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SRINMED, 2024; 1(3)

EDITORIAL TEAM

Scientific Reports in Medicine

- Adolescent Diseases
- Childhood Diseases
- Multisystem Diseases
- Physical Medicine and Rehabilitation
- Forensic Medicine
- Mental Health and Diseases
- Cardiovascular System Diseases
- Nervous System Diseases
- Neurosurgery
- Respiratory System Diseases
- Infectious Diseases
- Occupational Diseases
- Nuclear Medicine
- Oncological Diseases
- Sports Medicine
- Genetic Diseases
- Medical Pathology

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

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

Scientific Reports in Medicine is a scientific publication of Academician Publishing and published three times a year online.

It is an open access scientific journal, which publishes original contributions in medical disciplines pertaining to human medicine. In this context, the Journal publishes original researches, case reports, and reviews based on clinical and experimental studies in all areas of human medicine. It is a scientific, periodic journal based on the principles of blind peer-review process. The publication language is English. The Journal is published online three times a year on April, August, and December.

Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts submitted to the Journal are screened in terms of originality.

All manuscripts should be submitted by online system of the Journal.

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SRINMED, 2024; 1(2)

AUTHOR GUIDELINES

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

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

Audience

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

Manuscript Preparation

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

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

Process of Peer Review

The journal utilizes a standard online site (SRINMED), operated by Academician Publishing, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration

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

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

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

About the scientific language to be used in writing your manuscript

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

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

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

You can contact Academician Publishing to receive Editing and Proofreading services for a fee. You can click here to contact Academician Publishing.

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

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

Use of first person

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

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

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

Names made up of single word should not be abbreviated.

Instead of,

- Hypertension (HT) is one of the most …

Throughout the manuscript, you should use;

- Hypertension is one of the most …

Instead of,

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• Rituximab (RTX) is an IgG1 kappa chimeric monoclonal
Throughout the manuscript, you should use;
• Rituximab is an …
Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)
For example;
• In 2 studies, …
Should be replaced with;
• In two studies …
For example;
• … perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,
Should be replaced with;
• … perivascular lymphotic infiltration in only 10% of patients … in 7% of patients …
Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.
• determined to be high
Should be replaced with;
• … was found to be high.
Or throughout the entire manuscript;
• found to be significantly higher …
If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "… a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.
• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).
Should be replaced with;
While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Methods, Results [Findings], and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection

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of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

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

Sections

Abstract

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

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

Keywords

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

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

Introduction

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

Methods

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

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

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

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

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

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

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

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

Results [Findings]

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

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

Discussion

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

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote

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self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

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

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

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

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

Sample for in-text citation:

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

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

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

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4).

Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

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

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine,

its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

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

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

Reference List

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

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

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

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

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Scientific Reports in Medicine, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal. With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

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

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

Sample for Journal Article without DOI

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

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

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Sample for Journal Article with DOI

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

Article not in English

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

Books and Other Monographs

Personal author(s)

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

Editor(s), compiler(s) as author

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

Author(s) and editor(s)

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

Chapter in a book

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

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

Conference proceedings

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

Article published on the Internet ahead of the print version:

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

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

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

Thesis

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

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

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

Tables

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

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

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

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural.

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While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

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

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is

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to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

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

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 μm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

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

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

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

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing

size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

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

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EDITORIAL

As the journal Scientific Reports in Medicine (SRINMED), we are excited to share with you the excitement of continuing our publication journey and we are happy to share it with you, our valued science readers. I would like to thank all the authors who contributed to our fourth issue.

Editor-in-Chief

Assoc. Prof. Dr. Burak METE

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Investigation and Evaluation of Corneal Parameters in Patients withThyroid Ophthalmopathy

Evaluation of Corneal Parameters in Thyroid Ophthalmopathy

Burak Ulas[1], Altan Atakan Ozcan[2]

DOI 10.37609srinmed.36

Abstract: Objective: To evaluate corneal findings in patients with thyroid ophthalmopathy (TO) according to clinical activity score using corneal densitometry and corneal topography parameters.

Methods: This cross-sectional study was conducted in the department of Ophthalmology of Cukurova University between January 1, 2021, and June 31, 2022. The patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, fundoscopic examination, and hertel exophthalmometry. Clinical activity scores according to the European Group of Graves' Orbitopathy (EUGOGO) classification and retinal nerve fiber layer values were also recorded. Corneal densitometry and topography data recorded for 3 months were noted, and evaluated together according to the EUGOGO classification.

Results: Fifty eyes of 25 thyroid ophthalmopathy cases (15 female, 10 male) with a mean age of 52.6±12.87 years were included in the study. For corneal densitometric measurements in the first month of evaluation, there were significant differences in 2-6 mm zone specifically in anterior and posterior layers (p<0,040, p<0,010), 6-10 mm zone specifically in anterior, center, posterior layers and total diameter (p<0,008, p<0,002, p<0,002, p<0,003). When it comes to corneal topography, changes were detected in Sim K values especially a decrease in K1 and Avg in patients with mild and severe TO (p<0,046, p<0,010) and in patients with mild and moderate TO (p<0,027, p<0,017). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO (p<0,029).

Conclusion: Mechanical and inflammatory factors play a significant role in the ocular findings of TO, and can change corneal biomechanical properties. The present study showed differences in corneal topography and densitometry parameters among the patients with thyroid ophthalmopathy.

Keywords: Thyroid ophthalmopathy, corneal densitometry, corneal topography.

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INTRODUCTION

Graves' disease is an autoimmune disease associated with an imbalance in thyroid hormone levels. The most common cause of hyperthyroidism is Graves' disease. Graves' disease is typically seen in middle aged (40-60 years) period. Thyroid ophthalmopathy (TO), is the most common extrathyroidal manifestation of Graves' disease which is characterized by orbital inflammatory infiltration and activation of orbital fibroblasts resulting in their activation of orbital inflammation and tissue remodeling (1). TSH receptors are also found on orbital fibroblasts and this is the primary mechanism of ophthalmopathy. Previous studies showed that approximately 60% of the patients have mild symptoms like redness, proptosis, eyelid retraction, and lag exophthalmos (1,2). The others experience extraocular muscles involvement that causes diplopia, intraocular hypertension and as well as optic neuropathy due to optic nerve compression (2). Risk factors include smoking, high serum level of thyrotropin receptor antibodies, radioactive iodine (RAI) treatment, thyroid dysfunction and hypercholesterolemia. Eventhough, there are a variety of scoring systems used to classify TO, our study classified thyroid patients as mild, moderate and severe according to EUGOGO (European Group on Graves' Orbitopathy) classification (1-3). On the other hand, in order to minimize irreversible damages a stage-adapted anti-inflammatory therapy is of great importance. TO classification is based on clinical activity score (CAS). Treatment decisions are based on clinical activity, severity, and duration of Graves' orbitopathy (GO) (2,3). In this study, we aimed to evaluate the effects of systemic and thyroid ophthalmopathy findings via using optical cohorence tomography (OCT), corneal densitometry, and corneal topography parameters according to clinical activity score in thyroid patients.

METHODS

This cross-sectional study was conducted in the Department Ophthalmology of Cukurova University between January 1, 2021, and June 31, 2022. This study included 50 eyes of 25 thyroid patients who applied to the Oculoplasty unit of Cukurova University, Department of Ophthalmology. This study was approved by the Institutional Ethics Review Board of Cukurova University (03.06.2022-123/22), and informed consent was obtained from each patient, and all research adhered to the tenets of the Declaration of Helsinki. All patients fulfilled the TO comprehensive diagnostic criteria and were diagnosed by same ophthalmologists (BU, AAO). During the study period, 25 patients who met all diagnostic criteria and continued their full follow-up were included in the study.

The patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, ultrasonic pachymetry, eyelid laxity evaluation, fundoscopic examination and hertel exophthalmometry. Clinical activity scores according to the European Group of Graves' Orbitopathy (EUGOGO) classification and retinal nerve fiber layer values were also recorded. Cases with lymphoma, idiopathic orbital inflammation, cellulitis, orbital tumors, glaucoma, uveitis, retinal and corneal disease, a history of ocular trauma or surgery, and patients using eye drops and contact lenses were excluded from the study. Corneal densitometry and topography (CSO, Italy) data recorded for 3 months were noted and evaluated together according to the EUGOGO classification. The densitometry measurements are expressed in gray scale unit and measurements range from 0 (no clouding, maximum transparency) to 100 (completely opaque cornea, no transparency) depending on the degree of light scatter from the cornea.

Statistical analysis

Statistical analysis of the data was conducted using the Statistical Packages for the Social Science (SPSS 20.0, IBM corp. IBM SPSS Statistics for Windows, Version 20.0.Armonk, NY). The variables were investigated using analytical methods (Kolmogorov-Smirnov/

Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables while medians and interquartile range for the non-normally distributed and ordinal variables. Student's t-test was used to find differences between independent groups, and Chi-square analysis was used for qualitative data comparison. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Fifty eyes of 25 thyroid orbitopathy cases (15 female, 10 male) with a mean age of 52.6±12.87 years were included in the study. For corneal densitometric measurements, the cornea was divided into four concentric radial zones (0-2mm, 2-6mm, 6-10mm, 10-12mm and total) and anterior, central, and posterior layers according to corneal thickness. In the first month of evaluation, there were significant differences in 2-6 mm zone specifically in anterior and posterior layers (p<0,040, p<0,010), 6-10 mm zone specifically in anterior, center, posterior layers and total diameter (p<0,008, p<0,002, p<0,002, p<0,003) and in overall corneal thickness specifically in anterior, center, posterior layers and total diameter (p<0,008, p<0,004, p<0,002, p<0,007) (Table 1). During the second month of evaluation, there were significant differences in posterior layers of 0-2mm and 2-6mm zones (p<0,045, p<0,034), and in the central layers of 2-6mm zone and overall corneal thickness (p<0,037, p<0,041) (Table 2). In the third month of evaluation only in the anterior layer of total corneal thickness a significant difference is seen (p<0,039) (Table 3). When it comes to corneal topography, changes were detected in Sim K values especially a decrease in K1 and Avg in patients with mild and severe TO (p<0,046, p<0,010) and in patients with mild and moderate TO (p<0,027, p<0,017). Another decrease is also seen in K2 values specifically in patients with mild and severe disease (p<0,005) during the first month of evaluation. Hertel exophthalmometry measurements when compared between groups (mild - moderate - severe) significant differences were seen in the 1st month in mild and severe TO patients (p<0,041) and 3rd month especially in patients with mild-moderate (p<0.025) and mild-severe TO (p<0,020). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO (p<0,029).

DISCUSSION

TO is an autoimmune disease affecting the thyroid gland and eye (4). Mechanical and inflammatory factors play a significant role in the ocular findings of TO and can change ocular, corneal biomechanical and densitometric properties (5). Reduced tear production and rubbing of eyes, common in Graves' disease, is a known precipitant of keratoconus (KC). Our study showed some differences in corneal biomechanical properties among the patients with TO disease. By using Pentacam all the patients were evaluated and the results of this analysis demonstrate the haziness score at three layers of corneal depth: the anterior layer, comprising 120 μm of anterior cornea; the posterior layer, comprising 60 μm of the extreme posterior cornea; and the central layer, located between the anterior and posterior layers. A total densitometry score is also reported that represents the volume between the epithelium and endothelium. Eventhough there are not enough studies related with the effects of TO on corneal densitomery, we found out that there were significant differences in anterior and posterior layers of 2-6 mm zone (p<0,040, p<0,010), all layers of 6-10 mm zone (p<0,008, p<0,002, p<0,002, p<0,003) and in all layers of overall corneal thickness (p<0,008, p<0,004, p<0,002, p<0,007). During the second month of evaluation, there were significant differences in posterior layers of 0-2mm and 2-6mm zones (p<0,045, p<0,034), and in the central layers of 2-6mm zone and overall corneal thickness (p<0,037, p<0,041). In the last month of evaluation only in the anterior layer of total corneal thickness a significant difference is seen (p<0,03). We can say that every stage of TO has effect on corneal densitometry and the most affected one is the anterior layer which is

supposed to lead to the thinning of epithelial layer. Previous studies have analyzed mostly corneal densitometries of keratoconus, primary congenital glaucoma and outcomes after keratoplastic surgeries. Lopes et al.[5] found out a higher densitometry in all layers of the central cornea (p<0.001). The difference was marked in all layers of 0-2mm and 2-6mm zones and these values were detected in different stages of KC (5). Monitoring the cornea in patients with TO using Pentacam may help to show the presence of subclinical inflammation and regulate the follow-up and treatment protocols. For this reason larger sample sizes and prospective design studies are needed to reach more conclusive results.

It is known that increased expression of inflammatory mediators in tears of GO patients suggests that the lacrimal glands could be a target for immune responses and this may play role in the pathogenesis of tear film and ocular surface stability (6). The pathophysiologic alterations of active TO could result in an increase in orbital soft tissue volume, which pushes the globe anteriorly, leading to raised retrobulbar pressure and progression of proptosis (7). In our study, hertel exophthalmometry measurements increased during the severity of TO and significant differences were seen in the 1st month in mild and severe TO patients (p<0,041) and 3rd month especially in patients with mild-moderate (p<0.025) and mild-severe TO (p<0,020). Same results were found in the study of Tran et al.[8], where at initial presentations 41% of their patients demonstrated asymmetric proptosis (8). Upon reaching the stable phase, asymmetric proptosis persisted in only 22% of patients. A decline in the rate asymmetric proptosis was greatest within the first 3 months of the active phase (8). During the third month the retinal nerve fiber layer values were significantly thinner in patients with moderate-severe TO (p<0,029). Luo et al.[9], no statistically significant differences were found between the mild thyroid-associated opthalmopathy group and the control group in nerve fiber layers of patients (9). In the moderate-to-severe thyroid-associated opthalmopathy group, temporal and nasal peripapillary nerve fiber layer thicknesses were lower compared to the control group ($p = 0.041$, $p = 0.012$). The thinning of RNFL might be a strong suggestion for closer vision follow-up and earlier decompression surgery.

Almost 50% of patients with TO symptoms are mild (10). If the diagnosis couldn't be performed at the active phase, some cases might have severe sight-threating form of disease(11-13). TO is disfiguring and diabling autoimmune condition (14,15). Thyroid ophthalmopathy has been commonly seen in female patients who are 30-50 years old period (12-15). Consistent with the literature, the majority of patients in our study were female and their average age was approximately 50 years. Therefore, when evaluating TO patients, it is important to first examine demographic data.

Limitations of the study

There were several limitations to present study that including relatively few parameters. The main limitation is the retrospective nature of the study, followed by a relatively small number of patients. The difference in the sample size between the groups is another limitation. Despite the inherent limitations, there is a paucity of data about corneal findings of thyroid ophthalmopathy in the literature, and this study is important because it is one of the rare studies about thyroid ophthalmopathy from Southern Turkey.

Table 1. Corneal densitometry parameters of 1st month.					
1.month					
		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,00	24,36	28,34	>0,05
	SANTRAL	16,02	16,50	18,13	>0,05
	POSTERIOR	13,10	12,96	14,13	>0,05
	TOTAL	16,70	17,94	20,19	>0,05
2-6mm	ANTERİOR	20,13	22,37	29,10	0,040
	SANTRAL	14,76	14,95	19,23	>0,05
	POSTERIOR	12,32	11,94	14,99	0,010
	TOTAL	15,75	16,42	21,11	>0,05
6-10mm	ANTERIOR	26,61	24,21	41,88	0,008
	SANTRAL	21,38	17,99	32,51	0,002
	POSTERIOR	17,96	14,79	24,05	0,002
	TOTAL	21,99	19,00	32,81	0,003
TOTAL	ANTERIOR	24,43	25,26	36,21	0,008
	SANTRAL	19,01	17,74	25,69	0,004
	POSTERIOR	15,98	14,22	19,63	0,002
	TOTAL	19,86	19,08	27,16	0,007

Table 2. Corneal densitometry parameters of 2nd month.					
2.months					
		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,72	23,66	28,69	>0,05
	SANTRAL	16,11	16,26	18,03	>0,05
	POSTERIOR	13,13	12,76	14,10	0,045
	TOTAL	16,98	17,53	20,28	>0,05
2-6mm	ANTERIOR	20,87	22,11	23,38	>0,05
	SANTRAL	14,85	14,97	18,85	0,037
	POSTERIOR	12,31	12,04	14,63	0,034
	TOTAL	16,04	16,41	20,63	>0,05
6-10mm	ANTERIOR	26,61	24,21	41,88	>0,05
	SANTRAL	21,38	17,99	32,51	>0,05
	POSTERIOR	17,96	14,79	24,05	>0,05
	TOTAL	21,99	19,00	32,81	>0,05
TOTAL	ANTERIOR	24,43	25,26	36,21	>0,05
	SANTRAL	19,01	17,74	25,69	0,041
	POSTERIOR	15,98	14,22	19,63	>0,05
	TOTAL	19,86	19,08	27,16	>0,05

Table 3. Corneal densitometry parameters of 3rd month.

3. month		Mild GO	Moderate GO	Severe GO	P
0-2mm	ANTERIOR	21,25	21,77	23,34	>0,05
	SANTRAL	15,91	16,37	17,00	>0,05
	POSTERIOR	13,05	13,20	13,92	>0,05
	TOTAL	16,73	17,10	18,10	>0,05
2-6mm	ANTERIOR	20,21	20,34	23,91	>0,05
	SANTRAL	14,78	15,03	17,21	>0,05
	POSTERIOR	12,31	12,37	13,82	>0,05
	TOTAL	15,77	15,92	18,31	>0,05
6-10mm	ANTERIOR	27,00	24,21	34,73	>0,05
	SANTRAL	21,81	19,46	27,94	>0,05
	POSTERIOR	18,07	16,47	21,60	>0,05
	TOTAL	22,24	20,03	28,09	>0,05
TOTAL	ANTERIOR	24,78	23,30	30,36	0,030
	SANTRAL	18,98	18,08	22,84	>0,05
	POSTERIOR	15,94	15,03	18,01	>0,05
	TOTAL	19,91	18,80	23,74	>0,05

CONCLUSION

Thyroid ophthalmopathy is the most common extrathyroidal manifestation of Graves' disease. Mechanical and inflammatory factors play a significant role in the ocular findings of TO and can change ocular, corneal biomechanical and densitometric properties. The present study showed differences in corneal biomechanical properties among the patients with TO disease.

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The relationship the mobbing situation of healthcare workers and their conflict action styles

Mobbing in Healthcare Workers

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Abstract: **Objective**: This study aims to examine whether there is a relationship between exposure to mobbing behaviors and conflict action styles among healthcare workers in Karabük Province.

Material and Method: This is a descriptive and cross-sectional study conducted with 225 healthcare workers in Karabük between May 15, 2023, and August 15, 2023. The data were collected using the Sociodemographic Information Questionnaire, the Mobbing Scale, and the Conflict Action Styles Scale.

Results: The participants' average score on the mobbing scale was found to be 82.15±44.10. Among the sub-dimensions of the mobbing scale, the highest score was obtained in the "relationships with colleagues" sub-dimension. Participants scored the highest in the "facilitating approach" sub-dimension of the Conflict Action Styles Scale. A significant difference was found between healthcare workers' exposure to mobbing and their marital status, profession, workplace, weekly working hours, job satisfaction, and smoking status. Additionally, significant differences were found between conflict action styles and gender, education, profession, weekly working hours, and job satisfaction.

Conclusion: Healthcare professionals are at risk of experiencing mobbing. This is an important issue that needs attention in terms of employee satisfaction and quality of life. Emphasizing mobbing and conflict action styles in training, implementing more comprehensive legal regulations, and improving working conditions are considered to be beneficial measures.

Keywords: Healtcare workers, Mobbing, Conflict action styles.

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INTRODUCTION

Mobbing is defined as psychological harassment, violence, intimidation, pressure, and similar behaviors carried out by one or more individuals in the same work environment towards an employee (1). It is described as any form of abusive, repetitive, and systematic behavior that jeopardizes an individual's dignity, physical, or mental integrity (2). The word "mobbing" is derived from the Latin term "mobile vulgus," which means an unstable crowd, originating from the root "Mob." In the dictionary, "Mob" is defined as "a disorderly crowd that engages in illegal violence" or "bullying" (3, 4).

The concept of mobbing was first scientifically introduced into the workplace context by Swedish psychiatrist Heinz Leymann in the 1980s. Leymann coined the term to describe a specific form of bullying towards employees in the workplace (5). He also used the term "psychological terrorism" in relation to mobbing in workplaces (6). Mobbing has become a recognized international workplace issue in the literature. This issue is evident in any country and culture (7). Mobbing can occur in both the private and public sectors, and every individual in the workforce is a potential victim of mobbing (8).

All employees in the healthcare sector can be subjected to mobbing behaviors. Factors contributing to mobbing in the healthcare sector include the need for various professional groups to work together, continuous work demands, stressful work environments, insufficient wages, bureaucratic barriers, lack of medical facilities, and unclear job descriptions (9). Due to the matrix organizational structure in hospitals, communication problems between employees are frequently encountered. Insufficient communication leads to misunderstandings and problems among employees (10). A study conducted internationally concluded that healthcare workers in hospitals, due to their unique structures, are exposed to mobbing behaviors 16 times more than those working in other service sectors (11). A retrospective study on 60 physician suicides in Italy over the past decade found that 20% of them were related to work problems involving mobbing (12).

Conflict is described as a situation where one person's demands, expectations, and interests are opposed, resisted, or differentiated by another group or individuals, creating the perception that reconciliation is no longer possible (13). In organizations where people come together for a common purpose, conflicts are natural due to differences in abilities, knowledge, skills, and experience among employees (14). Although conflict is often seen negatively, not all conflicts are destructive. A well-managed conflict can lead to positive outcomes, such as reviewing issues, becoming aware of problems, creating solutions, and improving relationships (15). Unresolved conflict, however, can escalate into mobbing behaviors, and as the intensity of the conflict increases, individuals may begin to experience psychological symptoms. Continuing unresolved issues negatively affect both the physical and psychological well-being of the individual (16).

Conflict styles refer to the behavioral actions that individuals resort to in order to cope with conflict situations (17). In conflict management, the styles developed by Rahim (1985) are defined as "integration," "accommodation," "compromise," "competition," and "avoidance" (14).

This study was conducted to evaluate the extent to which healthcare workers are exposed to mobbing behaviors, to examine whether there is a relationship between the level of mobbing exposure and conflict action styles based on various demographic characteristics of healthcare workers, and to raise awareness about mobbing.

MATERIALS AND METHODS

Type and Purpose of the Study: This study is a descriptive and cross-sectional study conducted to determine the relationship between healthcare workers' exposure to mobbing and their conflict action styles.

Study Location and Period: The research was carried out between May 15, 2023, and August 15, 2023, in healthcare institutions affiliated with the Ministry of Health in Karabük province, including physicians, midwives-nurses, and other healthcare professionals.

Population and Sample of the Study: The study population consisted of physicians, midwives-nurses, and other healthcare personnel (medical secretaries, technicians, laboratory staff, cleaning personnel, physiotherapists) actively working in Karabük and willing to participate in the study Eleven healthcare personnel who reported experiencing mobbing were excluded from work. Based on a study in the literature examining the relationship between psychological violence and conflict management styles among nurses, the calculated sample size (G-POWER) analysis determined that the minimum sample size required to achieve 80% power and a 95% confidence interval was 246.

Data Collection: The subject, content, and purpose of the study were explained to healthcare workers in written form, and participation was voluntary. The survey was conducted using Google Forms, with data collection tools (scales and survey forms) sent to healthcare workers via a link.

Data Collection Tools: The survey form consisted of three sections. The first section included the Sociodemographic Information Questionnaire, the second section contained the Mobbing Scale, and the third section comprised the Conflict Action Styles Scale.

The Sociodemographic Information Questionnaire included 17 questions about participants' age, gender, education level, marital status, and professional groups.

The Mobbing Scale, in the second section, was developed by Aiello, Deitinger, Nardella, and Bonafede (2008) to measure the exposure of healthcare workers to mobbing. The Turkish version of the Mobbing Scale was validated and tested for reliability by Ayşegül Laleoğlu and Prof. Dr. Emine Özmete in 2013. The Cronbach's alpha internal consistency coefficient of the survey was 0.948. In this study, the Cronbach's alpha coefficient was found to be α=0.978. The statements in the scale were scored on a seven-point Likert scale, ranging from "Strongly Agree – 7" to "Strongly Disagree – 1." A high score on the scale indicated greater exposure to mobbing behaviors, whereas a low score suggested less exposure. Factor analysis results revealed five sub-factors representing mobbing behaviors. The validity and reliability study of the Mobbing Scale by Laleoğlu and Özmete (2013) identified the sub-dimensions as "relationships with colleagues," "threat and harassment," "work and career," "interference with private life," and "commitment to work". The first subdimension consists of 17 items, the second subdimension consists of 7 items, the third subdimension consists of 8 items, the fourth subdimension consists of 4 items, and the fifth subdimension consists of 2 items. The scoring range of the scale is between 38 and 266. The Cronbach's alpha values for these factors were 0.961, 0.904, 0.902, 0.867, and 0.931, respectively.

The Conflict Action Styles Scale, in the third section, was developed by Johnson and Johnson (2008) and was first published in 1981, undergoing multiple revisions over time. The Turkish adaptation of the scale was based on the revision conducted by Prof. Dr. Engin Karadağ and Assoc. Prof. Dr. Ülkü Tosun (2014). The scale consists of 35 attitudinal statements and is divided into five subscales: avoidant, forcing, facilitating, compromising, and oppositional. Each subscale's reliability analysis yielded Cronbach's alpha values of 0.79, 0.76, 0.77, 0.78, and 0.72, respectively. In this study, the Cronbach's alpha values for the sub-dimensions were found to be 0.70, 0.70, 0.75, 0.72, and 0.73. Each subscale was assessed separately, and no total score was calculated. The scores for each subscale ranged from 5 to 35, with higher scores indicating a greater tendency to adopt that particular conflict action style. The scale was designed based on a five-point Likert format, with response options ranging from (1) "I never behave this way" to (5) "I mostly behave this way."

Data Analysis: Statistical analyses were performed using the SPSS 27.0 statistical software. Descriptive statistics such as frequency, percentage, mean, and standard deviation were used. The reliability of the data was assessed using Cronbach's alpha coefficient. The Kolmogorov-Smirnov test was used to determine whether the data followed a normal distribution (n≥30). Since the Mobbing Scale did not show normal distribution, the Mann-Whitney U test (U-table value) was used to compare the measurement values of two independent groups, and the Kruskal-Wallis test (H-table value) was used for comparisons among three or more groups. Dunnett's test was applied as a post-hoc analysis to determine differences between groups. Since the Conflict Action Styles Scale showed normal distribution, the independent t-test (t-table value) was used to compare two independent groups, and One-Way ANOVA (F-table value) was applied for comparisons among three or more groups. Bonferroni's test was used as a post-hoc analysis to identify group differences. The relationships between the scales were determined using Spearman correlation analysis. All comparisons were evaluated at a 95% confidence interval, with statistical significance set at $p<0.05$.

Ethical Approval: Research permission was obtained by applying to the Karabuk University Non-Interventional Clinical Research Ethics Committee, and ethical approval was granted on 08.05.2023 with decision number 2023/1343. Before participating in the study, healthcare workers provided both verbal and written informed consent.

RESULTS

The average age of the 225 healthcare workers who agreed to participate in the study is 32.37 years (30.00±6.839). According to Table 1, 47.5% of the 225 participating healthcare workers are in the 20-29 age group, 65.8% are female, 57.3% are married, and 55.1% have a bachelor's degree. Among the participants, 51.1% are midwives-nurses, while 90.7% work in a training and research hospital. In the study, 69.3% of the participants work in a mixed day-night shift system, 54.2% work 40-47 hours per week, 72.9% are satisfied with their unit, and 59.1% do not regularly smoke (Table 1).

In our study, the total mean score of the healthcare workers on the mobbing scale was determined as 82.15±44.10 (Min: 38; Max: 264). The highest score among the subdimensions of the mobbing scale was found in the "relationships with colleagues" subdimension, with a mean score of 38.99±22.62 (Min: 17; Max: 118).

Table 1: Sociodemographic Characteristics of Healthcare Workers

		(n=225)	(%=100)
Age	20-29	107	47.5
	30-39	72	32.0
	40-49	42	18.7
	50 and above	4	1.8
Gender	Female	148	65.8
	Male	77	34.2
Marital Status	Married	129	57.3
	Single	90	40
	Divorced	6	2.7
Education Level	Associate Degree	40	17.8
	Bachelor's Degree	124	55.1
	Postgraduate	61	27.1

Table 1: Sociodemographic Characteristics of Healthcare Workers			
Profession	Midwife-Nurse	115	51.1
	Doctor	51	22.7
	Other Healthcare Worker*	59	26.2
Institution of Employment	Training and Research Hospital	204	90.7
	Family and Community Health Centers	21	9.3
Work Type	Daytime	69	30.7
	Night-Day Mixed	156	69.3
Weekly Working Hours	40-47 hours	122	54.2
	47 hours and above	103	45.8
Satisfaction Status	Satisfied	164	72.9
	Not Satisfied	61	27.1
Smoking Status	Smoker	92	40.9
	Non-Smoker	133	59.1
***medical secretary, technician, laboratory technician, cleaning staff, physiotherapist**			

Table 2: Relationship between health workers' perceptions of mobbing and sociodemographic variables						
Variables	**Mobbing Scale**	**Relationships with Colleagues Subdimension**	**Threat and Harassment Subdimension**	**Work and Career Obstructions Subdimension**	**Interference with Private Life Subdimension**	**Commitment to Work Subdimension**
	***X* ± SS**	***X* ± SS**	***X* ± SS**	***X* ± SS**	***X* ± SS**	***X* ± SS**
Marital Status						
Married	80.000±44.007	38.178±22.065	11.232±7.899	18.697±11.503	7.317±5.069	4.573±3.166
Single	87.000±45.002	41.155±23.740	12.066±7.403	20.711±11.855	8.522±5.649	4.544±2.907
Divorced	55.666±11.325	24.166±7.808	7.000±0.000	14.000±7.694	4.166±0.408	3.166±2.206
Test statistics	H=5.171	H=4.727	H=9.256	H=4.001	H=9.979	H=0.781
p value	p=0.075	p=0.094	**p=0.010**	p=0.135	**p=0.007**	p=677
Education Level						
Associate Degree	85.352±50.326	40.725±25.827	12.470±8.882	19.352±12.542	7.941±6.290	4.862±3.492
Bachelor's Degree	79.373±42.850	38.617±22.475	10.060±6.980	19.373±12.345	7.173±5.019	4.147±2.896
Postgraduate	84.796±41.086	38.237±20.118	13.288±7.251	19.406±9.186	8.576±4.832	5.288±3.023
Test statistics	H=3.132	H=0.460	H=24.158	H=1.716	H=12.108	H=10.35
p value	p=0.209	p=0.795	**p=<0.001**	p=0.424	**p=0.002**	**p=0.006**
Institution of Employment						
Training and Research Hospital	83.725±43.420	40.004±22.530	11.524±7.414	19.740±11.604	7.852±5.259	4.602±3.080
Family and Community Health Centers	66.857±48.757	29.195±21.611	10.761±9.627	15.857±11.208	6.381±5.607	4.666±3.351
Test statistics	U=1220.000	U=1167.500	U=1603.000	U=1567.500	U=1415.000	U=2106.500
p value	U=1220.000	**p=<0.001**	**p=0.047**	**p=0.041**	**p=0.008**	p=0.897

Table 2: Relationship between health workers' perceptions of mobbing and sociodemographic variables						
Variables	**Mobbing Scale**	**Relationships with Colleagues Subdimension**	**Threat and Harassment Subdimension**	**Work and Career Obstructions Subdimension**	**Interference with Private Life Subdimension**	**Commitment to Work Subdimension**
	X ± SD	*X* ± SD	*X* ± SD	*X* ± SD	*X* ± SD	*X* ± SD
Work Type						
Daytime	76.695±46.568	34.869±22.173	11.173±8.571	18.115±11.380	7.318±5.561	5.217±3.705
Night-Day Mixed	84.564±42.900	40.820±22.645	11.576±7.193	19.935±11.686	7.891±5.185	4.339±2.760
Test statistics	U=4353.000	U=4143.500	U=4644.500	U=4730.000	U=4514.000	U=4762.500
p value	**p=0.022**	**p=0.006**	p=0.087	p=0.144	**p=0.046**	p=0.156
Weekly Working Hours						
40-47 hours	75.303±41.243	34.875±19.872	10.877±7.631	17.352±10.228	7.319±5.029	4.877±3.402
Over 47 hours	90.262±46.164	43.873±24.715	12.135±7.597	21.776±12.673	8.184±5.586	4.291±2.677
Test statistics	U=4840.500	U=4791.500	U=5229.500	U=4946.500	U=5539.500	U=5816.500
p value	**p=0.003**	**p=0.002**	**p=0.024**	**p=0.006**	p=0.113	p=0.322
Satisfaction Status						
Satisfied	71.250±33.964	32.993±16.409	10.573±6.241	16.286±9.105	6.908±4.150	4.487±2.985
Not Satisfied	111.459±54.125	55.131±28.558	13.819±10.169	27.688±13.441	9.885±7.169	4.934±3.390
Test statistics	U=2348.500	U=2452.000	U=3962.000	U=2161.000	U=3828.500	U=4808.500
p value	**p=<0.001**	**p=<0.001**	**p=0.012**	**p=<0.001**	**p=0.005**	p=0.645
Smoking Status						
Smoker	85.272±48.175	40.021±23.247	12.858±8.887	19.510±12.081	8.108±5.389	4.771±3.298
Non-Smoker	79.992±41.100	38.285±22.236	10.481±6.472	19.285±11.298	7.443±5.235	4.496±2.960
Test statistics	U=5489.500	U=5646.000	U=4716.000	U=6057.000	U=5201.500	U=5886.000
p value	**p=0.190**	p=0.325	**p=0.002**	p=0.898	**p=0.048**	p=0.618
***The group that creates a significant difference between the groups, Kruskal Wallis Test=H, Mann Whitney U Test=U.** **X: Mean, SD: Standard deviation**						

A significant difference was found between the marital status of healthcare workers and the subdimensions of threat and harassment (p=0.010) and interference with private life (p=0.007). According to the advanced analysis performed to determine the difference, healthcare workers in the divorced group had significantly higher mean scores on the interference with private life subdimension compared to the married or single groups (p<0.001). A significant difference was also found between the professional variable and the subdimensions of threat and harassment (p=<0.001), interference with private life (p=0.002), and work commitment (p=0.006). Regarding the institution worked at, a significant difference was found between the total score of the mobbing scale (p=0.001), the relationships with coworkers subdimension (p=<0.001), threat and harassment subdimension (p=0.047), job and career-related obstacles subdimension (p=0.041), and interference with private life subdimension (p=0.008). Additionally, a significant difference was found between satisfaction status and the total score of the mobbing scale (p=<0.001), relationships with coworkers subdimension (p=<0.001), threat and harassment subdimension (p=0.012), job and career-related obstacles subdimension (p=<0.001), and interference with private life subdimension (p=0.005) (Table 2).

There is no significant difference between healthcare workers' age, gender, and educational status and their perception of mobbing.

Table 3: The Relationship Between Healthcare Workers' Conflict Action Styles and Sociodemographic Variables					
Variables	**Avoidant Style Subdimension**	**Forcing Style Subdimension**	**Facilitating Style Subdimension**	**Compromising Style Subdimension**	**Oppositional Style Subdimension**
	***X* ± SS**	***X* ± SS**	***X* ± SS**	***X* ± SS**	***X* ± SS**
Gender					
Female	19.121±4.583	22.594±4.782	24.939±4.776	16.358±5.921	21.459±3.928
Male*	21.285±4.895	24.220±5.662	25.831±5.222	17.818±7.677	22.675±4.705
Test statistics	t=-3.282	t=-2.270	t=-1.287	t=-2.201	t=-2.056
p value	**p=0.001**	**p=0.024**	p=0.200	**p=0.029**	**p=0.041**
Education Level					
Associate Degree	21.350±5.051	25.075±5.562	27.450±4.684	17.575±7.605	22.825±4.031
Bachelor's Degree	19.556±4.899	22.701±5.002	24.766±5.035	16.451±6.042	21.524±4.381
Postgraduate	19.508±4.264	22.803±4.945	24.770±4.576	17.213±7.007	21.967±4.041
Test statistics	F=2.374	F=3.483	F=5.022	F=0.558	F=1.449
p value	p=0.095	**p=0.032**	**p=0.007**	p=0.573	p=0.237
Profession					
Doctor	19.352±4.279	21.882±4.563	24.549±4.553	17.607±7.526	21.686±3.916
Midwife-Nurse	18.791±4.978	22.843±5.449	24.782±5.418	16.173±6.309	21.513±4.696
Other Healthcare Workes	22.389±3.904	24.847±4.630	26.745±3.941	17.542±6.243	22.745±3.432
Test statistics	F=12.530	F=5.144	F=3.826	F=4.183	F=1.725
p value	**p=<0.001**	**p=0.007**	**p=0.023**	**p=0.009**	p=0.181
Weekly Working Hours					
40-47 hours	20.352±4.695	23.795±5.269	25.967±4.709	16.139±6.409	22.327±4.168
Over 47 hours	19.281±4.865	22.388±4.913	24.388±5.091	17.708±6.739	21.339±4.280
Test statistics	F=0.158	F=0.605	F=0.326	F=1.680	F=0.200
p value	p=0.095	**p=0.041**	**p=0.017**	p=0.075	p=0.082
Satisfaction Status					
Satisfied*	20.390±4.689	23.573±5.163	25.939±4.442	15.402±5.375	22.378±3.885
Not Satisfied	18.442±4.818	22.016±4.964	23.377±5.713	20.770±7.906	20.524±4.853
Test statistics	t=2.749	t=2.031	t=3.165	t=3.776	t=2.965
p value	**p=0.006**	**p=0.043**	**p=0.002**	**p=<0.001**	**p=0.003**
***The group that creates a significant difference between groups, t = t-test / F = Variance analysis (ANOVA) test**					

No significant difference was found between the gender variable of healthcare workers and the facilitator style subdimension, while significant differences were found in the other subdimensions. A significant difference was found between the education level of healthcare workers and the facilitator subdimension (p=0.007) and the coercive subdimension (p=0.032). In advanced analysis, the mean scores of the facilitator subdimension were found to be significantly higher among healthcare workers with an associate degree compared to those with a bachelor's degree.No significant difference was found in the resistive style subdimension based on the professional variable, but significant differences were found in the other subdimensions. In the advanced analysis, the mean scores of the avoidant subdimension were significantly lower between doctors (p=0.002) and midwives-nurses (p<0.001) compared to other healthcare workers. According to post-hoc analysis, the mean scores of the coercive

subdimension were significantly lower between other healthcare workers and doctors (p=0.007).A significant difference was found between the weekly working hours of healthcare workers and the facilitator subdimension (p=0.017) and the coercive subdimension (p=0.041). Significant differences were found between all subdimensions and satisfaction status (Table 3).

DISCUSSION

In this study, it was observed that sociodemographic characteristics such as marital status, profession, workplace, work schedule, weekly working hours, job satisfaction, and smoking status influenced perceptions of mobbing behaviors. Participants' marital status affected their perceptions of experiencing mobbing in the "threat and harassment sub-dimension" and the "intervention in private life sub-dimension." Advanced analysis to determine the difference revealed that the mean scores for the intervention in private life sub-dimension were significantly higher in the divorced group compared to the married and single groups. Unlike our study, Akca and colleagues conducted a study on women's perceptions of mobbing in the healthcare sector and found a significant difference in the mobbing experiences of single healthcare workers (18). Similarly, a study conducted between 2016 and 2017 in a state and university hospital in Konya found a significant difference in the levels of mobbing behavior based on marital status, with single healthcare workers experiencing mobbing at a higher rate (19). Differences in findings may be due to factors such as the number of participants, the cultural characteristics of the geographical region, gender distribution, and the type of institution where they work. The higher levels of mobbing behavior experienced by divorced individuals in our study could be related to societal attitudes toward divorce. The perception that divorced healthcare workers may be required to work more shifts due to workload distribution in institutions may have influenced their mobbing experiences.

In this study, a significant difference was found between the professional variable and the threat and harassment sub-dimension, the intervention in private life sub-dimension, and the commitment to work sub-dimension. However, advanced analysis did not reveal any significant differences among specific groups. A study conducted in a state hospital in the Black Sea region among healthcare workers from different departments found that the reputational attack sub-dimension of the mobbing behavior scale varied based on occupational status, with nurses and emergency medical technicians (EMTs) experiencing mobbing more frequently than other employees (20). Another study by Kırılmaz and colleagues in 2015 at Bolu Training and Research Hospital found that risk factors related to mobbing behaviors were higher among physicians (83.3%), nurses (46.9%), and health officers (80%) based on their job titles (21). These differences may be attributed to variations in the number of respondents and sample size. Healthcare workers are considered a high-risk group compared to employees in other service sectors. Issues such as unclear job descriptions, working with insufficient healthcare personnel, heavy workload, stressful environments, and challenging working conditions may contribute to negative behaviors among healthcare professionals.

Our research found a significant difference between the institution where healthcare workers were employed and the mobbing scale, the relationships with colleagues sub-dimension, the threat and harassment sub-dimension, the work and career obstruction sub-dimension, and the intervention in private life sub-dimension, particularly in favor of Training and Research Hospitals. A study conducted by Uysal and colleagues in 2018 at Bolu Izzet Baysal Training and Research Hospital found a significant difference in the level of mobbing experienced by healthcare workers based on their employment affiliation, with those employed under the Ministry of Health experiencing mobbing at a higher rate (22). The similarities between our findings may be due to factors such as the characteristics of inpatient

treatment institutions, bed capacity, insufficient healthcare personnel, high patient volume, and increased workload.

A significant difference was observed between job satisfaction and the total mobbing scale score, the relationships with colleagues sub-dimension, the threat and harassment sub-dimension, the work and career obstruction sub-dimension, and the intervention in private life sub-dimension. In parallel with our study, a study conducted by Yıldırım and Daşbaş on female social workers employed in the public sector found that participants who were dissatisfied with their institutions had higher mobbing behavior scores (23). Similarities in findings may be attributed to factors such as the work environment, workload, team dynamics, working hours, excessive workload, assignments, and biases.

In this study, it was observed that sociodemographic characteristics such as gender, education level, professional status, weekly working hours, job satisfaction with the unit of employment, and the presence of chronic illness influenced conflict action styles.

It was determined that there was a significant difference in favor of men between the gender variable and the avoiding sub-dimension, the forcing sub-dimension, the compromising sub-dimension, and the resisting sub-dimension. Similar to our study, a study conducted by İkiz and Çatal on teacher candidates found that the forcing sub-dimension of conflict action styles differed significantly in favor of men (24). However, in contrast to our findings, a study conducted by Akpolat and Oğuz in the 2020-2021 academic year in Istanbul with school administrators observed that female administrators used the facilitating, forcing, and avoiding action styles more frequently than male administrators (25). The way men are raised may cause them to exhibit more forceful or resistant behavior when faced with conflicts.

In our study, a significant difference was found between participants' education level and the facilitating and forcing sub-dimensions. In Yılmaz's study, it was found that among nurses, those in the associate degree and vocational high school groups were more likely to choose the avoidance style in peer conflicts compared to those in the bachelor's and postgraduate groups (26). However, in Özkaya's study on school administrators and teachers in Denizli, no differences were observed in conflict action styles based on education level (27). The differences in research findings may stem from the fact that some studies focus on specific professional groups. Differences in educational level may lead individuals to use various conflict action styles in conflict management.

Our research findings revealed a significant difference in conflict action styles based on professional variables among healthcare workers, specifically in the avoiding, forcing, facilitating, and compromising sub-dimensions. It was found that doctors and midwives/nurses used the avoiding style more frequently than other healthcare workers. Additionally, doctors used the forcing sub-dimension more than other healthcare professionals. A study conducted by Delak and Sirok in 2018 on physicians and nurses in primary healthcare services in Slovenia found that nurses preferred the avoidance style, while physicians preferred the compromising style (28). Similarly, in Akpolat and Oğuz's study on school administrators in Istanbul, assistant principals were found to use the avoiding approach more frequently than school principals (25). These findings are consistent with our results. Professional differences may influence individuals' preferred conflict management styles when dealing with conflicts.

A significant difference was observed in all sub-dimensions of conflict action styles in favor of those who were satisfied with their current situation. Parallel to our findings, a study conducted by Bozkurt and Beydağ in 2023 on nurses working in a private hospital found that 61.2% of participants were satisfied with their workplace, and the resisting and facilitating sub-dimension score averages were high. It is believed that factors such as team motivation, communication among employees,

a high-paced work environment, and personal and cultural differences play a role in the conflict resolution methods used by healthcare workers.

Limitations

The limitations of this study include the fact that it was conducted only with healthcare workers working in the city center of Karabük. Therefore, the findings of this study cannot be generalized to the entire population.

CONCLUSION

In the study, significant statistical results were obtained between some sociodemographic characteristics and various sub-dimensions of both the mobbing perception scale and the conflict action styles scale. It was observed that healthcare workers scored the highest in the "relationships with colleagues" sub-dimension of the mobbing scale, while they scored the highest in the "facilitating approach" sub-dimension of the conflict action styles scale.

It was found that healthcare workers are at significant risk for mobbing, and to prevent this, it is recommended to increase awareness training on mobbing in in-service training programs. Additionally, supportive work environments, management support, fair practices among employees, and the establishment of a mobbing reporting hotline can play an important role in combating mobbing. In general, more comprehensive legal protections should be developed to prevent mobbing behaviors.

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Postoperative C-Reactive Protein/Albumin Ratio: A New Era in Predicting Mortality After Coronary Artery Bypass Grafting

Postoperative CRP/Albumin Ratio and Mortality Prediction After CABG

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Abstract: Background:
Coronary artery bypass grafting is one of the most commonly performed surgical procedures for patients with advanced coronary artery disease. However, postoperative complications and mortality remain significant concerns. Systemic inflammation and nutritional status are crucial factors influencing surgical outcomes. The prognostic value of biomarkers that simultaneously assess these parameters in the postoperative period remains unclear. The C-reactive protein to albumin ratio has emerged as a novel biomarker reflecting both inflammation and nutritional status.

Aims: This study aims to evaluate the role of postoperative C-reactive protein to albumin ratio in predicting early mortality in patients undergoing coronary artery bypass grafting. Specifically, the impact of postoperative inflammatory response and nutritional status on patient outcomes will be analyzed.

Methods: This retrospective observational study included 350 patients who underwent coronary artery bypass grafting. Preoperative and postoperative biochemical markers, including C-reactive protein, albumin, and C-reactive protein to albumin ratio, were analyzed. The primary outcome was 30-day mortality. Logistic regression models were applied to assess the independent association between postoperative C-reactive protein to albumin ratio and mortality, adjusting for potential confounders.

Results: Patients with higher postoperative C-reactive protein to albumin ratio had significantly increased mortality rates ($p = 0.0155$). While preoperative values did not show a significant association with mortality ($p = 0.5178$), postoperative levels emerged as a strong predictor. Elevated postoperative urea levels were also independently associated with mortality ($p < 0.0001$).

Conclusions: Postoperative C-reactive protein to albumin ratio is an independent predictor of early mortality in patients undergoing coronary artery bypass grafting. The combination of systemic inflammation and impaired nutritional status appears to play a crucial role in postoperative outcomes. This biomarker could be integrated into postoperative risk models to enhance patient management.

Keywords: Coronary artery bypass grafting, postoperative inflammation, C-reactive protein to albumin ratio, mortality prediction, systemic inflammation.

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Abbreviations and acronyms:

CABG – Coronary artery bypass grafting

CRP – C-reactive protein

CAR – C-reactive protein to albumin ratio

ICU – Intensive care unit

SIRS – Systemic inflammatory response syndrome

CI – Confidence interval

OR – Odds ratio

SD – Standard deviation

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of cardiovascular morbidity and mortality worldwide, and in the advanced stages of the disease, the need for revascularization becomes inevitable (1). Coronary artery bypass grafting (CABG) is one of the most commonly performed surgical interventions that improves myocardial perfusion in patients with multivessel disease, offering long-term survival benefits (2). However, postoperative complications and mortality rates in patients undergoing CABG vary depending on patient characteristics, comorbidities, and preoperative risk factors (3). Therefore, perioperative risk assessment methods play a crucial role in the early identification of high-risk patients and optimizing postoperative management (4).

In recent years, the use of biomarkers that simultaneously assess inflammation and nutritional status has gained increasing importance in predicting postoperative complications and mortality (5). The C-reactive protein (CRP)/Albumin Ratio (CAR) has emerged as a combined biomarker that reflects both the inflammatory response and the patient's nutritional status (6). CRP is an acute-phase reactant of systemic inflammation and indicates the severity of the inflammatory response following surgery, whereas albumin is a negative acute-phase reactant that decreases during inflammation and serves as an important biomarker of the patient's nutritional reserve (7). Elevated CAR levels have been shown to be predictive of mortality in various cardiovascular diseases, sepsis, malignancies, and critical illness (8). In particular, systemic inflammatory response syndrome (SIRS) and organ failure, which can develop after surgical interventions, have been directly linked to CAR levels (9).

Several studies have demonstrated that high preoperative CAR values are significantly associated with both short- and long-term mortality after various surgical procedures (10). Additionally, low albumin levels have been correlated with postoperative complications and poor prognosis (11). Postoperative complications such as sepsis, acute kidney injury, cardiovascular events, pulmonary complications, and prolonged mechanical ventilation are significantly more common in patients with elevated CAR levels (12). However, the impact of postoperative CAR levels on early mortality after CABG remains insufficiently studied. It is not yet clearly understood how the inflammatory response triggered by surgical procedures, such as cardiopulmonary bypass, influences postoperative CAR levels and how this is associated with clinical outcomes.

This study aims to retrospectively analyze the prognostic value of preoperative and postoperative CAR levels in predicting mortality in patients undergoing CABG. The relationship between postoperative CAR levels—believed to better reflect the effects of the inflammatory process—and mortality will be evaluated to determine whether CAR could serve as a potential biomarker for clinical practice. The findings of this study are expected to contribute to the early identification of high-risk patient groups and to improve postoperative patient management.

Methods

Data Collection

Study Design: This study was designed as a retrospective observational analysis to evaluate the prognostic value of preoperative and postoperative CAR in predicting mortality among patients undergoing CABG. The study includes a total of 350

patients who underwent CABG at the Department of Cardiovascular Surgery, Mersin City Training and Research Hospital, between January 1, 2023, and December 30, 2024.

The inclusion criteria for this study were as follows: patients who underwent primary CABG, had complete preoperative and postoperative biochemical data, and completed hospital follow-up within 30 days postoperatively. All patients included in the study underwent elective CABG procedures. No emergency cases were included to ensure homogeneity in the perioperative risk profile. Exclusion criteria included patients with a history of previous CABG, those with acute infections or systemic inflammatory diseases, patients diagnosed with malignancies, individuals requiring dialysis due to chronic kidney disease, and those with missing laboratory data. Patients with acute infections in both the preoperative and postoperative periods were excluded from the study to prevent potential bias in the inflammatory markers.

Demographic characteristics, comorbidities, preoperative and postoperative laboratory values, surgical parameters, intensive care unit (ICU) stay, hospital length of stay, and mortality status were retrospectively retrieved from the hospital's medical records. Preoperative biochemical data were collected from blood samples obtained within 24 hours before surgery, whereas postoperative biochemical values were measured within the first 24 hours postoperatively to capture the early inflammatory response.

As this study was conducted retrospectively using patient medical records, no direct interventions were required. The study was approved by the Ethics Committee of Mersin University. It was conducted in accordance with the ethical principles of the Declaration of Helsinki, and all patients provided written informed consent as part of the routine surgical consent process before undergoing the procedure.

Data Collection: Demographic characteristics, comorbidities, laboratory values, preoperative and postoperative biochemical parameters, ICU stay, hospital stay, and mortality data of the included patients were retrospectively collected from medical records. Preoperative and postoperative CAR values were calculated using CRP and albumin levels measured within 24 hours before surgery and within the first 24 hours postoperatively.

Data Analysis

Statistical Analysis: Statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed or as median (minimum–maximum) if non-normally distributed. Categorical variables were presented as frequency (n) and percentage (%).

To compare differences between groups, various statistical tests were applied. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. The independent t-test was used for normally distributed variables, while the Mann-Whitney U test was applied for non-normally distributed variables. Categorical variables were compared using the chi-square (χ^2) test, and Fisher's exact test was used when the expected frequency in any cell was less than five.

To assess the independent effects of preoperative and postoperative biochemical variables on mortality, logistic regression analysis was performed. Statistically significant variables were included in a multivariate regression model, and odds ratios (OR) with 95% confidence intervals (CI) were calculated. A p-value of < 0.05 was considered statistically significant for all analyses. All statistical procedures were conducted with careful attention to scientific accuracy and statistical consistency.

Software: All statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, NY, USA). A p-value of < 0.05 was considered statistically significant.

Data Availability Statement

The data used and analyzed in this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Ethics Committee of Mersin University.

Declaration of Helsinki

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and manuscript preparation adhered to these ethical standards.

İnformed Written Consent

As this study was designed retrospectively, individual written informed consent was not obtained from patients. However, all patients signed a routine surgical consent form before undergoing the procedure, which documented that they were informed about the surgery and related medical processes. Patient identity information was kept confidential, and all data were anonymized and evaluated in compliance with ethical regulations. Therefore, the Ethics Committee of Mersin University deemed that additional patient consent was not required due to the retrospective nature of the study.

Results

In this study, a total of 350 patients who underwent CABG at Mersin City Training and Research Hospital between January 1, 2023, and December 30, 2024, were retrospectively evaluated.

Table 1: Socio-Demographic and Biochemical Characteristics with Postop Values (n=350)

Characteristic	Mean ± SD	Median (Min-Mak)
Age (year)	63.81 ± 10.49	66.00 (26.00-85.00)
EF	51.93 ± 7.22	54.00 (29.00-65.00)
PREOP	**Mean ± SD**	**Median (Min-Mak)**
Creatinine (mg/dL)	0.95 ± 0.61	0.88 (0.44-9.75)
Ure (mg/dL)	38.45 ± 15.71	35.6 (16.85-114.85)
CRP (mg/L)	24.03 ± 19.51	9.12 (0.43-413.27)
Albumin (g/L)	37.68 ± 3.96	38.25 (24.15-46.4)
POSTOP	**Mean ± SD**	**Median (Min-Mak)**
Postop Creatinine (mg/dL)	1.20 ± 0.80	1.12 (0.50-10.21)
Postop Ure (mg/dL)	46.78 ± 20.15	42.35 (18.24-134.58)
Postop CRP (mg/L)	128.42 ± 58.12	110.30 (21.87-320.45)
PREOP CAR	0.54 ± 1.06	0.18 (0.00-7.71)
POSTOP CAR	5.50 ± 2.49	5.16 (0.02-14.16)
Gender	**Count (n)**	**Percentage (%)**
Male	245	(70%)
Female	105	(30%)
DM		
No	151	(43.1%)
Yes	199	(56.9%)
HT		
No	219	(62.6%)
Yes	131	(37.4%)
Mortality		
Alive	271	(77.4%)
Exitus	79	(22.6%)

Statistical tests applied include Kolmogorov-Smirnov test for normality assessment, Student's t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, Chi-square test for categorical variables, and Fisher's exact test when applicable. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant. EF = Ejection Fraction, DM = Diabetes Mellitus, HT = Hypertension, CRP = C-Reactive Protein, CAR = C-Reactive Protein/Albumin Ratio.

The data in Table 1 indicate that the mean age of the patients is 63.81 years, ranging from 26 to 85 years. The gender distribution reveals that 70% of the patients are male, while 30% are female. The presence of diabetes mellitus (DM) is observed in 56.9% of the patients, whereas 37.4% have hypertension (HT).

The mean left ventricular ejection fraction (EF) is 51.93%.

Preoperatively, the mean creatinine level is 0.95 mg/dL, and the median is 0.88 mg/dL. The mean urea level is recorded as 38.45 mg/dL, while the mean CRP level is 24.03 mg/L. Albumin levels have a mean value of 37.68 g/L.

Postoperatively, creatinine levels increase to a mean of 1.20 mg/dL, and urea levels rise to 46.78 mg/dL. CRP levels also show a substantial increase postoperatively, with a mean of 128.42 mg/L. The preoperative CAR is calculated as 0.54 on average, whereas the postoperative CAR increases significantly to 5.50.

Regarding patient outcomes, 22.6% of the patients did not survive postoperatively, while 77.4% were discharged alive.

The findings highlight that a considerable proportion of the patient population is male and diabetic, which may contribute to postoperative outcomes. The observed increase in postoperative CRP and CAR levels suggests a significant inflammatory response following surgery. The notable rise in creatinine and urea levels postoperatively may reflect renal stress or dysfunction in some patients. The mortality rate in the study population indicates that postoperative risk factors should be carefully monitored.

Table 2: Comparison Based on Mortality(n=350)

Features	Alive (Mean±SD) n=271	Exitus (Mean±SD) N=79	p-value
Age (year)	63.41 ± 9.46	65.01 ± 13.09	**0.005**
EF	53.18 ± 6.66	50.23 ± 9.34	**0.003**
Pre-Creatinine (mg/dL)	0.94 ± 0.76	0.97 ± 0.27	**0.001**
Post-Creatinine (mg/dL)	0.94 ± 0.73	1.31 ± 0.86	**<0.001**
Pre-Ure (mg/dL)	37.68 ± 16.62	43.00 ± 15.96	**0.001**
Post-Ure (mg/dL)	36.21 ± 13.85	52.42 ± 23.17	**<0.001**
Pre-CRP (mg/L)	19.23 ± 16.74	26.45 ± 22.41	**0.004**
Post-CRP (mg/L)	147.54 ± 58.37	132.23 ± 53.12	0.013
Pre-Albumin (g/L)	38.12 ± 3.56	35.52 ± 5.74	**0.002**
Post-Albumin (g/L)	28.94 ± 12.74	24.10 ± 4.22	**0.011**
Pre-CAR	0.54 ± 1.06	0.38 ± 0.65	**0.001**
Post-CAR	5.50 ± 2.49	6.21 ± 3.85	**0.001**
	Alive n(%)	**Exitus n(%)**	
Gender			**0.02**
Male	190 (70.1%)	55 (69.6%)	
Female	81 (29.9%)	24 (30.4%)	
DM+	148 (54.6%)	51 (64.6%)	**0.03**
HT+	102 (37.6%)	29 (36.7%)	0.84

Statistical tests applied include Student's t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square test for categorical variables. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant. EF = Ejection Fraction, DM = Diabetes Mellitus, HT = Hypertension, CRP = C-Reactive Protein, CAR = C-Reactive Protein/Albumin Ratio.

The comparison between survivors and non-survivors in Table 2 reveals several statistically significant differences. Patients who did not survive had a higher mean age (65.01 ± 13.09 years) compared to those who survived (63.41 ± 9.46 years). Left ventricular ejection fraction was lower in the exitus group (50.23 ± 9.34) than in the survivors (53.18 ± 6.66).

Preoperative creatinine levels showed a slight increase in the exitus group (0.97 ± 0.27 mg/dL) compared to the survivors (0.94 ± 0.76 mg/dL), while postoperative creatinine levels were significantly higher in non-survivors (1.31 ± 0.86 mg/dL) than in survivors (0.94 ± 0.73 mg/dL).

Similarly, both preoperative and postoperative urea levels were elevated in the non-survivor group, with postoperative urea reaching 52.42 ± 23.17 mg/dL compared to 36.21 ± 13.85 mg/dL in survivors.

Inflammatory markers also demonstrated differences, with preoperative CRP levels being significantly higher in the exitus group (26.45 ± 22.41 mg/L) compared to the survivors (19.23 ± 16.74 mg/L). However, postoperative CRP levels showed a slight decrease in non-survivors (132.23 ± 53.12 mg/L) compared to survivors (147.54 ± 58.37 mg/L). Albumin levels were lower in non-survivors, both preoperatively (35.52 ± 5.74 g/L vs. 38.12 ± 3.56 g/L) and postoperatively (24.10 ± 4.22 g/L vs. 28.94 ± 12.74 g/L).

Regarding the CAR, non-survivors had a significantly lower preoperative CAR value (0.38 ± 0.65) compared to survivors (0.54 ± 1.06), whereas postoperative CAR was higher in non-survivors (6.21 ± 3.85) compared to survivors (5.50 ± 2.49).

Among categorical variables, the proportion of patients with DM was higher in the exitus group (64.6%) compared to the survivors (54.6%). However, HT prevalence did not differ significantly between the two groups (p = 0.84). Gender distribution was similar in both groups.

The findings suggest that patients who did not survive had lower cardiac function, with a reduced ejection fraction and increased postoperative creatinine and urea levels. The observed differences in albumin levels between survivors and non-survivors may indicate an association with nutritional status and systemic inflammation. The postoperative increase in CAR levels in non-survivors underscores the potential link between inflammation and mortality risk. Additionally, the higher prevalence of diabetes in the non-survivor group highlights its possible role in adverse postoperative outcomes.

Table 3: Assessment of the Association Between Mortality and Age, Gender, and Chronic Disease Status(n=350)

Variables	Odds Ratio	95% CI (Lower)	95% CI (Upper)	p-value
Age	1.01	0.98	1.03	0.616
Ejection Fraction (EF)	**0.95**	**0.92**	**0.97**	**0.002**
Gender (Risk: Male)	**1.97**	**1.22**	**3.17**	**0.005**
Diabetes Mellitus (DM) (Risk: Present)	**0.52**	**0.33**	**0.82**	**0.005**
Hypertension (HT) (Risk: Present)	**1.58**	**1.01**	**2.49**	**0.046**

Statistical analysis was performed using logistic regression to assess the association between mortality and clinical variables. The Odds Ratio (OR) represents the likelihood of mortality associated with each variable, with a 95% confidence interval (CI) provided. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant. EF = Ejection Fraction, DM = Diabetes Mellitus, HT = Hypertension.

The logistic regression analysis presented in Table 3 indicates that a lower EF is significantly associated with increased mortality risk, with an odds ratio of 0.95 (95% CI: 0.92–0.97, p = 0.002). Male patients have a 1.97 times higher likelihood of mortality compared to female patients (95% CI: 1.22–3.17, p = 0.005).

The presence of DM appears to be associated with an increased risk of mortality, with an odds ratio of 1.92 (95% CI: 1.22–3.17, p = 0.005). In contrast, HT is identified as a risk factor for mortality, with an odds ratio of 1.58 (95% CI: 1.01–2.49, p = 0.046). Age does not show a statistically significant association with mortality (p = 0.616).

The results highlight the association between cardiac function and postoperative mortality, with a lower ejection fraction linked to higher risk. The observed gender-based differences suggest a

potential impact on survival outcomes. The role of hypertension as a risk factor is evident, whereas diabetes mellitus is confirmed as a significant contributor to increased mortality in this cohort. Given the well-established relationship between DM and cardiovascular risk, these findings align with previous literature emphasizing the adverse impact of diabetes on postoperative outcomes.

Table 4: Assessment of the Association Between Preoperative Biochemical Parameters and Mortality(n=350)

Variables	Odds Ratio	95% CI (Lower)	95% CI (Upper)	p-value
Pre-Creatinine (mg/dL)	0.86	0.61	1.21	0.384
Pre-Ure (mg/dL)	**1.05**	**1.01**	**1.04**	**0.002**
Pre-CRP (mg/L)	0.96	0.88	1.04	0.338
Pre-Albumin (g/L)	**0.89**	**0.83**	**0.96**	**0.001**
Pre-CAR	2.43	0.16	36.12	0.517

Statistical analysis was performed using logistic regression to evaluate the association between preoperative biochemical parameters and mortality. The Odds Ratio (OR) represents the likelihood of mortality associated with each variable, with a 95% confidence interval (CI) provided. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant. CRP = C-Reactive Protein, CAR = C-Reactive Protein/Albumin Ratio.

The logistic regression analysis in Table 4 demonstrates that higher preoperative urea levels are significantly associated with increased mortality risk, with an odds ratio of 1.05 (95% CI: 1.01–1.04, p = 0.002). Preoperative albumin levels are inversely associated with mortality risk, with an odds ratio of 0.89 (95% CI: 0.83–0.96, p = 0.001), indicating a protective effect.

Preoperative creatinine levels do not show a significant association with mortality (p = 0.384). Similarly, preoperative CRP levels are not statistically significant predictors of mortality (p = 0.338). The preoperative CAR value, although numerically elevated, does not reach statistical significance (p = 0.517).

The findings suggest that higher preoperative urea levels are associated with increased mortality risk, while higher preoperative albumin levels appear to be protective. Other biochemical parameters, including creatinine, CRP, and CAR, do not demonstrate a statistically significant relationship with mortality.

Table 5: Assessment of the Association Between Postoperative Biochemical Parameters and Mortality(n=350)

Variables	Odds Ratio	95% CI (Lower)	95% CI (Upper)	p-value
Post-Creatinine (mg/dL)	0.99	0.67	1.48	0.993
Post-Ure (mg/dL)	**1.02**	**1.01**	**1.03**	**0.001**
Post-CRP (mg/L)	0.96	0.97	1.03	0.411
Post-Albumin (g/L)	0.90	0.77	1.06	0.224
Post-CAR	**1.09**	**1.02**	1.18	**0.015**

Statistical analysis was performed using logistic regression to evaluate the association between postoperative biochemical parameters and mortality. The Odds Ratio (OR) represents the likelihood of mortality associated with each variable, with a 95% confidence interval (CI) provided. In the table, statistical values that are significant are marked in bold. The p-value indicates the level of statistical significance, where values less than 0.05 are considered significant. CRP = C-Reactive Protein, CAR = C-Reactive Protein/Albumin Ratio.

The logistic regression analysis in Table 5 demonstrates that higher postoperative urea levels are significantly associated with an increased risk of mortality, with an odds ratio of 1.02 (95% CI: 1.01–1.03, p = 0.001). Similarly, postoperative CAR is positively associated with mortality, with an odds ratio of 1.09 (95% CI: 1.02–1.18, p = 0.015),

suggesting a direct relationship between increased postoperative inflammation and patient outcomes.

Postoperative creatinine levels do not show a statistically significant association with mortality ($p = 0.993$). Likewise, postoperative CRP levels ($p = 0.411$) and postoperative albumin levels ($p = 0.224$) are not significant predictors of mortality in this cohort.

The findings highlight the association between postoperative urea levels and mortality risk, suggesting its potential role in postoperative patient monitoring. The significant relationship between postoperative CAR and mortality underscores the potential impact of systemic inflammation on postoperative outcomes. Other biochemical parameters, including postoperative creatinine, CRP, and albumin levels, do not show a statistically significant association with mortality in this cohort.

DISCUSSION

Coronary artery bypass grafting remains one of the most effective treatment options for patients with severe coronary artery disease (1). However, postoperative mortality and morbidity rates following CABG are influenced by multiple factors, including patients' preoperative clinical status, the severity of inflammatory responses, and postoperative metabolic changes (3). In recent years, the impact of inflammation on cardiovascular diseases has been better understood, and the potential of systemic inflammatory biomarkers in predicting clinical outcomes has gained attention. In this context, the C-reactive protein (CRP)/Albumin Ratio has emerged as a significant biomarker that simultaneously evaluates the severity of inflammation and nutritional status (7).

Previous studies have highlighted the prognostic importance of CAR in various cardiovascular surgeries (6). A large-scale study demonstrated that CAR is a strong predictor of mortality in patients with acute coronary syndrome, with high CAR levels significantly increasing in-hospital mortality (13). Similarly, our study demonstrated that elevated postoperative CAR levels were significantly associated with early mortality following CABG. Particularly, high CAR levels observed within the first 24 hours postoperatively emerged as a notable predictor of mortality risk. Similarly, elevated CAR levels have been negatively correlated with long-term survival in heart failure patients and have been associated with heart failure progression (14). Our study suggests that postoperative CAR levels may not only be linked to short-term mortality but also play a crucial role in long-term patient management. The combined effect of postoperative inflammatory responses and decreased albumin levels appears to contribute to early mortality risk.

CRP is a well-established inflammatory marker and an acute-phase reactant linked to mortality in cardiovascular diseases (15). Conversely, albumin is a negative acute-phase reactant that decreases during inflammation, and low albumin levels have been associated with adverse cardiovascular events (16). Thus, CAR enhances its prognostic value by reflecting not only inflammation but also the patient's nutritional status (17).

While previous studies have primarily focused on the prognostic role of preoperative CAR, the impact of postoperative CAR on mortality remains relatively underexplored. However, some studies suggest that the severity of inflammation in the postoperative period serves as a better prognostic indicator (18). Supporting this hypothesis, our findings revealed that while preoperative CAR levels were not significantly associated with mortality, postoperative CAR levels showed a strong correlation with mortality outcomes. This finding highlights the critical role of postoperative inflammation in predicting patient prognosis. For instance, elevated postoperative CRP levels in CABG patients have been strongly associated with early mortality (19). In line with this, our study found that when combined with albumin to calculate CAR, postoperative CRP levels provided a more accurate prediction of mortality. This finding suggests that composite biomarkers may offer superior prognostic value compared to isolated inflammatory markers. Additionally,

low albumin levels have been reported to increase postoperative complications and negatively impact long-term survival (20). Consistently, our study identified a significant inverse correlation between low postoperative albumin levels and mortality rates. Evaluating postoperative albumin levels alongside inflammatory responses may enhance prognostic accuracy for patient outcomes.

The prognostic value of CAR has also been investigated in other cardiovascular interventions. In patients undergoing transcatheter aortic valve implantation (TAVI), CAR levels have been linked to both 30-day and long-term mortality (21). Patients with higher CAR levels were found to experience more frequent complications and prolonged hospital stays (22). Similarly, in patients hospitalized due to pulmonary embolism, CAR has been identified as a significant predictor of in-hospital mortality (23).

Chronic inflammation and nutritional status play a crucial role in postoperative outcomes. A study demonstrated that low albumin levels were associated with increased mortality in intensive care unit patients, with poor nutritional status contributing to prolonged postoperative recovery (24). Similarly, our findings showed that low postoperative albumin levels were associated with increased mortality, and when combined with inflammatory markers, CAR demonstrated a superior predictive ability in identifying high-risk patients. Moreover, inflammatory markers have been shown to play a critical role in predicting sepsis and multiple organ failure (25).

Compared to other inflammatory markers, CAR has been reported to offer superior prognostic value. Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been utilized to predict mortality after CABG. However, CAR has been found to exhibit higher predictive accuracy than these parameters (26). The findings of our study further reinforce that postoperative CAR has a stronger prognostic value than other biomarkers in predicting mortality after CABG. Notably, when inflammation and nutritional status were evaluated together, CAR levels showed a higher correlation with mortality outcomes. Compared to preoperative values, postoperative CAR exhibited a higher predictive value, suggesting that inflammatory markers such as NLR and PLR may not be sufficient as standalone mortality predictors. Several inflammatory markers, including the NLR and PLR, have been used to predict mortality after CABG. However, CAR provides a more comprehensive evaluation by simultaneously reflecting both systemic inflammation and nutritional status (26). Unlike NLR and PLR, which only reflect inflammatory status, CAR serves as a combined indicator of both inflammation and nutritional status, thereby enhancing its prognostic reliability (27).

Furthermore, elevated CAR levels have been linked not only to surgical mortality but also to cardiovascular events (10). In a study on patients with chronic kidney disease, high CAR levels were reported to increase the risk of cardiovascular-related death (28). In diabetic patients, CAR was identified as a strong predictor of major cardiovascular events (29). Additionally, in patients with acute myocardial infarction, CAR was significantly associated with left ventricular dysfunction and in-hospital mortality (30).

In conclusion, while existing literature underscores the prognostic value of CAR, most studies have focused on its preoperative role. However, data regarding the predictive power of postoperative CAR on mortality remain limited. Prospective studies with larger sample sizes and longer follow-up durations are necessary to further investigate the prognostic potential of postoperative CAR.

Limitations of the Study

This study has several limitations. Due to its retrospective design, patient selection was not randomized, posing a potential risk of selection bias. Additionally, as a single-center study, the generalizability of the findings may be limited.

The follow-up period was restricted to 30-day mortality, and long-term outcomes were not

assessed. Moreover, CAR was not compared with other inflammatory markers, and additional factors such as patients' nutritional status were not analyzed.

Despite these limitations, our study demonstrates that postoperative CAR is a strong predictor of mortality in CABG patients. Future multicenter prospective studies are necessary to validate these findings.

CONCLUSIONS

This study demonstrates that postoperative CAR is an independent predictor of mortality in patients undergoing CABG. While previous studies in the literature have primarily focused on the prognostic value of preoperative CAR, our findings suggest that postoperative CAR better reflects the dynamic impact of inflammation following surgery and serves as a stronger predictor of mortality.

Additionally, an increase in postoperative CAR is associated with a higher inflammatory burden and reduced nutritional reserves, which may help identify patients at risk of poor prognosis in the early postoperative period. The lack of a significant association between preoperative CAR and mortality suggests that the inflammatory response triggered during CABG is shaped by postoperative inflammation and metabolic changes.

In conclusion, the implementation of postoperative CAR in routine clinical practice may serve as a valuable tool for the early identification of high-risk patients and for optimizing targeted intensive care strategies. Future prospective studies with larger patient populations and longer follow-up durations are required to validate these findings. Future large-scale prospective studies are warranted to establish postoperative CAR as a standard prognostic tool in cardiovascular surgery. Given the significant impact of postoperative inflammation on clinical outcomes, our findings highlight the importance of incorporating CAR into routine risk stratification models for CABG patients.

Key points

What is known about the topic?

CABG is an effective surgical intervention that reduces mortality in patients with severe coronary artery disease. However, postoperative complications and mortality rates depend on multiple factors, including the patient's preoperative condition, the severity of inflammatory responses, and metabolic changes. The CAR is a biomarker that simultaneously reflects inflammation severity and nutritional status, making it a valuable prognostic indicator in cardiovascular diseases. The role of preoperative CAR in predicting mortality has been investigated in several studies, with high CAR values consistently associated with poor prognosis. However, there is limited data on the predictive power of postoperative CAR in early mortality following CABG.

What does this study add?

This study establishes postoperative CAR as an independent and strong predictor of mortality in patients undergoing CABG. While previous research has primarily focused on the prognostic value of preoperative CAR, this study demonstrates that postoperative CAR better reflects the dynamic impact of inflammatory processes and exhibits a stronger correlation with mortality. Our findings indicate that elevated postoperative CAR is directly associated with increased inflammation and deteriorating nutritional status, suggesting its potential use in clinical practice to identify patients at risk of poor prognosis in the early postoperative period.

This study highlights the need for incorporating postoperative CAR into routine clinical practice to facilitate early identification of high-risk patients and optimize targeted treatment strategies. Future large-scale prospective studies are necessary to validate these findings and further strengthen the clinical significance of postoperative CAR in predicting mortality following CABG.

Authorship Contribution Statement

All authors have made significant contributions to the work reported, which may include the conception, study design, execution, acquisition of data, analysis and interpretation, or all of these areas; drafting, revising, or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and accepting responsibility for all aspects of the work.

Conflict Of Interest Statement

We have no conflict of interest.

Statement On The Use Of Artificial Intelligence

No artificial intelligence application was used.

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Scientific Reports in Medicine

The effect of emergency medicine internship on the knowledge levels of intern physicians on approaching emergency medical situations

Impact of EM Internship on Interns' Knowledge

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Abstract: Objective: In this study, it was aimed to investigate the knowledge levels of intern physicians regarding the approach to emergency conditions and the impact of the emergency medicine internship on these knowledge levels.

Method: This study evaluated the approach and knowledge levels of 154 volunteer intern physicians to emergency conditions using 40 case-based questions. These questions were derived from common, essential, and treatment-requiring cases in emergency medicine. The questions, which included topics such as basic and advanced life support, ECG arrhythmia interpretation, radiography and tomography imaging, and critical patient diagnosis and treatment, were prepared by our team in accordance with the 2020 National Core Education Program (UÇEP) guidelines.

Results: Among the 154 students who voluntarily participated in the study, a statistically significant increase in knowledge levels was observed in 37 out of 40 questions after the emergency medicine internship. For the remaining three questions, knowledge levels improved but not to a statistically significant extent. Notably, significant improvements were observed in ECG interpretation, advanced life support, and the approach to critical patients.

Conclusion: This study demonstrated that intern physicians had insufficient knowledge in approaching emergency conditions prior to the emergency medicine internship, but their knowledge levels improved significantly after the rotation. However, it was concluded that the duration of the emergency medicine internship is insufficient for preparing interns to work as general practitioners in emergency departments, or more effective educational activities should be implemented during this period.

Keywords: Intern Physician, Emergency Medicine, Internship, Medical Education

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INTRODUCTION

The emergency medicine internship is a crucial rotation that provides medical students with knowledge, skills, and experience in the management of emergency conditions while also offering significant gains for their future medical careers. During the emergency medicine internship, students have the opportunity to evaluate patients with a wide variety of clinical presentations (1,2). The management of emergency conditions requires not only knowledge, skills, and experience but also patience, composure, and courage. Today, the majority of medical school graduates in our country are assigned to emergency medicine clinics. In some cases, they are required to work alone on-call in rural areas. The emergency medicine internship in our country and worldwide is typically a two-month rotation during the final year of medical education; however, this duration is insufficient to achieve all the intended learning outcomes. Therefore, it is necessary to implement specialized educational activities that can engage and interest intern physicians during their emergency medicine training.

Some studies have shown that final-year medical students feel inadequate in terms of professional skills, clinical scenarios, symptom management, and the knowledge and skills targeted by the National Core Education Program (UÇEP) (3). For this reason, initiatives have been undertaken in recent years to improve the quality of medical education, and a national core education program (UÇEP) has been established to ensure standardized training across institutions (3,4).

This study aimed to evaluate the approach of intern physicians who have just begun their internship to emergency conditions and their ability to diagnose critically ill patients. The knowledge levels of intern physicians at the beginning and end of their rotation regarding critical patient scenarios they may encounter in general practice, imaging interpretation, electrocardiography evaluation, and the application of basic and advanced life support were assessed. Through this, the role of the emergency medicine internship in enhancing their knowledge levels was investigated.

METHOD

This study is a descriptive research study. It includes 154 final-year medical students who completed their internship at Kırşehir Ahi Evran University between 2022 and 2024. Ethical approval for the study was obtained from the Kırşehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee on 22.06.2021, with approval number 2021-11/133. Participation in the study was based on voluntary consent. Prior to the implementation, participants were informed about the study through an informed consent form, and written consent was obtained from the students.

Data was collected at the beginning and end of the emergency medicine internship during the 2022-2024 academic year through face-to-face testing using 40 case-based questions. The questions were designed in accordance with the clinical learning objectives outlined in the National Core Education Program (UÇEP). They included scenarios frequently encountered in the emergency department, which are critically important and must be well understood by emergency physicians.

The study began by preparing 40 critical

Table 1. Questions asked to intern physicians	
No.	Question
1	During your shift in the emergency department of a district state hospital, a 26-year-old woman develops symptoms such as tongue swelling, throat swelling, and shortness of breath following a penicillin injection. What is the first medication you will administer, and what are the appropriate dosages?
2	A nurse in the emergency department obtains an ECG for a patient. Based on the ECG findings provided, what diagnosis would you consider?
3	A nurse in the emergency department obtains an ECG for a patient. Based on the ECG findings provided, what diagnosis would you consider?
4	A patient presents to the emergency department with complaints of palpitations and shortness of breath. The nurse obtains an ECG. Based on the ECG findings, what diagnosis would you consider?
5	What pharmacological treatment would you recommend for the patient described in Question 4?
6	A 26-year-old male patient presents to the emergency department with palpitations. The nurse obtains an ECG. Based on the ECG findings, what is your primary diagnosis?
7	What is the first-line intervention for the patient described in Question 6?
8	A patient presents to the emergency department with syncope and hypotension. The ECG findings are provided. What is your preliminary diagnosis?
9	A patient presents to the emergency department with a severe headache, blood pressure of 170/100 mmHg, and persistent nausea and vomiting. What is your initial diagnosis, and what diagnostic test would you order?
10	A patient presents to the emergency department with a headache. A tomography image is provided. What is your diagnosis?
11	A 23-year-old male patient presents to the emergency department with sudden-onset chest pain and shortness of breath that began 20 minutes ago. A chest X-ray is provided. What is your primary diagnosis?
12	A 22-year-old male patient sustains a head injury after falling from a height. A brain tomography scan is provided. What is your diagnosis?
13	A 74-year-old patient loses consciousness after a fall at home. A tomography scan is provided. What is your diagnosis?
14	You are attempting to intubate a critically ill patient in a district hospital. The patient has severe trismus (jaw clenching). Which medication and dosage would you administer to facilitate intubation?
15	A patient presents to the emergency department with tachypnea (40 breaths per minute) but stable vital signs. What is the first diagnostic test you would order?
16	A patient presents to the emergency department with respiratory distress and agitation. After administering 5 mg of morphine, the patient experiences respiratory arrest. Which antidote should you administer alongside intubation?
17	A trauma patient is administered 5 mg of midazolam intravenously for sedation prior to tomography. The patient suddenly stops breathing. Which antidote should be administered in addition to initial resuscitation measures?
18	A patient in the emergency department suddenly develops convulsions, cyanosis, and respiratory arrest. What is your preliminary diagnosis, and what steps would you take for differential diagnosis?
19	What is the first action to take if a person exhibits symptoms of respiratory obstruction while eating?
20	Where should chest compressions be applied during cardiopulmonary resuscitation (CPR) in adults?
21	How much should the sternum be depressed during chest compressions in adult CPR?
22	What is the correct recovery position for an unconscious patient?
23	What is the recommended ratio of rescue breaths to chest compressions during adult CPR?
24	What is the sequence of actions for providing first aid to an unconscious adult found lying motionless on the ground?
25	If CPR is performed without rescue breaths, what is the recommended rate of chest compressions?
26	What is the sequence of actions for rescuing a drowning child who is unconscious and not breathing?
27	What should be done for an unconscious person with a completely obstructed airway?

Table 1. Questions asked to intern physicians	
No.	Question
28	Which of the following statements about cardiac massage is incorrect?
29	Which of the following statements about basic life support for infants and children is incorrect?
30	A patient with a myocardial infarction is brought to the emergency department after receiving CPR for 2 minutes. The patient has no pulse, and the following rhythm is observed on the monitor. What is the next step in management?
31	A 54-year-old male patient presents to the emergency department with sudden-onset chest and back pain lasting 1 hour. He has a history of hypertension, but his ECG is unremarkable. A chest X-ray is provided. What is your primary diagnosis?
32	A patient involved in a traffic accident presents with head, thoracic, and abdominal lacerations and pain. While awaiting blood results and radiology interpretation, the patient deteriorates. Based on the tomography images provided, what is your primary diagnosis?
33	A 74-year-old female patient is brought to the emergency department after a fall at home. A radiograph is provided. What is your preliminary diagnosis?
34	A 37-week pregnant patient presents to the emergency department with abdominal pain and suddenly develops seizures. What is your preliminary diagnosis, and what is the first-line treatment?
35	A 67-year-old male patient presents to the emergency department with weakness, poor general condition, and hyperventilation. ECG and venous blood gas results are provided (pH: 7.22, HCO3: 11, PO2: 58, Sat O2: 64, Na: 146, Ca: 1.16, K: 6.8, glucose: 132 mg/dL). What is your initial diagnosis, and what treatment should be initiated?
36	A patient presents to the emergency department after a fall. A radiograph is provided. What is your diagnosis?
37	A 38-year-old female patient presents with sudden, severe lower abdominal pain, cold sweats, nausea, and vomiting. She has no significant medical history. Physical examination reveals tenderness, guarding, and rebound in the lower abdomen. Vital signs and laboratory results are provided (BP: 90/65 mmHg, Pulse: 96/min, Temp: 36.7°C, Sat O2: 98%, WBC: 14,800/mm3, Hb: 8.7 g/dL, Platelets: 265,000/mm3, ALT: 18, AST: 29, BUN: 34, Cr: 0.98, CRP: 0.8). What are the two most likely diagnoses?
38	A patient treated for constipation in the emergency department returns with severe abdominal pain and subsequently experiences cardiac arrest. An abdominal tomography is provided. What is the most likely cause of cardiac arrest in this patient?
39	A 32-year-old female patient presents to the emergency department with fatigue, nausea, and worsening abdominal pain over 4 days. She has a history of moderate-severe persistent asthma but has been non-compliant with her medications. Vital signs and laboratory results are provided (BP: 86/53 mmHg, Pulse: 100/min, Temp: 35.9°C, WBC: 2000/mm3, Na: 126 mmol/L, K: 5.8 mmol/L, Glucose: 63 mg/dL). What is the most likely clinical condition, and what treatment should be initiated?
40	A patient with a history of hypertension and diabetes mellitus is presented to the emergency department after a sudden fall at home 4 hours ago. Physical examination reveals right-sided hemiparesis and slurred speech. Blood pressure is 180/100 mmHg. Two radiological images are provided. What imaging modalities are used, and what are their purposes? What is the patient's diagnosis, and how would you manage the current blood pressure?

patient case questions **(Table 1).**

On the first day of their emergency medicine internship, a pretest for all interns using these questions was administered, ensuring that both the questions and answers remained confidential. Subsequently, the same questions were reapplied at the end of the emergency medicine internship to assess the increase in knowledge among the physician candidates. These test questions were administered to each intern group over three years, and strict confidentiality of the questions was maintained. During the emergency medicine internship, regular training sessions were conducted for residents. Additionally, training to interns on fundamental topics was provided; however, no training was conducted on these specific questions

or their answers for any intern group. The test questions aimed to achieve two objectives: first, to determine students' level of knowledge regarding the approach to emergency conditions over the five years, and second, to enhance their motivation to learn about emergency conditions by demonstrating the critical patient scenarios they would encounter immediately after graduation.

Statistical analysis

The data were analyzed using the SPSS 21 program. The data are presented as mean, standard deviation, median, number, and percentage. The Kolmogorov-Smirnov test was used as the normality test. Parametric tests were used for data that followed a normal distribution, while non-parametric tests were preferred for data that did not follow a normal distribution. In the analyses, the McNemar test and Wilcoxon test were used. A p-value of <0.05 was considered statistically significant.

RESULTS

When comparing the intern physicians' correct answer rates on the pre-training pre-test and post-training post-test, a statistically significant increase in correct answers was observed for all questions except questions 1, 27, and 33 (Table 2).

A statistically significant increase was also found when comparing the overall correct answer rates of the intern physicians in the pre-training pre-test and post-training post-test. The effect size of the training

Table 2. Comparison of response distributions before and after training

	Pre-test correct answer rate		Post-test correct answer rate		
Questions	**n**	**%**	**n**	**%**	**p**
Q1	125	81.2	138	89.6	,281
Q2	132	85.7	151	98.1	,004 [c]
Q3	114	74.0	152	98.7	,000 [c]
Q4	45	29.2	125	81.2	,000
Q5	36	23.4	129	83.8	,000
Q6	35	22.7	141	91.6	,000
Q7	33	21.4	141	91.6	,000
Q8	80	51.9	145	94.2	,000
Q9	121	78.6	152	98.7	,000 [c]
Q10	70	45.5	145	94.2	,000
Q11	101	65.6	147	95.5	,000
Q12	105	68.2	147	95.5	,000
Q13	99	64.3	149	96.8	,000
Q14	9	5.8	50	32.5	,000 [c]
Q15	89	57.8	141	91.6	,000
Q16	21	13.6	135	87.7	,000
Q17	9	5.8	114	74.0	,000 [c]
Q18	9	5.8	75	48.7	,000
Q19	123	79.9	135	87.7	,040
Q20	130	84.4	147	95.5	,001
Q21	130	84.4	150	97.4	,000 [c]
Q22	146	94.8	152	98.7	,000 [c]
Q23	149	96.8	152	98.7	, [063c]
Q24	55	35.7	96	62.3	,000
Q25	135	87.7	149	96.8	, 001[c]

Table 2. Comparison of response distributions before and after training					
	Pre-test correct answer rate		Post-test correct answer rate		
Questions	**n**	**%**	**n**	**%**	**p**
Q26	76	49.4	115	74.7	,000
Q27	115	74.7	124	80.5	,112
Q28	128	83.1	143	92.9	,008
Q29	62	40.3	99	64.3	,000
Q30	29	18.8	102	66.2	,000
Q31	74	48.1	112	72.7	,000
Q32	70	45.5	146	94.8	,000
Q33	151	98.1	152	98.7	,500 [c]
Q34	62	40.3	134	87.0	,000
Q35	57	37.0	130	84.4	,000
Q36	144	93.5	152	98.7	.008c
Q37	53	34.4	115	74.7	,000
Q38	35	22.7	126	81.8	,000
Q39	12	7.8	64	41.6	, [002c]
Q40	82	53.2	137	89.0	,000
[c] **Mc Nemar test**					

was determined to be very large.

As can be understood from the responses given by the intern physicians, they initially demonstrated good performance in basic life support questions, which they frequently encountered during the first five years. However, it was observed that their knowledge levels further increased after the emergency medicine internship **(Table 3).**

Table 3. Comparison of pretest and post-test total correct answer numbers										
	N	Mean	Std. Deviation	Min.	Max.	25th	50th (Median)	75th	p	Cohen's d
Pretest total	154	21.11	5,051	8	34	17.00	21.00	24.25	**<0.001***	**6.13**
posttest total	152	33.36	3,341	21	38	32.00	34.00	36.00		
*Wilcoxon test										

While they generally had a good level of knowledge in imaging-related questions, their knowledge levels in ECG-related questions were initially very low but showed a significant improvement after the emergency medicine internship.

DISCUSSION

The internship year, which constitutes the final year of medical school, is an observational and predominantly practical process. During the internship, formal examinations are not typically conducted; however, the interns' attitudes, knowledge, and skills are evaluated, along with their adherence to good medical practices.

In Türkiye, the majority of intern physicians aim to specialize in a specific field after graduation (5). Driven by the goal of passing the specialization exam, many prefer to spend this period studying rather than gaining clinical experience. However, they should not neglect rotations such as the emergency medicine internship, which provides valuable clinical exposure. Studies by Akman et al. and Kaygusuz et al. (1,5) have indicated that the majority of intern physicians prioritize studying for the specialization

exam over gaining clinical experience, resulting in low levels of clinical skill acquisition. This situation leads to interns graduating without fully benefiting from clinical rotations and subsequently facing significant challenges when assigned to emergency departments.

In their study, Kaygusuz et al. (5) reported that final-year students did not feel confident in performing procedures such as intubation and advanced cardiac life support. Özvarış et al. (6) found that while final-year students had adequate theoretical knowledge, they needed more opportunities to practice and apply their skills. In a study by Tortum et al. (7) on the approach of intern physicians to emergency conditions, it was noted that interns' knowledge of anaphylaxis management increased from 39% before the internship to 95% after the internship. In our study, we observed that interns' knowledge of anaphylaxis increased from 81% before the internship to 90% afterward. We attribute this improvement to the strong emphasis placed on anaphylaxis during their first five years of training.

Hartman et al. (8) highlighted in their study that as physicians gain more clinical experience, their ability to interpret ECGs improves. Burns et al. (9) noted that the lack of a robust ECG training program in medical education results in interns being inadequately prepared in this area. Similarly, this study found that interns had insufficient basic ECG knowledge at the beginning of the rotation but demonstrated significant improvement in recognizing critical ECG findings by the end of the emergency medicine internship.

Two studies in the literature (10,11) have shown that ECG simulator-based training significantly improves knowledge levels. Although ECG simulators were not used in our emergency department, training sessions to ensure that interns could recognize essential arrhythmias were organized. As a result, we observed a notable increase in ECG knowledge levels in our study. This study represents a rare type of research in the literature, with the primary goal of ensuring that intern physicians are well-trained.

Limitations of the study

This study has several limitations, including being conducted at a single center, using a limited number of questions, and not including a practical examination component.

CONCLUSION

It was determined that intern physicians had insufficient knowledge in electrocardiography interpretation and diagnosing critical conditions before the emergency medicine internship, while their theoretical knowledge of imaging interpretation and basic life support was at a good level. However, it was observed that the emergency medicine internship significantly improved their knowledge levels in many areas. Providing high-quality training during the emergency medicine internship dramatically contributes to their competence as general practitioners.

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Delayed Presentation of Transfusion-Related Acute Lung Injury in the Emergency Department

Delayed Transfusion-Related Acute Lung Injury

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Abstract: Transfusion-related acute lung injury (TRALI) is a life-threatening complication of blood transfusion, characterized by acute hypoxemia and bilateral pulmonary infiltrates within 6–72 hours post-transfusion. Delayed TRALI, occurring 6–72 hours after transfusion, is underrecognized due to its temporal dissociation from the transfusion event, posing diagnostic challenges. We present the case of an 80-year-old woman with hypertension and atrial fibrillation who developed delayed TRALI 48 hours after receiving erythrocyte suspension for upper gastrointestinal bleeding. She presented with dyspnea, hypoxemia, and bilateral pulmonary edema, with no evidence of volume overload or infection. Management included non-invasive ventilation and diuresis, leading to rapid recovery. This case highlights the importance of considering delayed TRALI in elderly patients with new respiratory symptoms post-transfusion, even with non-plasma products. Early recognition and supportive care are critical, as delayed TRALI can progress to severe respiratory failure. Preventive strategies, such as using fresher blood units and male-donor plasma, may reduce risk. Clinicians must maintain a high index of suspicion for TRALI in high-risk populations to improve outcomes.

Keywords: Transfusion-related acute lung injury, transfusion-associated circulatory overload, Blood products, Transfusion

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INTRODUCTION

TRALI is a severe and potentially fatal complication of blood transfusion, characterized by acute hypoxemia and bilateral pulmonary infiltrates occurring within 6–72 hours post-transfusion (1). TRALI is categorized into two subtypes: immediate TRALI (onset ≤6 hours) and delayed TRALI (onset 6–72 hours). The latter is less frequently reported and often underdiagnosed due to its temporal dissociation from the transfusion event, making it a diagnostic challenge (2). The pathogenesis of TRALI is commonly explained by the "two-hit" model: the first hit involves patient-specific factors (e.g., inflammation, surgery, or critical illness) that prime neutrophils and endothelial cells, while the second hit arises from transfusion-derived biological response modifiers (e.g., anti-HLA antibodies, bioactive lipids) that trigger immune-mediated lung injury (3). Delayed TRALI is particularly concerning because its symptoms often overlap with other conditions, such as transfusion-associated circulatory overload (TACO), sepsis, or cardiac failure, leading to potential misdiagnosis and delayed treatment (4).

Despite significant advances in donor screening protocols, such as deferring multiparous female donors to reduce the risk of HLA antibodies, TRALI remains one of the leading causes of transfusion-related mortality, accounting for approximately 15% of reported fatalities (5). Elderly patients with comorbidities such as hypertension or atrial fibrillation are at heightened risk due to increased endothelial vulnerability, making them particularly susceptible to delayed TRALI (6). This case report presents an 80-year-old woman who developed delayed TRALI following erythrocyte transfusion for upper gastrointestinal bleeding, highlighting the importance of vigilance in high-risk populations and the need for early recognition and management.

CASE

An 80-year-old female patient with a medical history of hypertension and atrial fibrillation presented to the emergency department with complaints of dyspnea, fatigue, and generalized body pain. Two days prior, she had been hospitalized for upper gastrointestinal bleeding and received two units of erythrocyte suspension. Upon admission, she was tachypneic (respiratory rate: 27 breaths/min), agitated, and fatigued, with a Glasgow Coma Scale score of 14/15. Her vital signs included a blood pressure of 100/60 mmHg, oxygen saturation of 77% on room air, a heart rate of 101 beats/min, and a temperature of 37.3°C. Physical examination revealed accessory muscle use, diffuse crackles on auscultation, and short-sentence speech, consistent with mild to moderate respiratory distress. Electrocardiography showed atrial fibrillation without acute ischemic changes.

Laboratory results were unremarkable except for mild thrombocytopenia (platelet count: 100,000/μL). Hepatic and renal function tests were within normal limits. Transthoracic echocardiography performed by a cardiologist demonstrated a preserved left ventricular ejection fraction (55%) and chronic right atrial enlargement, with no evidence of systolic or diastolic dysfunction or significant valvular pathology. Chest radiography **(Figure 1)** and non-contrast thoracic computed tomography (CT) revealed new-onset bilateral pulmonary edema **(Figure 2).**

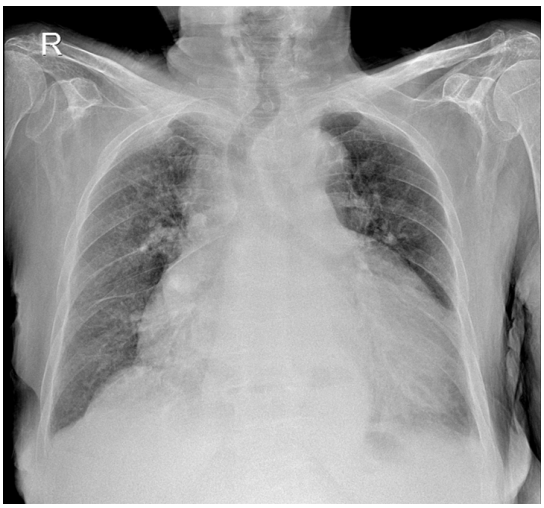

Figure 1. Chest radiography showed bilateral diffuse coarse reticular pattern

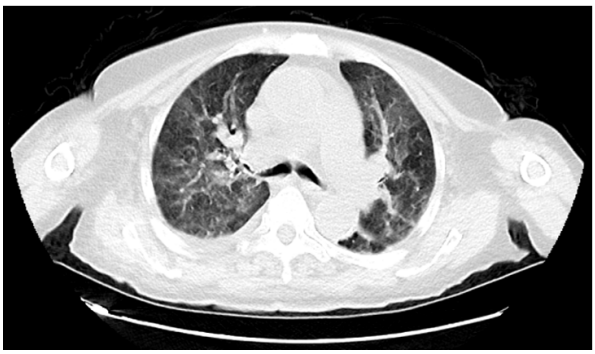

Figure 2. Non-contrast thoracic computed tomography demonstrated bilateral pulmonary edema

The patient required non-invasive ventilator support and was transferred to the intensive care unit. Diuresis with intravenous furosemide (40 mg/day) was initiated, leading to the gradual resolution of pulmonary edema. Respiratory support was weaned, and she was discharged on the fourth hospital day after complete symptom resolution.

DISCUSSION

This case exemplifies delayed TRALI, occurring 48 hours post-transfusion. The patient's advanced age, hypertension, and atrial fibrillation likely contributed to endothelial dysfunction, fulfilling the "first hit" in TRALI pathogenesis (7). The "second hit" may have involved transfusion-derived mediators, such as anti-HLA antibodies or bioactive lipids from stored erythrocytes. While HLA antibodies are classically implicated in TRALI, recent studies emphasize the role of bioactive lipids (e.g., lysophosphatidylcholines) in neutrophil priming, particularly in delayed cases (8). Notably, the patient received erythrocyte suspensions, which carry a lower TRALI risk than plasma-rich products (9). However, older blood units accumulate higher levels of pro-inflammatory lipids, potentially exacerbating lung injury (10).

Delayed TRALI diagnosis requires the exclusion of alternative etiologies. In this case, TACO was ruled out due to the absence of volume overload signs (e.g., elevated BNP, jugular venous distension) and rapid response to diuresis (11). Normal cardiac function on echocardiography further supported non-cardiogenic pulmonary edema. Thrombocytopenia, though mild, is a recognized feature of TRALI and may reflect platelet consumption in lung microvasculature (12). The absence of fever or leukocytosis helped exclude infectious causes.

This case underscores the importance of considering delayed TRALI in elderly patients with new respiratory symptoms following transfusion, even when plasma-rich products are not used. The delayed onset of symptoms can obscure the connection to the transfusion event, leading to diagnostic delays and potentially worse outcomes. Early recognition is critical, as delayed TRALI can rapidly progress to severe respiratory failure if not promptly managed (13).

Current TRALI management focuses on supportive care, including oxygen therapy and judicious fluid administration (14). Non-invasive ventilation, as used in this case, is preferred to avoid ventilator-induced lung injury (15). Diuresis remains controversial but may alleviate hydrostatic pressure in patients with concurrent volume overload (16). The patient's rapid recovery aligns with typical TRALI outcomes, where 80% of cases resolve within 96 hours with supportive measures (17).

This case highlights the need for heightened suspicion of delayed TRALI in elderly transfused patients, even when non-plasma products are administered. Implementing preventive strategies, such as using male-donor plasma and fresher blood units, could mitigate risk (18). Biomarkers like interleukin-8 (IL-8) or soluble CD40 ligand (sCD40L) may aid in early diagnosis but require further validation (19). Additionally, this case emphasizes the importance of multidisciplinary collaboration in managing TRALI, particularly in high-risk populations.

The delayed onset of symptoms, combined with the patient's complex medical history, underscores the need for clinicians to maintain a high index of suspicion for TRALI, even beyond the immediate post-transfusion period. Furthermore, this case highlights the potential role of bioactive lipids in delayed TRALI pathogenesis, suggesting that even

non-plasma products like erythrocyte suspensions can pose a risk, especially when older blood units are used. This has important implications for blood bank practices and transfusion protocols, particularly in elderly and critically ill patients.

CONCLUSION

Delayed TRALI is a rare but consequential complication of transfusion therapy, particularly in vulnerable populations such as the elderly. Clinicians must maintain a high index of suspicion in patients with new respiratory symptoms post-transfusion, even beyond the immediate 6-hour window. Multidisciplinary collaboration, adherence to preventive protocols, and ongoing research into pathogenetic mechanisms are essential to reduce TRALI-related morbidity and mortality. This case serves as a reminder of the importance of early recognition and prompt management of delayed TRALI, particularly in high-risk patients.

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Hypertension Measurement Methods and Differential Diagnosis

Hypertension and differential diagnosis

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Abstract: Hypertension, a prevalent global health concern, significantly contributes to cardiovascular morbidity and mortality. Accurate diagnosis and management are essential to mitigate its complications. This review highlights the importance of various blood pressure (BP) measurement methods, including office BP (OBP), ambulatory BP monitoring (ABPM), and home BP monitoring (HBPM), emphasizing their roles in identifying conditions such as white coat hypertension (WCH) and masked hypertension (MH). ABPM and HBPM are preferred for their superior predictive value for target organ damage and cardiovascular risk compared to OBP. Central aortic BP (cBP) and arterial stiffness, assessed via pulse wave velocity (PWV), provide additional insights into vascular aging and cardiovascular risk. The review also explores subtypes of hypertension, including WCH, MH, nocturnal hypertension, and secondary hypertension, discussing their pathophysiology, clinical implications, and management strategies. Lifestyle modifications, such as dietary changes and exercise, remain pivotal in hypertension management, with the DASH diet and sodium restriction being particularly effective. Pharmacological interventions, including renin-angiotensin-aldosterone system inhibitors and SGLT2 inhibitors, demonstrate efficacy in BP control and cardiovascular risk reduction. Additionally, the impact of comorbid conditions like obstructive sleep apnea (OSA) and the role of antihypertensive therapies during COVID-19 are discussed. Emerging evidence underscores the need for individualized treatment approaches, incorporating advanced diagnostic tools and addressing modifiable risk factors. This comprehensive review aims to enhance understanding of hypertension's complexities, guiding clinicians toward improved diagnostic accuracy and therapeutic outcomes.

Keywords: Hypertension, Blood pressure measurement, Central aortic blood pressure

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Introduction

Hypertension, commonly known as high blood pressure (BP), is a significant public health concern that can lead to serious complications if left untreated. Understanding the differential diagnosis is crucial for identifying underlying causes and ensuring appropriate management of the condition. Hypertension is most commonly defined as systolic arterial BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg; however, these definitions may vary depending on professional societies and cardiovascular risk profiles (1, 2). Hypertension is also a major risk factor for cardiovascular diseases and mortality (3).

The diagnosis of hypertension can vary depending on the measurement method (4). The 2018 European Hypertension Management Guidelines recommend that the diagnosis of hypertension should not rely solely on office BP (OBP) but also include "out-of-office" measurements, such as ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) (5). This approach provides a more accurate diagnosis, especially in cases of WCH and masked hypertension (MH). This review aims to discuss the clinical conditions that must be considered in the differential diagnosis and management of hypertension.

A. The Importance of Arterial Blood Pressure Measurement Methods

1. Office Blood Pressure Measurement (OBP)

OBP is typically performed as a single measurement in a clinical setting and can be influenced by external factors such as stress and white coat hypertension (WCH). Some guidelines define hypertension as an OBP of ≥ 140/90 mmHg, while others set the threshold at ≥ 130/80 mmHg (5, 6). OBP is affected by several limitations, including its inability to accurately diagnose WCH and MH, the use of faulty devices, methodological errors, and the lack of standardization in measurement conditions. Due to these and other shortcomings, current guidelines now recommend OBP as a screening method only, while ABPM or HBPM are preferred as diagnostic methods for hypertension (7). Additionally, the correlation between OBP and target organ damage is weaker compared to other measurement methods (8). This diminished correlation suggests that relying solely on OBP could lead to an incomplete understanding of a patient's cardiovascular health. Consequently, more reliable methods like ABPM or HBPM are advocated to ensure accurate diagnosis and effective management of hypertension.

2. Ambulatory Blood Pressure Monitoring (ABPM)

The ABPM is a type of out-of-office BP monitoring, typically assessed using the oscillometric method. Studies have shown that elevated BP measured via ABPM is a stronger predictor of target organ damage and cardiovascular events compared to OBP (9).

In clinical practice, ABPM is used to identify various conditions, including WCH, MH, white coat effect, masked uncontrolled hypertension, nocturnal hypertension, and BP dipping patterns (e.g., dipper, non-dipper, extreme dipper, and reverse dipper) (10). Additionally, ABPM can monitor the effectiveness of antihypertensive drug therapy and evaluate conditions such as orthostatic, postprandial, and drug-induced hypotension, as well as hypotension caused by autonomic dysfunction (10, 11).

The thresholds for elevated BP in ABPM are generally defined as follows:

- Daytime BP ≥ 135/85 mmHg
- 24-hour BP ≥ 130/80 mmHg
- Nighttime BP ≥ 120/70 mmHg (11).

These ABPM thresholds correspond to an OBP of ≥ 140/90 mmHg and are consistent with the thresholds recommended in international guidelines (5, 12). While some studies suggest that ABPM may be superior to HBPM in terms of prognostic value, the overall data remain insufficient to definitively conclude whether ABPM or HBPM is superior for assessing cardiovascular risk (13, 14).

3. Home Blood Pressure Monitoring

The HBPM involves measurements taken by individuals in their homes. However, as it usually

reflects only a single time point measurement, it may not accurately represent the dynamic variability of BP. On the other hand, the primary advantage of out-of-office BP measurement lies in its ability to perform multiple readings with reduced white coat effects and observer bias, providing a more reliable assessment of true BP (15). The preferred duration for HBPM is 7 days, with measurements taken in the morning and afternoon each day (16). Once BP is controlled, 1–3 days of monitoring is considered sufficient (17). In the literature, HBPM has been reported to predict subclinical target organ damage as effectively as ABPM in untreated hypertensive patients (18). Furthermore, several studies have indicated that HBPM is more closely associated with target organ damage compared to OBP and even ABPM (19, 20).

Key Considerations for HBPM

1. The patient's arm should be supported, such as resting on a table.
2. The cuff should be placed directly over the antecubital fossa.
3. The center of the bladder should align with the artery of the upper arm (16).

B. Central Aortic Blood Pressure Measurement and Arterial Stiffness

Central Aortic BP (cBP) Arterial Stiffness and BP levels change with aging, characterized by a typical increase in systolic BP and pulse pressure (systolic-diastolic BP), while diastolic BP decreases. Aging and hypertension collectively result in progressive structural and functional alterations of the large arteries, involving inflammatory processes and remodeling. In large arteries, such as the aorta, the thinning of elastin fibers combined with the relative increase in collagen content results in changes to arterial wall architecture, leading to vascular stiffness. Inflammatory processes and vascular calcification make these changes and the loss of elasticity and compliance in the arteries even worse (21–23). Endothelial dysfunction is another hallmark of vascular degeneration associated with aging and hypertension (24). Age-associated structural and functional alterations accelerate and intensify in hypertensive patients, resulting in a phenomenon known as "early vascular aging" in hypertension (25). Reliable techniques are being developed to evaluate vascular aging in clinical practice. Pulse wave velocity (PWV) and cBP, which measure how stiff a large artery is, give a more accurate picture of vascular aging and may be better at predicting cardiovascular risk (26).

In elastic arteries, reflected waves typically reach the central aorta in late systole or predominantly during diastole, minimizing their impact on central aortic systolic BP. However, with reduced elasticity in stiffer arteries, reflected waves move more quickly and arrive in the ascending aorta during early systole. Consequently, central aortic systolic pressure increases, diastolic pressure decreases, and this leads to increased central pulsatility (i.e., higher pulse pressure) and elevated PWV (27).

This rise in left ventricular afterload contributes to left ventricular hypertrophy and diastolic dysfunction. Simultaneously, a reduction in central diastolic pressure can compromise coronary perfusion and predispose to myocardial ischemia (28). Arterial hypertension accelerates these changes earlier in life (29). When the central elastic arteries get stiffer, pressure waves travel outwards. This puts stress on the brain and kidneys' microcirculation, which normally widens the blood vessels. This process can lead to complications like cerebral lacunar infarcts and albuminuria. Moreover, aortic stiffness increases the risk of ischemic and hemorrhagic strokes due to vessel dissection and ruptured intracranial aneurysms. Similarly, kidneys, being high-flow, low-resistance organs, experience increased pressure in the glomerular capillary network, leading to glomerular damage and proteinuria, eventually progressing to kidney failure (30, 31).

Measuring Vascular Stiffness and cBP: The PWV is calculated as the distance between two points in the arterial tree divided by the travel time of the pulse wave over that distance (32). The PWV is influenced by the stiffness of the vessels it traverses; stiffer arteries propagate the wave faster. With aging, central arteries stiffen earlier than peripheral

arteries. Carotid-femoral PWV is used to assess central arterial stiffness, while carotid-brachial PWV is utilized for peripheral stiffness evaluation (23). PWV remains the most accurate and valuable index for assessing arterial stiffness. Despite the widespread use of brachial cuff measurements for diagnosing hypertension, cBP more accurately reflects the hemodynamic load on the heart and large arteries. Among individuals with similar brachial pressures, significant variations in central pressure exist. Pharmacological interventions may also exert differential effects.

Most of the time, non-invasive methods are used to measure cBP because invasive cardiac catheterization with specialized catheters to record pressures in the ascending aorta is not practical in clinical practice (31). For example, oscillometric signals that show intra-arterial pressure waveforms have been used in cuff-based techniques to estimate cBP (67, 68). The cBP values that are normalized for age and sex can help doctors evaluate and treat patients.

Interventions for Arterial Stiffness: Exercise, weight loss, low-sodium diets, moderate alcohol consumption, and non-pharmacological strategies such as garlic powder, alpha-linolenic acid, dark chocolate, and fish oil may reduce arterial stiffness (34, 35).

While most antihypertensive therapies effectively lower brachial BP, only certain treatments demonstrate greater efficacy in reducing cBP. For example, beta blockers lack significant effects on cBP compared to renin-angiotensin-aldosterone system inhibitors. However, beta blockers with alpha-blockade activity (e.g., carvedilol) or nitric oxide-releasing properties (e.g., nebivolol) may show beneficial effects, though clinical evidence is inconclusive. Calcium channel blockers (CCBs) and diuretics reduce both brachial and cBP proportionally, showing parallel decreases in systolic and diastolic pressures. Notably, olmesartan/CCB regimens are more effective than olmesartan/diuretic combinations in lowering cBP (36).

Current guidelines for high BP say that people should start with a combination of ACEi/ARBs, CCBs, or thiazides to stop any organ damage caused by high BP(5). About 70% of people with high-normal brachial systolic BP also have cBP levels that are the same as those with stage I hypertension. Also, 30% of men and 10% of women with normal brachial BP also have cBP levels that are the same as those with stage I hypertension. These results suggest that patients with high cBP may not be getting enough treatment if only looking at brachial BP thresholds. More research is needed to see if making clinical decisions based on cBP is good for patients in the long term.

Lastly, sacubitril/valsartan, which was just approved to treat heart failure with low ejection fraction, looks like it could be useful for changing central parameters in people with high BP. It reduces vascular wall stress through diuresis, natriuresis, and increased levels of natriuretic peptides (31). Targeting cardiovascular risk factors, including diabetes, dyslipidemia, and smoking, may delay arterial aging. Statins have also demonstrated improvements in arterial stiffness, further supporting their role in cardiovascular prevention (38).

C. Types of Hypertension

1. White Coat Hypertension (WCH)

WCH, also referred to as isolated office or isolated clinical hypertension, describes a condition where BP is elevated in a clinical or office setting but remains within normal limits (<140/90 mmHg) outside of the office. Its prevalence is estimated to be 10–20%. Although the exact etiology remains unclear, anxiety may play a role. Patients with WCH are at risk of developing sustained hypertension over time. WCH is associated with increased cardiovascular morbidity and mortality compared to normotensive individuals. Lifestyle modifications and periodic BP monitoring are recommended to reduce cardiovascular risk. Routine pharmacological treatment is not necessary. However, treatment may be considered for patients with evidence of target organ damage or very high cardiovascular risk (5).

2. Masked Hypertension

MH refers to a condition where OBP measurements are <140/90 mmHg, but elevated BP is detected during home or ABPM. Its prevalence in the general population ranges from 8.5% to 16.6% (39, 40). MH is associated with an increased risk of cardiovascular morbidity and mortality, similar to that observed in patients with sustained hypertension (40).

Types and Causes of Masked Hypertension:

- **Morning Hypertension:** The most common form of MH, often caused by natural circadian rhythms, evening alcohol consumption, or the use of short-acting antihypertensive medications.

- **Daytime Hypertension**: May result from lifestyle factors such as habitual smoking, mental or physical stress.

- **Nighttime Hypertension**: Commonly associated with high salt intake, kidney disease, obesity, sleep apnea, and autonomic dysfunction (41).

Management of Masked Hypertension: Management should focus on aggressively addressing modifiable risk factors associated with MH, such as obesity, diabetes, sleep apnea, smoking, and alcohol consumption. A treatment approach for MH involves using antihypertensive medications to lower out-of-office BP, even in the absence of elevated OBP. Periodic ABPM is recommended during treatment to assess out-of-office BP levels and guide therapy adjustments (40).

3. Physiological Causes of Hypertension (Pain and Anxiety)

Anxiety and pain are among the physiological causes of hypertension (42). For instance, some individuals find visiting a doctor to be an anxiety-inducing situation, potentially leading to WCH. Conversely, individuals with MH with WCH might have previously undergone unpleasant experiences, such as undesired medical diagnoses and painful medical procedures in a doctor's office, which could lead to transient anxiety and a concurrent rise in BP (45). Monitoring BP at home or using an automatic device to measure BP while the patient is alone in the physician's office can help reduce errors that may lead to inaccurate results (42).

In normal physiology, acute pain signals triggered by tissue trauma and hypersensitivity evoke protective responses to minimize risk and promote tissue healing. Acute pain generates increased sympathetic nervous system activity. This process leads to heightened peripheral resistance, heart rate, and stroke volume. Additionally, the response involves activation of the neuroendocrine system, particularly the hypothalamic-pituitary-adrenal axis, as well as further activation of the sympathetic system by the adrenal glands (46). Therefore, painful conditions can elevate BP.

4. Labile Hypertension

Even in normotensive individuals, it is normal for BP to vary and fluctuate daily due to numerous factors, such as physical activity, emotions, body position, respiratory cycle, diet, salt intake, alcohol consumption, sleep deprivation, and others. However, there is no clear definition or quantitative criterion distinguishing normal from abnormal lability. Although most physicians are familiar with the term labile hypertension, it is more of a clinical impression than a specific diagnosis. Most cases attribute it to emotional stress, despite the lack of a clear and universally accepted definition. Patients may report being symptomatic or asymptomatic during episodes. Emotional stress-triggered sympathetic nervous system activation may link the etiology to increases in BP. Both genetic and environmental factors may contribute to exaggerated BP responses in patients with labile hypertension. Because the sympathetic nervous system may play a part in labile hypertension, it has been suggested that combined alpha and beta blockers and central alpha agonists be used to treat the condition (47). It remains uncertain whether the variable component of BP impacts cardiovascular outcomes, whether different medications have varying effects on BP variability, and whether reducing BP variability affects cardiovascular outcomes.

5. Paroxysmal Hypertension (Pseudopheochromocytoma)

Although the terms paroxysmal hypertension and labile hypertension are sometimes used interchangeably, they are considered distinct concepts due to differences in their clinical presentation and management. Unlike patients with labile hypertension, those with paroxysmal hypertension (pseudopheochromocytoma) typically experience hypertensive episodes that occur without evident emotional distress. Patients often describe these episodes as sudden and abrupt. The attacks typically begin unexpectedly and may last for minutes, hours, or even days. The abrupt increases in BP are accompanied by prominent and distressing physical symptoms such as headaches, palpitations, flushing, weakness, or dyspnea. The episodes often trigger fears of death or stroke; however, such fears usually occur after the onset of physical symptoms, not before. The fear of recurrent symptomatic episodes can lead to restrictions in lifestyle and functionality (48, 49). Biochemical screening for pheochromocytoma is mandatory; however, such a tumor is found in fewer than 2% of patients with paroxysmal hypertension (50). Catecholamine studies are generally normal but may exhibit mild abnormalities during or between paroxysmal episodes, possibly reflecting activation of the sympathetic nervous system (49). The differential diagnosis should include pheochromocytoma, labile hypertension, and panic disorder (47).

For patients with severe increases in BP, intravenous antihypertensives such as labetalol or nitroprusside may be considered. For those without extreme BP elevations, the use of an anxiolytic agent like alprazolam may be considered. The efficacy of any daily antihypertensive regimen in preventing, reducing the severity, or decreasing the frequency of paroxysmal episodes has not been adequately studied. Furthermore, the use of such regimens is limited by the risk of hypotension in patients whose BP returns to normal between paroxysmal episodes (47).

Due to the syndrome's similarity to panic disorder, experts have suggested using antidepressant medications to prevent attacks. Importantly, most patients report that antidepressants, when used at recommended dosages for treating panic disorder, prevent recurrent paroxysmal conditions. There is no evidence indicating that one class of antidepressants is more effective than another. Additionally, an approach incorporating psychotherapeutic interventions should also be considered (47).

6. Nocturnal Hypertension

A 10-20% reduction in systolic BPduring the night is considered a physiological dip (dipper). Nocturnal hypertension refers to high BP that occurs during sleep. It is defined as an average nighttime systolic BP of ≥120 mm Hg and/or an average diastolic BP of ≥70 mm Hg, as detected by ABPM (51). Nocturnal hypertension increases the risk of cardiovascular events and all-cause mortality, independent of daytime BP (52-54).

Nighttime BP reduction, compared to daytime BP, is categorized into four patterns: extreme dipper (>20% reduction), dipper (10–20% reduction), nondipper (<10% reduction), and reverse dipper (nighttime BP is higher than daytime BP) (51). Isolated systolic nocturnal hypertension is another type of nocturnal hypertension. This type of hypertension is marked by an average BP of ≥120/70 mm Hg at night, as measured by ABPM without the use of antihypertensive drugs, while daytime BP does not meet the diagnostic threshold for hypertension (55).

Orthostatic hypotension and supine nocturnal hypertension can happen in some older patients. These conditions are often linked to stiffer arteries, less sensitive baroreflexes, and problems with the autonomic nervous system (56). These patients have autonomic nervous system disorders characterized by systemic vasoconstriction and insufficient compensatory increases in heart rate to maintain BP (56).

The principles of treatment include:

1. Identify and aim to eliminate causal factors, if possible.

2. Implement lifestyle modifications alongside medications and other treatment measures.
3. Use long-acting antihypertensive agents at full doses or combination therapy to control nighttime hypertension.
4. Select an individually effective nighttime BP-lowering treatment strategy.

For example, in patients consuming high-salt diets, salt intake should be strictly restricted. Patients with uncontrolled nighttime hypertension caused by inappropriate use of short- or medium-acting antihypertensive medications should switch to long-acting antihypertensives. Recommendations for other hypertensive patients are also applicable here, such as adopting a healthy diet, quitting smoking, moderating alcohol consumption, engaging in regular physical exercise, controlling weight, improving sleep patterns, and reducing mental stress.

7. Pseudohypertension

Pseudohypertension is a condition in which BP measured indirectly using a cuff overestimates the actual intra-arterial BP (57). It is defined as a cuff-measured diastolic BP that is at least 15 mmHg higher than simultaneous intra-arterial BP measurements (58). This condition is observed in elderly patients with calcified and stiff arteries who exhibit very high BP readings but minimal or no target organ damage. In such patients, an excessively high cuff pressure is required to compress the artery, leading to an erroneously elevated BP measurement. In summary, it occurs due to medial sclerosis and/or calcification of the arteries, which significantly diminish the arteries' ability to collapse.

A particularly high BP reading without significant target organ damage is an important clue and can be detected using a simple diagnostic method called the "Osler maneuver." Definitive diagnosis is made by comparing directly measured intra-arterial BP with indirectly measured BP (59, 60). When the cuff is inflated to a level that stops brachial arterial sounds, the Osler maneuver is considered positive as long as the radial artery can still be felt (60). While this maneuver can serve as a cost-effective screening tool in resource-limited settings, it has low sensitivity and specificity (57). Additionally, calcification of small- and medium-sized arteries in these patients may appear as a "railroad track sign" on X-ray imaging (57).

Elderly hypertensive patients are particularly susceptible to the side effects of antihypertensive medications. Part of this susceptibility may stem from overtreatment due to overestimation of arterial BP caused by pseudohypertension in this age group. This overtreatment can lead to excessive reductions in arterial BP, resulting in inadequate blood flow to various vital organs such as the brain, heart, and kidneys (61).

8. Secondary Hypertension

Secondary hypertension refers to arterial hypertension caused by identifiable underlying conditions and affects approximately 5-10% of the general hypertensive population. The reported prevalence of the most common causes of secondary hypertension in hypertensive patients is as follows (58, 62):

- Obstructive sleep apnea (OSA): 5-15%
- Renal parenchymal disease: 1.6-8%
- Renal artery stenosis (RAS): 1-8%
- Primary hyperaldosteronism (PHA): 1.4-10%
- Thyroid diseases: 1-2%
- Cushing's syndrome: 0.5%
- Pheochromocytoma: 0.2-0.5%
- Coarctation of the aorta: <1%

Due to their rarity, secondary forms of hypertension should only be screened in patients with clinical suspicion, as the diagnostic workup can be time-consuming and costly. Finding general clinical clues that suggest secondary hypertension during the initial evaluation of hypertensive patients is one way to diagnose it (58, 62):

- Early-onset hypertension (e.g., before the age of 30) in patients without other risk factors (e.g., family

history, obesity) or elevated BP in prepubescent children

- Resistant hypertension

- Severe hypertension (>180/110 mmHg) or hypertensive emergencies

- Sudden increases in BP in previously stable patients

- Non-dipper or reverse-dipper patterns observed during 24-hour ABPM

- Presence of target organ damage (e.g., left ventricular hypertrophy, hypertensive retinopathy)

Age: Young adults (<30 years) without a family history of hypertension or other risk factors should be screened for secondary forms. In older adults with known atherosclerosis, severe hypertension or acute increases in BP may suggest a secondary form (58, 62).

Body Mass Index (BMI): Overweight patients with resistant hypertension should be screened for OSA and endocrine causes of hypertension (e.g., Cushing's syndrome, hypothyroidism) (58).

Blood Pressure Level: Patients with resistant hypertension despite adequate treatment, severe hypertension at baseline (>180/110 mmHg), or hypertensive emergencies should undergo screening for secondary forms of hypertension (58). Non-dipping during ABPM (i.e., <10% nocturnal reduction in BP compared to daytime values) is associated with secondary forms of hypertension (e.g., OSA, RAS); non-dipper or reverse-dipper patients should therefore be screened (63, 64).

Prevalence of Atherosclerosis: Among hypertensive patients with widespread atherosclerosis (e.g., coronary artery disease, peripheral vascular disease, and cerebrovascular disease), approximately 15–30% have significant RAS (≥50% stenosis) (65).

Resistant Hypertension: Resistant hypertension is defined as uncontrolled BP (>140/90 mmHg) despite concurrent use of three classes of antihypertensive medications (e.g., a long-acting CCB, a renin-angiotensin system blocker, and a diuretic) prescribed at their maximum or maximum tolerable doses. Screening for secondary forms should be conducted in these patients. However, before initiating screening, medication adherence should be confirmed and the white coat effect excluded (66).

Certain situations during antihypertensive treatment can also suggest the presence of secondary hypertension (58, 62):

- Excessive decline in glomeruler filtration rate(GFR) with ACE inhibitor treatment (suggestive of RAS, particularly in bilateral cases)

- Hypokalemia with diuretic therapy (suggesting PHA or other endogenous/exogenous mineralocorticoid excess)

- Resistant hypertension

- Fluctuating BP that remains uncontrolled despite treatment

Drug-Induced Hypertension: Several medications can cause hypertension associated with treatment resistance. The most well-known are NSAIDs and corticosteroids, potentially due to sodium and fluid retention. Some medicines, like stimulants (like cocaine and amphetamines) and decongestants (like phenylephrine hydrochloride and naphazoline hydrochloride), can raise BP by activating the sympathetic nervous system. Licorice elevates BP by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism (58, 67). Oral contraceptives (estrogen + progestin) cause hypertension in about 5% of women. Antidepressants (e.g., venlafaxine, monoamine oxidase inhibitors) may increase BP dose-dependently, likely through noradrenergic stimulation. Immunosuppressive agents, especially cyclosporine A, raise BP through sympathetic activation and direct vasoconstriction (68). Lastly, vascular endothelial growth factor inhibitors (e.g., bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenib) can also elevate BP (69).

Renal Artery Stenosis (RAS): RAS is a significant cause of secondary hypertension. In younger patients, fibromuscular dysplasia is the most common cause, while in adults, atherosclerosis is

the leading etiology. The prevalence of RAS in the general hypertensive population ranges from 1% to 8%, but it can be as high as 25%–35% in patients with widespread atherosclerosis (70). Hemodynamically significant atherosclerotic RAS (>70%) is found in approximately 10% of resistant hypertension cases in patients over the age of 65 (71). Clinical clues indicating RAS in adult patients include an abdominal bruit, deterioration in renal function with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, severe or sudden worsening of hypertension in smokers or diabetic patients, the presence of widespread atherosclerosis, and recurrent episodes of flash pulmonary edema (5).

Primary Hyperaldosteronism (PHA): PHA is a form of endocrine hypertension characterized by low renin, hypokalemia, and metabolic alkalosis resulting from excessive aldosterone production by one or both adrenal glands. The most common etiological causes are bilateral adrenal hyperplasia or aldosterone-producing adenomas. Excessive aldosterone production can lead to sodium retention, hypokalemia, and cardiovascular complications such as heart failure and atrial fibrillation. However, frequent observations also indicate normocalemic hypertension (72, 73).

Which patients should we suspect of having PHA (74)?

1. The patient has a history of hypertension and hypokalemia, which can be either spontaneous or induced by diuretics.
2. Resistant hypertension.
3. Coexisting adrenal incidentaloma with hypertension or hypokalemia.
4. Hypertension associated with sleep apnea.
5. Early-onset hypertension (under 40 years of age) or a history of cerebrovascular events.
6. Persistently elevated BP of ≥150/100 mmHg on three separate readings on different days.
7. History of hypertension in a first-degree relative diagnosed with PHA

Aldosterone-to-Renin Ratio (ARR) > 30 ng/dL is the most reliable screening test for PHA. Ideally, if hypokalemia is present, it should be corrected with oral potassium supplements before testing. Hypokalemia inhibits aldosterone secretion, potentially leading to a false-negative screening result. Prior to testing, medications such as ACE inhibitors, ARBs, beta blockers, diuretics, direct renin inhibitors, and aldosterone antagonists should be discontinued 2–4 weeks before the test, if possible. Amlodipine and alpha blockers are considered safe for use. Some tests, like the oral sodium loading test, saline infusion test, captopril test, or fludrocortisone suppression test, must be used to confirm biochemically that the PHA level is higher than 30 ng/dL.

The next step after biochemical confirmation of hyperaldosteronism is to perform computed tomography imaging of the adrenal glands. Finally, adrenal venous sampling to determine the lateralization of excessive aldosterone secretion helps guide the decision between surgical and medical treatment (74).

D. Hypertension and COVID-19: It is known that angiotensin-converting enzyme-2 (ACE2) expression can be upregulated by ACEI and ARB (75). Since ACE2 facilitates cellular entry of SARS-CoV-2, concerns were raised during the pandemic that treatment with these drugs might increase the risk of severe COVID-19 (5, 75, 76).

In March 2020, the European Society of Cardiology recommended continuing regular antihypertensive treatment with ACEI or ARB, as there was no conclusive evidence that treatment with these agents was harmful during SARS-CoV-2 infection. Subsequent studies have confirmed that ACEI and ARB are not associated with an increased risk of severe COVID-19 progression (77, 78). It can be hypothesized that the long-term use of these medications may also have beneficial effects during COVID-19 through their favorable cardiovascular effects.

E. Sleep Apnea and Hypertension: OSA is considered one of the most common causes of secondary hypertension. It is characterized by recurrent obstructive apneas and hypopneas caused by the collapse of the upper airways during sleep. The severity of OSA is classified based on the apnea-hypopnea index (AHI), which represents the number of apneas and hypopneas per hour of sleep: mild (AHI 5-15), moderate (AHI 16-30), and severe (AHI >30).

Most patients with OSA complain of excessive daytime sleepiness, snoring, morning headaches, difficulty concentrating, and irritability. Typical clinical findings include obesity, a thick neck, and macroglossia. Both nighttime (non-dipping) and daytime BP levels are elevated in OSA patients (79).

Proposed mechanisms for increased BP in OSA include elevated sympathetic nerve activity and changes in the renin-angiotensin-aldosterone system resulting from recurrent nighttime hypoxemia (80, 81). Furthermore, hypoxemia is associated with endothelial dysfunction caused by oxidative stress (82). Additionally, studies have shown a reduction in both nighttime and daytime BP following successful treatment with continuous positive airway pressure (CPAP) therapy for OSA (83).

F. Hypertension Treatment: Dietary Approaches

Effective lifestyle modifications can be sufficient to delay or even prevent the initiation of medication in patients with stage 1 hypertension (5). While lifestyle changes can enhance the efficacy of antihypertensive therapy, medication should not be delayed in hypertensive patients with high cardiovascular risk. Therefore, hypertension management guidelines emphasize lifestyle modifications, such as limiting salt intake, reducing alcohol consumption, increasing vegetable and fruit intake, and adopting a healthy diet (5).

The role of sodium in BP regulation is well-established. To lower high BP and improve cardiovascular outcomes, a daily salt intake of less than 5 grams is recommended (5).

One of the most significant dietary approaches in hypertension management is the Dietary Approaches to Stop Hypertension (DASH) (84). This diet emphasizes the consumption of fruits, vegetables, whole grains, lean proteins, and low-fat dairy products while reducing saturated fats, cholesterol, and sodium. Thus, salt restriction and lifestyle modifications remain effective options in the treatment of hypertensive patients with low cardiovascular risk. These approaches not only help manage BP but also contribute to overall cardiovascular health.

G. Hypertension and SGLT-2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) is a glucose transporter located in the proximal tubules of the nephrons in the kidney. In the kidney, SGLT2 facilitates glucose reabsorption from the tubular filtrate back into the bloodstream (85). SGLT2 inhibitors are a class of drugs that block the function of SGLT2, thereby preventing glucose reabsorption and promoting its excretion through urine (86). Beyond their glucose-lowering effects, SGLT2 inhibitors have been shown to have secondary effects, such as lowering BP independently of blood glucose levels (87, 88).

Therefore, the 2019 European Diabetes Management Guidelines recommend considering the BP-lowering effects of SGLT2 inhibitors during treatment (89). These medications appear advantageous in the treatment of cardiovascular disease, particularly heart failure, regardless of the presence of diabetes (90).

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A Drop of Blood: Newborn Heel Blood Screening Programmes, Innovations, and Contrary Voices in Türkiye and The World

Heel Blood Screening: Innovations and Oppositions

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Abstract: Congenital metabolic diseases are mostly autosomal recessive diseases that can be detected in the neonatal period and can lead to disability and even death if left untreated. Screening programmes for early diagnosis are organised worldwide to prevent such diseases. Heel Blood Screening (HBS), which is widely used in Türkiye and in the world, is an example of this. In our country in Türkiye, HBS is performed for phenylketonuria, biotidinase deficiency, cystic fibrosis, hypothyroidism, adrenal hyperplasia and spinal muscular atrophy. However, in recent years there has been opposition to heel prick screening among some people for different reasons. For families, navigating the abundance of available health information and making informed decisions is becoming increasingly complex. Today, when the influence of the media is stronger than ever, parents are exposed to so much information, opinions and messages about what they 'should' or 'should not' do about their children's health that it is difficult to distinguish right from wrong.

Keywords: Newborn, Heel Blood, Screening, Differences, Innovations, Oppositions

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INTRODUCTION

Congenital metabolic diseases are mostly autosomal recessive diseases that can be detected in the neonatal period and lead to disability and even death if left untreated (1). According to World Health Organization (WHO) data, 3 out of every 100 children born in the general population have congenital anomalies due to any cause. In addition, in a study conducted in 2018, it was found that the cause of death in newborns was consanguineous marriage in 25.4% of cases, and the most common cause of death in cases with consanguineous marriage was first-degree cousin marriage (46.2%). In Türkiye, 300.000 newborns die for this reason every year (2, 3).

Screening is a public health approach that aims to prevent disease development by detecting asymptomatic patients at an early stage of the disease. Some of the genetic and metabolic diseases that hinder mental and physical development can be detected and treated at an early stage with blood samples taken by heel blood screening (HBS) in the first forty-eight hours of newborns' lives. HBS, defined with the slogan 'One drop of heel blood, no more tears', is one of them. HBS in newborns is a health procedure for the diagnosis of metabolic, endocrinological or genetic disorders that may not have phenotypic and functional symptoms but require rapid intervention. Family education, appropriate treatment and follow-up are part of the disease management process. In Türkiye, capillary dry blood is analysed for phenylketonuria (PKU), biotidinase deficiency (BD), cystic fibrosis (CF), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and spinal muscular atrophy (SMA) (4).

History of Heel Blood Screening in the World and in Türkiye

HBS, also known as the Gutherie test, was developed in the United States of America (USA) in 1961 by Dr Robert Gutherie at the Buffalo Children's Hospital to screen for PKU. The first official newborn PKU screening programme was initiated in Massachusetts in 1962. The program was implemented in thirty-two US states by 1965. Galactosemia was the second disease detected by the Gutherie test. In 1973 screening methods for CH were developed and in 1974 screening programme was initiated in the Canadian province of Quebec. These developments were followed by maple syrup urine disease, CAH and BD. Other countries followed this innovation initiated in the USA. For example, screening for PKU was introduced in the Canadian province of Alberta in 1967, in the UK in 1969 and in the Netherlands in 1974. In these countries, the test was included in secondary screening for CH. The subsequent development of tandem mass spectrometry enabled the identification, quantification and elucidation of the molecular structure of compounds in samples. In 1990, this measurement method was integrated into the newborn screening programme (NSP), enabling the identification and quantification of the acyl carnitine profile and the detection of organic aciduria. This facilitated the detection of amino acid disorders. With this method, more than thirty metabolic disorders were added to the NSP (5-9).

Newborn screening programmes in Türkiye started with PKU screening in 1983 and became a national programme in 1994. With the addition of CH to PKU screening in 2006, the name of the programme was changed to the National Newborn Screening Programme (NNSP). Later, BD was added in 2008, CF in 2015, CAH in 2017 and finally SMA in 2022. Currently, comprehensive screening programmes are offered free of charge by the Ministry of Health in family health centres (10).

With advances in technology and screening methods, the number of diseases screened has increased. The diseases included in screening vary from country to country. While 6 diseases are screened in Türkiye, different screening strategies are applied in other countries. For example, 51 diseases are screened with HBS in New York, USA, 40 in Italy, 32 in Australia, 26 in Norway, Ontario, Canada and the Netherlands, 19 in Germany and Denmark, 16 in Saudi Arabia, 12 in Israel and 9 in the UK. These diseases are mostly genetic, metabolic and immune

system diseases. The diseases screened by HBS in these countries are shown in Table 1 (11-23).

Objectives of the Expanded Newborn Screening Program in Türkiye

The report of the Turkish Grand National Assembly Research Commission published in March 2020 stated that in addition to screening for 6 diseases, 32 more diseases are targeted to be added to expand the scope of screening. These diseases include genetic and metabolic diseases. Metabolic Diseases Targeted to be Included in the HBS Programme in Türkiye are shown in Table 2 (24).

Table 1. Diseases Screened by Heel Blood in Different Countries

DENMARK	Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency, Carnitine Transporter Deficiency, Phenylketonuria, Hereditary Tyrosinemia Type 1, Argininosuccinate Lyase Deficiency, Maple Syrup Urine Disease, Methylmalonic Acidemia, Propionic Acidemia, Isovaleric Acidemia, Glutaric Acidemia Type 1, Holocarboxylase Synthetase Deficiency, Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Severe Combined Immunodeficiency, Tetrahydrobiopterin Deficiency, Hyperphenylalaninemia, Multiple Acyl-CoA Dehydrogenase Deficiency, Spinal Muscular Atrophy, Galactose-1-Phosphate Uridyltransferase Deficiency, Homocystinuria, Mucopolysaccharidosis Type I-Hurler, Pompe Disease, Adrenoleukodystrophy.
UNITED KINGDOM	Cystic Fibrosis, Sickle Cell Disease, Congenital Hypothyroidism, Phenylketonuria, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Maple Syrup Urine Disease, Isovaleric Acidemia, Glutaric Acidemia Type 1, Homocystinuria.
ISRAEL	Phenylketonuria, Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Severe Combined Immunodeficiency, Maple Syrup Urine Disease, Homocystinuria, Tyrosinemia Type 1, Methylmalonic Acidemia, Propionic Acidemia, Glutaric Acidemia Type 1, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, Galactose-1-Phosphate Uridyltransferase Deficiency.
ITALY	Phenylketonuria, Homocystinuria, Disorders of Biopterin Regeneration / Biosynthesis, Tyrosinemia Type 1, Tyrosinemia Type 2, Tyrosinemia Type 3, Maple Syrup Urine Disease, Cystathionine Beta-Synthase Deficiency, Methylenetetrahydrofolate Reductase Deficiency, Galactosemia, Isovaleric Acidemia, Beta-Ketothiolase Deficiency, HMG-CoA Lyase Deficiency, Propionic Acidemia, Methylmalonic Acidemia Mutase Type, Cobalamin C Deficiency, Cobalamin D Deficiency, 2-Methylbutyrylglutaconic Aciduria, Methylmalonyl-CoA Mutase Deficiency, 3-Methylcrotonyl-CoA Carboxylase Deficiency, Citrullinemia Type 1, Carnitine Transporter Deficiency Type 2, Argininosuccinate Synthetase Deficiency, Argininosuccinate Lyase Deficiency, Citrullinemia Type 2, Carnitine Palmitoyltransferase 1 Deficiency, Carnitine-Acylcarnitine Translocase Deficiency, Carnitine Palmitoyltransferase 2 Deficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, Trifunctional Protein Deficiency, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Glutaric Acidemia Type 2 / Multiple Acyl-CoA Dehydrogenase Deficiency, Glycine N-Methyltransferase Deficiency, Methionine Adenosyltransferase Deficiency, S-Adenosylhomocysteine Hydrolase Deficiency, 3-Methylglutaconic Aciduria, 3-Methylcrotonyl-CoA Carboxylase Deficiency, Isobutyryl-CoA Dehydrogenase Deficiency, Short-Chain Acyl-CoA Dehydrogenase Deficiency.

Table 1. Diseases Screened by Heel Blood in Different Countries	
AUSTRALIA	Argininemia or Arginase Deficiency, Argininosuccinic Aciduria, Citrullinemia, Tyrosinemia Type 1, Homocystinuria, Maple Syrup Urine Disease, Phenylketonuria, Pterin Defects, Tyrosine Aminotransferase Deficiency, Beta-Ketothiolase Deficiency, Cobalamin C Defect, Glutaric Acidemia Type 1, Holocarboxylase Synthetase Deficiency, 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency, Isobutyryl-CoA Dehydrogenase Deficiency, Isovaleric Acidemia, Methylmalonic Acidemias, Propionic Acidemia, 2-Methylbutyryl-CoA Dehydrogenase Deficiency, 3-Methylglutaconyl-CoA Hydratase Deficiency, Carnitine-Acylcarnitine Translocase Deficiency, Carnitine Transporter Defect, Carnitine Palmitoyltransferase I Deficiency, Carnitine Palmitoyltransferase II Deficiency, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency, Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Trifunctional Protein Deficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, Cystic Fibrosis, Congenital Hypothyroidism, Galactosemia.
NORWAY	Methylmalonic Acidemia/Propionic Acidemia, Propionic Acidemia, Carnitine Deficiency, Glutaric Acidemia Type 1 (Infant), Maple Syrup Urine Disease, Cystathionine Beta-Synthase Deficiency, Tyrosinemia Type 1, Hyperammonemia Syndrome, HMG-CoA Lyase Deficiency, Beta-Ketothiolase Deficiency, Biotinidase Deficiency, Carnitine Transporter Deficiency, Carnitine Palmitoyltransferase 1A Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Carnitine Palmitoyltransferase 2/Carnitine-Acylcarnitine Translocase Deficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency, Long-Chain Acyl-CoA Dehydrogenase Deficiency, Trifunctional Protein Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency / Glutaric Acidemia Type 2.
UNITED STATES OF AMERICA (NEW YORK)	2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency, 2-Methylbutyryl-CoA Dehydrogenase Deficiency, 2,4-Dienoyl-CoA Reductase Deficiency, 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency, 3-Methylcrotonyl-CoA Carboxylase Deficiency, 3-Methylglutaconic Acidemia, Type 1, Adrenoleukodystrophy, Argininemia, Argininosuccinic Acidemia Deficiency, Beta-Ketothiolase Deficiency, Biotinidase Deficiency, Carnitine Acylcarnitine Translocase Deficiency, Carnitine Palmitoyltransferase 2 Deficiency, Carnitine Palmitoyltransferase 1 Deficiency, Carnitine Uptake Defect, Citrullinemia, Cobalamin A,B Coenzyme Deficiency, Cobalamin C, D Coenzyme Deficiency, Congenital Adrenal Hyperplasia, Congenital Hypothyroidism, Cystic Fibrosis, Galactosemia, Glutaric Acidemia, Type I, Guanidinoacetate Methyltransferase Deficiency, Homocystinuria, Hypermethioninemia, Isobutyryl-CoA Dehydrogenase Deficiency, Isovaleric Acidemia, Krabbe Disease, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Malonic Acidemia, Maple Syrup Urine Disease, Medium-Chain 3-Ketoacyl-CoA Thiolase Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Medium / Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Methylmalonyl-CoA Mutase Deficiency, Mucopolysaccharidosis Type I, Multiple Acyl-CoA Dehydrogenase Deficiency, Multiple Carboxylase Deficiency, Phenylketonuria, Pompe Disease, Propionic Acidemia, Severe Combined Immunodeficiency, Short-Chain Acyl-CoA Dehydrogenase Deficiency, Sickle Cell Disease and Other Hemoglobinopathies, Spinal Muscular Atrophy, Trifunctional Protein Deficiency, Tyrosinemia Type I, Tyrosinemia Type II, Tyrosinemia Type III, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency.
SAUDI ARABIA	Phenylketonuria, Argininosuccinate Lyase Deficiency, Maple Syrup Urine Disease, Citrullinemia, Propionic Acidemia, Methylmalonic Acidemia, Glutaric Acidemia Type I, Isovaleric Acidemia, 3-Methylcrotonyl-CoA Carboxylase Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency, Beta-Ketothiolase Deficiency, Galactosemia, Congenital Hypothyroidism, Congenital Adrenal Hyperplasia, Biotinidase Deficiency.

Table 1. Diseases Screened by Heel Blood in Different Countries	
CANADA (ONTORIO)	Argininosuccinic Acidemia, Biotinidase Deficiency, Carnitine Uptake Defect, Citrullinemia, Cobalamin A and B Defects, Congenital Adrenal Hyperplasia, Cystic Fibrosis, Galactosemia, Glutaric Acidemia Type 1, Guanidinoacetate Methyltransferase Deficiency, Homocystinuria, Hurler Syndrome, Isovaleric Acidemia, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Maple Syrup Urine Disease, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Methylmalonic Acidemia, Phenylketonuria, Propionic Acidemia, Severe Combined Immunodeficiency, Hemoglobin SC Disease, Sickle Cell Anemia, Sickle Cell Beta-Thalassemia, Tri-functional Protein Deficiency, Tyrosinemia Type 1, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency.
GERMANY	Congenital Adrenal Hyperplasia, Carnitine-Acylcarnitine Translocase Deficiency, Cystic Fibrosis, Carnitine Palmitoyltransferase I Deficiency, Carnitine Palmitoyltransferase II Deficiency, Glutaric Acidemia Type I, Hyperphenylalaninemia, Immunoreactive Trypsinogen, Isovaleric Acidemia, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency, Trifunctional Protein Deficiency, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Maple Syrup Urine Disease, Phenylketonuria, Severe Combined Immunodeficiency, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency.
NETHERLANDS	Congenital Adrenal Hyperplasia, Cystic Fibrosis, Congenital Hypothyroidism, Severe Combined Immunodeficiency, Sickle Cell Anemia, Hemoglobin H Disease, Beta-Thalassemia Major, 3-Methylcrotonyl-CoA Carboxylase Deficiency, Biotinidase Deficiency, Galactosemia, Glutaric Acidemia Type 1, HMG-CoA Lyase Deficiency, Isovaleric Acidemia, Maple Syrup Urine Disease, Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Methylmalonic Acidemia, Mucopolysaccharidosis Type 1, Multiple CoA Carboxylase Deficiency, Phenylketonuria, Propionic Acidemia, Trifunctional Protein Deficiency / Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency, Tyrosinemia Type 1, Very Long-Chain Acyl-CoA Dehydrogenase Deficiency.

Table 2. Diseases Targeted for Inclusion in the Heel Blood Screening Program in Türkiye	
Fatty Acid Oxidation Disorders	Medium-Chain Acyl-CoA Dehydrogenase Deficiency, Long-Chain Acyl-CoA Dehydrogenase Deficiency, Short-Chain Acyl-CoA Dehydrogenase Deficiency, Multiple Acyl-CoA Dehydrogenase Deficiency (Glutaric Acidemia Type II), Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency, Trifunctional Protein Deficiency.
Carnitin Cycle Disorders	Carnitine Transporter Deficiency, Carnitine Palmitoyltransferase I Deficiency, Carnitine Palmitoyltransferase II Deficiency, Carnitine / Acyl Carnitine Translocase Deficiency.
Organic Acidemias	Methylmalonic Acidemia, Beta-Ketothiolase Deficiency, 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency, 3-Methylcrotonyl-CoA Carboxylase Deficiency, Isovaleric Acidemia, 3-Methylglutaconyl-CoA Hydratase Deficiency, 2-Methylbutyryl-CoA Dehydrogenase Deficiency, Isobutyryl-CoA Dehydrogenase Deficiency, Propionic Acidemia, Glutaric Acidemia Type I, 3-Ketothiolase Deficiency, Holocarboxylase Deficiency.
Urea Cycle Disorders	Argininosuccinate Synthase Deficiency, Argininosuccinate Lyase Deficiency, Arginase Deficiency.
Amino Acid Metabolism Disorders	Tyrosinemia, Homocystinuria, Tetrahydrobiopterin Deficiencies, Maple Syrup Urine Disease, Cobalamin Disorders, Methylene Tetrahydrofolate Deficiency

Current Developments in Newborn Screening

Immune Deficiency Panel

Severe Combined Immunodeficiency (SCID) is a large group of inherited diseases in which the development and function of the T cells of the adaptive immune system are impaired, causing babies to be born without a functioning immune system. These disorders are also called primary immunodeficiency disorders. Humoral immunodeficiencies start to show signs from the 6th month of life on average due to the protection of antibodies passed from the mother, whereas in cellular or combined immunodeficiencies, the child usually becomes symptomatic within the first 3 months. Secondary immunodeficiencies can occur at any stage of life depending on the underlying factor (25). The immunodeficiency panel in heel prick screening is a screening test that allows early diagnosis of SCID detected by a drop of blood sample. The panel, which was first launched in the USA in 2008, was implemented in 50 states until 2018. According to the data of the Primary Immunodeficiency Treatment Consortium, 94% of babies who are transplanted before the age of 3.5 months survive, while the survival rate drops to 50% in babies with active infection and those who are transplanted later (26, 27).

Immunological parameters such as T cell receptor excision circle (TREC), CD3+ T cells, CD4+ T cell new thymic migrants (CD4RTE) and lymphocyte proliferation are measured in the immunodeficiency panel. With these parameters, naive T cells produced by the thymus, the proportion of immature T cells, the response of T cells to cytokines and absolute lymphocyte count (ALC) are evaluated. Haematopoietic stem cell transplantation, gene therapy or enzyme replacement are initiated in diagnosed infants and improve the survival of infants with SCID (27).

X-linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a congenital metabolic disorder caused by a mutation in the ABCD1 gene on the X chromosome. This disease develops due to a defect in ABCD1, a peroxisomal transmembrane protein that transports very long chain fatty acids. ALD is characterised by adrenal insufficiency and white matter lesions in the brain and spinal cord. In 2013, the US state of New York was the first region to add ALD to its newborn screening panel. Following this, in 2015, it was recommended that ALD be added to the newborn screening panel in the Netherlands and a pilot study was initiated. The screening strategy in the Netherlands was planned to cover only male infants. The reason for this is that ALD is fatal in males if left untreated, but in females it is usually symptomatic between 40 and 60 years of age. Detection of ALD in newborn screening is performed by quantitative analysis of C26:0-LPC in heel blood samples by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Increased levels of C26:0-LPC indicate a defect in peroxisomal beta-oxidation; however, this finding is not specific for ALD. Therefore, exon sequencing analysis of the ABCD1 gene is required for definitive diagnosis. Between 2010 and 2018, a total of 32 different states in the USA were included in the screening programme. In addition, ALD was included in the national NSP in the Netherlands, Georgia and Thailand. In 2021, pilot studies were initiated in Italy and Japan (28-30).

Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) is a rare inherited lysosomal storage disease that results from the inability to degrade glycosaminoglycans (GAGs) due to lysosomal enzyme deficiencies. It constitutes 30% of all lysosomal storage diseases. This accumulation leads to progressive damage in various organs and systems. MPS is classified into different types depending on the enzyme deficiency and the clinical features of each type may vary (31). The rarity and heterogeneous clinical course of MPS cause difficulties in the diagnosis and treatment of the disease. Therefore, newborn screening is important in the early diagnosis of MPS.

In recent years, some countries have started to include MPS types in newborn HBS programmes. For example, Taiwan initiated a national screening programme for MPS I (Hurler syndrome) in 2015 and measured α-L-iduronidase enzyme activity by tandem mass spectrometry (MS/MS) (32). In 2017, the US state of Illinois initiated newborn screening for five lysosomal storage diseases, including mucopolysaccharidosis type I (MPS I). In this programme, MPS I screening was performed by measuring α-L-iduronidase enzyme activity in dried blood drop samples by MS/MS. In the first 15 months, 219,973 newborns were screened and one case of MPS I was detected (33). A pilot NSP for various lysosomal storage diseases, including MPS I, was conducted in New York State between 2013 and 2017. In this programme, enzyme activities were measured using MS/MS and 65,605 newborns were screened. The results showed that such screening is effective in detecting late-onset diseases (34).

Arguments Against Heel Blood Screening

For families, navigating the abundance of health information available and making informed decisions is becoming increasingly complex. Today, when the influence of the media is stronger than ever, parents are exposed to a plethora of information, opinions and messages about what they 'should' or 'should not' do regarding their children's health, making it difficult to distinguish between right and wrong. In this confusion of information, it is also observed that some families develop opposing attitudes towards newborn screening. In January 2025, the "Grand National Assembly of Türkiye Commission for the Investigation of Violence and Abuse Against Children" stated that the refusal to HBS has increased approximately five times compared to previous years. The reasons for this opposition include people's belief that heel blood is smuggled abroad and used for genetic changes, the belief that the state sells blood samples abroad, the belief that it causes drug addiction, that the pain felt causes developmental retardation and that the procedure causes infertility (35).

There are also those who think that families do not want to see their children crying and that the pain caused by this practice is more harmful than beneficial. Based on this pain, a study was conducted in India in 2017 to compare the pain caused by two different methods (lancet and 26-gauge needle) used in heel blood collection, which is frequently applied in newborns and described as a painful procedure among the public, to determine which of the lancet and 26-gauge needle is less painful and more tolerable. In infants followed up in the neonatal intensive care unit (NICU), pain levels were evaluated using the Preterm Baby Pain Profile (PBPP) score and the effects of both methods were examined. Heel blood collection using lancet resulted in shorter duration of crying in newborns compared to needle ($p = 0.03$). However, no statistically significant difference was found between the two methods in terms of PBPP scores assessing pain level ($p = 0.052$). Both methods provided adequate sampling (36).

In Türkiye, different reasons are put forward for opposition in perception operations using the powerful influence of social media and these reasons are supported by the public. To cite an example that has been on the agenda on social media; a citizen raised a question: 'Why are the reproductive points on the feet of newborn babies pierced when there is no difference between blood taken from the heel and blood taken from the arm, hand or vein?' and submitted his complaint to the Ministry of Health. He tried to support his opinion by referring to the Reflexology table created by Eunice Ingham, an American physiotherapist in the 1930s. The Ministry of Health responded to the complaint by stating that reflexology is a method of practice and that it has not been approved to have any effect on the diagnosis and treatment of diseases. In addition, he emphasised the difficulty of blood sampling in newborns and stated that heel blood is a method that is selected considering the anatomy and physiology of the baby and is accepted and applied all over the world. The social media post shared by the citizen received five thousand likes and one thousand retweets (37, 38).

Another opposing view was shared on social media in 2023, criticising HBS in newborns. In the post in question, it was claimed that the pain felt by babies during screening was ignored, psychological pressure was applied to parents and there was a risk of infection. He also characterised this practice offered by modern medicine as 'Rockefeller Medicine'. To support his theory, he gave the example of the refusal of 'Amish people' to undergo screening. He argued that those who refused to be screened were healthier. This controversial post attracted attention on social media; it received a thousand likes and a thousand retweets, creating interaction (39). In addition to these public discourses, unfortunately there are also health professionals who support the opposition. They claim that HBS is unnecessary, that this is the reason why children walk on tiptoe, and that HBS can lead to phobias in the future (40).

Overview of Heel Blood Screening in Migrant Families Living in Türkiye and in the World

In 2022, forty-one migrant women registered at the Migrant Health Centre, a primary health care institution in Istanbul, were interviewed to learn migrant women's perspectives on HBS. Screening knowledge and attitudes were questioned during the interviews. It was observed that the participants had heard of the programme and understood its importance for early diagnosis. However, it was observed that almost all of the participants did not have information about the content of the programme and the diseases screened. While most participants felt that the benefits of the programme were high, some were more hesitant to accept the test. At the end of the interview, all participants agreed to have heel blood taken from their children (41).

The NSP is a non-compulsory practice in the Netherlands and is carried out with the consent of the families. A survey study was conducted in the Netherlands with parents who participated and did not participate in the screening programme between 2019-2021. In the study, parents' views on NSP, their experiences with the HBS process, and their suggestions for expanding the scope of NSP were evaluated. Socio-cultural characteristics of non-participating families were focussed on. The total number of parents who completed the questionnaire was 852, of whom 804 participated in the NSP and 48 did not participate. It was found that the participants who had the screening had higher levels of education compared to the general population than those who did not. Parents who did not participate in NSP were more likely to be 'fathers' (19% vs. 8%, p=0.3). These parents were found to have strong religious beliefs and were more prone to alternative medical practices. Parents who did not participate generally stated that they did not plan to vaccinate for infectious diseases. Factors such as life views and beliefs, the idea that it is a painful procedure for children, uncertainties about how the child and personal data are processed (conspiracy theories), and the coronavirus pandemic stood out among the reasons for not participating in the screening (42).

HBS, which is also practised in Ontario, Canada, is a process based on parental consent. Parents are informed in advance and their consent is obtained. In 2016, a study was conducted in Ontario with a total of 51 people using the interview method with parents and healthcare professionals. These included 32 parents and 19 health professionals. As a result of the study, it was determined that there were three parents who refused screening. One parent refused the test in the second child because of pain during the HBS of the first child, another parent refused the screening because of pain during the screening, and another parent refused consent because she found the blood collection disgusting (43).

Legal Processes and Court Decisions in Türkiye

In Türkiye, judicial processes related to HBS have led to a debate on the balance between individual rights and public health policies. In 2012, a family started a legal struggle after a heel blood sample was taken from their newborn baby without their consent. At the first stage, the court ruled that the screening was compulsory, citing public health. However, in

2014, the same family filed a new lawsuit claiming violation of the 'right to protection and development of material and moral existence' under Article 17 of the Constitution. This time, the court ruled in favour of the family and ruled that compulsory HBS constituted a violation of rights and the case proceeded to the next stage. The Constitutional Court stated that the discretionary power of public authorities in interventions against the bodily integrity of the individual is limited, but that the NSP did not exceed these limits. The Constitutional Court concluded the case in favour of the newborn HBS programme, stating that the HBS was carried out in a limited number for the diagnosis of certain diseases and that there were necessary regulations in terms of health. As a result, the Constitutional Court ruled that compulsory HBS does not violate the individual's right to the protection of his/her material and moral existence. This decision sets a precedent for cases to be filed on similar grounds (44).

A similar case was filed in Kars in 2024. The case of a family who refused HBS was taken to court by the Kars Provincial Health Directorate. However, the court stated that HBS was a hegemonic dictate imposed by the WHO and claimed that its positive results had not been proven. The court cited Aidin Salih, an alternative medicine expert, as saying that HBS is 'one of the greatest evils to be done to a child'. As a result, the Kars Provincial Health Directorate's court application was rejected. Numerous civil society organisations and associations opposed the decision and complained to the judge presiding over the process. The case was appealed to the Court of Appeal, which ruled that the Kars Family Court's decision, which threatened the best interests of the child and public health, should be annulled (45).

International Perspective: Heel Blood Data Controversy in the USA

Discussions on the storage and unauthorised use of biological data are not limited to Türkiye. Similar debates have also taken place in the USA, and especially the use of data collected without parental consent has turned into an important legal struggle.

In 2009, nine families in Minnesota and five families in Texas filed lawsuits against state health departments, stating that the storage and use of heel blood samples without parental consent was unlawful. As a result of the lawsuits, a new regulation was introduced in Texas and parental consent became mandatory for the storage of heel blood samples. However, the lawsuit filed in Minnesota resulted against the parents (46).

Conclusion

Heel blood screening, which started with PKU in the world to ensure a healthy life for newborns with genetic and metabolic disorders, has developed with technology and turned into a large-scale programme. Pilot studies continue to be carried out in order to move health programmes forward and benefit more people. Türkiye is also taking many steps in this direction. Developing technology has gained an important place not only in science but also in our social life and the circulation of ideas has increased. With the influence of social media, various perceptions, different opinions have started to form and oppositions have started to be seen. These views continue to increase because people do not have enough information. While Türkiye is trying to progress on the path of science as in developed countries, people's opposition to scanning by characterising it as privacy and individual rights has initiated legal processes. The fact that state institutions in Türkiye are pursuing this issue and our courts have ruled in favour of the HBS programme is an indication that the society is trying to protect children with the perspective of 'not the child of a family but the child of the whole country'.

In the future, clearer frameworks on the applicability and legal basis of compulsory health screenings will need to be determined. In this context, it is critical to develop balanced solutions that will protect both public health and individual rights.

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