to the Kellgren–Lawrence classification who received a total of four sessions of ozone injections at 4-day intervals (n=27). In the first session, 10 ml of 25 mcg; in the second session, 10 ml of 20 mcg; and in the third and fourth sessions, 10 ml of 10 mcg of IA knee ozone injection were administered. Dose selection aimed to provide relatively anti-inflammatory doses in the first two applications and relatively inductive doses in the last two applications.

During the treatment period, patients were provided with a home exercise program that included isometric strengthening exercises and joint range-of-motion exercises targeting the knee joint. All patients were screened for contraindications to ozone therapy, such as G6PDH deficiency, uncontrolled hyperthyroidism, and

Table 1. Demographic data

Demographic parameter		Mean (range)
Age (years)		67 (44-82)
Body mass index (kg/m^2)		29 (24-36)
	n	**%**
Gender		
Male	4	14.8
Female	23	85.1
Kellgren lawrence stage		
Stage 2	8	29.6
Stage 3	10	37.03
Stage 4	9	33.3
Heat sensation		
Present	4	14.8
Absent	23	85.1
Joint effusion		
Present	11	40.74
Absent	16	59.25
Crepitus		
Present	27	100
Absent	0	0

pregnancy. Furthermore, patients were evaluated in terms of age, sex, body mass index, presence of increased heat, presence of crepitus, and presence of effusion. Increased heat in the knee was detected by palpation. Crepitus was identified by palpation during joint movement. The ballottement test was applied to determine the presence of knee effusion.

All injections were administered by the same clinician using the same technique, with patients in the seated position and under appropriate sterilization conditions. During the injection, a 10 cc ozone-resistant syringe and a 21-gauge, 16 mm needle were used. The injection was administered via an anterolateral approach to the knee. Patients were informed about the treatment, and written consent was obtained. Patients who had received any physical therapy modalities or IA injection methods within the previous six months, as well as those who used NSAIDs, analgesic drugs, or any supportive oral joint preparations or lower limb orthoses during the treatment period, were excluded from the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Health Sciences University Hamidiye Scientific Research Ethics Committee on June 4, 2021, with approval number 19/14.

Statistical Analysis

Patient records were evaluated at baseline (T0), at 2 weeks (T1), at 1 month (T2), and at 3 months (T3) post-treatment. The evaluation included the Visual Analog Scale (VAS) for resting pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Lequesne Knee Index for functionality, and the Nottingham Health Profile for quality of life. The Turkish validity and reliability of these instruments have been scientifically established [16–18]. Follow-up assessments were conducted by the same physician.

Statistical analysis was performed using the SPSS 22.0 Statistical Program. Due to the retrospective nature of the study and the available data from 27 patients, a sample size analysis was not performed. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Descriptive statistics are presented as median values with minimum and maximum values. As the data did not show a normal distribution, the Friedman test was used for intragroup comparisons. In post hoc analysis of significant results, the Wilcoxon test was applied for pairwise comparisons.

Results

The mean age of the 27 patients included in the study was 64.81±11.41 years (range 44–82). Of these patients, 23 were female and 4 were male. Other demographic characteristics of the patients are summarized in Table 1.

Table 2. Pre-treatment and post-treatment evaluations

Assessment parameter	T0 (mean±SD)	T1 (mean±SD)	T2 (mean±SD)	T3 (mean±SD)	p*	p# (α)	p# (β)	p# (ɤ)
VAS	7.37±2.25	4.55±2.84	4.59±3.07	4.33±3.12	**0.001**	**0.001**	**0.001**	**0.001**
WOMAC	58±16.29	47.03±16.11	46.74±16.25	46.55±17.80	**0.001**	**0.001**	**0.001**	**0.001**
Nottingham	42.55±15.23	44.48±14.92	44.88±14.77	45.40±13.84	**0.001**	**0.001**	**0.001**	**0.001**
Lequesne	14.07±4.74	11.81±4.64	11.70±4.71	11.62±5.43	**0.001**	**0.001**	**0.001**	**0.001**

*: Friedman test; #: Wilcoxon test; (α): Pre-Treatment to 2 Weeks Post-Treatment; (β): Pre-Treatment to 1 Month Post-Treatment; (ɤ): Pre-Treatment to 3 Months Post-Treatment. VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; Pre-Treatment: T0; Post-Treatment: T1 (2 weeks; T2 (1 month); T3 (3 months); SD: Standart deviation.

Compared with the pre-treatment period, a statistically significant improvement was observed at 2 weeks post-treatment ($p<0.05$). This positive effect was found to persist at the 1st- and 3rd-month evaluations (Table 2). No significant differences were observed between the evaluations at 2 weeks, 1 month, and 3 months ($p>0.05$). No adverse effects were observed.

Discussion

The treatment of osteoarthritis remains an active area of research, with various therapeutic options under investigation. In this study, we examined the effects of intra-articular ozone therapy, which is low-cost and associated with minimal side effects, on pain scores, functional status, and activities of daily living in patients with knee osteoarthritis. It was observed that the significant positive effect, which began at the second week compared with baseline, persisted up to the third month.

In a study conducted by Lopes de Jesus et al. [19] in 2017, 61 patients were treated with eight sessions of 10 ml of 20 mcg/ml intra-articular ozone injection, while a second group of 35 individuals received eight sessions of intra-articular oxygen therapy. Patients were evaluated using the Visual Analog Scale (VAS), Lequesne Index, and Short Form-36 (SF-36) at baseline and at 1, 2, and 4 months. The results demonstrated a significant improvement in patients treated with intra-articular ozone compared with the placebo group. Unlike our study, eight sessions were administered with a constant dose of 20 mcg of ozone in each session, and a control group was included. In addition, the treatment protocol began with four sessions at 25 mcg and ended with a maintenance dose of 10 mcg. There is currently no established standard regarding the number of sessions or the optimal dosage of ozone in intra-articular ozone therapy.

In a study by Hashemi et al. [20] in 2016, 72 patients with stage 2–3 knee osteoarthritis were divided into two groups. The first group received eight sessions of 10 ml of 40 mcg/ml intra-articular ozone and 5 ml of periarticular ozone, with three sessions in the first week, two sessions in the second week, and the remaining three sessions administered weekly. The second group underwent genicular nerve block and intra-articular radiofrequency treatment. Pain scores were evaluated at baseline and at the third month. Both groups showed improvement, and no significant difference was observed between them. In contrast to our study, periarticular ozone injection was applied in addition to intra-articular ozone injection. Comparative studies are needed to evaluate the relative effectiveness of intra-articular and periarticular ozone injections. It should also be noted that this study included patients with stage 2–3 knee osteoarthritis.

In addition to comparisons with placebo and non-pharmacological treatments, ozone injection has also been compared with other infiltrative treatment modalities. In 2017, Duymus et al. [21] conducted a study including 102 patients with stage 2–3 knee osteoarthritis. The first group received four sessions of 2 ml of lidocaine and 15 ml of 30 mcg/ml intra-articular ozone injection. The second group received two sessions of platelet-rich plasma (PRP), and the third group received a single dose of 1.6 million Dalton hyaluronic acid (HA). Patients were evaluated using VAS and WOMAC scores at baseline and at 1, 3, 6, and 12 months. All three groups demonstrated similar positive outcomes at 1 month; however, at 3 months, the PRP and HA groups continued to improve, whereas the effect in the ozone group diminished. At 6 months, the most pronounced response was observed in the PRP group compared with the HA group, and the effect of ozone therapy had completely disappeared. In contrast to these findings, in our study, the positive effects of intra-articular ozone therapy that began at the second week persisted up to the third month. Further studies are required to clarify the duration of the therapeutic effect of ozone injection.

In a study by Hashemi et al. [22] in 2015 including 80 patients, participants were divided into two groups. The first group received three sessions of 5 ml of 15 mcg/ml intra-articular ozone injection, whereas the second group received three sessions of 12.5% intra-articular hypertonic dextrose. Patients' pain and WOMAC scores were assessed at baseline and at the third month. Both groups showed significant improvement, with no significant difference between them. In this study, ozone injection was administered in 5 ml doses. Findings from previous studies indicate considerable variability in the standard dosage and number of sessions for ozone injection.

In 2019, Ata et al. [23] compared intra-articular ozone therapy with polynucleotide gel injection in patients with stage 2–3 knee osteoarthritis. The first group of 30 patients received a total of four sessions at 1-week intervals, with doses starting at 20 ml and 20 mcg/ml, followed by 15 mcg/ml, 10 mcg/ml, and 10 mcg/ml. The second group of 32 patients received a single 2 ml injection of 20 mg/ml polynucleotide gel. Both groups were evaluated for pain scores at baseline and at 5 and 12 weeks. Significant improvement was observed in both groups, with no significant difference between them. Unlike our study, a 20 ml ozone injection with varying doses was used, and the sessions were scheduled weekly. Further studies are needed to determine the optimal intervals between ozone injection sessions.

The primary limitation of our study is its retrospective design. Another limitation is the absence of a comparison between intra-articular ozone therapy and other treatment modalities. Patient responses were evaluated up to the 3-month follow-up period, indicating the need for longer-term follow-up studies.

Conclusion

In patients with knee osteoarthritis, intra-articular ozone injection may have positive effects on pain, functional status, and activities of daily living in the short and medium term. Further large-scale and comprehensive studies are needed to determine the standard dose, volume, and number of sessions for intra-articular ozone therapy, its effectiveness across different disease stages, and the duration of its therapeutic effects.

Ethics Committee Approval: The study was approved by University of Health Sciences Hamidiye Scientific Research Ethics Committee (No: 19/14, Date: 04.06.2021).

Use of AI for Writing Assistance: This article was not written by artificial intelligence, and artificial intelligence was not used in the writing process. However, standard software tools were used for grammar and spelling checks.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – E.A., F.Y.; Design – E.A.; Supervision – E.A., F.Y.; Fundings – Z.C., S.A.; Materials – Z.C., S.A.; Data collection &/or processing – Z.C.; Analysis and/or interpretation – Z.C.; Literature search – Z.C.; Writing – Z.C.; Critical review – E.A., F.Y.

Conflict of Interest: The authors declare that there is no conflict of interest.

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

References

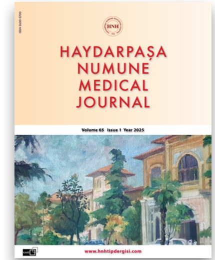
1. Ashkavand Z, Malekinejad H, Vishwanath B.S. The pathophysiology of osteoarthritis. J Pharm Res 2013;7:132–8. [CrossRef]
2. Mabey T, Honsawek S. Cytokines as biochemical markers for knee osteoarthritis. World J Orthop 2015;6:95–105. [CrossRef]
3. Azim S, Nicholson J, Rebecchi MJ, Galbavy W, Feng T, Rizwan S, et al. Interleukin-6 and leptin levels are associated with preoperative pain severity in patients with osteoarthritis but not with acute pain after total knee arthroplasty. Knee 2018;25:25–33. [CrossRef]
4. Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP injections for the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Cartilage 2021;13(1_suppl):364S–75S. [CrossRef]
5. Allaeys C, Arnout N, Van Onsem S, Govaers K, Victor J. Conservative treatment of knee osteoarthritis. Acta Orthop Belg 2020;86:412–21.
6. Jones IA, Togashi R, Wilson ML, Heckmann N, Vangsness CT Jr. Intra-articular treatment options for knee osteoarthritis. Nat Rev Rheumatol 2019;15:77–90. [CrossRef]
7. Daif ET. Role of intra-articular ozone gas injection in the management of internal derangement of the temporomandibular joint. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:e10–4. [CrossRef]
8. Manoto SL, Maepa MJ, Motaung SK. Medical ozone therapy as a potential treatment modality for regeneration of damaged articular cartilage in osteoarthritis. Saudi J Biol Sci 2018;25:672–9. [CrossRef]
9. Rahimzadeh P, Imani F, Azad Ehyaei D, Faiz SHR. Efficacy of oxygen-ozone therapy and platelet-rich plasma for the treatment of knee osteoarthritis: a meta-analysis and systematic review. Anesth Pain Med 2022;12:e127121. [CrossRef]
10. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, Salman Roghani R, Fathi M, Gharooee Ahangar A, et al. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord 2021;22:134. [CrossRef]
11. Liao CD, Chen HC, Huang MH, Liou TH, Lin CL, Huang SW. Comparative efficacy of intra-articular injection, physical therapy, and combined treatments on pain, function, and sarcopenia indices in knee osteoarthritis: a network meta-analysis of randomized controlled trials. Int J Mol Sci 2023;24:6078. [CrossRef]
12. Borrelli E, Alexandre A, Illiakis E, Alexandre A, Bocci V. Disc herniation and knee arthritis as chronic oxidative stress diseases: the therapeutic role of oxygen ozone therapy. J Arthritis 2015;4:1–7. [CrossRef]
13. Vaillant JD, Fraga A, Díaz MT, Mallok A, Viebahn-Hänsler R, Fahmy Z, et al. Ozone oxidative postconditioning ameliorates joint damage and decreases pro-inflammatory cytokine levels and oxidative stress in PG/PS-induced arthritis in rats. Eur J Pharmacol 2013;714:318–24. [CrossRef]
14. Niu T, Lv C, Yi G, Tang H, Gong C, Niu S. Therapeutic effect of medical ozone on lumbar disc herniation. Med Sci Monit 2018;24:1962–9. [CrossRef]
15. Chen H, Yu B, Lu C, Lin Q. The effect of intra-articular injection of different concentrations of ozone on the level of TNF-α, TNF-R1, and TNF-R2 in rats with rheumatoid arthritis. Rheumatol Int 2013;33:1223–7. [CrossRef]
16. Basaran S, Guzel R, Seydaoglu G, Guler-Uysal F. Validity, reliability, and comparison of the WOMAC osteoarthritis index

and Lequesne algofunctional index in Turkish patients with hip or knee osteoarthritis. Clin Rheumatol 2010;29:749–56. [CrossRef]

17. Kücükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, et al. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res 2000;23:31–8. [CrossRef]
18. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis Cartilage 2005;13:28–33. [CrossRef]
19. Lopes de Jesus CC, Dos Santos FC, de Jesus LMOB, Monteiro I, Sant'Ana MSSC, Trevisani VFM. Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study. PLoS One 2017;12:e0179185. Erratum in: PLoS One 2024;19:e0314494. [CrossRef]
20. Hashemi M, Nabi BN, Saberi A, Sedighinejad A, Haghighi M, Farzi F, et al. The comparison between two methods for the relief of knee osteoarthritis pain: radiofrequency and ıntra-periarticular ozone ınjection: a clinical trial study. Int J Med Res Health Sci 2016;5:539–46.
21. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc 2017;25:485–92. [CrossRef]
22. Hashemi M, Jalili P, Mennati S, Koosha A, Rohanifar R, Madadi F, et al. The effects of prolotherapy with hypertonic dextrose versus prolozone (intraarticular ozone) in patients with knee osteoarthritis. Anesth Pain Med 2015;5:e27585. [CrossRef]
23. Ata E, Kösem M. The comparison of the effects of intra-articular ozone and polynucleotide gel injections in pain management of knee osteoarthritis. Med J Mugla Sitki Kocman Univ 2019;6:56–9.

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.97947
Haydarpasa Numune Med J 2025;65(4):357–362



hnhtipdergisi.com

ORIGINAL ARTICLE

Comparison of the Effects of Paravertebral Ozone, Local Anesthetic, and Normal Saline Injection on Pain, Disability, and Quality of Life in Chronic Low Back Pain: A Retrospective Clinical Study

Selda Çiftci İnceoğlu[1], Aylin Ayyıldız[2], Alperen İnceoğlu[2], Figen Yılmaz[3]

[1]Department of Physical Medicine and Rehabilitation, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye
[2]Department of Physical Medicine and Rehabilitation, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye
[3]Department of Physical Medicine and Rehabilitation, Private Clinic, İstanbul, Türkiye

Abstract

Introduction: The aim of this study is to compare the effects of paravertebral ozone, local anesthetic (LA), and normal saline (NS) injections on pain, disability, and quality of life (QoL) in patients with chronic low back pain (CLBP).

Methods: Patients who underwent lumbar paravertebral ozone (Group 1), LA (Group 2), and NS (Group 3) injections due to CLBP between March and September 2023 were retrospectively screened. Patients with a history of surgery, injection, or physical therapy for the lumbar region in the last 6 months, as well as those with radicular spread or neurological deficits, were excluded from the study. Pain levels were assessed with the Numeric Rating Scale (NRS) for rest, movement, and night pain, disability levels with the Istanbul Low Back Pain Disability Index (ILBPDI), and QoL with the Nottingham Health Profile (NHP). Pre-treatment and post-treatment 3rd-month results were compared.

Results: In Group 1 (n=15), significant improvement was observed in NRS, ILBPDI, and NHP scores before and after treatment compared to baseline. In Group 2 (n=15), significant improvement was observed in NRS and ILBPDI, and in Group 3 (n=15), significant improvement was observed only in rest NRS scores ($p<0.05$). Group 1 showed significant improvement compared to Group 3 in all evaluation parameters ($p<0.05$). In Group 2, a more significant improvement was observed only in ILBPDI scores compared to Group 3 ($p<0.05$). Significant improvement was found in night NRS and NHP evaluations in Group 1 compared to Group 2 ($p<0.05$). No significant difference was observed in other pairwise comparisons ($p>0.05$).

Discussion and Conclusion: Lumbar paravertebral ozone is an effective treatment for pain, QoL, and disability in CLBP. Paravertebral ozone injection is a preferable treatment due to its advantages over LA and NS.

Keywords: Chronic low back pain; intramuscular injection; local anesthesia; normal saline; ozone; paravertebral.

Chronic low back pain (CLBP) can be defined as pain between the distal rib and the inferior gluteal fold lasting for more than 3 months [1]. A worldwide review found a midpoint prevalence of 18.3%, with a positive correlation shown between the human development index and low back pain [2]. Seventy percent of the general adult population suffers from low back pain at least once in their lifetime [3]. One of the most important goals of clinical trials

Correspondence: Selda Çiftci İnceoğlu, M.D. Department of Physical Medicine and Rehabilitation, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye
Phone: +90 541 485 78 50 **E-mail:** seldavd@gmail.com
Submitted Date: 30.04.2025 **Revised Date:** 20.08.2025 **Accepted Date:** 10.09.2025
Haydarpaşa Numune Medical Journal

is to find low-cost and effective treatments for low back pain, which poses a major burden on the health system worldwide [4,5].

Drug therapy, primarily non-steroidal anti-inflammatory drugs (NSAIDs), is recommended in the treatment of CLBP. Treatments involving injection or radiofrequency are also defined in the guidelines. In cases of disc herniation, widespread degenerative changes, or instability, surgical treatments may be considered [4]. Exercise therapy is also an effective treatment for both pain and disability [6]. Complementary and alternative medicine (CAM) methods are also effective options in the treatment of CLBP [7].

Ozone is a molecule consisting of 3 oxygen atoms and is a colorless gas. It is thought that subcutaneous and intramuscular applications to the lumbar region in low back pain help eliminate proinflammatory substances and reduce peripheral sensitivity through an immune regulatory effect [8]. However, ozone therapy is not widely accepted as a treatment option for CLBP and remains an empirical treatment [9]. Local anesthesia (LA) is also frequently used for myofascial pain [10]. LA injection is recommended with a low level of evidence in the presence of trigger points in CLBP [11]. Normal saline (NS) injection, 0.9% NaCl serum, may also be used as a treatment due to its low cost, good safety profile, and proven efficacy in myofascial pain [10,12].

The aim of this study was to investigate the effects of intramuscular ozone, LA, and NS injections on pain, disability, and quality of life (QoL) in the treatment of CLBP.

Materials and Methods

Study Design

The study was planned as a retrospective controlled study. It was conducted between March 2023 and September 2023 at the Physical Medicine and Rehabilitation (PM&R) Clinic. Ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Şişli Etfal Training and Research Hospital (15.11.2022/Approval No: 3723). Informed consent was obtained from the patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Patients who applied to the PM&R Clinic for low back pain lasting 3 months or longer were retrospectively screened through the hospital system. Patients aged 18 years and older who received local injections to the paravertebral muscles were included in the study. Patients with a history of injections, physical therapy, or surgery to the lumbar region in the last 6 months, those with low back pain with radicular spread and neurological deficits, and those with a history of malignancy were excluded.

Interventions

The patients were divided into 3 groups. Group 1 consisted of patients who received paravertebral ozone, Group 2 consisted of patients who received paravertebral LA, and Group 3 consisted of patients who received paravertebral NS injections. The injection protocol was applied to the lumbar paravertebral muscles intramuscularly at 4 points bilaterally in all 3 patient groups, completed in 2 sessions, 1 week apart. Ozone treatment in Group 1 was applied as 20 cc of a total of 15 µg/ml doses per session. In Group 2, LA injection was applied as a total of 8 cc of a 1/1 ratio of 2% prilocaine and 0.9% NaCl serum mixture. In Group 3, 0.9% NaCl serum was injected as 8 cc. All injections were performed by the same physician working in the injection clinic. Additionally, home exercises were demonstrated to all patients, and they were advised to do them at least 3 times a week.

Clinical Assessments

In the outpatient injection clinic of PM&R, some forms are routinely filled out to evaluate the results of the treatment for all patients who undergo the procedure. Data recorded in the hospital system before and after treatment were used for this study. Before treatment, pain levels were assessed with the Numerical Rating Scale (NRS) for rest, movement, and night pain. Low back pain disability was assessed with the Istanbul Low Back Pain Disability Index (ILBPDI). The ILBPDI is a scale consisting of 18 questions and scored between 0–90. As the score increases, the person's disability due to low back pain increases [13]. The Nottingham Health Profile (NHP) was used for QoL assessments. The NHP consists of two sections: the first section includes pain, emotional reactions, sleep, social isolation, physical activity, and energy subsections. These subheadings are assessed between 0–600 points, with each section worth 100 points. Calculations can be made without the second section. As the score increases, the QoL decreases [14]. Pre-treatment evaluations were compared with the evaluations performed at the routine control 3 months after treatment.

Statistical Analysis

Numerical variables in the descriptive data are given as percentage, mean, and standard deviation (for normally distributed data). Differences between groups in categorical variables were evaluated with the Chi-square test. Statistical significance between independent groups was evaluated with ANOVA and Kruskal-Wallis tests. Post-hoc analysis (Tukey, DSCF, respectively) was applied to data that revealed statistically significant differences in parameters evaluated with ANOVA and Kruskal-Wallis tests. P-values of post-hoc analyzed data are given with Bonferroni correction. In dependent groups, the Paired T-test was used for normally distributed data, and the Wilcoxon test was used for data that were not normally distributed. The statistical analysis of the study was performed using "The jamovi project (2024)" jamovi (Version 2.5) (Computer Software) (retrieved from https://www.jamovi.org).

Results

A total of 53 patients' data were obtained from hospital records. Five patients were excluded due to the presence of exclusion criteria, and three patients' data were missing. The study was completed with 45 patients, 15 in each group (Fig. 1). The mean age of Group 1 was 40.07±9.85 years, the mean age of Group 2 was 42.33±14.17 years, and the mean age of Group 3 was 42.40±11.01 years. The pain duration of Group 1 was 12.27±6.36 months, the pain duration of Group 2 was 15.73±14.94 months, and the pain duration of Group 3 was 14.04±7.71 months. There were no significant differences between the groups in terms of age, gender, and pain duration (p>0.05). Initial resting NRS, movement NRS, nighttime NRS, ILBPDI scores, and NHP scores were similar between the groups (Table 1).

In within-group evaluations, significant improvement was observed in all evaluations, including resting NRS, movement NRS, night NRS, ILBPDI scores, and NHP scores before and 3 months after treatment in Group 1 (p<0.05). In Group 2, post-treatment evaluations showed significant regression in resting NRS, night NRS, and ILBPDI (p<0.05). However, no significant change was found in NHP values (p>0.05). In Group 3, pre- and post-treatment evaluations revealed significant regression only in resting NRS values (p<0.05), while no significant change was observed in other assessment parameters (p>0.05) (Table 2).

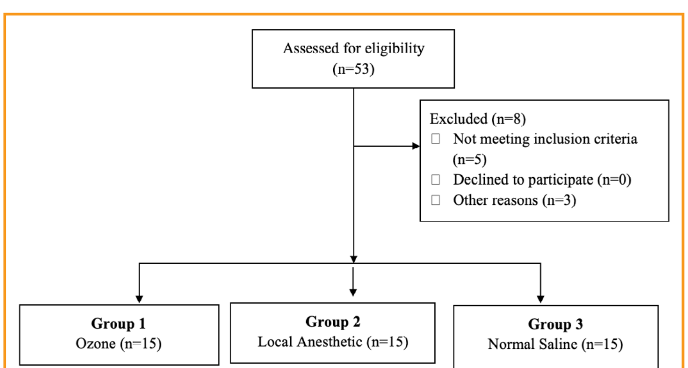


Figure 1. Flow diagram of the study. Adapted from the CONSORT 2010 Statement (www.consort-statement.org).

When the changes in resting NRS and movement NRS were compared between the groups, a significant difference was found (p=0.034, p<0.001, respectively). Pairwise comparisons revealed a significant difference between Group 1 and Group 3 (p=0.031, p<0.001, respectively), while no significant difference was found between other pairwise comparisons (p>0.05). When the groups were compared in terms of night NRS, a significant difference was found (p<0.001). A significant difference was observed between Group 1 and the other groups (p=0.009, p=0.002, respectively), but no significant difference was found between Group 2 and Group 3 (p=0.834). When the changes in ILBPDI were compared between the groups, no significant difference was found between Group 1 and Group 2 (p=0.629), while the change in Group 3 was significantly lower than in Group 1 and Group 2 (p=0.001, p=0.014, respectively). When the changes in NHP were compared between the groups, a significant difference was found (p<0.001). A significant difference was observed between Group 1 and the other groups (p<0.001), but no significant difference was observed between Group 2 and Group 3 (p=0.695) (Table 2).

Table 1. Demographic variables of patients and pre-treatment assessments

	Group 1 (n=15)	**Group 2 (n=15)**	**Group 3 (n=15)**	**p**
Age (year)	40.07±9.85	42.33±14.17	42.40±11.01	0.828†
Gender (n, %)				
Female	12 (80)	11 (73.3)	12 (80)	0.879+
Male	3 (20)	4 (26.7)	3 (20)	
Pain duration (month)	12.27±6.36	15.73±14.97	14.07±7.71	0.832*
Rest NRS	6.20±1.37	6.47±1.55	6.00±1.20	0.653†
Movement NRS	6.87±1.06	7.40±1.64	6.27±1.28	0.082†
Night NRS	5.67±1.45	5.60±1.80	5.60±1.12	0.989†
ILBPDI	47.93±17.42	42.13±23.39	47.47±15.57	0.656†
NHP	48.13±10.17	55.40±7.60	53.33±11.71	0.109†

†: ANOVA; +: Chi-Square test; *: Kruskal Wallis Test. NRS: Numeric rating scale; ILBPDI: Istanbul low back pain disability index; NHP: Nottingham health profile.

Table 2. Pre-treatment and post-treatment changes within and between groups

	Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=15)	p
Rest NRS				
Pre-treatment	6.20±1.37	6.47±1.55	6.00±1.20	0.034†
3rd month	3.51±1.30	4.93±1.89	4.93±1.33	
Mean change	- (2.67±1.54)	- (1.53±1.60)	- (1.07±1.83)	
p	<0.001p	0.005w	0.041p	
Movement NRS				
Pre-treatment	6.87±1.06	7.40±1.64	6.27±1.28	<0.001†
3rd month	3.80±1.52	5.40±1.72	5.67±1.45	
Mean change	- (3.07±1.62)	- (2.00±1.46)	- (0.60±1.92)	
p	<0.001p	<0.001p	0.246p	
Night NRS				
Pre-treatment	5.67±1.45	5.60±1.80	5.60±1.12	<0.001†
3rd month	2.87±1.51	4.60±2.20	4.93±1.10	
Mean change	- (2.80±1.78)	- (1.00±1.41)	- (0.67±1.54)	
p	<0.001p	0.021w	0.116p	
ILBPDI				
Pre-treatment	47.93±17.42	42.13±23.39	47.47±15.57	<0.001†
3rd month	25.93±13.48	24.60±13.23	44.20±15.17	
Mean change	-(22.00±12.25)	- (17.53±14.58)	- (3.27±12.81)	
p	<0.001p	<0.001p	0.340p	
NHP				
Pre-treatment	48.13±10.17	55.40±7.60	53.33±11.71	<0.001*
3rd month	32.40±7.35	52.33±8.97	49.27±11.22	
Mean change	-(15.73±6.05)	-(3.07±8.00)	-(4.07±7.79)	
p	<0.001p	0.160p	0.063p	

†: ANOVA; *: Kruskal Wallis Test; p: Paired T-test; w: Wilcoxon test. NRS: Numeric rating scale; ILBPDI: Istanbul low back pain disability index; NHP: Nottingham health profile.

Discussion

This study aimed to compare different types of paravertebral injections commonly used in the treatment of low back pain. Local injections are emerging as a significant treatment modality, particularly for patients who cannot receive systemic medication. The paravertebral ozone injection resulted in a decrease in NRS scores, a reduction in disability, and a significant improvement in quality of life compared to pre-treatment levels. The present study also examined the effects of paravertebral LA injection on both NRS scores and disability. The results demonstrated a decrease in NRS scores and an improvement in disability; however, these improvements did not reach statistical significance. Conversely, the paravertebral saline injection showed a reduction in resting NRS scores, but no significant impact on pain intensity was observed. Furthermore, paravertebral ozone injections demonstrated significant improvements in resting and movement NRS values in comparison with the saline group, and statistically significant improvements in nighttime NRS and NHP values when compared with both the LA and saline groups. In light of these findings, paravertebral ozone injection emerges as a potential therapeutic modality for CLBP.

Intramuscular ozone injection can be used in cases related to low back and neck pain [15,16]. A systematic review published in 2018 stated that further studies are needed due to the small number and low quality of studies on the effect of ozone therapy on low back pain and disc herniation [17]. However, studies on this treatment have been increasing in recent years. A study published after this review showed that paravertebral ozone injection may be beneficial in lumbar disc herniation, radicular pain, or mechanical low back pain [18]. A recently published study showed that paravertebral ozone injection reduced pain levels and improved Oswestry Disability Index (ODI) scores [15]. A study comparing paravertebral ozone injection with epidural steroid-hyaluronidase injection in patients with lumbar stenosis showed that both treatments were effective for pain relief, with paravertebral ozone being even more effective [19]. Another retrospective comparative study showed that adding paravertebral ozone injection to physiotherapy had a more significant positive effect on Visual Analog Scale (VAS) and ODI scores compared to physiotherapy alone [20]. Despite these positive results, the fact that the studies were retrospective observational studies or lacked control groups limits the reliability of the findings. Current evidence suggests that the benefits of ozone therapy in the general approach to low back pain are limited [21]. In our study, significant differences were found in the paravertebral ozone injection group compared to the other treatment groups, supporting the findings in the literature.

LA can be applied alone or mixed with different injectates such as NS and steroids for pain control. LA injections, especially in low doses, can be applied in the treatment of trigger points that cause myofascial pain [10]. It is known that treatments such as local anesthetic injection or dry needling can be used for trigger point injection in individuals with subacute low back pain or CLBP who do not respond to medical treatment. However, it is recommended to apply it alongside an active exercise program [11]. Percutaneous procedures are not recommended for non-specific low back pain [22]. A recent meta-analysis reported that interventional applications, including intramuscular LA injection, did not significantly reduce pain, or reduced it only minimally, compared to sham treatment applications in non-cancer chronic spine pain [23]. In fact, this finding is similar to the results of our study. In our study, the results in the LA group were similar to those in the NS group, except for the ILBPDI score. This suggests the applicability of NS injection in patients who cannot receive LA injection due to allergies or other reasons.

In a study comparing the effects of NS and lidocaine+steroid trigger point injections on pain in patients with myofascial pain, it was determined that the effect of NS on pain was similar to that of the other group [12]. Another study showed that NS injection was effective for pain in myofascial pain and could be applied because it did not cause major side effects [24].

It must be acknowledged that there are certain limitations associated with our study. The present study adopts a retrospective design, and the relatively small number of patients is one limitation. Despite the recommendation of exercise therapy for all patients following injections, the retrospective design of the study precluded the assessment of exercise adherence. The limited number of patients and the possibility of a Type 2 error should be considered for data sets exhibiting no significant difference. Conducting prospective studies with a larger cohort would provide more robust evidence. Furthermore, while all patients were classified as CLBP cases, the absence of a comparison between different etiologies necessitates analogous studies in specific low back pain cases. Nevertheless, the significant differences between the treatment groups, the relatively low costs, the demonstrated effectiveness of the treatments, and the comparison of injections containing three different treatments are features that render our study robust.

Conclusion

CLBP paravertebral injection is a feasible and cost-effective treatment. Paravertebral intramuscular ozone, LA, and NS (only rest NRS) injections showed significant changes after treatment in the respective groups. Lumbar paravertebral ozone injection may provide more favorable results than LA and NS on pain and QoL, as well as more favorable results than NS on disability.

Ethics Committee Approval: The study was approved by University of Health Sciences Şişli Etfal Training and Research Hospital Clinical Research Ethics Committee (No: 3723, Date: 15.11.2022).

Use of AI for Writing Assistance: Artificial intelligence programs were not used in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – S.Ç.İ., F.Y.; Design – S.Ç.İ., F.Y.; Supervision – A.A., F.Y.; Fundings – S.Ç.İ., A.A.; Materials – S.Ç.İ., A.A., A.İ.; Data collection and/or processing – S.Ç.İ., A.A.; Analysis and/or interpretation – A.İ.; Literature search – S.Ç.İ.; Writing – S.Ç.İ.; Critical review – A.A., F.Y.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

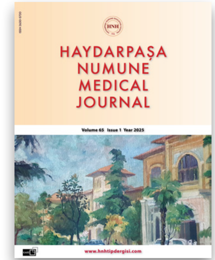
References

1. Rozenberg S. Chronic low back pain: definition and treatment. Rev Prat 2008;58:265–72. [Article in French]
2. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum 2012;64:2028–37. [CrossRef]
3. Cunha LL, Mayrink WC. Influence of chronic pain in the quality of life of the elderly. Rev Dor 2011;12:120–4. [Article in Portuguese] [CrossRef]
4. Oliveira CB, Maher CG, Pinto RZ, Traeger AC, Lin CC, Chenot JF, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. Eur Spine J 2018;27:2791–803. [CrossRef]
5. Li J, Jia Y, Sun T, Bai Z, Dong X, Hou X. Interventions used in

control group against cupping therapy for chronic nonspecific low back pain: A systematic review and network meta-analysis. Complement Ther Med 2025;90:103167. [CrossRef]
6. Hayden JA, Ellis J, Ogilvie R, Malmivaara A, van Tulder MW. Exercise therapy for chronic low back pain. Cochrane Database Syst Rev 2021;9:CD009790. [CrossRef]
7. Ketenci A, Zure M. Pharmacological and non-pharmacological treatment approaches to chronic lumbar back pain. Turk J Phys Med Rehabil 2021;67:1–10. [CrossRef]
8. Biazzo A, Corriero AS, Confalonieri N. Intramuscular oxygen-ozone therapy in the treatment of low back pain. Acta Biomed 2018;89:41–6.
9. Carlos AJ, Silvia CV. Evaluation of the usefulness of ozone - O3 in the treatment of low back pain. is it really something more than an empirical concept? systematic review of the literature. World Neurosurg 2024;182:e319–33. [CrossRef]
10. Anwar N, Wei X, Jie Y, Hongbo Z, Jin H, Zhu Z. Current advances in the treatment of myofascial pain syndrome with trigger point injections: A review. Medicine (Baltimore) 2024;103:e39885. [CrossRef]
11. Hegmann KT, Travis R, Andersson GBJ, Belcourt RM, Carragee EJ, Eskay-Auerbach M, et al. Invasive treatments for low back disorders. J Occup Environ Med 2021;63:e215–41. [CrossRef]
12. Roldan CJ, Osuagwu U, Cardenas-Turanzas M, Huh BK. Normal saline trigger point injections vs conventional active drug mix for myofascial pain syndromes. Am J Emerg Med 2020;38:311–6. [CrossRef]
13. Duruöz MT, Özcan E, Ketenci A, Karan A. Development and validation of a functional disability index for chronic low back pain. J Back Musculoskelet Rehabil 2013;26:45–54. [CrossRef]
14. Kücükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, Arasil T. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res 2000;23:31–8. [CrossRef]
15. Latini E, Nusca SM, Curci ER, Boaretto D, Santoboni F, Trischitta D, et al. Intramuscular paravertebral oxygen-ozone therapy for chronic neck pain and low back pain: evaluation of 6-month clinical outcomes. Med Gas Res 2024;14:6–11. [CrossRef]
16. Ucar D, Uçar S, Özcan Ç, Polat Ö, Çaçan MA, Uçar BY. Retrospective observational study of intramuscular oxygen-ozone therapy for the treatment of neck pain: cervical paravertebral injection. Med Gas Res 2020;10:170–3. [CrossRef]
17. Costa T, Linhares D, Ribeiro da Silva M, Neves N. Ozone therapy for low back pain. A systematic review. Acta Reumatol Port 2018;43:172–81.
18. Özcan Ç, Polat Ö, Çelik H, Uçar BY. The effect of paravertebral ozone injection in the treatment of low back pain. Pain Pract 2019;19:821–5. [CrossRef]
19. Parvin R, Farpour HR, Khoshnazar S, Jahromi LSM. Comparative effectiveness of paravertebral Ozone injection and caudal epidural steroid-hyaluronidase injection in lumbosacral spinal stenosis. Br J Neurosurg 2024;38:451–6. [CrossRef]
20. Yalçın Ü. Paravertebral intramuscular ozone therapy in lumbar disc hernia: A comprehensive retrospective study. J Back Musculoskelet Rehabil 2021;34:597–604. [CrossRef]
21. Llombart-Blanco R, Mariscal G, Cordón V, Barrios C, Benlloch M, Llombart-Ais R. The effectiveness of ozone infiltration on patient-reported outcomes in low back pain: a systematic review and meta-analysis. Life (Basel) 2024;14:1406. [CrossRef]
22. Chenot JF, Greitemann B, Kladny B, Petzke F, Pfingsten M, Schorr SG. Non-specific low back pain. Dtsch Arztebl Int 2017;114:883–90. [CrossRef]
23. Wang X, Martin G, Sadeghirad B, Chang Y, Florez ID, Couban RJ, et al. Common interventional procedures for chronic non-cancer spine pain: a systematic review and network meta-analysis of randomised trials. BMJ 2025;388:e079971. [CrossRef]
24. Kongsagul S, Vitoonpong T, Kitisomprayoonkul W, Tantisiriwat N. Ultrasound-guided physiological saline injection for patients with myofascial pain. J Med Ultrasound 2019;28:99–103. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.73549
Haydarpasa Numune Med J 2025;65(4):363–368



hnhtipdergisi.com

ORIGINAL ARTICLE

Positivity Rate of Rotavirus and Adenovirus in Acute Gastroenteritis Patients: A Three-Year Analysis Based on Age, Season, and Gender

Mehmet Akif Durmuş, Nurhadiye Kuru

Department of Medical Microbiology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye

Abstract

Introduction: Acute gastroenteritis (AGE) is a significant cause of morbidity and mortality, particularly in children under five years of age. Among viral pathogens, rotavirus and adenovirus are the leading causes of both endemic and epidemic AGE worldwide. This study aims to investigate the positivity rate of rotavirus and adenovirus among gastroenteritis-suspected patients in Istanbul, focusing on demographic factors and seasonal distribution.

Methods: Between May 1, 2020, and May 1, 2023, stool samples from 16,064 patients who presented to Başakşehir Çam ve Sakura City Hospital in Istanbul were retrospectively evaluated. Rotavirus and adenovirus antigens were analyzed using two different immunochromatographic rapid tests employed during the study period: the CerTest® RotaAdeno Card Test (CerTest Biotec, Spain) and the Rotavirus Adenovirus Rapid Antigen Test (Türklab, Türkiye). Patients were categorized by age groups (0–12, 13–36, 37–60 months, 6–18 years, and >18 years), gender, and seasons. Statistical analyses were conducted using Chi-square and Z-tests, with $p<0.05$ considered statistically significant.

Results: A total of 2,270 (14.1%) patients tested positive for rotavirus, and 595 (3.7%) tested positive for adenovirus. The highest positivity rate for rotavirus occurred in the 13–36 months age group (20.3%), while adenovirus was most common in the 37–60 months age group (4.8%) ($p<0.001$). When the positivity rates between genders were examined, no significant difference was found (rotavirus: female and male 14.1%; adenovirus: female 3.9%, male 3.5%; $p>0.05$). Rotavirus infections peaked in spring and summer (14.7%-14.5%), whereas adenovirus infections peaked in autumn (4.5%) ($p<0.05$). The co-infection rate was 0.58% (n=93).

Discussion and Conclusion: Rotavirus has become a more dominant pathogen causing AGE than adenovirus. Both viruses showed high levels of positivity, especially in early childhood. The seasonal patterns indicate that rotavirus peaks in spring and summer, while adenovirus sees an increase in autumn. These insights are crucial for developing targeted preventive measures for managing AGE in specific age groups.

Keywords: Acute gastroenteritis; adenovirus; rotavirus.

Acute gastroenteritis (AGE) is defined by the International Pediatric Gastroenterology, Hepatology Associations Federation, and the Nutrition Working Group as a condition characterized by diarrhea. Diarrhea is identified as a change in stool consistency and/or an increase in the frequency of bowel movements, occurring three or more times within a 24-hour period, regardless of whether there is accompanying fever or vomiting [1]. Since norovirus was

Correspondence: Mehmet Akif Durmuş, M.D. Department of Medical Microbiology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye
Phone: +90 554 467 15 61 **E-mail:** drmehmetakifdurmus@gmail.com
Submitted Date: 24.06.2025 **Revised Date:** 04.09.2025 **Accepted Date:** 15.09.2025
Haydarpaşa Numune Medical Journal

discovered in 1972 as the cause of what was previously known as acute infectious nonbacterial gastroenteritis, our scientific understanding of viral gastroenteritis has evolved significantly. It is now widely accepted that a small number of viruses are the primary causes of acute gastroenteritis worldwide, affecting both high-income and low-income regions [2]. Viral gastroenteritis is an etiological category that can clinically manifest in a wide range of diseases, depending on the specific pathogen and various host-related factors [1]. Rotavirus (family Reoviridae), norovirus (family Caliciviridae), and adenovirus (family Adenoviridae) are the primary viral causes of both endemic and epidemic gastroenteritis in children worldwide. In addition to these, human astrovirus (family Astroviridae), sapovirus (family Caliciviridae), and aichivirus (family Picornaviridae) are also viruses that can be associated with gastroenteritis [3,4]. AGE remains a significant cause of childhood morbidity and mortality worldwide, particularly affecting children under five years old in low-income regions [5]. According to the Global Health Data Exchange, in 2016, diarrhea was the eighth leading cause of death globally, and it became the fifth leading cause of death among children under five years old [6]. According to data from the Centers for Disease Control and Prevention (CDC), viral gastroenteritis infections lead to the deaths of over 200,000 children worldwide each year [7,8].

This study aims to determine the frequency of rotavirus and adenovirus antigens in stool samples of gastroenteritis-suspected patients sent to our laboratory using an immunochromatographic rapid test kit and to examine the distribution of these pathogens based on gender, age, and season.

Materials and Methods

This study analyzed stool samples sent to the Medical Microbiology Laboratory of Başakşehir Çam ve Sakura City Hospital in Istanbul between May 1, 2020, and May 1, 2023. These samples were collected from various outpatient clinics and departments, where there was a clinical suspicion of acute gastroenteritis, and a request for testing for rotavirus and adenovirus was made. A qualitative immunochromatographic rapid test method, utilizing specific monoclonal antibodies, was employed to detect rotavirus and adenovirus antigens in the stool samples. For this purpose, two different commercial kits were used during the study period: the CerTest® RotaAdeno Card Test (CerTest Biotec, Spain) and the Rotavirus Adenovirus Rapid Antigen Test (Türklab, Türkiye). The application of the test and the evaluation of results were carried out according to the protocols recommended by the manufacturer. Participants in the study were categorized into five age groups: 0–12 months, 13–36 months, 37–60 months, 6–18 years, and over 18 years.

Ethical Approval

The study was approved by the Başakşehir Çam ve Sakura City Hospital Ethical Committee on November 20, 2023, with approval number 568. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Chi-square (χ^2) tests were used to test the differences in proportions between groups based on gender, age, and seasons for positivity rates. For each virus, seasonal periods (December–February, March–May, June–August, September–November), age groups (0–12, 13–36, 37–60 months, 6–18 years, and >18 years), and gender (female/male) categories were analyzed separately. Positivity rates were determined based on the positive isolate rates calculated from the total number of tested samples. The statistical significance level was set at p=0.05, and a two-tailed test approach was adopted. All statistical analyses were conducted using IBM SPSS Statistics (Version 26.6, IBM Corp., NY, USA).

Results

The microbiology laboratory analyzed 16,064 patient samples. Of these, 2,270 tested positive for rotavirus, while 595 tested positive for adenovirus. Additionally, both viruses (rotavirus and adenovirus) were found to be positive together in 93 patients. For the rotavirus test results, out of the 2,270 positive samples, 965 (42.5%) were from female patients, and 1,305 (57.5%) were from male patients. When examining positivity rates by age groups, the highest rate was observed in the 13–36 months group at 20.3%, followed by the 37–60 months group at 16.9%, and the 0–12 months group at 15.6%. The positivity rate decreased to 8.9% in the 6–18 years group and dropped to 3.6% in the >18 years group. Gender distribution revealed that the positivity rates for female and male patients were similar, with both genders having a rate of 14.1%. Detailed data on these rates are presented in Table 1. For the adenovirus test results, 269 (45.2%) of the 595 positive samples were from female patients, while 326 (54.8%) were from male patients. The highest positivity rate for adenovirus was found in the 37–60 months group at 4.8%, followed by the 0–12 months group at 4.2%, and the 13–36 months group at 3.9%. The positivity rate decreased to 2.8% in the 6–18 years group and to 1.5% in the >18 years group. Similar positivity rates were also observed

Table 1. Distribution of rotavirus positivity by age and gender

The age range	Positive (n)		Total (n)		Positivity rate (%)		The overall positivity rate (%)
	Female	Male	Female	Male	Female	Male	
The 0–12 months age group	459	624	2942	3982	15.6	15.7	15.6
The 13–36 months age group	238	323	1171	1598	20.3	20.2	20.3
The 37–60 months age group	116	166	713	952	16.3	17.4	16.9
The 6–18 years age group	127	168	1296	2037	9.8	8.2	8.9
The >18 years age group	25	24	705	668	3.5	3.6	3.6
Total	965	1305	6827	9237	14.1	14.1	14.1

Table 2. Distribution of adenovirus positivity by age and gender

The age range	Positive (n)		Total (n)		Positivity rate (%)		The overall positivity rate (%)
	Female	Male	Femal	Male	Female	Male	
The 0-12 months age group	122	171	2942	3982	4.1%	4.3	4.2
The 13-36 months age group	58	50	1171	1598	5.0%	3.1	3.9
The 37-60 months age group	37	43	713	952	5.2%	4.5	4.8
The 6-18 years age group	41	52	1296	2037	3.2%	2.6	2.8
The >18 years age group	11	10	705	668	1.6%	1.5	1.5
Total	269	326	6827	9237	3.9%	3.5	3.7

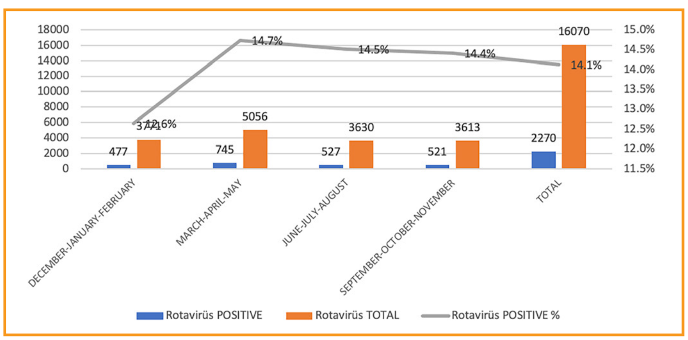


Figure 1. Distribution of rotavirus positivity by seasons.

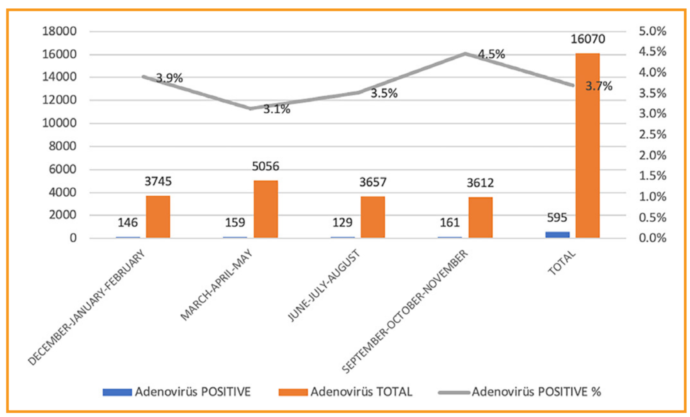


Figure 2. Distribution of adenovirus positivity by seasons.

between female and male patients. Data on these rates are presented in Table 2. Overall, the positivity rate for adenovirus was significantly lower than that for rotavirus.

Figure 1 illustrates the seasonal distribution of rotavirus positivity, while Figure 2 depicts the seasonal distribution of adenovirus positivity.

Discussion

Viral gastroenteritis remains a significant public health concern and is one of the leading causes of diarrhea-related deaths, especially in children under the age of five [6,9]. Rotavirus and adenovirus are known to be the most common viral pathogens responsible for acute gastroenteritis worldwide [3,4].

In our study, the rotavirus positivity rate was 14.1%, consistent with rates of 4.7% to 14% reported in similar studies from Türkiye [10–15]. Adenovirus positivity was recorded at 3.7%, consistent with the range of 1.2% to 9.1% found in previous studies [10–15]. Additionally, co-infection of rotavirus and adenovirus was observed in a low proportion in 93 (0.58%) patients. Co-infections in viral gastroenteritis are quite common. The most frequently reported co-infection is the combination of norovirus and rotavirus, while the combination of rotavirus and adenovirus is seen less often [16,17].

A study conducted in Spain examined stool samples from children aged five years and younger who visited outpatient clinics with symptoms of gastroenteritis of unknown cause. When the cause could not be identified through routine examinations—such as tests for enteropathogenic bacteria (including Salmonella spp., Shigella spp., Yersinia spp., Aeromonas spp., and Campylobacter spp.) and immunochromatographic tests for rotavirus or adenovirus—the researchers utilized the Polymerase Chain Reaction (PCR) method. This analysis revealed that viral co-infections were present in 21% of the cases examined [18]. In an 11-year study conducted in Italy by De Grazia et al. [17], co-infection was reported at a rate of 8.3%. A separate study in Türkiye revealed that the rate of virus-virus co-infections in cases of acute gastroenteritis was 10.4%. The most frequently detected combinations were rotavirus-norovirus at 4.5% and adenovirus-norovirus at 4.1%. Additionally, the coexistence of rotavirus and adenovirus was observed in 1.2% of cases [16]. In another study by Aytaç et al. [13], the coexistence of adenovirus and rotavirus was found in 17 patients, accounting for 0.3%.

Our study found the highest rotavirus positivity rate in the 13–36 months age group, which was 20.3%. This was followed by the 37–60 months age group at 16.9%, and the 0–12 months age group at 15.6%. For adenovirus positivity, the highest rate was observed in the 37–60 months age group, at 4.8%. There were statistically significant differences in the positivity rates of rotavirus and adenovirus across the age groups (p<0.001). In their study, Vural et al. [11], found that the age group with the highest rotavirus positivity was children aged 2 to 5, with a rate of 24.5%. In contrast, adenovirus positivity increased with age, peaking at 35.8% in the group older than 18. Sert et al. [15] reported that the highest rotavirus positivity was observed in the 0–2-year age group (1.9%), and this rate decreased with age. A similar decline was observed for adenovirus positivity, with the highest positivity again found in the 0–2 years age group (4.8%). In the study conducted by Gündüz et al. [14], there was no significant difference in rotavirus positivity rates between the age groups of 0–2 years (49.9%) and those older than 2 years (50.1%). However, for adenovirus positivity, the researchers reported a rate of 42% in the 0–2 years group, compared to 58% in the group older than 2 years, and this difference was found to be statistically significant. Duran et al. [19] reported that rotavirus infections were most prevalent in the 3 to 5-year age group, with an incidence of 11.6%, followed closely by the 1 to 2-year age group at 11.2%. In contrast, adenovirus infections were primarily observed in the 6 to 9-year age group (8.4%) and the 1 to 2-year age group (6.3%). However, no significant differences were found between the various age groups for either pathogen. Aktaş et al. [16] reported that rotavirus infections were significantly higher in children aged 0–24 months. Aytaç et al. [13], conducted a study in Elazığ and found that the positivity rate for rotavirus was notably high in the 0–12 months age group (12.9%) and the 13–24 months age group (11.1%). In contrast, this rate decreased to 5.1% among individuals aged 5 years and older. Similarly, the positivity rate for adenovirus was higher in younger age groups, recorded at 3.7% for those aged 0–12 months and 2.6% for those aged 13–24 months, while it was found to be 1.7% in older age groups. Our study's distribution of test positivity rates according to age groups aligns with existing literature, suggesting that rotavirus and adenovirus infections are more prevalent, particularly during early childhood.

No significant difference was found in positivity rates related to gender for both rotavirus and adenovirus (p>0.05). The rotavirus positivity rate was 14.1% for both females and males, while the adenovirus positivity rate was 3.9% in females and 3.5% in males. These findings indicate that the distribution by gender is balanced, suggesting that gender is not a risk factor for infection. These results are consistent with findings from other studies [13,14,19].

When the seasonal distribution was examined, rotavirus positivity was found to be at the highest level in the spring (March–May) and summer (June–August) months, with 14.7% and 14.5%, respectively. In contrast, adenovirus positivity peaked in the autumn (September–November) at 4.5%. The seasonal difference was statistically significant for rotavirus (p=0.013) and adenovirus (p=0.030). Studies on the seasonal distribution of rotavirus and adenovirus infections present different findings in the literature. In their study, Genç et al. [10] reported that the rotavirus positivity rate was statistically significantly higher, especially in the autumn compared to other seasons; however, adenovirus positivity increased significantly in the summer. The study of Vural et al. [11] stated that both viral agents were detected positive most frequently in the spring and winter months. The seasonal distribution of rotavirus showed a statistically significant difference, but the seasonal difference was not significant for adenovirus. The study of Aytaç et al. [13] showed that the rotavirus positivity rate in the winter season was higher compared to other seasons, and this difference was significant. However, according to the seasons, no significant difference was determined in adenovirus infections. According to Sert et al. [15], rotavirus infections were observed with the highest frequency in December and generally in the winter season, while adenovirus infections occurred most frequently in March and spring. The seasonality of both types of infection was also determined at a high statistical significance level in this study. These findings show that rotavirus infections are generally more common in the winter months, while adenovirus infections are more variable regarding seasonal distribution. However, some studies reported them more frequently in the spring and summer. These different results suggest that geographical region and environmental factors (climate, humidity, etc.) may play a decisive role in the seasonal patterns of viral agents.

Conclusion

The results of our study indicate that the positivity rates of adenovirus are significantly lower than those of rotavirus. This finding confirms that rotavirus plays a more dominant role in the etiology of AGE compared to adenovirus. In conclusion, our study underscores the significance of both rotavirus and adenovirus in the causes of AGE, highlighting their positivity rate during childhood. Rotavirus is more common in the spring and summer, while adenovirus is typically observed in the autumn. Seasonal patterns may vary based on regional climate conditions, hygiene standards, vaccination rates, and the variants of the circulating viruses. Looking ahead, multicenter studies are necessary to assess vaccination status, explore serotype distributions, evaluate the clinical impacts of co-infections, and investigate regional differences in greater detail.

Ethics Committee Approval: The study was approved by Başakşehir Çam ve Sakura City Hospital Ethics Committee (No: 568, Date: 20.11.2023).

Use of AI for Writing Assistance: Grammarly was used for English grammar editing.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – M.A.D.; Design – M.A.D.; Supervision – M.A.D.; Materials –N.K.; Data collection and/or processing – N.K.; Analysis and/or interpretation – M.A.D.; Literature search – M.A.D.; Writing – M.A.D.; Critical review – M.A.D., N.K.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

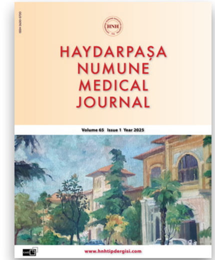
References

1. Guarino A, Lo Vecchio A, Dias JA, Berkley JA, Boey C, Bruzzese D, et al. Universal recommendations for the management of acute diarrhea in nonmalnourished children. J Pediatr Gastroenterol Nutr 2018;67:586–93. [CrossRef]
2. Flynn TG, Olortegui MP, Kosek MN. Viral gastroenteritis. Lancet 2024;403:862–76. [CrossRef]
3. Manouana GP, Nguema-Moure PA, Mbong Ngwese M, Bock CT, Kremsner PG, et al. Genetic diversity of enteric viruses in children under five years old in Gabon. Viruses 2021;13:545. [CrossRef]
4. Rossouw E, Brauer M, Meyer P, du Plessis NM, Avenant T, Mans J. Virus etiology, diversity and clinical characteristics in South African children hospitalised with gastroenteritis. Viruses 2021;13:215. [CrossRef]
5. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the sustainable development goals. Lancet Child Adolesc Health 2022;6:106–15. [CrossRef]
6. GBD 2016 Diarrhoeal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018;18:1211–28.
7. Stuempfig ND, Tobin EH, Seroy J. Viral gastroenteritis. 2025. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
8. King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 2003;52:1–16.
9. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210. Erratum in: Lancet 2017;390:e38.
10. Genç BY, Özüdoğru O, Acer Ö. The frequency of rotavirus and adenovirus in case of gastroenterit observed in Siirt region. Gevher Nesibe J Med Health Sci 2022;7:23–8. [Article in Turkish]
11. Vural DG, Torun EG, Bıyık İ, Çaycı YT, Bilgin K, Birinci A. Investigation of frequency of rotavirus and adenovirus in patients with acute gastroenteritis. Kırıkkale Üniv Tıp Fak Derg 2022;24:289–94. [Article in Turkish] [CrossRef]
12. Turna G, Sezgin FM, İlanbey B, Babaoğlu ÜT, Ünlü E. Retrospective evaluation of laboratory tests of patients with rotavirus and adenovirus positivity in Kırşehir province. Ahi Evran Med J 2020;4:103–8. [Article in Turkish] [CrossRef]
13. Aytaç Ö, Şenol FF, Oner P, Erkmen N, Aslan R, Doğukan M et al. Rotavirus and adenovirus frequency in acute gastroenteric diseases. Türk Hij Den Biyol Derg 2020;77:179–84. [Article in Turkish] [CrossRef]
14. Gündüz A. Prevalence of rotavirus-adenovirus positivity: 5-year retrospective evaluation. J Med Topics Updates 2022;1:50–3. [Article in Turkish]
15. Sert S, Erayman B. Frequency and seasonal distribution of adenovirus and rotavirus in children diagnosed with acute gastroenteritis: A single centre experience. J Contemp Med 2023;13:353–9. [CrossRef]
16. Aktaş O, Aydin H, Timurkan MO. A molecular study on

the prevalence and coinfections of Rotavirus, Norovirus, Astrovirus and Adenovirus in children with gastroenteritis. Minerva Pediatr 2019;71:431–7. [CrossRef]
17. De Grazia S, Bonura F, Bonura C, Mangiaracina L, Filizzolo C, Martella V, et al. Assessing the burden of viral co-infections in acute gastroenteritis in children: An eleven-year-long investigation. J Clin Virol 2020;129:104513. [CrossRef]
18. Vu DL, Sabrià A, Aregall N, Michl K, Rodriguez Garrido V, Goterris L, et al. Novel human astroviruses: prevalence and association with common enteric viruses in undiagnosed gastroenteritis cases in Spain. Viruses 2019;11:585. [CrossRef]
19. Duran H, Yücel FY. Frequency of rotavirus and adenovirus in children with diarrhea. J Contemp Med 2023;13:724–8. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.32815
Haydarpasa Numune Med J 2025;65(4):369–376



hnhtipdergisi.com

ORIGINAL ARTICLE

The Relationship Between C-Reactive Protein to Albumin Ratio and Heart Failure in Patients with Atrial Fibrillation

Ayça Arslan[1], Doğan İliş[1], İnanç Artaç[1], Muammer Karakayalı[1], Timor Omar[1], Ezgi Güzel[1], Özcan Yağcıbulut[2], Yavuz Karabağ[1], İbrahim Rencüzoğulları[1]

[1]Department of Cardiology, Kafkas University Faculy of Medicine, Kars, Türkiye
[2]Department of Cardiology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye

Abstract

Introduction: Heart failure (HF) is associated with morbidity, mortality, and diminished quality of life. One of the most common etiological factors for HF is atrial fibrillation (AFib). The development of HF during the course of AFib causes patients both to reveal HF's ominous outcomes and the worsening of AFib. Previous studies have shown that HF is associated with systemic inflammation, elevated C-reactive protein (CRP), and decreased serum albumin (SA) levels; however, the predictive value of the CRP to SA ratio (CAR) for diagnosing HF in patients with AFib is not fully demonstrated. This study aims to elucidate the diagnostic value of CAR in predicting the development of HF in AFib patients.

Methods: This retrospective study comprised 279 patients with permanent AFib attending our outpatient clinic. The study population was categorized into two groups based on left ventricular ejection fraction (LVEF): patients with LVEF <40% and those with LVEF ≥40%.

Results: In the study cohort, 75 patients (26.9%) were identified with HF with reduced ejection fraction (HFrEF). Patients with HFrEF exhibited elevated levels of neutrophils, CRP, and CAR, along with increased left ventricular end-diastolic diameter (LVEDD) and left atrial volume index (LAVI). Multivariate analyses demonstrated that LVEDD, LAVI, CRP, and CAR (OR: 1.414, 95% CI: 1.182–1.692; p<0.001) were independent predictors of HFrEF in patients with AFib.

Discussion and Conclusion: The relationship between HF presence and CAR in AFib patients has been revealed in the present study. Evaluation of CAR may be useful in diagnosing or anticipating HF in the course of AFib.

Keywords: Albumin; atrial fibrillation; C-reactive protein; heart failure.

Heart failure (HF), a prevalent chronic condition worldwide, is linked to increased mortality and morbidity rates, frequent hospitalizations, diminished quality of life, and compromised functional status [1]. Various clinical conditions, including ischemic heart disease, hypertension, valvular pathologies, and arrhythmias, can significantly contribute to the development of HF [2–4].

Atrial fibrillation (AFib) stands out as the most prevalent rhythm disorder among the adult population [5]. Previous studies have established its association with an elevated risk of stroke [6], cognitive dysfunction [7], and HF [8]. Although the role of inflammation has been previously demonstrated in the onset and perpetuation of AFib [9–11], the specific impact of inflammatory status and the

Correspondence: Ayça Arslan, M.D. Department of Cardiology, Kafkas University Faculy of Medicine, Kars, Türkiye
Phone: +90 506 810 31 76 **E-mail:** hivda.arslan@hotmail.com
Submitted Date: 01.07.2025 **Revised Date:** 26.08.2025 **Accepted Date:** 15.09.2025
Haydarpaşa Numune Medical Journal

role of inflammatory markers in the development of HF in patients with AFib remain unclear.

Recent studies have shown that increased C-reactive protein (CRP) and low serum albumin (SA) levels can be used as biomarkers of systemic inflammation and are associated with adverse cardiovascular events [12,13]. Furthermore, many studies have demonstrated that the CRP/SA ratio (CAR) is more sensitive than these two parameters separately in predicting systemic inflammatory status and adverse outcomes [12,14]. However, the role of these inflammatory parameters in the diagnosis of HF in AFib patients is not clear. Therefore, this study aims to elucidate the diagnostic value of CAR in the diagnosis of HF in patients with AFib.

Materials and Methods

Study Population

This retrospective study enrolled 279 consecutive patients over 18 years of age with atrial fibrillation (AFib) who presented to our outpatient clinic between 2022 and 2023. Patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention, malignancy, or active infection were excluded from the study. Additionally, patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or evidence of hepatopathy (ALT/AST >3 times the upper limit of normal) were excluded. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki.

Data Collection

Patients' baseline clinical and demographic characteristics, along with their medical histories, were extracted from hospital records. Upon admission, all patients underwent complete blood counts and blood biochemical analyses. Laboratory variables, including hemoglobin, blood glucose, creatinine, serum albumin (SA), and C-reactive protein (CRP) levels, were documented. The CRP to SA ratio (CAR) was calculated. Electrocardiograms were recorded upon admission, and AFib was defined according to the current guidelines [15]. Echocardiographic parameters were obtained from the Philips Epic 7c echocardiography device, following the recommendations of the American Society of Echocardiography. Left ventricular ejection fraction (LVEF) was determined using Simpson's rule from left ventricular end-diastolic and end-systolic volumes in apical four- and two-chamber views. Left atrial (LA) volume was determined using the biplane method of disks (modified Simpson's rule) with apical four-chamber and apical two-chamber views at ventricular end-systole (maximum LA size). The LA volume index was calculated by dividing LA volume by body surface area. All echocardiographic measurements were obtained by averaging five beats due to the presence of AFib [15,16].

Statistical Analyses

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). The normality of the data was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution were presented as mean±standard deviation and compared using analysis of variance. Non-normally distributed data were expressed as median (0.25–0.75 percentile) values and compared using the Kruskal–Wallis H-test. Categorical variables were reported as numbers (percentages) and compared using Fisher's exact test or the χ^2 test.

The risk factors for LVEF <40% were analyzed using multivariate Cox proportional hazard analyses of variables that showed statistically significant associations with mortality in univariate analyses. Multicollinearity between CAR and CRP and SA levels was assessed using the eigenvalue and condition index. Linearity was tested by interacting with the logarithmic transformation of each parameter. Multicollinearity was not observed. The receiver operating characteristic (ROC) curve was utilized to determine the best cut-off values of CAR for predicting LVEF using Youden's J statistic. Subsequently, the method proposed by DeLong et al. [17] was employed to compare the ROC curves of CAR, CRP, and SA for predicting LVEF. A p-value <0.05 indicated statistical significance.

Results

The study enrolled 279 patients diagnosed with AFib, with a mean age of 73±10 years, of whom 51.3% were female. Patients were categorized into two groups based on their LVEF: patients with LVEF < 40% (n=75, 26.9%) and patients with LVEF ≥ 40% (n=204, 73.1%). Among patients with LVEF < 40%, elevated levels of neutrophils, CRP, CAR, left atrial anterior-posterior (LA-AP) dimension, left atrial volume index (LAVI), and left ventricular end-diastolic diameter (LVEDD) were observed. Additionally, patients with LVEF < 40% exhibited lower levels of SA. Medication use, including beta-blockers, ACE inhibitors/ARBs, and spironolactone, showed no statistically significant differences between the groups. The distribution of patients' baseline characteristics, laboratory parameters, and echocardiographic findings is presented in Table 1.

Variables related to CAR were analyzed by dividing the study group into two based on the median value of

Table 1. Demographic, clinical, and laboratory characteristics of all patients with EF < 40 and EF ≥ 40 groups, with p-value

	EF<40 (n=75)		EF≥40 (n=204)		Total patients (n=279)		p
	n	%	n	%	n	%	
Age (years)	74±9		73±10		73±10		0.83
Female gender	32	44.0	111	53.9	143	51.3	0.08
Body surface area (m^2)	1.95±0.18		1.97±0.20		1.96±0.19		0.57
Hypertension	58	77.3	154	75.5	212	76.0	0.75
Diabetes mellitus	27	36.0	69	33.8	96	34.4	0.73
Hyperlipidemia	24	32.0	73	35.8	97	34.8	0.55
Smoking	12	16.0	38	18.6	50	17.9	0.61
ACEi/ARB (%)	63	84.0	149	73.0	212	76.0	0.07
DHP-CCB (%)	15	20.0	62	30.4	77	27.6	0.09
Beta-blocker (%)	57	76.0	159	77.9	216	77.4	0.73
Diltiazem/Verapamil (%)	11	14.7	15	7.4	26	9.3	0.06
Anticoagulant (%)							
Warfarin	18	24.0	52	25.5	70	25.1	0.79
Rivaroxaban	40	53.3	107	52.5	147	52.7	
Apixaban	6	8.0	20	9.8	26	9.3	
Dabigatran	3	4.0	4	2.0	7	2.5	
Edoxaban	8	10.6	21	10.3	29	10.4	
Statin (%)	28	37.3	76	37.0	104	37.3	0.99
SGLT-2 inh. (%)	11	14.7	18	8.8	29	10.4	0.16
Digoxin (%)	20	26.7	44	21.57	64	22.9	0.37
WBC (10^3/uL)	8.75±3.05		8.28±3.25		8.41±3.20		0.09
Neutrophil (10^3/uL)	6.03±2.39		5.43±2.64		5.59±2.59		0.01
Hemoglobin (g/dL)	13.19±2.33		13.34±2.02		13.3±2.1		0.69
Platelet (10^3/uL)	222±81		235±140		231±127		0.31
Creatinine (mg/dL)	1.15±0.39		1.10±0.42		1.11±0.42		0.08
Glucose (mg/dL)	126±48		131±59		130±56		0.85
Sodium (mmol/L)	138±3.6		139±3.3		139±3.4		0.02
Potassium (mmol/L)	4.07±0.5		4.17±0.51		4.14±0.51		0.15
CRP (mg/L)	27.6 (9.1–51.2)		7.4 (3.3–19.1)		9.6 (4.1–29.9)		<0.001
Serum albumin (g/L)	35.1±3.5		37.1±3.8		36.6±3.8		<0.001
CRP/serum albumin ratio	0.82 (0.34–1.51)		0.19 (0.09–0.51)		0.28 (0.12–0.84)		<0.001
Total cholesterol (mg/dl)	151.87±51.91		155.78±44.18		154.73±46.32		0.38
LDL-C (mg/dl)	94.56±40.42		93.16±35.48		93.54±36.8		0.87
Triglycerides (mg/dl)	98±43		105±66		103±60		0.85
HDL-C (mg/dl)	40.2±11.9		42.09±12.57		41.58±12.40		0.08
TSH (mIU/L)	1.20 (0.69–2.07)		1.40 (0.85–2.16)		1.39 (0.78–2.13)		0.32
Heart rate (bpm)	94±15		91±15		92±15		0.16
EF (%)	31.1±6.3		53.1±6.3		47.2±11.6		<0.001
LA-AP dimension (cm)	4.6±0.8		4.4±0.7		4.4±0.7		0.013
LAVI (mL/m^2)	39.0±14.6		33.4±14.2		34.9±14.5		0.003
LVEDD (cm)	5.1±0.8		4.7±0.8		4.8±0.8		0.001

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB: Dihydropyridine calcium channel blocker; SGLT 2 inh: Sodium glucose co-transporter 2 inhibitor; CRP: C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TSH: Thyroid Stimulating Hormone; WBC: White blood cell; LA-AP: Left atrial anterior-posterior; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter.

CAR (0.2778). Patients with CAR≤0.2778 were assigned to the low CAR group (n=139 patients), and those with CAR>0.2778 were assigned to the high CAR group (n=140 patients). The baseline characteristics of all patients, as well as those of the low and high CAR groups, are shown in Table 2. Patients with CAR>0.2778 were older and had

Table 2. Demographic, clinical, and laboratory characteristics of the study population according to C-reactive protein/serum albumin ratio

	CRP/albumin ratio ≤0.2778 (n=139)		CRP/albumin ratio >0.2778 (n=140)		p
	n	%	n	%	
Age (years)	72±10		75±9		0.002
Female gender	71	51.1	72	51.4	0.954
Body surface area (m^2)	1.97±0.20		1.96±0.19		0.896
Hypertension	105	75.5	107	76.4	0.862
Diabetes mellitus	48	34.5	48	34.3	0.965
Hyperlipidemia	51	36.7	46	32.9	0.502
Smoking	27	19.4	23	16.4	0.515
ACEi/ARB (%)	100	71.9	112	80.0	0.116
DHP-CCB (%)	37	26.6	40	28.6	0.716
Beta-blocker (%)	110	79.1	106	75.7	0.495
Diltiazem/Verapamil (%)	8	5.8	18	12.9	0.042
Anticoagulant (%)					
Warfarin	35	25.2	35	25.0	0.586
Rivaroxaban	70	50.4	77	55.0	
Apixaban	14	10.1	12	8.6	
Dabigatran	3	2.2	4	2.9	
Edoxaban	17	12.2	12	8.6	
Statin (%)	47	33.8	57	40.7	0.234
SGLT-2 inh. (%)	14	10.1	15	10.7	0.861
Digoxin (%)	27	19.4	37	26.4	0.165
WBC (10^3/uL)	7.86±2.39		8.95±3.77		0.019
Neutrophil (10^3/uL)	4.94±2.00		6.24±2.93		<0.001
Hemoglobin (g/dL)	13.63±1.99		12.97±2.16		0.012
Platelet (10^3/uL)	218 (177–268)		213 (176–267)		0.714
Creatinine (mg/dL)	1.01±0.27		1.21±0.50		<0.001
Glucose (mg/dL)	124.4±46.8		135.7±63.8		0.111
Sodium (mmol/L)	139.6±2.8		138.1±3.7		<0.001
Potassium (mmol/L)	4.1±0.5		4.1±0.5		0.657
CRP (mg/L)	4.2 (2.2–7.2)		29.3 (14.9–61.1)		<0.001
Serum albumin (g/L)	37.26±3.78		35.96±3.79		<0.001
CAR	0.12 (0.063–0.185)		0.84 (0.44–1.79)		<0.001
Total cholesterol (mg/dl)	158.25±45.54		151.23±46.97		0.079
LDL-C (mg/dl)	94.06±3556		93.02±38.12		0.491
Triglycerides (mg/dl)	87 (68–132)		81 (65–110)		0.063
HDL-C (mg/dl)	43.69±12.39		39.48±12.10		0.002
TSH (mIU/L)	1.4 (0.9–2.0)		1.4 (0.7–2.4)		0.939
Heart rate (bpm)	88.6±15.5		94.7±13.1		0.001
LA-AP dimension (cm)	4.4±0.8		4.4±0.7		0.386
LAVI (mL/m^2)	33.8±14.4		36.1±14.5		0.187
LVEDD (cm)	4.7±0.7		4.8±0.9		0.242
EF (%)	51.2±9.2		43.3±12.4		<0.001

ACEi: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blocker; DHP-CCB: Dihydropyridine calcium channel blocker; SGLT 2 inh: Sodium glucose co-transporter 2 inhibitor; CRP: C-reactive protein; CAR: CRP albumin ratio; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TSH: Thyroid Stimulating Hormone; WBC: White blood cell; LA-AP: Left atrial anterior-posterior; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter.

higher levels of white blood cells, neutrophils, creatinine, CRP, and heart rate, as well as lower levels of hemoglobin, sodium, SA, and HDL cholesterol.

Logistic regression analyses were performed to determine independent predictors of heart failure with reduced ejection fraction (HFrEF) using variables that had a p-value

Table 3. Univariate and multivariate logistic regression analysis of biochemical and echocardiographic parameters for diagnosis of heart failure prediction

	Univariate analysis of HFrEF (EF<40)			Multivariate analysis of HFrEF (EF<40)		
	Odds ratio	**95% CI**	**p**	**Odds ratio**	**95% CI**	**p**
Neutrophil	1.088	0.986–1.200	0.092	–	–	–
Na	0.917	0.848–0.991	0.029	–	–	–
LA-AP	1.544	1.064–2.241	0.022			
Albumin	0.872	0.809–0939	<0.001			
CRP	1.012	1.005–1.019	0.001	0.919	0.875–0.966	0.001
LAVI	1.026	1.008–1.045	0.005	1.029	1.008–1.049	0.006
LVEDD	1.849	1.296–2.640	0.001	1.887	1.278–2.784	0.001
CAR	1.680	1.315–2.148	<0.001	1.414	1.182–1692	<0.001

HFrEF: Heart failure with reduced ejection fraction; LA-AP: Left atrial anterior-posterior; CRP: C-reactive protein; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter; CAR: C-reactive protein serum albumin ratio; EF: Ejection raction; CI: Confidence Interval; Na: Sodium

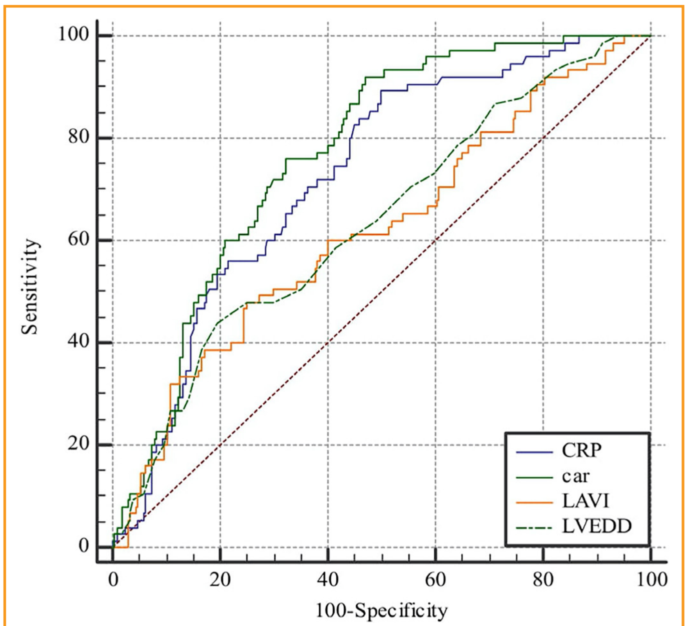


Figure 1. Receiver operating characteristic curves to detect the best variable for predicting HFrEF.

CRP: C-reactive protein; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter.

<0.1 in univariate analysis (neutrophil, Na, LA-AP dimension, albumin, CRP, LAVI, LVEDD, and CAR). In the multivariate analysis, independent predictors of HFrEF in patients with AFib were CRP, LAVI, LVEDD, and CAR (OR, 1.414; 95% CI, 1.182–1.692; p<0.001), as shown in Table 3.

The optimal cut-off value of CAR for predicting HFrEF was >0.2077, with a sensitivity of 92% and a specificity of 52.9% (area under the curve (AUC): 0.768; 95% CI: 0.714–0.816). To assess whether CAR has additional prognostic value over CRP, LAVI, and LVEDD, ROC curve comparison analyses were performed. ROC curve analyses revealed that CAR was a better predictor of HFrEF than CRP (AUC: 0.725, 95% CI: 0.669–0.777), LAVI (AUC: 0.616, 95% CI: 0.557–0.674), and LVEDD (AUC: 0.634, 95% CI: 0.574–0.691) (Fig. 1).

Discussion

Our findings underscore the notable association between CAR levels and HF, affirming CAR as an independent predictor for HFrEF in patients with AFib. Furthermore, CAR emerges as a more robust predictor for diagnosing HFrEF in patients with AFib.

HF is associated with poor survival, increased hospitalizations, financial burden, and diminished quality of life [1]. Its prevalence among adults ranges from 1% to 2%, with a notable increase with age, reaching over 10% in individuals aged 70 years or older [18–20]. Additionally, it carries a mortality rate of nearly 67% within five years post-diagnosis [21]. Given its widespread occurrence and adverse outcomes, the etiology of HF has been extensively studied. One of the most common etiological factors for HF is AFib [2,3], which leads to progressive atrial abnormalities and adversely affects ventricular function [22,23]. While stroke remains a significant complication of AFib, hospitalization rates due to HF are two to four times higher than those for stroke in patients with both AFib and HF undergoing oral anticoagulation therapy [24]. Furthermore, the leading cause of mortality among anticoagulated patients with AFib is attributed to HF, accounting for deaths resulting from progressive HF (14%) or sudden cardiac death (21%), rather than thromboembolism-related deaths (8%) [25,26]. In parallel to current knowledge [15], in our study, which was conducted on AFib patients, HF was observed at 26.8%.

Many demographic, biochemical, hematological, electrocardiographic, and morphological parameters have been shown to be associated with the development of HFrEF in AFib patients [3,4,8]. Although in our study there was no difference in demography between the two groups, in alignment with previous studies, impaired left atrial and left ventricular indexes were associated with HFrEF [4,27]. The impairment of left ventricular indexes, which is known as remodeling, mostly occurs by the loss of synchronized atrial contraction, impaired myocardial perfusion due to microvascular coronary dysfunction, and irregular/high ventricular rates [28,29].

In addition to remodeling mechanisms, HF is also linked to systemic inflammation and compromised endothelial function [30]. Previous studies have shown that in patients with HF, activated neutrophils may release significant quantities of pro-inflammatory cytokines and oxidative stress substances, potentially playing a role in the advancement of cardiovascular disease and the onset of HF [31]. Likewise, in the present study, neutrophil levels were higher in patients with HFrEF.

CAR is a parameter obtained by combining CRP and SA and has been demonstrated to have both diagnostic and prognostic effectiveness in acute coronary syndrome, pulmonary embolism, and HF [12,14,32]. In our study, patients had higher CAR and lower hemoglobin levels. The pathophysiologic mechanism of the lower hemoglobin levels could be attributed to the pro-inflammatory cytokines that influence iron metabolism, iron turnover, and ferritin synthesis, leading to low serum iron levels without clear evidence of iron deficiency [33]. Furthermore, in the present study, patients who had higher creatinine levels also had higher CAR levels, representing enhanced inflammation. Associations between damaged renal function and inflammation have been shown previously [34].

Earlier studies have established a direct correlation between elevated CRP levels and the progression of HF. It independently predicts adverse cardiovascular outcomes, regardless of whether the etiology is ischemic or non-ischemic [35,36]. SA acts as a negative acute-phase reactant, and its serum concentrations are anticipated to decrease in pro-inflammatory conditions, such as HF. Individuals with advanced HF may develop hypoalbuminemia due to suppressed appetite and reduced bowel absorption resulting from severe congestion, apart from basal inflammation [36]. Not only in HF but also in AFib, inflammation plays a crucial role in both the initiation and the progression of AFib. It is not newly documented that CRP and SA are associated with adverse events in AFib patients [37,38]. However, as a merged parameter, CAR has been shown to be superior in predicting adverse outcomes both in HF [14] and AFib [37] compared to CRP and SA alone. Nonetheless, the role of CAR in predicting HF in the course of AFib is not yet clear. The reason why inflammation is associated with HF could be attributed mainly to the myopathic effect of inflammation, the alteration of atrial fibroblast-cardiomyocyte distribution, and the promotion of atrial remodeling [39]. Increased wall stress results in the accumulation of damaged mitochondria and apoptogenic proteins, which then promote cardiomyocyte death in the failing heart through activation in recruited macrophages and neutrophils [40].

In our study, we hypothesized that CAR may be associated with the presence of HF in AFib patients due to its role in both AFib and HF. Indeed, according to our results, CAR was found to be an independent predictor of HF. Moreover, in accordance with studies that compare the predictive power of several parameters [12,14], in our study, CAR was stronger in predicting HF compared to CRP and SA in patients with AFib.

AFib, the most common arrhythmia in clinical practice, can lead to HF and facilitate cardiovascular mortality. Therefore, early diagnosis of HF is vital. CAR is an inexpensive, useful, and accessible parameter that could be used from the first contact onward to anticipate HF in patients with AFib.

Limitations of the Study

The present study has several limitations. First, it had a retrospective design and was based on a registry analysis. Previous studies have shown that HFrEF is linked to systemic inflammation. However, it is not fully clear which one initiates or potentiates the other. Due to the study's design, it cannot be conclusively stated that the high CAR level is the cause of HFrEF or vice versa, even though the relationship between the presence of HFrEF and high CAR level in AFib patients has been well established. Second, we did not evaluate energy expenditure and nutrient intake, which are potential factors influencing serum albumin levels. Finally, the study group included a relatively small number of patients. A larger volume of patients may improve the results.

Conclusion

Given the unfavorable outcomes associated with AFib, predicting newly emerging HFrEF may be crucial in the course of AFib. Although the association between HFrEF and inflammation has been clearly established, the relationship between the presence of HFrEF and CAR in AFib patients has been revealed for the first time in the present study. Based on evidence that CAR is a better predictor than CRP or SA, evaluating CAR may be useful in diagnosing or anticipating HFrEF in the course of AFib. While it is documented that HFrEF and inflammation may potentiate each other in AFib patients, high CAR levels should be monitored for HFrEF during the course of AFib.

Ethics Committee Approval: The study was approved by Kafkas University Ethics Committee (No: 80576354-050-99/397, Date: 31.01.2024).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – A.A., İ.R., D.İ., Ö.Y.; Design – A.A., E.G., D.İ., T.O., Ö.Y., M.K.; Supervision – D.İ., Ö.Y., A.A.; Data collection and/or processing – E.G., T.O., M.K.; Analysis and/or interpretation – İ.A., Y.K., T.O.; Literature search – Y.K., İ.A., E.G., M.K.; Writing – A.A., İ.R.; Critical review – A.A., İ.R., İ.A., Y.K.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

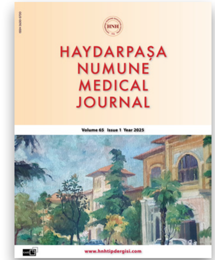
1. Lee JK, Son YJ. Gender differences in the impact of cognitive function on health literacy among older adults with heart failure. Int J Environ Res Public Health 2018;15:2711. [CrossRef]
2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13:368–78. [CrossRef]
3. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 2016;68:2217–28. [CrossRef]
4. Wijesurendra RS, Casadei B. Atrial fibrillation: effects beyond the atrium? Cardiovasc Res 2015;105:238–47. [CrossRef]
5. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American heart association. Circulation 2019;139:e56–28.
6. Ceornodolea AD, Bal R, Severens JL. Epidemiology and management of atrial fibrillation and stroke: review of data from four european countries. Stroke Res Treat 2017;2017:8593207. [CrossRef]
7. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med 2013;158:338–46. [CrossRef]
8. Ziff OJ, Carter PR, McGowan J, Uppal H, Chandran S, Russell S, et al. The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: Insights from the, United Kingdom ACALM registry. Int J Cardiol 2018;252:117–21. [CrossRef]
9. Harada M, Nattel S. Implications of inflammation and fibrosis in atrial fibrillation pathophysiology. Card Electrophysiol Clin 2021;13:25–35. [CrossRef]
10. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015;12:230–43. [CrossRef]
11. Boos CJ. Infection and atrial fibrillation: inflammation begets AF. Eur Heart J 2020;41:1120–2. [CrossRef]
12. Çağdaş M, Rencüzoğullari I, Karakoyun S, Karabağ Y, Yesin M, Artaç I, et al. Assessment of relationship between c-reactive protein to albumin ratio and coronary artery disease severity in patients with acute coronary syndrome. Angiology 2019;70:361–8. [CrossRef]
13. Yamada T, Haruki S, Minami Y, Numata M, Hagiwara N. The C-reactive protein to prealbumin ratio on admission and its relationship with outcome in patients hospitalized for acute heart failure. J Cardiol 2021;78:308–13. [CrossRef]
14. Çinier G, Hayıroğlu Mİ, Kolak Z, Tezen O, Yumurtaş AÇ, Pay L, et al. The value of C-reactive protein-to-albumin ratio in predicting long-term mortality among HFrEF patients with implantable cardiac defibrillators. Eur J Clin Invest 2021;51:e13550. [CrossRef]
15. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498. Erratum in: Eur Heart J 2021;42:507. Erratum in: Eur Heart J 2021;42:546–7. Erratum in: Eur Heart J 2021;42:4194.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63. [CrossRef]
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometric 1988;44:837–45. [CrossRef]
18. Authors/Task Force Members:; McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022;24:4–131. [CrossRef]
19. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure

incidence: a population-based study of 4 million individuals. Lancet 2018;391:572–80. [CrossRef]
20. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242–52. [CrossRef]
21. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC Heart Fail 2018;6:678–85. [CrossRef]
22. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. Circ Arrhythm Electrophysiol 2008;1:62–73. [CrossRef]
23. Cha YM, Redfield MM, Shen WK, Gersh BJ. Atrial fibrillation and ventricular dysfunction: a vicious electromechanical cycle. Circulation 2004;109:2839–43. [CrossRef]
24. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail 2013;6:451–60. [CrossRef]
25. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013;128:2192–201. [CrossRef]
26. Sharma A, Hijazi Z, Andersson U, Al-Khatib SM, Lopes RD, Alexander JH, et al. Use of biomarkers to predict specific causes of death in patients with atrial fibrillation. Circulation 2018;138:1666–76. [CrossRef]
27. Shah MA, Soofi MA, Jafary Z, Alhomrani A, Alsmadi F, Wani TA, et al. Echocardiographic parameters associated with recovery in heart failure with reduced ejection fraction. Echocardiography 2020;37:1574–82. [CrossRef]
28. Ling LH, Taylor AJ, Ellims AH, Iles LM, McLellan AJ, Lee G, et al. Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation. Heart Rhythm 2013;10:1334–9. [CrossRef]
29. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7:31–8. [CrossRef]
30. Drera A, Rodella L, Brangi E, Riccardi M, Vizzardi E. Endothelial dysfunction in heart failure: what is its role? J Clin Med 2024;13:2534. [CrossRef]
31. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science 2013;339:161–6. [CrossRef]
32. Artac I, Omar T, Karakayali M, Ilis D, Karabag Y, Rencuzogullari I. Assessment of the relationship between C-reactive protein to albumin ratio and late-term mortality in patients with acute pulmonary embolism. Asian Cardiovasc Thorac Ann 2023;31:332–9. [CrossRef]
33. Roy CN, Andrews NC. Anemia of inflammation: the hepcidin link. Curr Opin Hematol 2005;12:107–11. [CrossRef]
34. Baer PC, Koch B, Geiger H. Kidney inflammation, injury and regeneration 2020. Int J Mol Sci 2021;22:5589. [CrossRef]
35. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 2005;112:1428–34. [CrossRef]
36. Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. Circulation 2016;133:1696–703. [CrossRef]
37. Abuş S. C-reactive protein to albumin ratio in atrial fibrillation. Eur Res J 2023;9:674–9. [CrossRef]
38. Aronson D, Boulos M, Suleiman A, Bidoosi S, Agmon Y, Kapeliovich M, et al. Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. Am J Cardiol 2007;100:753–7. [CrossRef]
39. Wijesurendra RS, Casadei B. Mechanisms of atrial fibrillation. Heart 2019;105:1860–7. [CrossRef]
40. Nishida K, Otsu K. Sterile inflammation and degradation systems in heart failure. Circ J 2017;81:622–8. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.95815
Haydarpasa Numune Med J 2025;65(4):377–383

ORIGINAL ARTICLE



hnhtipdergisi.com

Prevalence and Associated Factors of Urinary Incontinence among Adults Attending a Family Medicine Clinic

Yağmur Gökseven Arda[1], Abdullah Ozan Polat[2], Güzin Zeren Öztürk[1]

[1]Department of Family Medicine, University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Türkiye
[2]Department of Family Medicine, University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye

Abstract

Introduction: This study aimed to determine the prevalence and subtypes of urinary incontinence (UI), as well as associated demographic and clinical factors, among adults attending a family medicine outpatient clinic.

Methods: A two-phase cross-sectional study was conducted between January and April 2018. In Phase 1, 794 participants aged 18 years and older completed the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF). Those identified with UI were invited to participate in Phase 2, in which a 25-item structured questionnaire was administered via face-to-face interviews to explore contributing factors. All statistical analyses were conducted using SPSS version 25.0. A p-value of less than 0.05 was considered statistically significant.

Results: Of the participants, 26.9% reported UI. The most common subtype was mixed incontinence (14.4%), followed by urge (6.5%) and stress incontinence (5.9%). UI was significantly more prevalent among women ($p<0.001$) and individuals aged 65 and older ($p<0.001$). In the second phase (n=130), mixed incontinence remained the predominant type (51.5%). Significant associations were found between UI type and menopausal status ($p=0.032$) and the sensation of incomplete bladder emptying ($p=0.016$). Although the prevalence of urinary incontinence is high, only 16.9% of affected individuals sought medical care. Most attributed this to feelings of embarrassment or perceiving the condition as unimportant.

Discussion and Conclusion: Urinary incontinence is a common but underreported condition that significantly affects quality of life, particularly among older adults and women. Routine screening in primary care settings is essential for early detection and effective management.

Keywords: Aging; mixed incontinence, prevalence; primary care; urinary incontinence.

Urinary incontinence (UI), defined as the involuntary leakage of urine, is a common yet underdiagnosed condition that significantly impacts quality of life. Reported prevalence rates vary widely, ranging from 5% to 70% across different populations and age groups, depending on study design and diagnostic criteria [1]. UI is generally classified into three primary subtypes: stress incontinence, urge incontinence, and mixed incontinence, each with distinct etiological and clinical characteristics [2].

The condition is more frequently reported among women and older adults, largely due to anatomical and physiological factors such as pelvic floor damage during childbirth and postmenopausal estrogen deficiency [3]. Although its high prevalence and negative influence on physical, emotional,

Correspondence: Abdullah Ozan Polat, M.D. Department of Family Medicine, University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye
Phone: +90 506 760 03 27 **E-mail:** ozanpolat1987@gmail.com
Submitted Date: 28.05.2025 **Revised Date:** 19.09.2025 **Accepted Date:** 20.09.2025
Haydarpaşa Numune Medical Journal

and social well-being, UI is often underreported by patients due to embarrassment or the misconception that it is a natural consequence of aging. This underreporting contributes to low diagnosis and treatment rates, leading to a significant burden on both individuals and healthcare systems [4].

Understanding the epidemiology of UI, including its associated risk factors and behavioral correlates, is essential for improving early diagnosis and preventive strategies, particularly in primary care settings. However, studies that evaluate the prevalence and contributing factors of UI in general adult populations attending family medicine clinics remain limited in number and scope.

Therefore, the aim of this study was to assess the prevalence and subtypes of urinary incontinence and to identify associated sociodemographic and clinical variables in individuals over the age of 18 who presented to a family medicine outpatient clinic.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted between January 1 and April 1, 2018, at the Family Medicine outpatient clinic of a tertiary research hospital. The study was carried out in two distinct phases. Ethical approval was obtained from the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Approval No: 1763, Date: November 14, 2017), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Study Population and Sampling

The study included adult patients aged 18 years and older who attended the family medicine clinic for any reason and agreed to participate. Exclusion criteria were as follows: individuals under 18 years of age, those with mental or communication disabilities, refusal to participate, and incomplete or erroneous questionnaire data.

Of the 3,124 individuals who visited the clinic during the study period, 794 participants met the inclusion criteria and were enrolled in Phase 1. Based on their responses to the ICIQ-SF, 214 participants were identified as having UI. In Phase 2, 130 of these individuals agreed to participate in a more detailed face-to-face interview.

Sample size was calculated using G*Power 3.1 software, with a power of 95%, a significance level of 0.05, and an effect size of 0.3. The minimum required sample size was determined as 124 individuals. The final sample exceeded this number, enhancing the study's statistical robustness.

Data Collection Tools and Procedures

In Phase 1, participants completed the International Consultation on Incontinence Questionnaire – Short Form (ICIQ-SF), a validated and widely used tool for assessing the frequency, severity, and impact of UI on quality of life. The Turkish version of the ICIQ-SF was validated by Çetinel et al. [5,6]. It consists of six items scored between 0 and 21, with higher scores indicating greater symptom severity [7].

In Phase 2, individuals who screened positive for UI completed a 25-item structured questionnaire administered through face-to-face interviews. This questionnaire collected detailed sociodemographic data, medical and surgical history, medication use, reproductive history (for females), and urinary symptom characteristics. UI was categorized into three types: stress, urge, and mixed incontinence, based on self-reported symptom patterns.

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated as mean and standard deviation for continuous variables, and as frequencies and percentages for categorical variables. For non-normally distributed variables, median values (min–max) were reported. Chi-square was used for comparing proportions. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Non-normally distributed variables were analyzed using the Mann–Whitney U test or Kruskal–Wallis test, while normally distributed variables were compared using One-Way Welch ANOVA. For post-hoc analyses, Tukey's HSD test was used following parametric ANOVA, while non-parametric comparisons between more than two groups were performed using the Kruskal–Wallis test, and when significant, post-hoc pairwise comparisons were conducted with Dunn's test using Bonferroni correction for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

First Phase Results

A total of 794 individuals participated in the study. Among them, 457 (57.6%) were between 40–65 years old. There were 594 women (74.8%). A history of urinary incontinence was reported by 214 participants (26.9%), while 590 participants (74.3%) had never experienced UI.

Participants reported varying frequencies and volumes of UI: 70 (8.8%) experienced UI once a week or less, 43 (5.4%) two or three times a week, 146 (18.4%) reported losing a small amount of urine, and 34 (4.3%) reported losing a large amount. The impact of UI on daily life was rated on a scale from 0 to 10, with 41 participants (5.2%) rating it a 10.

Regarding UI types, 52 participants (6.5%) had urge UI, 47 (5.9%) had stress UI, and 115 (14.4%) had mixed UI. The average ICIQ-SF score for the group was 10.83±5.37.

- Women with stress incontinence (n=47) had an average ICIQ-SF score of 5.87±0.41 (min: 3, max: 15).
- Women with urge incontinence (n=52) had an average ICIQ-SF score of 9.96±0.74 (min: 3, max: 21).
- Women with mixed incontinence (n=115) had an average ICIQ-SF score of 13.25±0.43 (min: 3, max: 21).

Among women with a history of UI (n=185), 95 (51.4%) had mixed incontinence, 47 (25.4%) had urge incontinence, and 43 (23.2%) had stress incontinence. Among men with a history of incontinence (n=29), 20 (69.0%) had mixed incontinence, 5 (17.2%) had urge incontinence, and 4 (13.8%) had stress incontinence.

Women had higher rates of incontinence frequency, volume, impact on daily life, history of incontinence, urgency, stress incontinence, and mixed incontinence compared to men ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.037$, respectively) (Table 1).

Table 1. Comparison of ICIQ-SF characteristics by gender and age groups of all participants

	Gender					Age						
	Male		Female			Under 40 years old		40-64 years old		65 years and older		
	n	%	n	%	p	n	%	n	%	n	%	p
Urinary incontinen-ce status												
Incontinence present	29	14.5	185	31.1	**<0.001**	27	17.2	107	23.4	80	44.4	**<0.001**
Never Incontinent	171	85.5	409	68.9		130	82.8	350	76.6	100	55.6	
How often do you leak urine?												
Never	171	85.5	409	68.9	**<0.001**	130	82.8	350	76.6	100	55.6	**<0.001**
About once a week or less often	11	5.5	59	9.9		14	8.9	43	9.4	13	7.2	
Two or three times a week	4	2.0	39	6.6		5	3.2	20	4.4	18	10	
About once a day	3	1.5	29	4.9		4	2.5	14	3.1	14	7.8	
Several times a day	7	3.5	29	4.9		3	1.9	16	3.5	17	9.4	
All the time	4	2.0	29	4,9		1	0.6	14	3.1	18	10	
How much urine do you usually leak? (whether you wear protection or not)												
None	171	85.5	409	68.9	**<0.001**	130	82.8	350	76.6	100	55.6	**<0.001**
A small amount	21	10.5	125	21		21	13.4	77	16.8	48	26.7	
A moderate amount	3	1.5	31	5.2		5	3.2	15	3.3	14	7.8	
A large amount	5	2.5	29	4.9		1	0.6	15	3.3	18	10	
How significantly does urinary incontinence impact your daily life?												
5 points or less	184	92.0	489	82.3	**0.001**	148	94.3	402	88.0	123	68.3	**<0.001**
6 points or more	16	8.0	105	17.7		9	5.7	55	12.0	57	31.7	
Leaking urine before reaching the toilet												
None	181	90.5	475	80.0	**<0.001**	144	91.7	392	85.8	120	66.7	**<0.001**
Present	19	9.5	119	20.0		13	8.3	65	14.2	60	33.3	
Leaking urine when coughing or sneezing												
None	190	95.0	474	79.8	**<0.001**	141	89.8	393	86	130	72.2	**<0.001**
Present	10	5.0	120	20.2		16	10.2	64	14	50	27.8	
Mixed type UI												
None	180	90.0	499	84.0	**0.037**	146	93.0	413	90.4	120	66.7	**<0.001**
Present	20	10.0	95	16.0		11	7.0	44	9.6	60	33.3	
Total	200	100.0	594	100.0		157	100.0	457	100.0	180	100.0	

Chi-Square analysis. ICIQ-SF: International Consultation on Incontinence Questionnaire – Short Form; UI: Urinary incontinence.

There was a significant difference between ICIQ-SF scores and gender (Z=-4.618, U=49281.0, p<0.001), with women scoring higher than men (Table 2).

Participants aged 65 and older had higher frequencies, volumes, impacts on daily life, histories of incontinence, urgency, stress incontinence, and mixed incontinence compared to other age groups (p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively). The distribution of UI by age group is shown in Table 1.

As presented in Table 2, the Kruskal–Wallis test indicated a significant difference in ICIQ-SF scores across age groups (H=49.62, p<0.001), with the highest scores observed in those aged 65 and older. Post-hoc Dunn's test with Bonferroni correction revealed that patients who were 65 years and older had significantly higher scores compared with patients younger than 40 years (p<0.001). There was no significant difference in ICIQ-SF scores between patients younger than 40 years and those aged 40–64 years (p=0.183).

Second Phase Results

Of the 214 participants with a history of UI, 130 were included in the second phase of the study. Of these individuals, 115 (88.5%) were female, and the mean age was 61.49±13.39 years (min: 26, max: 97). When the distribution according to UI types was examined, 42 individuals (32.3%) were diagnosed with urge-type UI, 21 individuals (16.2%) with stress-type UI, and 67 individuals (51.5%) with mixed UI.

The mean number of pregnancies among female participants was 5.06±3.31 (min: 0, max: 21), the mean number of births was 3.53±2.27 (min: 0, max: 11), and the mean number of abortions was 1.33±1.87 (min: 0, max: 15). The mean age at first birth was 20.41±3.71 years (min: 13, max: 40), and eight women (7.0%) had never given birth. The vaginal birth rate was 81.7% (n=94), and the cesarean birth rate was 11.3% (n=13). Vaginal, rectal, or bladder prolapse was detected in 16.5% (n=19) of the women, and atrophic urethritis or vaginitis was detected in 33.0% (n=38). The menopause rate was 74.8% (n=86), while 25.2% (n=29) were still menstruating. A statistically significant relationship was found between menopausal status and UI type (p=0.032).

Among male participants, 13.3% (n=2) had rectal or bladder prolapse, and 46.7% (n=7) had benign prostatic hyperplasia (BPH). When surgical history was examined, 53.3% (n=8) of the men had not undergone any previous surgery, and 20.0% (n=3) had undergone prostate surgery.

A total of 22 participants (16.9%) sought medical help due to UI, while 112 (83.1%) did not seek medical attention. Reasons for not seeking help included not perceiving the complaint as important (59.8%, n=67), embarrassment (29.4%, n=33), and the physician not asking about the condition (10.7%, n=12). In addition, 70.8% (n=92) of the participants stated that they avoided using public

Table 2. Comparison of ICIQ-SF scores by age groups and gender

	n	%	Mean±SD	Median* (min–max)	p	Post-hoc[c]
Age						
Under 40 years old[1]	157	19.8	1.36±0.28	0 (0–17)	**<0.001[a]**	3>1: **p<0.001**
40–64 years old[2]	457	57.6	2.35±0.23	0 (0–21)		3>2: **p<0.001**
65 years and older[3]	180	22.7	5.7±0.54	0 (0–21)		
Gender						
Male	200	25.1	1.47±4.03	0 (0–21)	**<0.001[b]**	–
Female	594	74.9	3.41±5.91	0 (0–21)		

[a]: Kruskal Wallis test; [b]: Mann-Whitney U test; [c]: Dunn post-hoc comparisons (Bonferroni corrected). *: Values are expressed as median (min–max) due to the large number of zero scores. ICIQ-SF: International Consultation on Incontinence Questionnaire – Short Form; SD: Standard deviation; UI: Urinary incontinence.

Table 3. Relationship between participants' ages and types of urinary incontinence

Age	Urge n=42	Stress n=21	Mixed n=67	F value	p	Post-hoc
Mean±SD	59.00±12.53	55.09±12.21	65.05±13.33	5.91	0.004	Urge-mixed: **0.048** Stress-mixed: **0.007**

Welch ANOVA and Türkiye HSD Post-Hoc. SD: Standard deviation.

toilets, 71.5% (n=93) reported frequent urination, and 63.8% (n=83) reported no urinary tract infection in the previous year.

A statistically significant relationship was found between UI type and the sensation of incomplete bladder emptying after urination (p=0.016). Among participants reporting this sensation, 68.7% (n=46) were in the mixed UI group, 47.6% (n=20) were in the urge UI group, and 38.1% (n=8) were in the stress UI group. Sociodemographic factors and their associations with UI are summarized in Table 3.

Discussion

One in every four patients who applied to a family medicine clinic reported UI, and the most common and effective type was found to be mixed UI. In a study covering approximately 19,000 individuals in five different countries, the overall UI prevalence was found to be 11.0% [8]. In a study conducted in Edirne, Türkiye, among individuals aged 20 years and older in the general population, the UI prevalence was reported as 19.3% [9]. The lower rate compared to our findings may be attributed to differences in the study setting, as our sample was drawn from a clinical population attending a family medicine outpatient clinic. According to a study in the literature, the prevalence of urinary incontinence during pregnancy was reported to be 56.1% [10]. In this study, the UI prevalence was found to be 27%, which is higher than in the literature and can be explained by the fact that the study included a certain regional hospital group.

The age of onset of mixed UI was found to be statistically significantly higher compared to urge and stress UI. In a meta-analysis study, 54 studies covering a total of 138,722 women between the ages of 10–90 were examined. It has been determined that the prevalence of UI varies between 2.8% (Nigeria) and 57.7% (Iran). The prevalence of general UI was 25.7%, stress type 12.6%, urge type 5.3%, and mixed type 9.1% [11]. In another study, stress UI was found to be 45.9%, urge UI 31.1%, and mixed UI 18.1%.

Despite the differences in mean ages in the study, the finding that mixed UI is more common in older ages and stress UI in younger ages is supported. In the literature, it is stated that women are at higher risk of UI, and this situation is attributed to factors such as a short urethra, pelvic floor damage due to childbirth, and postmenopausal estrogen decrease. In a study conducted in Europe, the prevalence of UI in women was reported as 13.1% [8]. In our study, the prevalence of UI in women was 31.1%, which is consistent with the literature [12].

It has been reported that the prevalence of UI in women aged 35 years and over is 42.8%, and 50% during menopause [13]. In this study, it was observed that both the prevalence of UI and ICIQ-SF scores increase with age. Although the relationship between menopause and UI is not fully clear, it is thought that estrogen deficiency may increase the risk of UI by weakening the pelvic muscles [2,14]. In the study, the prevalence of UI was found to be significantly high in women in menopause, and in particular, 80.4% of women with mixed UI and 78.9% of women with urge UI were found to be in menopause. In a study conducted in India, the most common types of UI after menopause were determined to be mixed (26%), urge (19%), and stress UI (13%) [3].

In a European study conducted on UI in men, the overall prevalence of UI was found to be 5.4% [8]. In Türkiye, the prevalence of UI in men aged 18 years and over varies between 4.9% and 13.5% [9]. In this study, the prevalence of UI in men was determined as 14.5%, which is consistent with the literature. A review reported the prevalence of UI in men as 17.3% [15]. Like many studies showing that UI increases with age, this study also determined that both the prevalence of UI and ICIQ-SF scores increase with age.

The frequency of UI in men increases with age. In one study, the prevalence of UI in the 40–44 age group was 12.2%, while it increased to 17.3% in the 55–59 age group and to 24.9% in the 60 and older age groups. The most common type of UI was mixed UI (10.3%), followed by stress UI (7.7%) and urge UI (6.9%). Studies examining the types of UI in men in Türkiye are quite limited. In one study, 41.5% had urge, 20.3% stress, 6.5% mixed, and 31.7% unclassified UI in men with UI [9]. In this study, the most common type of UI in men was mixed UI, followed by urge and stress UI. The reason for the difference from the order in the literature may be that cases that do not fully fit into a certain category are classified as mixed UI.

Although UI is common among elderly individuals, the rate of healthcare-seeking remains low. The main reasons include the perception of UI as a natural part of aging, feelings of embarrassment, and a lack of recognition of UI as a serious health concern [16]. In one study, it was reported that UI awareness is low in elderly individuals, and this situation negatively affects their behavior of seeking medical help [17]. In this study, only 17% sought medical help, while 59% of individuals who did not seek help did not see the complaint as important, 30% were embarrassed, and 10% stated that their doctors did not ask about this issue. In our study, only 17% of individuals with UI reported seeking medical care, consistent with previous findings indicating low help-seeking behavior. For instance, a systematic review by Yan et al. [16] found that help-seeking rates among older adults with UI varied from 12% to 38%, depending on cultural context and healthcare accessibility. Common barriers included embarrassment, the belief that UI is a normal part of aging, and lack of awareness about treatment options. These findings suggest that underreporting of UI is a global concern and highlight the need for public education and proactive screening in primary care settings to improve health-seeking behaviors.

The present study identified older age and female gender as significant risk factors associated with UI severity. Mixed UI is the most common and most affecting type among age groups, and is particularly strongly associated with menopause and the feeling of incomplete emptying of the bladder after urination.

Limitations

This study has several limitations. Due to the cross-sectional design and the selection of participants from a specific geography, cause-effect relationships could not be evaluated, and the findings were interpreted at the relational level. Since participation in the study was voluntary, the participants may not fully represent the entire population.

Conclusion

This study has shown that UI is significantly associated with age and female gender. However, UI is a common health problem that affects not only certain risk groups but also both men and women aged 18 and over, seriously reducing the quality of life. Due to reasons such as social stigma, lack of awareness, and acceptance as a natural consequence of aging, most patients avoid expressing UI and delay the diagnosis and treatment processes of this condition. Considering the negative effects of UI on the physical health, psychological state, and social life of individuals, this condition should be routinely screened in primary health care, regardless of whether symptoms are present or not. Future research should focus on developing more comprehensive approaches to the early diagnosis and management of UI. First of all, standard screening protocols should be established in primary health care to ensure early detection of the disease. In addition, more targeted preventive strategies should be developed by examining in detail the physiological and lifestyle factors that cause UI in women and men. The effectiveness of treatment approaches should be evaluated, individualized management plans should be created, and comparative analyses of different approaches such as behavioral therapy, pharmacological treatments, and surgical methods should be conducted. In addition, it is of great importance to organize community-based awareness and education programs, change the perception of UI, and encourage individuals' healthcare-seeking behaviors. Finally, the use of innovative technologies such as wearable technologies, telemedicine applications, and non-invasive diagnostic methods can be increased to make UI monitoring and management more effective. Further studies in these areas will contribute to a better understanding of UI, improve the quality of life of patients, and develop more effective approaches that will be integrated into the health system.

Ethics Committee Approval: The study was approved by University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (No: 1763, Date: 14.11.2017).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – A.O.P., Y.G.A., G.Z.Ö.; Design – A.O.P., Y.G.A., G.Z.Ö.; Supervision – A.O.P., Y.G.A., G.Z.Ö.; Fundings – A.O.P., Y.G.A., G.Z.Ö.; Materials – A.O.P., Y.G.A., G.Z.Ö.; Data collection and/or processing – A.O.P., Y.G.A.; Analysis and/or interpretation – A.O.P., Y.G.A., G.Z.Ö.; Literature search – A.O.P., Y.G.A., G.Z.Ö.; Writing – A.O.P., Y.G.A., G.Z.Ö.; Critical review – A.O.P., Y.G.A., G.Z.Ö.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

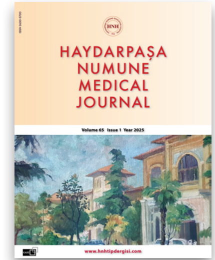
References

1. Milsom I, Gyhagen M. The prevalence of urinary incontinence. Climacteric 2019;22:217–22. [CrossRef]
2. Minassian VA, Hagan KA, Erekson E, Austin AM, Carmichael D, Bynum JPW, et al. The natural history of urinary incontinence subtypes in the Nurses' Health Studies. Am J Obstet Gynecol 2020;222:163.e1–e8. [CrossRef]
3. Deshmukh P, Nikhade N, Ghodey S. Prevalence and Risk factors for Urinary Incontinence in postmenopausal women. J Med Sci Clin Res 2019;7:695–9. [CrossRef]
4. Russo E, Caretto M, Giannini A, Bitzer J, Cano A, Ceausu I, et al. Management of urinary incontinence in postmenopausal women: An EMAS clinical guide. Maturitas 2021;143:223–30. [CrossRef]
5. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn 2004;23:322–30. [CrossRef]
6. Çetinel B, Özkan B, Can G. The validation study of ICIQ-SF Turkish version. Turk J Urology 2004;30:332–8. [Article in Turkish]

7. Ceyhan Ö, Göriş S, Zincir H. An important problems affecting sleep in elderly indıviduals: incontınence. J Health Sci 2018;27:29–35.
8. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50:1306–15. [CrossRef]
9. Dağdeviren N. Prevalence of urinary incontinence and factors affecting urinary incontinence in the population over the age of 20 in the center of Edirne. 2010. Available at: https://acikbilim.yok.gov.tr/handle/20.500.12812/396665. Accessed Aug 2, 2024.
10. Şahin F, Aktürk E, Adan R, Genç S, Mihmanlı V, Yurci A, et al. The effect of pregnancy-related urinary incontinence on incidence and quality of life. Ann Clin Anal Med 2023;14:502–5. [CrossRef]
11. Mostafaei H, Sadeghi-Bazargani H, Hajebrahimi S, Salehi-Pourmehr H, Ghojazadeh M, Onur R, et al. Prevalence of female urinary incontinence in the developing world: A systematic review and meta-analysis-A Report from the Developing World Committee of the International Continence Society and Iranian Research Center for Evidence Based Medicine. Neurourol Urodyn 2020;39:1063–86. [CrossRef]
12. Abufaraj M, Xu T, Cao C, Siyam A, Isleem U, Massad A, et al. Prevalence and trends in urinary incontinence among women in the United States, 2005-2018. Am J Obstet Gynecol 2021;225:166.e1–e12. [CrossRef]
13. Hu JS, Pierre EF. Urinary incontinence in women: evaluation and management. Am Fam Physician 2019;100:339–48.
14. Russo E, Giannini A, Caretto M, Mannella P, Simoncini T. Bladder dysfunction and urinary ıncontinence after the menopause: hormones, drugs, or surgery? Int Soc Gynecol Endocrinol Ser 2018. [CrossRef]
15. Cheng MC, Liu SP, Chuang YC, Hsu KCP, Chow PM. Prevalence and impacts of male urinary incontinence on quality of life, mental health, work limitation, and health care seeking in China, Taiwan, and South Korea (LUTS Asia): Results from a cross-sectional, population-based study. Investig Clin Urol 2022;63:71–82. [CrossRef]
16. Yan F, Xiao LD, Zhou K, Li Z, Tang S. Perceptions and help-seeking behaviours among community-dwelling older people with urinary incontinence: A systematic integrative review. J Adv Nurs 2022;78:1574–87. [CrossRef]
17. Bulgak M, Avcı İA. Methods of coping with factors affecting urinary incontinence awareness and frequency in elderly patients with urinary ıncontinence. J Nursol 2022;25:1–6. [Article in Turkish] [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.28482
Haydarpasa Numune Med J 2025;65(4):384–388



hnhtipdergisi.com

ORIGINAL ARTICLE

Vitamin D and Asthma: Association with Pulmonary Function and Eosinophilic Inflammation

Müzeyyen Eryılmaz[1], İlkay Keskinel[2]

[1]Department of Internal Medicine, İstanbul University of Health Sciences, Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Türkiye

[2]Department of Chest Diseases, Okan University Faculty of Medicine, İstanbul, Türkiye

Abstract

Introduction: Asthma is a chronic inflammatory airway disease marked by variable airflow obstruction and bronchial hyperresponsiveness. Vitamin D, known for its immunomodulatory properties, has been suggested to influence asthma pathophysiology, potentially affecting pulmonary function and eosinophilic inflammation. This study aims to investigate the differences in vitamin D levels between asthmatic patients and healthy individuals, and to analyze the correlation of vitamin D with pulmonary function, arterial oxygen saturation, and eosinophilic inflammation markers.

Methods: This retrospective observational study reviewed medical records from 147 asthmatic patients and 30 healthy controls at a research hospital from January 2022 to January 2023. Pulmonary function tests, arterial oxygen saturation, and eosinophilic markers (eosinophil count, eosinophil percentage, total immunoglobulin E (IgE), and eosinophil cationic protein (ECP) levels) were analyzed.

Results: No significant difference in vitamin D levels was observed between asthmatic patients and healthy controls (p=0.543). A weak positive correlation was found between vitamin D levels and peak expiratory flow (PEF)% (r=0.185, p=0.025). No significant correlations were observed between vitamin D levels and other pulmonary function parameters or eosinophilic markers.

Discussion and Conclusion: While vitamin D levels did not differ significantly between asthmatic and healthy individuals, a weak positive correlation with PEF% suggests a potential role in improving expiratory flow. No significant association was found with other pulmonary functions or eosinophilic inflammation markers. Further studies are needed to clarify the role of vitamin D in asthma management.

Keywords: Asthma; eosinophil cationic protein; immunoglobulin E; lung function tests; Vitamin D.

Asthma is a long-term inflammatory disorder of the airways, marked by intermittent airflow impairment, increased bronchial responsiveness, and airway remodeling [1]. Despite advancements in treatment options, it continues to pose a substantial global health challenge, affecting roughly 300 million people and contributing significantly to healthcare resource use [2,3]. Beyond environmental and genetic influences, vitamin D has emerged as a possible modulator of asthma due to its immune regulatory effects [4].

Vitamin D contributes to the regulation of innate and adaptive immunity. Its deficiency has been linked to heightened airway inflammation and greater vulnerability

Correspondence: İlkay Keskinel, M.D. Department of Chest Diseases, Okan University Faculty of Medicine, İstanbul, Türkiye
Phone: +90 532 255 98 18 **E-mail:** ilkaykeskinel@gmail.com
Submitted Date: 13.05.2025 **Revised Date:** 22.09.2025 **Accepted Date:** 29.09.2025
Haydarpaşa Numune Medical Journal

to respiratory tract infections [5,6]. Prior research has associated lower vitamin D levels with more severe asthma, frequent exacerbations, and increased airway reactivity [7,8]. It may also influence eosinophilic responses and allergy-related biomarkers like total immunoglobulin E (IgE) [9]. However, studies examining its relationship with lung function in asthma have yielded inconsistent results [10,11].

This study sought to determine whether vitamin D concentrations differ between asthmatic patients and healthy individuals and to explore possible correlations between vitamin D levels and pulmonary function, oxygenation, and eosinophilic markers in asthmatic patients.

Materials and Methods

This study was approved by the Clinical Research Ethics Committee of Univesity of Health Sciences, Istanbul Fatih Sultan Mehmet Training and Research Hospital (approval no: FSM EAH-KAEK 2023/88, decision date: 25 May 2023). The study was conducted in accordance with the Declaration of Helsinki. Patient records from asthmatic individuals and healthy controls attending routine check-ups between January 1, 2022, and January 1, 2023, were reviewed. Only stable asthma patients not experiencing exacerbations and without comorbidities were included.

Vitamin D levels were compared across groups. Additionally, associations between vitamin D and lung function [Forced vital capacity (FVC), FVC%, forced expiratory volume in 1 second (FEV_1), FEV_1%, FEV_1/FVC, peak expiratory flow (PEF), PEF%], oxygen saturation ($SatO_2$), eosinophil count and percentage, total IgE, and eosinophil cationic protein (ECP) levels were analyzed.

Data from healthy controls lacked IgE and ECP levels due to the retrospective nature of the study. All data were anonymized, and access was limited to the study team.

Statistical Analysis

Data analysis was performed using IBM SPSS version 26.0. Numerical variables were summarized using descriptive statistics, and normality was assessed through tests such as Shapiro-Wilk and Kolmogorov-Smirnov. Depending on data distribution, either Pearson or Spearman correlation tests were used. Group comparisons employed the Independent Samples t-test or Mann-Whitney U test as appropriate. Categorical variables were compared using the Chi-square test. A p-value <0.05 indicated statistical significance.

Results

The study involved 147 asthmatic patients (Group I) and 30 healthy controls (Group II). Gender distribution did not differ significantly (p=0.512) (Table 1). Age, asthma duration, and vitamin D levels also showed no gender-based differences (Table 2).

No significant correlations were found between vitamin D levels and FVC, FVC%, FEV_1, FEV_1%, FEV_1/FVC, or PEF. However, vitamin D levels were weakly correlated with PEF% (r=0.185, p=0.025) (Table 3, Fig. 1). Mean serum vitamin D levels increased across PEF (%) groups, being 20.3±9.3 ng/mL in patients with PEF < 80%, 23.4±8.9 ng/mL in those with PEF 80–100%, and 26.7±13.2 ng/mL in patients with PEF > 100% (Table 4).

No significant correlations were observed between vitamin

Table 1. Gender distribution between the groups

	Group I (n=147)	Group II (n=30)	p
Gender (n, %)			0.512^a
Female	104 (58.8)	23 (13.0)	
Male	43 (24.3)	7 (4.0)	

^{a}: Pearson's Chi-square test.

Table 2. Patients with asthma

Gender	Female (n=104)	Male (n=43)	p
Age (years)	41±11	40±12	0.597^b
Duration of asthma (years)	9.50±9.90	8.00±10.20	0.228^c
Vitamin D levels	23.65±9.36	22.00±8.96	0.325^b

^{b}: Independent samples t test; ^{c}: Mann-Whitney U test.

Table 3. Correlation between lung function parameters and vitamin D levels

	n	Pearson correlation coefficient (r)	p
FVC	147	-0.094	0.258
FVC%	147	0.086	0.303
FEV_1	147	-0.078	0.348
FEV_1%	147	0.078	0.351
FEV_1/FVC	147	0.007	0.929
PEF	147	0.037	0.659
PEF%	147	0.185	0.025*

*: Statistically significant. FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 second; PEF: Peak expiratory flow.

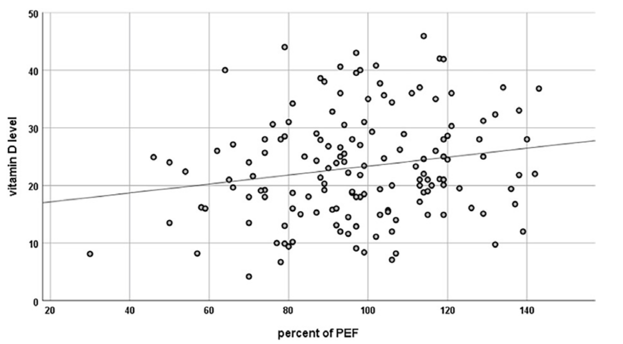


Figure 1. Correlation of PEF% with vitamin D levels of patients with asthma.

PEF: Peak expiratory flow.

Table 4. Vitamin D levels according to PEF (%) groups

PEF (%) group	Mean Vitamin D (ng/mL)±SD[b]	n
<80	20.3±9.3	33
80–100	23.4±8.9	53
>100	26.7±13.2	68

PEF: Peak expiratory flow; SD: Standard deviation.

Table 5. Correlation between eosinopil counts, total IgE, ECP and vitamin D levels

	n	Spearman's rho	p
Eosinophils/mm^3	137	0.101	0.238
Eosinophil %	136	0.154	0.074
Total IgE[a] (IU/mL)	121	0.150	0.099
ECP[b] (mcg/L)	102	-0.45	0.652

IgE: Immunoglobulin E; ECP: Eosinophil cationic protein.

Table 6. Eosinophil counts/mm^3 and eosinophil percentage of the groups

	Group I (n=137)	Group II (n=29)	p
Eosinophil/mm^3			[c]0.035*
Median	180.0	100.0	
%95 CI Level for median	160.0–210.0	100.0–200.0	
Mean±SD	226.8±190.0	157.0±88.5	
Min-max (range)	10.0–1240.0 (1230.0)	42.7–400.0 (357.3)	
%25-%75 perc	120.0–270.0	100.0–200.0	
Eosinophil %			[c]0.004*
Median	2.75	1.70	
%95 CI level for median	2.40–3.30	1.60–2.50	
Mean±SD	3.47±2.54	2.24±1.26	
Min-max (range)	0.10–16.10 (16.00)	0.70–6.30 (5.60)	
%25-%75 perc	1.90–4.25	1.30–2.80	

[c]: Mann-Whitney U Test; *: Statistically significant. CI: Confidence interval; SD: Standard deviation

Table 7. Vitamin D levels of the groups

	Group I (n=147)	Group II (n=30)	p
Vitamin D level			[b]0.543
Mean±SD	23.17±9.25	24.54±11.45	
Median	22.00	25.35	
%95 CI level for median	20.30–24.60	16.70–31.00	
Min-max (range)	4.19–45.90 (41.71)	5.62–45.60 (39.98)	
%25-%75 perc	16.00–28.60	15.80–32.00	

[b]: Independent samples t test. CI: Confidence interval; SD: Standard deviation.

D and eosinophil count, percentage, IgE, or ECP levels (Table 5). Eosinophil counts and percentages were significantly elevated in asthmatics compared to controls (Table 6). Vitamin D levels did not differ significantly between groups (Table 7), nor did they differ when grouped by SatO$_2$% (Table 8).

Discussion

This study examined the relationship between serum vitamin D concentrations and pulmonary function, eosinophilic inflammation, and allergic markers among individuals with asthma. Our analysis revealed no statistically significant difference in vitamin D levels between asthmatic patients and healthy controls. This contrasts with findings from previous research, which demonstrated lower vitamin D levels in asthmatic populations compared to non-asthmatic adults [12]. Similarly, Bai et al. [13] reported decreased vitamin D levels in children diagnosed with asthma compared to healthy peers.

Vitamin D has been the subject of considerable investigation in asthma due to its immunomodulatory potential [14,15]. Existing literature proposes that vitamin D deficiency could be linked to increased asthma severity and diminished lung function, likely through mechanisms involving airway inflammation and remodeling [16,17]. Nevertheless, our study did not establish a significant correlation between vitamin D levels and fundamental lung function metrics such as FEV$_1$ and FVC, with the exception of a weak yet statistically significant positive correlation with PEF%. This modest association may point to a limited but potential role of vitamin D in enhancing expiratory airflow, though further studies are necessary to confirm this finding.

Our results align with those of Mehrabi et al. [18], who also observed no significant connection between vitamin D deficiency and pulmonary function indicators. Conversely, a large-scale study involving 435,040 asthmatic individuals

Table 8. Vitamin D Levels in asthmatic patients (Group I) categorized by $SatO_2$%

$SatO_2$ %	97 (n=1)	98 (n=41)	99 (n=31)	p
Vitamin D				c0.316
Median	25.56	21.00	23.30	
%95 CI level for median	19.00–35.00	18.90–27.00	18.50–25.50	
Mean±SD	27.00±8.77	21.83±9.32	23.13±9.30	
Min-max (range)	16.00–43.00 (27.00)	4.19–42.00 (37.81)	7.10–40.80 (33.70)	
%25-%75 perc	19.00–35.00	15.70–29.00	14.90–26.60	

$SatO_2$: Oxygen saturation; CI: Confidence interval; SD: Standard deviation.

found that higher vitamin D levels were associated with improved FVC, FEV_1, and FEV_1/FVC ratios [19]. Likewise, a meta-analysis conducted by Liu et al. [20] suggested a positive, albeit statistically insignificant, association between vitamin D and parameters such as FEV_1/FVC and FVC%. Additionally, Tamašauskienė et al. [21] reported significantly lower vitamin D levels in asthmatic adults compared to healthy individuals, though no meaningful relationship was found between vitamin D levels and lung function, IgE concentrations, or eosinophil counts. In our cohort, no significant correlations were observed between serum vitamin D levels and FEV_1 or FVC values; however, mean vitamin D concentrations increased progressively across PEF (%) groups, suggesting a potential link between higher vitamin D status and better expiratory performance.

Eosinophilic inflammation is a hallmark feature of asthma pathophysiology. Consistent with this understanding, our data demonstrated significantly elevated eosinophil counts and percentages in the asthma group compared to controls. Although previous studies proposed that vitamin D could reduce eosinophilic airway inflammation, potentially by downregulating IL-5, our analysis did not reveal a significant correlation between vitamin D levels and eosinophil counts or percentages [22]. Some publications have described an inverse association between vitamin D and eosinophil counts [12], yet this was not reflected in our findings. Furthermore, we did not identify any significant relationship between vitamin D levels and total IgE or ECP. While Mohammadzadeh et al. [23] reported a strong negative correlation between vitamin D and IgE in pediatric asthma patients, and similar associations have been described in adults [12], other studies found no such link [17]. Regarding ECP, Lu et al. [24] demonstrated in a cell culture study that vitamin D deficiency led to elevated levels of ECP and other eosinophil-related mediators, including eosinophil peroxidase, eosinophil-derived neurotoxin, and major basic protein.

Several limitations of our study should be noted. First, its retrospective design prevents the establishment of causality. Second, the limited size of the healthy control group may have impacted the ability to detect minor differences in vitamin D status. Third, variables such as dietary habits, ultraviolet exposure, and genetic factors influencing vitamin D metabolism were not considered, all of which may contribute to individual variability.

Conclusion

In summary, our findings do not support a strong association between vitamin D levels and key pulmonary function indicators or eosinophilic inflammation in asthmatic patients. Although a weak positive correlation was identified between vitamin D and PEF%, further longitudinal and controlled studies with larger sample sizes are necessary to fully elucidate the role of vitamin D in the pathophysiology and clinical management of asthma.

Ethics Committee Approval: The study was approved by the University of Health Sciences Istanbul Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (No: FSM EAH-KAEK 2023/88, Date: 25.05.2023).

Use of AI for Writing Assistance: No artificial intelligence–based tools, including large language models, conversational systems, or image-generation technologies, were employed at any stage of this study, from its conception and execution to data analysis and manuscript preparation.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – M.E., İ.K.; Design – M.E., İ.K.; Supervision – M.E., İ.K.; Fundings – M.E., İ.K.; Materials – M.E., İ.K.; Data collection and/or processing – M.E., İ.K.; Analysis and/or interpretation – M.E., İ.K.; Literature search – M.E., İ.K.; Writing – M.E., İ.K.; Critical review – M.E., İ.K.

Conflict of Interest: None declared.

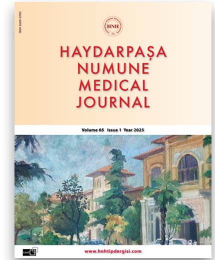
Financial Disclosure: The authors declare that this research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

References

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2023. Available at: https://ginasthma.org/. Accessed Jan 30, 2025.
2. Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J 2020;56:2002094. [CrossRef]
3. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:246. [CrossRef]
4. Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. Curr Opin Allergy Clin Immunol 2012;12:179–85. [CrossRef]
5. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008;181:7090–9. [CrossRef]
6. Pfeffer PE, Hawrylowicz CM. Vitamin D and lung disease. Thorax 2012;67:1018–20. [CrossRef]
7. Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med 2011;184:1342–9. [CrossRef]
8. Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009;179:765–71. [CrossRef]
9. El Abd A, Dasari H, Dodin P, Trottier H, Ducharme FM. Associations between vitamin D status and biomarkers linked with inflammation in patients with asthma: a systematic review and meta-analysis of interventional and observational studies. Respir Res 2024;25:344. [CrossRef]
10. Martineau AR, Cates CJ, Urashima M, Jensen M, Griffiths AP, Nurmatov U, et al. Vitamin D for the management of asthma. Cochrane Database Syst Rev 2016;9:CD011511. [CrossRef]
11. Forno E, Bacharier LB, Phipatanakul W, Guilbert TW, Cabana MD, Ross K, et al. Effect of Vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low Vitamin D levels: The VDKA randomized clinical trial. JAMA 2020;324:752–60. [CrossRef]
12. Al-Thagfan SS, Alolayan SO, Ahmed S, Emara MM, Awadallah MF. Impacts of deficiency in vitamin D derivatives on disease severity in adult bronchial asthma patients. Pulm Pharmacol Ther 2021;70:102073. [CrossRef]
13. Bai YJ, Dai RJ. Serum levels of vitamin A and 25-hydroxyvitamin D3 (25OHD3) as reflectors of pulmonary function and quality of life (QOL) in children with stable asthma: A case-control study. Medicine (Baltimore) 2018;97:e9830. [CrossRef]
14. Pfeffer PE, Hawrylowicz CM. Vitamin D in asthma: mechanisms of action and considerations for clinical trials. Chest 2018;153:1229–39. [CrossRef]
15. Zhang P, Xu Q, Zhu R. Vitamin D and allergic diseases. Front Immunol 2024;15:1420883. [CrossRef]
16. Sarıoglu N, Yalcın AD, Sahin F, Soyyigit S, Tepetam FM, Erel F. Does vitamin D deficiency in asthma affect clinical and functional parameters? A Turkish multicenter study. Allergy Asthma Proc 2021;42:e152–8. [CrossRef]
17. Plesa M, Gaudet M, Mogas A, Olivenstein R, Al Heialy S, Hamid Q. Action of 1,25(OH)2D3 on human asthmatic bronchial fibroblasts: implications for airway remodeling in asthma. J Asthma Allergy 2020;13:249–64. [CrossRef]
18. Mehrabi S, Toghraee E. Association between serum 25-hydroxy vitamin D levels and severity of asthma. Clin Nutr ESPEN 2022;49:197–200. [CrossRef]
19. Zhu Y, Jing D, Liang H, Li D, Chang Q, Shen M, et al. Vitamin D status and asthma, lung function, and hospitalization among British adults. Front Nutr 2022;9:954768. [CrossRef]
20. Liu J, Dong YQ, Yin J, Yao J, Shen J, Sheng GJ, et al. Meta-analysis of vitamin D and lung function in patients with asthma. Respir Res 2019;20:161. [CrossRef]
21. Tamašauskienė L, Gasiūnienė E, Lavinskienė S, Sakalauskas R, Šitkauskienė B. Evaluation of vitamin D levels in allergic and non-allergic asthma. Medicina (Kaunas) 2015;51:321–7. [CrossRef]
22. Cho SW, Kim JH, Choi JH, Lim DH. Preventive and therapeutic effects of vitamin D in a mouse model of allergic asthma. Asian Pac J Allergy Immunol 2019;37:130–7.
23. Mohammadzadeh I, Darvish S, Qujeq D, Hajiahmadi M, Vaghari-Tabari M. Association of serum 25-OH vitamin D_3 with serum IgE and the Pediatric Asthma Severity Score in patients with pediatric asthma. Allergy Asthma Proc 2020;41:126–33. [CrossRef]
24. Lu H, Xie RD, Lin R, Zhang C, Xiao XJ, Li LJ, et al. Vitamin D-deficiency induces eosinophil spontaneous activation. Cell Immunol 2017;322:56–63. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.67790
Haydarpasa Numune Med J 2025;65(4):389–393



hnhtipdergisi.com

ORIGINAL ARTICLE

A Current Perspective on Variations in Male Urogenital Development under Changing Environmental Conditions

Burcu Karakayalı[1], Nurdan Erol[2], Ömer Ceran[3]

[1]Department of Pediatric Neurology, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye
[2]Department of Pediatric Cardiology, University of Health Sciences, Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, İstanbul, Türkiye
[3]Department of Pediatrics, Bağcılar Medipol Mega University Hospital, İstanbul, Türkiye

Abstract

Introduction: In recent years, the deterioration of male reproductive health and the increasing incidence of urogenital anomalies such as hypospadias, cryptorchidism, and micropenis have been associated with environmental endocrine disruptors. This study aimed to assess the prevalence of micropenis and other urogenital anomalies in healthy full-term male newborns in our country. A secondary aim of the study was to contribute further to national data by recording penile measurements, along with gestational age, in infants in whom micropenis was not detected.

Methods: In this study, the findings of urogenital examinations performed by the same physician during routine neonatal check-ups were evaluated in healthy male infants born at term (38–42 weeks of gestation) within a one-month period, at Zeynep Kamil Women and Children's Hospital.

Results: Among the 230 newborns examined, the incidence of hypospadias was 0.43%, and hydrocele 8.2%, while no cases of cryptorchidism were observed. The mean penile length was found to be 3.14±0.36 cm, and the mean penile diameter was 1.5±0.24 cm, with no cases of micropenis detected.

Discussion and Conclusion: No significant increase in the prevalence of hypospadias and cryptorchidism was observed. A significant correlation was found between penile length and birth weight, but no such relationship was identified with gestational age. The findings emphasize the need for ethnic-specific reference standards and larger-scale studies to better understand the impact of endocrine disruptors on male reproductive health.

Keywords: Endocrine disruptors; hypospadias; mean penile length; micropenis; urogenital anomalies.

In recent years, reports from all over the world have highlighted a decline in male reproductive health [1–5]. These publications describe a drop in sperm quality together with a rising incidence of urogenital anomalies such as hypospadias and cryptorchidism, as well as an increase in testicular cancer. The principal culprit is thought to be growing exposure to environmental endocrine disruptors—synthetic hormones, plastic components, and pesticides being the best-known examples. Today's newborn is already exposed in utero to chemicals that infants born before 1920 never encountered.

According to current literature, a thorough urogenital examination is a critical component of the routine neonatal physical assessment [6]. This examination is indispensable

Correspondence: Burcu Karakayalı, M.D. Department of Pediatric Neurology, Marmara University Pendik Training and Research Hospital, İstanbul, Türkiye
Phone: +90 505 394 57 14 **E-mail:** burcukarakayali@hotmail.com
Submitted Date: 13.08.2025 **Revised Date:** 08.09.2025 **Accepted Date:** 29.09.2025
Haydarpaşa Numune Medical Journal

for distinguishing disorders of sex development, identifying life-threatening conditions such as congenital adrenal hyperplasia, and detecting urogenital anomalies such as micropenis, undescended testes, and hypospadias.

Micropenis is defined as a stretched penile length that falls more than 2.5 standard deviations below the mean for a given age [7,8]. Age-specific reference ranges for penile length have been established and serve as the benchmark in the diagnosis of micropenis. According to current data, the average penile length in full-term newborns is 3.5±0.7 cm, and the average penile diameter is 1.1±0.2 cm [7,8]. Values below 1.9 cm are considered indicative of micropenis and should prompt further investigation for underlying conditions [8]. These reference values are based on international data, but average measurements may vary by ethnic background [9]. However, studies conducted within our country on this topic remain limited.

Hypospadias is among the most common urogenital anomalies and is defined as an incomplete fusion of the penile urethra. Hypospadias is classified as Type I when the urethral meatus is located at the glans or subcoronal region, Type II when it is along the ventral penile shaft, and Type III when it is in proximal positions such as the penoscrotal, scrotal, or perineal region [10]. The incidence of hypospadias, reported as 2.02 per 1000 live births in 1970, increased to 3.97 per 1000 by 1993, corresponding to approximately 1 in every 250 live births [11,12]. Some researchers have linked the development of hypospadias to prenatal exposure to exogenous progestins, a type of endocrine disruptor [13]. The increased incidence of hypospadias in infants conceived through *in vitro* fertilization (IVF) further supports the potential role of endocrine disruptors in its etiology, although current evidence is not yet sufficient to establish a definitive causal relationship [14].

Cryptorchidism is another common congenital anomaly. Early recognition and appropriate treatment are crucial in preventing long-term complications such as infertility and malignancy [15,16].

Other conditions evaluated during routine neonatal urogenital examination include phimosis, paraphimosis, and hydrocele, which may signal underlying congenital adrenal hyperplasia [6,7].

This study aimed to determine the prevalence of micropenis and other urogenital anomalies in healthy full-term male newborns under local conditions. Additionally, penile length and diameter measurements, obtained during the assessment of infants without micropenis, were recorded alongside gestational age to provide supplementary data for national reference values.

Materials and Methods

This study was conducted at Zeynep Kamil Women and Children Diseases Training and Research Hospital. The gestational age of the neonates was determined based on the last menstrual period (LMP) as reported by the mothers.

Inclusion Criteria

1. Healthy male neonates born at term (38–42 weeks' gestation) based on LMP were included.

Exclusion Criteria

1. Premature infants were excluded.
2. Neonates with a history of undetermined maternal LMP were excluded.

Urogenital findings from the routine neonatal examination, all performed by the same physician, were analyzed.

This study was conducted following the ethical principles of the 1964 Declaration of Helsinki and its subsequent amendments, as well as comparable ethical standards. The measurements were performed as part of the routine physical examination of the neonates, with prior parental information and consent obtained. A total of 230 newborn boys met the inclusion criteria. For each infant, gestational age, mode of delivery, birth weight, and maternal data—age, gravidity, parity, number of miscarriages or terminations, illnesses during pregnancy, and use of iron, multivitamins, or other medications—were recorded. Family history variables (consanguinity, urogenital anomalies in male siblings or other relatives) were also documented.

During the standard physical examination, the urogenital system was assessed by inspection and palpation. Penile length and diameter were measured; a stretched penile length more than 2.5 SD below the mean for gestational age was classified as micropenis [7,8]. Additional findings such as hydrocele, hypospadias, epispadias, and cryptorchidism were noted. Hypospadias was defined by the presence of incomplete fusion of the penile urethra during clinical examination. Cases with any urogenital anomaly were referred, as per routine practice, to pediatric endocrinology and pediatric surgery.

Statistical Analysis

Data were analyzed with SPSS version 10.0 (SPSS Inc., Chicago IL, USA). Descriptive statistics (mean, SD, frequency, percentile) were calculated. Because continuous variables followed a normal distribution, Pearson correlation assessed relationships between continuous variables, and the chi-square test compared categorical variables. Results were considered significant at $p<0.05$ (95% confidence level).

Table 1. Penile length and diameter values in full-term male neonates

	Min-max (cm.s)	Mean±SD (cm.s)
Penile length	2.30-4.50	3.14±0.36
Penile diameter	0.90-1.70	1.15±0.12

Penile length and diameter are presented as mean±SD, with corresponding minimum and maximum values (cm). SD: Standard deviation.

Table 2. Correlation between penile length and birth weight & gestational age

	Penile Length	
	r	p
Birth weight	0.279	0.001**
Gestational age	0.046	0.485

**: p<0.01 indicates a statistically highly significant correlation. r: Pearson correlation coefficient.

Results

The mothers' mean age was 25.52±4.70 years (range 17–40). Mean gravidity was 1.99±1.11 (range 1–8) and mean parity 1.75±0.97 (range 1–7). Consanguinity was present in 28.7% of cases, and 3.0% had a male sibling with a urogenital disorder. Vaginal delivery accounted for 90.9% of births. Mean birth weight was 3371±453.9 g.

Measured penile lengths ranged from 2.30 cm to 4.50 cm, with a mean of 3.14±0.36 cm. Mean penile diameter was 1.5±0.24 cm (range 0.90–1.70). The minimum, maximum, and mean values of penile length and diameter (in centimeters) are presented in Table 1. Hydrocele was identified in 8.2% of cases (3.9% bilateral, 3% right-sided, and 1.3% left-sided). Hypospadias was detected in a single case (0.43%), and no instances of cryptorchidism were found.

A highly significant correlation emerged between penile length and birth weight ($p<0.001$), but not between penile length and gestational age ($p=0.485$; Table 2).

Discussion

A thorough urogenital examination is an essential component of the neonatal examination, enabling the early detection of conditions that can affect future health. As demonstrated in our cohort, such an approach facilitates the detection of urogenital anomalies.

Only one infant (0.43%) presented with hypospadias, classified as type 2. The case was evaluated by pediatric surgery, and corrective surgery was scheduled for age one year; no additional urogenital anomalies were present. Apart from a medically supervised course of antibiotics during pregnancy, the maternal history was unremarkable.

No cases of cryptorchidism were recorded, even though cryptorchidism is generally considered the most common congenital anomaly, with reported prevalences of 4–8% [7]. The absence of cryptorchidism in our 230 infants contrasts with both these figures and studies suggesting an increasing incidence.

In our cohort, hydrocele was identified as an additional physical examination finding in about 8% of infants assessed for insufficient virilization. All were placed under pediatric surgical follow-up; persisting hydroceles were slated for elective repair.

Current reference values for neonatal penile size derive mainly from international data: with lengths below 1.9 cm regarded as micropenis [8]. Ethnic variation clearly influences these parameters, yet local data remain limited [17–21]. In a 2005 Turkish study conducted in Diyarbakır by Akarsu et al. [22], mean penile length in 1,522 healthy term newborns was 3.5±0.7 cm (range 2.1–4.9 cm), with a minimum of 1.9 cm.

In our series, no cases of micropenis were identified. Mean length in our study is slightly lower than both the commonly used reference and the value reported by Akarsu et al. [22], whereas mean diameter aligns with the literature. Our analysis revealed that penile length showed a correlation with birth weight, but not with gestational age.

Endocrine disruptors are exogenous substances or mixtures that alter endocrine function in a healthy organism—or in its offspring—and thereby cause adverse health effects. The agents most frequently implicated include diethylstilbestrol (DES), persistent organochlorines (DDT, PCBs, bisphenol A), methoxychlor, alkylphenols, phthalates, anti-androgenic fungicides, and phytoestrogens [23–26]. DES, once used to prevent miscarriage, is known to increase the incidence of urogenital anomalies in male infants and vaginal adenocarcinoma in females [27]. Contemporary data documenting the rising prevalence of urogenital anomalies and the deterioration of male reproductive health often implicate endocrine disruptors. Multiple studies have demonstrated measurable levels of toxic substances in amniotic fluid, cord blood, placenta, and breast milk [28–31]. Epidemiologic evidence also indicates an elevated relative risk of cryptorchidism in boys whose mothers work in pesticide-treated environments [31].

Our study did not include direct assessment of exposure to these compounds; future research should adopt prospective designs with larger cohorts and objective measures of endocrine disruptor exposure.

Conclusion

The impact of endocrine disruptors on the male reproductive system remains a timely and compelling topic. This study offers a current investigation into the prevalence of urogenital anomalies in male infants in the setting of increasing environmental exposure to endocrine-disrupting chemicals. Our findings indicate that there has been no significant increase in the prevalence of hypospadias and cryptorchidism, which are well-recognized clinical indicators of impaired virilization associated with endocrine disruptors.

Ethics Committee Approval: The study was approved by Haydarpaşa Numune Training and Research Hospital Ethics Committee (No: 771/7/2025, Date: 29.07.2025).

Use of AI for Writing Assistance: No artificial intelligence(AI) or AI-assisted technology was used in the production of the submitted work.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – B.K., Ö.C.; Design – N.E.; Supervision – Ö.C.; Fundings – B.K.; Materials – B.K.; Data collection and/or processing – B.K.; Analysis and/or interpretation – B.K., Ö.C.; Literature search – B.K., N.E.; Writing – B.K., Ö.C.; Critical review – N.E., Ö.C.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research received no financial support from any funding agency in the public, commercial, or not-for-profit sectors.

References

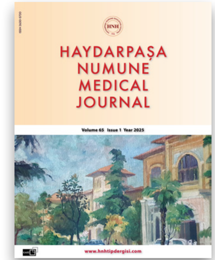
1. Goldman AS, Bongiovanni AM. Induced genital anomalies. Ann N Y Acad Sci 1967;142:755–67. [CrossRef]
2. Mau G. Progestins during pregnancy and hypospadias. Teratology 1981;24:285–7. [CrossRef]
3. Myers JP. Endocrine disruption: Emerging science vitally important for pediatric urologists. Dial Pediatr Urol 2000;23:2–3.
4. Cannarella R, Gül M, Rambhatla A, Agarwal A. Temporal decline of sperm concentration: role of endocrine disruptors. Endocrine 2023;79:1–16. [CrossRef]
5. Calivarathan L, Mathur PP. Effect of endocrine disruptors on testicular function. Adv Exp Med Biol 2025;1469:115–25. [CrossRef]
6. Hall DMB. Health for all children: report of the third joint working party on child health surveillance. Neonatal and 8-week examinations. New York: Oxford University Press; 1996. p.142–5.
7. Kurtoğlu K, Atabek ME. Yenidoğanın endokrin sorunları. In: Günöz H, Öcal G, Yordam N, Kurtoğlu S, editors. Pediatrik endokrinoloji. Pediatric Endokrinoloji ve Oksoloji Derneği Yayınları; 2003, p.653–92.
8. Lee PA, Mazur T, Danish R, Amrhein J, Blizzard RM, Money J, et al. Micropenis. I. Criteria, etiologies and classification. Johns Hopkins Med J 1980;146:156–63.
9. López-Soto Á, Bueno-González M, Urbano-Reyes M, Garví-Morcillo J, Meseguer-González JL, Martínez-Uriarte J, et al. Stretched penile length at birth: a systematic review. J Pediatr Endocrinol Metab 2021;34:1211–23. [CrossRef]
10. Baskin LS, Duckett JW. Hypospadias. Gillenwater J, editor. Adult and pediatric urology. 2nd ed. St. Louis, CV; Mosby; 1995.
11. Duckett JW. Hypospadias. In: Walsch PC, Retik AB, Vaughan ED Jr, Wein AJ, editors. Campbell's Urology. Philadelphia, WB Saunders; 1998. p.2093–119.
12. Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. Environ Health Perspect 1999;107:297–302. [CrossRef]
13. Aarskog D. Maternal progestins as a possible cause of hypospadias. N Engl J Med 1979;300:75–8. [CrossRef]
14. Macnab AJ, Zouves C. Hypospadias after assisted reproduction incorporating *in vitro* fertilization and gamete intrafallopian transfer. Fertil Steril 1991;56:918–22. [CrossRef]
15. Yılmaz Y, Özen İO. İnmemiş testis kliniğinde güncel yaklaşımlar. STED 2004;13:211–4. [Article in Turkish]
16. Virtanen HE, Main KM, Toppari J. Editorial: Update on epidemiology, endocrinology and treatment of cryptorchidism. Front Endocrinol (Lausanne) 2024;15:1435877. [CrossRef]
17. Vasudevan G, Manivarmane, Bhat BV, Bhatia BD, Kumar S. Genital standards for south Indian male newborns. Indian J Pediatr 1995;62:593–6. [CrossRef]
18. Al-Herbish AS. Standard penile size for normal full term newborns in the Saudi population. Saudi Med J 2002;23:314–6.
19. Ponchietti R, Mondaini N, Bonafè M, Di Loro F, Biscioni S, Masieri L. Penile length and circumference: a study on 3,300 young Italian males. Eur Urol 2001;39:183–6. [CrossRef]
20. Lian WB, Lee WR, Ho LY. Penile length of newborns in Singapore. J Pediatr Endocrinol Metab 2000;13:55–62. [CrossRef]
21. Cheng PK, Chanoine JP. Should the definition of micropenis vary according to ethnicity? Horm Res 2001;55:278–81. [CrossRef]
22. Akarsu S, Öcal C, Kurt A, Yılmaz E, Kurt ANÇ, Aygün AD. Sağlıklı çocuklarda penis uzunluğu ve testis çapı. Çocuk Derg 2005;5:259–63. [Article in Turkish]
23. Wolf C Jr, Lambright C, Mann P, Price M, Cooper RL, Ostby J, et al. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. Toxicol Ind Health 1999;15:94–118. [CrossRef]
24. Foster PM. Disruption of reproductive development in male rat offspring following in utero exposure to phthalate esters. Int J Androl 2006;29:140–85. [CrossRef]

25. Mínguez-Alarcón L, Gaskins AJ, Meeker JD, Braun JM, Chavarro JE. Endocrine-disrupting chemicals and male reproductive health. Fertil Steril 2023;120:1138–49. [CrossRef]
26. Das D, Dutta HK, Borbora D, Brahma RC, Das JM. Assessing the relationship between hypospadias risk and parental occupational exposure to potential endocrine-disrupting chemicals. Occup Environ Med 2023;80:93–6. [CrossRef]
27. Klip H, Verloop J, van Gool JD, Koster ME, Burger CW, van Leeuwen FE, et al. Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. Lancet 2002;359:1102–7. [CrossRef]
28. Rogan WJ, Bagniewska A, Damstra T. Pollutants in breast milk. N Engl J Med 1980;302:1450–3. [CrossRef]
29. Foster WG, Chan S, Platt L, Hughes CL Jr. Detection of phytoestrogens in samples of second trimester human amniotic fluid. Toxicol Lett 2002;129:199–205. [CrossRef]
30. Saxena MC, Siddiqui MK, Seth TD, Krishna Murti CR, Bhargava AK, Kutty D. Organochlorine pesticides in specimens from women undergoing spontaneous abortion, premature of full-term delivery. J Anal Toxicol 1981;5:6–9. [CrossRef]
31. Restrepo M, Muñoz N, Day N, Parra JE, Hernandez C, Blettner M, et al. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. Scand J Work Environ Health 1990;16:239–46. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.73669
Haydarpasa Numune Med J 2025;65(4):394–401

ORIGINAL ARTICLE



hnhtipdergisi.com

Association Between Neutrophil Percentage-to-Albumin Ratio and Clinical Outcomes in Myocardial Infarction with Non-obstructive Coronary Arteries Patients

Erkan Kahraman, Koray Kalenderoğlu, Fatih Furkan Yücedağ, Yalçın Velibey, Göktürk İpek

Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye

Abstract

Introduction: This study sought to analyze the predictive importance of neutrophil percentage/albumin ratio (NPAR) levels at hospitalization for one-year major adverse cardiovascular and cerebrovascular events (MACCE) in patients with non-obstructive myocardial infarction (MINOCA).

Methods: This retrospective cohort study included 495 patients. Patients were categorized into two groups: those with MACCE and those without. The neutrophil percentage-to-albumin ratio (NPAR), C-reactive protein (CRP)/albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation (SII) index, and advanced lung cancer inflammation index (ALI) were calculated for all patients, and the correlations of these inflammation-based biomarkers with 1-year MACCE were assessed.

Results: CRP, neutrophil count, neutrophil percentage, NLR, SII, CAR, and NPAR were significantly higher in MACCE (+) patients ($p<0.001$). In contrast, body mass index (BMI), lymphocyte count, albumin, and ALI values were markedly lower in the MACCE (+) group ($p<0.001$). In receiver operating characteristic (ROC) curve analysis, NPAR had a greater area under the curve (AUC: 0.970) value than either ALI (AUC: 0.932), SII (AUC: 0.927), or CAR (AUC: 0.928).

Discussion and Conclusion: Inflammatory biomarkers NPAR, CAR, SII, and ALI can predict one-year major adverse cardiovascular and cerebrovascular events for patients with MINOCA. NPAR shows better predictive value compared to other biomarkers.

Keywords: Adverse outcome, inflammatory biomarkers, MINOCA, neutrophil percentage-to-albumin ratio.

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinical condition defined by angiographic findings of myocardial infarction (MI) in the absence of significant obstructive coronary artery disease, comprising roughly 5–10% of all acute MI instances [1,2]. The diagnosis and prognosis of MINOCA are challenging due to its heterogeneous underlying mechanisms, including coronary microvascular dysfunction, plaque disruption, vasospasm, and myocarditis [3].

Inflammatory processes play a pivotal role in the initiation and progression of myocardial damage, influencing both obstructive coronary syndromes and MINOCA [4,5]. In recent years, numerous inflammatory biomarkers have been examined as potential prognostic indicators in acute coronary syndromes [6,7]. The neutrophil percentage-to-albumin ratio (NPAR) emerged as a novel inflammatory marker indicative of elevated neutrophilic response and diminished serum albumin levels. These features are often

Correspondence: Erkan Kahraman, M.D. Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye

Phone: +90 505 717 02 68 **E-mail:** erkan.kahraman@hotmail.com

Submitted Date: 01.10.2025 **Revised Date:** 15.10.2025 **Accepted Date:** 24.10.2025

Haydarpaşa Numune Medical Journal

associated with systemic inflammatory activity, oxidative stress, and poor nutritional condition [8–10].

Previous studies indicate that increased NPAR levels correlate with heightened morbidity and mortality in critically ill patients, as well as those suffering from sepsis, heart failure, and ischemic stroke [11–13]. Moreover, NPAR was identified as an independent predictor of in-hospital mortality in patients with acute ST-segment elevation myocardial infarction (STEMI) [14]. A further study identified NPAR as an independent predictor of all-cause mortality at 180 days and 365 days in critically ill patients with acute MI [15]. The predictive advantage of NPAR in patients with MINOCA remains largely unexplored. This study evaluated the correlation between NPAR levels upon admission and the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) within 1 year in patients diagnosed with MINOCA. In addition to NPAR, we evaluated and compared several other widely utilized inflammatory markers in this cohort, namely the C-reactive protein-to-albumin ratio (CAR), the systemic immune-inflammation index (SII), and the advanced lung cancer inflammation index (ALI).

Materials and Methods

Study Population and Design

This retrospective analysis encompassed 7,680 consecutive patients admitted to our tertiary cardiovascular center with acute myocardial infarction from 2015 to 2020. Patients were eligible if they were over 18 years old at the time of presentation, had an acute MI, and satisfied the MINOCA criteria. Patients who did not undergo coronary angiography, had experienced another type of acute myocardial infarction, or had a confirmed diagnosis of myocarditis or Takotsubo syndrome were excluded. In addition, patients with conditions that could potentially influence albuminuria—such as viral hepatitis (defined as positive serologic markers for hepatitis B or C virus and a physician-confirmed diagnosis), excessive alcohol consumption (defined as >1 alcoholic drink per day for women or >2 drinks per day for men), liver cancer, severe hepatic injury (characterized by aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transpeptidase [GGT] levels >500 IU/L), or evident malnutrition—were also excluded from the study. Our dataset comprised demographic information, transthoracic echocardiography (TTE) and electrocardiogram (ECG) parameters, laboratory results, prescribed medications, procedural details, and complications, all retrieved from hospital records and national health databases.

Definitions and Study Endpoints

The Fourth Universal Definition of Myocardial Infarction (2018) was applied to define MINOCA and other forms of acute MI. In patients admitted between 2015 and 2018 and included in the study, MINOCA was defined according to the most recent criteria established in 2018. Laboratory diagnosis of MI required elevated cardiac biomarkers above the 99th percentile with a rising or falling pattern, in addition to at least one of the following: ischemic symptoms, ECG changes consistent with ischemia, new regional wall motion abnormalities on TTE, or angiographic evidence of coronary thrombus. Coronary stenosis not resulting in significant obstruction was defined as <50% luminal narrowing. Coronary ectasia was defined as ≥50% dilatation compared with an adjacent normal segment, and coronary slow flow was defined as delayed opacification in the absence of significant epicardial coronary artery stenosis. Progression of index lesions in patients who underwent repeat angiography during follow-up was defined as a visually estimated increase of ≥10% in the degree of stenosis. Repeat angiography was performed due to the diagnosis of acute coronary syndrome or suspicion of coronary artery disease based on clinical, ECG, laboratory, exercise treadmill testing, and non-invasive imaging results. Dyslipidemia was defined as total cholesterol >200 mg/dL, triglycerides >150 mg/dL, LDL cholesterol >100 mg/dL, and/or HDL cholesterol <40 mg/dL [1,16–18].

Inflammatory indices were calculated as follows:

- NPAR: neutrophil percentage×100/serum albumin (g/dL),
- NLR: neutrophil count / lymphocyte count,
- CAR: C-reactive protein (CRP) (mg/dL) / albumin (g/dL),
- SII: platelet count×neutrophil count/lymphocyte count,
- ALI: body mass index × serum albumin / neutrophil-to-lymphocyte ratio (NLR).

The primary endpoint was the occurrence of MACCE within 12 months, defined according to the Academic Research Consortium-2 (ARC-2) consensus, and included cardiovascular death (MI, malignant arrhythmia, heart failure, or stroke), non-fatal MI, non-fatal cerebrovascular accident (ischemic stroke or transient ischemic attack), or cardiovascular rehospitalization due to MI, arrhythmia, heart failure, or stroke [19]. MACCE was evaluated based on hospital medical records, and a total of 495 patients meeting the inclusion criteria with accessible MACCE data were analyzed.

Laboratory Analyses

Laboratory parameters included complete blood counts, liver function tests, renal function tests, electrolytes, lipid profiles, and cardiac biomarkers measured at admission. High-sensitivity troponin levels were classified into three categories: <10-fold increase, 10–100-fold increase, and >100-fold increase above the upper reference limit.

Coronary Angiography

Coronary angiography was performed using the standard Judkins technique and analyzed by two experienced interventional cardiologists on an Axiom (Siemens Medical Solutions) workstation. Written informed consent was obtained from all patients prior to the procedure.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 30 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean±standard deviation or median with interquartile range, while categorical data are presented as counts and percentages. The Shapiro–Wilk test was applied to evaluate normality, and homogeneity of variance was assessed with Levene's test. For comparisons between two groups, the independent-samples t test was used when normal distribution was confirmed, whereas the Mann–Whitney U test was applied otherwise. Categorical variables were compared with Pearson's chi-square, Yates's chi-square, or Fisher's exact test, as appropriate. When a chi-square result was significant, subgroup comparisons were performed with Bonferroni-adjusted two-proportion Z tests. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. The predictive ability of biomarkers for MACCE was examined with Receiver Operating Characteristic (ROC) curve analysis. A two-sided p value of <0.05 was considered statistically significant.

Ethics Approval and Compliance Statement

The research followed the ethical guidelines specified in the Declaration of Helsinki. There was no utilization of AI-powered tools such as Large Language Models (LLMs), chatbots, or image generators in developing this article. The study received approval from the ethics committee on March 06, 2025, with reference number E-10840098-202.3.02-1849, under the supervision of the Scientific Research Applications Review Commission.

Results

A total of 495 patients were included in the study, of whom 356 were in the MACCE(–) group and 139 in the MACCE(+) group. The overall incidence of MACCE was higher in male patients compared to females (33.0% vs. 20.3%, p<0.05). Patients in the MACCE(+) group were significantly older than those in the MACCE(–) group. No significant differences were observed between the groups with respect to diabetes mellitus, hypertension, hyperlipidemia, or anemia. However, MACCE incidence was significantly higher in patients with chronic kidney disease (64.0% vs. 25.7%, p<0.001).

The presence of atrial fibrillation was not associated with MACCE. In contrast, a history of MI was strongly associated with MACCE (41.6% vs. 23.5%, p<0.05). Similarly, patients with prior revascularization and those with post-discharge adverse events developed MACCE at markedly higher rates compared to their counterparts (p<0.001 for both). Patients who developed MACCE had a significantly shorter follow-up duration. Troponin stratification did not show a significant association with MACCE.

Regarding laboratory parameters, glucose and creatinine levels were significantly higher in MACCE(+) patients. Conversely, low-density lipoprotein (LDL)-cholesterol and thyroid-stimulating hormone (TSH) levels were significantly lower in the MACCE(+) group.

Ejection fraction (EF) was strongly associated with outcomes: the incidence of MACCE was 72.2% in patients with EF <30%, 50.8% in those with EF 30–50%, and 22.3% in those with EF >50% (p<0.001). Patients with nonobstructive coronary artery stenosis (defined as <50% stenosis) had a significantly higher MACCE incidence compared with those without lesions (32.9% vs. 23.9%, p<0.05). The presence of coronary ectasia, STEMI, or Non-ST-elevation Myocardial Infarction (NSTEMI) presentation did not differ significantly between groups. Coronary slow flow was inversely associated with MACCE, with a lower incidence in patients with slow flow (16.0% vs. 29.7%, p<0.05).

Repeat angiography was significantly associated with MACCE (44.4% vs. 24.3%, p<0.01), as was the progression of native stenoses (53.8% vs. 24.5%, p<0.001).

Inflammatory indicators, including CRP, neutrophil count, neutrophil percentage, NLR, SII, CAR, and NPAR, were considerably higher in MACCE(+) patients compared to MACCE(–) patients (p<0.001). Conversely, BMI, lymphocyte count, albumin, and ALI values were markedly diminished in the MACCE(+) group compared to the MACCE(–) group (p<0.001).

In the comparisons presented in Table 1, parameters that showed significant differences between the MACCE(+) and MACCE(–) groups were further analyzed. The predictive performances of the ALI, SII, CAR, and NPAR for MACCE were evaluated in Table 2 using ROC curve analysis,

Table 1. Comparison of demographic, clinical characteristics, laboratory and angiographic parameters and medications of patients according to MACCE groups

Variable	MACCE (-) n=356		MACCE (+) n=139		Test statistic	p
	n	%	n	%		
Demographics						
Male	191	67.0	94	33.0	9.658	0.002
Female	165	79.7	42	20.3	–	–
Age, (years)	49.9±16.2		55.6±18.1		3.180	0.002
Diabetes	42	65.6	22	34.4	1.303	0.254
Hypertension	66	64.7	36	35.3	3.300	0.069
Dyslipidemia	216	70.4	91	29.6	1.632	0.201
Anemia	26	74.3	9	25.7	0.005	0.945
Chronic renal failure	9	36.0	16	64.0	15.545	<0.001
Atrial fibrillation	30	61.2	19	38.8	2.783	0.095
Prior MI	66	58.4	47	41.6	14.274	<0.001
Revascularization	0	0.0	30	100.0	79.821	<0.001
Death after discharge	0	0.0	102	100.0	336.831	<0.001
Smoking	25	71.4	10	28.6	0.000	1.000
Cerebrovascular disease	3	75.0	1	25.0	–	1.000
Laboratory parameters						
Troponin increase						
<10 fold	182	73.3	65	26.3	0.439	0.803
10–100 fold	90	70.9	37	29.1		
>100 fold	84	71.2	34	28.8		
Glucose (mg/dL)	106 (37.0)		113 (51.8)		2.346	0.019
Hemoglobin (g/dL)	13.58±1.68		13.53±1.75		0.344	0.731
PLT ($\times 10^3/\mu L$)	230.5 (76.3)		231.5 (81.5)		0.168	0.867
Creatinine (mg/dL)	0.80 (0.20)		0.90 (0.30)		4.339	<0.001
LDL (mg/dL)	106.0 (42.5)		98.5 (56.8)		2.027	0.043
TSH (mU/L)	1.51 (1.77)		1.28 (1.13)		3.321	0.001
Ejection fraction						
<30	5	27.8	13	72.2	40.215	<0.001
30–50	30	49.2	31	50.8		
>50	321	77.7	92	22.3		
Angiographic parameters						
Number of stenosed vessels						
Null	218	76.2	68	23.8	7.314	0.063
One	62	72.1	24	27.9		
Two	31	60.8	20	39.2		
Three	45	65.2	24	34.8		
Coronary lesion (<50%)	217	76.1	68	23.9	4.846	0.028
Ectasia	336	72.4	128	27.6	0.000	1.000
Coronary slow flow	293	70.3	124	29.7	5.330	0.021
NSTEMI	164	76.3	51	23.7	2.936	0.087
STEMI	351	72.8	131	27.2	–	0.149
Recurrent angiography	311	75.7	100	24.3	12.699	<0.001
Native stenosis change	332	75.5	108	24.5	18.523	<0.001
Medications						
Acetylsalicylic acid	265	71.6	105	28.4	0.404	0.525
Clopidogrel	206	74.4	71	25.6	1.281	0.258
Prasugrel	349	72.9	130	27.1	–	0.204

Table 1. Cont.

Variable	MACCE (-) n=356		MACCE (+) n=139		Test statistic	p
	n	%	n	%		
Ticagrelor	343	72.7	129	27.3	0.246	0.620
Beta-blockers	250	73.3	91	26.7	0.508	0.476
ACE inhibitors	241	73.5	87	26.5	0.615	0.433
Statins	232	72.3	89	27.7	0.003	0.955
BMI (kg/m^2)	28.80 (2.30)		28.00 (3.40)		5.173	<0.001
CRP	0.50 (1.50)		3.05 (3.24)		11.312	<0.001
Neutrophil (×10^3/μL)	5.30 (2.60)		7.75 (3.65)		8.803	<0.001
Neutrophil (%)	53.0 (8.0)		67.0 (12.0)		12.798	<0.001
Lymphocyte (×10^3/μL)	2.20 (1.20)		1.80 (1.10)		3.425	<0.001
NLR	2.41 (1.93)		3.67 (3.48)		7.690	<0.001
Albumin (mg/dL)	4.00 (0.20)		3.70 (0.98)		9.032	<0.001
ALI	48.27 (39.08)		26.97 (16.84)		10.137	<0.001
SII	567.7 (468.7)		860.8 (774.4)		7.328	<0.001
CAR	0.13 (0.37)		0.85 (0.86)		11.920	<0.001
NPAR	1329.2 (255.1)		1900.0 (415.3)		14.826	<0.001

MACCE: Major adverse cardiovascular and cerebrovascular events; PLT: Platelet count; LDL: Low-density lipoprotein; TSH: Thyroid-stimulating hormone; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-Elevation myocardial infarction; ACEIs: Angiotensin-converting-enzyme inhibitors; BMI: Body mass index; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio.

Table 2. Evaluation of Biomarker Performance in Predicting MACCE by receiver operating characteristic (ROC) Curve Analysis

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)	PPV (95.0% CI)	NPV (95.0% CI)
ALI*	0.932 (0.906–0.953)	<0.001	>39.26	96.3 (91.6–98.8)	78.7 (74.0–82.8)	63.1 (58.3–67.7)	98.2 (95.9–99.3)
SII*	0.927 (0.901–0.949)	<0.001	>526.2	92.6 (86.8–96.4)	79.5 (74.9–83.6)	63.1 (58.1–67.9)	96.6 (94.0–98.1)
CAR*	0.928 (0.902–0.949)	<0.001	>0.67	90.4 (84.1–94.8)	79.8 (75.2–83.8)	62.9 (57.8–67.7)	95.6 (92.9–97.3)
NPAR*	0.970 (0.951–0.983)	<0.001	>1487.8	94.1 (88.7–97.4)	91.6 (88.2–94.2)	80.9 (75.0–85.7)	97.6 (95.4–98.8)

*: The analysis was adjusted for age, sex, glucose, creatinine, LDL, TSH, BMI, CRP, NLR, albumin, chronic renal disease (CRD), ejection fraction (EF), coronary lesion, coronary slow flow, recurrent angiography, and changes in native stenosis. MACCE: Major adversecardiovascular and cerebrovascular events; AUC: Area under the curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio.

after adjustment for potential confounding variables (excluding prior MI, revascularization, post-discharge events, and time to death).

According to Table 2 and Figure 1, the area under the curve (AUC) values were 0.932 for ALI, 0.927 for SII, 0.928 for CAR, and 0.970 for NPAR, indicating discriminatory capacity for all indices. Among these, ALI demonstrated the highest sensitivity (96.3%), whereas NPAR exhibited the highest specificity (91.6%). Furthermore, NPAR had the highest positive predictive value (PPV, 80.9%), while ALI achieved the highest negative predictive value (NPV, 98.2%).

According to Table 3, correlation analyses were performed to further evaluate the relationships between NPAR and other inflammatory indices.

In the overall cohort, NPAR demonstrated a statistically significant moderate negative correlation with ALI, a weak positive correlation with SII, and a moderate positive correlation with CAR. In the MACCE(+) group, NPAR

Table 3. Spearman correlation coefficients showing the relationships between biomarkers in the entire patient group and MACCE groups

	All groups			MACCE (+)			MACCE (-)		
	SII	CAR	NPAR	SII	CAR	NPAR	SII	CAR	NPAR
ALİ	-0.876**	-0.432**	-0.524**	-0.893**	-0.280**	-0.361**	-0.824**	0.060ns	-0.303**
SII	–	0.343**	0.386**	–	0.262**	0.285**	–	-0.119ns	0.086ns
CAR	–	–	0.414**	–	–	0.108*	–	–	0.004ns

*: p<0.05, **: p<0.001. MACCE: Major adverse cardiovascular and cerebrovascular events; ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio; ns: Not significant.

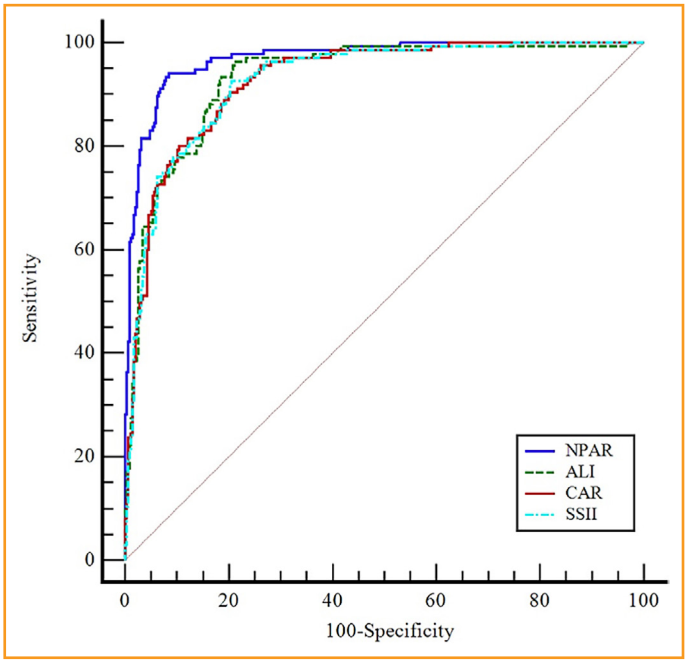


Figure 1. The receiver operating characteristic (ROC) curve analysis of ALI, SII, CAR and NPAR for predicting MACCE.

ALI: Advanced lung cancer inflammation index; SII: Systemic immune-inflammation index; CAR: C-reactive protein-to-albumin ratio; NPAR: Neutrophil percentage-to-albumin ratio; MACCE: Major adverse cardiovascular and cerebrovascular events.

showed a statistically significant weak negative correlation with ALI, a weak positive correlation with SII, and a very weak positive correlation with CAR. In the MACCE(–) group, NPAR exhibited a statistically significant weak negative correlation with ALI, whereas no significant correlations were observed between NPAR and either SII or CAR.

Discussion

This study identified higher NPAR, CAR, and SII, and lower ALI values as independent predictors of one-year MACCE occurrence in MINOCA patients. Among these biomarkers, NPAR was particularly prominent and demonstrated a stronger predictive capacity for 1-year MACCE development compared to other biomarkers. These findings highlight NPAR as a simple, cost-effective, and readily accessible biomarker that could potentially aid in clinical risk stratification and management of MINOCA patients, a group characterized by considerable heterogeneity and diagnostic uncertainty.

The pathophysiological mechanisms of MINOCA are multifaceted and frequently entail inflammatory processes, despite the lack of substantial coronary artery occlusion [20]. Inflammation significantly contributes to MINOCA and serves as a robust prognostic factor. Numerous studies emphasize the importance of inflammatory biomarkers in outcome prediction. Plasma biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6), indicate the extent of local vascular inflammation resulting from several non-atherosclerotic etiologies of MINOCA, such as coronary vasospasm and coronary microvascular dysfunction [21,22]. Increased neutrophil levels indicate an acute-phase systemic inflammatory response, linked to plaque destabilization, microvascular dysfunction, and myocardial damage. Neutrophils play a pivotal role in these processes through the release of proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps (NETs), contributing to endothelial dysfunction and a prothrombotic state [23,24]. On the other hand, hypoalbuminemia may signify chronic inflammation, inadequate nutritional status, or hepatic dysfunction, all of which are recognized predictors of unfavorable outcomes in cardiovascular disease [25,26]. All four biomarkers in our study showed strong associations with one-year MACCE, underscoring the clinical significance of systemic inflammation in MINOCA prognosis. However, our findings suggest that NPAR outperforms these markers, likely due to its ability to capture both increased innate immune activation (via neutrophil percentage) and decreased endogenous antioxidant/anti-inflammatory defenses (via serum albumin levels).

Recent studies demonstrate that NPAR serves as an inflammation-based prognostic predictor for several cardiovascular disorders, including STEMI and NSTEMI, which are elements of acute coronary syndrome, as well as chronic heart failure and atrial fibrillation (AF) [12,14,27,28]. In a comparable manner, a study by Huang et al. [29] similarly identified CAR as a predictor of MACCE in patients with STEMI and hypertension. Zhang et al. [30] conducted a study demonstrating that SII elevated the risk of MACCE in patients with STEMI undergoing coronary angiography. A study conducted by Trimarchi et al. [31] identified ALI as an independent predictive indicator for all-cause mortality in patients with STEMI. The study by Zhou et al. [22] established a correlation between various biomarkers and the incidence of MACE in patients with MINOCA. One such biomarker is SII. Zhao et al. [32] revealed that low ALI values independently predicted MACCE in patients with MINOCA. Despite these findings, the relationship between NPAR, CAR, and adverse outcomes in MINOCA had not been previously established. Our study fills this gap and suggests that NPAR, due to its accessibility and strong predictive power, may serve as a valuable tool for early risk assessment and personalized management strategies in MINOCA patients.

Limitations

This study possesses multiple limitations that warrant consideration. The principal restriction is its retrospective, single-center design. Secondly, biomarker levels were evaluated solely at baseline and may not represent temporal fluctuations. Third, although there is a considerable population from a particular patient category, the overall number may be inadequate to extrapolate our findings to all MINOCA patients. Fourth, even adjusting for many confounders, the potential for enduring confounding remains uneliminated. Additionally, the presence of albuminuria in patients with chronic kidney disease constituted an important limitation of the study, as it may have influenced serum albumin levels and, consequently, the interpretation of their prognostic value. Consequently, further rigorously planned, prospective, multicenter trials are required to validate and enhance our findings.

Conclusion

In MINOCA patients, this study identified higher NPAR, CAR, SII, and lower ALI values as independent predictors of 1-year MACCE development. In comparison to other biomarkers, NPAR reveals superior predictive value. Due to its simplicity, accessibility, and predictive capability, NPAR may function as an essential instrument for early risk categorization and tailored management measures in MINOCA.

Ethics Committee Approval: The study was approved by Medipol University Ethics Committee (No: E-10840098-202.3.02-1849, Date: 06.03.2025).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – E.K.; Design – E.K., K.K.; Supervision – E.K., Y.V.; Fundings – E.K., Y.V.; Materials – F.F.Y., G.İ.; Data collection and/or processing – F.F.Y., G.İ.; Analysis and/or interpretation – Y.V., E.K.; Literature search – E.K., K.K.; Writing – E.K., K.K., Y.V.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

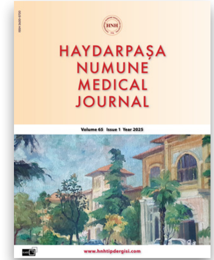
References

1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Glob Heart 2018;13:305–38. [CrossRef]
2. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017;38:143–53. [CrossRef]
3. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. Contemporary diagnosis and management of patients with myocardial ınfarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. Circulation 2019;139:e891–e908. [CrossRef]
4. Hjort M, Eggers KM, Lindhagen L, Agewall S, Brolin EB, Collste O, et al. Increased inflammatory activity in patients 3 months after myocardial infarction with nonobstructive coronary arteries. Clin Chem 2019;65:1023–30. [CrossRef]
5. Ryabov VV, Vorobeva DA, Kologrivova IV, Suslova TE. Pro-inflammatory biomarkers and progression of atherosclerosis in patients with myocardial infarction with non-obstructive coronary artery disease: 1-year follow-up. J Pers Med 2023;13:1669. [CrossRef]
6. Sun H, Liu H, Li J, Kou J, Yang C. Analysis of the clinical predictive value of the novel inflammatory indices SII, SIRI, MHR and NHR in patients with acute myocardial infarction and their extent of coronary artery disease. J Inflamm Res 2024;17:7325–38. [CrossRef]
7. Dziedzic EA, Gąsior JS, Tuzimek A, Paleczny J, Junka A, Dąbrowski M, et al. Investigation of the associations of novel inflammatory biomarkers-Systemic Inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI)-with the severity of coronary artery disease and acute coronary syndrome occurrence. Int J Mol Sci 2022;23:9553. [CrossRef]
8. Hu C, He Y, Li J, Zhang C, Hu Q, Li W, et al. Association between neutrophil percentage-to-albumin ratio and 28-day mortality in Chinese patients with sepsis. J Int Med Res 2023;51:3000605231178512. [CrossRef]

9. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. FEBS Lett 2008;582:1783–7. [CrossRef]
10. Granger CB, Kochar A. Understanding and targeting inflammation in acute myocardial infarction: an elusive goal. J Am Coll Cardiol 2018;72:199–201. [CrossRef]
11. Gong Y, Li D, Cheng B, Ying B, Wang B. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. Epidemiol Infect 2020;148:e87. [CrossRef]
12. Wang X, Zhang Y, Wang Y, Liu J, Xu X, Liu J, et al. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with chronic heart failure. BMC Cardiovasc Disord 2023;23:568. [CrossRef]
13. Xu S, Sun Y, Zhang S, Peng Y, Dai D, Zhao L. Relationship of neutrophil percentage-to-albumin ratio with stroke: evidence from NHANES 1999-2020. Brain Behav 2024;14:e70192. [CrossRef]
14. Cui H, Ding X, Li W, Chen H, Li H. The neutrophil percentage to albumin ratio as a new predictor of in-hospital mortality in patients with ST-Segment elevation myocardial infarction. Med Sci Monit 2019;25:7845–52. [CrossRef]
15. Lin Y, Lin Y, Yue J, Zou Q. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in critically ill patients with acute myocardial infarction. BMC Cardiovasc Disord 2022;22:115. [CrossRef]
16. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 1999;33:1756–824.
17. Kawsara A, Núñez Gil IJ, Alqahtani F, Moreland J, Rihal CS, Alkhouli M. Management of coronary artery aneurysms. JACC Cardiovasc Interv 2018;11:1211–23. [CrossRef]
18. Beltrame JF. Defining the coronary slow flow phenomenon. Circ J 2012;76:818–20. [CrossRef]
19. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45–60. [CrossRef]
20. Pasupathy S, Tavella R, McRae S, Beltrame JF. Myocardial infarction with non-obstructive coronary arteries - diagnosis and management. Eur Cardiol 2015;10:79–82. [CrossRef]
21. Xu X, Zhang G, Li Z, Li D, Chen R, Huang C, et al. MINOCA biomarkers: Non-atherosclerotic aspects. Clin Chim Acta 2023;551:117613. [CrossRef]
22. Zhou H, Li X, Wang W, Zha Y, Gao G, Li S, et al. Immune-inflammatory biomarkers for the occurrence of MACE in patients with myocardial infarction with non-obstructive coronary arteries. Front Cardiovasc Med 2024;11:1367919. [CrossRef]
23. Naruko T, Ueda M, Haze K, van der Wal AC, van der Loos CM, Itoh A, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation 2002;106:2894–900. [CrossRef]
24. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. Circ Res 2017;120:736–43. [CrossRef]
25. Gotsman I, Shauer A, Zwas DR, Tahiroglu I, Lotan C, Keren A. Low serum albumin: A significant predictor of reduced survival in patients with chronic heart failure. Clin Cardiol 2019;42:365–72. [CrossRef]
26. Zhu L, Chen M, Lin X. Serum albumin level for prediction of all-cause mortality in acute coronary syndrome patients: a meta-analysis. Biosci Rep 2020;40:BSR20190881. [CrossRef]
27. Karaca M, Gumusdag A. Prognostic role of neutrophil percentage-to-albumin ratio in patients with non-st-elevation myocardial ınfarction. Medicina (Kaunas) 2024;60:2101. [CrossRef]
28. Xu Y, Lin Z, Zhu C, Song D, Wu B, Ji K, et al. The neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with atrial fibrillation: a retrospective study. J Inflamm Res 2023;16:691–700. [CrossRef]
29. Huang J, Zhang J, Li L, Chen M, Li Y, Yu X, et al. Triglyceride-glucose index and hsCRP-to-albumin ratio as predictors of major adverse cardiovascular events in STEMI patients with hypertension. Sci Rep 2024;14:28112. [CrossRef]
30. Zhang W, Jia H, Zhao X, Song W, Sun W, Wang Q, et al. Predictive value of cumulative SII for MACE in STEMI patients after PCI. Medicine (Baltimore) 2025;104:e41983. [CrossRef]
31. Trimarchi G, Pizzino F, Lilli A, De Caterina AR, Esposito A, Dalmiani S, et al. Advanced lung cancer inflammation index as predictor of all-cause mortality in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. J Clin Med 2024;13:6059. [CrossRef]
32. Zhao HW, Wang CF. The relationship between advanced lung cancer inflammation index and adverse clinical outcomes in patients with myocardial infarction with no-obstructive coronary arteries. J Inflamm Res 2025;18:9907–17. [CrossRef]

HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.65632
Haydarpasa Numune Med J 2025;65(4):402–406



hnhtipdergisi.com

SYSTEMATIC META-ANALYSIS

Red Blood Cell Distribution Width in Migraine: A Systematic Review and Meta-Analysis

Giuseppe Lippi[1], **Camilla Mattiuzzi**[2]

[1]Department of Clinical Biochemistry, University of Verona, Verona, Italy
[2]Medical Director, Rovereto Hospital, Provincial Agency for Social and Health Services (APSS), Trento, Italy

Abstract

Introduction: Migraine is a prevalent and disabling neurological disorder with a complex and partially understood pathophysiology. Red blood cell distribution width (RDW), a routine hematological parameter, has emerged as a potential biomarker of systemic inflammation, which may be relevant in migraine.

Methods: We conducted a systematic review and meta-analysis of studies reporting RDW values in individuals with and without migraine. Electronic databases (PubMed, Scopus, Web of Science) and Google Scholar were searched through June 23, 2025. Inclusion criteria comprised case-control studies comparing RDW in migraineurs and healthy controls.

Results: Five case-control studies comprising 1,240 participants (709 with migraine and 531 without) met the inclusion criteria. RDW values were higher in migraine patients in four of the five studies. The overall pooled weighted mean difference (WMD) in RDW was 0.24 (95% CI: –0.15 to 0.62; I^2=97%). After excluding one outlier study, the WMD increased to 0.47 (95% CI: 0.18 to 0.76).

Discussion and Conclusion: Our findings suggest a trend toward elevated RDW in individuals with migraine. While promising, the results are limited by high heterogeneity and methodological inconsistencies across studies, underscoring the need for further standardized research.

Keywords: Migraine; RDW; red blood cell distribution width.

Migraine is a highly prevalent and disabling neurological disorder, affecting approximately 12–15% of the global population, with a marked female predominance and a peak incidence during the most productive years of life [1,2]. It also ranks among the leading causes of disability-adjusted life years (DALYs) worldwide [2], imposing substantial individual and societal burdens due to its recurrent, often severe attacks and the associated disability caused by a wide range of debilitating symptoms, including nausea (up to vomiting), dizziness or vertigo, photophobia, phonophobia, osmophobia, allodynia, and post-migraine fatigue [1].

The complex and multifactorial pathophysiology of migraine remains incompletely understood; however, it is thought to involve genetic predisposition, neurovascular dysfunction, cortical spreading depression, and inflammation [3]. In this context, the identification of accessible and reliable laboratory biomarkers that reflect underlying pathophysiological mechanisms, aid in risk assessment, support diagnosis, and enable monitoring of disease progression is of considerable clinical importance.

Red blood cell distribution width (RDW), a routinely reported parameter in the complete blood count (CBC),

Correspondence: Giuseppe Lippi, M.D. Department of Clinical Biochemistry, University of Verona, Verona, Italy
Phone: +39 045 812 43 08 **E-mail:** giuseppe.lippi@univr.it
Submitted Date: 23.06.2025 **Revised Date:** 27.08.2025 **Accepted Date:** 08.09.2025
Haydarpaşa Numune Medical Journal

reflects variability in the size of circulating erythrocytes [4]. Traditionally used in the differential diagnosis of anemia, RDW has more recently emerged as a potential biomarker of various pathological conditions characterized by systemic inflammation, oxidative stress, and endothelial dysfunction—key pathways that may also be implicated in the pathogenesis of migraine [5]. Accordingly, this systematic review and meta-analysis aimed to summarize the available evidence on RDW in patients with and without migraine and to evaluate whether this parameter may serve as a potential biomarker in this clinical setting.

Materials and Methods

We conducted a comprehensive electronic search in Medline (via PubMed), Scopus, and Web of Science using the keywords "red blood cell distribution width" OR "RDW" AND "migraine," applied to all searchable fields. Because anemia status was not consistently reported across studies, it was not feasible to apply anemia as an exclusion criterion in this meta-analysis. The search was performed without restrictions on date (up to June 23, 2025) or language. The protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An additional search was performed in Google Scholar using the same predefined keywords to capture studies not indexed in the primary databases, limited to the first 1000 items.

Titles, abstracts, keywords, and full texts of all retrieved records were systematically screened. Studies were included if they reported RDW values in individuals with (cases) and without (controls) a diagnosis of migraine based on the criteria of the International Headache Society [6]. The reference lists of the included studies were also manually screened using forward and backward citation tracking to identify additional potentially relevant studies.

Statistical Analysis

A pooled analysis was conducted to calculate the weighted mean difference (WMD) and corresponding 95% confidence intervals (95% CI) for RDW values between migraine and non-migraine subjects. A random-effects model was used to account for heterogeneity due to variations in study populations, hematological analyzers used to measure RDW, and measurement units. Heterogeneity was assessed using the χ^2 test and the I^2 statistic with the inverse variance heterogeneity (IVhet) model. All analyses were performed using MetaXL software, Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). This study was conducted in accordance with the principles of the Declaration of Helsinki and relevant local legislation. Ethical approval was not required, as the study was a meta-analysis and therefore exempt from local institutional review board requirements.

Results

A total of 22 articles were initially identified through searches of the three primary scientific databases (Fig. 1). Of these, 19 were excluded after title, abstract, or full-text screening for the following reasons: 14 did not specifically include patients with migraine, 3 did not report RDW values, and 2 were review articles. An additional two eligible studies were identified through manual searching in Google Scholar. Consequently, five studies comprising a total of 1,240 participants (709 with migraine and 531 without) met the inclusion criteria and were included in the pooled analysis, as summarized in Table 1 [7–11]. All included studies had a case-control design. Three studies reported the laboratory instruments used to measure RDW and specified the measurement unit as percentage (%), with each using a different hematological analyzer. In contrast, two studies did not report the type of analyzer

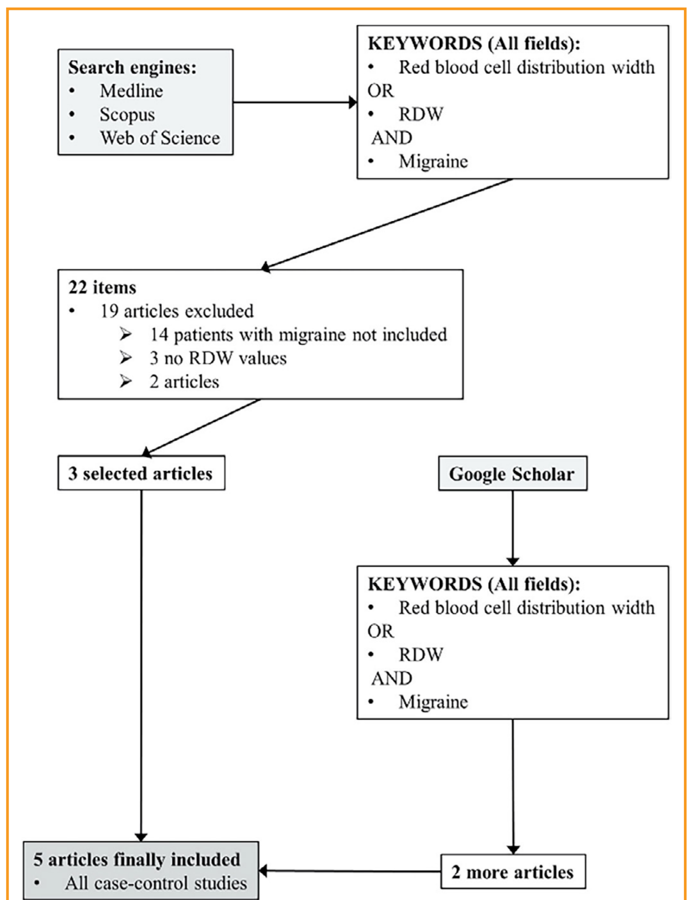


Figure 1. Flow-chart detailing search criteria, eligibility, exclusion/inclusion, and final outcome of our search.

RDW: Red blood cell distribution width.

Table 1. Summary of the studies included in the pooled analysis

Authors	Study design	Sample size (patients)	Instrumentation	Measure unit	Values (cases vs. controls)
Celikbilek et al. [7],	Case-control	200 (100 with migraine)	Coulter LH 750 (Beckman Coulter)	Percent (%)	13.8±0.5 vs. 13.1±0.3
Acar et al. [8],	Case-control	165 (100 with migraine)	Pentra DF Nexus (Hariba Medical)	Percent (%)	14.6±1.7 vs. 14.4±1.6
Gül et al. [9],	Case-control	167 (100 with migraine)	Non-available	Percent (%)	13.8±1.3 vs. 13.2±1.0
Meamar et al. [10],	Case-control	200 (100 with migraine)	Sysmex K1000 (Sysmex Corp)	Non-available	13.4±0.2 vs. 13.1±0.1
Kömürcü et al. [11],	Case-control	508 (309 with migraine)	Non-available	Non-available	13.3±0.8 vs. 13.9 ±1.1

used or the measurement unit. Although the measurement unit of RDW was not explicitly stated in two studies, it can reasonably be inferred that the values were expressed as percentages based on the reported data. The overall risk of bias was low across all included studies (Fig. 2). The funnel plot of the studies included in the meta-analysis is shown in Figure 3 and demonstrates marked asymmetry, suggesting the presence of potential publication bias or small-study effects, with studies of smaller sample size appearing to be unevenly distributed and clustering predominantly on one side of the pooled effect estimate. This asymmetry indicates that negative or non-significant results may be underrepresented in the available literature.

The results of the random-effects meta-analysis are presented in Figure 4. In all but one study, RDW values were higher in patients with migraine than in control subjects. The overall pooled weighted mean difference (WMD) in RDW between migraine and non-migraine groups was 0.24 (95%CI: –0.15 to 0.62), with substantial heterogeneity (Cochrane's Q: 150.9; I^2=97%). After logit transformation, the WMD was 0.37 (95%CI: 0.27–0.35). Following exclusion of the single study by Kömürcü et al. [11], which reported

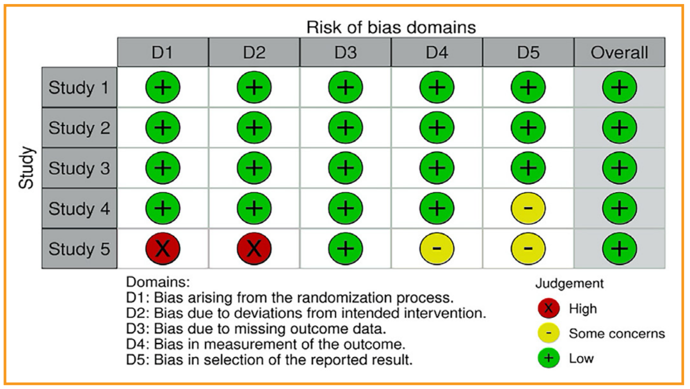


Figure 2. Risk of bias evaluated according to Risk of bias tools – ROBVIS.

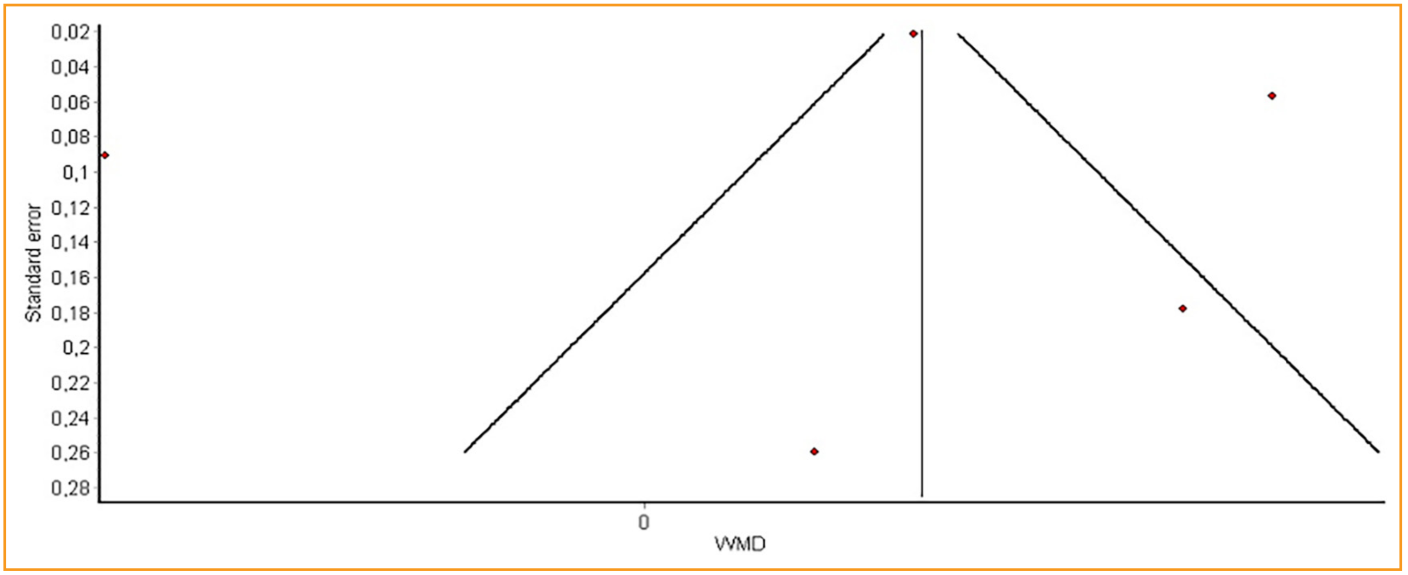


Figure 3. Funnel plot of studies included in the meta-analysis.

WMD: Weighted mean difference.

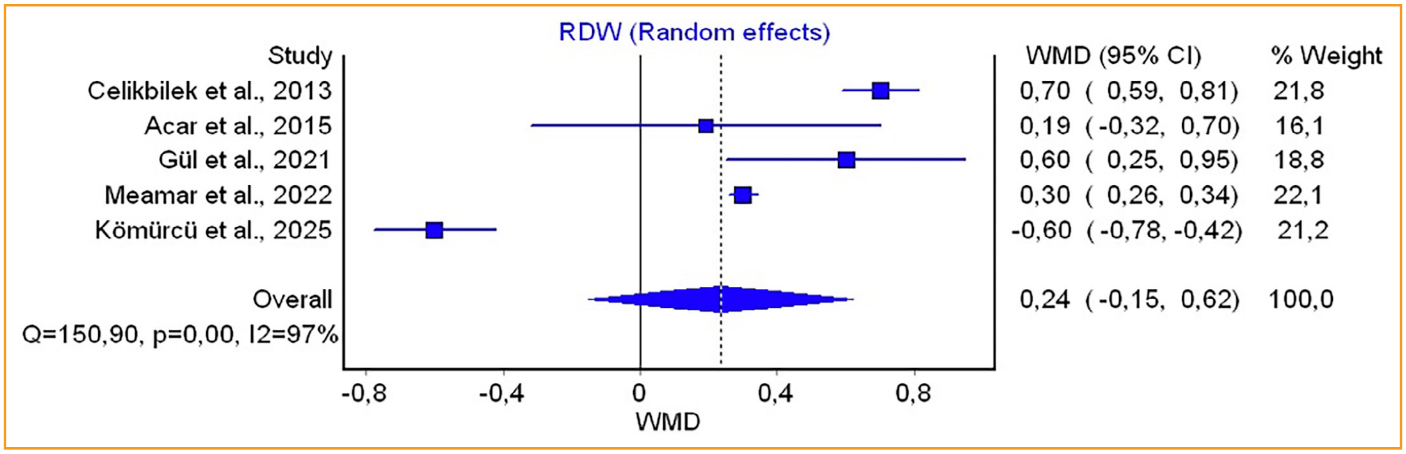


Figure 4. Weighted mean difference and 95% confidence interval (95% CI) of red blood cell distribution width (RDW) values in patients with or without migraine.

WMD: Weighted mean difference.

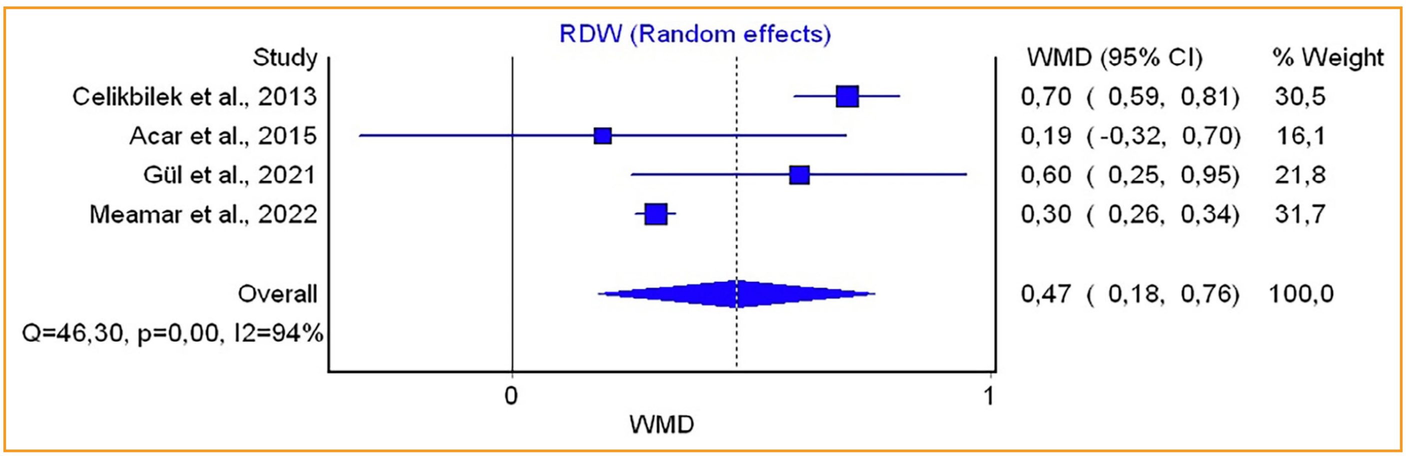


Figure 5. Weighted mean difference and 95% confidence interval (95% CI) of red blood cell distribution width (RDW) values in patients with or without migraine after excluding the study of Kömürcü et al. [11].

WMD: Weighted mean difference.

lower RDW values in migraine patients, the pooled WMD became statistically significant and positive (WMD=0.47; 95%CI: 0.18 to 0.76), although heterogeneity remained high (Cochrane's Q: 49.3; I^2=94%) (Fig. 5). After logit transformation, the WMD was 0.35 (95%CI: 0.31–0.39).

Discussion

RDW has gained increasing attention in recent years as a potential biomarker for a range of pathological conditions, many of which are characterized by persistent inflammation, oxidative stress, and endothelial dysfunction [4]. In general, an elevated RDW reflects increased heterogeneity in erythrocyte volume, which may ultimately influence cerebrovascular tone, nociceptive signaling, and immune responses [5]. Although RDW lacks specificity for any particular pathology, it is inexpensive, widely available, and relatively reproducible [12], making it a potentially attractive laboratory parameter in the context of migraine, provided that its diagnostic or prognostic utility is confirmed.

The aim of the present meta-analysis was to investigate the potential association between RDW and migraine by synthesizing data from the available scientific literature. Our pooled analysis indicates a trend toward higher RDW values in individuals with migraine compared with healthy controls. Specifically, four of the five included studies reported significantly elevated RDW levels among migraine patients, with individual WMDs consistently in the positive direction and with the overall trend becoming significant after logit transformation [7–10]. However, the study by Kömürcü et al. [11] markedly deviated from this pattern, reporting lower RDW values in migraine patients. Inclusion of this study substantially attenuated the overall pooled effect, rendering it statistically non-significant and increasing heterogeneity (I^2=97%) (Fig. 1). In a sensitivity analysis excluding the study by Kömürcü et al. [11], the pooled WMD increased and achieved statistical significance, (Fig. 5) although heterogeneity remained high (I^2=94%).

The study by Kömürcü et al. [11] may differ methodologically, most notably in its exclusive inclusion of migraine patients without aura, a subgroup that may represent a distinct clinical phenotype. Interestingly, while Celikbilek et al. [7] reported identical RDW values in patients with and without aura (13.7 vs. 13.7; p=0.732), Meamar et al. [10] observed a non-significant trend toward higher RDW values in the aura group (15.1 vs. 13.4). Potential sources of heterogeneity include differences in population demographics, migraine subtypes (e.g., with or without aura), disease duration, and comorbid conditions. An additional and important contributor to heterogeneity is variability in devices and laboratory protocols used for RDW measurement, which may yield systematically different results across studies. This methodological inconsistency, combined with clinical variability, likely explains the very high level of heterogeneity observed in the analysis (I^2>94%). Moreover, the limited number of eligible studies and the relatively small cumulative sample size reduce statistical power and restrict the robustness and generalizability of the findings. A comprehensive meta-regression analysis was not feasible due to insufficient reporting of key clinical and laboratory variables across the included studies. Taken together, these factors underscore the need for future studies employing standardized measurement techniques, larger sample sizes, and more homogeneous patient populations to validate and extend the present results.

Conclusion

Future research should address these limitations by employing larger, prospective cohorts, accounting for relevant confounding variables, and adopting standardized RDW assessment methods. Additionally, it would be informative to explore whether RDW correlates with migraine severity, frequency, duration, or therapeutic response, which could further clarify its clinical utility.

Ethics Committee Approval: Ethical approval was not required, as the study was a meta-analysis and therefore exempt from local institutional review board requirements.

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – G.L., C.M.; Design – G.L., C.M.; Data collection and/or processing – G.L.; Analysis and/or interpretation – G.L.; Literature search – G.L., C.M.; Writing – G.L.; Critical review – C.M.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: Not declared.

References

1. Safiri S, Pourfathi H, Eagan A, Mansournia MA, Khodayari MT, Sullman MJM, et al. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. Pain 2022;163:e293–309. [CrossRef]
2. Mattiuzzi C, Lippi G. Updates on migraine epidemiology. Eur J Neurol 2020;27:e13. [CrossRef]
3. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol 2018;17:174–82. [CrossRef]
4. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86–105. [CrossRef]
5. Lippi G, Cervellin G, Mattiuzzi C. Migraine and erythrocyte biology: a review. Int J Lab Hematol 2014;36:591–7. [CrossRef]
6. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808. [CrossRef]
7. Celikbilek A, Zararsiz G, Atalay T, Tanik N. Red cell distribution width in migraine. Int J Lab Hematol 2013;35:620–8. [CrossRef]
8. Acar E, Beydilli H, Karagöz Ü, Yıldırım B, Kırlı İ, Kılınç RM, et al. Neutrophil-lymphocyte ratio can distinguish migraine patients from other patients with nonspecific headache in the emergency department. Acta Med Mediterranea 2015;31:829–34.
9. Gül BZ, Gözübatık Çelik RG, Selçuk B, Aksoy S, Gül M, Soysal A. New indicator of inflammation in migraine: red blood cell distribution. Haydarpasa Numune Med J 2021;61:166–71.
10. Meamar R, Janghroban S, Ansari B, Saeedi A, Atefi A, Tavakoli F. Evaluation of red cell distribution width alterations with severity of migraine. Canon J Med 2022;3:15–8.
11. Kömürcü HF, Erkalaycı C, Gozke E. Hemogram and inflammatory indices in pain-free periods in migraine patients without aura. Neurol Res 2025;47:44–50. [CrossRef]
12. Lippi G, Pavesi F, Bardi M, Pipitone S. Lack of harmonization of red blood cell distribution width (RDW). Evaluation of four hematological analyzers. Clin Biochem 2014;47:1100–3. [CrossRef]