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The journal is published quarterly in March, June, September and December.

English Title: Bagcilar Medical Bulletin

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The journal is published quarterly in March, June, September and December.

Original clinical and experimental articles,interesting case studies, and literature reviews made from relevant authors in their brancheswill be accepted for evaluation in BMB.

Bagcilar Medical Bulletin is indexed in **TÜBİTAK/ULAKBİM, EBSCO, Gale, Türk Medline, Turkey Citation Index, Index Copernicus, ProQuest, J-Gate** and **ScopeMed.**

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Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin (BTB), Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi'nin süreli bilimsel yayınıdır. Uluslararası, hakem değerlendirmeli, İngilizce ve açık erişim olarak yılda 4 sayı (Mart, Haziran, Eylül, Aralık) yayınlanan bilimsel bir dergi olup, tıbbın tüm alanlarındaki bilgi birikiminin uluslararası bilimsel platformda yayılabilmesini amaçlamaktadır. Bu amaçla tıbbın her alanında yapılmış orijinal klinik ve deneysel çalışmalar ve ilginç olgu sunumları ile konusunda uzman yazarların yaptığı literatür derlemeleri yayın için değerlendirmeye alınır.

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Derginin editöryal ve yayın süreçleri ile etik kuralları International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), ve National Information Standards Organization (NISO) gibi uluslararası kuruluşların kurallarına uygun olarak şekillenmektedir. Dergimiz, şeffaf olma ilkeleri ve "Akademik Yayıncılıkta En İyi Uygulamalar İlkeleri" ile uyum içindedir.

Bağcılar Tıp Bülteni, **TÜBİTAK/ULAKBİM, EBSCO, Gale, Türk Medline, Türkiye Atıf Dizini, Index Copernicus, ProQuest, J-Gate** ve **ScopeMed** tarafından indekslenmektedir.

Dergi Adı (İngilizce): Bagcilar Medical Bulletin

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Açık Erişim Politikası

Bu dergi, araştırmaları kamuya ücretsiz olarak sunmanın daha büyük bir küresel bilgi alışverişini desteklediği ilkesine dayanarak içeriğine anında açık erişim sağlar.

Yazarlar ve telif hakkı sahipleri, Bağcılar Tıp Bülteni'nde yayınlanan makaleler için tüm kullanıcılara ücretsiz olarak erişim sağlar. Makaleler kaynak gösterilmek şartıyla kullanıma açıktır.

Açık Erişim Politikası, Budapeşte Açık Erişim Girişimi'nin (BOAI) kurallarına dayanmaktadır. "Açık erişim" ile, onun ücretsiz erişilebilirliğini kastedilmektedir. Herhangi bir kullanıcının bu makalelerin tam metinlerini okumasına, indirmesine, kopyalamasına, dağıtmasına, yazdırmasına, aramasına veya bağlantı vermesine, indeksleme için taramasına, yazılıma veri olarak iletmesine veya başka herhangi bir yasal amaç için internetin kendisine erişim elde etmekten ayrılamaz olanlar dışında finansal, yasal veya teknik engeller olmadan kullanmasına izin verir. Çoğaltma ve dağıtım üzerindeki tek kısıtlama ve bu alandaki telif hakkının tek rolü, yazarlara çalışmalarının bütünlüğü üzerinde kontrol ve uygun şekilde tanınma ve alıntılanma hakkı vermek olmalıdır.

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The editorial and publication process of the Journal of the Turkish Academy of Dermatology are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

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Identifying information such as names, initials, hospital numbers, dates, photographs, and family pedigree must be avoided, unless disclosure is allowed by written consent of patient or the legal custodian of the patient. Informed consent for this purpose requires that an identifiable patient be shown in the manuscript to be published. Patient consent should be written and archived either with the journal, the authors, or both, as dictated by local regulations or laws. It must be mentioned in the text that informed consent was obtained from the participants. Especially for case report, identifying information should be avoided as much as possible. Eye masking on photos is not sufficient to conceal the identity of the patient. Authors have to stipulate lack of impact on scientific significance in case of changing the identifying information. Written informed consent should be taken from the patients presented in case studies; and it should be indicated in the manuscript.

INSTRUCTIONS TO AUTHORS

Authors have to confirm in the section "Materials and Methods" that study has been conducted in compliance to above mentioned principles, approvals have been obtained from related institutional ethical committees and informed consents were collected.

When reporting experiments on animals, authors should indicate whether the institutional and national guides for the care and use of laboratory animals were followed as in "Guide for the Care and Use of Laboratory Animals" and approval from ethical committee should be taken. The editor and the publisher do not guarantee or accept responsibility for the published features or definitions of commercial products. If there is direct or indirect grant support, it should be acknowledged in the section titled "declaration of interest" and should include the full name of the sponsor and grant number. Existence or lack of sponsorship of any kind as well as the type of sponsorship (consulting etc.) has to be acknowledged, as well.

Adopts WAME's definition which states that conflict of interest exists when author, peer reviewer or editor has a competing interest that could unduly influence (or be reasonably seen to do so) his or her responsibilities in the publication process. The types of competing interests that should be declared include financial ties, academic commitments, personal relationships, political or religious beliefs, institutional affiliations. The conflict of interest is to be acknowledged in the manuscript.

All manuscripts submitted to the journal for publication are checked by Crossref Similarity Check powered by "iThenticate" software for plagiarism. If plagiarism is detected, relevant institutions may be notified. In this case, the authors might be asked to disclose their raw data to relevant institutions.

Language

The language of the Bagcilar Medical Bulletin is American English. In addition, abstracts of the articles are published in both English and Turkish, and abstracts in both languages are requested from the authour(s).

Manuscript Organization And Format

All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the Journal it is being submitted (i.e., original research article,brief research article, review article, case report or letter to the editor). In addition, a Copyright Transfer Form, Author Contribution Form and ICJME Form for Disclosure of Potential Conflicts of Interest must be submitted. Authors will be notified of the receipt of their paper and the number assigned to it. The number should be included in all further correspondence. All parts of the manuscript, including case reports, quotations, references, and tables, must be double-spaced throughout. All four margins must be at least 2.5 cm. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) acknowledgement 5) references, and 6) tables and/or figures. All pages must be numbered consecutively.

Title Page

On the title page, include full names of authors, academic or professional affiliations, and complete address with phone, fax number(s) and e-mail address (es) of the corresponding author. Acknowledgments for personal and technical assistance should be indicated on the title page.

Abstract and Keywords

Title of the manuscript in English should be written in English abstract, and a Turkish title must be for Turkish abstract.. All articles should include abstract and keywords. For abstracts are most distinct parts of an article and take place on the electronic databases, author should be sure that abstract represents the content of the article accurately. Abstract should inform about the basis of the study and include the purpose, basic procedures (selection of cases and laboratory animals, observatory and analytical methods), key findings and conclusions. New and significant apects of the study or observations should be stated. Up to 3-10 key words in English and in Turkish should be in accordance with National Library of Medicine's Medical Subjects Subheadings (MeSH).

Manuscript Types

Original Research

Original research articles report substantial and original scientific results within the journal scope. Original research articles comprised of Abstract, Key Words, Introduction, Material and Methods, Results, Discussion, Conclusion, References and Table/ Figures. The abstract should be structured as the following.

INSTRUCTIONS TO AUTHORS

Abstract

The abstract should be no longer than 500 words and structured as follows: objective, method, results, and conclusions. Objective -the primary purpose of the article; Material and Method(s) -data sources, design of the study, patients or participants, interventions, and main outcome measures; Results -key findings; Conclusions -including direct clinical applications.

Keywords

Up to 3-10 key words in English and in Turkish should be in accordance with National Library of Medicine's Medical Subjects Subheadings (MeSH).

Introduction

This section should contain a clear statement of the general and specific objectives as well as the hypotheses which the work is designed to test. It should also give a brief account of the reported literature. The last sentence should clearly state the primary and secondary purposes of the article. Only, the actual references related with the issues have to be indicated and data or findings related with the current study must not be included in this section.

Material and Methods

This section should contain explicit, concise descriptions of all procedures, materials and methods used in the investigation to enable the reader to judge their accuracy, reproducibility, etc. This section should include the known findings at the beginning of the study and the findings during the study must be reported in results section. Ethics Committee Approval of the research and written Informed Consent obtained from the participants should be indicated.

The selection and description of the participants

The election, source of population, inclusion and exclusion criteria of the people who participate to experimental or clinical study must be clearly defined in this section. The particular study sample must be explained by the authors (i.e., why the study is performed in a definite age, race or sex population, etc.)

Technical information

The methods, apparatus (the manufacturer's name and address in parentheses), and procedures in sufficient detail must be defined to allow others to reproduce the results. References to established methods, including statistical methods (see below) must be given and brief descriptions for methods that have been published but are not well-known must be provided; new or substantially modified methods must be described, the reasons for using them must be given, and their limitations of the methods must be evaluated. The all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration must be identified. Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

Statistics

The statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. If possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size must be avoided. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. The computer software used must be specified.

Results

The results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. The all the data in the tables or illustrations should not be repeated in the text; only the most important observations must

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be emphasized or summarized. Extra or supplementary materials and technical detail 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.

Discussion

The findings of the study, the findings and results which support or do not support the hypothesis of the study should be discussed, results should be compared and contrasted with findings of other studies in the literature and the different findings from other studies should be explained. The new and important aspects of the study and the conclusions that follow from them should be emphasized. The data or other information given in the Introduction or the Results section should not be repeated in detail.

Conclusions

Conclusions derived from the study should be stated. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice. The conclusions should be linked with the goals of the study but unqualified statements and conclusions not adequately supported by the data should be avoided. New hypotheses should be stated when warranted, but should be labeled clearly as such.

Tables, Graphics and Illustrations

Tables, graphics and illustrations should be numbered in Arabic numerals in the text. The places of the illustrations should be signed in the text. Detailed information is under the related heading in below.

Brief Research

Brief researches are similar to original research in that they follow the same format and guidelines, but they consider small-scale research or research that is in early stages of development. These may include preliminary studies that has a simple research design or a small sample size and that have produced limited pilot data and initial findings that indicate need for further investigation. Brief researches are much shorter than manuscripts associated with a more advanced, larger-scale research project. They are not meant to be used for a short version of an article about research that would otherwise qualify for a full original research manuscript or for publishing material on research that lacks significance, is not rigorous or, if expanded, would not qualify for a full article or for research.

Case Report

Case reports consider new, interesting and intriguing case studies in detail. They should be unique and present methods to overcome any health challenge by use of novel tools and techniques and provide a learning source for the readers. Case reports comprise of: Abstract (unstructured summary), Key-words, Introduction, Case Report, Discussion, Reference, Tables and Figures. Written informed consent of the patient should be obtained and indicated in the manuscript.

Review

Review articles are written by individuals who have done substantial work on the subject or are considered experts in the field. The Journal invites authors to write articles describing, evaluating and discussing the current level of knowledge regarding a specific subject in the clinical practice.

The manuscript should have an unstructured abstract representing an accurate summary of the article, key words, introduction, conclusion. Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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Letter to the Editor

Letter to the Editor is short and decisive manuscript. They should be preferably related to articles previously published in the Journal or views expressed in the Journal. The letter should not include preliminary observations that need a later study for validation.

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. Each table should be typed or printed with double spacing on a separate sheet of paper. The tables should be numbered consecutively in the order of their first citation in the text and a brief title for each table should be supplied. Any internal horizontal or vertical lines should not be used and a short or an abbreviated heading should be given to each column. Authors should place explanatory matter in footnotes, not in the heading. All nonstandard abbreviations should be explained in footnotes, and the following symbols should be used in sequence: *,†,‡,§,ǁ,¶,**,††,‡‡. The statistical measures of variations, such as standard deviation and standard error of the mean should be identified. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully. Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text. Such tables should be submitted for consideration with the paper so that they will be available to the peer reviewers.

Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as digital prints in photographic-quality. In addition to requiring a version of the figures suitable for printing, authors are asked for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, sharp, glossy, black-and-white or color photographic prints should be sent, usually 127 x 173 mm. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends--not on the illustrations themselves. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Photographs of potentially identifiable people must be accompanied by written permission to use the photograph. Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, the original source should be acknowledged and written permission from the copyright holder should be submitted to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. We publish illustrations in color only if the author pays the additional cost.

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The legends for illustrations should be typed or printed out using one spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each one clearly should be identified and explained in the legend. The internal scale should be explained and the method of staining in photomicrographs should be identified.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be in degrees Celsius, blood pressures should be in millimeters of mercury. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International

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System of Units (SI). Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

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

Acknowledgement(s)

All forms of support, including individual technical support or material support must be acknowledged in the author's footnote before references.

Case Reports and Word Limitation

Original papers and reviews have no specific word limitation. A case report must be strictly limited to 1000 words excluding abstract and have minimal figures, tables, and references. Letters to the Editor (maximum of 500 words, including references; no tables or figures) will be considered if they include the notation "for publication." A letter must be signed by all of its authors. Letters critical of an article published in the journal must be received within 12 weeks.

Preparation of Manuscripts

The Bagcilar Medical Bulletin follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals". Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.),

STROBE statement-checklist of items that should be included in reports of observational studies,

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.)

References

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. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can

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now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently. Using abstracts as references should be avoided.

References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source. Citing a "personal communication" should be avoided unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, written permission and confirmation of accuracy from the source of a personal communication must be obtained.

Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the National Library of Medicine for its databases. Authors should consult NLM's Citing Medicine for information on its recommended formats for a variety of reference types. References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals 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 in the list of Journals in National Library of Medicine sources. Accuracy of citation is the author's responsibility. All references should be cited in text. Type references in the style shown below. If there are more than 6 authors, list them followed by et al. Abbreviations of journal names should conform to the style used in National Library of Medicine. If a journal is not indexed in National Library of Medicine's MEDLINE/PubMed, it should not be abbreviated.

Examples for References:

1. For articles in journals:

For the published article from the journal which placed and abbreviated in MEDLINE:

Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166(12):1342-1346.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3:171-178.

2. For the supplement:

For the published article from the journal which placed and abbreviated in MEDLINE:

Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. For articles in press:

Cossrow N, Pawaskar M, Witt EA, Ming EE, Victor TW, Herman BK, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria. J Clin Psychiatry, 2016. (in press).

4. For the citations from books:

Books edited by one editor:

McKnight TL. Obesity Management in Family Practice. 1st ed., NewYork: Springer, 2005:47-51.

For the citation from a section of book edited by editor(s):

Jebb S, Wells J. Measuring body composition in adults and children. In Clinical Obesity in Adults and Children, Copelman P, Caterson I, Dietz W (editors). 1st ed., London: Blackwell Publishing, 2005:12-18.

If the authors of the cited section are the editors of the book:

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Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. First ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

For the citation from a translated book:

McGuffin P, Owen MJ, Gottsman II. Psikiyatri Genetiği ve Genomiği. Abay E, Görgülü Y (Çevirenler) 1st ed., Istanbul: Nobel Tıp Kitabevleri, 2009:303-341.

5. For the citation from thesis:

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6. For the citation from posters:

Akbaş Öncel D, Akdemir A. Üniversite öğrencilerinde diyet, beden algısı ve kendilik algısı arasındaki ilişkiler. 47. Ulusal Psikiyatri Kongresi Özet Kitabı, 26-30 Ekim 201, Antalya, 2011:102.

7. Online Article:

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 2006 Jul 4 [cited 2007 Jan 4];145(1):62-9. Available from:http://www.annals.org/cgi/reprint/145/1/62.pdf

SUBMISSION TO JOURNAL

All new manuscripts must be submitted through the Bagcilar Medical Bulletin online manuscript submission and peer review system. Complete instructions are available at the website (). A cover letter should accompany with manuscripts, including the knowledge of:

•The findings of previous same studies should be informed and should be cited. The copies of previous same studies should be sent with manuscripts that might help to the editor in the decision process.

•The knowledge of "all authors have read and accepted the study in its form, all authors meet the criteria for being in authorship" should be stated.

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SUBMISSION CHECKLIST

It is hoped that this list will be useful during the final checking of an article prior to sending it to the journal's editor for review. Please consult this Guide for Authors, for further details of any item.

Ensure that the following items are present:

• Cover letter to the editor

- The category of the manuscript
- Acknowledgement of "the paper is not under consideration for publication in another journal"
- Disclosure of any commercial or financial involvement
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Copyright Transfer Form

Author Contribution Form

ICJME Form for Disclosure of Potential Conflicts of Interest

-Permission of previous published material if used in the present manuscript

-Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000.

-Statement that informed consent was obtained after the procedure(s) had been fully explained.

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-Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in “Guide for the Care and Use of Laboratory Animals”.

-Title page

-The title of the manuscript both in Turkish and in English

-All authors and their affiliations

-All authors’ e-mail address, full postal address, GSM phone, business telephone and fax numbers

-Abstracts (400-500 words) Both in Turkish and in English

-Keywords: 3 to 10 words (in Turkish and in English)

-Body text

-Acknowledgement

-Reference

-All tables (including title, description, footnotes)

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Peer Review, Publication Ethics and Malpractice Statement

Peer- Review

Submission is considered on the conditions that papers are previously unpublished and are not offered simultaneously elsewhere; that authors have read and approved the content, and all authors have also declared all competing interests; and that the work complies with the ethical approval requirements and has been conducted under internationally accepted ethical standards. If ethical misconduct is suspected, the Editorial Board will act in accordance with the relevant international rules of publication ethics (i.e., COPE guidelines).

Editorial policies of the journal are conducted as stated in the rules recommended by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Accordingly, authors, reviewers, and editors are expected to adhere to the best practice guidelines on ethical behavior contained in this statement.

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For the experimental, clinical, and drug human studies, approval by the ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the Bagcilar Medical Bulletin together with the manuscript.

The approval of the ethics committee; a statement on the adherence to international guidelines mentioned above; and proof that the patient's informed consent is obtained should be indicated in the `Material and Method` section. These items are required for case reports whenever data/media could reveal the identity of the patient.

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The editor of the journal strives to meet the needs of readers and authors, and to provide a fair and appropriate peer-review process. The editor is also responsible for deciding which articles submitted to the journal should be published and guided by the policies subjected to legal requirements regarding libel, copyright infringement, and plagiarism. The editor might discuss such policies, procedures, and responsibilities with reviewers while making publication decisions. The editor is responsible for the contents and overall quality of the publication.

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Reviewers evaluate manuscripts without regard for the origin, gender, sexual orientation, or political philosophy of the authors. Reviewers also ensure a fair, blind peer review of the submitted manuscripts for evaluation.

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All the information relative to submitted articles is kept confidential. The reviewers must not be discussed with others except if authorized by the editor.

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Contribution to editor

Reviewers help the editor make publishing decisions and may also assist the author in improving the manuscript.

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Reviewers offer objective judgments and evaluations. The reviewers express their views clearly with appropriate supporting arguments.

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Reviewers ought to identify a relevant published study that the authors have not cited. Reviewers also call to the editor's attention any substantial similarity or overlap between the manuscript and any other published paper of which they have personal knowledge.

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A submitted manuscript should be original, and the authors ensure that the manuscript has never been published previously. Research data should be represented literally in the article. A manuscript should include adequate detail and references to allow others to replicate the study.

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Authors must ensure that their study is entirely original. References to the literature should be appropriately cited.

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Authors should not submit the same study to multiple journals. Simultaneous submission of the same study to more than one journal is unacceptable and constitutes unethical behaviour.

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Acknowledgement to the workof others must be given. Authors should cite publications of relevance to their own study. All of the sources for the author’s study should be noted.

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Authorship of a Paper

Authorship of a paper ought to be limited to those who have made a noteworthy contribution to the study. If others have participated in the research, they should be listed as contributors. Authorship also includes a corresponding author who is in communication with the editor of a journal. The corresponding author should ensure that all appropriate co-authors are included in a paper.

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YAZARLARA BİLGİ

Hakem Değerlendirmesi, Yayın Etiği ve Kötüye Kullanım

Hakem Değerlendirmesi

Makalelerin daha önce yayınlanmamış olması ve aynı anda başka bir yere gönderilmemiş olması koşuluyla başvuru kabul edilir; yazarlar, içeriği okuduğunu, onayladığını, tüm yazarların çıkar çatışmalarını beyan ettiğini, çalışmanın etik onaya uygun olduğunu ve uluslararası kabul görmüş etik standartlarda yürütüldüğünü kabul eder. Etik suistimalden şüphelenilmesi durumunda, Yayın Kurulu ilgili uluslararası yayın etiği kurallarına (COPE yönergelerine) uygun olarak hareket edecektir.

Derginin yayın politikaları, Bilim Konseyi Editörleri tarafından önerilen kurallarda belirtildiği gibi yürütülür ve ICMJE Biyomedikal Dergilere Gönderilen Makaleler için Tekdüzen Gereklilikler: Biyomedikal Yayın için Yazma ve Düzenleme'de yansıtılır. Buna göre yazarlar, gözden geçirenler ve editörlerin bu bildirimde yer alan etik davranışa ilişkin en iyi uygulama kılavuzlarına uymaları beklenmektedir.

Gönderilen yazılar çift-kör hakem değerlendirmesine tabi tutulur. Dergide yayımlanacak yazıların seçimine rehberlik eden bilim kurulu, derginin seçilmiş uzmanlarından ve gerekirse ilgili araştırma alanında ulusal ve uluslararası uzmanlardan seçilmiş uzmanlardan oluşur. Tüm yazılar editör, bölüm yardımcı editörleri ve en az üç dahili ve harici uzman hakem tarafından incelenir. Tüm araştırma makaleleri de bir istatistik editörü tarafından yorumlanır.

İnsan ve Hayvan Araştırmaları

Deneysel, klinik, ilaç ve insan çalışmaları için, etik kurul onayı ve çalışma protokolünün uluslararası anlaşmalara uygunluğuna dair bir beyan (World Medical Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," Ekim 2013) gereklidir. Deneysel hayvan çalışmalarında yazarlar, izlenen prosedürlerin hayvan haklarına uygun olduğunu (Laboratuvar Hayvanlarının Bakım ve Kullanım Kılavuzu) belirtmeli ve hayvan Etik Kurul Onayı almalıdır. Etik Kurul Onayı belgesi, makale ile birlikte Bağcılar Tıp Bülteni'ne gönderilmelidir.

Etik Kurul Onayı ile yukarıda belirtilen uluslararası kılavuzlara uyum ve hastanın aydınlatılmış onamının alındığına dair beyan "Materyal ve Yöntem" bölümünde belirtilmeli ve kullanılan veri/medyanın hastanın kimliğini ortaya çıkarabileceği durumlarda vaka raporları gerekmektedir. Yazarlar, kurumlar arasında çıkar çatışması beyanı, herhangi bir mali veya maddi desteğin kabulünün belirtilmesi makale gönderen yazarlar için zorunludur ve bu açıklama makalenin sonunda yer almalıdır. Hakemler, yazarlar veya kurumlar ile aralarında herhangi bir potansiyel çıkar çatışması varsa, bunu rapor etmelidir.

18 yaşın altındaki kişiler için, her iki ebeveynin veya kişinin yasal vasisi veya velisinin imzasını içeren bir onay formu gönderilmelidir.

İntihal ve Etik Suistimal

Bağcılar Tıp Bülteni, tüm makaleleri yayınlanmadan önce "iThenticate" kullanarak intihal taramasına tabi tutar. Dergi, iThenticate raporlarına göre benzerlik oranı %15'in üzerinde olan makaleleri kabul etmemektedir.

Yazarların aşağıda yazılanlar gibi her türlü intihal ve etik suistimalden kaçınmaları önemlidir:

İntihal: Başka bir yazarın yayınındaki bir içeriğin tamamını veya bir kısmını kaynak göstermeden yeniden yayınlamak.

Fabrikasyon (Uydurma): Var olmayan veri ve bulguları/sonuçları yayınlamak.

Çoğaltma: Bir makalenin farklı dillerde yeniden yayınlanmasını içeren başka bir yayından alınan verileri kullanmak.

Dilimleme (Salamizasyon): Bir çalışmanın sonuçlarını bölerek birden fazla yayın oluşturma.

Veri Manipülasyonu/Yanlışlığı: Yanlış bir izlenim vermek için araştırma verilerini manipüle etmek veya kasıtlı olarak çarpıtmak.

İntihal, fabrikasyon, çoğaltma, veri manipülasyonu ve dilimleme gibi etik olmayan uygulamaları ve yazarlık hediye etme, uygunsuz teşekkür ve COPE akış şemalarına uygun olmayan referanslar gibi uygulamalarla inceleme sürecini etkilemeye yönelik çabaları onaylamıyoruz.

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Gönderilen yazılar ayrıca otomatik yazılım tarafından intihal ve yayın değerlendirmesine tabi tutulur. Yazarlar, çalışma sonuçlarını tamamen veya kısmen özet şeklinde yayınlayıp yayınlamadıklarını bildirmekle yükümlüdür.

A. YAYINCININ GÖREVLERİ:

Etik Olmayan Yayınlama Davranışının Ele Alınması

Yayıncı, iddia edilen veya kanıtlanmış bilimsel suistimal, hileli yayın veya intihal durumlarında, söz konusu makaleyi editörlerle yakın iş birliği içinde değiştirmek için tüm uygun önlemleri alacaktır. Bu, en ciddi durumda, etkilenen çalışmanın bir yanlışlık sonucu yayınlanmasını, ifşa edilmesini veya geri çekilmesini içerir. Yayıncı, editörlerle birlikte, araştırma suistimalinin meydana geldiği makalelerin yayınlanmasını tespit etmek ve önlemek için makul adımları atacak ve hiçbir koşulda bu tür kötüye kullanımın gerçekleşmesine teşvik etmeyecek veya bilerek izin vermeyecektir.

Editöryal Özerklik

Bağcılar Tıp Bülteni, herhangi birinin veya ticari ortakların etkisi olmaksızın editöryal kararların özerkliğini sağlamayı taahhüt eder.

Fikri Mülkiyet ve Telif Hakkı

Bağcılar Tıp Bülteni, dergide yayınlanan makalelerin mülkiyetini ve telif haklarını korur ve her makalenin yayınlanmış kaydını tutar. Dergi, yayınlanan her makalenin bütünlüğünü ve şeffaflığını sağlar.

Bilimsel Suistimal

Bağcılar Tıp Bülteni'nin yayıncısı, hileli yayın veya intihal ile ilgili gerekli tüm önlemleri almaktadır.

B. EDİTÖRLERİN GÖREVLERİ:

Yayın Kararı ve Sorumluluğu

Dergi editörü, dergideki her şeyi kontrol altında tutar, okuyucuların ve yazarların ihtiyaçlarını karşılamaya çalışır. Editör ayrıca dergiye gönderilen makalelerin hangilerinin yayınlanması gerektiğine karar vermekten ve hakaret, telif hakkı ihlali ve intihal ile ilgili yasal gerekliliklere tabi politikalar tarafından yönlendirilmekten sorumludur. Editör, yayın kararları verirken hakemlerle tartışabilir. Yayının içeriğinden ve genel kalitesinden editör sorumludur. Editör, adil ve uygun bir hakemlik süreci sağlamalıdır.

Nesnellik

Dergiye gönderilen makaleler her zaman önyargısız olarak değerlendirilir.

Gizlilik

Editör, gönderilen bir makaleyle ilgili herhangi bir bilgiyi, editör kadrosu, hakemler ve yayıncı dışında hiç kimseye açıklamamalıdır.

Çıkar Çatışmaları ve İfşa

Bağcılar Tıp Bülteni, yazarlar, hakemler ve editörler gibi taraflar arasında herhangi bir çıkar çatışmasına izin vermez. Gönderilen bir makaledeki yayınlanmamış materyaller, yazarın açık izni olmaksızın hiç kimse tarafından kullanılmamalıdır.

Yayımlanan Eserlerde Temel Hatalar

Yazarlar, yayınlanan çalışmada önemli hatalar veya yanlışlıklar tespit edilirse, derhal dergi editörlerini veya yayıncısını bilgilendirmek ve makaleyi düzeltmek veya geri çekmek üzere onlarla iletişim sağlamakla yükümlüdür. Editörler veya yayıncı, yayınlanan bir çalışmanın önemli bir hata veya yanlışlık içerdiğini üçüncü bir taraftan öğrenirse, yazarlar makaleyi derhal düzeltmeli, geri çekmeli veya dergi editörlerine makalenin doğruluğuna dair kanıt sağlamalıdır.

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C. HAKEMLERİN GÖREVLERİ:

Değerlendirme

Hakemler, yazarların kökeni, cinsiyeti, cinsel yönelimi veya politik felsefesini gözetmeksizin yazıları değerlendirir. Hakemler ayrıca değerlendirme sırasında gönderilen yazılar için adil bir kör hakem incelemesi sağlar.

Gizlilik

Gönderilen makalelerle ilgili tüm bilgiler gizli tutulur. Hakemler, editör tarafından izin verilmedikçe başkalarıyla tartışılmamalıdır.

Çıkar Çatışmaları ve İfşa

Hakemlerin yazarlar, fon sağlayıcılar, editörler vb. taraflarla ilgili herhangi bir çıkar çatışması yoktur.

Editöre Katkı

Hakemler, editöre karar vermede ve makaleyi geliştirmede yardımcı olabilir.

Nesnellik

Daima objektif bir değerlendirme yapılır. Hakemler görüşlerini uygun destekleyici argümanlarla açıkça ifade eder.

Kaynakların Onaylanması

Hakemler, yazarların atıfta bulunmadığı ilgili yayınlanmış bir çalışmayı tanımlamalıdır. Hakemler ayrıca, makale ile kişisel bilgilerine sahip oldukları diğer yayınlanmış makaleler arasındaki önemli benzerlikleri veya örtüşmeleri editörün dikkatine sunarlar.

D. YAZARLARIN GÖREVLERİ:

Raporlama Standartları

Gönderilen bir makale orijinal olmalı ve yazarlar, makalenin daha önce herhangi bir dergide yayınlanmamış olmasını sağlamalıdır. Araştırmanın verileri makalede tam anlamıyla sunulmalıdır. Bir makale, başkalarının çalışmayı yeniden kopyalamasına izin vermek için gerekli ayrıntı ve referansları içermelidir.

Özgünlük

Çalışmalarını dergiye göndermek isteyen yazarlar, çalışmalarının tamamen özgün olduğundan emin olmalıdır. Literatürden alınan kelime ve cümleler uygun şekilde alıntılanmalıdır.

Çoklu Yayınlar

Yazarlar, aynı çalışmayı başka bir dergide yayınlanmak veya değerlendirilmek üzere göndermemiş olmalıdır. Aynı çalışmanın birden fazla dergiye aynı anda gönderilmesi kabul edilemez ve etik dışı bir davranış olarak nitelendirilir.

Kaynakların Belirtilmesi

Başkalarının çalışmalarının uygun bir şekilde alıntılanması gerekir. Yazarlar, çalışmayı belirlemede etkili olan yayınlara atıfta bulunmalıdır. Çalışmanın sürecini kapsayan tüm kaynaklar belirtilmelidir.

Makale Yazarlığı

Bir makalenin yazarlığı, çalışmaya kayda değer bir katkı yapmış olanlarla sınırlı olmalıdır. Başkaları araştırmaya katılmışsa, katkıda bulunanlar olarak listelenmelidir. Yazarlık aynı zamanda bir derginin editörü ile iletişim halinde olan bir sorumlu yazarı da içerir. Sorumlu yazar, tüm uygun ortak yazarların bir makaleye dahil edilmesini sağlamalıdır.

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Çıkar Çatışmaları ve İfşa

Tüm finansal destek kaynakları açıklanmalıdır. Tüm yazarlar, çalışmalarını oluşturma sürecinde (varsa) çıkar çatışmasını ifşa etmelidir. Gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali yardımlar veya diğer destekler, Bağcılar Tıp Bülteni Yayın Kurulu'na açıklanmalıdır. ICMJE Potansiyel Çıkar Çatışması Bildirim Formu, olası bir çıkar çatışmasını açıklamak için katkıda bulunan tüm yazarlar tarafından doldurulmalı ve gönderilmelidir. Derginin Yayın Kurulu, editörler, yazarlar veya hakemler arasında olası bir çıkar çatışması durumlarında COPE ve ICMJE yönergeleri kapsamında hareket eder.

Mali veya şahsi fayda sağlayan koşullar, bir çıkar çatışması doğurur. Bu durum, bilimsel sürecin ve yayınlanan makalelerin güvenilirliği, bilimsel çalışmaların planlanması, uygulanması, yazılması, değerlendirilmesi, düzenlenmesi ve yayınlanması sırasında çıkar çatışmalarının objektif olarak ele alınması ile doğrudan ilişkilidir.

Finansal ilişkiler en kolay tespit edilen çıkar çatışmalarıdır ve derginin, yazarların ve bilimin güvenilirliğini zedelemesi kaçınılmazdır. Bu çatışmalara bireysel ilişkiler, akademik rekabet veya entelektüel yaklaşımlar neden olabilir. Yazarlar, çalışmanın tüm verilerine ulaşmalarını veya makalelerini analiz etme, yorumlama, hazırlama ve yayınlama olanaklarını kısıtlayan kâr veya başka bir avantaj elde etme düşüncesiyle sponsorlarla anlaşmalardan mümkün olduğunca kaçınmalıdır. Editörler, çalışmaları değerlendirirken aralarında ilişki olabilecek kişileri bir araya getirmekten kaçınmalıdır. Makaleler hakkında nihai kararı verecek olan editörlerin, karar verecekleri konulardan hiçbiriyle kişisel, mesleki veya mali bağı olmamalıdır. Yazarlar, makalelerinin bağımsız bir değerlendirme süreci ile etik ilkeler çerçevesinde değerlendirilmesini sağlamak için olası çıkar çatışmalarını yayın kuruluna bildirmelidir.

Editörlerden birinin herhangi bir yazıda yazar olması durumunda editör, makale değerlendirme sürecinden çıkarılır. Herhangi bir çıkar çatışmasını önlemek için makale değerlendirme süreci çift kör olarak yapılmaktadır. Çift kör değerlendirme sürecinden dolayı Baş Editör dışında hiçbir yayın kurulu üyesine, uluslararası danışma kurulu üyesine veya hakemlere, makalenin yazarları veya yazarların kurumları hakkında bilgi verilmemektedir.

Yayın ekibimiz tüm bu durumları göz önünde bulundurarak değerlendirme sürecinin tarafsız bir şekilde yürütülmesi için özveriyle çalışmaktadır.

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Bağcılar Tıp Bülteni (Bagcilar Medical Bulletin), tıbbın her alanında araştırma makalelerini, güncel derleme yazılarını, olgu sunumlarını ve editöre mektupları İngilizce tam metin ve Türkçe özle yayınlayan hakemli bir dergidir. Dergi online olarak yılda 4 sayı yayınlanmaktadır. Tüm makaleler kabul edilir edilmez, online olarak pdf formatında bu web sitesinde, o dönemdeki sayının bir makalesi olarak yer alacaktır. Dergi Galenos Yayınevi tarafından yayımlanmaktadır.

Editoryal Politikalar ve Hakem Süreci

Yayın Politikası

Bağcılar Tıp Bülteni, yayınlanmak üzere gönderilen yazıları aşağıda belirtilen şekillerde kabul eder:

-Orijinal araştırmalar,

-Kısa araştırmalar,

-Olgu sunumları,

-Derlemeler,

-Editöre mektup

Dergi, Türkiye'de yapılan araştırmaların uluslararası bilim arenasına duyurulması, uluslararası bilim çevrelerince paylaşılması ve bu bağlamda Türkiye'nin tanıtılmasına katkıda bulunmayı misyon edindiğinden özellikle orijinal araştırma niteliğindeki yazıları yayınlamaya öncelik vermektedir. Dergide yayınlanacak derleme türündeki yazılar editör tarafından konu ile ilgili çalışan yetkin kişilere hazırlatılmaktadır.

Genel İlkeler

Daha önce yayınlanmamış ya da yayınlanmak üzere başka bir dergide halen değerlendirmede olmayan ve her bir yazar tarafından onaylanan makaleler dergide değerlendirilmek üzere kabul edilir. Yayın kurulu, yazarların iznini alarak yazıda değişiklikler yapabilir. Editör ve dil editörleri dil, imlâ ve kaynakların National Library of Medicine MEDLINE/PubMed Resources'da belirtildiği gibi yazılmasında ve ilgili konularda tam yetkilidir.

Eğer makalede daha önce yayınlanmış alıntı yazı, tablo, resim vs. mevcut ise makale yazarı, yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu makalede belirtmek zorundadır. Gerekli izinlerin alınıp alınmadığından yazar(lar) sorumludur.

Bilimsel toplantılarda sunulan özet bildiriler, makalede belirtilmesi koşulu ile kaynak olarak kabul edilir. Editör, dergiye gönderilen makale biçimsel esaslara uygun ise, gelen yazıyı yurtiçinden ve/veya yurtdışından en az iki hakemin değerlendirmesinden geçirtir, hakemler gerek gördüğü takdirde yazıda istenen değişiklikler yazarlar tarafından yapıldıktan sonra yayınlanmasına onay verir. Makale yayınlanmak üzere dergiye gönderildikten sonra yazarlardan hiçbirinin ismi, tüm yazarların yazılı izni olmadan yazar listesinden silinemez ve yeni bir isim yazar olarak eklenemez ve yazar sırası değiştirilemez. Yayına kabul edilmeyen makale, resim ve fotoğraflar yazarlara geri gönderilmez.

Yazar Hakları

Makalelerinin telif haklarını dergiye devreden yazarlar, yayınladıkları yazıdaki yazılarını diğer çalışmalarında kısmen veya tamamen, herhangi bir revizyon veya değişiklik yapmadan kullanma ve uygun gördükleri takdirde kitap haline getirme hakkını saklı tutarlar. Dergideki, CC BY-NC-ND 4.0 Lisansıvnda ve derginin Açık Erişim politikasında belirtildiği gibi açıkça yayınlanmalıdır. Makale, yazar tarafından bir kitap bölümü olarak veya bir koleksiyonda veya derlemede yeniden kullanılacaksa veya ticari amaçlarla bir kitap haline getirilecekse, atama veya feragat etme hakkını saklı tutan Dergi'den izin alınması gerekir. Bu yeniden kullanım için bedel ve dergide asıl yayına açıkça verilmek üzere uygun bir atıf yapılması gerekmektedir.

Yazarların Soru mluluğu

Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır. Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat

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sağlamalıdır. Uygulamadaki telif kanunları ve anlaşmaları gözetilmelidir. Telife bağlı materyaller (örneğin tablolar, şekiller veya büyük alıntılar) gerekli izin ve teşekkürle kullanılmalıdır. Başka yazarların, katkıda bulunanların çalışmaları ya da yararlanılan kaynaklar uygun biçimde kullanılmalı ve referanslarda belirtilmelidir.

Gönderilen makalede tüm yazarların akademik ve bilimsel olarak doğrudan katkısı olmalıdır, bu bağlamda "yazar" yayınlanan bir araştırmanın kavramsallaştırılmasına ve desenine, verilerin elde edilmesine, analizine ya da yorumlanmasına belirgin katkı yapan; yazının yazılması ya da bunun içerik açısından eleştirel biçimde gözden geçirilmesinde görev yapan; yazının yayınlanmak üzere nihai halini onaylayan ve çalışmanın herhangi bir bölümünün doğruluğuna ya da bütünlüğüne ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul eden kişi olarak görülür. Fon sağlanması, ya da araştırma grubunun genel süpervizyonu tek başına yazarlık hakkı kazandırmaz. Yazar olarak gösterilen tüm bireyler sayılan tüm ölçütleri karşılamalıdır ve yukarıdaki ölçütleri karşılayan her birey yazar olarak gösterilebilir. Çok merkezli çalışmalarda grubun tüm üyelerinin yukarıda belirtilen şartları karşılaması gereklidir. Yazarların isim sıralaması ortak verilen bir karar olmalıdır. Tüm yazarlar yazar sıralamasını Telif Hakkı Devir Formunda imzalı olarak belirtmek zorundadırlar. Yazarların tümünün ismi yazının başlığının altındaki bölümde yer almalıdır.

Yazarlık için yeterli ölçütleri karşılamayan ancak çalışmaya katkısı olan tüm bireyler Teşekkür (Acknowledgement) kısmında sıralanmalıdır. Bunlara örnek olarak ise sadece teknik destek sağlayan, yazıma yardımcı olan ya da sadece genel bir destek sağlayan kişiler verilebilir. Finansal ve materyal destekleri de belirtilmelidir.

Yazıya materyal olarak destek veren ancak yazarlık için gerekli ölçütleri karşılamayan kişiler "klinik araştırıcılar" ya da "yardımcı araştırıcılar" gibi başlıklar altında toplanmalı ve bunların işlevleri ya da katılımları "bilimsel danışmanlık yaptı", "çalışma önerisini gözden geçirdi", "veri topladı" ya da "çalışma hastalarının bakımını üstlendi" şeklinde belirtilmelidir. Teşekkür (Acknowledgement) kısmında belirtilen bu ifadeler için bu bireylerden de yazılı izin alınması gerekmektedir.

Bütün yazarlar, araştırmanın sonuçlarını ya da bilimsel değerlendirmeyi etkileyebilme potansiyeli olan finansal ilişkiler, çıkar çatışması ve çıkar rekabetini beyan etmelidirler. Bir yazar kendi yayınlanmış yazısında belirgin bir hata ya da yanlışlık tespit ederse, bu yanlışlıklara ilişkin düzeltme ya da geri çekme için yayın yönetmeni ile hemen temasa geçme ve işbirliği yapma sorumluluğunu taşır. Yazarların katkısını belirten Yazar Katkı Formu ve çıkar çatışması olup olmadığını belirten ICMJE Potansiyel Çıkar Çatışması Beyan Formu makale ile birlikte gönderilmelidir. Yazarların görevleri ve sorumlulukları ICMJE yönergelerine dayandırılmaktadır.

Editör ve Hakem Sorumlulukları ve Değerlendirme Süreci

Editörler, makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlarlar. Gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalacağını garanti ederler. Editörler içerik ve yayının toplam kalitesinden sorumludurlar. Gereğinde hata sayfası yayınlamalı ya da düzeltme yapmalıdırlar.

Genel Yayın Yönetmeni; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve Bağcılar Tıp Bülteni'nde yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür. Dergide yayın etiği hususunda COPE yönergeleri izlenmektedir.

Hakemler makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Araştırmayla ilgili, yazarlarla ve/veya araştırmanın finansal destekçileriyle çıkar çatışmaları olmamalıdır. Değerlendirmelerinin sonucunda tarafsız bir yargıya varmalıdırlar. Hakemler yazarların atıfta bulunmadığı konuyla ilgili yayınlanmış çalışmaları tespit etmelidirler. Gönderilmiş yazılara ilişkin tüm bilginin gizli tutulmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse Genel Yayın Yönetmeni`ne raporlamalıdırlar. Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, Baş Editör`e bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Editör makalelerle ilgili bilgileri (makalenin alınması, içeriği, gözden geçirme sürecinin durumu, hakemlerin eleştirileri ya da varılan sonuç) yazarlar ya da hakemler dışında kimseyle paylaşmaz.

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Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri topluma açık bir şekilde makaleleri tartışamazlar. Hakemlerin kendileri için makalelerin kopyalarını çıkarmalarına izin verilmez ve editörün izni olmadan makaleleri başkasına veremezler. Hakemler gözden geçirmelerini bitirdikten sonra makalenin kopyalarını yok etmeli ya da editöre göndermelidirler. Dergimiz editörü de reddedilen ya da geri verilen makalelerin kopyalarını imha etmelidir.

Yazarın ve editörün izni olmadan hakemlerin gözden geçirmeleri basılamaz ve açıklanamaz. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek hakemlerin bu süreçte aydınlatılması sağlanabilir. Değerlendirme süreciyle ilgili COPE yönergeleri izlenmektedir.

Açık Erişim İlkesi

Açık erişimli bir yayın olan Bağcılar Tıp Bülteni dergisinin tüm içeriği okura ya da okurun dahil olduğu kuruma ücretsiz olarak sunulur. Okurlar, yayıncı ya da yazardan izin almadan dergi makalelerinin tam metnini okuyabilir, indirebilir, kopyalayabilir, dağıtabilir, basabilir, arayabilir ve link sağlayabilir.

Yayın Etiği

İlke ve Standartlar

Bağcılar Tıp Bülteni yayın etiğinde en yüksek standartlara bağlıdır ve Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journals (ICJME) tarafından geliştirilen yayın etiği ilkelerini ve tavsiyelerini gözetir.

Gönderilen tüm makaleler orijinal, yayınlanmamış (konferans bildirilerindeki tam metinler de dahil) ve başka bir dergide değerlendirme sürecinde olmamalıdır. Her bir makale editörlerden biri ve en az iki hakem tarafından çift kör değerlendirmeden geçirilir. Gönderilen makaleleri intihal yazılımı ile denetleme hakkımız haklıdır. İntihal, veride hile ve tahrif (araştırma verisi, tabloları ya da imajlarının manipülasyonu ve asılsız üretimi), insan ve hayvanların araştırmada uygun olmayan kullanımı konuları denetimden geçmektedir. Bu standartlara uygun olmayan tüm makaleler yayından çıkarılır. Buna yayından sonra tespit edilen olası kuraldışı, uygunsuzluklar içeren makaleler de dahildir. Yayın etiği kurallarına bağlı olarak, intihal şüphesini ve duplikasyon durumlarını rapor edeceğimizi belirtiriz. Olası bilimsel hatalı davranışları ve yayın etiği ihlali vakalarını ele alırken COPE Ethics Flowcharts izlenir.

İnsan ve Hayvan Hakları, Bilgilendirilmiş Olur, Çıkar Çatışması

Bağcılar Tıp Bülteni, yayınladığı makalelerin ticarî kaygılardan uzak ve konu ile ilgili en iyi etik ve bilimsel standartlarda olması şartını gözetmektedir. Makalelerin etik kurallara uygunluğu yazarların sorumluluğundadır.

Bağcılar Tıp Bülteni, 2013 yılında revize edilen Helsinki Deklarasyonu “Ethical Principles for Medical Research Involving Human Subjects”e ve 2006 yılında revize edilen WMA Statement on Animal Use in Biomedical Research’e uymayı prensip edinmiştir. Bu yüzden dergide yayınlanmak üzere gönderilen yazılarda, klinik deneylere katılan denekler ile ilgili olarak yukarıda belirtilen etik standartlara uyulduğunun mutlaka belirtilmesi gerekmektedir. Ayrıca deneyin türüne göre gerekli olan yerel veya ulusal etik komitelerden alınan onay yazıları yazı ile birlikte gönderilmelidir. Bununla birlikte deneye katılan kişi/hastalardan, hastalar eğer temyiz kudretine sahip değilse vâsilerinden yazılı bilgilendirilmiş onam alındığını belirten bir yazı ile beraber tüm yazarlar tarafından imzalanmış bir belgenin editöre gönderilmesi gerekmektedir.

Hastalardan izin alınmadan mahremiyet bozulamaz. Hastaların ismi, isimlerinin baş harfleri ya da hastane numaraları gibi tanımlayıcı bilgiler, fotoğraflar ve soy ağacı bilgileri vb. bilimsel amaçlar açısından çok gerekli olmadıkça ve hasta (ya da anne-baba, ya da vâsisi) yazılı bilgilendirilmiş onam vermedikçe basılmazlar. Özellikle olgu bildirimlerinde, çok gerekli olmadıkça hasta ile ilgili tanımlayıcı ayrıntılar çıkarılmalıdır. Örneğin, fotoğraflarda göz bölgesinin maskelenmesi kimliğin gizlenmesi için yeterli değildir. Eğer veriler kimliğin gizlenmesi için değiştirildiyse yazarlar bu değişikliklerin bilimsel anlamı etkilemediği konusunda güvence vermelidirler. Olgu sunumlarında yer verilen hastalardan bilgilendirilmiş onam alınmalıdır. Bilgilendirilmiş onam alındığı da makalede belirtilmelidir.

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Bu tip çalışmaların varlığında yazarlar, makalenin YÖNTEM(LER) bölümünde bu prensiplere uygun olarak çalışmayı yaptıklarını, kurumlarının etik kurullarından ve çalışmaya katılmış insanlardan "bilgilendirilmiş onam" aldıklarını belirtmek zorundadırlar.

Çalışmada "hayvan" kullanılmış ise yazarlar, makalenin YÖNTEM(LER) bölümünde "Guide for the Care and Use of Laboratory Animals" doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadırlar. Hayvan deneyleri rapor edilirken yazarlar, laboratuvar hayvanlarının bakımı ve kullanımı ile ilgili kurumsal ve ulusal rehberlere uyup uymadıklarını yazılı olarak bildirmek zorundadırlar.

Editör ve yayıncı, reklâm amacı ile dergide yayınlanan ticari ürünlerin özellikleri ve açıklamaları konusunda hiçbir garanti vermemekte ve sorumluluk kabul etmemektedir. Eğer makalede doğrudan veya dolaylı ticarî bağlantı veya çalışma için maddî destek veren kurum mevcut ise yazarlar; kaynak sayfasında, kullanılan ticarî ürün, ilaç, ilaç firması vb. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar) bildirmek zorundadır.

Buna göre, yazar, hakem ya da editör sorumluluklarını aşırı düzeyde ve/veya haksızlığa yol açabilecek düzeyde etkileyebilecek ya da etkileyebileceği olası bir çıkar rekabeti içindeyse, çıkar çatışması söz konusudur ve bunun açıklanması gerekir. Açıklanması öngörülen çıkar çatışması tipleri, finansal bağlar, akademik taahhütler, kişisel ilişkiler, politik ya da dini inançlar, kurumsal bağlantılardır. Çıkar çatışması söz konusuysa bu makalede açıklanmalıdır.

Dergiye yayımlanmak üzere gönderilen tüm yazılar editör ve hakemlerin uzmanlığı ile Crossref Similarity Check "iThenticate" programı ve internet üzerinden arama motorlarında taranarak, intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar reddedilebilir. İntihal tespit edilmesi halinde, ilgili kurumlara yazarlar hakkında ihbar yapılabilir. Bu durumda yazarlar sorumlu kurumlara çalışmalarının ham sonuçlarını teslim etmek zorunda kalabilir.

Dil

Bağcılar Tıp Bülteni`nin yayın dili Amerikan İngilizcesi'dir. Ayrıca makalelerin özleri hem İngilizce, hem Türkçe yayınlanır. Her iki dildeki özler yazarlardan istenir.

Yazıların Hazırlanması

Aksi belirtilmedikçe gönderilen yazılarla ilgili tüm yazışmalar ilk yazarla yapılacaktır. Gönderilen yazılar, yazının yayınlanmak üzere gönderildiğini ve Bağcılar Tıp Bülteni`nin hangi bölümü (Orijinal Araştırma, Kısa Araştırma, Olgu Sunumu, Derleme, Editöre Mektup) için başvurulduğunu belirten bir mektup, yazının elektronik formunu içeren Microsoft Word 2003 ve üzerindeki versiyonları ile yazılmış elektronik dosya ile tüm yazarların imzaladığı 'Telif Hakkı Devir Formu' , Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışması Beyan Formu eklenerek gönderilmelidir. Yazıların alınmasının ardından yazarlara makalenin alındığı, bir makale numarası ile bildirilecektir. Tüm yazışmalarda bu makale numarası kullanılacaktır. Makaleler sayfanın her bir kenarından ,5 cm kenar boşluğu bırakılarak ve çift satır aralıklı yazılmalıdır. Makalelerde aşağıdaki sıra takip edilmelidir ve her bölüm yeni bir sayfa ile başlamalıdır: 1) başlık sayfası, 2) öz, 3) metin, 4) teşekkür / 5) kaynaklar ve 6) tablo ve/veya şekiller. Tüm sayfalar sırayla numaralandırılmalıdır.

Başlık

Başlık sayfasında, yazarların adları, akademik ünvanları ve yazışılacak yazarın tam adres, telefon ve faks numaraları ile e-mail adresi mutlaka bulunmalıdır. Yazıların Türkçe özlerinde mutlaka Türkçe başlık da yer almalıdır.

Öz ve Anahtar Sözcükler

Makalenin İngilizce başlığı İngilizce özde, Türkçe başlığı da Türkçe özde yer almalıdır. Bütün makaleler öz ve anahtar kelime içermelidir. Özler bir makalenin birçok elektronik veri tabanında yer alan en belirgin kısmı olduğundan, yazarlar özün makalenin içeriğini doğru olarak yansıttığından emin olmalıdır. Öz çalışmanın temeliyle ilgili bilgi vermeli ve çalışmanın amacını, temel prosedürleri (olguların ya da laboratuvar hayvanlarının seçimi, gözlemsel ve analitik yöntemler), ana bulguları (mümkünse özgül etki büyüklüklerini ve istatistiksel anlamlılıklarını vererek) ve temel çıkarımları içermelidir. Çalışmanın ya da gözlemlerin yeni ve önemli yönleri belirtilmelidir. Anahtar sözcükler, her türlü yazıda Türkçe ve İngilizce özlerin altındaki sayfada 3-10 adet

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verilmelidir. Anahtar sözcük olarak National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (Medical Subject Headings, MeSH) yer alan terimler kullanılmalıdır. MeSH'de yer alan terimlerin Türkçe karşılıklarına Türkiye Bilim Terimleri'nden erişilebilir.

Makale Türleri

Orijinal Araştırma

Orijinal araştırma makaleleri derginin kapsamına uygun konularda önemli, özgün bilimsel sonuçlar sunan araştırmaları raporlayan yazılardır. Orijinal araştırma makaleleri, Öz, Anahtar Kelimeler, Giriş, Yöntem ve Gereçler, Bulgular, Tartışma, Sonuçlar, Kaynaklar bölümlerinden ve Tablo, Grafik ve Şekillerden oluşur. Öz bölümü araştırma yazılarında aşağıda belirtilen formatta yapılandırılmış olmalıdır.

Öz

Araştırma yazılarında Türkçe ve İngilizce özler en fazla 500 kelime olmalı ve şu şekilde yapılandırılmalıdır: Amaç/Objective: Yazının birincil ve asıl amacı; Yöntem ve Gereçler/Material and Method(s): Veri kaynakları, çalışmanın iskeleti, hastalar ya da çalışmaya katılanlar, görüşme/değerlendirmeler ve temel ölçümler; Bulgular/Results: Ana bulgular; Sonuç(lar)/Conclusion(s):Doğrudan klinik uygulamalar, çıkartılacak sonuçlar belirtilmelidir.

Anahtar Kelimeler

National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (Medical Subject Headings, MeSH) yer alan terimler kullanılmalıdır, en az üç anahtar kelime belirtilmelidir.

Giriş

Giriş/Introduction bölümünde konunun önemi, tarihçe ve bugüne kadar yapılmış çalışmalar, hipotez ve çalışmanın amacından söz edilmelidir. Hem ana hem de ikincil amaçlar açıkça belirtilmelidir. Sadece gerçekten ilişkili kaynaklar gösterilmeli ve çalışmaya ait veri ya da sonuçlardan söz edilmemelidir.

Yöntem ve Gereçler

Yöntem ve Gereçler/Material and Methods bölümünde, veri kaynakları, hastalar ya da çalışmaya katılanlar, ölçekler, görüşme/değerlendirmeler ve temel ölçümler, yapılan işlemler ve istatistiksel yöntemler yer almalıdır. Yöntem bölümü, sadece çalışmanın planı ya da protokolü yazılırken bilinen bilgileri içermelidir; çalışma sırasında elde edilen tüm bilgiler bulgular kısmında verilmelidir. Yöntem ve Gereçler bölümünde olguların seçimi ve tanımlanması hakkında bilgi, teknik bilgi ve istatistik hakkında bilgi yer almalıdır. Araştırmanın Etik Kurul Onayı ve katılımcılardan alınan yazılı Bilgilendirilmiş Onam belirtilmelidir.

Olguların Seçimi ve Tanımlanması

Gözlemsel ya da deneysel çalışmaya katılanların (hastalar, hayvanlar, kontroller) seçimi, kaynak popülasyon, çalışmaya alınma ve çalışmadan dışlanma ölçütleri açıkça tanımlanmalıdır. Yaş ve cinsiyet gibi değişkenlerin çalışmanın amacıyla olan ilişkisi her zaman açık olmadığından yazarlar çalışma raporundaki kullanımlarını açıklamalıdır; örneğin yazarlar niçin sadece belli bir yaş grubunun alındığını ya da neden kadınların çalışma dışında bırakıldığını açıklamalıdır. Çalışmanın niçin ve nasıl belli bir şekilde yapıldığı açık bir şekilde belirtilmelidir. Yazarlar etnisite ya da ırk gibi değişkenler kullandıklarında bu değişkenleri nasıl ölçtüklerini ve geçerliklerini açıklamalıdır.

Teknik Bilgi

Diğer çalışmacıların sonuçları yineleyebilmesi için yöntem ve kullanılan araçlar (üretici firma ve adres paragraf içinde belirtilerek) ayrıntılı bir şekilde belirtilmelidir. Önceden kullanılan bilinen yöntemler için (istatistiksel yöntemler dahildir) kaynak gösterilmeli, basılmış ama iyi bilinmeyen bir yöntem için kaynak verilmeli ve yöntem açıklanmalıdır. Aynı şekilde yeni ya da belirgin olarak modifiye edilmiş yöntemler tanımlanmalı ve kullanılma nedenleri belirtilip kısıtlılıkları değerlendirilmelidir. Kullanılan tüm ilaç ve

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kimyasallar doğru olarak tanımlanıp jenerik isimleri, dozları ve kullanım biçimleri belirtilmelidir. Gözden geçirme yazısı gönderen yazarlar veriyi bulma, seçme, ayırma ve sentezleme yöntemlerini belirtmelidir. Bu yöntemler aynı zamanda özde de yer almalıdır.

İstatistik

İstatistiksel yöntem, orijinal veriye erişebilecek bilgili bir okuyucunun rapor edilen sonuçları onaylayabileceği bir ayrıntıda belirtilmelidir. Mümkünse, bulgular niceliksel hale getirilmeli ve hata ölçümleri (güvenlik aralıkları gibi) sunulmalıdır. Etki büyüklüğünü vermeyen, p değerlerinin kullanımı gibi, salt istatistiksel hipotez sınamasına dayanılmamalıdır. Çalışma deseni ve istatistiksel yönteme dair kaynaklar sayfalar belirtilerek mümkün olduğu sürece standart kaynaklar olmalıdır. İstatistiksel terimler, kısaltmalar ve semboller tanımlanmalıdır. Kullanılan bilgisayar programı belirtilmelidir.

Bulgular

Ana bulgular istatistiksel verilerle desteklenmiş olarak eksiksiz verilmeli ve bu bulgular uygun tablo, grafik ve şekillerle görsel olarak da belirtilmelidir. Bulgular yazıda, tablolarda ve şekillerde mantıklı bir sırayla önce en önemli sonuçlar olacak şekilde verilmelidir. Tablo ve şekillerdeki tüm veriyi yazıda vermemeli, sadece önemli noktaları vurgulanmalıdır. Ekstra materyal ve teknik bilgi ek kısmında verilerek yazının akışının bozulmaması sağlanmalı, alternatif olarak bunlar sadece elektronik versiyonda yer almalıdır.

Tartışma

Tartışma/Discussion bölümünde o çalışmadan elde edilen veriler, kurulan hipotez doğrultusunda hipotezi destekleyen ve desteklemeyen bulgular ve sonuçlar irdelenmeli ve bu bulgu ve sonuçlar literatürde bulunan benzeri çalışmalarla kıyaslanmalı, farklılıklar varsa açıklanmalıdır. Çalışmanın yeni ve önemli yanları ve bunlardan çıkan sonuçları vurgulanmalıdır. Giriş ya da sonuçlar kısmında verilen bilgi ve veriler tekrarlanmamalıdır.

Sonuçlar

Sonuçlar/Conclusions bölümünde çalışmadan çıkarılan sonuçlar sıralanmalıdır. Deneysel çalışmalar için tartışmaya sonuçları kısaca özetleyerek başlamak, daha sonra olası mekanizmaları ya da açıklamaları incelemek ve bulguları önceki çalışmalarla karşılaştırmak, çalışmanın kısıtlılıklarını özetlemek, gelecekteki çalışmalar ve klinik pratik için uygulamalarını belirtmek faydalıdır. Varılan sonuçlar çalışmanın amacıyla karşılaştırılmalı, ancak elde edilen bulgular tarafından yeterince desteklenmeyen çıkarımlardan kaçınılmalıdır. Yazarlar, eğer elde ettikleri veriler ekonomik veri ve analizler içermiyorsa, ekonomik çıkar ya da faydalarla ilgili yorumlardan özellikle kaçınılmalıdır. Gerektiğinde yeni hipotezler ortaya konmalı, ancak bunların yeni hipotezler olduğu belirtilmelidir.

Tablo, Grafik ve Şekiller

Yazı içindeki grafik, şekil ve tablolar Arap sayıları ile numaralandırılmalıdır. Şekillerin metin içindeki yerleri belirtilmelidir. Ayrıntılı bilgi aşağıda ilgili başlık altında yer almaktadır.

Kısa Araştırma

Kısa Araştırma makaleleri tarz ve format açısından Orijinal Araştırma makaleleri gibidir; ancak daha küçük ölçekli araştırmaları ya da geliştirme çalışmasının erken aşamalarında olan araştırmaları ele alır. Basit araştırma tasarımı kullanan ön çalışmalar, sınırlı pilot veri sağlayan küçük örnek kitle ile yapılan çalışmalar, ileri araştırma gereksinimine işaret eden başlangıç bulguları bu tür araştırmalar kapsamında sayılabilir. Kısa Araştırma makaleleri, büyük ölçekli gelişkin araştırma projelerini konu alan Orijinal Araştırma makalelerinden daha kısadır. Ancak Kısa Araştırma, Orijinal Araştırma makalesi olabilecek kalitede bir araştırma makalesinin kısa versiyonu olarak anlaşılmamalıdır; önem derecesi düşük, titizlikle yapılmamış bir araştırma hakkında bir yayın malzemesi hazırlamak için kullanılmamalıdır ya da genişletildiğinde Orijinal Araştırma makalesi ya da araştırma niteliği kazanmayacak bir içeriği değerlendirecek bir makale türü olarak anlaşılmamalıdır.

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Olgu Sunumu

Olgu sunumu makaleleri özgün vakaları rapor eden yazılardır. Derginin kapsamına giren konulara ilişkin bir problemin üstesinden gelen tedaviyle ilgili, yeni araçlar, teknikler ve metotlar göstererek okuyucular için bilgilendirme sağlamalıdır. Olgu sunumu yazıları Öz (özün araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Olgu Sunumu, Tartışma, Referanslar, gerekirse Tablo ve açıklayıcı bilgilerden oluşur. Olgu sunumunda yazılı bilgilendirilmiş onam alınmalı ve makalede belirtilmelidir.

Derleme

Derleme makaleleri alanında zengin birikime ve atıf alan çalışmalara sahip uzman kişilerce yazılan yazılardır. Klinik pratiğe ilişkin bir konuda mevcut bilgiyi tanımlayan, değerlendiren ve tartışan; geleceğe ilişkin çalışmalara yol gösteren derleme yazıları yazmaları için dergi belirlediği yazarlara davet gönderir. Derleme makaleleri, Öz (özün, araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Sonuç bölümlerinden oluşur. Derleme makale gönderen yazarların, makalede kullandıkları verinin seçimi, alınması, sentezi için kullandıkları yöntemleri tanımlayan bir bölüme de makalede yer vermeleri gerekir. Bu yöntemler Öz bölümünde de belirtilmelidir.

Editöre Mektup

Editöre Mektup, kısa ve net görüş bildiren yazılardır. Dergide daha önce yayınlanmış olan makalelerle ilgili olarak ya da dergide ifade edilmiş görüşlerle ilgili olarak yazılmış olması tercih edilir. Editöre Mektup yazıları, daha sonra yeni bir yazı ile geçerlilik ispatı gerektirebilecek ön görüş bildiren yazılar olmamalıdır.

Tablolar

Tablolar bilgileri etkin bir şekilde gösterir ve ayrıca bilginin istenen tüm ayrıntı seviyelerinde verilmesini sağlar. Bilgileri metin yerine tablolarda vermek genelde metnin uzunluğunu kısaltır.

Her tablo ayrı bir sayfaya çift aralıklı olarak basılmalıdır. Tablolar metindeki sıralarına göre numaralanıp, her birine kısa bir başlık verilmelidir. MS Word 2003 ve üstü versiyonlarında otomatik tablo seçeneğinde "tablo klasik 1" ya da "tablo basit 1" seçeneklerine göre tablolar hazırlanmalıdır. Başlık satırı ve tablo alt üst satırları dışında tablonun içinde başka dikey ve yatay çizgiler kullanılmamalıdır. Her sütuna bir başlık verilmelidir. Yazarlar açıklamaları başlıkta değil, dipnotlarda yapmalıdır. Dipnotlarda standart olmayan tüm kısaltmalar açıklanmalıdır. Dipnotlar için sırasıyla şu semboller kullanılmalıdır: (*,†,‡,§,ǁ,¶,**,††,‡‡).

Varyasyonun standart sapma ya da standart hata gibi istatistiksel ölçümleri belirtilmelidir. Metin içinde her tabloya atıfta bulunulduğuna emin olunmalıdır. Eğer yayınlanmış ya da yayınlanmamış herhangi başka bir kaynaktan veri kullanılıyorsa izin alınmalı ve onlar tam olarak bilgilendirilmelidir. Çok fazla veri içeren tablolar, çok yer tutar ve sadece elektronik yayınlar için uygun olabilir ya da okuyuculara yazarlar tarafından doğrudan sağlanabilir. Böyle bir durumda uygun bir ifade metne eklenmelidir. Bu tip tablolar, hakem değerlendirmesinden geçmesi için makaleyle beraber gönderilmelidir.

Şekiller

Şekiller ya profesyonel olarak çizilmeli ve fotoğraflanmalı ya da fotoğraf kalitesinde dijital olarak gönderilmelidir. Şekillerin basıma uygun versiyonlarının yanı sıra JPEG ya da GIF gibi elektronik versiyonlarda yüksek çözünürlükte görüntü oluşturacak biçimlerde elektronik dosyaları gönderilmeli ve yazarlar göndermeden önce bu dosyaların görüntü kalitelerini bilgisayar ekranında kontrol etmelidir.

Röntgen, CT, MRI filmleri ve diğer tanısal görüntülemeler yüksek kalitede basılmış olarak gönderilmelidir. Bu nedenle şekillerin üzerindeki harfler, sayılar ve semboller açık ve tüm makalede eşit ve yayın için küçültüldüklerinde bile okunabilecek boyutlarda olmalıdır. Şekiller mümkün olduğunca tek başlarına anlaşılabilir olmalıdır. Fotomikrografik patoloji preparatları iç ölçekler içermelidir. Semboller, oklar ya da harfler fonla kontrast oluşturmalıdır. Eğer insan fotoğrafı kullanılacaksa, ya bu kişiler fotoğraftan tanınmamalıdır ya da yazılı izin alınmalıdır (Etik bölümüne bakınız).

Şekiller metinde geçiş sıralarına göre numaralandırılmalıdır. Eğer önceden yayınlanmış bir şekil kullanılacaksa, yayın hakkını elinde bulunduran bireyden izin alınmalıdır. Toplum alanındaki belgeler hariç yazarlığa ve yayıncıya bakılmadan bu izin gereklidir.

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Basılacak bölgeyi gösteren ek çizimler editörün işini kolaylaştırır. Renkli şekiller editör gerekli gördüğünde ya da sadece yazar ek masrafı karşılarsa basılır.

Şekillerin Dipnotları

Ayrı bir sayfadan başlayarak şekiller için tablo başlıkları ve dipnotları tek aralıklı olarak ve Arap sayıları ile hangi şekle karşı geldikleri belirtilerek yazılmalıdır. Semboller, oklar, sayılar ya da harfler şeklin parçalarını belirtmek için kullanıldığında, dipnotlarda her biri açıkça tanımlanmalıdır. Fotomikrografik patoloji preparatlarında iç ölçek ve boyama tekniği açıklanmalıdır.

Ölçüm Birimleri

Uzunluk, ağırlık ve hacim birimleri metrik (metre, kilogram, litre) sistemde ve bunların onlu katları şeklinde rapor edilmelidir. Sıcaklıklar Celsius derecesi, kan basıncı milimetre civa cinsinden olmalıdır. Ölçü birimlerinde hem lokal hem de Uluslararası Birim Sistemleri (International System of Units, SI) kullanılmalıdır. İlaç konsantrasyonları ya SI ya da kütle birimi olarak verilir, alternatif olarak parantez içinde de verilebilir.

Kısaltmalar ve Semboller Sadece standart kısaltmaları kullanın, standart olmayan kısaltmalar okuyucu için çok kafa karıştırıcı olabilir. Başlıkta kısaltmadan kaçınılmalıdır. Standart bir ölçüm birimi olmadıkça kısaltmaların uzun hali ilk kullanılışlarında açık, kısaltılmış hali parantez içinde verilmelidir.

Teşekkür(ler)

Yazının sonunda kaynaklardan önce yer verilir. Bu bölümde kişisel, teknik ve materyal yardımı gibi nedenlerle yapılacak teşekkür ifadeleri yer alır.

Kelime Sayısı Sınırlandırması

Türkçe ve İngilizce özler en fazla 500 kelime olmalıdır. Orijinal makaleler ve derleme yazılarında özel bir kelime sayısı sınırlandırması yoktur. Olgu sunumları öz /abstract hariç 1000 kelime ile sınırlandırılmalı ve en az sayıda şekil, tablo ve kaynak içermelidir. Editöre mektuplar (en fazla 1000 kelime, tablosuz ve şekilsiz) olmalı ve mektup, tüm yazarlar tarafından imzalanmış olmalıdır. Bağcılar Tıp Bülteni`nde yayınlanmış olan bir yazı ile ilgili eleştiri ya da değerlendirme niteliğindeki mektuplar sözü edilen yazının yayınlanmasından sonraki 12 hafta içinde alınmış olmalıdır.

Makale Hazırlığı

"Bağcılar Tıp Bülteni", Tıp Dergilerinde Bilimsel Çalışmaların Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanmasına İlişkin Yönergeleri takip eder "(Uluslararası Tıp Dergisi Editörleri Komitesi ICMJE). Makalenin sunulması üzerine, yazarlar deneme/araştırma türünü belirtmeli ve uygun olduğunda aşağıdaki kuralların kontrol listesini sağlamalıdır:

Randomize çalışmalar için CONSORT beyanı (CONSORT Grubu için Moher D, Schultz KF, Altman D. CONSORT beyanı paralel grup randomize çalışmaların raporlarının kalitesini iyileştirmek için önerileri gözden geçirdi. JAMA 2001; 285: 1987-91),

Sistematik gözden geçirmeler ve meta-analizler için tercih edilen raporlama maddeleri için PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Grubu. Sistematik İncelemeler ve Meta-Analizler için Tercih Edilen Raporlama Maddeleri: PRISMA Beyanı. PLoS Med 2009; 6 (7): e1000097.),

Tanısal doğruluk çalışmalarının raporlanması için STARD kontrol listesi (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, vd, STARD Grubu için. Teşhis doğruluğu çalışmalarının eksiksiz ve doğru raporlanmasına yönelik: STARD girişimi, Ann Intern Med 2003; 138: 40-4.),

STROBE gözlemsel çalışma raporlarında yer alması gereken maddelerin kontrol listesi,

Gözlemsel çalışmaların meta-analizi ve sistemik incelemeleri için MOOSE yönergeleri (Stroup DF, Berlin JA, Morton SC, vd.) Epidemiyolojideki gözlemsel çalışmaların meta-analizi: Epidemiyoloji (MOOSE) grubundaki gözlemsel çalışmaların Meta-analizini bildirme önerisi JAMA 2000; 283: 2008-12),

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CARE kuralları, vaka raporlarının doğruluğunu, şeffaflığını ve kullanışlılığını artırmak için tasarlanmıştır. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Grubu. CARE Yönergeleri: Konsensüs Tabanlı Klinik Vaka Raporlama Rehberinin Geliştirilmesi).

Kaynaklar

Kaynaklarla İlgili Genel Konular

Gözden geçirme yazıları okuyucular için bir konudaki kaynaklara ulaşmayı kolaylaştıran bir araç olsa da, her zaman orijinal çalışmayı doğru olarak yansıtmaz. Bu yüzden mümkün olduğunca yazarlar orijinal çalışmaları kaynak göstermelidir. Öte yandan, bir konuda çok fazla sayıda orijinal çalışmanın kaynak gösterilmesi yer israfına neden olabilir. Birkaç anahtar orijinal çalışmanın kaynak gösterilmesi genelde uzun listelerle aynı işi görür. Ayrıca günümüzde kaynaklar elektronik versiyonlara eklenebilmekte ve okuyucular elektronik literatür taramalarıyla yayınlara kolaylıkla ulaşabilmektedir.

Özler kaynak olarak gösterilmemelidir. Kabul edilmiş ancak yayınlanmamış makalelere atıflar "basımda" ya da "çıkacak" şeklinde verilmelidir; yazarlar bu makaleleri kaynak gösterebilmek için yazılı izin almalıdır ve makalelerin basımda olduğunu ispat edebilmelidir. Gönderilmiş ancak yayına kabul edilmemiş makaleler, "yayınlanmamış gözlemler" olarak gösterilmeli ve kaynak yazılı izinle kullanılmalıdır. Genel bir kaynaktan elde edilemeyecek temel bir konu olmadıkça "kişisel iletişimlere" atıfta bulunulmamalıdır. Eğer atıfta bulunulursa parantez içinde iletişim kurulan kişinin adı ve iletişimin tarihi belirtilmelidir. Bilimsel makaleler için yazarlar bu kaynaktan yazılı izin ve iletişimin doğruluğunu gösterir belge almalıdır.

Referans Stili ve Formatı

Tek tip kurallar esas olarak National Library of Medicine, tarafından uyarlanmış olan bir ANSI standart stilini kabul etmiştir. Kaynak atıfta bulunma örnekleri için yazarlar NIH Samples of Formatted References for Authors of Journal Articles sitesine başvurabilirler. Dergi isimleri National Library of Medicine kaynağında yer alan şekilleriyle kısaltılmalıdır. Kaynaklar yazının sonunda (Kaynaklar/References) başlığı altında metindeki geçiş sırasına göre numaralandırılıp dizilmelidir. Metin içinde ise parantez içinde belirtilmelidir. Kaynakların listesiyle metin içinde yer alış sırası arasında bir uyumsuzluk bulunmamalıdır.

Kaynaklar yazının sonunda (Kaynaklar/References) başlığı altında metindeki geçiş sırasına göre numaralandırılıp dizilmelidir. Metin içinde ise () şeklinde parantez içinde referans numarası belirtilmelidir. Kaynakların listesiyle metin içinde yer alış sırası arasında bir uyumsuzluk bulunmamalıdır.

Kaynakların doğruluğundan yazar(lar) sorumludur. Tüm kaynaklar metinde belirtilmelidir. Kaynaklar aşağıdaki örneklerdeki gibi gösterilmelidir. Altı yazardan fazla yazarı olan çalışmalarda ilk altı yazar belirtilmeli, sonrasında "ve ark." ya da "et al." ibaresi kullanılmalıdır. Kaynak dergi adlarının kısaltılması National Library of Medicine'de belirtilen kısaltmalara uygun olmalıdır. National Library of Medicine'da indekslenmeyen bir dergi kısaltılmadan yazılmalıdır.

Kaynaklar için örnekler aşağıda belirtilmiştir:

1. Dergilerdeki makaleler için örnekler: MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166(12):1342-1346.

MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3:171-178.

2. Ek sayı için: MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. Baskıdaki makale için: Cossrow N, Pawaskar M, Witt EA, Ming EE, Victor TW, Herman BK, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria. J Clin Psychiatry, 2016. (in press).

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4. Kitaptan alıntılar:

Tek yazarlı kitaptan alıntı için:

McKnight TL. Obesity Management in Family Practice. 1st ed., New York:Springer, 2005:47-51.

Kitaptan bir bölüm için, editör(ler) varsa:

Jebb S, Wells J. Measuring body composition in adults and children. In Clinical Obesity in Adults and Children, Copelman P, Caterson I, Dietz W (editors). 1st ed., London: Blackwell Publishing, 2005:12-18.

Editörler aynı zamanda kitabın içindeki metin ya da metinlerin yazarı ise: Önce alınan metin ve takiben kitabın ismi yine kelimeler büyük harfle başlatılarak yazılır.

Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. 1st ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

Çeviri Kitaptan Alıntı için:

McGuffin P, Owen MJ, Gottsman II. Psikiyatri Genetiği ve Genomiği. Abay E, Görgülü Y (translation editors) 1st ed., Istanbul: Nobel Tıp Kitabevleri, 2009:303-341.

5. Tezden alıntı için: Keçeli F. Yeme bozukluğu hastalarında obsesif kompulsif bozukluk ve kişilik bozukluğu. Thesis, T.C. Sağlık Bakanlığı Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul:2006.

6. Kongre bildirileri için: Akbaş Öncel D, Akdemir A. Üniversite öğrencilerinde diyet, beden algısı ve kendilik algısı arasındaki ilişkiler. 47. Ulusal Psikiyatri Kongresi Özet Kitabı, 26-30 Ekim 201, Antalya, 2011:102.

7. Online Makale:

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 4 Temmuz 2006 [Atıf tarihi:4 Ocak 2007];145(1):62-9. Erişim adresi:http://www.annals.org/cgi/reprint/145/1/62.pdf

Makalenin Dergiye Gönderilmesi

Çevrimiçi gönderim (online submission) ile birlikte Bağcılar Tıp Bülteni web sitesinin (www.ijfed.org) ilgili kısımlarındaki talimatlara uyarak makale gönderilebilmekte, hakem süreçleri de bu yolla yapılabilmektedir.

Makalelere eşlik eden ve aşağıdaki bilgileri içeren bir kapak mektubu olmalıdır.

• Aynı ya da çok benzer çalışmadan elde edilen raporların daha önce yayına gönderilip gönderilmediği mutlaka belirtilmelidir. Böyle bir çalışmaya özgül olarak atıfta bulunulmalı ve ayrıca yeni makalede de eskisine atıfta bulunulmalıdır. Gönderilen makaleye bu tip materyalin kopyaları da eklenerek editöre karar vermesinde yardımcı olunmalıdır.

• Eğer makalenin kendisinde ya da yazar formunda belirtilmemişse çıkar çatışmasına neden olabilecek mâli ya da diğer ilişkileri belirten bir ifade olmalıdır.

• Makalenin tüm yazarlar tarafından okunup kabul edildiğini, önceden belirtilen şekilde yazarlık ölçütlerinin karşılandığını, her yazarın makalenin dürüst bir çalışmayı yansıttığına inandığını belirten bir ifade olmalıdır. Mektup editöre yardımcı olabilecek tüm diğer bilgileri içermelidir. Eğer makale önceden başka bir dergiye gönderilmişse önceki editörün ve hakemlerin yorumları ve yazarların bunlara verdiği cevapların gönderilmesi faydalıdır. Editör, önceki yazışmaların gönderilmesini hakem sürecini dolayısıyla yazının yayınlanma sürecini hızlandırabileceğinden istemektedir.

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Peri-postoperative Atrial Fibrillation in Non-cardiothoracic Surgeries: Approach of the Anesthesiologist

Kardiyotorasik Olmayan Cerrahilerde Peri-postoperatif Dönem Atriyal Fibrilasyon: Anesteziyolog Yaklaşımı

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Abstract

In this study, our aim was to summarize the current knowledge on the epidemiology, pathophysiology and management of new-onset perioperative and postoperative atrial fibrillation (POAF) in non-cardiothoracic surgery and to provide a practical approach for anesthesiologists and non-cardiologist clinicians. Various findings such as age, hypertension, diabetes mellitus, cardiac risk factor, premature beats on preoperative electrocardiogram, left anterior fascicular block or left ventricular hypertrophy pose an elevated risk for POAF. The first thing to do in patients with POAF is to determine the origin of the arrhythmia. In most cases, identifying and eliminating the triggering cause will suffice. On the other hand, hemodynamic data should be evaluated. The primary goal of treatment in patients with life-threatening symptoms is to maintain hemodynamic stability. Deterioration of hemodynamic stability and development of shock with AF with high ventricular rate is a condition that requires immediate cardioversion. Rate control therapy increasing dose with continuous cardiac monitoring to a heart rate <110 should be performed on hemodynamically stable patients with POAF. β-blockers and non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are used for rate control in AF. If there is peripheral vascular disease, congestive heart failure, diabetes, hypertension or history of thromboembolic event, attention should be paid and postoperative bleeding risk should be calculated. There is a risk of bleeding in the postoperative period and POAF usually lasts less than 24 hours and improves spontaneously, and the use of heparin at a therapeutic dose is not required. As a general rule, therapeutic doses of anticoagulants are recommended for POAF lasting longer than 48 hours and for frequent recurrent AF attack.

Keywords: Anesthesia, atrial fibrillation, non-cardiothoracic surgery

Öz

Bu makalede, anesteziyologlar ve kardiyolog olmayan klinisyenler için kardiyotorasik olmayan cerrahilerde yeni başlayan perioperatif ve postoperatif atriyal fibrilasyonun (POAF) epidemiyolojisi, patofizyolojisi ve yönetimine ilişkin mevcut bilgileri özetlemeyi ve pratik bir yaklaşım sağlamayı amaçladık. Yaş, hipertansiyon, diabetes mellitus, kardiyak risk faktörü, preoperatif elektrokardiyogramda erken atımlar, sol anterior fasiküler blok veya sol ventrikül hipertrofisi gibi çeşitli bulgular POAF için daha yüksek risk oluşturur. POAF'li hastalarda yapılması gerekenlerin başında, bu aritminin altında yatan nedenin belirlenmesi gelmektedir. Çoğu durumda, tetikleyici nedenin tespit edilip ortadan kaldırılması yeterli olacaktır. Bununla birlikte hemodinamik veriler değerlendirilmelidir. Yaşamı tehdit eden semptomatik hastalarda tedavinin ilk amacı, hemodinamik stabiliteyi sağlamaktır. Yüksek ventrikül hızlı AF ile hemodinamik stabilitenin bozulması, şok tablosunun gelişimi acil kardiyoversiyon gerektiren bir durumdur. POAF'si olan hemodinamik olarak stabil hastalara, kalp hızı <110 olacak şekilde sürekli kardiyak monitörizasyon yapılarak artan dozda hız kontrol tedavisi yapılmalıdır. β-blokerler ve dihidropiridin grubu olmayan kalsiyum kanal blokerleri (diltiazem ve verapamil), AF'de hız kontrolünün sağlanmasında kullanılır. Konjestif kalp yetmezliği, hipertansiyon, diyabet, geçirilmiş tromboembolik olay, periferik damar hastalığı varsa dikkat edilmeli ve ameliyat sonrası kanama riski hesaplanmalıdır. Postoperatif süreçte kanama riskinin olması ve POAF'nin çoğunlukla 24 saatten daha kısa sürüp kendiliğinden geçmesi tedavi dozunda heparin kullanımını gerektirmez. Genel bir kural olarak 48 saatten uzun sürenlerde ve sık tekrar eden AF ataklarında tedavi edici dozda antikoagülan önerilmektedir.

Anahtar kelimeler: Anestezi, atriyal fibrilasyon, kardiyotorasik dışı cerrahi

***One of the authors of this article (KE) is a member of the Editorial Board of this journal. He was completely blinded to the peer review process of the article.**

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Introduction

Atrial fibrillation (AF) is the condition caused by supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and this leads to inefficient atrial contraction. Irregular R-R intervals despite usual atrioventricular conduction, missed obvious P wave repeats, and irregularities in atrial activation are the electrocardiographic characteristics of AF (1). New-onset atrial arrhythmias have been reported to develop in 16-46% of patients after cardiac surgery, in 3-30% of patients after thoracic surgery, and in up to 8% of non-cardiothoracic surgery patients (2). Following non-cardiothoracic surgery, AF usually occurs within the first four postoperative days. In this article, we aimed to summarize the up-to-date knowledge on the epidemiology, pathophysiology and management of new-onset perioperative and postoperative AF (POAF) in non-cardiothoracic surgery and to provide a practical approach for anesthesiologists and non-cardiologist clinicians.

Perioperative AF is common in cardiothoracic surgeries and is thought to occur secondary to direct mechanical myocardial or pericardial irritation (3). However, the pathophysiology of AF associated with non-cardiothoracic surgery remains elusive. Its cause is suggested to be a preoperative or postoperative inflammatory response triggering the dysregulation in the electrical activity in atrial myocytes (4). Moreover, increased sympathetic activity due to stress from surgery and anesthesia predisposes the patient to arrhythmias. Clinical conditions including intraoperative hypotension, hypovolemia, anemia, trauma and pain may have an impact on sympathetic activity. Several other mechanisms that may trigger arrhythmia includes electrophysiological disorders and metabolic dysregulations like hypoglycemia and electrolyte imbalance. Hypoxia may also cause arrhythmias via vasoconstriction of pulmonary vein and may lead to increase in the right ventricular pressure and right atrial distension. In addition, hypoxia may lead to ischemia of atrial myocardial cells by changing the conductive system in the cardiac tissue. Hypovolemia is also suggested to be another contributing mechanism that may lead to AF development. Increased intravascular volume caused by hypervolemia leads causes stretching of the right atrium and triggers the development of AF (5).

Prevention

Several studies have reported several predictors for POAF (2,6,7). Knowing these predictors and being prepared are important for the management of AF. Age is an important predictor of POAF when demographic data are considered. The incidence of AF increases with age. The incidence of AF is 2.3% in people older than 40 years, and this rate increases to 5.9% in people older than 65 years (8,9). Men have been reported to have a higher POAF incidence compared to women (10). On the other hand, the effect of body mass index (BMI) on AF is controversial. Although BMI has been defined as a risk factor for AF in some cardiac surgery studies, no significant effect of BMI on AF development has been demonstrated in some studies (11-13).

It is well established that hypertension is a risk factor for POAF, as indicated by both animal and human studies (6,14). Possible hemodynamic mechanisms and left atrial distension and pressure, as well as an increased thickness of left ventricular wall, predispose to AF.

Studies have reported that diabetes mellitus (DM)-related inflammation may contribute to the pathophysiology of AF (15,16). In addition, in a study by Iguchi et al. (7), DM was shown to be an independent factor associated with AF. It is very important whether the patients have a previous cardiac risk factor for the POAF development. In the study of Christians et al. (17) on non-cardiothoracic surgery patients, 67% of the patients exhibited at least one cardiac risk factor (18). Besides the clinical factors, various findings on the preoperative electrocardiogram including premature atrial complexes, left anterior fascicular block, or left ventricular hypertrophy constitute the higher risk factors of POAF.

Management

The first thing to do in patients with POAF is to determine the underlying cause of this arrhythmia. In most cases, identification and elimination of the triggering cause will suffice. On the other hand, hemodynamic data should be evaluated. The primary goal of treatment in patients with life-threatening symptoms is to maintain hemodynamic stability. Deterioration of hemodynamic stability and development of shock with AF with high ventricular rate is a condition that requires immediate cardioversion [Class I-European Society of Cardiology (ESC)] (Table 1). Direct transthoracic cardioversion is effective in converting the heart rhythm of the patient to sinus rhythm. Moreover, the need for anesthesia-analgesia should not be overlooked, as there will be pain and discomfort in cardioversion where high-energy electrical shocks are applied.

Rate control therapy including increasing dose with continuous cardiac monitoring to a heart rate <110

Table 1. Peri-postoperative atrial fibrillation in non-cardiothoracic surgeries: Practical approach

Management of peri-postoperative atrial fibrillation

Identify and treat the factors that trigger AF!
Hypoxia?-Infection?
Electrolyte abnormality?-Hypovolemia?
CAD or CHF?-Bleeding?

Stable hemodynamics
Rate control to aim for HR <110
If decompensate HF or EF <35%, administer amiodarone, NOT betablocker or CCB.
1. Apart from this, administer metoprolol 2 mg IV (for 1 minute), repeat every 5-10 minutes if a positive response is obtained and no side effects occur, the initial maximum IV dose should be 10 mg in total.
2. If there is no response or insufficient response to >4 mg metoprolol, administer diltiazem 5 mg (within 1 min), if positive response is obtained and no side effects occur, top up to a maximum of 20 mg at 10-minute intervals.

Unstable hemodynamics
Pale, shock, hypotension, decreased peripheral pulses, pulmonary edema, chest pain
Synchronized cardioversion at 200 joule monophase

Resistant ventricular HR or side effects are present
1: Digoxin 0.5 mg IV then 0.25 mg IV in 6 h. and if renal function is normal, 0.25 mg IV in 12 h (Not first-choice drug alone. It can be combined with beta-blocker and CCB in resistant AF).
2: Amiodarone 150 mg IV over 10 min followed by infusion for rate and rhythm control (decompensated heart failure, patient with EF <35)

Resistant AF lasting more than 48 hours

Patient group with risk
(Congestive heart failure, hypertension, diabetes, previous thromboembolic event, peripheral vascular disease, cerebrovascular disease etc.)
▪ Consult cardiology!
▪ What is the bleeding risk?
Low risk of bleeding: Start warfarin
High risk of bleeding: Electrical cardioversion and low molecular weight heparin (LMWH) are recommended after control with TEE.

Patient group without risk
▪ Daily oral acetylsalicylic acid treatment recommended

CAD: Coronary artery disease, HR: Heart rate, IV: Intravenous, EF: Ejection fraction, CHF: Cardiac heart failure, CCB: Calcium channel blocker, AF: Atrial fibrillation, TEE: Transesophageal echo

(class I-ESC) should be performed in hemodynamically stable patients with POAF (Table 1). β-blockers and non-dihydropyridine calcium channel blockers (CCB) (diltiazem and verapamil) are used for rate control in AF (19). After non-cardiac surgery, β-blockers accelerate the conversion of AF to sinus rhythm. Moreover, preoperative use of β-blockers has been associated with better control of arrhythmia in several studies. Digoxin alone itself is not the drug of first choice in acute AF, except for patients with congestive heart failure. Nevertheless, digoxin can be used in combination with beta-blockers and CCB in resistant AF (20). Amiodarone is generally preferred when other antiarrhythmic drugs are ineffective or cannot be used due to its serious side effects (heart block, bradycardia, hypotension, pulmonary fibrosis, and thyroid and hepatic dysfunction). In patients with decompensated heart failure or with ejection fraction <35%, amiodarone should be given instead of beta-blockers and CCBs because of their negative inotropic effects (20).

There is a risk of bleeding in the postoperative period and POAF usually lasts less than 24 hours and improves spontaneously, and the use of heparin at a therapeutic dose is not required. As a general rule, therapeutic doses of anticoagulants are recommended for POAF lasting longer than 48 hours and for frequent recurrent AF attack (21,22). Before starting anticoagulant therapy, it should be personalized for the patient. In the cases of hypertension, congestive heart failure, diabetes, history of thromboembolic event and peripheral vascular disease, attention should be paid and postoperative bleeding risk should be calculated (Table 1) (22).

In the postoperative period, AF usually occurs within the first four days, and the hearth rhythm of most patients who develop AF returns to spontaneous sinus rhythm. Therefore, many physicians question the necessity of diagnosing and treating this self-limiting arrhythmia that does not usually result in hemodynamic deterioration and mortality. Nevertheless, evidence obtained since the 1980s indicates poor prognosis with an increased risk of postoperative complications of POAF (19,22). POAF should not be underestimated as a temporary complication occurring only in the perioperative period because it can cause serious and fatal problems in non-cardiothoracic surgery. Previous studies indicated that POAF could recur in patients, leading to cardiac complications and embolic

events (23). In addition, higher mortality rates were observed in patients with POAF (16,24,25). Therefore, documentation of POAF is necessary even in asymptomatic patients.

To decrease the risk of POAF, prophylactic treatment with β-blocking agents, amiodarone, CCB, and magnesium may be acknowledged in the pre-surgical period. Notwithstanding, considering the side effects of these drugs, which will only benefit a few patients in prevention of POAF, it is pointless to use them in all patients. Prophylaxis can be considered to decrease the incidence and severity of POAF only in high-risk patients (uncontrolled DM, coronary artery disease, heart failure, cerebrovascular events, etc.); however, more studies regarding the safety and efficacy of this approach are required (16).

Although POAF is not as common as in cardiac surgery, it can also be encountered in non-cardiothoracic surgery. In particular, POAF, which affects hemodynamics, should be treated quickly. In addition, β-blockers and CCB have a high efficacy in the intervention of POAF in patients with stable hemodynamics. Amiodarone should be preferred in heart failure patients. Anticoagulant therapy should be considered in AF attacks lasting more than 48 hours or frequently recurring. Anesthesiologists must be prepared for POAF and also document it, even in asymptomatic patients.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: H.Y.A., K.T., K.E., Design: H.Y.A., K.T., K.E., Literature Search: H.Y.A., K.T., K.E., Writing: H.Y.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Evaluation of the Efficacy of PET/CT in Gynecological Cancers: A Retrospective Study

Jinekolojik Kanserlerde PET/BT'nin Etkinliğinin Retrospektif Olarak Değerlendirilmesi

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Abstract

Objective: To evaluate the efficacy of preoperative positron emission tomography/computed tomography (PET/CT) to detect lymph node metastasis in gynecologic malignancies.

Method: This study included a total of 78 patients who underwent surgery for gynecological cancer at the Gynecology and Obstetrics Clinic, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital between January 2016 and November 2017. Data on age, menopausal status, clinical diagnoses, definitive pathology reports and PET/CT findings were obtained from the Hospital Information Management System and the patient files. The histological type and pelvic and/or paraaortic lymph node involvement status of the tumor based on a definitive pathology report, and the maximum standardized uptake value (SUV_{max}) values of the primary tumor and lymph nodes with pathological involvement in the PET/CT were recorded.

Results: Of the 78 patients, 42 had endometrial cancer, 10 had uterine sarcoma, 14 had cervical cancer and 12 had ovarian cancer. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of PET/CT in predicting lymph node metastasis were 54.5%, 96.7%, 85.7%, 85.7%, and 85.7%, respectively, in patients with endometrial cancer; 100%, 89.9%, 90%, 50%, and 100%, respectively, in patients with uterine sarcoma; 0%, 92.3%, 85.7%, 0%, and 92.3%, respectively, in patients with cervical cancer; and 62.5%, 75%, 66.7%, 83.3%, and 50%, respectively, in patients with ovarian cancer. When all of the patients were assessed together, these values were found to be 57.1 %, 92.9%, 83.3%, 75%, and 85.4%, respectively.

Öz

Amaç: Bu çalışmanın amacı, jinekolojik malignitelerde operasyon öncesi yapılan pozitron emisyon tomografi/bilgisayarlı tomografinin (PET/BT) lenf nodu metastazını saptamadaki etkinliğini değerlendirmektir.

Yöntem: Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'nde Ocak 2016 ile Kasım 2017 yılları arasında jinekolojik kanser nedeni ile opere olan 78 hasta çalışmaya dahil edildi. Hastane veri sisteminden ve hasta dosyalarından hastaların yaşına, menopozal durumuna, klinik tanılarına, nihai patoloji raporlarına ve PET/BT bulgularına ulaşıldı. Nihai patoloji raporundaki tümörün histolojik tipi, pelvik ve/veya paraaortik lenf nodu tutulumları, PET/BT'de patolojik tutulum izlenen lenf nodlarının ve primer tümörün maksimum standart tutulum değeri (SUV_{maks}) kaydedildi.

Bulgular: Çalışmaya alınan 78 hastanın 42'si endometrium kanseri, 10 hasta uterin sarkom, 14 hasta serviks kanseri ve 12 hasta over kanseriydi. Endometrium kanser tanısı almış hasta grubunda PET/BT'nin lenf nodu metastazını tahmin etmedeki sensitivitesi, spesifitesi, doğruluğu, pozitif prediktif değeri ve negatif prediktif değeri sırasıyla %54,5, %96,7, %85,7, %85,7 ve %85,7 idi. Uterin sarkomda bu değerler sırasıyla %100, %89,9, %90, %50 ve %100'dü. Serviks kanserinde sırasıyla %0, %92,3, %85,7, %0 ve %92,3 ve son olarak over kanserinde sırasıyla %62,5, %75, %66,7, %83,3 ve %50 idi. Tüm hasta grubu incelendiğinde bu değerler sırasıyla %57,1, %92,9, %83,3, %75 ve %85,4 olarak bulundu.

Sonuç: PET/BT tanı testleri bakımından en iyi başarı uterin sarkomlarda elde edilmiştir. Ayrıca, çalışmamızda metabolik parametrelerden ortalama SUV_{maks} değerlerinin yalnızca over kanserinde lenf nodu

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Conclusion: The highest diagnostic yield of PET/CT was obtained for uterine sarcoma. Furthermore, among the metabolic parameters, the mean SUV_{max} value was found to be associated with lymph node metastasis only in patients with ovarian cancer and was not predictive in other gynecologic malignancies.

Keywords: Gynecological neoplasms, lymphatic metastasis, ^{18}F-FDG PET/CT

metastazı ile ilişkili olduğu, diğer jinekolojik malignitelerde anlamlı olmadığı saptanmıştır.

Anahtar kelimeler: Jinekolojik neoplazmlar, lenfatik metastaz, ^{18}F-FDG PET/BT

Introduction

Gynecological cancers are important in the female population in terms of causing morbidity and mortality. According to 2018 data reported by the American Cancer Society, it was stated that 32,120 of the estimated 110,070 patients newly diagnosed with gynecological cancer would die (1).

The most important factor determining prognosis in gynecologic cancers is disease stage. In gynecological malignancies other than cervical cancer, lymph node metastasis is among the prognostic factors owing to its inclusion in the International Federation of Gynecology and Obstetrics (FIGO) staging system. That said, although not included in the FIGO stating system, lymph node metastasis is very important when deciding upon treatment and predicting outcomes in cervical cancer (2). Lymph node dissection prolongs the operation time and increases the rates of such complications as bleeding, lymphocyte formation and lower extremity edema, and for this reason, non-invasive imaging methods are important in determining lymph node metastasis in the preoperative period (3). Imaging modalities include ultrasonography, magnetic resonance imaging, computed tomography (CT), and positron emission tomography/CT (PET/CT), and PET/CT in particular is gaining increasing importance among the imaging methods.

Our study evaluates the effectiveness of the determination of lymph node metastasis by ^{18}F-fluoro-2-deoxy-G-glucose (^{18}F-FDG) PET/CT in patients with endometrial carcinoma, uterine sarcoma, cervical cancer, and ovarian cancer.

Materials and Methods

Study Population

The study was conducted in the Obstetrics and Gynecology Clinic of the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital. The patient files and records of 120 patients who underwent surgery for a gynecologic cancer between January 2016 and November 2017 were obtained from the hospital information management system and were reviewed retrospectively. Patients who were considered to have a high operation risk and so precluded from lymph node dissection and those being treated for another concurrent malignancy were excluded from the study. Of the remaining 78 patients included in the study, 42 had endometrial cancer, 10 had uterine sarcoma, 14 had cervical cancer, and 12 had ovarian cancer. Of the 12 patients with ovarian cancer, three had recurrent ovarian cancer and also had a minimum of 3 months between the time of the PET/CT scan and the last treatment. Data on age, menopausal status, clinical diagnoses, definitive pathology reports and PET/CT findings were obtained from the hospital information management system, and the patient files. The histological type and pelvic and/or paraaortic lymph node involvement status of the tumor based on a definitive pathology report, and the maximum standardized uptake value (SUV_{max}) values of the primary tumor and lymph nodes with pathological involvement in the PET/CT were recorded.

Surgical Procedure

All patients were operated on by gynecologic oncology specialists of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital within 30 days of the PET/CT examinations. The surgical procedures included radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymphadenectomy, omentectomy and peritoneal cytology. Unlike in other cancer types, patients with endometrial cancer did not undergo a systematic lymphadenectomy. In these patients, the risk of metastasis was preoperatively evaluated with respect to the histological type, tumor grade and PET/CT findings, and a sentinel lymph node dissection was made to the patients having low risk for metastasis. Pelvic and paraaortic lymphadenectomies and omentectomies were performed on three patients with recurrent ovarian cancer.

Data Analysis

In the present study, the standard protocol was applied for the histopathological evaluation of lymph nodes. Fine cuts

were performed so as not to miss any micrometastases. Pathological specimens obtained during the operations were evaluated by pathology specialists experienced in gynecologic oncology in the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. In the patients who underwent surgery after PET/CT imaging, the PET/CT findings were evaluated along with their definitive pathology reports. The PET/CT findings of the pelvic and paraaortic lymph nodes were compared with the corresponding findings related to these lymph nodes mentioned in the pathology report. In the PET/CT report, lesions with pathological ^{18}F-FDG uptake and metastasis in the pathology report were considered true positives; lesions with pathological ^{18}F-FDG uptake but no metastasis in the pathology report were considered false positives; lesions with no pathological ^{18}F-FDG uptake but metastasis in the pathology report were considered false negatives; and lesions with no pathological ^{18}F-FDG uptake and no metastasis in the pathology report were considered true negatives. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of PET/CT for the detection of lymph node metastasis were calculated.

In order to predict the presence of nodal metastasis, the SUV_{max} values of the primary tumor were recorded from the PET/CT reports. The staging was performed using the FIGO staging system in all patients.

Statistical Analysis

The normality of the distribution of the data was tested with the Shapiro-Wilk test. A Student's t-test was used to compare data with a normal distribution between two independent groups and the Mann-Whitney U test was used to compare data with a skewed distribution between two independent groups. One-Way Analysis of Variance and least significant difference multiple comparison tests were employed to compare continuous data with a normal distribution between more than two independent groups. The Kruskal-Wallis and all-pairwise multiple comparison tests were used to compare data with a skewed distribution between more than two groups. The correlations between variables were tested with the Spearman's correlation test. A receiver operating characteristic (ROC) analysis was performed to estimate cut-off values for continuous variables. The cut-off value was determined with respect to the activity level of the area under the ROC curve (AUC). Mean ± standard deviation values were given for numerical variables, and categorical variables were expressed as numbers and frequencies. The SPSS for Windows version 24.0 package program was used for the statistical analysis, and a p-value of <0.05 was considered as statistically significant.

Results

Patient Population

There were 78 patients in our study. Of them, 42 had endometrial cancer, 10 had uterine sarcoma, 14 had cervical cancer and 12 had ovarian cancer. The age of the patients ranged from 21 to 80 years and the mean age was 55.69±11.95 years.

Histopathological data and demographic information of the patients with clinical diagnoses of endometrial cancer, uterine sarcoma, cervical cancer and ovarian cancer are presented in Tables 1 and 2, respectively.

Histopathological Findings

The total number of pelvic lymph nodes removed from the patients was 1,221 (mean 15.65±11.13), and the total number of paraaortic lymph nodes was 586 (mean 7.51±10.25). The definitive pathological report recorded 40 (3.2%) of the 1,221 pelvic lymph nodes and 94 (16.04%) of the 586 para-aortic lymph nodes as metastatic.

PET/CT Findings

Table 3 presents the statistical parameters of PET/CT in predicting lymph node metastasis in patients with endometrial cancer, uterine sarcoma, cervical cancer and ovarian cancer. In endometrial cancer, there was no statistically significant difference between different stages and between patients with myometrial invasion of <50% and those with ≥50% in terms of the mean SUV_{max} values of the primary tumor on a PET/CT examination.

In the present study, 42 patients with endometrial cancer were categorized with respect to the risk classification system described jointly by the European Society for Medical Oncology, the European Society for Radiotherapy & Oncology and the European Society of Gynecological Oncology. Based on this system, 19 (45.2%) patients were in the low-risk group, 8 (19%) were in the middle-risk group and 15 (35.7%) were in the high-risk group. There were no patients in the high-middle risk group. The mean SUV_{max} value of the primary tumor was 14.40±6.79 in the low-risk group, 18.06±7.32 in the medium-risk group, and 16.55±7.87 in the high-risk group. After evaluating all risk groups, the mean SUV_{max} values were found to be statistically insignificant.

Table 1. Descriptive characteristics and histopathological findings of endometrial cancer patients

Parameters	Number
Age	58.83±10.24 (38-80)
Menopausal condition	
Postmenopausal	33 (78.6%)
Premenopausal	9 (21.4%)
Histopathological subtype	
Type 1	37 (88.1%)
Type 2	5 (11.9%)
FIGO stage	
IA	19 (45.2%)
IB	9 (21.4%)
II	2 (4.8%)
IIIA	1 (2.4%)
IIIC1	5 (11.9%)
IIIC2	6 (14.3%)
Myometrial invasion	
<50%	19 (45.2%)
≥50%	23 (54.8%)
Risk group	
Low	19 (45.2)
Intermediate	8 (19%)
High	15 (35.7%)
Grading	
1	13 (30.9%)
2	17 (40.4%)
3	12 (28.5%)
Lymph node metastasis	
Yes	11 (26.1%)
No	31 (73.8%)
CSI	
Yes	8 (19%)
No	34 (81%)
LVSI	
Yes	8 (19%)
No	34 (81%)

CSI: Cervical stromal involvement, LVSI: Lymphovascular space invasion

The use of the mean SUV_{max} values of the primary tumor in a PET/CT examination to discriminate between patients with and without lymphatic metastasis with respect to the pathology report was evaluated by a ROC analysis (Figure 1). The 95% confidence interval of the AUC of the ROC curve was calculated as 0.697 (p=0.073). The ROC curve analysis was not statistically significant. In addition, the optimum cutoff value was determined as 19.20, which corresponds to a sensitivity of 66.7% and a specificity of 78.8%.

When we evaluated patients with endometrial cancer, there was no significant correlation between the mean SUV_{max} value of the primary tumor and histological subtype, LVSI, or cervical stromal involvement (Table 4). The mean SUV_{max} value of the primary tumor in patients with uterine sarcoma was 16.92±8.68 (range 5.3 to 32.4). The relationship between the mean SUV_{max} value and lymphatic metastases of the primary tumor based on the definitive pathology report could not be estimated owing to the insufficient number of patients.

When the mean SUV_{max} values of patients with cervical cancer were compared according to FIGO stages, an insignificant difference was found. However, nine of the 14 patients with cervical cancer had squamous cell carcinomas and five had adenocarcinomas with respect to the histopathology. The mean SUV_{max} of the primary tumor was 10.25±6.065 in patients with squamous cell carcinoma and 12.25±11.01 in patients with adenocarcinoma. There was no statistically significant difference between these two groups in terms of the mean SUV_{max} values of the primary tumor upon a PET/CT examination.

The lesion-based mean SUV_{max} in PET/CT was 9.92±4.71 (range 2.66-15.40) in ovarian cancer. The lesion-based mean SUV_{max} value of the patients who had lymph node metastases based on a pathological examination was 9.96±5.55, and the mean SUV_{max} value of the patients who had no lymph node metastasis was 9.79±1.19 (Table 5). There was a statistically significant difference between these two groups (p=0.041).

Discussion

Our study assessed the efficacy of preoperative ^{18}F-FDG PET/CT to detect lymph node metastasis in patients who underwent surgery and lymphadenectomy for endometrial cancer, uterine sarcoma, cervical cancer or ovarian cancer, and found that the highest diagnostic yield of PET/CT was for uterine sarcomas. Furthermore, we found that the mean SUV_{max} value was the only variable among the metabolic parameters of PET/CT that was used and there was an important relationship between lymph node metastasis and SUV_{max} only in patients who had ovarian cancer.

In terms of determining lymph node metastasis, there have been many studies in the literature comparing the non-invasive medical imaging techniques. Some of these studies have only investigated the yield of ^{18}F-FDG PET/CT in predicting lymph node metastasis. One such study, carried out by Crivellaro et al. (4), investigated 76 patients who had

Table 2. Descriptive characteristics and histopathological findings of patients with uterine sarcoma, cervical cancer, and ovarian cancer

		Uterine sarcoma	Cervical cancer		Ovarian cancer	
Parameters		**Number**	**Number**		**Number**	
Age		56.6±14.28 (33-77)	47.64±9.14 (37-63)		53.33±14.71 (21-73)	
Menopausal condition	Postmenopausal	8 (80%)	6 (42.9%)		10 (83.3%)	
	Premenopausal	2 (20%)	8 (57.1%)		2 (16.7%)	
Histological subtype	Leiomyosarcoma	2 (20%)	Adenocarcinoma	5 (35.7%)	Granulosa cell tumor	1 (8.3%)
	Carcinosarcoma	6 (60%)	SCC	9 (64.3%)	Serous cancer	11 (91.7%)
	USS	2 (20%)				
FIGO stage	IA	1 (10%)	IA1	1 (7.1%)	IA	2 (22.2%)
	IB	6 (60%)	IA2 IB1	1 (7.1%) 9 (64.5%)		
	IC	2 (20%)	IB2	1 (7.1%)	IIIC	7 (77.8%)
	IIIC2	1 (10%)	IIA1 IIA2	1 (7.1%) 1 (7.1%)		

USS: Undifferentiated uterine sarcoma, SCC: Squamous cell carcinoma

Table 3. PET/CT findings

Endometrial cancer	Sensitivity	54.5%
	Specificity	96.7%
	Accuracy	85.7%
	PPV	85.7%
	NPV	85.7%
Uterine sarcoma	Sensitivity	100%
	Specificity	89.9%
	Accuracy	90%
	PPV	50%
	NPV	100%
Cervical cancer	Sensitivity	0%
	Specificity	92.3%
	Accuracy	85.7%
	PPV	0%
	NPV	92.3%
Ovarian cancer	Sensitivity	62.5%
	Specificity	75%
	Accuracy	66.7%
	PPV	83.3%
	NPV	50%
Total	Sensitivity	57.1%
	Specificity	92.9%
	Accuracy	83.3%
	PPV	75%
	NPV	85.4%

PPV: Positive predictive value, NPV: Negative predictive value, PET/CT: Positron emission tomography/computed tomography

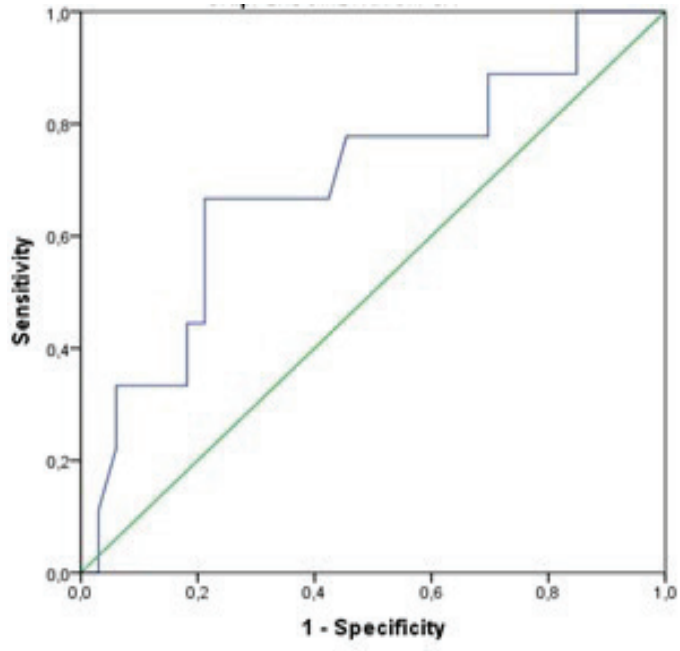

Figure 1. Evaluation of lymph node metastasis in endometrial cancer through a receiver operating characteristic curve analysis

high-risk endometrial cancer and found that 66 patients had endometrioid, seven patients had carcinosarcoma and the remaining patients had a non-endometrioid histology. The sensitivity, specificity, accuracy, PPV and NPV of PET/CT in detecting lymph node metastasis were 78.6%, 98%, 94.7%, 91.7%, and 95.3%, respectively. In a study by Atri et al. (5), comparing the success of PET/CT in predicting lymph node metastasis in cervical cancer with CT, the sensitivity and specificity of PET/CT were found to be 81% and 69%, respectively, and PET/CT was thus reported to be superior to CT. Jiafu et al. (6) compared the sensitivity,

specificity, and accuracy of PET/CT with CT in predicting lymph node metastasis in 28 patients (17 with cervical cancer, four with endometrial cancer and seven with ovarian cancer), and they reported sensitivity, specificity and accuracy of 100%, 61.54% and 82.14%, respectively, for PET/CT, and these values were higher than in CT. They also found no relationship between the mean SUV_{max} value and lymph node metastasis.

In the present study, no comparison was made among PET/CT and other imaging techniques, as only the performance of ^{18}F-FDG PET/CT was investigated. The statistical values of PET/CT in predicting lymph node metastasis in patients with endometrial cancer were comparable with those of similar studies, aside from the sensitivity of PET/CT in endometrial cancer. The relatively low sensitivity was attributed to the fact that most of the patients with endometrial cancer in the present study were at an early stage of the disease. We speculate that ^{18}F-FDG PET/CT may perform better in advanced stage endometrial cancer.

Considering the statistical parameters in Table 3, the sensitivity of PET/CT in detecting lymph node metastasis in patients who had cervical cancer was found to be quite low when compared to other studies in literature, although it should not be concluded that ^{18}F-FDG PET/CT does not achieve good success in cervical cancer, as the low number of patients with cervical cancer in the present study may have led to a type 1 error.

When we analyzed the statistical parameters in Table 3, the PET/CT examination achieved a very high success rate to predict lymph node metastasis in cases of uterine sarcoma when compared to other studies in literature. Uterine sarcoma's a very rare gynecological malignity, and there have been very few studies to date investigating PET/CT in the identification of patients with this form of cancer. The efficacy of PET/CT in uterine sarcomas has been evaluated in conjunction with endometrial cancer in previous studies, although uterine sarcomas have not been classified separately in these studies. There is little doubt that the findings of the present study of patients with uterine sarcoma will contribute significantly to literature, but it should be supported by larger scale studies.

In addition, the statistical values that were found by PET/CT in ovarian cancer are in parallel with those of other similar studies. When we consider the statistical values of the PET/CT examination in the total study population of 78 patients, there are currently insufficient data on the performance of ^{18}F-FDG PET/CT in these four cancer types together, and so it is not possible to compare these values with those of other studies.

The SUV_{max} value, which is a semi-quantitative parameter obtained from PET/CT, is a measure of ^{18}F-FDG concentration in metabolically active tissue, and is widely used as a marker of tumor aggressiveness and prognosis in many cancers (7). Recently, measures of metabolic tumor burden, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have been used as important prognostic markers in many cancers (8). However, only the SUV_{max} value was used in the present study, while the other metabolic parameters of MTV and TLG were not used.

Table 4. Correlation analysis

		Mean SUV_{max} value of primary tumor
Histological subtype	r	-0.216
	p	0.098
	n	41
LVSI	r	0.168
	p	0.199
	n	41
CSI	r	-0.034
	p	0.792
	n	41
Mean SUV_{max} value of primary tumor	r	-
	p	-
	n	-

LVSI: Lymphovascular space invasion, CSI: Cervical stromal involvement, r: Spearman correlation coefficient, n: Number of patients

Table 5. Comparison of lesion-based mean SUV_{max} values of patients with ovarian cancer and lymph node metastasis

		N	Mean ± SD	Minimum	Maximum	p
Lymphatic metastasis in PET/CT	Yes	6	8.96±5.76	2.66	15.40	0.500[a]
	No	6	11.52±2.30	8.95	13.40	
Lymphatic metastasis in pathology	Yes	8	9.96±5.55	2.66	15.40	0.041*[a]
	No	4	9.79±1.19	8.95	10.63	

N: Number of patients, SD: Standard deviation, PET/CT: Positron emission tomography/computed tomography, [a]Student's t-test, *p<0.05

When we have reviewed the literature, there are many studies related to metabolic parameters. Antonsen et al. (9) reported that a high SUV_{max} value in endometrial carcinoma was related to lymph node metastasis, and they observed that high SUV_{max} values were significantly associated with advanced FIGO stage, deep myometrial invasion, and cervical stromal involvement. In another study conducted with 56 patients diagnosed with endometrial cancer, the study population was classified as having low or high-risk cancer, and the high-risk group had significantly higher MTV and TLG values than the low-risk group. They showed no differences in mean SUV_{max} values among the groups (10).

Miccò et al. (11) reported that the SUV_{max} value was not associated with lymph node metastasis in a retrospective study involving 49 patients with cervical cancer. Takagi et al. (12) reported that the use of the SUV_{max} value contributed to the differentiation between benign and malign ovarian tumors, as well as between uterine myomas and uterine sarcomas.

In our study, no significant correlation was found between the mean SUV_{max} values of the primary tumor and lymph node metastasis, histopathological subtype, deep myometrial invasion, LVSI or cervical stromal involvement in patients diagnosed with endometrial cancer. When evaluated according to risk groups, the mean SUV_{max} values were found to be similar to each other and were not statistically significant. No significant relationship was found in the present study between the mean SUV_{max} values of the primary tumor and histological type, FIGO stage or lymph node metastasis in patients with cervical cancer. Due to the small number of patients with uterine sarcoma, the relationship between the mean SUV_{max} value of the primary tumor and other study parameters could not be clearly determined. Finally, in the patients with ovarian cancer in the present study, the lesion-based mean SUV_{max} values were associated with lymph node metastasis.

While the SUV_{max} values have been related to lymph node metastasis, FIGO stage, histological subtype, deep myometrial invasion and risk groups in some studies, no such associations have been noted in others. Relatively new metabolic parameters such as MTV and TLG have been shown to provide a better diagnostic yield than SUV_{max}, and their use could potentially provide better results in the present study.

In the present study, the demographic characteristics of the patients were similar to those of other studies in literature. It is well-known that physiological ^{18}F-FDG uptake may be observed in the endometrium, which changes cyclically in the premenopausal period (13). Ovarian ^{18}F-FDG uptake may also be physiological in the premenopausal period, but is considered abnormal in the postmenopausal period (14). The rates of postmenopausal and premenopausal patients were similar in the present study and similar studies in the literature. In the present study, ^{18}F-FDG uptake was not evaluated separately in postmenopausal and premenopausal patients, and this limitation may have influenced the assessment of the association between the mean SUV_{max} values and lymph node metastasis.

One of the strongest points of our study is that the effectiveness of PET/CT was evaluated separately for four gynecological cancer types and was specifically investigated also for uterine sarcomas.

Study Limitations

The present study has some limitations, the first of which relates to the low number of patients, especially those with cervical cancer, uterine sarcoma, and ovarian cancer. And, the absence of a balanced distribution of some study variables among some cancer groups is another limitation. Secondly, the effect of SUV_{max} values on treatment outcomes, recurrence, progression-free survival or overall survival was not investigated. Thirdly, relatively new metabolic parameters such as MTV and TLG were not evaluated in the present study. Finally, the only non-invasive imaging method utilized in the study was PET/CT.

Conclusion

PET/CT was found to provide the best diagnostic yield in uterine sarcomas, and the mean SUV_{max} values of metabolic parameters were only associated with lymph node metastasis in ovarian tumor, but not in other gynecologic malignancies.

Ethics

Ethics Committee Approval: Ethics committee approval dated 19/12/2017 and numbered 785 was obtained from University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee before the study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.T., V.M., Concept: N.T., V.M., G.D., Design: N.T., V.M., G.D., Data Collection

or Processing: Y.K., D.Y.Y.K., H.C.U., Analysis or Interpretation: Y.K., D.Y.Y.K., H.C.U., Literature Search: Y.K., D.Y.Y.K., H.C.U., Writing: Y.K., D.Y.Y.K., G.D.

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ORIGINAL RESEARCH

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Evaluation of Complicated and Uncomplicated Brucellosis Cases in the Endemic Region

Endemik Bölgede Komplike ve Komplike Olmayan Bruselloz Olgularının Değerlendirilmesi

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Abstract

Objective: It was aimed to investigate the clinical and laboratory changes in complicated and uncomplicated brucellosis cases.

Method: Within the scope of the study, 268 brucellosis patients (aged ≥18 years) hospitalized in the infectious diseases unit or seen in outpatient clinics were evaluated retrospectively. The complicated and uncomplicated brucellosis cases were assessed.

Results: In the study, 268 brucellosis patients were evaluated and it was observed that 80.7% of the patients consumed fresh cheese. Also, 93.2, 90.8, 88.8 and 84% of the cases had symptoms such as arthralgia, weakness, sweating and fever, respectively. Anemia, leukopenia, leukocytosis, thrombocytopenia and increased C-reactive protein (CRP) were also detected in 25.9, 4.9, 7.2, 9.2 and 60.2% of patients, respectively. It was found that 32.4% of the patients developed complications, and the complications were osteoarticular in 59 patients (67.8%), genitourinary in 17 (19.5%) and hematological in three (3.44%) cases. The complications were more common in male patients. CRP and neutrophil/lymphocyte ratios (NLR) were also found higher in complicated cases.

Conclusion: Since values such as gender, CRP and NLR were significantly different in complicated brucellosis cases from the non-complicated group, it is considered that a significant increase may have been detected in infection parameters due to the longer exposure time to the microorganism. For this reason, early detection of complications and timely diagnosis play a vital role to improve the prognosis.

Keywords: Brucellosis, complication, C-reactive protein, neutrophil/lymphocyte ratio

Öz

Amaç: Komplike ve komplike olmayan bruselloz olgularında klinik ve laboratuvar değişikliklerin araştırılması amaçlandı.

Yöntem: Çalışmada enfeksiyon hastalıkları biriminde yatan veya polikliniklerde izlenen 268 bruselloz hastası (≥18 yaş) retrospektif olarak değerlendirildi. Komplike ve komplike olmayan bruselloz olguları incelendi.

Bulgular: Çalışmada 268 bruselloz olgusu değerlendirilmiş olup; hastaların %80,7'sinde taze peynir tüketimi mevcuttu. Ayrıca olguların sırasıyla %93,2, %90,8, %88,8 ve %84'ünde artralji, halsizlik, terleme ve ateş gibi semptomlar vardı. Anemi, lökopeni, lökositoz, trombositopeni ve C-reaktif protein (CRP) artışı da sırasıyla hastaların %25,9, %4,9, %7,2, %9,2 ve %60,2'sinde saptandı. Hastaların %32,4'ünde komplikasyon geliştiği, 59 hastada (%67,8) osteoartiküler, 17 hastada (%19,5) genitoüriner ve üç olguda (%3,44) hematolojik komplikasyon geliştiği saptandı. Komplikasyonlar erkek hastalarda daha sıktı. Komplike olgularda CRP ve nötrofil/lenfosit oranları da (NLR) daha yüksek bulundu.

Sonuç: Komplike bruselloz olgularında cinsiyet, CRP ve NLR gibi değerlerin komplike olmayan gruptan anlamlı olarak farklı olması nedeniyle, mikroorganizmaya maruz kalma süresinin daha uzun olmasından dolayı enfeksiyon parametrelerinde anlamlı bir artış saptanmış olabileceği düşünülmektedir. Bu nedenle komplikasyonların erken tespiti ve zamanında teşhis, prognozu iyileştirmede hayati bir rol oynamaktadır.

Anahtar kelimeler: Bruselloz, C-reaktif protein, komplikasyon, nötrofil/lenfosit oranı

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Introduction

Although brucellosis, known as a disease since ancient times, has been eradicated in various parts of the world, it still keeps being witnessed in many continents and 500,000 new cases are reported to be seen per annum by the World Health Organization (1-4). Basically, leading to infections in animals, *Brucella* spp. is transmitted to humans as a result of direct/indirect contact with contaminated milk/dairy products or infected animals, and can mimic many diseases by affecting various organs of the body (5-10). The condition with non-specific symptoms, such as fever, sweating, malaise and anorexia, appears to be an acute complication or chronic brucellosis (8,9). In this study, 268 cases of brucellosis were retrospectively investigated, primarily to guide clinicians working in areas where brucellosis is endemic, and to contribute to the literature by comparing the clinical and laboratory findings obtained as a result of the study with other brucellosis series.

Materials and Methods

The study was conducted between 1st January 2018 and 31st December 2018 in the departments of infectious diseases and clinical microbiology. A total of 268 brucellosis patients who were hospitalized in the infectious diseases department or seen in their outpatient clinics were evaluated retrospectively. However, since only adult patients were followed in our clinic, patients under the age of 18 years and patients over the age of 18 years who applied to the clinic more than once were excluded from the study. The demographic, epidemiological, clinical and laboratory findings, the methods used to diagnose the disease, antimicrobial regimens and duration of the treatment used in the treatment process were obtained from the patients' hospital records. Besides, as radiological imaging techniques, additional imaging methods such as X-ray, ultrasonography (USG), magnetic resonance imaging and echocardiography were peformed, as well as cranial computed tomography performed in all neurobrucellosis cases.

The cases of brucellosis were diagnosed in light of the following criteria in the presence of positive clinical signs and symptoms:

1. The determination through the standard tube agglutination (STA) (Cromatest, Linear Chemicals, Spain) as titer ≥1/160 and/or,

2. Observing a two-fold increase in two serological evaluations performed at 2 or 3-week intervals after the symptoms compatible with brucellosis started and/or,

3. The methods of isolating the microorganisms with automated culture identification system BACTEC 9240 (Becton-Dickinson, Sparks, MD, USA) in blood cultures, tissue samples or other body fluids and defining the microorganisms as *Brucella* spp. After positive signals passage was made from the blood culture bottles, gram stains and biochemical tests were performed from the colonies grown as a result of incubation for 48 hours. *Brucella* bacteria were identified as "catalase and oxidase positive Gram-negative *Coccobacilli*".

All of the cases were subdivided as acute brucellosis (0-2 months), subacute brucellosis (2-12 months) and chronic brucellosis (>12 months) according to the duration of symptoms (8).

Descriptions of Complicated and Non-complicated Patients

As a result of imaging and physical examination, the detection of infection findings in a certain anatomical region of a patient was defined as "complicated brucellosis". The definitions made according to the area of the organ involvement are as follows.

1. Osteoarticular involvement: The involvement was defined as the presence of inflammatory manifestations in any joint, such as increased temperature, skin erythema, pain, edema or loss of function. The diagnosis of osteoarticular involvement was supported by joint culture sampling and radiological examinations according to the osteoarticular region of involvement.

2. Neurobrucellosis: The condition was defined as the presence of STA positivity in any titer along with abnormal cerebrospinal fluid (CSF) findings, the isolation of *Brucella* spp. in the blood or bone marrow culture of a patient with abnormal CSF findings or the isolation of *Brucella* spp. in CSF of a patient with suspected brucellosis findings.

3. Gastrointestinal (GI) involvement: GI involvement was defined as a four-fold increase in aspartate aminotransferase and alanine aminotransferase values which cannot be explained by a different etiological condition, and/or the condition of total bilirubin value >2.5 g/dL.

4. Hematological involvement: The involvement was defined as the hematological abnormalities seen in the laboratory findings and the clinical findings -such as epistaxis, bleeding, petechia, purpura, disseminated intravascular coagulation and thrombophlebitis- witnessed upon excluding the asymptomatic cytopenias with weak symptoms or coagulation disorders.

5. Genitourinary involvement: In patients with brucellosis, the epididymal and testicular sensitivity accompanied by arthralgia and arthritis, skin erythema/inflammation in the scrotum and detection of epididymo-orchitis on USG were defined as genitourinary involvement.

6. Obstetric involvement: Challenges such as spontaneous abortus, early membrane rupture (EMR), intrauterine fetal death (IUF), the threat of abortus or development of preterm delivery during/after the treatment of brucellosis among brucellosis patients with pregnancy or the diagnosis of brucellosis in addition to spontaneous abortus, EMR, IUF, the threat of abortus or preterm delivery within such an obstetric condition, or the production of *Brucella* spp. in the blood culture of the newborn were defined as obstetric involvement.

7. Mucocutaneous involvement: Due to the immune response developing due to brucellosis, mucocutaneous involvement was defined as witnessing the features such as erythematous papular lesions, purpura, dermal cysts and Steven-Johnson syndrome in the early stage of the disease.

Modalities of Treatment

The standard combination treatment of doxycycline (100 mg every 12h) and rifampicin (600 mg every 24 h) was administered to the patient groups without complications for 6 weeks. Furthermore, an additional treatment modality was also developed as streptomycin (1g every 24 h) for 14-21 days at the initial treatment for the cases with osteoarticular involvement. In neurobrucellosis patients, however, intravenous ceftriaxone (2 g every 12 h) or trimethoprim sulfamethoxazole (TMP-SXT) (160/800 every 12 h) treatment was also added to the standard treatment. Other treatment regimens including ciprofloxacin or TMP-SXT (160/800 every 12 h) were preferred for the patients developing lactation, GI intolerance or other side effects, including allergic reactions such as rash or drug-induced hematological changes. The drug combinations and duration of treatment were determined according to some parameters such as the patient's anatomical region involved, response to treatment, side effects, and physician's approach. Patients diagnosed with complicated brucellosis were allowed to receive treatment for 3 months, 6 months or 1 year depending on the area of involvement. While the patients with the poor health conditions were treated and followed up by hospitalization, all of the out-patients were followed up through hospital visits every two weeks. In addition, all patients were followed up for one year after antibiotic treatment was completed. No relapse or recurrence was detected in any of these patients.

Ethics committee approval: The approval was obtained from the Non-Invasive Research Ethics Committee of the University of Health Sciences Turkey, Van Training and Research Hospital (date: 21st March 2019 and no: 2019/06).

Statistical Analysis

Statistical analyses of the study findings were performed with the Statistical Package for the Social Sciences Software Version 18.0 (SPSS Inc., Chicago, IL, USA). In addition, the appropriateness of laboratory parameter levels to the normal distribution was investigated using visual (histogram and probability graphics) and analytical (the Kolmogorov-Smirnov test) methods. For the comparisons between both groups, the chi-square, Fisher's Exact and Mann-Whitney U tests were used and if a p-value was lower than 0.05, it was considered to be significant.

Results

Of the patients included in the study, 60.4% (162) were male and 39.6% (106) were female. It was found that the development of complications was higher in males. While the mean age of all patients in the study was 38.7±14.5 years, the mean age was 37.2±13.6 years in complicated cases. When the relationship between the development of complications and age was examined, no significant relationship was found. The findings of the overall patients were arthralgia (93.2%), fatigue (90.8%), sweating (88.8%) and fever (84%), low-back pain (55.2%), and weight loss (51.6%). It was observed that symptoms such as arthralgia (96.4%), fever (90.2%), weight loss (69.9%) and low back pain (66.3%) were higher in patients with complications compared to uncomplicated cases. It was determined that 84.8% of the cases in the study had acute brucellosis and 1.3% had chronic brucellosis. Subacute brucellosis was more common in 20.0% of complicated cases. In all patients, 60.2% CRP (>8 mg/L), 34.3% ESR (>30 mm/h), 29.1% elevated transaminase, 25.9% anemia, 7.2% leukocytosis, 9.2% thrombocytopenia and 4.9% leukopenia were measured. Unlike similar studies, anemia, leukopenia, leukocytosis, thrombocytopenia, CRP and ESR were found to be higher in complicated patients. The findings are presented in Table 1.

STA was found to be 160 and above in all patients. *Brucella* spp. was isolated in 76.3% of 38 patients who underwent blood culture testing. The number of complicated and non-complicated patients was determined as 87 and 181,

Table 1. Socio-demographic, clinical and laboratory data of the patients

Characteristics		Complicated patients, n (%)	Non-complicated patients, n (%)
Age (yrs), mean ± SD		37.2±13.6	39.5±14.9
Symptoms, n, %	Fever (n=250)	74 (90.2)	136 (80.9)
	Sweating (n=249)	72 (87.8)	149 (89.2)
	Fatigue (n=249)	74 (90.2)	152 (91.0)
	Low-back pain (n=250)	55 (66.3)	83 (49.7)
	Arthralgia (n=251)	80 (96.4)	154 (91.7)
	Weight loss (n=250)	58 (69.9)	71 (42.5)
Disease stages	Acute	63 (78.7)	144 (87.8)
	Subacute	16 (20.0)	18 (10.9)
	Chronic	1 (1.3)	2 (1.3)
Laboratory findings, n, %	Anemia (Hgb g/dL) (women <12 and men <14)	27 (31.8)	40 (22.9)
	Leukopenia (<4.000/mm^3) (n=263)	5 (5.8)	8 (4.5)
	Leukocytosis (>12.000/mm^3) (n=263)	10 (11.6)	9 (5.1)
	Thrombocytopenia (<150.000/mm^3) (n=260)	10 (11.6)	14 (8.0)
	ESR (>30 mm/h) (n=216)	26 (42.6)	48 (30.9)
	CRP (>8 mg/L) (n=266)	70 (80.5)	90 (50.2)
	Transaminase height (AST >30 IU/mL, n=261) ALT 30>IU/mL, n=262)	24 (28.9)	52 (29.2)

ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, STA: Standard tube agglutination, Hgb: Hemoglobin

respectively. The rates of osteoarticular, genitourinary and hematological complications were also found to be 67.8% (n=59), 19.5% (n=17) and 3.44% (n=3), respectively (Table 2).

The combination of doxycycline (D) and rifampicin (R) was frequently preferred in complicated and non-complicated patients. In addition, it was determined that regimens containing streptomycin or gentamicin were frequently preferred combinations in both groups of patients (Table 3).

No deaths were observed in the brucellosis patients and all patients successfully completed the treatment process. The characteristic and laboratory parameters of the patients who developed complications are shown in Table 4. Accordingly, the complications were detected to develop more frequently in male patients in the study. In addition, CRP (>8 mg/dL) and NLR were also found to be higher in the cases with complications.

Table 2. Distribution of complications

Complications		n (%)
Osteoarticular (Spondylitis/spondylodiscitis/arthritis/tendinitis/bursitis etc.)		59 (67.8)
Genitourinary (Epididymo-orchitis/epididymitis/orchitis)		17 (19.5)
CNS*	Meningitis	2 (2.29)
	Brain abscess	1 (1.14)
Hematologic		3 (3.44)
Obstetric	Abortus	2 (2.29)
	Premature birth	1 (1.14)
Mucocutaneous		1 (1.14)
Hepatobiliary		1 (1.14)
Total		87

CNS*: Central nervous system

Discussion

Brucellosis, which presents with non-specific clinical findings and laboratory changes, complicates the treatment of patients by causing organ involvement. Many organs can also be affected by the complications arising from brucellosis. The involvements may develop in various organs due to brucellosis at different rates ranging from less than 1% to over 50% (8). In previous studies conducted to date, the osteoarticular, hematological, GI and genitourinary involvements have been seen at varying rates, such as 21.3-68%, 22-55%, 2.5-51% and 1-20%, respectively (11-13). In this study, 32.4% of the patients were complicated and 3.44% of the patients had hematological, 67.8% had osteoarticular, 19.5% had genitourinary involvement (Table 2). Moreover, it was revealed that different from osteoarticular involvement, which is frequently reported in other studies, various organ involvements ranging from obstetric and mucocutaneous involvement, which are

more rarely encountered, could develop. This fact shows that complicated brucellosis cases can be encountered not only by infection physicians, but also by clinicians working in different specialties and it is an important issue for providing appropriate treatment for patients.

Brucellosis is clinically staged according to the time of symptom onset (8). Complicated brucellosis is frequently seen in subacute and chronic brucellosis stages (8). The longer the contact time with the microorganism, the higher the probability of the disease being complicated. As it is known that the immune system is of a dynamic nature in which the regulatory molecules -such as cytokines composed of lymphocytes and granulocytes including neutrophils, eosinophils, basophils, mast cells, dendritic cells, monocyte-macrophages and phagocytes- are active (14). Neutrophils constitute the first line of defense mechanism against the infectious agents and among the target of neutrophils are bacteria, fungi, protozoa, viruses, and virus-infected cells (15). In recent years, there has been an increasing interest in the rates of leukocyte subgroups in reflecting the inflammation level in chronic and several acute diseases (16). Routine laboratory tests alone are not sufficient for the diagnosis of brucellosis cases, and in addition, complete blood count (CBC), ESR, CRP and liver function tests can be used to help support the diagnosis (9). The lipopolysaccharide structure on the cell surface of *Brucella* species prevents the formation of an immune response or the triggering of the alternative complement system (17). This situation enables the microorganism to easily invade tissues such as the liver, lymph node, and bone marrow and make laboratory changes (18). Laboratory findings such as leukocytosis (especially in those with focal complications), leukopenia, thrombocytopenia, anemia, ESR, CRP and increased liver enzymes can be seen in brucellosis (11,19). As seen in Table 1, hematological changes were observed more prominently in this study, especially in complicated brucellosis cases.

Neutrophil, lymphocyte, monocyte, and platelet counts are the components of CBC parameters and are routinely used in the follow-up of brucellosis patients. NLR is a simple and

Table 3. Distributions of treatment regimes

Patient groups	Treatment protocols	n (%)
Non-complicated cases	D+R	140 (77.3)
	S (14/21) + D + R	6 (3.3)
	G (7) + D + R	12 (6.6)
	Other combinations (TMP-SXT+D. TMP-SXT+R. D+CIPRO. D+R+TMP-SXT. TMP-SXT+RIF. D+R+CIPRO. D+G+TMP-SXT. CRO+SXT. D+SXT+S)	23 (12.8)
Complicated cases	D+R	30 (34.5)
	S (14/21) +D+R	28 (32.2)
	G (7) +D+R	17 (19.5)
	Other combinations (TMP-SXT+D. TMP-SXT+R. D+CIPRO. D+R+TMP-SXT. TMP-SXT+RIF. D+R+CIPRO. D+G+TMP-SXT. CRO+TMP-SXT. D+TMP-SXT+S. CRO+D+R)	12 (13.8)

CIPRO: Ciprofloxacin, CRO: Ceftriaxone, D: Doxycycline, G: Gentamycin, R: Rifampicin, S: Streptomycin, TMP-SXT: Trimethoprim sulfometaxazole

Table 4. The effects of patients' laboratory findings and general characteristics on the development of complications

All cases	Complicated mean, n	SD (%)	Non-complicated mean, n	SD (%)	p
Gender					
Male	60	37.0	102	63.0	0.048
Female	27	25.5	79	74.5	
Age (yrs)	37.2	13.6±1.5	39.5	14.9±1.1	0.289
CRP	51.6	58.6±6.3	22.9	35.4±2.6	**<0.001**
Sedimentation	27.9	20.6±2.6	21.9	17.4±1.4	0.060
AST	39.6	45.8±5.1	31.1	27.5±2.1	0.778
ALT	45.2	60.1±6.6	32.3	27.9±2.1	0.716
Platelets	262534	116860	254454	77952	0.711
Hgb	13.6	1.8±0.2	14.0	1.9±0.1	0.346
MPV	9.4	1.3±0.1	9.4	1.2±0.1	0.760
Neutrophil/lymphocyte	2.26	2.25±0.25	1.84	2.07±0.16	**0.007**
Monocyte/lymphocyte	0.23	0.13±0.01	0.25	0.41±0.03	0.152
Platelet/lymphocyte	114.4	67.8±7.4	111.5	49.5±3.9	0.802

ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, Hgb: Hemoglobin, MPV: Mean platelet volume, SD: Standard deviation

inexpensive parameter that can be used in many areas to indicate the inflammatory or infectious pathologies and postoperative complications as a strong prognostic factor in the classification of major cardiac events and various types of cancer (20-22). In the study where the association of brucellosis and healthy volunteers with hematological parameters was investigated by Olt et al. (23), an important correlation was found between hemoglobin and NLR through the receiver operating characteristic curve analysis. In the study conducted by Kayaaslan et al. (10) on the patients with complicated brucellosis, the rates of anemia ($p<0.001$), increased CRP ($p=0.005$), ESR ($p=0.021$), and positivity of blood culture ($p=0.014$) were determined to be more frequent in complicated patients (10). In the study of Tekin et al. (24) -comparing the inflammatory markers of adult and pediatric brucellosis patients with the control group- the NLR and PLR values were significantly lower in adult patients than those in the control group subjects.

Based on the results of the above studies, it can be suggested that NLR and PLR ratios are inflammatory markers that can be used in brucellosis patients. This situation is also valid for MPV value investigated for many systemic inflammatory diseases including brucella (25). Changes in the release of proinflammatory cytokines by affecting macrophages can affect the number and structure of platelets (26). In some studies, it is stated that platelet count, MPV, neutrophil and monocyte are important markers in brucellosis (27,28). It was aimed to investigate the role of hematological parameters in complicated brucellosis cases. In addition, changes in MPV, NLR, MLR and PLR values and abnormalities in anemia, CRP, ESR and other laboratory parameters were also investigated. Anemia, thrombocytopenia, leukocytosis and leukopenia were more common in complicated cases, but this was not statistically significant. While it was found that complicated cases were more common in male patients ($p<0.05$), it was also observed that CRP and NLR values were higher in complicated cases ($p<0.05$). In the light of the data obtained, it would be appropriate to determine and support the cutoff values for NLR, MLR and PLR with different studies on brucellosis cases.

Study Limitations

The limitations of our study are;

1. Its retrospective nature,

2. The fact that a group having all complications had to be formed because there were not enough cases to separately evaluate each complication due to brucella in groups.

Conclusion

In this study, the rate of complicated brucellosis cases was observed to be higher among the male gender, as well as findings of higher CRP and NLR values. Moreover, it was found that NLR value was an important parameter in this patient group in addition to male gender and CRP values in complicated brucellosis cases. In previous studies, it has been emphasized that there is a relationship between the development of complications in brucellosis and the exposure time to the microorganism. As a result of these studies, this parameter is taken into consideration in the clinical staging of the disease. In addition to previous studies, it was revealed that the NLR value was a useful parameter as well as the exposure time to the microorganism in the clinical classifications of brucellosis in this study. However, since the study was performed at a single center and no cut-off value was detected in NLR values in cases with brucellosis, we consider that our study findings cannot be generalized to the other regions in Turkey and further studies are needed to support the data.

Ethics

Ethics Committee Approval: The approval was obtained from the Non-Invasive Research Ethics Committee of the University of Health Sciences Turkey, Van Training and Research Hospital (date: 21st March 2019 and no: 2019/06).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: M.S.S., D.B., D.B.Ö., Design: M.S.S., D.B., Data Collection or Processing: M.S.S., Analysis or Interpretation: D.B.Ö., Literature Search: M.S.S., Writing: M.S.S., D.B., D.B.Ö.

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ORIGINAL RESEARCH

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The Relationship Between Thyroid Dysfunctions and Symptom Severity and Functionality in Patients with Carpal Tunnel Syndrome

Karpal Tünel Sendromu Olan Hastalarda Tiroit Fonksiyon Bozukluklarının Semptom Şiddeti ve İşlevsellik ile İlişkisi

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Abstract

Objective: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy caused by compression of the median nerve in the wrist. This study aimed to examine the relationship between thyroid dysfunctions and symptom severity and functional status in patients with CTS.

Method: Forty-four consecutive patients who were clinically and electrophysiologically diagnosed with CTS and met the inclusion criteria were included in the study. Demographic characteristics, thyroid hormone levels and electroneuromyography results of the patients were recorded. Boston questionnaire-symptom severity scale (BQ-SSS) and Boston questionnaire-functional status scale (BQ-FSS) were used to evaluate symptom severity and functionality, respectively. The patients were divided into two groups: Group 1 (n=25) included CTS patients with normal thyroid function and group 2 (n=19) included CTS patients with thyroid dysfunction.

Results: There was no significant difference between the two groups in terms of age, gender, body mass index, symptomatic side, electrophysiologically determined CTS severity, and BQ-FSS (all p>0.05). The mean symptom duration was 10.64±3.08 months in group 1 and 24.63±14.06 months in group 2 (p<0.001). The mean BQ-SSS score was 36.48±5.85 in group 1 and 42.00±8.10 in group 2 (p=0.013).

Conclusion: It was observed that CTS symptoms were more severe and symptom duration was longer in CTS patients with thyroid dysfunction. Therefore, detection and treatment of thyroid dysfunctions in patients with CTS may be beneficial in improving symptoms.

Keywords: Functional status, karpal tunnel syndrome, thyroid hormones

Öz

Amaç: Karpal tünel sendromu (KTS) el bileğinde medyan sinirin sıkışması ile ortaya çıkan en sık rastlanan tuzak nöropatidir. Bu çalışma, KTS'li hastalarda tiroid fonksiyon bozuklukları ile semptom şiddeti ve fonksiyonel durum arasındaki ilişkiyi incelemeyi amaçladı.

Yöntem: Çalışmaya klinik ve elektrofizyolojik olarak KTS tanısı konan ve dahil edilme kriterlerini karşılayan 44 ardışık hasta alındı. Hastaların demografik özellikleri, tiroid hormon düzeyleri ve elektronöromiyografi sonuçları kaydedildi. Semptom şiddeti ve işlevselliği değerlendirmek için sırasıyla Boston anketi-semptom şiddet ölçeği (BQ-SSS) ve Boston anketi-fonksiyonel durum ölçeği (BQ-FSS) kullanıldı. Hastalar iki gruba ayrıldı: Grup 1 (n=25) normal tiroid fonksiyonu olan KTS hastalarını ve grup 2 (n=19) tiroid fonksiyon bozukluğu olan KTS hastalarını içerdi.

Bulgular: İki grup arasında yaş, cinsiyet, vücut kitle indeksi, semptomatik taraf, elektrofizyolojik olarak belirlenen KTS şiddeti ve BQ-FSS açısından fark yoktu (tümü p>0,05). Ortalama semptom süresi grup 1'de 10,64±3,08 ay ve grup 2'de 24,63±14,06 aydı (p<0,001). Ortalama BQ-SSS skoru grup 1'de 36,48±5,85 ve grup 2'de 42,00±8,10 idi (p=0,013).

Sonuç: Tiroit fonksiyon bozukluğu olan KTS'li hastalarda, KTS semptomlarının daha şiddetli ve semptom süresinin daha uzun olduğu görüldü. Bu nedenle KTS'li hastalarda tiroit fonksiyon bozukluklarının saptanması ve tedavisi semptomların iyileştirilmesinde faydalı olabilir.

Anahtar kelimeler: Fonksiyonel durum, karpal tünel sendromu, tiroid hormonları

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Introduction

Carpal tunnel syndrome (CTS), known as neuropathy due to entrapment of the median nerve at the wrist level, is one of the most common peripheral entrapment neuropathies. Its prevalence in the general community varies between 3.7% and 5.8% (1).

CTS presents with pain, numbness and tingling localized in the first three fingers and the lateral side of the fourth finger, and symptoms that can progress to loss of strength in some patients (2). Therefore, it affects daily activities and quality of life in many patients and may cause loss of workforce (3). CTS is generally idiopathic (4). However, conditions such as obesity, osteoarthritis, Colles' fractures, amyloidosis, acromegaly and rheumatoid arthritis may facilitate the development of CTS by disrupting the structure of the joint or metabolic diseases such as diabetes mellitus causing deterioration in the structure of the nerve (5). In addition, it has been reported that thyroid dysfunctions are effective in the development of CTS (6). Nerve conduction studies found that 29% of hypothyroid patients were accompanied by CTS. It has been suggested that myxedema and accumulation of pseudo-mucinous material play a role in median nerve compression in hypothyroidism (7). Moreover, Roquer and Cano (8) have defined CTS associated with hyperthyroidism. However, the relationship of thyroid dysfunction with symptom severity and functional status in patients with CTS is not clear.

Few studies have examined the effect of thyroid dysfunction on CTS operation outcomes, but different results have been revealed (9,10). In this study, it was aimed to examine the relationship between thyroid dysfunctions and symptom severity and functional status in patients with CTS.

Materials and Methods

This study was approved by Ankara City Hospital the Local Ethics Committee of the Medical Center (E1-22-2412). Informed consent was obtained from all participants included in the study. The study was conducted in accordance with the Declaration of Helsinki. In this study, patients who applied to Orthopedics and Traumatology outpatient clinic of a tertiary hospital between January 2021 and December 2021 and were diagnosed with CTS were reviewed retrospectively.

The study was conducted with 44 patients who met the inclusion criteria. Patients who were diagnosed with CTS by anamnesis, physical and electrophysiological examination, aged between 18 and 65 years, whose thyroid hormone levels were evaluated and who had the necessary data for the study were included. Patients who received any treatment for CTS in the last three months, had a known chronic disease history (diabetes mellitus, Colles' fracture, amyloidosis, acromegaly, rheumatoid arthritis, etc.), were pregnancy, and had missing demographic and clinical data were excluded. Patients' age, gender, body mass index (BMI), symptomatic side, symptom duration, thyroid hormone levels [thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4)], electroneuromyography (ENMG) results, and symptom severity and functional status evaluated with the Boston questionnaire were recorded in the patient follow-up form created by the authors.

The thyroid hormone levels of the patients at the time of admission were recorded. Patients were divided into two groups according to their TSH, fT3 and fT4 values as euthyroid group (group 1) and thyroid dysfunction group (hypothyroid or hyperthyroid, group 2). Decreased fT3 and/or fT4 hormone levels with increased TSH levels were defined as hypothyroidism; increased fT3 and/or fT4 hormone levels with decreased TSH level were defined as hyperthyroidism. Normal thyroid hormone levels were defined as euthyroidism. Subclinical hypothyroidism and subclinical hyperthyroidism were included in the group with thyroid dysfunction. Increased TSH and normal fT3 and fT4 hormone levels were defined as subclinical hypothyroidism; decreased TSH and normal fT3 and fT4 hormone levels were defined as subclinical hyperthyroidism (11). The reference range of thyroid hormones was as follows: 0.55-4.78 mU/L for TSH, 2.3-4.2 ng/L for fT3, and 0.89-1.76 ng/dL for fT4.

Electrophysiological evaluation was performed using Nihon Kohden 4-channel (China) ENMG device according to American Association of Neuromuscular and Electrodiagnostic medicine diagnostic criteria. CTS was classified as mild, moderate and severe according to the severity of compression of the median nerve in the electrophysiological evaluation (12). The Boston questionnaire assesses symptom severity and functional status in patients with CTS and consists of two parts: Symptom severity scale (BQ-SSS) and functional status scale (BQ-FSS) (13). This questionnaire was developed by Levine et al. (13), and its Turkish validity and reliability was demonstrated by Sezgin et al. (14). BQ-SSS is evaluated with 11 questions and BQ-FSS with 8 questions. Each question is

scored between 1 and 5. The mean score is calculated by dividing the total score by the number of questions. The mean score is determined separately for symptom severity and functional status. High scores correlate with symptom severity and impaired functionality (13).

The estimation of sample size was made using the G Power software (3.1.9.4). It was assigned that based on the study of Roshanzamir et al. (9), the minimum number of patients for each group was 17, with 95% power and 5% type I error probability.

Statistical Analysis

The research data were uploaded to the computer and analyzed via "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". The Kolmogorov-Smirnov test was performed to obtain whether the variables were normally distributed. Mean ± standard deviation or median and minimum-maximum values were used for continuous data for normally or abnormally data, respectively. Frequency (percent) was used for categorical data. The chi-square test was performed to compare categorical variables. The Student's t-test or Mann-Whitney U test was used to compare continuous variables for normally or abnormally distributed data, respectively. A p-value <0.05 was considered statistically significant.

Results

The mean age of 44 patients included in the study was 55.47±10.85 years, 31 (70.5%) were female and 13 (29.5%) were male. The symptomatic side was right in 24 patients (54.5%), left in 19 patients (43.2%) and bilateral in 1 patient (2.3%). The mean symptom duration was 16.68±11.71 months and BMI was 32.42±5.20 kg/m^2. In ENMG examination, mild CTS was found in 3 (6.8%), moderate in 12 (27.3%), and severe in 29 (65.9%) patients. The mean BQ-SSS score of the patients was 38.79±7.33 and the mean BQ-FSS score was 26.39±5.29. Twenty-five (56.8%) patients were euthyroid (group 1, n=25) and 19 (43.1%) patients had thyroid dysfunction (group 2, n=19).

There was no significant difference between the two groups in terms of age, gender, BMI, symptomatic side, severity of CTS, and BQ-FSS (all p>0.05). The mean symptom duration was 10.64±3.08 months in group 1 and 24.63±14.06 months in group 2 (p<0.001). The mean BQ-SSS score was 36.48±5.85 in group 1 and 42.00±8.10 in group 2 (p=0.013). Table 1 shows the demographic and clinical parameters of the two groups.

Discussion

This study compared the functional status and symptom severity of CTS patients with and without thyroid dysfunction. It was observed that CTS symptoms were more severe and symptom duration was longer in patients with thyroid dysfunction. However, there was no difference between the two groups in terms of functional status and electrophysiologically determined nerve compression severity.

CTS is associated with various diseases and occupational risk factors (15,16). A number of studies have reported that thyroid dysfunctions increase the risk of peripheral neuropathy (8,17,18). In a study, 43% of patients with thyroid disfunction had mononeuropathy and polyneuropathy, and 30% had entrapment neuropathy (19). It has been stated that the most common neuropathy associated with hypothyroidism is CTS (17,20). In addition, in a study investigating the etiological factors of CTS, it was shown that 23.7% of patients with CTS had thyroid dysfunction (21). In this study, thyroid dysfunctions were found in 43.1% of the patients. We think that this high rate is due to the fact that only the patients whose thyroid function tests were examined were included in the study.

Previous studies have proposed various hypotheses regarding peripheral nerve compression in thyroid dysfunctions. It has been suggested that pseudomucinous substances accumulating in the median nerve sheath cause compression of the nerve in hypothyroidism (22). In addition, it has been reported that in hyperthyroidism, the nerve may be more open to compression and the carpal ligaments may be compressed more due to stiffness, and as a result, axonal function may be impaired (8). In fact, although it is known that thyroid dysfunctions are a risk factor for CTS, the relationship between thyroid dysfunctions and symptom severity and functional status in these patients is not clear because, in the literature, the data on this subject are limited and have revealed contradictory results (9,10). In a study examining the factors affecting symptom severity and functional status in patients with CTS, no effect of hypothyroidism on symptoms was found (10). In another study conducted in patients with CTS who were operated on, it was found that euthyroid patients had more improvement in their symptoms compared to hypothyroid patients (9). Our study determined that the symptoms of patients with thyroid dysfunction were more severe than those of euthyroid patients.

Table 1. Comparison of the demographic and clinical characteristics of the groups

	Group 1 (n=25)	Group 2 (n=19)	p
Age (years), mean ± SD	55.24±12.68	55.78±8.18	0.870
BMI (kg/m²), mean ± SD	32.31±5.33	32.58±5.17	0.875
Gender, n (%)			0.682
Male	8 (32)	5 (26)	
Female	17 (68)	14 (74)	
Symptom duration (months), mean ± SD	10.64±3.08	24.63±14.06	<0.001*
Symptom side, n (%)			0.228
Right	16 (64)	8 (42)	
Left	9 (36)	10 (53)	
Bilateral	0 (0)	1 (5)	
ENMG, n (%)			0.117
Mild	0 (0)	3 (16)	
Moderate	7 (28)	5 (26)	
Severe	18 (72)	11 (58)	
BQ-SSS, mean ± SD	36.48±5.85	42.00±8.10	0.013*
BQ-FSS , mean ± SD	26.32±3.37	26.50±7.29	0.914

SD: Standard deviation, BMI: Body mass index, ENMG: Electroneuromyography, BQ-BSSS: Boston questionnaire-symptom severity scale, BQ-FSS: Boston questionnaire-functional status scale, * Statistically significant, p-value <0.05

In this study, although symptom severity of patients with thyroid dysfunction increased significantly compared to those with euthyroidism, functionality did not differ between the two groups. However, Sharief et al. (19) showed a significant relationship between symptom severity and functionality in patients with CTS, and functionality decreased as symptom severity increased. The difference for the lack of functional status between the groups in this study may be due to the fact that the sensory conduction of the median nerve is mostly affected in patients with hyperthyroidism and hypothyroidism, as reported in the study of Somay et al. (23). In addition, although this is not significant, it may be due to the higher number of patients with moderate and severe CTS in the euthyroid group.

Studies have reported that the incidence of CTS increases with age (24,25). It has been mentioned that female gender is an independent risk factor for CTS (24). Moreover, it has been shown that BMI and obesity are strongly associated with CTS, and a one-unit increase in BMI increases the risk of CTS by 8% (26). In our study, there was no difference between the two groups in terms of age, gender and BMI values. Therefore, we think that the effect of these parameters on symptom severity is minimized and the relationship between thyroid functions and symptom severity is better reflected.

Suresh and Morris (27) stated that routine screening for thyroid dysfunction in patients with CTS was not necessary. In our study, although the mean age was similar in both groups, symptom duration was significantly longer in those with thyroid dysfunction. This result suggests that CTS presents with symptoms at an earlier age in patients with thyroid dysfunction, or that thyroid dysfunction may exist in those whose CTS symptoms occur at an early age. Therefore, we think that it may be useful to evaluate the thyroid functions of patients with CTS symptoms at an early age. However, prospective controlled studies are needed on this subject.

The current study showed that thyroid dysfunctions are associated with duration and severity of CTS symptoms. Therefore, this study may be beneficial for future research assessing whether symptoms regress after thyroid dysfunction treatment, whether surgery is still required in patients with thyroid dysfunction, or whether the post-surgical recovery of the patients with and without thyroid dysfunction is different.

Study Limitations

The main limitation of this study is its retrospective design and another limitation is the small number of patients included in the study.

Conclusion

In conclusion, the symptoms of CTS patients with thyroid dysfunction may be more severe than those with CTS alone. In addition, the symptoms of these patients may begin at an earlier age. Therefore, diagnosis and treatment of thyroid dysfunctions in patients with CTS may be beneficial in improving symptoms.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Ankara City Hospital the Local Ethics Committee of the Medical Center (E1-22-2412).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: N.K., Design: N.K., Data Collection or Processing: N.K., İ.K., Critical Revision of Manuscript: N.K., İ.K., Writing: N.K., İ.K.

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ORIGINAL RESEARCH

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Clinical and Imaging Consequences in Pediatric Head Trauma

Pediyatrik Kafa Travmalarında Klinik ve Görüntüleme Sonuçları

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Abstract

Objective: Cases of childhood head trauma constitute a common patient group in emergency departments and computed tomography (CT) is a frequently preferred imaging method for these cases. We aimed to retrospectively evaluate the cranial tomography results of pediatric patients, along with their admission clinics, hospitalization, and survival status.

Method: Four-hundred pediatric patients admitted to the emergency department with head trauma between 1 January 2019 and 31 December 2020 were included in this retrospective cross-sectional study. Demographic characteristics, trauma patterns, symptoms, clinical findings, CT findings, hospitalization, consultation, and survival status of the patients were recorded and evaluated.

Results: The mean age of evaluated patients was 6.87±4.96 (range 0-17) years. Among the 400 cases in the study, the most common type of trauma was falling in 260 (65%) cases, the most common symptom was headache in 99 (24.8%) cases, and 264 (66%) patients had CT imaging. Although 137 (34.3%) of all patients had no complaints, they had CT imaging. Although 56 (14%) of all patients did not have any complaints, there was a lesion in their tomography. While 288 patients had no CT lesions, the most common CT findings included 80 (20%) cephalohematomas and 21 (5.3%) fractures, respectively. The relationship of clinical symptoms with both the presence of radiological imaging and the presence of a lesion on CT was significant (p=0.001). Four (1%) patients were in the exitus group.

Conclusion: Tomography imaging is a very important examination in pediatric patients with head trauma and is directly related to symptoms, clinic, and mortality. There is a requirement for multicenter prospective studies on this subject to establish realistic and reliable algorithms for cranial CT preference in patients.

Keywords: Child, emergency department, head trauma, tomography

Öz

Amaç: Pediyatrik kafa travma olguları acil servislere sıklıkla başvurmaktadır ve bilgisayarlı tomografi (BT) bu olgularda sıklıkla tercih edilen bir görüntüleme yöntemidir. Acil serviste değerlendirilen kafa travmalı çocuk hastaların kraniyal tomografi sonuçlarını, klinik bulgularını hospitalizasyon ve sağkalım durumları eşliğinde retrospektif olarak değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif kesitsel çalışmaya 1 Ocak 2019 ile 31 Aralık 2020 tarihleri arasında acil servise kafa travması ile başvuran 400 çocuk olgu dahil edildi. Hastaların demografik özellikleri, travma mekanizmaları, semptomları, klinik bulguları, BT bulguları, yatış, çıkış, konsültasyon ve sağkalım durumları kaydedilerek değerlendirildi.

Bulgular: Çalışmadaki hastaların yaş ortalaması 6,87±4,96 (dağılım 0-17) idi. Çalışmadaki 400 olgu içerisinde, en sık görülen travma tipi 260 (%65) olgu ile düşme, en sık görülen semptom 99 (%24,8) olgu ile baş ağrısı idi ve 264 (%66) hastanın BT görüntülemesi vardı. Tüm hastaların 137'sinin (%34,3) şikayeti olmamasına rağmen BT görüntülemesi vardı. Tüm hastaların 56'sının (%14) herhangi bir şikayeti olmamasına rağmen tomografisinde lezyon vardı. İki yüz seksen sekiz hastanın BT lezyonu yokken, en sık BT bulguları sırasıyla 80 (%20) sefalohematom ve 21 (%5,3) kırık idi. Klinik semptomlarının hem radyolojik görüntüleme varlığı hem de BT'de lezyon varlığıyla ilişkisi anlamlıydı (p=0,001). Dört (%1) hastada mortalite gözlendi.

Sonuç: Kafa travmalı çocuk hastalarda BT görüntülemesi oldukça önemli bir tetkik olup, semptom, klinik ve mortalite ile direk ilişkilidir. Hastalarda kraniyal BT tercihi için gerçekçi ve güvenilir algoritmalar oluşturulması amacıyla bu konuda çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Acil servis, çocuk, kafa travması, tomografi

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Introduction

Trauma is a condition that is increasingly common in developed or developing countries and can cause serious health problems. Although it is seen at all ages, it is a public health problem that can occur with different etiologies, frequently in children, and it causes morbidity and mortality as well as serious loss of workforce (1). In trauma cases in childhood, head traumas are quite common with isolated or accompanying traumas. From an early age, children apply to emergency services due to head trauma for many reasons. In addition to traumas occurring during birth, fall cases in infancy and childhood, child abuse, and traffic, domestic and sports accidents at advanced ages are the most common causes of head trauma (1,2).

It is very important to determine whether patients who present to the emergency department with head trauma need emergency intervention and surgical treatment after a rapid evaluation (3). Trauma is a common cause of mortality in children, and head trauma is the most common cause of death among trauma cases (1,2).

Head injuries can cause many symptoms, depending on the type, severity, and location of the injury. The child's neurological symptoms may include loss of consciousness, headache, dizziness, nausea and vomiting, difficulty walking, slurred speech, amnesia, seizures, and hemiparesis or hemiplegia. Cranial computed tomography (CT) is generally preferred to evaluate the initial intracranial injury. Head trauma is the most common indication for CT imaging in the emergency department in pediatric patients (2,4,5). It is currently the gold standard for the emergency diagnosis of intracranial injuries. Although pathology is not observed in more than 90% of CT scans, signs of injury requiring acute intervention are detected in up to 1% of cases (6). It can be thought that most of the CTs expose patients to radiation unnecessarily and may be harmful in the long term (7,8). On the other hand, failure to perform clinically indicated CT imaging as a part of the evaluation of a patient with traumatic brain injury may result in an overlooked injury and direct and immediate harm to the patient (9).

In our study, we aimed to retrospectively evaluate the cranial tomography results of pediatric patients with head trauma in the emergency department, along with their admission clinics, hospitalization, and survival status.

Materials and Methods

Study Design and Population

This retrospective, observational and cross-sectional study included 400 patients aged 0-18 years, who applied to the emergency medicine clinic between January 01, 2019 and December 31, 2020 due to isolated head trauma. During this two-year period, 96,864 patients presented to our emergency department's trauma department, with 10,260 having a head injury statement. Among 4,102 pediatric patients aged 0-18 years, 400 patients with isolated head trauma without additional trauma and no missing data in the hospital registry system were included in the study. Demographic characteristics, trauma patterns, symptoms, clinical findings, tomography findings, hospitalization, discharge, consultation, and survival status of the patients were recorded and evaluated. The data were obtained from the hospital automation system. In the study, patients who fell from a height of 1 meter or less were considered "fall", and patients who fell from a height of 1 meter or more were considered "fall from height".

Patients under the age of 18 years, whose isolated head trauma admission records were specified in the patient file or forensic report records were evaluated. Patients with complete history, physical examination findings, radiological data, neurosurgery consultation information, hospitalization information, discharge or mortality status in the patient file and hospital automation system were included in the study. Patients aged 18 years and over, who had trauma in an additional localization (spinal, thoracic, abdominal, or extremities) other than head trauma, and whose patient file and data we evaluated in the hospital automation system were missing, were excluded from the study. In addition, cases with a history of congenital or acquired chronic central nervous system involvement were not included in the study.

Data about the patients' age, gender, type of trauma, clinical symptoms, clinical findings, whether CT examination was performed or not, the presence of a lesion in CT, the presence of neurosurgery consultation, hospitalization status and location, survival and mortality status were recorded. The patients were divided into five groups according to the type of trauma: "Fall, fall from height, traffic accident, collision, assault". The patients were divided into nine groups according to their clinical symptoms as "no, nausea vomiting, headache, dizziness, unconsciousness, sleep tendency, headache + nausea vomiting, headache + dizziness, seizure". The patients were divided into two groups according to whether they had radiological CT imaging or not. The patients were divided into eight groups as "no, cephalohematoma, fracture, contusion, epidural hemorrhage, fracture + epidural hemorrhage, fracture + pneumocephalus, fracture + multiple hemorrhage" according to the presence of lesions in CT imaging. In

addition, the patients were divided into two groups according to the presence of neurosurgery consultations, three groups as "discharge from emergency, service admission, intensive care hospitalization" according to their hospitalization status, and two groups as "healing/discharge, exitus" according to their survival status. The study was conducted in accordance with the Declaration of Helsinki, and Ethics Committee approval was received on November 18, 2021 with the number E-10840098-772.02-5921 from Medipol University. The study was made in accordance with the Declaration of Helsinki for human research. It meets ICMJE criteria, including all relevant legislation.

Statistical Analysis

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used in the analysis. The Kolmogorov-Smirnov test was utilized to assess the normality of continuous variables. In the study, categorical variables were presented as frequency (n) and percentage (%), whereas continuous variables were presented as mean ± standard deviation and median (smallest and largest) values. Since the age parameter of the variables did not follow a normal distribution, the Kruskal-Wallis H test was utilized to compare the means of the groups. Using the chi-square analysis, the gender variable was compared to trauma mechanisms. All other tests analyzed categorical variables using the chi-square test. The statistical significance level in the study was accepted as $p<0.05$.

Results

There were 200 (50%) male participants in the study. The average age of all patients was 6.87±4.96 years (range: 0 to 17 years; males: 6.70±4.68, females: 7.03±5.23). There was a significant relationship between age and trauma types (p=0.001). In 260 (65%) patients, falls represented the most common type of trauma. There were 54 (13.5%) collision cases, 42 (10.5%) fall from height cases, 24 (6%) assault cases, and 20 (5%) traffic accident cases. Male patients accounted for 15 (3.8%) of assault cases. There was no relationship between gender and types of trauma (p=0.232, Table 1).

There was access to tomography for 137 (34.3%) of the patients who had no complaints. CT imaging was performed on 45 (11.3%) of 49 (12.3%) individuals with nausea and vomiting. Of the 99 (24.8%) cases with headache, the most prevalent symptom, approximately 47 (11.8%) had no imaging. CT scans were performed on all 7 (1.8%) patients with seizures or multiple symptoms. The relationship between CT imaging and symptoms was statistically significant (p=0.001, Table 2).

In the evaluation of trauma types by the presence of CT examination and the presence of a lesion on CT, 264 (66%) of all patients had a cranial CT. While CT imaging was conducted on 181 (45.3%) patients in the fall group, CT imaging was performed on 33 (8.3%) of 42 (10.6%) patients

Table 2. Relationship between the presence of cranial imaging and clinical symptoms

Cranial CT	No	Yes	All patients	p
	n (%)	n (%)	n (%)	
Clinical symptom				
No complaint	75 (18.8)	137 (34.3)	212 (53)	
Nausea vomiting	4 (1)	45 (11.3)	49 (12.3)	
Headache	47 (11.8)	52 (13)	99 (24.8)	
Dizziness	8 (2)	12 (3)	20 (5)	**0.001**
Unconsciousness	1 (0.3)	7 (1.8)	8 (2)	
Sleep tendency	1 (0.3)	4 (1)	5 (1.3)	
Headache +nausea vomiting	0 (0)	2 (0.5)	2 (0.5)	
Headache + dizziness	0 (0)	3 (0.8)	3 (0.8)	
Seizure	0 (0)	2 (0.5)	2 (0.5)	

Chi-square analysis, bold values indicate significance of p<0.05, CT: Computed tomography

Table 1. Age, gender and trauma mechanism

Trauma mechanism		All patients	Fall	Fall from height	Traffic accident	Collision	Assault	p
		Mean ± SD						
Age (year)		6.87±4.96	6.17±4.56	6.38±5.10	7.80±5.51	6.87±4.96	7.92±5.05	**0.001***
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Gender	**Male**	200 (50)	135 (33.8)	15 (3.8)	9 (2.3)	26 (6.5)	15 (3.8)	0.232**
	Female	200 (50)	125 (31.3)	27 (6.8)	11 (2.8)	28 (7.0)	9 (2.3)	
	Total	400 (100)	260 (65)	42 (10.5)	20 (5)	54 (13.5)	24 (6.0)	

SD: Standard deviation, *Kruskal-Wallis-H test and **chi-square analysis, bold values indicate significance of p<0.05

admitted with fall from height. The association between the type of trauma and the existence of cranial CT imaging (p=0.004) and the presence of a lesion on cranial CT was statistically significant (p=0.001, Table 3).

CT scans revealed lesions in 66 (16.5%) of male patients and 46 (11.5%) of female patients. On CT, there was no association between gender and the presence of lesions (p=0.117). Although 56 of the patients (14%) had no complaints, tomographic imaging revealed a lesion. The relationship between patients' clinical symptoms and the existence of the lesion on radiological imaging was statistically significant (p=0.001, Table 4).

Three (0.8%) patients in the exitus group were unconscious, while one (0.3%) suffered headache. When CT lesions were analyzed in this group, it was observed that 1 patient (0.3%) had no CT lesions while 1 patient (0.3%) had only a contusion. An association between CT results and survival was revealed (p=0.001, Table 5).

Twenty-three patients (5.7%) in the service admission group and four patients (1%) in the intensive care hospitalization group exhibited tomographic lesions (p=0.001). Survival was observed in 396 (99%) patients (p=0.001). While 20 (5%) patients without CT abnormalities did not receive neurosurgical consultation, 49 (12.3%) patients had both CT findings and consultation reports. The relationship between consultation requests and CT findings was statistically significant (p=0.001, Table 6).

Table 4. Relationship of the presence of cranial CT lesion with gender and clinical symptoms

Cranial CT lesion & clinical symptom	No	Yes	All patients	p
	n (%)	n (%)	n (%)	
Gender				
Male	134 (33.5)	66 (16.5)	200 (50)	0.117
Female	154 (38.5)	46 (11.5)	200 (50)	
Clinical symptoms				
No complaint	156 (39)	56 (14)	212 (53)	
Nausea vomiting	28 (7)	21 (5.3)	49 (12.3)	
Headache	79 (19.8)	20 (5)	99 (24.8)	
Dizziness	18 (4.5)	2 (0.5)	20 (5)	**0.001**
Unconsciousness	2 (0.5)	6 (1.5)	8 (2)	
Sleep tendency	2 (0.5)	3 (0.8)	5 (1.3)	
Headache, nausea, vomiting	1 (0.3)	1 (0.3)	2 (0.5)	
Headache, dizziness	1 (0.3)	2 (0.5)	3 (0.8)	
Seizure	1 (0.3)	1 (0.3)	2 (0.5)	

Chi-square analysis, bold values indicate significance of p<0.05, CT: Computed tomography

Discussion

Studies have shown that 50% of childhood deaths are caused by head trauma. Pediatric head traumas are also a frequent reason for admission to emergency services and can occur by many different mechanisms. In addition, it causes serious morbidity rates and financial burden in terms of health even in developed countries (10). Head trauma can occur for

Table 3. Relationship of trauma mechanisms with the presence of cranial CT imaging and CT findings

Trauma mechanism & cranial CT	Fall	Fall from height	Traffic accident	Collision	Assault	All patients	p
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Cranial CT imaging							
No	79 (19.8)	9 (2.3)	8 (2)	28 (7)	12 (3)	136 (34)	**0.004**
Yes	181 (45.3)	33 (8.3)	12 (3)	26 (6.5)	12 (3)	264 (66)	
Cranial CT finding							
No	186 (46.5)	22 (5.5)	15 (3.8)	44 (11)	21 (5.3)	288 (72)	
Cephalohematoma	60 (15)	8 (2)	2 (0.5)	7 (1.8)	3 (0.8)	80 (20)	
Fracture	10 (2.5)	9 (2.3)	1 (0.3)	1 (0.3)	0 (0)	21 (5.3)	
Contusion	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	**0.001**
Epidural hemorrhage	1 (0.3)	1 (0.3)	0 (0)	0 (0)	0 (0)	2 (0.5)	
Fracture + epidural hemorrhage	1 (0.3)	0 (0)	1 (0.3)	1 (0.3)	0 (0)	3 (0.8)	
Fracture + pneumocephalus	1 (0.3)	1 (0.3)	0 (0)	1 (0.3)	0 (0)	3 (0.8)	
Fracture + multiple hemorrhage	0 (0)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	2 (0.5)	

Chi-square analysis, bold values indicate significance of p<0.05, CT: Computed tomography

different reasons in every age group. Studies on this subject are very important in order to determine the differences in etiological causes and demographic data among societies. In the study conducted by Cooper et al. (11), 59% of pediatric traumas were reported as traffic accidents, 13% as falls from a height, 12% as bicycle accidents, and 16% as other causes. In the study of Efendioğlu et al. (12), the most common cause of trauma was shown to be falls (77.6%), traffic accidents (10.2%), and other causes (10.2%). In our study, we evaluated 400 pediatric patients with head trauma with a mean age of 6.87±4.96 years. In addition, we attribute the significant relationship between age and trauma type to the change in social interaction according to age groups and the age determines the type of trauma that the child is likely to be exposed to. With 260 (65%) of the patients in the fall group and 42 (10.5%) in the fall from height group, it was similar to other studies. These were followed by traffic accident and assault cases. Assault cases were also more common in boys. We attribute the high incidence of falling and falling from a height in our region to active childhood and insufficient parental involvement. The fact that assault cases are more prevalent among boys may also be due to the fact that boys are more likely to engage in joking and physical contact compared to girls.

Table 5. Relationship between clinical symptoms and survival

Survival	Healing/ discharge	Exitus	All patients	p
	n (%)	n (%)	n (%)	
Clinical symptom				
No complaint	212 (53)	0 (0)	212 (53)	
Nausea vomiting	49 (12.3)	0 (0)	49 (12.3)	
Headache	98 (24.5)	1 (0.3)	99 (24.8)	**0.001**
Dizziness	20 (5)	0 (0)	20 (5)	
Unconsciousness	5 (1.3)	3 (0.8)	8 (2)	
Sleep tendency	5 (1.3)	0 (0)	5 (1.3)	
Headache, nausea, vomiting	2 (0.5)	0 (0)	2 (0.5)	
Headache, dizziness	3 (0.8)	0 (0)	3 (0.8)	
Seizure	2 (0.5)	0 (0)	2 (0.5)	
Cranial CT finding				
No	287 (71.7)	1 (0.3)	288 (72)	
Cephalohematoma	80 (20)	0 (0)	80 (20)	**0.001**
Fracture	21 (5.3)	0 (0)	21 (5.3)	
Contusion	0 (0)	1 (0.3)	1 (0.3)	
Epidural hemorrhage	2 (0.5)	0 (0)	2 (0.5)	
Fracture + epidural hemorrhage	3 (0.8)	0 (0)	3 (0.8)	
Fracture + pneumocephalus	2 (0.5)	1 (0.3)	3 (0.8)	
Fracture + multiple hemorrhage	1 (0.3)	1 (0.3)	2 (0.5)	

Chi-square analysis, bold values indicate significance of p<0.05, CT: Computed tomography

The clinical presentation of children with head trauma can be extremely variable, depending on the severity of the trauma. In general, neurological examination findings appear at the time of injury, and new clinical signs may indicate further progression of pathological changes due to head injuries. Some authors recommend using clinical symptoms and signs as screening tools to determine which patients need radiographic imaging following head trauma (13). Some authors have stated that abnormalities in neurological examination and clinical symptoms are not reliably present in children with traumatic brain injury (14). In the study of pediatric patients with head trauma, Hacioglu (15) revealed that the most common complaint was vomiting, followed by headache, loss of consciousness, amnesia, and seizures. In the study conducted by Andrade et al. (16) on 1,006 pediatric trauma patients, it was observed that 35% of the patients complained of somnolence, 33.5% of them vomiting, and 20% of them headache. In our study, 212 (53%) of our patients did not have any complaints. Headache (24.8%) was the most common complaint, followed by nausea, vomiting, and dizziness, respectively. In addition, 56 (14%) patients had a lesion in their CT although they had no complaints. Even though there are no complaints, we believe that the high rate of post-traumatic

Table 6. Relationship of hospitalization, survival, and consultations with CT findings

Cranial CT lesion & hospitalization/ prognosis	No	Yes	All patients	p
	n (%)	n (%)	n (%)	
Hospitalization				
Discharge from emergency	286 (71.5)	85 (21.3)	371 (92.8)	**0.001**
Service admission	1 (0.3)	23 (5.7)	24 (6)	
Intensive care hospitalization	1 (0.3)	4 (1)	5 (1.3)	
Survival				
Healing/discharge	287 (71.8)	109 (27.2)	396 (99)	**0.001**
Exitus	1 (0.3)	3 (0.8)	4 (1)	
Neurosurgery consultation				
No	268 (67)	63 (15.8)	331 (82.8)	**0.001**
Yes	20 (5)	49 (12.3)	69 (17.3)	

Chi-square analysis, bold values indicate significance of p<0.05, CT: Computed tomography

admission is a result of the ease of access to health services in modern times and the anxious attitude of parents of pediatric patients. Considering that the headache complaint is typically considered as equivalent to the pain in the trauma localization, the frequency of the absence of any complaints may be higher.

Short-term disadvantages of CT use include higher healthcare costs, more sedation procedures, longer emergency department stays, and increased parental discontentment. Early exposure to ionizing radiation, which is linked to an increased risk of cancer and mortality, is the most significant long-term disadvantage of CT use (8). Unfortunately, the increased use of CT leads to increased costs as well as increased radiation exposure, and its benefit, therefore, needs to be carefully evaluated (17). McKinlay et al. (18), in their study with 159 cases with head trauma, showed that children could not fully explain their complaints to the family, and as a result, the clinical severity could not be fully understood. In the study of Hacioglu (15) with 2,321 patients, cranial CT imaging was performed on 1,708 (71.46%) patients. In this study, in which cephalohematoma was not counted among the CT findings, bone fractures were the most common, followed by subdural hemorrhage, in 146 (6.11%) patients (15). In the study of Atmış et al. (19), epidural bleeding was observed most frequently after bone fracture. In the study, 264 (66%) patients had cranial CT imaging. The frequency of CT scanning was higher in cases of falls and falls from height. We believe that this number has increased due to both the severity of trauma and the prevalence of falls. We attribute the higher lesion frequency in CT, compared to other studies, to the fact that we defined cephalohematoma as a pathological lesion in our study. We attribute the high rate of patients with no complaints, who have not undergone imaging, and the high rate of patients who have undergone imaging despite having no complaints to the fact that numerous physicians have adopted varying perspectives and evaluation methods on this issue. A group of physicians requested tomography imaging in response to concerns such as legal malpractice and documented instances of positive CT findings in the absence of complaints.

Despite the fact that patient clinics and follow-ups determine the imaging plan and results, studies may report different recommendations. In a study involving 916 patients conducted by Güzel et al. (20), it was determined that CT was performed on 318 patients, CT was abnormal in 19.8% of those patients, and 13.8% of all patients required hospitalization. In a recent study conducted in England, it has been determined that the number of pediatric patients with head trauma who have sought emergency care has increased over the past decade, while the number of traumatic brain injuries and surgical interventions has remained unchanged. In recent years, mortality and length of hospital stay have decreased according to the same study (21).

Studies on hospitalization and mortality in head traumas have been conducted. Işık et al. (22) evaluated 851 children with head trauma, who also had additional trauma, and discovered a 3.8% mortality rate. Furthermore, Cecen et al. (23) examined 157 pediatric patients under the age of three years, who had moderate to severe trauma with head trauma, and they discovered a 3.18% mortality rate. In our study, 4 (1%) cases resulted in clinical death. There were 4 (1%) patients who were discharged from the intensive care unit with full recovery, and 1 (0.3%) patient who were exitus. Three (0.8%) patients died in the emergency department. We think that the reason why most of the cases resulted in death in the emergency room is due to the high severity of the trauma, the instability of the clinic, and the fact that they occur without being hospitalized. We attribute the survival of 99% of the patients to the fact that our hospital is a qualified trauma center and that it is due to the effective evaluation of the trauma patient. Furthermore, we attribute the higher mortality rate in comparable articles to the fact that moderate-to-severe cases were evaluated in other studies and our patients had isolated head trauma with no additional injuries. In addition, the high number of applications and the fact that the severity of trauma in most of them is not severe enough to result in mortality can also be cited as a reason.

Study Limitations

One of the limitations of our study may be that the way of grouping the risk and severity of trauma in children presenting with head trauma could not be done adequately in the emergency department. Uncertainty about the rate of protective equipment and precautions during trauma and the inability to predict which type of trauma will result in more severe consequences can be counted among the limitations. In addition, the possibility that the data obtained from pediatric patients in both history and physical examination are not realistic due to communication and interaction difficulties can be stated as another limitation.

Conclusion

The data show that the mechanism, clinical symptoms, and findings in head trauma cannot provide clear data for CT imaging with current analyses and studies. In general, the choice of imaging differs according to the clinician's

experience and evaluation of the patient, and forensic concerns. We think that a large number of multicenter prospective studies are needed to standardize this medically and to establish certain criteria among physicians and health institutions.

Ethics

Ethics Committee Approval: Ethics committee approval was received on 18.11.2021 with the number E-10840098-772.02-5921 from Medipol University.

Informed Consent: Our study is retrospective and was carried out on data processing data without using patient names.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: B.A., A.C., B.D., Design: B.A., A.C., B.D., B.Ç., Data Collection or Processing: B.A., B.D., H.K., Analysis or Interpretation: B.A., A.C., B.Ç., Literature Search: B.A., B.D., H.K., B.Ç., Writing: B.A., H.K.

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ORIGINAL RESEARCH

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Renal Involvement in Children with Henoch-Schönlein Purpura

Henoch-Schönlein Purpuralı Çocuklarda Renal Tutulum

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Abstract

Objective: Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in childhood. In this study, we aimed to retrospectively analyze the clinical and laboratory findings and treatment results in terms of renal involvement features in pediatric patients diagnosed with HSP who were hospitalized or applied to our outpatient clinic.

Method: This study included 50 patients who were diagnosed with HSP, admitted to the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Pediatrics Clinic between 2012 and 2015, and followed up regularly for at least 9 months.

Results: The patients included in the study were between the ages of 3 and 16 years (mean age 6.9 years). Thirty-one patients with kidney involvement were between the ages of 5 and 16 years (mean age 10.1 years). 30% of the cases were female (n=15) and 70% were male (n=35). Of the patients with kidney involvement, 11 (35%) were female and 20 (65%) were male. The disease was more common in males, consistent with the literature (p<0.05). The season in which the disease occurred was determined as winter in 10 cases (20%), spring in 11 cases (22%), summer in 10 cases (20%), and autumn in 19 cases (38%). Skin involvement was found in the form of petechiae purpura in all cases (100%), gastrointestinal involvement in 29 patients (58%), joint involvement in 21 patients (42%), kidney involvement in 31 patients (62%), and neurological involvement in 1 (2%) patient. During the follow-up, recurrence was detected in 13 (26%) of the patients. Renal findings developed in 64.6% of the patients within the first 4 weeks and in 35.4% of the patients in the later period. Hematuria was found in all 31 patients with renal involvement, proteinuria in 5 (10%) patients, massive proteinuria in 2 (4%) patients, urea and creatinine elevation in 2 (4%) patients, and high blood pressure in 4 (8%) patients. Renal involvement was found in 23 (79%) of 29 patients with gastrointestinal involvement. Renal involvement was detected in 8 (38%) of the remaining 21 patients. These results were significant in terms of gastrointestinal involvement and renal involvement (p<0.05).

Öz

Amaç: Henoch-Schönlein purpurası (HSP) çocukluk çağının en sık görülen vaskülitidir. Biz bu çalışmada kliniğimizde yatarak tedavi gören veya poliklinik takibine aldığımız HSP'li çocuklarda özellikle renal tutulum başta olmak üzere klinik bulguları, labaratuvar bulgularını ve tedavi sonuçlarını retrospektif olarak incelemeyi amaçladık.

Yöntem: Bu çalışmada, 2012-2015 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği'ne başvuran ve HSP tanısı alan ve en az 9 ay izlemi yapılan 50 hasta yer aldı.

Bulgular: Çalışmaya alınan hastalar 3-16 yaş aralığındaydı (ortalama 6,9). Böbrek tutulumu olan 31 hasta ise 5-16 yaş aralığında (ortalama 10,1) idi. Olguların %30'u kız (n=15), %70'i erkek (n=35) idi. Böbrek tutulumu olan hastaların ise, 11'i (%35) kız, 20'si (%65) erkekti. Hastalık literatürle uyumlu olarak erkeklerde daha sık gözlendi (p<0,05). On olguda (%20) hastalığın görüldüğü mevsim kış, 11 olguda (%22) ilkbahar, 10 olguda (%20) yaz, 19 olguda (%38) sonbahar olarak belirlendi. Olguların tamamında peteşi purpura şeklinde deri tutulumu (%100), 29 hastada gastrointestinal tutulum (%58), 21 hastada (%42) eklem tutulumu, 31 hastada böbrek tutulumu (%62) saptandı. Hastalarımızdan 32 no'lu olgu ilk olarak santral sinir sistemi tutulumu ile başvurdu. İzlemde hastaların 13'ünde (%26) nüks saptandı. Renal bulgular hastaların %64,6'sında hastalığın ortaya çıktığı ilk 4 haftada belirirken %35,4'ünde daha sonra ortaya çıktı. Renal tutulumu olan 31 hastanın tamamında hematüri, 5'inde (%10) proteinüri, 2'sinde (%4) masif proteinüri, 2'sinde (%4) üre, kreatinin yüksekliği, 4'ünde (%8) yüksek kan basıncı saptandı. Gastrointestinal tutulum saptanan 29 hastanın 23'ünde (%79) renal tutulumun da mevcut olduğu saptandı. Geriye kalan 21 hastanın 8'inde (%38) renal tutulum saptandı. Bu sonuçlar gastrointestinal tutulum ve renal tutulum birlikte görülmesi açısından anlamlı bulundu (p<0,05).

Sonuç: HSP'nin üst solunum yolu enfeksiyonlarının artış gösterdiği sonbahar mevsiminde sık görülebileceği, purpurik döküntüden sonra en sık rastlanan bulgunun renal tutulum olduğu, renal tutulumun da hematüri,

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Conclusion: The most common finding of HSP after purpuric rash is renal involvement, and renal involvement may develop with hematuria, proteinuria, nephrotic syndrome, hypertension, and acute kidney failure. It was determined that renal involvement occurred especially in the first 4 weeks, and the probability of renal involvement increased in patients with gastrointestinal involvement. Considering the wide spectrum of renal involvement in patients with HSP, it was emphasized that the importance of follow-up and monitoring for possible serious renal disease in proteinuria and hypertensive patients, together with angiotensin receptor blocker treatment, as in IgA nephropathy, can yield extremely positive results.

Keywords: Children, Henoch-Schönlein purpura, renal involvement

proteinüri, nefrotik sendrom, hipertansiyon, akut böbrek yetmezliği gibi tablolarla ortaya çıkabileceği görüldü. Renal tutulumun özellikle ilk 4 hafta içerisinde ortaya çıktığı, gastrointestinal tutulumu olan hastalarda renal tutulum olasılığının arttığı saptandı. HSP'li hastaların renal tutulumun geniş spektrumu da dikkate alınarak takiplerinin önemi ve proteinürili, hipertansif olgularda olası ciddi renal hastalık yönünden izlem ile birlikte IgA nefropatisinde olduğu gibi anjiyotensin reseptör blokeri tedavisi ile son derece olumlu sonuçlar alınabileceği vurgulanmıştır.

Anahtar kelimeler: Böbrek tutulumu, çocuk, Henoch-Schönlein purpurası

Introduction

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood. This disease, which is characterized by leukocytoclastic vasculitis, progresses with the deposition of immunoglobulin A (IgA) in the small vessels of the skin, joints, gastrointestinal tract, and kidneys (1). Although the exact etiology is not known, it has been reported that it is seen after allergen contact in some cases and after upper respiratory tract infection caused by streptococcus or other microorganisms in some cases (2). The annual incidence of HSP in children is 14-20/100,000. The disease is more common in children than adults, and more often in boys than girls. The incidence in boys and girls was reported as 1.2/1-1.8/1, respectively. 90% of HSP cases seen in childhood are seen between the ages of 3 and 10 years (1). HSP usually occurs in autumn, winter, and spring. It can rarely be seen in summer (3). The disease is seen at a lower incidence in black children compared to white Asian children (4).

HSP is a syndrome that includes non-thrombocytopenic purpura, arthritis, arthralgia, gastrointestinal symptoms, and nephritis. Palpable purpura or accompanying abdominal pain and/or joint pain is the first finding in more than 70% of the patients (5). Typically, skin rashes in the form of palpable purpura appear first on the gluteal regions and lower extremities. Rarely, rashes can be seen on the body and face. Oligoarthritis is present in the large joints of the lower extremities (ankles and knees) in 50-80% of the patients (6-9). These findings usually heal within a few days without any sequelae but may recur later on. Gastrointestinal manifestations occur in 50-75% of cases. Bleeding in the intestinal wall causes colic-like pain and melena. Invagination and perforation are rare. Renal involvement may occur in 20-40% of cases. Oliguria, hematuria, hypertension, nephrotic syndrome, and rarely chronic renal failure can be seen (6). In this study, we aimed to retrospectively analyze the clinical and laboratory findings and treatment results in terms of renal involvement features in pediatric patients diagnosed with HSP, who were hospitalized or admitted to our outpatient clinic.

Materials and Methods

This study included 50 patients who were diagnosed with HSP and were followed up in an outpatient or inpatient clinic at the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Pediatrics Outpatient Clinic, Pediatric Emergency Outpatient Clinic, Pediatric Service and Pediatric Nephrology Outpatient Clinic between the years of 2012 and 2015. For the diagnosis of HSP, the diagnostic criteria determined by the European Rheumatism Union in 2006 (10) were used. These were as follows:

Mandatory criterion: The presence of rash in the form of palpable purpura, which is common especially in the lower extremities, was determined as the absolute criterion.

Other criteria:

Abdominal pain

Histopathological findings (leukocytolastic vasculitis or proliferative glomerulonephritis with excessive IgA deposition)

Arthritis/arthralgia

Renal involvement (proteinuria; >0.3 g/24 hours or albumin/creatinine >30 mmol/mg or microscopic hematuria or erythrocyte count >5 at high magnification).

Criteria required for diagnosis: The diagnosis was made by the presence of at least one of the above 4 criteria, especially palpable purpura in the lower extremities, the absolute criterion.

System involvements in the patients were evaluated as skin involvement, joint involvement, gastrointestinal system involvement, kidney involvement, and other system involvements according to physical examination and laboratory findings. Fifty cases included in the study were those who did not have underlying kidney, gastrointestinal, primary immunological, endocrine or other systemic diseases, and other causes of purpura were excluded. Children aged 2-15 years were included in the study. Data about identity information, age, gender, weight, height values, detailed physical examinations, blood pressure, and season of the disease were recorded for patients diagnosed with HSP. Complete blood count, complete urinalysis, proteinuria amount in 24-hour urine, serum urea, serum creatinine, serum albumin liver function tests, (aspartate aminotransferase) alanine aminotransferase), gama glutamyl transferase, C-reactive protein, sedimentation, and occult blood in the stool were evaluated. The presence of more than 5 erythrocytes at 40° magnification in the urine sample centrifuged at 3000 rpm, macroscopic hematuria, proteinuria (under 4 mg/m^2/hour in 24-hour urine, 4-40 mg/m^2/hour and 40 mg/hour in patients with strip protein positive m^2/h), serum albumin level in patients with proteinuria, measurements above the 95th percentile and deterioration in renal function tests (increase in serum creatinine, deterioration in creatinine clearance) were evaluated with reference to the Report of the Second Task Force on Blood Pressure Control in Children for High Arterial Blood Pressure.

Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 16.06.2016, number: 2016/481).

Statistical Analysis

In this study, statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation) in the evaluation of the data, independent t-test was used in the comparison of paired groups, and chi-square test was used in the comparison of qualitative data. The results were evaluated at the significance level of $p<0.05$.

Results

Fifty patients aged 3-16 years (mean 6.9±3 years) were included in the study. Thirty-one patients with renal involvement were between the ages of 5 and 16 years (mean age 10.1 years). There was no significant difference between the mean age of the patients without kidney involvement and the patient groups with kidney involvement (p=0.359).

30% of the cases were girls (n=15) and 70% were boys (n=35), and the female-male ratio was 0.43 (Table 1). On the other hand, 11 (35%) of the patients with kidney involvement were female and 20 of them (65%) were male. There was no significant difference in gender distribution between those with and without kidney involvement.

The season in which the disease occurred was determined as winter in 10 cases (20%), spring in 11 cases (22%), summer in 10 cases (20%), and autumn in 19 cases (38%) (Table 1).

Skin involvement in the form of petechiae purpura was found in all cases (100%), gastrointestinal involvement in 29 patients (58%), joint involvement in 21 patients (42%), and kidney involvement in 31 patients (62%). The case numbered 32 of our patients first applied with central nervous system involvement. During the follow-up, recurrence was detected in 13 (26%) of the patients (Table 1).

In the treatment of the patients, those with skin involvement were followed up by suggesting rest without medical treatment. Non-steroidal anti-inflammatory drugs were started to reduce pain in those with joint involvement.

Table 1. Clinical features of patients with Henoch-Schönlein purpura

		All groups	
Season of disease occurrence	**Winter**	10	20.00%
	Spring	11	22.00%
	Summer	10	20.00%
	Autumn	19	38.00%
Gender	**Female**	15	30.00%
	Male	35	70.00%
Rash	**Yes**	50	100.00%
Arthritis	**No**	29	58.00%
	Yes	21	42.00%
Gastrointestinal involvement	**No**	21	42.00%
	Yes	29	58.00%
Renal involvement	**No**	19	38.00%
	Yes	31	62.00%
Recurrence	**No**	37	74.00%
	Yes	13	26.00%
Treatment	**Follow-up**	27	54.00%
	Steroid	21	42.00%
	Angiotensin receptor blocker	2	4.00%

Hydration and short-term steroids were given to those with gastrointestinal involvement. In patients with renal involvement, anqiotensin receptor blackar (ARB) was started in patients with high blood pressure and/or massive proteinuria. The treatment of the case having central nervous system involvement with corticosteroids was successfully completed (Table 1).

Onset of renal findings was at the first week of the onset of the disease in 15 patients (48.3%), at the second week in 2 patients (6.4%), at the third week in 1 patient (3.2%), at the fourth week in 2 patients (6.4%), and in later period in 11 patients (35.4%) (Table 2).

Urea and creatinine levels were found to be high in 2 (4%) patients. Elevated blood pressure was found in 4 (8%) of the patients. Hematuria was detected in 31 cases (62%), proteinuria in 5 cases (10%), and massive proteinuria in 2 cases (4%) (Table 2).

Table 2. Features of renal involvement in children with Henoch-Schönlein purpura

		n	%
Time of appearance of renal findings	1st week	15	48.39
	2nd week	2	6.45
	3rd week	1	3.23
	4th week	2	6.45
	>5 week	11	35.48
Blood pressure	Normal	27	87.10
	High	4	12.90
Creatinine	Normal	31	100.00
Urea	Normal	30	96.77
	High	1	3.23
Albumin	Normal	30	96.77
	Low	1	3.23
Hematuria	Yes	31	100.00
	No	24	77.42
Proteinuria	Yes	7	22.58

The urea, creatinine, serum albumin and blood pressures of cases numbered 9, 17 and 24 were normal. Proteinuria disappeared spontaneously in the follow-up of patients with proteinuria less than 500 mg/m^2/day.

Case numbered 26 had proteinuria of 3.4 g/m^2/day. ARB was started for the patient. In the follow-up, urea and creatinine values returned to normal and proteinuria disappeared.

In case numbered 29, high urea and creatinine levels were also present along with high blood pressure. The patient was started on a short-term anti-hypertensive (ARB). In the follow-up, urea creatinine values and blood pressure regressed to normal.

Case numbered 32 with neurological involvement was admitted to our emergency department with confusion and convulsions. The disease-specific rash appeared after neurological involvement. Renal involvement (hematuria) and high blood pressure were also present. Steroids were started for central nervous system involvement. Blood pressure returned to normal without the need for antihypertensive use and renal involvement improved in the follow-up. ARB was started in case numbered 14 because of high blood pressure and proteinuria (1.76 gr/m^2/day). In the follow-up, blood pressure returned to normal and proteinuria disappeared. In case numbered 15, high blood pressure resolved spontaneously without the need for antihypertensive use.

No recurrence was observed in 12 (57%) of 21 patients who were given steroids, and in 9 (31%) of 29 patients who were not given steroids. It was found that the steroid did not have a significant role in preventing recurrence (p=0.2).

While recurrence was detected in 12 (41%) of 29 patients with gastrointestinal involvement, recurrence was found in 1 (4%) of 21 patients without gastrointestinal involvement. It was found that the disease recurred more in cases with gastrointestinal involvement (p=0.004). Recurrence was

Table 3. Comparison of the relationship of recurrence with age, treatment, gastrointestinal involvement, and gender

		Relapse (-) n=37		Relapse (+) n=13		p
Age		9.54±3.71		10.54±2.90		0.384
Treatment	**Follow-up**	23	62.16%	4	30.77%	0.062
	Steroid	12	32.43%	9	69.23%	
	ARB	2	5.41%	0	0.00%	
Gastrointestinal involvement	**No**	20	54.05%	1	7.69%	**0.004**
	Yes	17	45.95%	12	92.31%	
Gender	**Female**	11	29.73%	4	30.77%	0.944
	Male	26	70.27%	9	69.23%	

ARB: Angiotensin receptor blocker

Table 4. Examination of the relationship between kidney involvement and age, the season of onset of the disease, gender, rash, arthritis, gastrointestinal involvement, recurrence, and treatment

		Renal involvement (-) n=19		Renal involvement (+) n=31		p
Age		9.21±3.75		10.16±3.38		0.359
Season of disease occurrence	**Winter**	2	10.53%	8	25.81%	**0.043**
	Spring	5	26.32%	6	19.35%	
	Summer	1	5.26%	9	29.03%	
	Autumn	11	57.89%	8	25.81%	
Gender	**Female**	4	21.05%	11	35.48%	0.281
	Male	15	78.95%	20	64.52%	
Rash	**Yes**	19	100.00%	31	100.00%	
Arthritis	**No**	10	52.63%	19	61.29%	0.547
	Yes	9	47.37%	12	38.71%	
Gastrointestinal involvement	**No**	13	68.42%	8	25.81%	**0.003**
	Yes	6	31.58%	23	74.19%	
Relapse	**No**	16	84.21%	21	67.74%	0.198
	Yes	3	15.79%	10	32.26%	
Treatment	**Follow-up**	15	78.95%	12	38.71%	**0.019**
	Steroid	4	21.05%	17	54.84%	
	ARB	0	0.00%	2	6.45%	

ARB: Angiotensin receptor blocker

found in 4 (26%) of 15 female patients, while it was found in 9 (25%) of 35 male patients. There was no significant relationship between relapse and gender (p=0.062) (Table 3).

Renal involvement was also found in 23 (79%) of 29 patients with gastrointestinal involvement. Renal involvement was detected in 8 (38%) of the remaining 21 patients. These results were found to be significant in terms of gastrointestinal involvement and renal involvement (p<0.05) (Table 4).

Joint involvement was found in 9 (47%) of 19 patients without kidney involvement, and in 12 (38%) of 31 patients with kidney involvement. These results were not significant in terms of joint involvement and kidney involvement (p=0.567) (Table 4).

Recurrence was detected in 3 (15%) of 19 patients without kidney involvement and in 10 (32%) of 31 patients with kidney involvement, showing that there was no significant relationship between these results and the incidence of renal involvement and recurrence (p=0.198) (Table 4).

Discussion

HSP is a disease, the frequency of which increases in winter, spring, and autumn (11-13). However, in our cases, autumn (38%) stood out as the season in which this disease was observed most commonly. Considering that upper respiratory tract infections, which are thought to play a role in the etiology of the disease, increase in this season (14,15), the prominence of the autumn season can be considered significant.

It was reported that HSP was 1.5 times more common in boys than in girls (16). However, in the present study, the incidence in boys was found to be higher than that in the literature (male/female: 2.3). Renal involvement is also common in males, but the male/female ratio was found to be 1.85.

HSP is known as a vasculitic syndrome that generally concerns young children and peaks around the age of 4-7 years (15,17). The mean age of our cases was found to be 6.9±3 (3-16) years. However, the disease can also be seen in adults and has a more serious clinical course especially in terms of renal involvement (18). The mean age of our patients with kidney involvement was found to be 10.1 (5-16) years. The fact that the mean age of patients with renal involvement is older may be significant in terms of more serious clinical course and the emergence of renal findings as the age increases.

Renal involvement in HSP is reported as 20-100% in the literature, and renal involvement occurs in the first four weeks of the disease in 80% of the cases (19-22). In our study,

renal involvement was detected in 62% of our patients. On the other hand, the time of appearance of kidney findings was observed in the first 4 weeks (64.6% of the patients) in line with the literature.

According to a study investigating the factors affecting the prognosis in HSP, it was claimed that while the probability of renal involvement increased in patients with severe gastrointestinal involvement, persistent purpura, and decreased Factor XIII activity, steroid therapy reduced renal involvement (15). Gastrointestinal involvement was detected in 29 (58%) of our patients. Renal involvement was present in 23 (79%) of the cases. Detection of renal involvement in 8 (38%) of the remaining 21 patients was found to be significant in terms of the coexistence of serious symptoms such as gastrointestinal involvement and renal involvement.

On the other hand, it has been suggested that one of the most important factors affecting the prognosis in HSP is the initial findings of renal involvement. According to a study in which it was found that 20% of patients with renal involvement developed chronic renal failure in a 20-year follow-up, end-stage renal disease was initially found in 5% of cases with only microscopic hematuria, in 15% of cases with proteinuria that did not reach the nephrotic level or in nephritic syndrome, in 40% of cases with nephrotic syndrome, and in 50% of cases with both nephrotic and nephritic syndrome (23). It was reported that 1.7% of all children followed in the renal replacement program in Europe were caused by HSP nephritis (4). In our study, no chronicity was detected in the cases we followed up for at least 9 months of follow-up.

However, the absence of a definite specific treatment for HSP nephritis is an important problem. There are also studies suggesting ARB, as in IgA nephropathy, with corticosteroids, immunosuppressives such as cyclophosphamide, and possible severe renal disease in proteinuria and hypertensive cases (19,23,24).

Proteinuria was found in 5 of the cases in our study. In 3 of them, proteinuria was <500 mg/m^2/day, and urea, creatinine, albumin and blood pressure values were normal. In the follow-up, the proteinuria of these patients resolved spontaneously without the need for any treatment. In one of the other 2 cases, proteinuria and urea and creatinine levels were also high. Serum albumin and blood pressure values were normal. In the follow-up of the patient who was started on ARB, urea and creatinine values returned to normal and proteinuria disappeared. In the other case, blood pressure was high together with proteinuria. Urea, creatinine and albumin values were normal. Blood pressure and proteinuria improved in the follow-up of the patient who was started on ARB.

The recurrence rate reported for HSP in the literature varies and is given as 15-35% (24,25). In our study group, recurrence was found to be 26% (13 in 50 cases), which is consistent with the literature. Recurrence was detected in 32% (10 cases) of 31 patients with renal involvement. No recurrence was observed in 12 (57%) of 21 patients who were given steroids and in 9 (31%) of 29 patients who were not given steroids. In our study, it was observed that steroids could not prevent recurrence.

Study Limitations

The limitation of our study is that it is retrospective.

Conclusion

The most common finding of HSP after purpuric rash is renal involvement, and renal involvement may occur with hematuria, proteinuria, nephrotic syndrome, hypertension, and acute kidney failure. It was determined that renal involvement occurred especially in the first 4 weeks, and the probability of renal involvement increased in patients with gastrointestinal involvement. Considering the wide spectrum of renal involvement in patients with HSP, it was emphasized that the importance of follow-up and monitoring for possible serious renal disease in proteinuria and hypertensive patients, together with ARB treatment, as in IgA nephropathy, can yield extremely positive results.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 16.06.2016, number: 2016/481).

Informed Consent: Written informed consent was obtained in accordance with the Declaration of Helsinki.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: S.U., Ö.Y., Design: S.U., Ö.Y., Data Collection or Processing: S.U., Analysis or Interpretation: S.U., Writing: S.U., Ö.Y.

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ORIGINAL RESEARCH

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Characteristics of COVID-19 Related Stroke: A Single-center Prospective Study

COVID-19 İlişkili İnmenin Özellikleri: Tek Merkezli Bir Prospektif Çalışma

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) seems more related to stroke than other respiratory viruses. Acute stroke has become increasingly conspicuous during a typical COVID-19 infection. In the present study, we aim to evaluate stroke characteristics in the context of COVID-19 infection.

Method: We conducted a single-center prospective study and evaluated characteristics of stroke patients who had concomitant definite COVID-19 (dCOV) (n=24), suspected COVID-19 (sCOV) (n=31), and no COVID-19 (CG) (n=19). Then we classified all participants into two groups according to the modified Rankin scale (mRS) scores (0-2 indicating good outcome, 3-6 indicating poor outcome). A logistic regression analysis and a receiver operating characteristic area under the curve were performed to evaluate the variables, which predict a poor prognosis.

Results: Just over half of the patients in the dCOV were admitted with stroke symptoms and diagnosed with COVID-19 at admission, and nearly half of the patients initially had a COVID-19 diagnosis. They had developed stroke after a gap of 4-21 days. Ischemic stroke was the most common stroke subtype in dCOV. The dCOV had higher mRS indicating poor outcomes. Patients with poor outcomes had higher levels of D-dimer, neutrophil-to-lymphocyte ratio (NLR), procalcitonin, and aspartate aminotransferase. NLR reliably predicts poor outcome, overall with an accuracy of 86%.

Conclusion: COVID-19 related stroke is associated with high inflammatory biomarkers, poor outcome, and high mortality. NLR is a potential, cost-effective, and easy-to-use marker for poor prognosis in COVID-19 related stroke.

Keywords: Cerebrovascular disease, COVID-19, neutrophil-to-lymphocyte ratio, prognosis, stroke

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) diğer solunum yolu virüslerine kıyasla inme ile daha çok ilişkili gibi görünmektedir. Tipik bir COVID-19 enfeksiyonu sırasında akut inme giderek daha göze çarpar hale gelmiştir. Bu çalışmada COVID-19 enfeksiyonu bağlamında inme özelliklerini değerlendirmeyi amaçladık.

Yöntem: Bu tek merkezli prospektif çalışmada kesin COVID-19 tanısı olan (dCOV) (n=24), şüpheli COVID-19 tanısı olan (sCOV) (n=31) ve COVID-19 tanısı olmayan (CG) (n=19) inme hastasının özellikleri değerlendirildi. Ardından tüm katılımcılar modifiye Rankin skalası (mRS) skorlarına göre iki gruba ayrıldı (0-2 iyi sonlanım, 3-6 kötü sonlanım göstergesi). Lojistik regresyon analizi ve receiver operating characteristic eğri altında kalan alan analizi yapılarak kötü prognozu öngören değişkenler değerlendirildi.

Bulgular: dCOV grubundaki hastaların yarısından biraz fazlası inme semptomlarıyla başvurdu ve beraberinde COVID-19 tanısı aldı. Yaklaşık yarısı ise başvuru sırasında halihazırda COVID-19 tanısına sahipti. Bu hastalarda COVID-19 tanısından 4-21 gün sonra inme semptomları ortaya çıkmıştı. dCOV grubunda en fazla görülen inme türü iskemik inmeydi. dCOV grubu diğerlerine kıyasla daha yüksek mRS'ye sahipti. Kötü sonlanımı olan hastalar daha yüksek D-dimer, nötrofil-lenfosit oranı (NLR), prokalsitonin ve aspartat aminotransferaz düzeyine sahipti. NLR kötü sonlanımı genel olarak %86 doğrulukla öngörmekteydi.

Sonuç: COVID-19 ile ilişkili inme, yüksek enflamatuvar biyoişaretleyiciler, kötü sonlanım ve yüksek mortaliteyle ilişkilidir. NLR, COVID-19 ile ilişkili inmede potansiyel, uygun maliyetli ve kullanımı kolay bir kötü prognoz belirtecidir.

Anahtar kelimeler: COVID-19, inme, nötrofil-lenfosit oranı, prognoz, serebrovasküler hastalık

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Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2, has been declared as a global pandemic by the World Health Organization in March 2020. Although this new syndrome is characterized by respiratory symptoms, accumulated evidence shows that it may also involve many other systems and organs including the nervous system, resulting in manifestations such as anosmia, headache, stroke, acute confusional state, and encephalitis (1).

Although it is known that many viral infections and sepsis may trigger stroke, COVID-19 seems more related to stroke than other respiratory viruses, seven-fold greater compared to influenza (2).

In a retrospective study, 36% of the patients with COVID-19 had neurological complications, 5.7% of them had an acute stroke, mainly in patients with severe respiratory symptoms (3).

The incidence of acute stroke in COVID-19 patients has been reported as 0.4-8.1% in the subsequent studies (4), more commonly in older patients with stroke risk factors (RF) (3,5,6), and ischemic stroke has been reported to be more frequent than hemorrhagic stroke (4). COVID-19 related stroke patients have a poor prognosis (7,8).

It is still not known whether there is a causal relationship between COVID-19 and stroke, and the pathophysiological mechanism is still unclear. Still, inflammation, hypercoagulability, and hypoxia appear to be major contributors (9).

Perhaps the most critical point for clinicians during the COVID-19 pandemic was to separate patients with and without COVID-19 infection with precision and to ensure the isolation of patients in inpatient wards. Reverse transcriptase-polymerase chain reaction (RT-PCR) assay is the primary diagnostic tool for COVID-19. Still, the sensitivity of RT-PCR has been reported between 42% and 83% (10), and false-negative results have also been reported (11,12). Since the RT-PCR test takes hours to days, chest computed tomography (CCT) has been used for faster evaluation in clinical practice as a first-line screening tool. To standardize the various reported CCT findings of COVID-19, the COVID-19 reporting and data system (CO-RADS) was proposed (10).

In the present study, we aim to evaluate stroke characteristics in COVID-19 by comparing demographic, clinical, radiological, and laboratory findings of stroke patients who had concomitant definite COVID-19 (dCOV), suspected but unproven COVID-19 (sCOV), and no COVID-19 (nCOV).

Materials and Methods

Participants

The study was performed between January 2021 and May 2021, and a total of 171 patients who were diagnosed with acute cerebrovascular disease (aCVD) were prospectively included.

The CCT was used to evaluate all patients, which is a part of the hospital inpatient admission policy. CO-RADS scores were determined by experienced radiologists. Among them, those having a travel history to another country within the last two weeks, a contact history with a known COVID-19 patient, respiratory symptoms, or suggestive CCT findings underwent a nasopharyngeal swab RT-PCR. Those with a positive RT-PCR were included in the dCOV group. If the two consecutive RT-PCRs were negative, they were included in the sCOV group. If all the four criteria for an RT-PCR test were absent, the patient was included in the nCOV group, which also served as the candidate control group (CG).

After the initial workup for COVID-19, all the nCOV patients were followed up for infectious diseases (other system infections, sepsis) during the hospital stay and for respiratory symptoms for two weeks. Those who did not develop respiratory symptoms and whose relatives were not diagnosed with COVID-19 within that period and those who did not develop other infectious diseases during the stay were included in the final CG.

According to a protocol approved by the Local Ethics Committee of the University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (date: 15/01/2021, number: 2021.01.1.12.213.r1.012) and the relevant committee of the Turkish Ministry of Health, written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

After excluding patients who did not consent to the study, 24 patients were included in the dCOV group, 31 patients in the sCOV group, and 19 patients in the CG.

Data on RF, medication, electrocardiography (ECG) (sinus rhythm or atrial fibrillation), CO-RADS score, outcome (home discharge, transfer to another center, being still hospitalized, in-hospital death), admission platelet, hemoglobin, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer,

procalcitonin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and fibrinogen were collected and recorded.

Stroke types were classified as ischemic stroke, transient ischemic attack, and hematoma. Ischemic stroke was further classified into four main groups, including total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI), and lacunar infarction (LACI) according to the Bamford clinical classification (13).

Hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, heart failure, previous stroke, smoking, obesity, and dyslipidemia were the RFs for stroke.

The temporal relationship of COVID-19 diagnosis with stroke diagnosis and delay of stroke after the onset of COVID-19 were recorded if applicable.

Echocardiography and computed tomography angiography (CTA) results were evaluated by two neurologists (Z.Y., S.O.), and echocardiography results were classified as normal, mild findings, low ejection fraction (EF), and/or akinetic wall, aortic stenosis, cardiac mass/intracardiac thrombus, prosthetic valve. CTA results were classified as normal, atherosclerotic changes, symptomatic stenosis, asymptomatic stenosis, and vasculitic findings.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean, standard deviation, median, minimum, maximum, frequency, and percentage. Then all participants were classified into two groups according to the modified Rankin scale (mRS) scores. Group 1 included participants with mRS scores of 0-2, indicating good outcome, and group 2 included participants with mRS scores of 3-6, indicating poor outcome. In the comparison of demographic and clinical data, the Kruskal-Wallis and Mann-Whitney U tests were used. In the presence of a significant difference in the Kruskal-Wallis test, the Tamhane's T2 test was used for the paired comparison of subgroups. The Pearson chi-square and Fisher's Exact tests were employed to compare the frequencies and percentages.

A logistic regression analysis (LRA) was performed with outcome groups as the dependent variable and the significantly different variables between these two outcome groups as the predictors.

A "receiver operating characteristic" (ROC) area under the curve (AUC) was used in the statistical evaluation of the sensitivity and specificity of the NLR.

Results

The comparison of the demographic and clinical variables of CG, sCOV, and dCOV groups are shown in Table 1. There were no significant differences among the groups in terms of age (p=0.437), gender (p=0.226), the RF (p=0.672), medication (p=0.796), type of stroke (p=0.879), ECG findings (p=0.387), echocardiography findings (p=0.386), CTA findings (p=0.419), outcome (p=0.65), WBC (p=0.634), hemoglobin (p=0.158), ESR (p=0.107), D-dimer (p=0.265), procalcitonin (p=0.271), BUN (p=0.136), and creatinine (p=0.773).

All sCOV patients and 13 patients from the dCOV had synchronous COVID-19 (suspected or definite) and CVD diagnoses. They were admitted for stroke and evaluated for COVID-19 for safety reasons. On the other hand, 11 patients from the dCOV had CVD symptoms 4-21 days after the onset of COVID-19. While there was no significant difference among the groups regarding outcome (p=0.650), mRS scores were significant between the groups (p=0.006). Post-hoc analysis revealed that the mRS score of the dCOV was significantly higher than that of the CG (p=0.002). Also, mortality rate was 16.7% (n=4) in dCOV and 9.7% (n=3) in sCOV, while there was no mortality in the CG.

Platelet count (p=0.041), NLR (p=0.007), CRP (p=0.027), AST (p=0.004), ALT (p=0.001), and fibrinogen (p=0.002) were significantly different among the three groups. While post-hoc analysis revealed no significant difference between the groups with regard to platelet count, NLR of the dCOV was significantly higher than that of CG (p=0.004). CRP level of the dCOV was significantly higher than that of CG (p=0.009). AST level was higher in dCOV than in CG (p=0.005) and sCOV (p=0.011). ALT level of dCOV was higher than that of CG (p=0.001). Fibrinogen level of CG was lower compared to both the sCOV (p=0.036) and the dCOV (p=0.004).

The proportion of patients aged under 65 years and over in the groups was compared. 50% (n=12) of the dCOV, 22.6% (n=7) in sCOV and 42.1% (n=8) in CG were under 65 years. Although the proportion of younger patients was higher in dCOV, there was no significant difference between the groups (p=0.094).

There was a single hemorrhagic case in dCOV, and the etiology was arteriovenous malformation.

Six patients in dCOV who had no prior RF for stroke are listed in Table 2.

Two patients in CG had no prior RF. One of them had intracardiac thrombus, and one was cryptogenic. Six

Table 1. Demographic, clinical, radiological, and laboratory findings according to the diagnostic groups and according to the outcome groups

	CG (n=19)	sCOV (n=31)	dCOV (n=24)		Good outcome mRS 0-2 (n=37)	Poor outcome mRS 3-6 (n=37)	
	n mean ± SD	n mean ± SD	n mean ± SD	p	n mean ± SD	n mean ± SD	p
Group							
dCOV	NA	NA	NA		7	17	0.043‡*
sCOV	NA	NA	NA		18	13	
CG	NA	NA	NA		12	7	
Age (range)	65.7±16.6 (40-94)	69.2±13.4 (33-89)	64.3±15.5 (28-93)	0.437†	66.2±15.3 (28-93)	67.2±14.7 (33-94)	0.922‖
≤65 y	8	7	12	0.094‡	13	14	0.809‡
Gender (Female: Male)	7:12	16:15	7:17	0.226‡	17:20	13:24	0.344‡
Temporal relationship COVID-19 diagnosis with stroke diagnosis					NA	NA	NA
Synchronous	NA	31	13	<0.001§*			
Asynchronous		-	11				
Delay of stroke after the onset of COVID-19 (range)	NA	NA	11.5±5.4 (4-21)	NA	NA	NA	NA
Risk factors and comorbidities							
1 RF	4	10	5	0.672§	13	6	0.222§
2 RF	9	9	6		11	13	
≥3 RF	4	4	6		4	10	
No RF	2	6	6		7	7	
Malignancy	0	2	1		2	1	
Medication							
None	4	11	8	0.796§	14	9	0.287§
Antiaggregants	5	11	8		12	12	
Anticoagulants	1	1	2		1	3	
Other	8	7	6		8	13	
Irregular use of antiaggregants	1	1	0		2	0	
Stroke type							
TACI	2	3	5	0.879‡	3	7	0.780‡
PACI	8	11	11		16	14	
POCI	3	6	4		6	7	
LACI	4	6	2		7	5	
TIA	0	2	1		2	1	
Hematoma	2	3	1		3	3	
ECG							
Sinus rhythm	18	25	21	0.387§	32	32	1.000‡
Atrial fibrillation	1	6	3		5	5	
CO-RADS							
1	19	0	0		12	7	0.038§*
2	0	0	0		0	0	
3	0	5	0	<0.001§*	4	1	
4	0	11	0		8	3	
5	0	15	0		6	9	
6	0	0	24		7	17	

Echocardiography							
Normal	2	3	4	0.386§	6	3	0.082§
Mild findings	7	14	8		14	15	
Low EF and/or akinetic wall	3	2	4		6	3	
Aortic stenosis	0	1	0		0	1	
Cardiac mass/intracardiac thrombus	3	1	0		4	0	
Prosthetic valve	1	0	0		0	1	
CTA							
Normal	6	9	7	0.419§	14	8	0.580§
Atherosclerotic changes	4	6	3		6	7	
Symptomatic stenosis	5	9	11		10	15	
Asymptomatic stenosis	2	3	2		4	3	
Vasculitic findings	1	0	0		1	0	
Outcome							
Home discharge	15	24	17	0.650§	33	23	0.019§*
Transfer to another center	1	2	1		1	3	
Still hospitalized	3	2	2		3	4	
In-hospital death	0	3	4		0	7	
mRS	1.8±1.5	2.5±1.9	3.9±1.6	0.006†*	NA	NA	
Blood biochemistry							
WBC	9.4±2.6	9.8±3.6	9.4±4.3	0.634†	9.1±3.5	10.2±3.7	0.112‖
Hemoglobin	13.4±2.8	12.7±2.1	12.6±1.7	0.158†	13.0±1.8	12.7±2.5	0.799‖
Platelet	242.2±81.7	304.4±103.1	262.7±119.8	0.041†*	269.6±93.9	280.2±117.9	0.841‖
NLR	3.3±1.7	4.2±3.9	6.1±3.4	0.007†*	3.0±1.6	6.7±4.1	<0.001‖*
CRP	16.8±14.4	32.1±58.3	73.2±82.8	0.027†*	29.4±50.7	53.5±74.3	0.077‖
ESR	26.6±29.7	36.1±24.4	44.3±29.6	0.107†	30.5±29.0	40.0±27.2	0.115‖
D-dimer	0.9±0.6	0.6±0.8	1.1±1.1	0.265†	0.6±0.8	1.1±0.9	0.033‖*
Procalcitonin	0.9±2.4	0.4±1.5	0.9±2.2	0.271†	0.3±1.5	0.9±2.3	0.002‖*
AST	21.9±6.9	29.3±10.1	33.6±15.0	0.004†*	24.7±8.3	32.9±13.8	0.009‖*
ALT	15.5±6.8	19.8±13.4	29.8±16.4	0.001†*	20.7±14.6	23.1±13.9	0.284‖
BUN	38.1±14.6	44.4±15.5	50.6±23.6	0.136†	40.1±14.3	49.4±21.4	0.074‖
Creatinine	0.9±0.2	0.9±0.3	0.9±0.3	0.773†	0.9±0.3	0.9±0.2	0.280‖
Fibrinogen	433.1±87.4	451.3±149.9	559.5±99.0	0.002†*	461.9±135.8	505.8±180.5	0.394‖

CG: Control group, sCOV: Suspected COVID-19, dCOV: Definite COVID-19, RF: Vascular risk factors, TIA: Transient ischemic attack, ECG: Electrocardiography, EF: Ejection fraction, CTA: Computed tomography angiography, mRS: Modified Rankin scale, WBC: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, COVID-19: Coronavirus disease-2019, SD: Standard deviation, *p<0.05, †Kruskal-Wallis test, ‡Pearson chi-square test, §Fisher's Exact test, ‖Mann-Whitney U test

patients in sCOV had no prior RF. Three of them had hyperlipidemia, and three of them had large vessel occlusion.

The comparison of the demographic and clinical variables of outcome groups is shown in Table 1. When all participants were divided into two groups according to mRS scores, three diagnostic groups showed significant differences indicating that the poor outcome in the dCOV group was higher than the sCOV and CG (p=0.043). There was a significant difference in terms of CO-RADS scores (p=0.038), NLR (p<0.001), D-dimer (p=0.033), procalcitonin (p=0.002) and AST (p=0.009) between the two groups.

RFs, medication, echocardiography and CTA were then classified into two groups as normal vs. abnormal, and outcome was classified into three groups as home discharge, still hospitalized and death in order to improve the quality of statistical analysis. There were no significant differences among the CG, sCOV, and dCOV groups in terms

Table 2. Six patients in COVID-19 definite group who had no prior risk factors for stroke

	Age	Infarct location	Echocardiography	CTA	Detected risk factors
Patient 1	48	Unilateral multifocal posterior circulation	Normal	Normal	ANA +
Patient 2	53	Right large MCA territory	NA	Right ICA stenosis	Hyperlipidemia and large vessel occlusion
Patient 3	55	Bilateral anterior circulation multifocal	Normal	Normal	Lupus anticoagulant +
Patient 4	28	Bilateral anterior circulation multifocal	Normal	Normal	Cryptogenic
Patient 5	63	Bilateral anterior and posterior circulation	Normal	Normal	Hyperlipidemia
Patient 6	46	Bilateral anterior and posterior circulation	Normal	Normal	Hyperlipidemia

CTA: Computed tomography angiography, ANA: Antinuclear antibody, MCA: Middle cerebral artery, ICA: Internal carotid artery, COVID-19: Coronavirus disease-2019

Table 3. Predictor variables of outcome groups

	B	p	Exp (B)	95% CI for EXP (B)
D-dimer	0.376	0.452	1.456	0.546-3.881
NLR	1.246	0.004*	3.478	1.480-8.172
Procalcitonin	0.302	0.157	1.353	0.890-2.055
AST	0.002	0.970	1.002	0.907-1.107

NLR: Neutrophil-to-lymphocyte ratio, AST: Sspartate aminotransferase, CI: Confidence interval, *Whole model test p<0.001

of RFs (p=0.483), medication (p=0.541), echocardiography (p=0.587), CTA (p=0.971), and outcome (p=0.421). There were also no significant differences among the good outcome and poor outcome groups in terms of RFs (p=0.234), medication (p=1.0), echocardiography (p=0.293), and CTA (p=0.799).

An LRA was performed with outcome groups as the dependent variable and D-dimer, NLR, procalcitonin, and AST as the predictor variables. A total of 43 cases were analyzed, and the full model was significantly reliable (chi-square =30.6, df =4, p<0.001). This model accounted for between 50.9% and 67.9% of the variance in the outcome groups, with 90.5% of the good outcome participants successfully predicted, and 81.8% of the poor outcome participants successfully predicted. Overall, 86.0% of predictions were accurate. Predictor variables are shown in Table 3. Only NLR reliably predicted good and poor outcome (odds ratio =3.478, confidence interval =1.480-8.172, p=0.004).

ROC analysis was applied to determine the cut-off values where NLR had high sensitivity and specificity in distinguishing patients with poor outcomes from the patients with a good outcome. It was found that NLR indicated patients with poor outcome with an 0.831 AUC. The optimum cut-off was 3.7 as the sensitivity and specificity were both 75.7% (Figure 1).

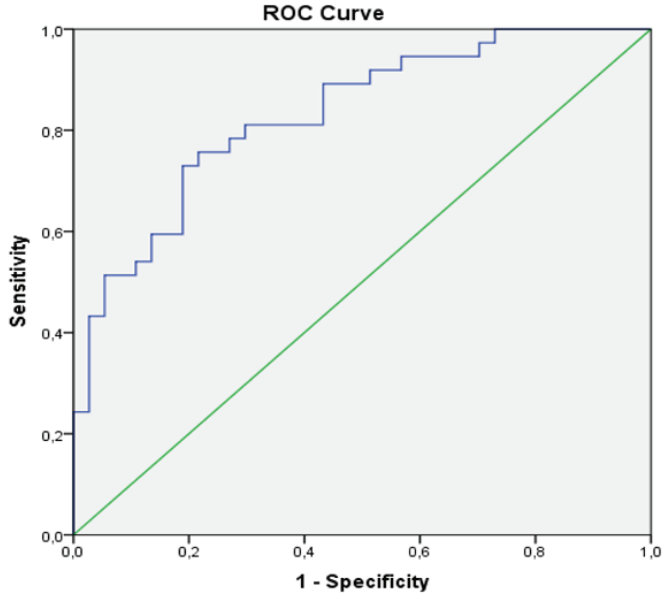

Figure 1. Neutrophil-to-lymphocyte ratio prediction of poor outcome

Area under curve: 0.831

Discussion

In this prospective study, three groups of stroke patients were evaluated. There were no differences among the groups in terms of demographical, clinical, and neuroradiological features. In the dCOV, just over half of the patients were admitted with stroke symptoms and diagnosed with COVID-19 at admission, and nearly half of the patients initially had a COVID-19 diagnosis. They were treated at home or hospital, and after a gap of 4-21 days, they had developed a stroke. Ischemic stroke was the most common stroke subtype in dCOV. The dCOV group had higher mRS scores indicating poor outcomes. Higher mortality was evident in dCOV and sCOV groups than CG. There was a trend in abnormal NLR, CRP, AST, ALT, and fibrinogen findings for the dCOV. Patients with poor outcomes had higher levels of D-dimer, NLR, procalcitonin,

and AST. NLR predicts reliably poor outcomes, overall with an accuracy of 86.0%.

Consistent with the literature (5,14), 75% (n=18) of the dCOV had at least one RF. Younger patients with COVID-19 and stroke have been reported in early reports of the pandemic (15). Still, subsequent studies and meta-analyses have shown that older age, male gender, and vascular RF are associated with COVID-19 related stroke (16). COVID-19 may trigger the pathogenesis in older patients with COVID-19, especially those with traditional RF (2).

In our study, as in previous literature, ischemic stroke was predominant in dCOV (17).

Delay of stroke after the onset of COVID-19 has been reported in several studies as 8.8 (6.3-11.6) days (4), 12 days (6), 8-24 days (18). This delay stands for the late thromboembolism complications of immune-mediated coagulopathy (16,19).

In the meta-analyses and the large studies, a male predominance has been reported (4,16,17). The majority of COVID-19 patients in our study were also male, but there was no difference among the groups in terms of gender.

Several pathogenic mechanisms such as coagulopathy, inflammation, and platelet activation for COVID-19-related stroke have been proposed (2). Elevated D-dimer and fibrinogen levels, both of which are the biomarkers of inflammation and hypercoagulable state (20), are the most reported findings in COVID-19 patients with stroke (3,6) and proposed to be the source of venous and arterial thromboembolism (21-24). Although D-dimer levels were elevated in all groups in our patients, there was no significant difference between the diagnostic groups. The poor outcome group had higher levels of D-dimer than the good outcome group. D-dimer greater than 1 mg/mL was associated with severe COVID-19 and mortality (25). A D-dimer level greater than 1 mg/mL was found in the dCOV group in our study. Elevated inflammatory markers such as interleukin, ESR, and CRP have also been reported (6). COVID-19 related stroke patients also have higher lactate dehydrogenase, ALT, and AST levels than COVID-19 negative stroke patients (7). Similar to the previous studies, the dCOV group in our study also had higher levels of inflammatory markers, ALT, and AST. Interleukin-6 levels were not available in this study.

The dCOV group in our study had a higher NLR than the CG. The poor outcome group had higher NLR, D-dimer, procalcitonin, and AST. The NLR levels predicted poor outcome. NLR is another inflammatory marker that is associated with poor outcome, higher intensive care requirement, and higher complications of COVID-19 and has also been reported as a predictor of poor outcome in ischemic stroke (20,26,27). Increased level of NLR is thought to be evidence of dysregulated neutrophil extracellular traps (NETs). NETs are networks of extracellular fibers including chromatin, proteins, antimicrobial peptides, and enzymes (26,27), which may promote platelet adhesion and thrombus formation (28). The relationship between NETs and ischemic stroke and NETs and COVID-19 have been described (26), but the role of NETs in COVID-19 related stroke still needs to be clarified. Our study showed that higher NLR levels are also a predictor of the poor outcome in COVID-19 related stroke with an optimum cut-off value of 3.7. The cut-off value of NLR has previously been reported as 4.795, with 83.9% sensitivity and 75.0% specificity for the severity of COVID-19 (29).

The positivity of anti-phospholipid antibodies has also been reported in COVID-19 related stroke patients (30). One patient had ANA positivity, and one patient had lupus anticoagulant positivity in our study.

Most importantly, the dCOV group in our study had worse outcomes and higher mortality. A more extended stay in the hospital, increased mortality, and higher need for intensive care unit have been reported in COVID-19 related stroke patients (2,7,31).

Although this study cannot provide a causality between COVID-19 and stroke, it clarifies the clinical characteristics of COVID-19 related stroke. In addition to highlighting higher mortality in COVID-19 related stroke, it also shows that NLR levels higher than 3.7 are a predictor of poor outcome in COVID-19 related stroke.

Study Limitations

This study has several limitations. First, this is a single-center study with a limited number of patients. Second, our study did not include patients who had acute stroke treatment because our center does not have an acute stroke unit, and we cannot perform acute treatment of patients with thrombolysis and thrombectomy. Such patients are referred to appropriate centers by the emergency call center. Third, our group definitions are not sufficiently precise due to diagnostic challenges. The sCOV group is theoretically a heterogeneous group that we are not sure whether they have COVID-19 pneumonia or another viral pneumonia. And we could not totally rule out COVID-19 diagnosis in the CG; there may be asymptomatic carriers.

Conclusion

COVID-19 related stroke is associated with high inflammatory biomarkers, poor outcome, and high mortality rates. Therefore COVID-19 related stroke should be a priority for public health. NLR is a potential, cost-effective, and easy-to-use marker of poor prognosis in COVID-19 related stroke. Further studies, especially multi-center large studies, are needed to better understand the relationship between these two clinical entities.

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Ethics

Ethics Committee Approval: According to a protocol approved by the Local Ethics Committee of the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date:15/01/2021, number: 2021.01.1.12.213.rl. 012) and the Relevant Committee of the Turkish Ministry of Health, all participants provided written informed consent, per the Declaration of Helsinki.

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Concept: Z.Y., S.Ö., E.Ç., N.K., Design: Z.Y., S.Ö., E.Ç., N.K., Data Collection or Processing: Z.Y., S.Ö., E.Ç., N.K., Analysis or Interpretation: Z.Y., S.Ö., Literature Search: Z.Y., S.Ö., Writing: Z.Y., S.Ö., E.Ç., N.K.

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ORIGINAL RESEARCH

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Should the Paramedian Approach be the First Choice in Spinal Anesthesia of Geriatric Patients? Prospective Randomized Clinical Trial

Geriatrik Hastaların Spinal Anestezisinde Paramedyan Yaklaşım İlk Tercih Olmalı mı? Prospektif Randomize Klinik Çalışma

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Abstract

Objective: There are significant technical difficulties in spinal anesthesia for geriatric patients. Spinal anesthesia can be applied with a median or paramedian approach. This study aimed to evaluate the success rates and intraoperative complications of two approaches in spinal anesthesia for geriatric patients.

Method: This prospective randomized study included 110 patients aged 60 years and older with ASA II-III status. The patients were randomly divided into the median (M) and paramedian (P) groups. Spinal anesthesia was performed on the patients at the L3-4 level. In case of failure in both approaches despite three attempts, an alternative method was applied. The patients' demographic data, the number of interventions, the duration of the procedure, bone contact during the process, the need for an alternative approach, and intraoperative complications were recorded.

Results: While the success rate at the first attempt was 56.6% in group M, it was 78.1% in group P. The duration of spinal anesthesia was significantly lower in group P (18±13 vs. 41±27 seconds, p<0.001). The mean number of attempts and bone contact were also significantly lower in group P (1.1±0.3 vs. 1.4±0.7, p=0.02, 30.9% vs. 52.8%, p=0.02, respectively). No significant difference was observed in terms of intraoperative complications.

Conclusion: This study showed that the procedure time was significantly shortened in the paramedian approach in spinal anesthesia in geriatric patients, and there was less bone contact during the procedure. We think the paramedian approach may be the first choice in spinal anesthesia for geriatric patients.

Keywords: Geriatrics, regional anesthesia, spinal anesthesia

Öz

Amaç: Geriatrik hastaların spinal anestezisinde önemli teknik zorluklar mevcuttur. Spinal anestezi medyan veya paramedyan yaklaşımla uygulanabilir. Bu çalışmada, geriatrik hastaların spinal anestezisinde iki farklı yaklaşımın başarı oranlarını ve intraoperatif komplikasyonlarını değerlendirmek amaçlanmıştır.

Yöntem: Prospektif randomize bu çalışmaya ASA II-III statüsüne sahip 60 yaş ve üzeri 110 hasta dahil edildi. Hastalar randomize olarak grup mediyan (M) ve grup paramedyan (P) olarak ikiye ayrıldı. Tüm hastalara L3-4 seviyesinde spinal anestezi uygulandı. Her iki grupta üç denemeye rağmen spinal anestezide başarısız olunması durumunda diğer yaklaşım uygulandı. Hastaların demografik verileri, girişim sayıları, işlem süresi, işlem sırasındaki kemik teması, alternatif yaklaşım ihtiyacı ve intraoperatif komplikasyonları kaydedildi.

Bulgular: Demografik veriler gruplar arasında benzerdi. Grup M'de ilk denemede başarı oranı %56,6 iken grup P'de %78,1 idi. Spinal anestezi süresi grup P'de anlamlı olarak düşüktü (18±13'e karşın 41±27 saniye, p<0,001). Ayrıca girişim sayıları ve kemik teması da grup P'de anlamlı olarak düşük bulundu (sırasıyla, 1,1±0,3'e karşın 1,4±0,7, %30,9'a karşın %52,8, p=0,02). İntraoperatif komplikasyonlar açısından anlamlı farklılık gözlenmedi.

Sonuç: Bu çalışmada geriatrik hastaların spinal anestezisinde paramedyan yaklaşımında işlem süresinin anlamlı olarak kısaldığı ve işlem sırasında daha az kemik teması olduğu gösterilmiştir. Geriatrik hastaların spinal anestezisinde paramedyan yaklaşımın ilk tercih olabileceğini düşünüyoruz.

Anahtar kelimeler: Geriatrik, rejyoner anestezi, spinal anestezi

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Introduction

Spinal anesthesia (SA), also known as subarachnoid block, is a low-cost neuraxial anesthesia method that can be applied, which has a high success rate and allows rapid mobilization. It is frequently preferred in lower abdomen, inguinal, urogenital, rectal, and lower extremity operations. Compared to general anesthesia, it has advantages such as rapid recovery, early mobilization and discharge, lower pulmonary embolism and venous thrombosis, less surgical bleeding and transfusion need, and early return of bowel functions (1).

SA can be performed with the median approach (MA) or the paramedian approach (PA). Although MA is most frequently preferred in routine practice, its application becomes difficult due to changes in the vertebrae of geriatric patients. The PA has been reported to be more successful due to the decreased joint distances with aging, limitation of joint movements, highly calcified interspinous ligament, and osteophyte formation (2). However, there are limited studies on the median and PAs in SA of geriatric patients in the literature.

This study was conducted to compare the effectiveness of the median and PAs in SA of geriatric patients regarding success rates, difficulties, advantages, and early complications.

Materials and Methods

This prospective randomized study was conducted at the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital after the approval of the Local Ethics Committee (date: 09.02.2022, number: 19). The principles of the Declaration of Helsinki complied with the study. The study included one hundred ten patients with the American Society of Anesthesiologists (ASA) II-III status, who underwent elective orthopedic operation under SA and obtained an informed consent form.

The study's inclusion criteria included patients aged 60 years and over and were scheduled for elective surgery under SA in the sitting position. Exclusion criteria of the study included patients who did not accept SA, who were under the age of 60 years, who would undergo SA in the lateral decubitus position, who were allergic to any drug in SA, for whom SA was contraindicated, and who were not successful in SA despite repeated attempts. After creating two sets of 55 unique numbers from 1 to 110 for each group using an internet-based program (www.randomize.org), the patients were randomly allocated to one of the two groups as group median (M) (n=55, SA with a MA) and group paramedian (P) (n=55, SA with PA). A flow chart demonstrating patient selection is presented in Figure 1.

After 8 hours of fasting, the patients were taken to the operating table for the procedure. Standard ASA monitoring was applied throughout the process, including the non-invasive arterial blood pressure, heart rate, and pulse oximetry. A peripheral intravenous cannula (18-20 G) was placed. A crystalloid infusion was started. Routine iv fluid loading was not performed before SA in our clinic. Before the procedure, patients were premedicated with 0.02-0.5 mg kg^{-1} midazolam.

The puncture site of the patients, placed in a sitting position by the healthcare personnel, was cleaned under aseptic conditions. The classical method, connecting the tops of both iliac crests (Tuffier's line), was used to determine the level at which SA would be applied. This level was accepted as L4 spinous process or L4-L5 vertebral space, and the first intervention level was determined as L3-L4 in all patients. For group M, SA was performed using 25 µg fentanyl and 10-15 mg bupivacaine heavy, according to the operation, using 22 G Quincke needles at the L3-4 level with the MA. L4-L5 levels were optionally used as an alternative in patients whose first attempt failed. The PA was tried in group M patients when SA could not be performed despite three attempts.

For group P, 22 G Quincke needles were advanced 10-15 degrees medially and 60 degrees cephalad from 1 cm lateral and 1 cm caudal distance of the interspinous space at the L3-4 level. The operation performed SA with 25 µg fentanyl and 10-15 mg bupivacaine heavy. Likewise, L4-L5 levels were optionally used as an alternative in patients who failed the first attempt. The MA was tried in group P patients with a similar method when SA could not be performed despite three attempts. Surgery was allowed after adequate block levels were achieved. General anesthesia was started when the procedure was unsuccessful or there was not enough block.

The same anesthesiologist performed all SA interventions, and the same anesthesia technician recorded the procedure times. The demographic data of the patients, the number of interventions, the duration (seconds) of the procedure after skin disinfection, the success rates according to the groups, the levels of vertebrae used for SA, bone contact during the process, and the transition to an alternative approach were recorded. In addition, hypotension, bradycardia,

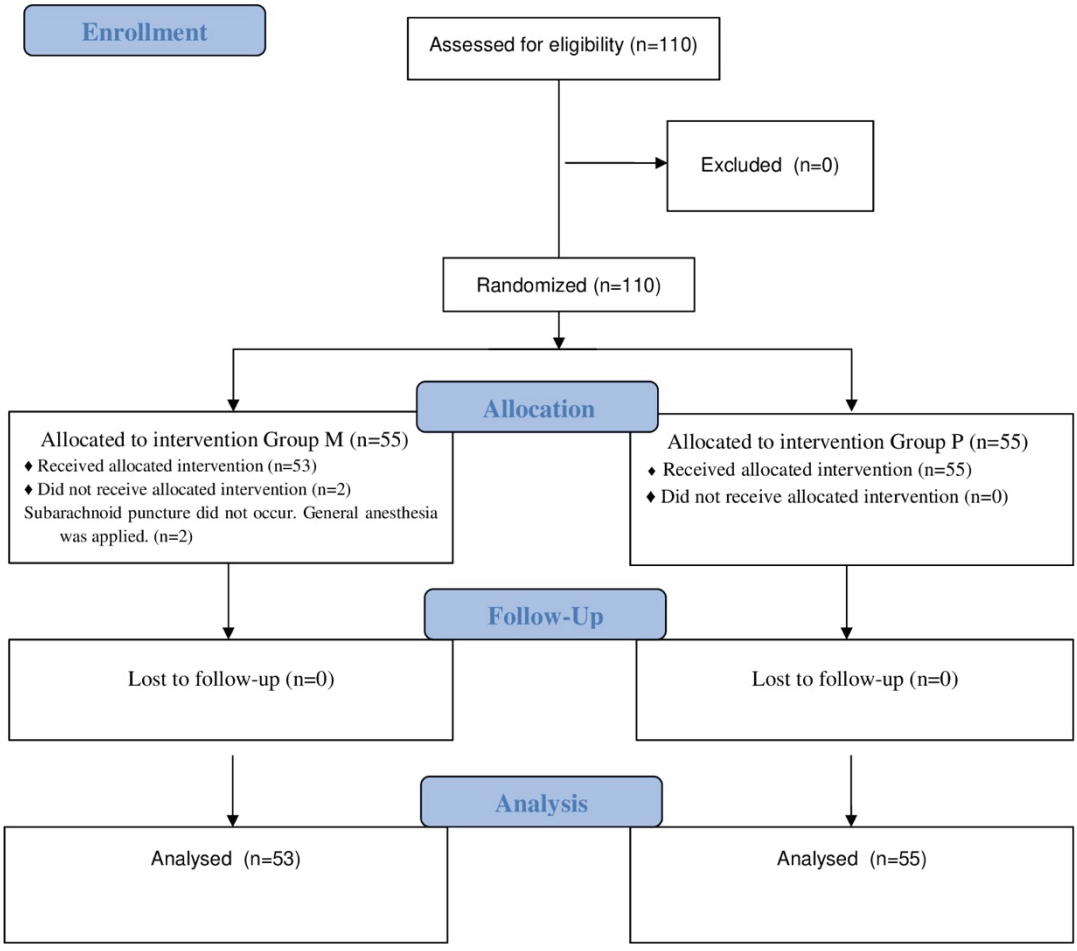

Figure 1. Flow chart of the study

nausea-vomiting, total or high spinal block, cardiac arrest, hemorrhagic tap due to venous puncture, failure in SA, and paresthesia development were recorded between the groups.

Statistical Analysis

G*Power 3.1 program was used to calculate the sample size. For t-tests, with an effect size of 0.5, α: 0.05, and study power (1-β): 0.8, 51 patients in each group were evaluated. One-hundred ten patients, 55 from both groups, were included in our study.

The IBM SPSS 22 statistical package program was used for data analysis. The Shapiro-Wilk test and histogram were used to examine the compatibility of the data for normal distribution. Categorical data were expressed as absolute and relative frequencies. Continuous variables were expressed as means and standard deviation. The chi-square and Fisher's Exact test were used to compare categorical variables between the two groups. The Mann-Whitney U test was used to analyze quantitative data that did not show normal distribution. An independent sample t-test was used to compare the normally distributed quantitative data. $p<0.05$ was considered statistically significant.

Results

One hundred ten patients, including 55 patients in each group, were included in the study. General anesthesia was applied since subarachnoid puncture did not occur in 2 patients in group M. As a result, 108 patients, 53 in group M and 55 in group P, were included in the study (Figure 1). The characteristics of patients and findings related to SA are presented in Table 1. There was no significant difference between the groups regarding age, gender, ASA status, and body mass index [p=0.52, p=0.54 (χ^2:0.36, df:1), p=0.34 (χ^2:0.88, df:1), p=0.49 respectively].

Table 1. The characteristics of patients and findings related to spinal anesthesia

	All population (n=108)	Group M (n=53)	Group P (n=55)	p	χ^2
Age (years)	70.4±8.3	70.4±9.3	70.4±7.3	0.52*	
Gender, n (%)				0.54†	0.36
Female	60 (55.6)	31 (58.5)	29 (52.7)		
Male	48 (44.4)	22 (41.5)	26 (47.3)		
ASA, n				0.34†	0.88
II	64	29	35		
III	44	44	20		
BMI (kg/m²)	27.5±4.7	27.5±5.6	27.6±3.5	0.49‡	
Duration of process (sec)	30.0±24.3	41.7±27.8	18.8±13.0	<0.001*	
Number of attempts	1.3±0.5	1.4±0.7	1.1±0.3	0.02*	
Touching the bone? n (%)				0.02†	5.33
Yes	45 (41.7)	28 (52.8)	17 (30.9)		
No	63 (58.3)	25 (47.2)	38 (69.1)		

Data are given as mean ± standard deviation, number of patients (n), and percentage.
ASA: American Society of Anesthesiologists status, BMI: Body mass index, sec: Seconds, data obtained by using the chi-square (χ^2) are given in the analysis. *Mann-Whitney U test, †Chi-square test, ‡Independent sample t-test

The duration of SA was significantly lower in group P (p<0.001). The rate of a successful subarachnoid block at the first attempt was 56.6% in group M and 78.1% in group P. The number of SA interventions was significantly lower in group P (p=0.02). Attempts to achieve SA in the groups are shown in Table 2.

Bone contact rate was significantly lower in group P (p=0.02, χ^2:5.33, df:1) (Table 1). The alternative level L4-L5 range was used in 18.8% (n=10) of the patients in group M and 12.7% (n=7) of the patients in group P. Although the need for SA from a different level was less in group P, no significant difference was found (p=0.38).

Hypotension was accepted as a 25% decrease in the patient's baseline blood pressure. Hypotension was resolved quickly by administering 5-10 mg of ephedrine hydrochloride as a vasoconstrictor and fluid resuscitation. There was no significant difference between the groups regarding hypotension and bradycardia (p=0.74, p=1.00, respectively). Complications observed during SA of the patients are shown in Table 3.

Table 2. Number of attempts for spinal anesthesia

Number of attempts	Group M	Group P
First attempt	**30 (56.6%)**	**43 (78.1%)**
Second attempt	8	9
Third attempt	5	0
Another approach	10	2

Data are given as the number and percentage of patients

Table 3. Complications observed in spinal anesthesia

Complications	Group M	Group P	p
Hypotension	5	4	0.74*
Bradycardia	4	4	1.00*
Cardiac arrest	-	-	-
Total or high spinal anesthesia	-	-	-
Hemorrhagic tap	3	2	-
Nausea-vomiting	1	1	-
Inadequate spinal anesthesia	2	2	-
Paresthesia	0	0	-

Data are given as the number of patients (n). *Fisher's Exact test

Discussion

The subarachnoid block is widely used in the lower abdomen and lower extremity operations because it reduces postoperative morbidity and complications. The MA is the most commonly used method. At the same time, it has technical advantages, such as requiring less frequent three-dimensional imaging and easier detection of the operation site since the broadest part of the ligamentum flavum is in the median part (3). However, this approach is problematic in elderly patients due to degenerative changes in the structural elements of the spine. In the MA, the supraspinous, interspinous ligaments, and ligamentum flavum are passed after the skin, and subcutaneous tissue is given. After passing the skin and subcutaneous tissue, the ligamentum flavum is directly reached in the PA. Since the paravertebral muscles are replaced by the supraspinous

and interspinous ligaments, difficulties due to degenerative change can be avoided in elderly patients (4).

Bayındır et al. (4) reported the success rate of SA as 70% with the PA and 95% with the MA in young patients aged 30-40 years. In contrast, Singh et al. (5) found a success rate of 100% in the PA and 90% in the MA. Similarly, Kartal et al. (6) reported the success of SA in geriatric patients as 79.1% with the MA and 90.5% with the PA. In our study, the success rate of SA was 81.1% with the MA and 96.3% with the paramedian method. Cerebrospinal fluid (CSF) flow was not observed in 18.8% (n=10) of the patients in group M after three attempts. SA was performed with the PA. In the PA, CSF flow was not observed in 3.6% (n=2) of the patients despite three attempts, and successful SA was achieved with the MA. The incidence of SA with the other approach was significantly higher in group M (p=0.01). In our study, the success of SA was found to be higher with the PA in the geriatric population, which is consistent with the literature. Bayındır et al. (4) reported higher success of the MA in their study. We think this is related to the patient population being in the young-middle age range.

Rabinowitz et al. (2) reported that the procedure time was short in the PA with continuous SA in elderly patients. However, no significant difference was observed. Kartal et al. (6) reported that the application time of SA was significantly shorter in the PA compared to the median approach. In our study, the application time of SA was 41±27 seconds in group M and 18±13 seconds in group P. Consistent with the literature, we found that the procedure time was significantly shorter in the PA (<0.001). As stated in the literature, we think that in the PA, bypassing the interspinous and supraspinous ligaments and avoiding stenosis and degeneration in the interspinous space shorten the procedure time. At the same time, the difficulty in positioning during the procedure in the geriatric population also contributed to the shorter procedure time in the PA (2,4,6).

Singh et al. (5) reported the success rate in the first trial as 70% in the MA and 90% in the PA. In another study, the success rate in the first attempt was 68% in the MA and 92% in the PA (7). In our research, the success rate in the first trial was 56.6% in the MA and 78.1% in the PA. Consistent with the literature, the PA had a higher success rate in the first attempt.

Bayındır et al. (4) compared the number of interventions and the duration of SA in SA performed with the median and PAs. They found that the number of interventions and the duration of SA were higher in the MA (4). Kartal et al. (6) reported that while there was no significant difference in the number of interventions, the duration of SA administration was significantly higher. In our study, the number of interventions and the time of application were substantially lower in the paramedian group, consistent with the literature (p=0.02, p<0.001, respectively).

It is difficult and uncomfortable to place geriatric patients in a forward flexion position during subarachnoid block application. The contact of the spinal need with the bone at the intervention site may also cause pain. Podder et al. (8) reported that young patients with lower extremity trauma felt less pain with the PA approach in SA. Kartal et al. (6) said that patients had lower bone contact rates in the paramedian method but it was not significantly different. In their study, 60% of the patients who underwent the PA did not have bone contact. In our study, bone contact was not observed in 69% of the patients who underwent the PA. Consistent with the literature, bone contact was significantly lower in the PA (p=0.02).

Positioning for SA in elderly patients is difficult, especially in orthopedic surgery because the procedure is painful and positioning is difficult. Similar to the studies in the literature, a sitting position was preferred for SA in our study (6-8). Rabinowitz et al. (2) reported that the intervention rate from another space was 5% with PA and 30% with MA due to failure in SA applied in the lateral decubitus position. Kartal et al. (6) reported that intervention from another space was performed at 27% with PA and 36.8% with MA. Our study performed SA at the L4-L5 level, an alternative level, in 18.8% in the MA and 12.7% in the PA. Considering that the higher success rate of the PA reduces the need for intervention from another level, this difference was not significant in our study (p=0.38).

Hypotension is a common complication of SA. The literature's improvement rate varies between 8.2% and 57.9%. The rate of cardiac arrest due to SA has been reported to be between 0.018% and 0.029% (9). One of the acute effects of the sympathetic blockade after SA is that it triggers reflexes and causes bradycardia with a decrease in cardiac venous return. A study evaluating 612 SA cases reported complications in 148 patients, including bradycardia in 25.7%, nausea and vomiting in 13.5%, post-spinal headache in 29.1%, urinary retention in 2.7%, hypotension in 21.6%, 3.4% inadequate SA was found in 2% and unsuccessful application in 2% (10). In our study, hypotension was observed at a rate of 8.3% and bradycardia at a rate of 7.4%,

while no significant difference was observed between the groups (p=0.74, p=1.00, respectively). Respiratory arrest and cardiac arrest were not observed in any patient.

During the procedure, nausea and vomiting in SA often develop due to hypotension or retraction of the peritoneum. Hypotension that occurs should be treated with fluid resuscitation or vasoconstrictor agents. In our study, it was seen in 1.8% of the patients. It was resolved in a short time with fluid resuscitation and vasoconstrictor administration. We think that the geriatric patients in our study resulted in lower rates of nausea and vomiting than in the literature.

Post-spinal headache (PSHA) is one of the common complications of SA. Its incidence increases with younger age, increased needle size, use of sharp-pointed needles, and recurrent puncture of the dura mater. Its incidence varies between 0.1% and 36% (3). Firdous et al. (1) applied SA with two different approaches using a pencil-tipped needle in 120 patients undergoing cesarean section. They found the incidence of PSHA in the PA lower than in the MA (1.6% vs. 5%). However, no significant difference was observed (1). In their study, Haider et al. (11) found the incidence of PSHA with the PA as significantly lower than with the MA. In another study conducted on 150 middle-aged patients undergoing orthopedic surgery, the incidence of PSHA was reported to be similar to the two approaches (12). Kartal et al. (6) did not register PSHA in their study with geriatric patients. PSHA was not evaluated because our study focused on the success of the median and PAs and was rarely seen in old orthopedic surgery in our hospital.

In a study investigating the causes and failures of neuraxial blocks, the failure rate in SA was reported as 3.9% in 6966 patients (13). In our study, SA was inadequate in 3.7% (n=2) of the patients in group M and 3.6% (n=2) of the patients in group P. In these cases, spontaneous breathing is preserved, and the depth of anesthesia is increased with intravenous analgesics, or general anesthesia is started.

Study Limitations

This study has several limitations. First, this study was conducted in a single center. Secondly, our study focused on the success of SA. Early intraoperative complications of SA were investigated, but late complications were not evaluated. In addition, diseases such as ankylosing spondylitis and anatomical variations of the vertebral column, which limit vertebral movements, were not determined.

Conclusion

As a result, SA in geriatric patients is complex due to anatomical changes in the vertebrae and patient compliance. The PA makes direct access to the dura possible from the paravertebral muscles without encountering the supraspinous and interspinous ligaments. This study showed that the procedure time was significantly shortened in the PA in SA of geriatric patients, and there was less bone contact during the procedure. Anesthesiologists' experience in SA approaches can also affect the duration and success of the procedure. We think that the PA may be the first choice in SA for geriatric patients.

Ethics

Ethics Committee Approval: After the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee, a prospective placebo-controlled randomized study was started (date: 09.02.2022, number: 19).

Informed Consent: An informed consent form was obtained from the patients participating in the study.

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Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., A.S.Ş., Design: K.A., A.S.Ş., Data Collection or Processing: K.A., Analysis or Interpretation: K.A., A.S.Ş., Literature Search: K.A., A.S.Ş., Writing: K.A.

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ORIGINAL RESEARCH

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Correlation Between Coronary Lesion Severity Detected in Fractional Flow Reserve with Systemic Immune Inflammation Index and Atherogenic Plasma Index

Fraksiyonel Akım Rezervi Kullanılarak Saptanan Koroner Lezyon Ciddiyeti ile Sistemik İmmün Enflamasyon İndeksi ve Aterojenik Plazma İndeksi Arasındaki Korelasyon

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Abstract

Objective: Systemic immune inflammation index (SII) and atherogenic plasma index (AIP) are indices that have been defined in recent years and play an important role in the process of atherosclerosis and inflammation. In this study, we aimed to investigate the relationship between the severity of atherosclerotic lesions detected and AIP and SII in patients who underwent fractional flow reserve (FFR) in coronary angiography.

Method: In this study, 119 patients who underwent elective FFR in coronary angiography were retrospectively analyzed. According to the severity of FFR lesion, two groups were formed as FFR <0.8 group (77 patients) and FFR >0.8 group (42 patients). SII, AIP, demographic data and other parameters were compared between the two groups.

Results: In the FFR applied groups, there was a statistically significant difference between the two groups in terms of high-density lipoprotein (p=0.001), platelet (p=0.007), mean platelet volume (MPV) (p=0.016), monocytes (p<0.001), lymphocyte (p<0.001), SII (p<0.001), AIP (p=0.009) and HbA1c (p<0.001). In the univariable regression analysis, we found that HbA1c [odds ratio (OR): 10; 95% confidence interval (CI): 3.2-3.5, p<0.001], monocytes (OR: 273.8; 95% CI: 24.8-3015.3, p<0.001), MPV (OR: 0.6; 95% CI: 0.39-0.91, p=0.02), SII (OR: 1.06; 95% CI: 1.03-1.09, p<0.001) and AIP (OR: 3.7; 95% CI: 1.6-10, p=0.01) parameters were predictors. In the multivariable regression analysis, we found that HbA1c (OR: 9.41; 95% CI: 1.89-46.73, p=0.006), monocytes (OR: 108.2; 95% CI: 6.8-1726.2,

Öz

Amaç: Sistemik immün enflamasyon indeksi (SII) ve aterojenik plazma indeksi (AIP) son yıllarda tanımlanmış, ateroskleroz ve enflamasyon sürecinde önemli rol alan indekslerdir. Bu çalışmamızda koroner anjiyografide fraksiyonel akış rezervi (FFR) uygulanan hastalarda, tespit edilen aterosklerotik lezyon ciddiyeti ile AIP ve SII arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Bu çalışma kapsamında, koroner anjiyografide elektif FFR işlemi uygulanan 119 hasta retrospektif olarak incelendi. FFR lezyon ciddiyetine göre; FFR <0,8 grup (77 hasta), FFR >0,8 grup (42 hasta) şeklinde iki grup oluşturuldu. İki grup arasında SII, AIP, demografik veriler ve diğer parametreler karşılaştırıldı.

Bulgular: FFR uygulanan gruplarda yüksek yoğunluklu lipoprotein (p=0,001), platelet (p=0,007), ortalama trombosit hacmi (MPV) (p=0,016), monosit (p<0,001), lenfosit (p<0,001), SII (p<0,001), AIP (p=0,009) ve HbA1c (p<0,001) açısından iki grup arasında istatistiksel olarak anlamlı derecede farklılık saptandı. Yapılan tek değişkenli regresyon analizinde HbA1c [olasılık oranı (OO): 10; %95 güven aralığı (GA): 3,2-3,5, p<0,001], monosit (OO: 273,8; %95 GA: 24,8-3015,3, p<0,001), MPV (OO: 0,6; %95 GA: 0,39-0,91, p=0,02), SII (OO: 1,06; %95 GA: 1,03-1,09, p<0,001) ve AIP'nin (OO: 3,7; %95 GA: 1,6-10, p=0,01) birer prediktör olduğu saptandı. Yapılan çok değişkenli regresyon analizinde ise HbA1c (OO: 9,41; %95 GA: 1,89-46,73, p=0,006), monosit (OO: 108,2; %95 GA: 6,8-1726,2, p=0,001) ve

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p=0.001) and SII (OR: 1.005; 95% CI: 1.002-1.008, p=0.004) parameters were independent predictors. With the applied ROC analysis, SII predicted FFR lesion severity with 75% sensitivity and 72% specificity [area under the curve (AUC): 0.79; 95% CI: 0.72-0.87, p<0.001], and AIP with 62% sensitivity and 60% specificity (AUC: 0.64; 95% CI: 0.54-0.75, p=0.008).

Conclusion: In this study, we would like to emphasize that simple, fast and low-cost methods such as AIP and SII may be parameters related to lesion severity detected in FFR. These parameters are easily accessible, reproducible and widely used.

Keywords: Atherogenic plasma index, coronary angiography, fractional flow reserve, systemic immune inflammation index

SII (OO: 1,005; %95 GA: 1,002-1,008, p=0,004) parametrelerinin bağımsız birer prediktör olduğu saptandı. Uygulanan ROC analizi ile SII %75 sensitivite %72 spesifite ile [eğrinin altındaki alan (AUC): 0,79; %95 GA: 0,72-0,87, p<0,001], AIP %62 sensitivite %60 spesifite ile (AUC: 0,64; %95 GA: 0,54-0,75, p=0,008) FFR lezyon ciddiyetini öngörmekteydi.

Sonuç: Bu çalışmamızda özellikle AIP ve SII gibi basit, hızlı ve düşük maliyetli yöntemlerin, FFR'de saptanan lezyon ciddiyeti ile ilişkili parametreler olabileceğine vurgu yapmak istiyoruz. Bu parametreler kolay ulaşılabilir, tekrarlanabilir ve yaygın olarak kullanılabilmektedirler.

Anahtar kelimeler: Aterojenik plazma indeks, fraksiyonel akış rezervi, koroner anjiyografi, sistemik immün enflamasyon indeks

Introduction

Cardiovascular diseases associated with atherosclerosis are still the leading cause of death worldwide (1). Coronary angiography (CAG) is the most important diagnostic method in the evaluation of coronary artery lesions. However, the visual assessment of the severity of the lesion in the coronary arteries by CAG is not always reliable. It is important to measure fractional flow reserve (FFR) in the coronary arteries, especially when the level of stenosis is 40-70% (i.e., moderate). FFR is a reliable method especially for the functional assessment of lesion severity (2). Coronary atherosclerosis formation is multifactorial and atheromatous plaque is affected by many parameters (3). In some studies, the importance of triglycerides in atherosclerosis has been emphasized (4). A high triglyceride concentration stimulates the activity of the cholesteryl ester transfer protein. This enables the lipoprotein particles to be enriched with triglycerides, making them better substrates for lipolysis. This leads to more high-density lipoprotein (HDL) catabolism and more low-density lipoprotein (LDL) particles to form (5). In addition to the atherogenic plasma index (AIP) serum cholesterol levels, cholesterol esterification rates are based on the relationship of lipoprotein particle size and residual lipoproteinemia. And this index has been shown to be a marker of plasma atherogenicity (6,7). However, data on changes in coronary atherosclerosis depending on AIP levels are limited. It is known to be effective in the formation of atherosclerosis and inflammation as well as lipid parameters. Therefore, parameters associated with inflammation have often been the subject of research. These parameters are mostly hematological inflammatory markers such as platelets, neutrophils and/or lymphocyte cells. Among them, platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) are some inflammation markers that can be easily obtained by looking at the complete blood count. The association of these markers with mortality and adverse clinical outcomes in cardiovascular diseases has been reported (8). Previous studies have revealed that PLR and NLR correlate with the anatomical severity of atherosclerotic lesions in the coronary arteries (9). In addition, it has been reported to be associated with hemodynamically severe coronary artery stenosis (10). The systemic immune inflammation index (SII) is a new definition that combines these three hemogram parameters and is an indicator of inflammation. SII is an important marker of adverse clinical outcomes in many cancer types (11). In addition, in a recent study, SII was reported to be a marker for functionally severe coronary stenosis in patients with a diagnosis of chronic coronary syndrome (12).

In this study, we aimed to examine the relationship between the severity of atherosclerotic stenosis and AIP and SII in patients evaluated with FFR in CAG.

Materials and Methods

Study Population

This study was planned as a retrospective, single-center study. Within the scope of the study, patients who underwent CAG at Dicle University Faculty of Medicine between January 2013 and November 2019 were examined. Patients with angina unresponsive to medical treatment and stable angina pectoris, who showed high-risk markers in non-invasive imaging methods, were analyzed consecutively. Among these patients, 119 consecutive patients who underwent elective FFR were included in the study. Inclusion criteria for the study were determined as patients who were evaluated as stable angina pectoris and underwent FFR procedure under elective conditions. Exclusion criteria included patients with acute coronary syndrome, severe arrhythmia, hemodynamic instability, previous history of revascularization (percutaneous coronary intervention

or coronary artery bypass graft), moderate/severe heart valve pathology, acute decompensated and/or severe heart failure patients with severe kidney and liver failure, active infection, malignancy, hematological diseases, patients receiving steroid therapy, familial history of hyperlipidemia, rheumatological disease, life expectancy <1 year, age <18 and >90 years. A signed informed consent form was obtained from each patient participating in the study. The study was designed in accordance with the principles of the Declaration of Helsinki. Our clinical study was approved by the ethics committee of İzmir Bakırçay University with the date of 29.04.2021 and number 264.

Demographic and Laboratory Data

Venous blood samples were obtained from all patients included in the study after they were admitted to our cardiology clinic, and after an overnight fasting period. Blood was drawn from the anterior surface of the forearm in the supine position. For complete blood count, blood was drawn into tubes containing standard EDTA and measurements were made immediately after blood collection. Measurements of lipid levels were made in serum separated by centrifugation at 3000 rpm at room temperature. Total cholesterol, triglyceride, and HDL were evaluated in Konnelab kits, Konnelab 60i and Thermo Clinical Labsystems (Thermo Clinical Labsystems Oy Ratostic 2, Vantae, Finland) devices. LDL cholesterol levels in patients were calculated with the Friedewald formula. Drugs used by the patients, demographic and echocardiographic data were obtained from hospital records.

Definitions

Hypertension (HT) was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure ≥90 mmHg or using antihypertensive medication. Hyperlipidemia was defined as a total cholesterol level >200 mg/dL or an LDL level >130 mg/dL. Smoking was defined as currently smoking in the past 6 months. AIP was obtained by applying logarithmic transformation to the triglyceride/HDL ratio (13). SII was determined as the ratio of absolute platelet count x absolute neutrophil count/absolute lymphocyte count (14).

CAG and FFR

Selective CAG was performed on the patients with a right-left femoral or radial approach, using 6F or 7F catheters with the Judkins technique. CAG images were evaluated by two experienced cardiologists, who were unaware of the laboratory values and clinical features of the patients. The degree of stenosis in the coronary arteries was decided on the basis of the projection showing the greatest stenosis. Evaluation by applying the FFR was left to the discretion and discretion of the cardiologists. After an intra-arterial bolus of 5000 units of heparin, the coronary arteries were visualized using a guide catheter without side holes. A 0.014 inch pressure monitoring guidewire (PrimeWire, Volcano, San Diego, CA, USA) was placed distal to the stenosis after calibration. Before FFR measurements, 200 µg bolus nitroglycerin was administered intracoronally. Initially, distal intracoronary pressures of the patients were recorded. Hyperemia was triggered by administering gradually increasing doses of intracoronary adenosine until the last value where the FFR value decreased. FFR value was determined as the ratio between the mean distal intracoronary pressure and the mean aortic pressure, at which time the highest level of hyperemia was observed. An FFR value of <0.80 was defined as functionally significant. According to FFR lesion severity, two groups were formed, as FFR <0.8 group (77 patients) and FFR >0.8 group (42 patients).

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) software version 25.0 for Windows (IBM Co., Armonk, NY, USA). The conformity of numerical variables to the normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Numerical variables are given as mean and standard deviation. In order to compare the two groups in terms of numerical variables, the independent samples t-test was used if normal distribution was achieved, and the Mann-Whitney U test was used if not. Categorical variables were shown as numbers (n) and ratios (%). The relationship between categorical variables was examined with the Pearson chi-square and Fisher's Exact tests. Relationships between SII and AIP were evaluated using the Spearman's RHO analysis. The power of SII and AIP values in predicting FFR lesion severity was evaluated with univariable and multivariable analyses. Odds ratio (OR) and 95% confidence interval (CI) values were recorded. In addition, ROC analysis was performed for SII and AIP cut-off values. Cut-off value was determined according to Youden index. Descriptive data were expressed as mean ± standard deviation values for normally distributed continuous variables, and median (minimum-maximum) values for non-normally distributed variables. The significance level for all hypotheses was accepted as <0.05.

G Power 3.1.9.7 programme was used for the sample size calculation. Estimated sample size was calculated using the Student's t-test with 0.95 (1-β err probe) power, α=0.05 error level and Cohen (d) effect size =0.8. Accordingly, it was found appropriate to complete the study with at least 70 (group 1 =35 patients, group 2 =35 patients) patients. G Power 3.1.9.7 programme was used for post-hoc power. Difference between two independent means tests was applied. The power (1-β err probe) was determined as 0.993 with alpha 0.05 error level, Cohen (d) effect size =0.8.

Results

Patients included in the study were divided into groups as group-I: FFR>0.8; group-II, with FFR<0.8. The mean age of the patients included in the study was 58.3 (±9.8) years, and 66.4% of them were male. When the means of age and gender were compared between the groups, there was no statistically significant difference [57.9 (±10.2) vs. 58.4 (±9.6), p=0.764; 71.4% vs. 63.6%, p=0.390, respectively]. 94.1% of the patients were in the NYHA class-I category. The most common symptoms among the patients included in the study were chest pain and shortness of breath (90.8% and 21%, respectively). Between the two groups, no significant difference was found in terms of smoking (33.4% versus 42.9%, p=0.310), HT (47.6% versus 39%, p=0.36), coronary artery disease (CAD) (50% versus 54.5%, p=0.635), and hyperlipidemia (57.1% vs 50.6%, p=0.498) (Table 1). Other demographic data and comorbid diseases between the groups are given in Table 1.

When the biochemical and hemogram parameters were examined, there was a statistically significant difference between the two groups in terms of HDL (p=0.001), platelet (p=0.007), MPV (p=0.016), monocytes (p<0.001), lymphocyte (p<0.001), SII (p<0.001), AIP (p=0.009) and HbA1c (p<0.001). When the left ventricular ejection fraction values [53.3 (±8.4) vs. 54.7 (±7.9), p=0.356] were compared, there was no statistically significant difference between the two groups (Table 2). Other hemogram, biochemical and echocardiographic parameters are summarized in Table 2.

The medical treatments received by the patients are compared in Table 3. The results of the CAG data are shown in Table 4.

In the univariable regression analysis performed among the factors affecting the severity of the lesion detected in FFR, we found that HbA1c (OR: 10; 95% CI: 3.2-3.5, p<0.001), monocytes (OR: 273.8; 95% CI: 24.8-3015.3, p<0.001), MPV (OR: 0.6; 95% CI: 0.39-0.91, p=0.02), SII (OR: 1.06; 95% CI: 1.03-1.09, p<0.001) and AIP (OR: 3.7; 95% CI: 1.6-10, p=0.01) parameters were each a predictor. In the multivariable regression analysis, we found that HbA1c (OR: 9.41; 95% CI: 1.89-46.73, p=0.006), monocytes (OR: 108.2; 95% CI: 6.8-1726.2, p=0.001) and SII (OR: 1.005; 95% CI: 1.002-1.008, p=0.004) parameters were each an independent predictor (Table 5).

ROC analysis was used to reveal the power of SII and AIP parameters to predict lesion severity detected in FFR. According to the results obtained, SII predicted FFR lesion severity with 75 % sensitivity and 72% specificity (AUC: 0.79; 95% CI: 0.72-0.87, p<0.001), and AIP with 62% sensitivity and 60% specificity (AUC: 0.64; 95% CI: 0.54-0.75, p=0.008) (Figure 1).

Discussion

In this study, SII, a new marker that includes neutrophil, platelet, and lymphocyte counts, as well as AIP, a marker that includes triglycerides and HDL, were independently associated with coronary artery lesions, which were evaluated by FFR measurement and considered functionally significant. In addition, SII was superior to AIP in predicting hemodynamically significant coronary obstruction. FFR is a technique that guides the operator in the decision of percutaneous intervention in moderate to severe lesions during CAG (15). Functionally severe coronary stenosis is associated with ischemia in addition to adverse clinical outcomes (16). Therefore, in this study, FFR measurements were used to identify hemodynamically severe lesions, instead of visually evaluating them in angiography.

It is known that atherosclerosis and inflammation are in a cause-effect relationship. Many inflammatory parameters have a role from the onset of CAD to its progression (17). Neutrophils, lymphocytes and platelet cells play an important role in this process (17,18). Neutrophil infiltration into endothelial tissue initiates the atherosclerotic process, and this is the event that initiates increased damage to the endothelium. In addition, neutrophil cells secrete parameters and markers related to acute inflammation after tissue damage (18). It has been described that low lymphocyte cell counts in the blood cause CAD and adverse clinical outcomes (19). When chronic inflammation develops in the body, a decrease in the number of lymphocyte cells occurs in response to the stress process (19). Lymphocytes are often the regulators of the immune system and have positive contributions to the immune system. On the contrary, neutrophils are associated with negative events in the inflammatory response (20). Platelets are cells that play

Table 1. Demographic and comorbid characteristic results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Age, (years)	57.9 (±10.2)	58.4 (±9.6)	58.3 (±9.8)	0.764
Male sex, n (%)	30 (71.4)	49 (63.6)	79 (66.4)	0.390
SBP, mmHg	129.3 (±16.8)	127.7 (±16.5)	128.3 (±16.5)	0.614
DBP, mmHg	70.7 (±10.6)	70.6 (±10.2)	70.7 (±10.3)	0.964
Heart rate, minute	75.7 (±12.1)	73.7 (±12.5)	74.4 (±12.3)	0.403
NYHA class I, n (%)	41 (97.6)	71 (92.2)	112 (94.1)	0.231
Chest pain, n (%)	36 (85.7)	72 (93.5)	108 (90.8)	0.161
Dyspnea, n (%)	10 (23.8)	15 (19.5)	25 (21.0)	0.580
Palpitation, n (%)	10 (23.8)	5 (6.5)	15 (12.6)	**0.007**
Tiredness, n (%)	7 (16.7)	4 (5.2)	11 (9.2)	**0.039**
Dizziness, n (%)	3 (7.1)	4 (5.2)	7 (5.9)	0.666
Syncope, n (%)	0 (0)	1 (1.3)	1 (0.8)	0.458
Smoking, n (%)	14 (33.4)	33 (42.9)	47 (39.5)	0.310
Alcohol use, n (%)	1 (2.4)	4 (5.2)	5 (4.2)	0.465
Hypertension, n (%)	20 (47.6)	30 (39.0)	50 (42.0)	0.360
CAD, n (%)	21 (50.0)	42 (54.5)	63 (52.9)	0.635
Hyperlipidemia, n (%)	24 (57.1)	39 (50.6)	63 (52.9)	0.498
COPD, n (%)	8 (19.0)	11 (14.3)	19 (16.0)	0.498
Thyroid disease, n (%)	4 (9.5)	6 (7.8)	10 (8.4)	0.745
Stroke/TIA, n (%)	1 (2.4)	6 (7.8)	7 (5.9)	0.231
CKD, n (%)	1 (2.4)	2 (2.6)	3 (2.5)	0.943
Peripheral artery disease, n (%)	1 (2.4)	4 (5.2)	5 (4.2)	0.465
Pacemaker/ICD/CRT, n (%)	0 (0)	2 (2.6)	2 (1.7)	0.292
Malignancy, n (%)	1 (2.4)	1 (1.3)	2 (1.7)	0.661
Anemia, n (%)	1 (2.4)	2 (2.6)	3 (2.5)	0.943

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NYHA: New York heart association, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary diseases, TIA: Transient ischemic attack, CKD: Chronic kidney disease, ICD: Implantable cardioverter defibrillator, CRT: Cardiac resynchronization therapy, Group I: FFR>0.8, Group II: FFR<0.8

a serious role in inflammation and atherogenesis as well as thrombosis. Therefore, it is associated with these three pathological events and acts as a bridge. It also mediates the recruitment of leukocytes and progenitor cells to damaged sites in vascular tissue. In addition, these parameters reveal chemokines together with cytokines that mediate vascular inflammation (21). Biomarkers obtained using these three parameters have been the subject of extensive research in recent years, as they are inexpensive, easy to calculate and easy to obtain. In a study conducted, it has been reported that high mean platelet volume/lymphocyte ratio and mean platelet volume/platelet ratio are associated with mortality in patients with GFR <60 mL/min and admitted with the diagnosis of acute myocardial infarction (22). SII, which is formulated by considering neutrophil, thrombocyte and lymphocyte parameters, has been defined and researched recently. It reveals the relationship between the inflammatory process and the immune system status (11). SII has also been used as a prognostic marker in many cardiovascular diseases and malignancies (9,14,23). Recently, Yang et al. (24) reported that higher SII values were associated with CAD, myocardial infarction, and stroke. They also found that SII was a better predictor than traditional markers (24). Consistent with these studies and available data, we demonstrated a strong association with the severity of coronary artery stenosis, and assessed it using the SII FFR method.

In addition to inflammatory parameters, abnormal lipid metabolism also plays a serious role in the progression of coronary atherosclerosis, formation of calcified plaque and unstable plaque formation (25). Lipid deposition in the vascular intima layer is a very important event in the emergence and progression of the atherosclerotic process. In a study conducted, high monocyte/HDL ratio

Table 2. Hemogram, biochemical and echocardiographic results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Urea, mg/dL	33.80 (±13.32)	34.02 (±10.52)	33.94 (±11.53)	0.921
Creatinine, mg/dL	1.07 (±0.99)	0.89 (±0.20)	0.95 (±0.61)	0.123
Uric acid, mg/dL	5.54 (±1.02)	5.28 (±0.89)	5.37 (±0.94)	0.162
Total cholesterol, mg/dL	190.55 (±52.37)	198.73 (±44.18)	195.84 (±46.57)	0.362
Triglyceride, mg/dL	156.72 (±84.62)	184.18 (±129.09)	174.49 (±115.74)	0.218
HDL, mg/dL	44.10 (±10.86)	37.51 (±9.39)	39.83 (±10.38)	**0.001**
LDL, mg/dL	112.67 (±53.60)	128.66 (±83.30)	123.10 (±74.48)	0.269
Hemoglobin, g/dL	13.56 (±1.29)	13.56 (±1.54)	13.56 (±1.45)	0.981
Platelet, $x10^3$/µL	243.19 (±46.54)	277.65 (±72.91)	265.49 (±66.71)	**0.007**
Leukocyte, $x10^3$/µL	8.63 (±2.42)	8.44 (±1.55)	8.50 (±1.89)	0.593
MPV, fL	8.72 (±0.89)	8.29 (±0.92)	8.44 (±0.93)	0.016
Neutrophil, $x10^3$/µL	4.80 (±1.68)	5.27 (±1.53)	5.10 (±1.59)	0.123
Monocyte, $x10^3$/µL	0.72 (±0.20)	0.95 (±0.21)	0.87 (±0.23)	**<0.001**
Lymphocyte, $x10^3$/µL	2.88 (±1.04)	2.11 (±0.53)	2.38 (±0.83)	**<0.001**
Fasting glucose, mg/dL	97.93 (±10.83)	99.56 (±10.95)	98.98 (±10.89)	0.438
TSH, µIU/Ml	2.03 (±1.37)	2.18 (±1.49)	2.12 (±1.45)	0.588
T4, ng/dL	1.37 (±0.40)	1.45 (±0.50)	1.42 (±0.47)	0.319
Calcium, mg/dL	9.31 (±0.55)	9.38 (±0.58)	9.36 (±0.57)	0.578
Sodium, mmol/L	137.21 (±15.64)	140.81 (±13.43)	139.54 (±14.29)	0.191
Potassium, mmol/L	4.47 (±0.48)	4.39 (±0.49)	4.42 (±0.49)	0.429
AST, U/L	26.07 (±19.32)	24.69 (±15.03)	25.18 (±16.60)	0.666
ALT, U/L	23.02 (±10.17)	20.19 (±8.28)	21.19 (±9.04)	0.103
SII	426.61 (±152.41)	753.29 (±428.16)	637.99 (±388.23)	**<0.001**
AIP	0.52 (±0.25)	0.65 (±0.25)	0.60 (±0.26)	**0.009**
HbA1c, %	5.56 (±0.39)	5.98 (±0.59)	5.83 (±0.56)	**<0.001**
Sinus rhythm, n (%)	42 (100)	71 (92.2)	113 (95.0)	0.063
LVEF, %	53.3 (±8.4)	54.7 (±7.9)	54.2 (±8.0)	0.356
LVEDD, cm	48.45 (±5.31)	47.08 (±4.91)	47.56 (±5.07)	0.159
LVESD, cm	30.93 (±6.42)	28.56 (±5.45)	29.39 (±5.90)	**0.036**
LVDD, n (%)	26 (61.9)	55 (71.4)	81 (68.1)	0.287

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MPV: Mean platelet volume, TSH: Thyroid stimulating hormone, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, HbA1C: Hemoglobin A1c, LVEF: Left Ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter; LVDD: Left ventricular diastolic dysfunction, Group I: FFR>0.8, Group II: FFR<0.8

Table 3. Results of drugs used by patients

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
Beta-blockers, n (%)	24 (57.1)	48 (62.3)	72 (60.5)	0.580
ACE-I, n (%)	9 (21.4)	25 (32.5)	34 (28.6)	0.203
Statine, n (%)	26 (61.9)	41 (53.2)	67 (56.3)	0.363
Antiaggregant, n (%)	28 (66.7)	52 (67.5)	80 (67.2)	0.923
Anticoagulant, n (%)	2 (4.8)	6 (7.8)	8 (6.7)	0.528
ARBs, n (%)	8 (19.0)	12 (15.6)	20 (16.8)	0.629
Dihydropyridine CCB, n (%)	7 (16.7)	11 (14.3)	18 (15.1)	0.729
Loop diuretic, n (%)	3 (7.1)	12 (15.6)	15 (12.6)	0.185
Aldosterone antagonist, n (%)	3 (7.1)	8 (10.4)	11 (9.2)	0.559
Thiazide diuretic, n (%)	5 (11.9)	20 (26.0)	25 (21.0)	0.072
Non-dihydropyridine CCB, n (%)	0 (0)	4 (5.2)	4 (3.4)	0.133

ACE-I: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium channel blockers, Group I: FFR>0.8, Group II: FFR<0.8

was found to be significant in predicting mixed plaques in asymptomatic intermediary carotid artery stenosis (26). In addition, AIP predicts CAD; triglyceride is more valuable than LDL, HDL and total cholesterol (27). An increase in the AIP value leads to a decrease in LDL particle, an increase in the emergence of foam cells. It has also been reported that there is an increase in the ratio of small dense low-density lipoprotein-cholesterol (sdLDL), which is a marker supporting the development of atherosclerotic plaque (28). Studies show that the AIP value is the determining factor and parameter in the atherosclerotic process and cardiovascular diseases (29). Onat et al. (30) have reported that high AIP is a risk factor for CAD in both men and women in the Turkish population. In another recent study, AIP revealed that increases in monocyte/lymphocyte ratio and triglyceride-glucose index were strong markers and indices associated with subclinical CAD (31). In a previous study, we revealed that the AIP value might be an indicator of the level of collateral development in patients with chronic coronary occlusion (32). In the light of all these findings, the result we obtained in the study is compatible with the data in the literature. In addition, in a previously published study, we demonstrated a strong correlation between HbA1c value and FFR lesion severity (33). These parameters are important in terms of showing them as predictors in the process of atherosclerosis, since they are inexpensive and easily accessible and they are obtained from blood tests. Researching these markers in newly defined indexes

Table 4. Coronary angiography results

Parameters	Group I (n=42)	Group II (n=77)	Total (n=119)	p
LMCA	2 (4.8)	2 (2.6)	4 (3.4)	0.58
LAD proximal	12 (28.6)	22 (28.5)	34 (28.6)	1.0
LAD mid	16 (38.1)	30 (39)	46 (38.7)	0.92
LAD distal	1 (2.4)	5 (6.5)	6 (5)	0.32
Cx proximal	5 (11.9)	5 (6.5)	10 (8.4)	0.30
Cx mid	3 (7.1)	5 (6.5)	8 (6.7)	0.89
Cx distal	1 (2.4)	0	1 (0.8)	0.17
RCA proximal	1 (2.4)	4 (5.2)	5 (4.2)	0.46
RCA mid	1 (2.4)	3 (3.9)	4 (3.4)	0.66
RCA distal	0	1 (1.3)	1 (0.8)	0.45

LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, Group I: FFR>0.8, Group II: FFR<0.8

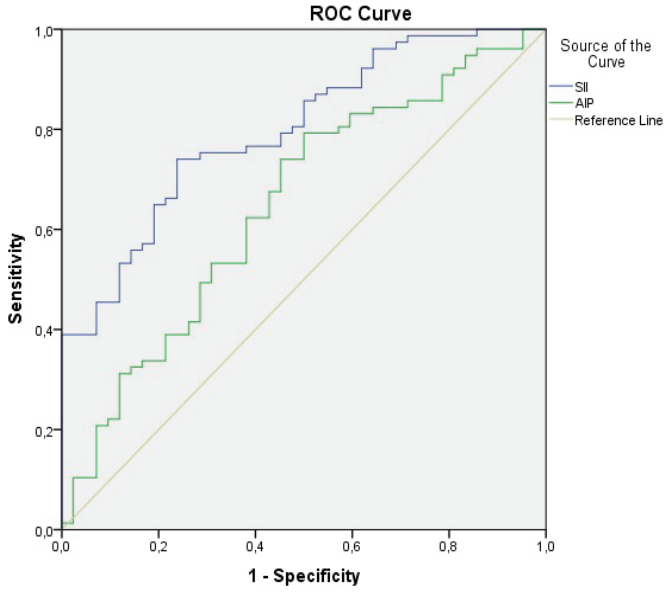

Figure 1. The cut-off values of SII and AIP associated with FFR in the ROC curve analysis

SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, FFR: Fractional flow reserve

Table 5. Univariable and multivariable regression analyses for determining predictor of FFR lesion severity

Parameters	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.006 (0.96-1.04)	0.76	-	-
Gender	1.42 (0.63-3.22)	0.39		
Hypertension	0.7 (0.32-1.5)	0.36	-	-
Hyperlipidemia	1.2 (0.6-2.7)	0.49	-	-
LVEF	1.02 (0.97-1.07)	0.35	-	-
HbA1c	10 (3.2-3.5)	**<0.001**	9.41 (1.89-46.73)	**0.006**
Monocyte	273.8 (24.8-3015.3)	**<0.001**	108.2 (6.8-1726.2)	**0.001**
MPV	0.6 (0.39-0.91)	**0.02**	0.85 (0.45-1.58)	0.600
SII	1.06 (1.03-1.09)	**<0.001**	1.005 (1.002-1.008)	**0.004**
AIP	3.7 (1.6-10)	**0.01**	6.73 (0.68-66.70)	0.103

LVEF: Left ventricular ejection fraction, HbA1C: Hemoglobin A1c, MPV: Mean platelet volume, SII: Systemic immune inflammation index, AIP: Atherogenic plasma index, OR: Odds ratio, CI: Confidence interval, FFR: Fractional flow reserve

instead of evaluating them separately increases the power of studies in this field.

Study Limitations

Our study has some limitations as well as strengths. The study was designed retrospectively. The number of patients included in the study was relatively small. Prospective studies with larger numbers of patients are needed. Many other important markers of inflammation, such as CRP and albumin, were not used in this study (it is unlikely to conduct a study that could include and examine all types of inflammation markers). Our analyses were based on a single value of platelets, neutrophils, lymphocytes, triglycerides, and HDL. In other words, we did not examine temporal changes and variations in these inflammatory parameters.

Conclusion

In this study, we would like to emphasize that simple, fast and low-cost methods such as AIP and SII may be parameters related to lesion severity detected in FFR. These parameters are easily accessible, reproducible and widely used. Therefore, we think that these parameters can be an alternative option in cases where it is difficult to apply invasive methods due to patient preference or other reasons.

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Ethics

Ethics Committee Approval: Our clinical study received ethics committee approval on 29.04.2021 from İzmir Bakırçay University, with the number 264.

Informed Consent: Verbal and written consent was obtained from all patients.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.G., Concept: T.G., Design: M.K., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., Literature Search: T.G., Writing: T.G.

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ORIGINAL RESEARCH

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Complete Blood Count Parameters in Apheresis Platelet Donors According to ABO and Rh Blood Groups

Aferez Trombosit Donörlerinde ABO ve Rh Kan Gruplarına Göre Tam Kan Sayımı Parametreleri

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Abstract

Objective: Data about the effects of blood groups on complete blood count parameters are limited. We aimed to examine the relationship between complete blood count parameters and ABO-Rh blood groups in this study.

Method: Three thousand volunteer apheresis donors were examined. The records of these cases were evaluated retrospectively and age, gender, complete blood count parameters, and ABO and Rh blood groups were recorded. Statistical evaluations were made by the SPSS 21 program.

Results: A significant correlation was found between the ABO blood group and erythrocyte distribution width-standard deviation and plateletcrit values (p=0.01, p=0.009, respectively). Neutrophil and mean erythrocyte hemoglobin concentration values were statistically significantly higher in Rh-negative cases than in Rh-positive cases (p=0.04, p=0.01, respectively). Neutrophil count was lower in the A blood group than in the non-A blood group (p=0.03). Lymphocyte count was significantly higher in cases with the B blood group than in cases with the non-B blood group (p=0.002).

Conclusion: We found a significant relationship between ABO and Rh blood groups and some complete blood count parameters. Therefore, one of the factors affecting hemogram parameters may be ABO and Rh blood group.

Keywords: ABO blood group, hemoglobin, lymphocyte, neutrophil, platelet, Rh blood group

Öz

Amaç: Kan gruplarının tam kan sayımı parametreleri üzerindeki etkilerine ilişkin veriler sınırlıdır. Bu çalışmada tam kan sayımı parametreleri ile ABO-Rh kan grupları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntem: Üç bin gönüllü aferez bağışçısı incelendi. Bu olguların kayıtları geriye dönük olarak değerlendirilerek yaş, cinsiyet, tam kan sayımı parametreleri, ABO ve Rh kan grupları kaydedildi. İstatistiksel değerlendirmeler SPSS 21 programı ile yapıldı.

Bulgular: ABO kan grubu ile eritrosit dağılım genişliği-standart sapma ve plateletcrit değerleri arasında anlamlı bir ilişki bulundu (sırasıyla p=0,01, p=0,009). Nötrofil ve ortalama eritrosit hemoglobin konsantrasyonu değerleri Rh negatif olgularda Rh pozitif olgulara göre istatistiksel olarak anlamlı derecede yüksekti (sırasıyla p=0,04, p=0,01). Nötrofil sayısı A kan grubunda A olmayan kan grubuna göre daha düşüktü (p=0,03). Lenfosit sayısı B kan grubuna sahip olgularda B olmayan kan grubuna sahip olgulara göre anlamlı olarak daha yüksekti (p=0,002).

Sonuç: ABO ve Rh kan grupları ile bazı tam kan sayımı parametreleri arasında anlamlı bir ilişki bulduk. Bu nedenle hemogram parametrelerini etkileyen faktörlerden biri de ABO ve Rh kan grubu olabilir.

Anahtar kelimeler: ABO kan grubu, hemoglobin, lenfosit, nötrofil, Rh kan grubu, trombosit

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Introduction

In addition to the history and physical examination findings, laboratory tests play an important role in the diagnosis and follow-up of the diseases. Complete blood count (CBC) is the most commonly used diagnostic hematological laboratory test in clinical practice. It provides information about the numbers of erythrocyte, leukocyte, and platelet, their shapes, and structural features. CBC is used for both diagnosis and follow-up of diseases such as anemia, leukemia, infection, and bleeding disorders. CBC containing more than 20 sub parameters can be performed by the auto analyzers in a very short time.

The results of the CBC parameters are evaluated according to the reference ranges determined by the manufacturer. However, age, race, gender, hunger status, altitude, pregnancy, technical equipment used, and environmental factors may affect CBC parameters (1-4). It is reported that dietary habits also affect the reference ranges of hemogram parameters (5). For this reason, determining the factors affecting the CBC parameters and arranging the reference ranges according to these factors provide an accurate interpretation of CBC parameters. The International Federation of Clinical Chemistry and Laboratory Medicine and the Clinical and Laboratory Standards Institute recommend that each laboratory establish its reference range for the CBC test.

Blood group identification was first made in 1901 by Karl Landsteiner as A, B, and O according to the type of antigen found on the erythrocyte surface (6). Sturli and Von Castelo defined the AB blood group in 1902. Currently, 339 blood group antigens and 33 blood group systems have been listed by the International Blood Transfusion Association study committee. The relationship between the ABO blood group and esophagus, stomach, prostate, colorectal, liver, and prostate cancers was reported (7-10). In addition, the relationship between coronary artery disease (CAD) and the ABO blood group was investigated, and CAD was found to be more common in patients with non-O blood group (11). Increased mean platelet volume (MPV) and platelet distribution width (PDW) values are also potential biomarkers for CAD. For this reason, it is thought that the reason why coronary artery disease is common in some blood groups may be related to PDW and MPV values. Studies investigating the relationship between the ABO blood group and MPV, PDW values were conducted. However, there are a few studies examining the effects of blood groups on all CBC parameters. Therefore, in this study, we aimed to investigate the effects of ABO and Rh blood groups on hemogram parameters.

Materials and Methods

Ethical approval was obtained from the Atatürk University Ethics Committee for this study (date: 17.12.2020, number: B.30.2.ATA.0.01.00/18). The study design was made in accordance with the Declaration of Helsinki. Three thousand volunteer apheresis donors who applied to the blood center of our hospital were analyzed in this study. All of the subjects included in the study were healthy and they had no history of systemic disease, drug use, or active infection. The medical files of all cases were evaluated retrospectively and age, gender, hemoglobin (hb), hematocrit (hct), erythrocyte (RBC), leukocyte (WBC), neutrophil (PNL), lymphocyte, monocyte, eosinophil, basophil, mean erythrocyte volume (MCV), mean erythrocyte hemoglobin (MCH), mean erythrocyte hemoglobin concentration (MCHC), erythrocyte distribution width-standard deviation (RDW-SD), erythrocyte distribution width-coefficient of variation (RDW-CV), plateletcrit (PCT), MPV, PDW, platelet-larger cell ratio (P-LCR) values, ABO and Rh blood groups were recorded. For the CBC test, a blood sample was taken into a tube with ethylenediaminetetraacetic acid (EDTA) and studied by Sysmex XN 1000 (Germany) automatic CBC device. ABO and Rh blood groups of the cases were determined by Galileo Immucor Gamma (Microplate, Germany) device. Cases with positive D antigen were considered as Rh-positive.

Statistical Analysis

Statistical evaluations were made by SPSS 21 windows software (Armonk, NY: IBM Corp). Descriptive data were defined as number and percentage for categorical variables, and mean ± standard deviation for numeric variables. For the comparison of the two groups, the Student's t-test was used in the presence of a normal data distribution, and the Mann-Whitney U test was used when there was no normal data distribution. Comparison of numeric values among three or more groups was performed using a One-Way analysis of variance (ANOVA) test for the data with normal distribution, and the Kruskal-Wallis test for the non-normally distributed data. A value of $p<0.05$ was considered as statistical significance.

Results

The mean age of all cases in our study was 33.97±11.04 (18-65) years; 2456 (81.9%) cases were men, and 544 (18.1%) were women. The distribution of ABO and Rh blood groups in all cases is shown in Table 1. A significant correlation between AB in the O blood group and RDW-SD and PCT

values (p=0.01, p=0.009, respectively) was detected through the ANOVA test. In subgroup comparisons, the RDW-SD value was found to be significantly higher in the A blood group compared to the B blood group and AB blood group (p=0.03, p=0.018, respectively). PCT value was significantly higher in the A blood group than in the AB blood group (p=0.04). A significant relationship was not determined between other hemogram parameters and the ABO blood group (Table 2).

Neutrophil count and MCHC value were statistically significantly higher in Rh-negative cases than in Rh-positive cases (p=0.04, p=0.01, respectively) (Table 3). There was no significant relationship between other hemogram parameters and the Rh blood group.

In only male cases, a significant relationship was found between the ABO blood group and RBC, RDW-SD values (p=0.01, p=0.01, respectively). In the subgroup examination, the RDW-SD value was found to be significantly higher in the A blood group than in the B blood group (p=0.026), and the RBC value in the AB blood group was significantly higher than in the A blood group (p=0.008). Neutrophil and MCHC values in Rh-negative cases were significantly higher than in Rh-positive cases (p=0.03, p=0.01, respectively). In male cases, no significant relationship was found between other hemogram parameters and ABO, Rh blood groups.

In only female cases, a significant association between hb, hct values, and ABO blood group was determined (p=0.004, p=0.002, respectively). In the subgroup evaluation, the hb value in the A blood group was found to be significantly higher than in the B, AB, and O blood groups (p=0.004, p=0.012, p=0.039, respectively). Hct value was also found significantly higher in the A blood group compared to B, AB, and O blood groups in accordance with the hb value

Table 1. The distribution of blood groups

Blood group	Male n (%)	Female n (%)	Total n (%)
A Rh(+)	885 (29.5%)	165 (5.5%)	1050 (35%)
A Rh(-)	157 (5.2%)	31 (1%)	188 (6.3%)
B Rh(+)	352 (11.7%)	78 (2.6%)	430 (14.3%)
B Rh(-)	60 (2%)	13 (0.4%)	73 (2.4%)
AB Rh(+)	162 (5.4)	60 (2%)	222 (7.4%)
AB Rh(-)	38 (1.3%)	7 (0.2%)	45 (1.5%)
O Rh(+)	602 (20.1%)	147 (4.9%)	749 (25%)
O Rh(-)	200 (6.7%)	43 (1.4%)	243 (8.1%)

Table 2. CBC parameters according to the ABO blood group

CBC parameters	Blood group					p
	A	B	AB	O	Total	
WBC (µL)	8155±1709	8314±1692	8115±1754	8203±1800	8194±1741	0.31
Lymphocyte (µL)	2803±751	2885±768	2805±784	2767±0.734	2805±752	0.42
Neutrophil (µL)	4496±121.8	4576±1279	4446±1297	4568±1358	4529±1295	0.32
Monocyte (µL)	630±174	628±163	637±194	638±175	633±174	0.63
Eosinophil (µL)	179±127	177±121	182±139	181±142	180±132	0.95
Basophil (µL)	46±21	46±23	43±21	45±21	45±21	0.33
RBC (µL)	5511±421	5533±418	5539±437	5489±440	5510±4290	0.17
Hb (g/dL)	16.05±1.22	16.06±1.25	16.03±1.28	15.98±1.25	16.03±1.24	0.53
Hct (%)	47.2±3.2	47.29±3.38	47.2±3.3	47.07±3.32	47.21±3.31	0.46
MCV (fL)	85.9±3.8	85.5±3.8	85.39±4.1	85.9±4.2	85.81±3.98	0.09
MCH (pg)	29.1±1.6	29.08±1.66	29±1.88	29.18±1.78	29.15±1.71	0.32
MCHC	33.9±1.25	33.98±1.3	33.95±1.3	33.96±1.25	33.96±1.26	0.98
RDW-SD	39.47±2.56	39.11±2.57	39.33±2.59	39.56±2.66	39.43±2.6	0.01
RDW-CV	12.62±0.78	12.57±0.83	12.66±0.77	12.66±0.84	12.63±0.81	0.16
PLT (µL)	270853±53594	269918±54323	264940±50275	270599±58214	270143±55092	0.58
MPV (fL)	10.07±0.81	10.16±0.83	10.08±0.87	10.11±0.83	10.10±0.83	0.3
PCT (%)	0.27±0.05	0.27±0.05	0.26±0.05	0.27±0.05	0.27±0.05	0.009
PDW	11.64±1.72	11.84±1.83	11.66±1.93	11.72±1.79	11.70±1.78	0.33
P-LCR	25.80±6.47	26.44±6.64	25.80±7.18	26.23±6.49	26.04±6.58	0.49

WBC: White blood cell, RBC: Red blood cell count, hb: Hemoglobin, hct: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, RDW-CV: Erythrocyte distribution width-coefficient of variation, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio

(p=0.009, p=0.007, p=0.005, respectively). Basophil, MCH and MCHC values were low in Rh-positive group compared to Rh-negative group (p=0.04, p=0.04, p=0.009, respectively). In female cases, there was no significant relationship between other CBC parameters and ABO, Rh blood groups.

The cases were compared as A Rh(+) and A Rh(-), B Rh(+) and B Rh(-), AB Rh(+) and AB Rh(-), O Rh(+) and O Rh (-). In addition, the cases were compared as A Rh (+) and non-A Rh (+), B Rh(+) and non-B Rh(+), O Rh(+) and non-O Rh(+), AB Rh(+) and non-AB Rh (+),A Rh(-) and non-A Rh (-), B Rh (-) and non-B Rh(-), O Rh(-) and non-O Rh(-), AB Rh(-) and non-AB Rh (-). Statistically significant results were shown in Tables 4, 5, respectively.

The cases were also grouped as A and non-A, B and non-B, AB and non-AB, and O and non-O blood groups. The neutrophil count in the A blood group (4496±121.8 µL) was significantly lower than in the non-A blood group (4613±1304 µL) (p=0.03). The lymphocyte count was found significantly higher in the B blood group (2885±768 µL) than in the non-B blood group (2697±757 µL) (p=0.002). There was no relationship between other hemogram parameters and these blood groups.

Table 3. CBC parameters according to Rh blood group

CBC parameters	Rh-positive	Rh-negative	p
Leukocyte (µL)	8167±1744	8314±1726	0.07
Lymphocyte (µL)	2804±756	2810±735	0.86
Neutrophil (µL)	4506±1287	4631±1326	0.04
Monocyte (µL)	630±174	644±177	0.09
Eosinophil (µL)	179±135	181±120	0.77
Basophil (µL)	45±22	46±21	0.43
RBC (µL)	5510±425	5512±444	0.9
Hb (g/dL)	16.02±1.24	16.07±1.23	0.41
Hct (%)	47.24±3.34	47.08±3.21	0.31
MCV (fL)	85.86±3.94	85.59±4.16	0.14
MCH (pg)	29.13±1.69	29.22±1.79	0.25
MCHC (g/dL)	33.92±1.26	34.13±1.28	0.01
RDW-SD	39.45±2.59	39.33±2.63	0.35
RDW-CV	12.63±0.81	12.64±0.81	0.84
PLT (µL)	273370±53543	271250±55825	0.41
MPV (fL)	10.11±0.83	10.14±0.76	0.46
PCT (%)	0.27±0.05	0.27±0.05	0.83
PDW	11.73±1.77	11.77±1.64	0.71
P-LCR	25.99±6.7	26.24±6.13	0.5

RBC: Red blood cell count, hb: Hemoglobin, hct: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, RDW-CV: Erythrocyte distribution width-coefficient of variation, PLT: Platelet, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, P-LCR: Platelet-larger cell ratio

Table 4. CBC parameters in B Rh(+) and B Rh(-), AB Rh(+) and AB Rh(-), O Rh(+) and O Rh(-) blood groups

CBC parameters	Blood group		p
	B Rh(+) (mean ± SD)	B Rh(-) (mean ± SD)	
Leukocyte (µL)	8339 ±1696	8834±1609	0.025
Neutrophil (µL)	4530±1267	4960±1253	0.010
MCV (fL)	85.44±3.91	86.68±3.71	0.015
MCH (pg)	28.99±1.67	29.59±1.47	0.006
	AB Rh (+) (mean ± SD)	AB Rh(-) (mean ± SD)	
MCH (pg)	28.86±1.91	29.55±1.80	0.034
MCHC (g/dL)	33.79±1.31	34.49±1.33	0.002
	O Rh(+) (mean ± SD)	O Rh(-) (mean ± SD)	
PLT (µL)	273310±60280	262180±50470	0.010
PCT (%)	0.27±0.05	0.26±0.05	0.025
MCV (fL)	86.11±4.09	85.30±4.78	0.016
MCHC (g/dL)	33.91±1.25	34.14±1.27	0.022

MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, PLT: Platelet, PCT: Plateletcrit, SD: Standard deviation, CBC: Complete blood count

Table 5. CBC parameters in B Rh(+) and non-B Rh(+), O Rh(+) and non-O Rh(+), B Rh(-) and non-B Rh(-), AB Rh(-) and non-AB Rh(-), O Rh(-) and non-O Rh(-) blood groups

CBC parameters	Blood group		p
	B Rh(+) (mean±SD)	Non-B Rh(+) (mean±SD)	
MCV (fL)	85.44 ±3.9	85.9±4.05	0.041
MCH (pg)	28.99±1.67	29.18±1.73	0.049
RDW-SD	39.09±2.59	39.49±2.62	0.006
PDW	11.87±1.88	11.67±1.76	0.042
	O Rh (+) (mean ± SD)	Non-O Rh(+) (mean ± SD)	
RBC (µL)	5470±430	5510±420	0.042
	B Rh(-) (mean ± SD)	Non-B Rh(-) (mean ± SD)	
Leukocyte (µL)	8281±2377	7537±2662	0.018
Lymphocyte (µL)	2823±1023	2568±1061	0.047
Neutrophil (µL)	4955±1253	4526±1293	0.006
MCH (pg)	29.59±1.47	29.14±1.73	0.032
	AB Rh(-) (mean ± SD)	Non-AB Rh(-) (mean ± SD)	
MCHC (g/dL)	34.49±1.33	33.95±1.27	0.006
	O Rh(-) (mean ± SD)	Non-O Rh(-) (mean ± SD)	
MCV (fL)	85.31±4.77	85.88±3.96	0.045
MCHC (g/dL)	34.13±1.27	33.94±1.27	0.035
PLT (µL)	261967±50442	270865±55434	0.016
PCT (%)	0.26±0.05	0.27±0.05	0.04

MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW-SD: Erythrocyte distribution width-standard deviation, PLT: Platelet, PCT: Plateletcrit, PDW: Platelet distribution width, SD: Standard deviation, RBC: Red blood cell count, CBC: Complete blood count

Discussion

The frequency of ABO and Rh blood groups is affected by ethnicity. In ABO blood group distribution worldwide, A blood group was 41%, O blood group was 47%, B blood group was 9%, and AB blood group was 3% (12). In the United States, the blood group distribution was found as 37.1%, 46.7%, 12.2%, and 4.1% according to the same order (13). Akbay et al. (14) investigated the ABO blood group frequency in Turkey and they determined the distribution of A, O, B, and AB blood groups as 42.84%, 32.67%, 16.46%, and 8.03%, respectively. Eren and Çeçen (15) studied 2198 platelet donors and they found the blood group distribution of these cases as A Rh(+): 37.2%, O Rh(+): 33.3%, B Rh(+): 11.7%, A Rh(-) and O Rh(-): 5.2%, AB Rh(+): 5.1%, B Rh(-): 1.2% and AB Rh(-): 1%. Rh positivity in Turkey was determined as 88.54%. The blood group distribution in our study was A>O>B>AB and this result was similar to blood group distribution in our country. However, we detected Rh positivity in 66.7% of our cases. This rate is lower than in Turkey and around the world. This may be due to ethnic differences. There are more male cases than female cases who voluntarily applied to healthcare institutions to become platelet and erythrocyte donors (16,17). The reason for this condition may be that anemia is more common in women due to menstrual bleeding and pregnancy. In our study, in accordance with the literature, the number of male donors was more than women.

Several studies have been conducted to examine the effects of ABO and Rh blood groups on platelet count and parameters. Eren and Çeçen (15) reported that the platelet count in Rh-positive individuals was higher than in Rh-negative individuals. They detected the platelet count as higher in the O Rh(+) group than in the O Rh(-) group. However, there was no statistically significant difference between the two groups. MPV shows the mean platelet volume and is an important biomarker of platelet activation (18). PDW measures the distribution of platelet sizes and is a marker showing platelet function. Celik et al. (19) evaluated the association between platelet parameters and the ABO blood group of 301 healthy volunteers. They found the MPV value lower in the O and A blood groups than in the AB and B blood groups. On the other hand, PDW value was lower in individuals with O and A blood groups than in cases with B blood group. In our study, a significant relationship was found between the ABO blood group and plateletcrit value. PCT value was significantly higher in the A blood group compared to the AB blood group. Plt and PCT values were lower in the O Rh(-) blood group than in the O Rh(+) and non-O Rh(-) blood groups. In addition, the PDW value was higher in B Rh(+) individuals than in non-B Rh(+) individuals. We did not find a significant relationship between ABO and Rh blood groups and MPV, P-LCR values.

Khan et al. (20) determined the association between the hb value and ABO, Rh blood groups of 1796 people in Abha city. They did not find a significant relationship between ABO, Rh blood groups, and hb value. In the study conducted by Ramalingam and Raghavan (21) 158 male and 111 female cases were examined. They found that the hb value in O Rh(+) individuals was significantly higher than in A Rh(+) individuals. They also declared that the O blood group had a higher hb value than the A and B blood groups. In our study, we found that individuals in the A blood group had significantly higher hb and hct values than the other groups in only female cases. Seyfizadeh et al. (22) examined 792 healthy pregnant women and found the RBC count higher in the AB blood group than in the A and O blood groups. However, they did not find a significant difference between the groups in terms of hb and hct values. In our study, the RBC count was higher in the AB blood group than in the A and O blood groups in only male cases. Also, the RBC value was lower in the O Rh(+) group than in the non-O Rh(+) group in our study. Ramalingam and Raghavan (21) found the hb value to be lower in the Rh-negative group than in the Rh-positive group. In our study, no relationship was found between the Rh blood group and the hb value. However, we found the MCHC value was higher in the Rh(-) group than in the Rh(+) group. RDW is a test that shows the difference in the size of erythrocytes. It is a parameter used to distinguish between iron deficiency anemia and thalassemia carriage. In our study, we found that the RDW-SD value was significantly higher in the O blood group.

In our study, the neutrophil count in the A blood group was found to be statistically significantly lower than in the non-A blood group. In the B blood group, the lymphocyte count was higher than in the non-B blood group. The results of our study could not be compared with the literature, because there were no studies in the literature about the effect of ABO and Rh blood groups on leukocyte, lymphocyte, monocyte, eosinophil, and basophil counts.

Conclusion

A CBC is a cheap test and it can be performed in any hospital. However, reference ranges for hemogram parameters have not been fully standardized. Therefore, it is recommended that each laboratory establish its reference range for CBC. All factors affecting hemogram parameters should be evaluated to determine reference ranges. In this study, we

detected that ABO and Rh blood groups affected some CBC parameters.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Ethics Committee for this study (date: 17.12.2020, number: B.30.2.ATA.0.01.00/18).

Informed Consent: Patients consent form was waived (not required) because the study was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.S., F.E., Design: E.B., S.S., Data Collection or Processing: G.S., S.S., F.E, Analysis or Interpretation: E.B., Literature Search: G.S., S.S., F.E., Writing: G.S., S.S., E.B., Manuscript Review, and Revision: F.E., G.S., S.S., E.B.

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ORIGINAL RESEARCH

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Evaluation of the Relationship Between Axillary Lymph Node Involvement with Frequently Evaluated Prognostic Factors in Breast Cancer

Meme Kanserlerinde Aksiller Lenf Nodu Tutulumunun Sık Değerlendirilen Prognostik Faktörlerle İlişkisinin Değerlendirilmesi

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Abstract

Objective: We aimed to evaluate the effect of hormone receptor and immunohistochemistry data on the incidence of primary tumor type and lymph node positivity in breast cancer cases.

Method: Demographic, immunohistochemical data of 62 patients who were biopsied in the institute's interventional radiology clinic and long axis of primary tumor in ultrasonography (USG) were retrospectively evaluated.

Results: The age of the patients, cell type, c-erb B-2 score and axillary lymph node positivity were not significantly correlated with the assessed data, whereas the long axis of primary tumor, estrogen and progesterone receptor severity and prevalence, ki-67 proliferation index affected lymph node involvement ratio.

Conclusion: Evaluation of lymph node involvement with second-line detailed USG before the operation, especially in malignant tumors refer to surgical or interventional radiology departments with negative, high ki-67 PI and C-erb B-2 values in estrogen and progesterone receptors, and the presence of recent axillary USG examination of the cases for breast biopsy regardless of the results, will provide important contribution in the diagnosis and treatment stages.

Keywords: Axillary lymph node, breast cancer, hormone receptors, immunohistochemical data

Öz

Amaç: Meme kanseri olgularında hormon reseptör ve immünohistokimyal verilerinin, primer tümör tipinin ve büyüklüğünün lenf nodu pozitif olma sıklığına etkisini araştırmayı amaçladık.

Yöntem: Enstitümüz girişimsel radyoloji kliniğinde biyopsi aldığımız 62 olgunun demografik immünohistokimyasal verileri ve ultrasonografide (USG) primer tümör uzun ekseni retrospektif olarak değerlendirilmiştir.

Bulgular: Değerlendirilmeye alınan verilerden hastaların yaşı, hücre tipi, c-erb B-2 skoru, değerlerinin aksiller lenf nodu pozitifliğine anlamlı katkısı bulunamaz iken primer tümörün uzun ekseni, östrojen ve progesteron reseptör şiddeti ve yaygınlığı, ki-67 proliferasyon indeksi lenf nodu tutulumuna etki etmektedir.

Sonuç: Özellikle östrojen ve progesteron reseptörlerine negatif, yüksek ki-67 PI ve C-erb B-2 değerleri elde edilmiş malign tümörlerde, operasyon öncesi ikinci bakı detaylı USG ile lenf nodu tutulumu değerlendirilmesi ve sonuçlar ne olursa olsun meme biyopsisi alınması için cerrahi veya girişimsel radyoloji departmanlarına refere edilen olguların yanlarında son dönemde elde olunmuş aksiller bölge USG incelemesinin bulunmasını sağlamak tanı ve tedavi aşamalarında önemli katkılar sağlayacaktır.

Anahtar kelimeler: Aksiller lenf nodu, hormon reseptörleri, immünohistokimyasal veriler, meme kanseri

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Introduction

Malignant tumors of the breast are the second most common cause of cancer death in women after lung. A woman's risk of death due to breast cancer is 1 in 37 (approximately 2.7%) (1). Although lymph node involvement affects the prognosis, it is not the only indicator. In recent studies, the 5-year survival rate has been determined as 99% only in the presence of breast cancer. This rate decreases to 85% in the spread of local lymph nodes and to 26% in the presence of distant metastases (2). In addition to histopathological examination, staging, immunohistochemical evaluation is frequently performed because it determines the patient's prognosis and contributes to treatment planning. In recent studies, the relationship of immunohistochemical data with prognosis and treatment continues to be evaluated.

Lymph node pathologies are common, and many different entities can affect their size and shape. These may be due to infectious, metabolic, neoplastic or physiological reasons (3). Imaging-guided lymph node biopsies are generally performed using two different methods. These are fine needle biopsy (FNAB) and core needle biopsy (CRI). With CRI, liquid and small particle-containing material is obtained by using a 14-20 G, thicker needle vacuum device (VIB) compared to fine needle. In both methods, local anesthesia can be used if necessary (4).

The aim of the study is to evaluate the relationship between the frequency of sentinel lymph node involvement, histological diagnosis, primary tumor size, cell type, estrogen-progesterone receptor severity-prevalence, c-erb B-2 score and ki-67 proliferation index parameters in cases diagnosed with histopathologically breast cancer.

Materials and Methods

Patients diagnosed with breast cancer histopathologically were included in our study. Age of the patients, long axis of the primary tumor, cell type and immunohistochemical findings were recorded to compare. In the evaluation of hormone receptors, the severity and prevalence of estrogen and progesterone receptors were evaluated together.

Biopsy Procedure

Before the procedure, all patients were questioned about possible contraindications and the presence of anxiety. After sterilization, a topical 10% lidocaine solution (Vemcaine Pump Spray; Nobel Farma medical) was applied to the procedure area. In addition, 5-10 mL of Bupivacaine (Marcaine solution; Pfizer) was applied as a local anesthetic for VIB. 22 G injectors were used for FNAB and 18 G vacuum biopsy needles were used for vacuum biopsy (Figure 1). USG device was Aplio 500 (Toshiba Medical Systems Europe) and 7.2-14 MHz linear probe was used.

Statistical Analysis

Anova (single factor) was used in the data analysis. The p-value less than 0.05 were considered significant. For statistical evalution Microsoft Excel pack programme (version 2206) was used.

All procedures performed in studies involving human participants were performed in accordance with institutional and/or national research ethical standards and the 1964 Declaration of Helsinki and its later revisions. The patient data were obtained retrospectively from the archives of our institute and from the patients who underwent true breast and fine-vacuum needle lymph node biopsy in the interventional radiology department. Informed consent was obtained from the patients participating in the study before the procedure.

Ethical approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our IRB (date: 06.02.2018, no: 825).

Results

A total of 62 female cases participated in our study. The mean age was 48.2 (27-83). Age, cell type, c-erb B-2 score values of the patients were not found to contribute significantly to sentinel lymph node positivity. In addition, it was observed that the long axis of the tumor, estrogen and progesterone receptor severity and extent, and ki-67 proliferation index parameters affected lymph node involvement (Table 1).

FNAB was used in 11 cases and VAP was used in 51 cases. Histopathological results of the cases: Invasive ductal

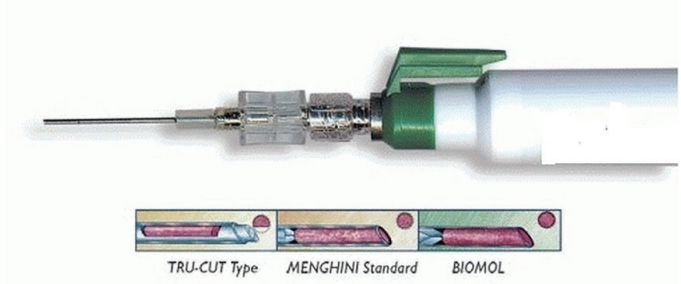

Figure 1. Instrument used for vacuum biopsy

carcinoma in 55 cases and invasive lobular carcinoma in 7 cases (Table 2).

Discussion

USG was used as guide imaging in our study. This modality is the most preferred method because it can clearly show the superficial structures, does not use ionizing radiation, is non-invasive, allows real-time examination, and is inexpensive (5). As the lymph node biopsy technique, VIB was preferred in a significant part of our cases (82.3%). Despite the use of thicker needles, it is a well tolerated method when local anesthesia is used. In our study, no major complications were encountered with this method. Subcutaneous hemorrhage, which can be limited with subcutaneous ice therapy, was observed in only two cases. The only disadvantage of this method is that it is more expensive. In recent years, especially VIB has been replacing excisional surgical techniques. Considering the diagnostic accuracy, sensitivity and specificity, although similar results are obtained, it is a minimally invasive method and is more advantageous in terms of morbidity and cost (6-10). At this point, it should be noted that although micrometastases are present in the sentinel lymph nodes in many cases, residual tumor remains due to false negative results in biopsy, even if it is detected on USG, and it is reported to be an important cause of recurrence (Figure 2).

When the demographic data of the cases were evaluated, it was observed that all cases were female. In the literature, breast cancer is reported to be 100 times more common in women compared to men (11). There was no statistically significant difference between the mean age of the cases with and without axillary lymph node involvement.

In our study, it was observed that tumors with large long axis had more frequent lymph node involvement. Here, the long axis can be defined as the primary tumor burden indicator in the breast. Malignant tumors reaching larger volumes are more likely to spread to sentinel lymph nodes and other distant tissues.

According to our results, high ki-67 PI increases the possibility of lymph node metastasis. Similarly, in previous studies, high PI was associated with younger patient age, high histological grade, estrogen receptor negativity, and increased risk of metastatic involvement (12-14). A more aggressive course and shorter average survival can be expected in breast cancer cases diagnosed at a young age. Especially the presence of distant metastases (extra-axillary) negatively affects the prognosis.

Presence of estrogen and progesterone receptors in immunohistochemistry studies reduces the possibility of lymph node involvement. Presence of estrogen and progesterone receptors can be defined as a positive prognostic factor in this respect, as it will increase the chance of cure of the tumor with hormone therapy and lymph node involvement will be less expected. Similar to our study, there are many studies in the literature reporting the positive contribution of hormone receptor positivity to clinical course and axillary involvement (15-18).

In our study, although increased C-erb B-2 expression was found to be higher in cases with axillary lymph node involvement, the difference was not statistically significant. The results obtained in the literature on this subject are controversial. There are studies reporting that axillary lymph node involvement is increased in cancers with

Table 2. The distrubution of patologic results and biopsy procedure

		No of nodes	%
Diagnosis	Invasive ductal carcinoma	55	88.7
	Invasive lobular carcinoma	7	11.3
Technic	FNAB	11	17.7
	VAB	51	82.3

FNAB: Fine needle biopsy

Table 1. Relation of immunohistochemical data with axillary lymph node

Findings	Sentinel lymph node negative	Sentinel ymph node positive	p
Long axis of the primary tumor	20.36±11.1 mm	31.4±12.2 mm	<0.01
The mean age of patients	60.23±11.5	58.33±13.12	0.32
Ki-67 PI %	12.42±11	18.16±13.18	0.012
Estrogen receptor x diffusiveness (%)	66.88±30.87	50.66±32.67	0.028
Progesteron receptor x diffusiveness (%)	56.74±35.75	38.33±34.03	0.026
The mean C-erb B-2 score	0.67±1.07	1.17±1.31	0.11
Invasive ductal ca	22	33	0.13
Invasive lobuler ca	3	4	

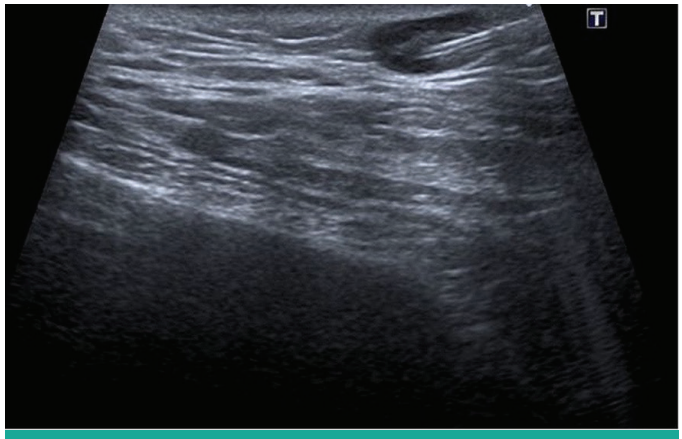

Figure 2. Fifty-three years old female case. Since the axillary lymph node has a benign appearance (oval shaped, fatty hilus intact) radiologically, histopathological examination was not performed. Biopsy was recommended because estrogen and progesterone receptors were negative. Micrometastasis was found as a result of the fine needle biopsy

increased expression (19,20). However, Tweedie et al. (21) stated that it had no reverse effect.

Finally, it was determined that the cell type did not affect the probability of axillary lymph node metastasis. In our study, the diagnosis of most of the cases was invasive ductal carcinoma, in line with the literature. Seven of our cases were diagnosed with invasive lobular carcinoma. Detection of only two cell types in histopathological results may affect the judgment that axillary involvement is not cell type dependent. We might have had a different outcome had our case group had neuro-endocrine carcinomas or micropapillary carcinomas, which were described as potentially more aggressive. Of course, since these entities are rare, a study with a larger series is needed.

Although there are many studies on this subject in the literature, the number of studies in which axillary lymph node involvement, which is an important prognostic indicator, is evaluated in isolation is very few. In most of the studies, the correlation of immunohistochemical data with the survival time of the cases was evaluated. In addition, studies conducted in recent years tend to classify breast cancers according to the results of immunohistochemical data and to predict prognosis according to this classification.

Study Limitations

The first limitation of our study is that not all lymph node biopsies were performed with VIB. Because there are studies indicating that VAP has a higher sensitivity in detecting the presence of axillary lymph node metastasis in breast cancer compared to FNAB (22,23). The second limitation is the relatively small number of cases. Similar studies in this area with more cases will contribute to the literature.

Conclusion

When the results of our study are evaluated, we recommend that axillary lymph node involvement be evaluated with detailed USG in the second look before biopsy and operation in malignant tumors that do not have estrogen and progesterone receptors and have high ki-67 PI and C-erb B-2 values. However, regardless of the immunohistochemical results, ensuring that the cases referred to surgery or interventional radiology departments for breast biopsy are accompanied by recent axillary region USG examinations will provide important contributions in the diagnosis and treatment stages.

Ethics

Ethics Committee Approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our IRB (date: 06.02.2018, no: 825).

Informed Consent: Informed consent was obtained from the patients participating in the study before the procedure.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ö., M.Ö., Concept: D.Ö., M.Ö., Design: D.Ö., M.Ö., Data Collection or Processing: D.Ö., M.Ö., Analysis or Interpretation: D.Ö., M.Ö., Literature Search: D.Ö., M.Ö., Writing: D.Ö., M.Ö.

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ORIGINAL RESEARCH

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Smell and Taste Impairment in COVID-19 Positive Pediatric Patients: A Prospective Cohort on Different Stages of The Disease

COVID-19 Pozitif Pediyatrik Hastalarda Koku ve Tat Bozukluğu: Hastalığın Farklı Evrelerinde Prospektif Bir Kohort

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Abstract

Objective: To evaluate the smell and taste impairment in Coronavirus disease-2019 (COVID-19) pediatric patients according to the disease severity.

Method: Ninety polymerase chain reaction test-confirmed COVID-19 patients were enrolled from January 2021 to July 2021. Patients were categorized into three main groups according to the stage of disease (stage 1: Outpatients, stage 2: Inpatients, stage 3: Intensive care unit patients). There were 30 pediatric patients in each group. Subjects were evaluated with a questionnaire. Visual analog scale was used to evaluate smell and taste impairment patients.

Results: The impairment of smell and taste were evaluated separately, and the rates were found to be 31.1% and 35.6%, respectively. The impairment of smell showed a statistically significant difference between the groups (p=0.002). The rate of smell impairment in the outpatients was found to be significantly higher than in the patients treated in the intensive care unit. The taste impairment did not show a statistically significant difference between the groups (p=0.109; p>0.01). Persistence of smell and taste impairment was found in 5.5% of the patients.

Conclusion: The rate of smell impairment in the outpatients was found to be significantly higher than in the cases treated in the intensive care unit.

Keywords: COVID-19, olfactory impairment, pediatrics, smell, taste

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pediyatrik hastalarda koku ve tat bozukluğunu hastalığın ciddiyetine göre değerlendirmektir.

Yöntem: Ocak 2021'den Temmuz 2021'e kadar 90 polimeraz zincir reaksiyonu testi doğrulanmış COVID-19 hastası kaydedildi. Hastalar, hastalığın evresine göre üç ana gruba ayrıldı (evre 1: Ayakta tedavi olan hastalar, evre 2: Yatan hastalar, evre 3: Yoğun bakım hastaları). Her grupta 30 çocuk hasta vardı. Denekler bir anket ile değerlendirildi. Koku ve tat bozukluğu olan hastaları değerlendirmek için görsel analog skalası kullanıldı.

Bulgular: Koku ve tat bozukluğu ayrı ayrı değerlendirildi ve sırasıyla %26,7 ve %27,8 olarak bulundu. Koku alma bozukluğu gruplar arasında istatistiksel olarak anlamlı farklılık gösterdi (p=0,002). Ayakta tedavi gören hastalarda koku bozukluğu oranı yoğun bakımda tedavi edilen hastalara göre anlamlı derecede yüksek bulundu. Tat bozukluğu gruplar arasında istatistiksel olarak anlamlı bir fark göstermedi (p=0,109; p>0,01). Hastaların %5,5'inde koku ve tat bozukluğunun kalıcılığı olduğu görüldü.

Sonuç: Ayaktan tedavi gören hastalarda koku bozukluğu oranı yoğun bakımda tedavi edilen olgulara göre anlamlı derecede yüksek bulundu.

Anahtar kelimeler: COVID-19, koku, koku bozukluğu, pediatri, tat

***One of the authors of this article (EŞ) is a member of the Editorial Board of this journal. She was completely blinded to the peer review process of the article.**

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Introduction

Despite the increasing vaccination rates all over the world, the 2019 Coronavirus pandemic continues to affect the whole world with 254,606,286 confirmed cases and 5,122,842 deaths (as of November 16, 2021) worldwide (1). Although it presents with different symptoms, olfactory dysfunctions are the most prominent ones among ear, nose, and throat symptoms with the earlier variants (2-7). In adults, the smell and taste impairment is presented extensively in the literature. However, data on children are in limited number.

Coronavirus disease-2019 (COVID-19) has a variable course starting from asymptomatic infection to death (2,3). Previous studies have suggested that the course of disease may be adversely linked with the smell and taste impairment. In the milder forms of COVID-19, the smell and taste impairment rates were found to be high. In contrast, the smell and taste impairment rates were found to be low in critically ill patients (4). The upper respiratory tract involvement was regarded as a protective factor for lower airway involvement and more severe disease (8).

In this study, our aim is to examine the rates of smell and taste disorders in 3 groups of pediatric patients having COVID-19 with different prognosis. Although there are evaluations in terms of pediatric COVID-19 symptoms in the literature, our study differs from other studies because it examines the relationship between the stage of the disease and the olfactory disorder.

Materials and Methods

The study was approved by our Institutional Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital with study number 2021-50. According to power analysis, a total of 90 children with COVID-19 infection were enrolled. All cases were patients with definite COVID-19 infection, confirmed by real-time reverse transcriptase-polymerase chain reaction materials taken from naso-oropharyngeal swabs). Patients with asymptomatic infection, those with a known co-infection with other viruses and co-incidentally positive patients were excluded from the study. We classified the study population based on disease stage (stage 1 mild type: Outpatient, stage 2 moderate type: Inpatient, stage 3 severe type: Intensive care unit). There were 30 pediatric patients in each group.

The American Academy of Otolaryngology-Head and Neck Surgery Anosmia Reporting Tool was used as questionnaire (4). A clinical history was taken from the parents and from the patient if the patient was old enough to answer the questions. Patients' demographic data (age, gender, weight, height, body mass index) and concomitant symptoms were recorded. The patients were asked to rate their smell sensation at its worst point during the infection, as normal, partial (hyposmia), or complete (anosmia) loss of smell. All the patients were asked if they had any alteration in taste or not. Visual analog scale (VAS) was used to evaluate hyposmia and hypogeusia patients.

Power Analysis

Power Analysis was performed to determine the sample size by using G*Power (v3.1.7). According to the Cohen's effect size coefficients, assuming the evaluation being made between 3 independent groups will have a small effect size (d=0.2), the results indicated that a total sample of 90 participants with 3 equally sized groups of 30 would be required to achieve a power of 0.80.

Statistical Analysis

While evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, quantitative variables were shown with mean, standard deviation, median, minimum, and maximum values, and qualitative variables were shown with descriptive statistical methods such as frequency and percentage. The Shapiro-Wilks test and Box Plot graphics were used to evaluate the conformity of the data to the normal distribution. The Kruskal-Wallis test was used for the comparison of the parameters that did not show normal distribution, and the Dunn test was used to determine the group that caused the difference. The Pearson chi-square test and Fisher-Freeman-Halton test were used to compare qualitative data. The results were evaluated at the significance level of $p<0.05$.

Results

The study was carried out with 90 cases, including 44.4% (n=40) female and 55.6% (n=50) male patients. The ages of the subjects participating in the study ranged from 4 to 17 ($p>0.05$) years. There was no statistically significant difference in the gender distribution, mean age, height, and body mass index of the cases according to the groups ($p>0.05$ for all comparisons). The mean weight values differed statistically significantly between the groups

(p=0.044; p<0.05). According to the pairwise comparisons made to determine the difference, the mean weight of the patients treated in the intensive care unit was found to be statistically significantly lower than that of the patients treated in the inpatient unit (p=0.021; p<0.05) (Table 1).

Of the subjects participating in the study, 72.2% (n=65) had fever, 41.1% (n=37) had fatigue, 33.3% (n=30) had headache, 37.8% (n=34) had muscle pain, 31% (n=28) had diarrhea, and 32.2% (n=29) had cough complaints. Other complaints are given in Table 2. Fever and fatigue were the most frequently reported symptoms in all study groups. In our study, the impairment of smell and taste was evaluated separately and the rates were found to be 26.7% and 27.8%, respectively.

When the smell impairment of the cases was examined, it was observed that 23.3% (n=21) could not smell (anosmia) at all, 7.8% (n=7) had a partial smell (hyposmia), and 68.9% (n=62) did not have an olfactory disorder. Hyposmia evaluation VAS scores of the subjects participating in the study ranged from 5 to 7. Smell impairment developed in 32.1% (n=9) of the cases within 1-2 days, in 39.3% (n=11) within 3-4 days, and in 28.6% (n=8) within 5 days and later. In 82.1% (n=23) of the cases with a smell disorder, this complaint was completely recovered. The impairment of smell revealed a statistically significant difference according to the groups (p=0.002). The rate of smell impairment in the outpatients was found to be significantly higher than in the patients treated in the intensive care unit.

When taste impairment of the cases was examined, it was detected that 17.8% (n=16) had no taste (ageusia) at all, 16.7% (n=15) tasted partially (hypogeusia), 1.1% (n=1) had different tastes (parageusia), and 64.4% (n=58) had no taste impairment. Hypogeuisa evaluation VAS scores of the subjects participating in the study ranged from 5 to 8. Taste impairment developed in 31.3% (n=10) of cases within 1-2 days, in 40.6% (n=13) within 3-4 days, and in 28.1% (n=9) within 5 days and later. In 84.4% (n=27) of the cases with a taste disorder, the taste disorder was completely recovered. Taste impairment did not show a statistically significant difference between the groups (p=0.109; p>0.05) (Table 3).

Table 2. Distribution of complaints according to groups

		Stage 1	Stage 2	Stage 3	p
		n (%)	n (%)	n (%)	
Fever	Absent	16 (53.3)	7 (23.3)	2 (6.7)	[a]**0.001 ** **
	Present	14 (46.7)	23 (76.7)	28 (93.3)	
Fatigue	Absent	26 (86.7)	17 (56.7)	28 (93.3)	[a]**0.001 ** **
	Present	4 (13.3)	13 (43.3)	2 (6.7)	
Feeding difficulties	Absent	27 (90.0)	25 (83.3)	26 (86.7)	[c]**0.926**
	Present	3 (10.0)	5 (16.7)	4 (13.3)	
Tiredness	Absent	15 (50.0)	15 (50.0)	23 (76.7)	[a]**0.053**
	Present	15 (50.0)	15 (50.0)	7 (23.3)	
Headache	Absent	15 (50.0)	20 (66.7)	25 (83.3)	[a]**0.024 ***
	Present	15 (50.0)	10 (33.3)	5 (16.7)	
Muscle pain	Absent	18 (60.0)	15 (50.0)	23 (76.7)	[a]**0.099**
	Present	12 (40.0)	15 (50.0)	7 (23.3)	
Stomachache	Absent	27 (90.0)	25 (83.3)	19 (63.3)	[a]**0.031 ***
	Present	3 (10.0)	5 (16.7)	11 (36.7)	
Vomiting	Absent	29 (96.7)	24 (80.0)	14 (46.7)	[a]**0.001 ** **
	Present	1 (3.3)	6 (20.0)	16 (53.3)	
Diarrhea	Absent	28 (93.3)	20 (66.7)	14 (46.7)	[a]**0.001 ** **
	Present	2 (6.7)	10 (33.3)	16 (53.3)	
Cough	Absent	23 (76.7)	18 (60.0)	20 (66.7)	[a]**0.380**
	Present	7 (23.3)	12 (40.0)	10 (33.3)	
Throat ache	Absent	20 (66.7)	21 (70.0)	25 (83.3)	[a]**0.303**
	Present	10 (33.3)	9 (30.0)	5 (16.7)	
Shortness of breath	Absent	29 (96.7)	25 (83.3)	20 (66.7)	[a]**0.010***
	Present	1 (3.3)	5 (16.7)	10 (33.3)	
Nasal congestion	Absent	23 (76.7)	23 (76.7)	30 (100.0)	[c]**0.008 ** **
	Present	7 (23.3)	7 (23.3)	0 (0.0)	
Runny nose	Absent	27 (90.0)	25 (83.3)	30 (100.0)	[c]**0.091**
	Present	3 (10.0)	5 (16.7)	0 (0.0)	
Other	Absent	28 (93.3)	27 (90.0)	18 (60.0)	[a]**0.001****
	Present	2 (6.7)	3 (10.0)	12 (40.0)	

Other symptoms: Rash, low back pain, forgetfulness, hoarseness. [a]: Pearson chi-square test, [c]: Fisher-Freeman-Halton test, *p<0.05 **p<0.01

Table 1. Examination of demographic characteristics by groups

		Stage 1 (n=30)	Stage 2 (n=30)	Stage 3 (n=30)	p
Gender	Female	16 (53.3)	13 (43.3)	11 (36.7)	[a]0.425
	Male	14 (46.7)	15 (56.7)	19 (63.3)	-
Age	Median (Q1-Q3)	12.5 (10-15)	12 (10-13)	11 (8.5-13.3)	[b]0.266
Height	Median (Q1-Q3)	159 (147-166.5)	152.5 (142-168)	147.5 (125.5-160)	[b]0.074
Weight	Median (Q1-Q3)	50 (40-56)	51 (38-65)	41 (29-50)	[b]0.044 *
BMI	Median (Q1-Q3)	19.9 (17.2-22)	21.4 (19.2-24)	18.9 (17-22)	[b]0.088

[a]: Pearson chi-square test, [b]: Kruskal-Wallis test, *p<0.05, Q1-Q3: 25% percentile -75% percentile, BMI: Body mass index

Table 3. The comparison of smell and taste impairment according to groups

		Stage 1	Stage 2	Stage 3	p
		n (%)	n (%)	n (%)	
Smell impairment	**Normal (n=62)**	16 (53.3)	19 (63.3)	2 (90.0)	[c]**0.019***
	Anosmia (n=21)	11 (36.7)	8 (26.7)	2 (6.7)	
	Hyposmia (n=7)	3 (10.0)	3 (10.0)	1 (3.3)	
Recovery (n=28)	**Yes (n=23)**	11 (78.6)	9 (81.8)	3 (100.0)	[c]**1.000**
	No (n=5)	3 (21.4)	2 (18.2)	0 (0.0)	
Hyposmia VAS	**n**	3	3	1	-
	Median (Q1-Q3)	6 (5-7)	6 (6-6)	6 (6-6)	
Taste impairment	**Normal (n=58)**	18 (60.0)	15 (50.0)	25 (83.3)	[a]**0.109**
	Ageuasia (n=17)	6 (20.0)	8 (26.7)	3 (6.7)	
	Hypogeusia (n=14)	6 (20.0)	6 (20.0)	2 (10.0)	
	Parageusia (n=1)	0 (0.0)	1 (3.3)	0 (0.0)	
	Normal (n=58)	18 (60.0)	15 (50.0)	25 (83.3)	[c]**0.021***
	Abnormal (n=32)	12 (40.0)	15 (50.0)	5 (16.7)	
Hypogeuisa VAS	**n**	6	6	2	-
	Median (Q1-Q3)	5.5 (6-7)	6 (6-6)	6 (6-6)	
Recovery (n=32)	**Yes (n=27)**	10 (83.3)	12 (80.0)	5 (100.0)	[c]**0.832**
	No (n=5)	2 (16.7)	3 (20.0)	0 (0.0)	

[a]: Pearson chi-square test, [c]: Fisher-Freeman-Halton test, *p<0.05, **p<0.01, Q1-Q3: 25% percentile -75% percentile, VAS: Visual analog scale

Discussion

In the present study, our aim was to examine the rates of smell and taste disorders in 3 groups of pediatric COVID-19 patients with different stages. Overall, the rates of smell and taste impairment were found to be 31.1% and 35.6%, respectively. The rate of smell impairment in the outpatients was found to be significantly higher than in the patients treated in the intensive care unit. The taste impairment did not show a statistically significant difference between the groups.

With the progression of this pandemic, despite the constant stream of new and interesting literature, the scarcity of systematic reviews and meta-analyses on various aspects of severe acute respiratory syndrome-coronavirus-2 infection in pediatric patients (0.04%) prompted us to do this study (6).

Although the pandemic continues at full speed, the clinical course of pediatric patients is very variable. A treatment modality other than a vaccine that could be a glimmer of hope is not on the horizon. Therefore, it is important to understand the clinical course of the disease. In this study, clinical symptoms and smell and taste disorders were evaluated by survey studies according to their clinical courses in 3 groups of patients. In the literature, it has been shown that previously self-reported subjective smell impairment results are correlated with objective methods (7).

A prospective comparative study of smell and taste disorders with pediatric patients could not be found in the literature review (5). Also, information on smell and taste disorders of pediatric intensive care patients is not available in the literature. This may be due to relatively small number of critically ill pediatric patients which required intensive care unit stay. In fact, only one study has been found in the literature on adult intensive care patients. Sayın et al. (8) reported that smell and taste disorders were detected in 43.2% of the intensive care unit COVID-19 patients. Barry et al. (9) found the rate of loss of smell as 9.1% in hospitalized severely ill adult patients with COVID-19. Lechien et al. (10) reported only %38.3 smell impairment rate in severe hospitalized COVID-19 adult patients. There is a publication that argues the opposite and states that the severity of the disease is not associated with smell and taste disorders (11). It is not known whether the differences in the rapid recovery of smell and taste disorders can be attributed to the patient's forgetting the situation. Kaye et al. (12) stated that 85% of patients had anosmia healed within 10 days.

The low mortality rate (0.1%) in pediatric patient groups and the clinical picture are different from those in adults, which is being tried to be explained by various hypotheses (13). The exact pathophysiology of smell and taste impairment in COVID-19 patients is still unknown (14). Human angiotensin-converting enzyme 2 (ACE 2) is the important key factor for entering coronaviruses.

Although low *ACE 2* gene expression has been implicated in children, a prospective observational cohort study found no age-related differences (15). One of the other blamed factors is the immaturity of immunological development in children, which is important in the milder course of the clinical course (16). Except that the immune system is immature, the lack of maturity in the receptors, to which ACE 2 binds, is used to explain the fact that pediatric taste and odor disorders are less frequent than in adults (16). Another implicated hypothesis is that smoking increases the expression of ACE 2, thus facilitating the entry of the coronavirus into the pulmonary epithelium (17). There is no doubt that the smoking rate of adults is higher than that of pediatric patients, which protects children from serious infections (13).

Two forms of COVID-19 infection were hypothesized in the literature. One is the "nasal form" and the other is "pulmonary form" (8). In early variants of COVID-19 infection, the characteristic of infection is the presence of smell and taste impairment in the absence of nasal blockage (3,4). The presence of smell and taste impairment was the sign of upper respiratory tract involvement and when this occurred, the nasal as well as systemic responses were triggered. In the absence of smell and taste impairment, immune responses may not be triggered. Second mechanism is that the lungs may be the first reservoir and the upper respiratory involvement may not be the case (18). Yan et al. (18), in their study, published that partially mild outpatient cases might be a result of nasal-centered viral spread, while patients requiring hospitalization might be experiencing a more pulmonary-centered infection. However, very few data are available regarding the effect of disease severity on chemosensory findings (19).

Saniasiaya et al. (5) were able to include only 9 studies in their systematic review between December 1, 2019 and April 30, 2021, examining COVID-19 positive pediatric patients with olfactory dysfunction. Only one of the studies included in this review studied on 141 patients, which is higher than our number of patients. In their study, they reported the prevalence of smell and taste disorders in children and adolescent patients to be 28.4% in COVID-19 (14). Rusetsky et al. (2) stated that, in the pediatric population, olfactory dysfunction was an early and warning symptom. Within a month, 93.4% of patients' complaints regress. Sayin et al. (4) reported changes in smell and taste in children aged 7-15 years at the rate of 10.4-13.1%. When the smell and taste impairment develops, it mostly occurs as partial loss and recovers early and spontaneously (20).

Our prospective study was the first study that evaluated smell and taste impairment according to different stages of COVID-19 infection. This study also serves as the first study that evaluated COVID-19 pediatric patients that required intensive care unit stay. Our findings were consistent with the literature which highlighted that the presence of smell and taste impairment was related to milder disease. There are some limitations of this study. First, we did not use an objective testing method. However, using objective testing in a pediatric group of patients was challenging, and it is also not the case for the patients that required ICU stay. Second, we performed the present study with a small effect size. This is why pediatric patients requiring ICU stay are in a limited number. The fact that the intensive care data of pediatric patients are not included in the previous papers on this topic in the literature makes it difficult to interpret our own data in light of the literature. Although we could evaluate the smell with the questions that we asked the children, we had difficulties in the evaluation of taste. Finally, we could not present the long-term outcomes for those who did not experience a recovery in smell and taste impairment.

Conclusion

In our study, smell and taste impairment was evaluated in different stages of COVID-19 pediatric patients. The rate of smell impairment in the outpatients was found to be significantly higher than in the patients treated in the intensive care unit. Further studies will clarify the relationship between smell and taste impairment and disease severity.

Ethics

Ethics Committee Approval: The study was approved by our Institutional Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital with study number 2021-50.

Informed Consent: Written informed consent for publication was obtained from the parents on behalf of the patients.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., B.M., N.S., Concept: Z.M.Y., N.S., N.A., B.M., N.H., Design: Z.M.Y., N.S., N.A., B.M., Data Collection or Processing: N.S., N.A., B.M., Analysis or Interpretation: Z.M.Y., İ.S., Critical Review: İ.S., E.Ş., N.S., Writing: Z.M.Y., E.Ş., N.H., Supervision: E.Ş., N.H., İ.S., Z.M.Y.

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ORIGINAL RESEARCH

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The Relationship of Familial EEG Characteristics with Age and Gender in Primary Generalized Epilepsy

Primer Jeneralize Epilepside Ailesel EEG Özelliklerinin Yaş ve Cinsiyet ile İlişkisi

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Abstract

Objective: Epilepsy is basically a group of electrical brain dysfunctions, in which many factors play a role in its etiology. Less is known about primary generalized epilepsies than focal epilepsies. Most forms of them are thought to have a genetic basis. In recent years, interest in genetics has also increased in epilepsy, and family studies and epidemiological studies have shown that some forms of epilepsy are inherited. Electroencephalography (EEG) is one of the most important examinations that show the cerebral bioelectric activity and the changes therein. The aim of this study is to examine the EEGs of primary generalized epilepsy patients with typical EEG findings and the EEGs of their first-degree relatives, and to show the genetic effect here.

Method: Patients diagnosed with primary generalized epilepsy according to the International Classification of Epilepsy and Epileptic Syndromes (ILAE-1998) criteria were selected among epilepsy patients who were admitted to neurology outpatient clinic. EEG examination was performed in the first-degree relatives of these patients who could also be reached.

Results: One hundred patients (59 females, 41 males) were included in the study. The seizures of these patients were primary generalized type (PGE), which presented as a generalized tonic-clonic seizure, myoclonic seizure, absence seizure, or combinations of these. Two hundred-nineteen first-degree relatives of 100 patients with PGE, who could be reached, were examined with EEGs. Ten of them had seizures and 48 of them had EEG pathology.

Conclusion: As a result of this study, it was understood that the cerebral bioelectrical activity characteristics of patients with PGE showed a significant difference according to age and gender, although this was

Öz

Amaç: Epilepsi temel olarak etiyolojisinde birçok faktörün rol oynadığı, elektriksel olan bir grup beyin fonksiyonu bozukluğudur. Primer jeneralize epilepsiler hakkında ise fokal epilepsilere göre daha az şey bilinmektedir. Bunların çoğu formunun genetik temellere dayandığı düşünülmektedir. Son yıllarda epilepside de genetiğe olan ilgi artmıştır, aile çalışmaları ve epidemiyolojik çalışmalar ile epilepsinin bazı formlarının kalıtsal olduğu gösterilmiştir. Elektroansefalografi (EEG) ise serebral biyoelektrik aktiviteyi ve buradaki değişiklikleri gösteren en önemli tetkiklerdendir. Bu çalışmanın amacı tipik EEG bulgusu gösteren primer jeneralize epilepsi hastalarının EEG'leri ile bu hastaların 1. derece yakınlarının EEG'leri incelenerek, buradaki genetik etkinin gösterilmesidir.

Yöntem: Nöroloji polikliniğine başvuran epilepsi hastaları arasından International Classification of Epilepsy and Epileptic Syndromes (ILAE -1998) kriterlerine göre primer jeneralize epilepsi tanısı almış hastalar seçildi. Bu hastaların arasından ulaşılabilen 1. derece yakınlarında da EEG incelemesi yapıldı.

Bulgular: Çalışmaya 100 hasta (59 kadın, 41 erkek) alındı. Bu hastaların nöbetleri primer jeneralize tipte olup, jeneralize tonik klonik nöbet, miyoklonik nöbet, absans nöbet veya bunların kombinasyonları şeklinde prezente olmaktaydı. Yüz primer jeneralize epilepsili hastanın ulaşılabilen 219 birinci derece yakınının EEG'leri incelendi. Bunların 10'unda nöbet, 48'inde ise EEG patolojisi saptandı.

Sonuç: Bu çalışmanın sonucunda primer jeneralize epilepsili hastaların serebral bioelektrik aktivite özelliklerinin istatistiksel olarak desteklenmemekle birlikte yaşa ve cinsiyete göre önemli bir farklılık gösterdiği anlaşılmıştır. Bu da epileptogenez üzerindeki etkisi ve

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not supported statistically. This shows the necessity of more detailed genetic studies in order to understand its effect on epileptogenesis and the differences in cerebral sensitivity.

Keywords: Electroencephalography, epilepsy, genetic

serebral duyarlılıktaki farklılıkların anlaşılması için daha ayrıntılı genetik incelemelerin gerekliliğini göstermektedir.

Anahtar kelimeler: Elektroansefalografi, epilepsi, genetik

Introduction

Idiopathic generalized epilepsies (IGEs) constitute a large portion (39-59%) of all epilepsies. Now also known as genetic generalized epilepsies, they are diagnosed on the basis of specific electroencephalographic findings as well as clinical features. Bilateral synchronous, symmetrical, and generalized spike-wave discharges are diagnostic electrophysiological features (1). Other common features include polyspike and polyspike wave discharges. Although less common, other EEG abnormalities in IGE include occipital intermittent rhythmic delta activity and photoparoxysmal response (PPR) (2,3).

IGEs have different subgroups, such as juvenile myoclonic epilepsy, childhood absence epilepsy, and juvenile absence epilepsy. This group of epilepsies has the most genetic characteristics among all types of epilepsy. Chromosomal localization of some epileptic syndromes has been achieved. Changes have been detected in 6p11-12, 15q14, and 5q34 in juvenile myoclonic epilepsy; 22q in benign familial neonatal convulsion; and chromosome 8q (and 16p12, according to some studies) in childhood absence epilepsies (4-7).

Among epilepsy examinations, electroencephalography (EEG) gives us information and allows us to record the bioelectric activity of the brain. Whether there is a genetic influence on EEG findings has been a remarkable issue in terms of the importance of genetics in both epilepsy and the electrical activity of the brain. Studies have shown the genetic characteristics of some basal activity variants and epileptiform discharges in EEG (2).

This study aimed to investigate whether there were genetic features in terms of both clinical presentation and EEG by examining first-degree relatives of IGE patients.

Materials and Methods

Patients who were diagnosed with primary generalized epilepsy with anamnesis, clinical and electroencephalographic features according to the International Classification of Epilepsy and Epileptic Syndromes (ILAE-1998) criteria were selected among the patients who were admitted to the neurology outpatient clinic. This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (25.3.2019/61-13).

Inclusion criteria: Patients with diffuse bilateral synchronous and symmetrical spike-wave discharges, which are characteristic of primary generalized epilepsy, on their EEG were examined.

The exclusion criteria from the study included; 1) A trauma or an operation that might be a risk for epilepsy, 2) A pathology that might pose a risk for epileptic seizure in routine hemogram or biochemistry screenings, 3) Having another neurological disease other than epilepsy, and 4) Pathology in cranial magnetic resonance imaging determination.

EEGs of patients' relatives with and without a history of seizures were examined. They were divided into two groups as those with normal and abnormal EEG. These were grouped as those with spontaneous multiple spike waves, those with spike-wave discharge complex, those with sharp waves, those with 4-7 Hz/min theta rhythm, and those with photosensitivity.

Statistical Analysis

SPSS 26.0 program was used in the analysis (Statistical Package for the Social Sciences, version 26.0 for Windows, SPSS Inc., Chicago, IL). Descriptive data for categorical variables were expressed as numbers and percentages. Relationships between categorical variables were evaluated with the chi-square test. The statistical significance level in the analyses was accepted as $p<0.05$.

Results

One hundred patients (59 females, 41 males) aged between 12 and 37 years were included in the study. Generalized tonic-clonic seizure (GTCS) was observed in 87 patients, myoclonic seizures in 6, absence seizures in 1, both GTCS and myoclonic seizures in 16, and combinations of both GTCS and absence seizures in 12 patients (Table 1).

Two hundred-nineteen first-degree relatives of 100 IGE patients who could be reached were examined with EEGs. History of seizure was detected in 10 relatives of 100 patients

before or during the study. One of 10 relatives who had this seizure was the mother of the patient and the other 9 were siblings. Eight of them had GTCS and 3 of them had myoclonic seizures. Both GTCS and myoclonic seizures were detected in 1 patient's relative. EEG disorder was found in 9 of these relatives with seizures, and the EEG of 1 patient's relative was found to be normal (Table 2).

EEG pathology without seizures was detected in first-degree relatives of 48 patients. The relatives of the patients who had no seizures but had EEG disorder were 10 fathers, 7 mothers, 28 siblings, and 3 children. In EEG disorders, 10 bilateral synchronous spike waves, 32 sharp waves, 13 theta activity, and 7 both sharp and theta wave paroxysms were observed. Most of EEG disorders were observed in siblings (Table 3). When these people were evaluated according to their age groups, 27 of them were found to gather in the 2nd and 3rd decades. (Graph 1, Table 4). When 48 first-degree relatives of patients with EEG disorders were evaluated according to gender, it was observed that 31 were female and 17 were male, which was not found to be statistically significant (Table 5).

PPR were examined as another parameter in the EEG. PPR was found to be positive in 23 (23%) of the patients and in 16 relatives of these 23 patients.

Table 1. demographic features of patients

Number of cases	277
Number of cases excluded	177
Number of cases included	100
Gender	
Male	41
Female	59
Age	
0-9	0
10-19	64
20-29	26
30-39	10
40-49	0
50-59	0
Seizure type	
GTCS	87
MS	6
AS	1
GTCS+MS	16
GTCS+AS	12

GTCS: Generalized tonic clonic seizure, MS: Myoclonic seizure, AS: Absence seizure

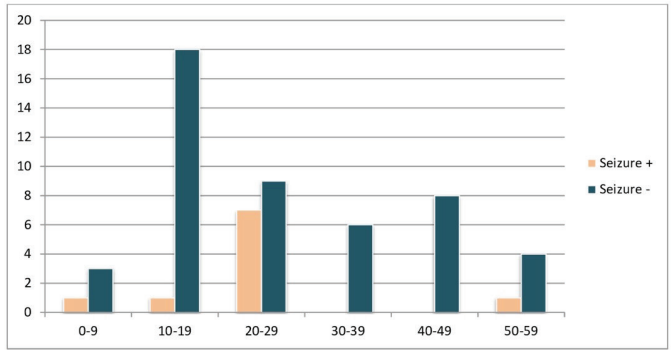
Table 2. Distribution of first-degree relatives of patients with EEG disorders and seizure

n	10
Relatives	
Mother	1
Sibling	9
Seizure type	
GTCS	8
MS	2
GTCS + MS	1
EEG pathologies	
(+)	9
(-)	1

GTCS: Generalized tonic clonic seizure, MS: Myoclonic seizure, EEG: Electroencephalography

Discussion

EEG shows the bioelectrical activity of the brain and is the most important epilepsy examination technique. It allows for the diagnosis of IGEs with specific findings, such as bilateral synchronous spike-wave discharges. Whether there is a genetic effect on EEG is an important issue, both



Graph 1. Distribution of first-degree relatives of patients with EEG disorders by age

EEG: Electroencephalography

Table 3. Distribution of EEG disorders among family members

	Mother	Father	Sibling	Child
n	7	10	28	3
EEG pathologies				
Sharp wave	5	8	18	1
Spike wave	1	0	7	2
Slow wave	2	5	6	0
Sharp + slow wave	1	3	3	0
Spike + slow wave	0	0	0	0

EEG: Electroencephalography

Table 4. Chi-square test findings on the distribution of family members with impaired EEG by age

Age	EEG pathologies	
	+ (%)	(-) (%)
0-9	14 (82.4)	3 (17.6)
10-19	35 (67.3)	17 (32.7)
20-29	38 (79.2)	10 (20.8)
30-39	29 (82.9)	6 (17.1)
40-49	30 (78.9)	8 (21.1)
50-59	15 (78.9)	4 (21.1)
Total	161 (77.0)	48 (23.0)
	X^2=3.965 p=0.555	

EEG: Electroencephalography

Table 5. Distribution of relatives with impaired EEG by gender

		EEG abnormality		Total
Gender		(-)	(+)	
Woman	n	80	31	111
	%	72.1	27.9	100
Man	n	81	17	98
	%	82.7	17.3	100
Total	n	161	48	209
	%	77	23	100
	X^2=2.723 p=0.099			

EEG: Electroencephalography

in terms of epilepsy and the role of genetics in the electrical activity of the brain (8-10). When the patients with IGE included in our study were evaluated, the majority were gathered in childhood, adolescence, and young adulthood. In the literature, childhood absence epilepsy is seen in 13-17% of children, and JME has been reported in 11% of adults and 3% of children. GTCSs are seen at a rate of 27-31% in adults (11). Our patient group was predominantly composed of young adult and adolescent patients, and, as in the literature, GTCSs were more common than absence or myoclonic seizures (4,8).

In our study, the first-degree relatives of patients with IGE were examined. The extent to which genetic characteristics were reflected in EEG in this type of epilepsy and the features of this reflection were investigated.

The majority of all epilepsies are IGEs. In monozygous twin studies conducted in these patient groups, it was found that epilepsy had a transmission rate of 90% (12). Metrakos and Metrakos (13) showed that among 211 patients with centrencephalic epilepsy, 13% of the patients' siblings also had seizures, and 37% had EEG pathology without seizures. In our study, 10% of the patients' relatives had seizures, and 48% had EEG pathology without seizures. This finding suggests that pathological cerebral neural activity may be common among patients' relatives despite the lack of seizure activity. On the other hand, in a study by Jayalakshmi et al. (14), EEG examinations were performed on 132 first-degree relatives of 31 JME patients in India; 12% of those had seizures, and EEG pathology was found in 12.9% of those without seizures. Although fewer EEG disorders were found in the relatives of asymptomatic patients, there was another remarkable feature: While the average age of cases with seizure-free EEG disorders was 19.6 years, the average age of those with normal EEGs was 32.4 years (14). This raises the question of whether the younger age group may be more sensitive to EEG disorders.

Metrakos and Metrakos (13) also supported this finding. The genetic characteristics of paroxysmal bilateral synchronous 3 Hz spike and wave discharges were investigated in patients with petit mal and grand mal seizures. The study demonstrated that centrencephalic-type EEG pathology had autosomal dominant inheritance. However, it was also found that this transition might differ depending on age, and there was a transition characteristic almost completely specific to those aged 4.5-16.5 years (13). Although it was not statistically significant, a peak in the number of patients with EEG pathology in the second decade was observed in our study (Table 4). The ages of patients' relatives who did not show pathology on EEG were concentrated in the third and fourth decades. In a similar study by Degen and Degen (15), 83 siblings of 54 patients with epilepsy were scanned with EEG, and epileptiform activity was observed in 41%. The highest rate of epileptiform activity was also found in the age group of 6-14 years (15). Detecting EEG pathology is important in terms of increased risk of epilepsy.

Determining the risk of cerebral seizures in individuals with spike wave discharges is difficult. Baier and Doose (8) found that the risk of seizures was 33% in patients with spike wave discharges in the relatives of patients with IGE with minor seizures. There was no difference in patients with only PPR or 4-7 Hz slow-wave pathology compared to those with normal EEGs.

Another important feature in our study was gender affinity (Table 5). Among the relatives of patients who had pathological EEGs, 64.5% were women and 35.5% were men. Similarly, Degen and Degen (15) examined the siblings of patients with absence epilepsy; EEG pathology was found in 54.5% of the patients' sisters but in only 30% of

their brothers. In the study conducted by Baier and Doose (8) the brothers and sisters of patients with IGE with minor seizures were examined, pathological EEG was detected in 24% of sisters, while this rate was found to be 11% in men. A similar relationship was shown in another study conducted on patients with JME (8). This has shown us that, gender is also an important parameter in genetic transition as well as age, and the female gender is at higher risk in terms of EEG pathology among patient relatives.

Another remarkable result is the genetic transition feature observed in photo paroxysmal response. PPR was found to be positive in 23 patients and in 16 (59%) of the relatives of these 23 patients. PPR is an EEG finding that is observed at a rate of 15% to 40% in all IGEs, especially in JMEs. In different studies including twin groups, the genetic inheritance feature of PPR has been emphasized (14-16). For example, in the study conducted by Doose and Waltz (17), in 49% of patients with positive PPR, PPR was found to be positive in their siblings.

It is known that many EEG features and clinical features may have a genetic inheritance in epileptic patients. Resistance to epilepsy or hypersensitivity to epilepsy is under the control of many endogenous and exogenous factors, including genetic features. In addition to factors such as sleep, wakefulness, HPV, sound, or light, hereditary traits play an important role. However, heredity has an important place among the endogenous features. Genetic properties play a very important role in the development of pathological discharges as well as in the regulation of the bioelectrical ground activity of the brain. The presence of EEG pathologies such as bilateral synchronous spike-wave discharge and bilateral 4-7 Hz theta waves, which are specific to PGE, also highlights the role of the heredity in asymptomatic relatives. The results of our study have suggested that this situation may be related to age and gender, and the increase in the incidence of pathological discharges between the ages of 5 and 17 years was remarkable. The authors demonstrated changes in EEG background activity during some developmental periods. This may reflect a period correlated with an increase in cerebral sensitivity to convulsions and may explain the tendency to EEG pathology that occurs in an age-dependent manner.

An important question is the type of genetic inheritance. Variables such as the type of seizure, the age at the onset of the seizure, and the activation methods used in the relatives of the patient affect the cerebral activity. This suggests a polygenic mode of heredity.

Conclusion

Our findings showed the importance of the effect of genetics on EEG in IGE. Pathologies detected in the EEG in the relatives of patients with IGE may reflect the hereditary feature in cerebral sensitivity and indicate that there are genetic determinants of cerebral excitability. Especially in women, susceptibility to genetic effects may be more pronounced in childhood and adolescence.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (25.3.2019/61-13).

Informed Consent: The consent of the patients was obtained for the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ö.B.M., M.F.Ö., Design: Ö.B.M., M.F.Ö., Data Collection or Processing: Ö.B.M., Analysis or Interpretation: Ö.B.M., M.F.Ö., Critical Revision of Manuscript: M.F.Ö., Writing: Ö.B.M., M.F.Ö.

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ORIGINAL RESEARCH

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Cytopenias in Treatment-naive HIV Patients: A Comparison of Turkey and Somalia

Tedavi Almamış HIV Hastalarında Sitopeniler: Türkiye ve Somali Karşılaştırması

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Abstract

Objective: Cytopenias are common complications in HIV-positive individuals, generally correlated with the stage of the disease. Prevalence of cytopenias depends on the stage of HIV infection, gender, race, geographic location, and nutritional status. The objective of this study was to determine the frequency of cytopenias in treatment-naive HIV infected patients in two ethnically, geographically and socio-economically different countries, Turkey and Somalia.

Method: The study participants were all newly diagnosed adult HIV-positive patients, not on any antiretroviral treatment. The exclusion criteria included being at the age of <18 years, the presence of hematologic and oncologic disorders, having HIV-positivity with malignancy, chronic renal failure, hepatic disease, pregnancy, acute illness (i.e., pneumonia, or gastroenteritis), opportunistic infections and congenital hematological disorders.

Results: In our study, the most common type of cytopenia was normocytic normochromic anemia. Anemia was significantly more common among Somalia patients than their Turkish counterparts. The second common hematological abnormality was leucopenia among Somalian patients and thrombocytopenia among Turkish patients. Leucopenia was rare in Turkish patients.

Conclusion: The hematological findings of our study have implications for the selection of antiretroviral drugs and other agents in HIV-positive individuals and also in monitoring the development of side effects. These results vary between countries with socio-economic and geographical differences.

Keywords: Acquired immune deficiency syndrome, anemia, cytopenia, Somalia, Turkey

Öz

Amaç: Sitopeni, HIV pozitif bireylerde yaygın olarak görülen ve genellikle hastalığın evresi ile ilişkili komplikasyonlardır. Sitopenilerin prevalansı HIV enfeksiyonunun evresine, cinsiyete, ırka, coğrafi konuma ve beslenme durumuna bağlıdır. Bu çalışmanın amacı etnik, coğrafi ve sosyo-ekonomik olarak farklı iki ülkede, Türkiye ve Somali'de tedavi görmemiş HIV ile enfekte hastalarda sitopeni sıklığını değerlendirmektir.

Yöntem: Çalışmaya katılanların tümü, herhangi bir antiretroviral tedavi almayan, yeni teşhis edilmiş yetişkin HIV pozitif hastalardı. Dışlama kriterleri, 18 yaşından küçük olmak, hematolojik ve onkolojik bozuklukların varlığı, malignitesi olan HIV pozitif hastalar, kronik böbrek yetmezliği, karaciğer hastalığı, hamilelik, akut hastalık (yani, pnömoni veya gastroenterit), fırsatçı enfeksiyonlar ve konjenital hematolojik bozukluklar idi.

Bulgular: Bu çalışmada en sık görülen sitopeni normositik normokromik anemi idi. Anemi, Somalili hastalarda Türk hastalara göre önemli ölçüde daha yaygındı. Somalili hastalarda ikinci sık görülen hematolojik anormallik lökopeni, Türk hastalarda ise trombositopeni idi. Türk hastalarda lökopeni nadirdi.

Sonuç: Çalışmamızın hematolojik bulguları, HIV pozitif bireylerde antiretroviral ilaçların ve diğer ajanların seçiminde ve ayrıca yan etkilerin gelişiminin izlenmesinde çıkarımlara sahiptir. Bu sonuçlar sosyo-ekonomik ve coğrafi farklılıklara sahip ülkeler arasında farklılık göstermektedir.

Anahtar kelimeler: Anemi, edinsel immün yetmezlik sendromu, sitopeni, Somali, Türkiye

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Introduction

One of the most common complications in people with human immunodeficiency virus (HIV) is hematological changes. Cytopenias are characterized by reduction in blood cell lines and lead to anemia, thrombocytopenia, and leucopenia (1,2). They are generally correlated with the stage of the disease in the incidence and the severity, increasing as the progression of the disease from the asymptomatic HIV-positive state to the advanced state (3-5). Low CD4+ T-cell numbers, high viremia, later stages of the disease, increased age and side effects of drugs given for HIV are the risk factors for cytopenias in HIV-infected patients (6-8). The pathophysiology of cytopenias in HIV infection is complex and multifactorial. Direct bone marrow suppression of HIV or indirect abnormal production due to cytokine impaired hematopoiesis especially causes anemia or leucopenia. On the other hand, thrombocytopenia usually results from immune-mediated destruction of platelets (9-12). Other causes of cytopenia in HIV infected patients include nutritional deficiencies (e.g., iron deficiency, folic acid deficiency), opportunistic infections, malignancies, decreased erythropoietin, infiltrative diseases of the bone marrow, opportunistic infection or co-existing medical problems and treatment-related adverse events (13,14). Cytopenias play an important role in HIV-related morbidity and morbidity (10,15,16). In addition, cytopenias have a major impact on patients' quality of life (15). Prevalence of cytopenias has been shown to vary geographically (17,18). In recent years, studies conducted all around the world have shown highly different results regarding the cytopenias in HIV patients (8,17-19). Anemia is the most common cytopenia observed in patients with HIV-infection and is often associated with leucopenia or thrombocytopenia. The level of anemia correlates with the stages of HIV infection (20). In previous studies, the prevalence rates of anemia have been reported between 6.3% and 84% depending on the stage of HIV infection, gender, race, geographic location, nutritional status, and definition of anemia (21,22). In some studies, the prevalence of anemia has been estimated to be 30% in asymptomatic patients and 63-95% in HIV-infected patients in late-stage (18,21,22-26). Geographical differences in the prevalence of anemia in HIV infected individuals have been reported all over the world. In Europe and in the United States, anemia occurs in about 35-65% of treatment-naive patients (27,28).

The second most frequent hematological complication seen in HIV infected patients is the thrombocytopenia found in 3-40% of patients. Thrombocytopenia can be seen at any stage of the disease. The frequency of thrombocytopenia varies among countries, while race and ethnicity may affect the prevalence of thrombocytopenia (18,19,24,29,30). The geographical distribution of thrombocytopenia differs from that of leucopenia and anemia in HIV infected patients (17).

The prevalence of leukopenia also varies widely among patients with HIV, ranging from 10% to 50%. The most common form of leucopenia is neutropenia, which has been reported in 0% to 28.3% of treatment-naive patients. Its incidence rises from 13% to 44% with disease progression from HIV to AIDS (19,24,25,31).

The objective of this study was to determine the frequency of cytopenias in treatment-naive HIV infected patients in two ethnically, geographically and socio-economically different countries.

Materials and Methods

Study Design and Patient Selection

This cross-sectional study was conducted among treatment-naive HIV infected individuals at two hospitals in two geographically different countries. One of them was Recep Tayyip Erdoğan Training and Research Hospital in Mogadishu, Somalia and the other was Koç University Hospital in İstanbul, Turkey. The patient groups in these hospitals had very different socio-economic conditions and belonged to different ethnic groups and races. Ethics committee permission was obtained from Recep Tayyip Erdoğan Training and Research Hospital, Mogadishu, Somalia for this study (date: 25.11.2019, no: 153). It was carried out in accordance with the 1975 Declaration of Helsinki, as revised in 2000. After informing participants about the objectives of the study, written informed consent was taken from all the participants.

The study focused on HIV-positive patients from Somalia and from Turkey. All descriptive data, consisting of demographics, diagnosis, and laboratory findings, were obtained from the hospital's medical records at Recep Tayyip Erdoğan Training and Research Hospital, Mogadishu, Somalia between January 2017 and November 2019 and at Koç University Hospital, İstanbul, Turkey between January 2016 and December 2019.

The study participants were all newly diagnosed adult HIV-positive patients, not on any antiretroviral treatment. The exclusion criteria included being at the age of <18 years, the presence of hematologic and oncologic disorders, having HIV-positivity with malignancy, chronic renal failure, hepatic disease, pregnancy, acute illness (i.e., pneumonia,

or gastroenteritis), opportunistic infections and congenital hematological disorders.

Measurement of Laboratory Parameters

Blood samples were collected into EDTA (ethylenediaminetetraa- cetic acid) containing tubes. Hematological parameters of Somalian patients and Turkish patients were determined using automated hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) and Sysmex XN-3100 (Sysmex Corporation, Kobe, Japan), respectively. In this study, we only evaluated baseline information. The hematological profiles of the patients were collected at the initial baseline visit.

Anemia in adults was defined using the World Health Organization criteria, as hemoglobin (Hb) <13 g/dL in males and <12 g/dL in non-pregnant females. Anemia severity was classified as: Mild for 11-11.9 g/dL in females and for 11-12.9 g/dL in males, moderate for 8-10.9 g/dL in both sexes, and severe for <8 g/dL in both sexes. Anemia was defined as normocytic, if the mean corpuscular volume (MCV) was between 80 and 100 fL. MCV <80 fL was considered as microcytic and MCV >100 fL as macrocytic (32,33).

The platelet count less than 150×10^9/L was considered as thrombocytopenia. It was further classified into mild ($100\text{-}150\times10^9$/L cells), moderate ($50\text{-}99\times10^9$/L) and severe thrombocytopenia ($<50\times10^9$/L). Leucopenia was defined as total white blood cell (WBC) count less than 4×10^9/L. Neutropenia was defined as an absolute neutrophil count $<1.5\times10^9$/L and subcategorized as mild ($1.0\text{-}1.5\times10^9$/L), moderate ($0.5\text{-}1\times10^9$/L), and severe ($<0.5\times10^9$/L). Lymphopenia was considered when absolute lymphocyte count was less than 1.0×10^9/L (34,35).

We categorized patients based on their cytopenias. Patients with isolated anemia, thrombocytopenia or neutropenia were defined as patients with unicytopenia. Bicytopenia was defined as having any two of the three lineage cell counts (neutrophils, Hb, or platelets) that were below the levels designated above. Pancytopenia was defined as having three lineage cell counts below the levels designated above.

An initial enzyme-linked immunosorbent assay (ELISA), followed by a confirmatory Western blot if the initial ELISA was positive, was made for the diagnosis of HIV to all patients. Polymerase chain reaction (PCR, RealStar®, Altona Diagnostics, Germany) test was performed to detect the HIV RNA titre.

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean and standard deviation (SD).

The differences between the groups were analyzed by using independent student t-test. Categorical variables were presented as frequencies and percentage of each category. Comparison of categorical variables was performed using the chi-square test. The statistical tests were two-tailed, and $p<0.05$ was considered to be statistically significant.

Results

A total of 327 HIV-positive treatment-naive patients, of which 208 (63.6%) from Somalia and 119 (36.4%) from Turkey were included in this study. The age range of the patient were between 18 and 90 years old. The mean age was found to be 40.2±13.3 years. The majority of the study participants were males (67.3%) and the ratio of males to females was 2.05:1. Statistically there was no significant difference between mean ages of Somalian and Turkish patients (39.5±13.6 vs. 41.6±12.7 respectively, p=0.17). The majority of cases (n=138, 42.2%) were in the age group of 31-45 years and followed by 90 (27.5%) cases in 18 to 30 years age group. Demographic characteristics of treatment-naive HIV positive patients is seen in Table 1. The male/female ratio was significantly higher among Turkish patients compared to Somalian patients (Table 1).

The hematological parameters of treatment-naive HIV-positive patients is given in Table 2. The mean ± SD Hb concentration for the study population was 12.6 ±2.46 g/dL (range 4.6-17.5), it was 14.1±1.69 g/dL and 11.8±2.47 g/dL for Turkish and Somalian patients, respectively. Demographic characteristics of treatment-naive HIV positive patients is seen in Table 1. The difference in Hb concentration between the Turkish and Somalian patients groups was statistically significant ($p<0.001$) (Table 2).

The prevalence of anemia in treatment-naive HIV-positive patients was 44.3% (145/327). The overall anemia prevalence was higher in Somalian patients compared to Turkish patients [58% (120/208) vs 21% (25/119)] and this difference was statistically significant ($p<0.001$) (Table 2).

Anemia was significantly more common in female patients compared to male patients [60.7% (65/107) vs 36.4% (80/220) $p<0.001$]. In the Turkish patient group, the proportion of female patients was very small (6.8%

Table 1. Demographic characteristics of treatment-naive HIV positive patient groups

Variable	Total patients (n=327)	Somalian patients (n=208)	Turkish patients (n=119)	p-value between Somalia and Turkish patients
Age (in years)				
Mean age	40.2±13.3	39.5±13.6	41.6±12.7	0.17
18-30	90 (27.5%)	66 (31.7%)	24 (20.1%)	**0.024**
31-45	138 (42.2%)	81 (39%)	57 (47.9%)	0.115
46-60	72 (22%)	44 (21.2%)	28 (23.6%)	0.618
>60	27 (8.3%)	17 (8.1%)	10 (8.4%)	0.942
Sex				
Male	220 (67.3)	109 (52.4%)	111 (93.2%)	**<0.001**
Female	107 (32.7%)	99 (47.6%)	8 (6.8%)	**<0.001**

Table 2. Hematological parameters of treatment-naive HIV-positive patient groups

	All HIV+ patients (n=327) mean ± SD	Somalian HIV+ patients (n=208) mean ± SD	Turkish HIV+ patients (n=119) mean ± SD	p-value
WBC	6.643±3.29	6.850±3.83	6.280±2.03	0.08
TLC	1.856±1.02	1.802±1.058	1.949±0.946	0.213
ANC	4.339±3.783	4.747±4.080	3.625±1.872	**<0.001**
HGB	12.59±2.46	11.79±2.47	14±1.69	**<0.001**
MCV	85.3±7.8	84.95± 8.47	85.9±6.5	0.26
RDW	14.45±2.67	14.87±3.04	13.72±1.62	**<0.001**
PLT	255.2±113.6	266.7±126.9	235.1±82.1	**0.007**
MPV	9.49±1.37	9.25±1.51	9.92±0.95	**<0.001**

SD: Standard deviation, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, TLC: Layer chromatography, ANC: Absolute neutrophil count, PLT: Platelet count, HGB: Hemoglobin

in Turkish patients vs 47.6% in Somalian patients). In the comparison of only male patients, the frequency of anemia was 53% in Somalian male patients and 20% in Turkish male patients.

Anemia was present at mild level in 67 (46%) of cases and at moderate level in 62 (43%) of cases. Yet, 11% (n=16) of the anemic patients had severe anemia (Hb <8 g/dL). Among Somalian HIV-positive patients, 40% had mild level, 47.5% had moderate level, and 12.5% had severe level anemia. These rates were 76%, 20%, and 4%, respectively, in Turkish HIV positive patients. The prevalence of mild anemia was significantly higher among Turkish patients than Somalian ones.

The most common pattern of anemia was normocytic anemia (in 61% of all patients). Microcytic anemia was present in 28.9% of patients. Macrocytic anemia was uncommon (seven cases only).

The mean ± SD platelet count of the study population was 255.2±113.6×10^9 (range 16-836) /L, it was 235.1±82.1×10^9/L and 266.7±126.9×10^9/L for the Turkish and Somalian patient groups, respectively. The difference in thrombocyte counts of two groups was statistically significant (p=0.007). On the other hand, there was also statistically significant difference in thrombocyte counts between male and female patients (241.6±103.6 and 283.3±127.9×10^9/L, respectively p=0.004).

Thrombocytopenia (platelet count <150×10^9/L) was detected in 12.8% (n=42) of study participants. Frequency of thrombocytopenia was similar in men (13.2%) and women (12.4%) patients (p=0.79). Twenty-seven patients (64%) had mild thrombocytopenia and 16 patients (36%) had moderate or severe thrombocytopenia. The overall prevalence of thrombocytopenia was 11.8% (14/119) and 13.5% (28/208) for Turkish and Somalian patients, respectively. There was no significant difference in the prevalence of thrombocytopenia between Turkish and Somalian patients (p=0.66).

The mean ± SD leukocyte count for the study population was 6.643±3.298×10^9 (range 0.690-21.580)/L, it was 6.280±2.029 and 6.850±3.829×10^9/L for the Turkish patient group and for the Somalian patient group, respectively. There was no statistically important difference in WBC counts between patient groups (p=0.08).

Table 3. Cytopenias in treatment-naive HIV positive Somalian and Turkish patients

	All HIV + patients (n=327)	Somalian HIV + patients (n=208)	Turkish HIV + patients (n=119)	p-value between Somalia and Turkish patients
Any cytopenia	178 (54.4%)	136 (65.4%)	42 (35.3%)	**<0.001**
Pancytopenia	9 (2.8%)	9 (4.3%)	0 (0%)	**0.029**
Bicytopenia	43 (13.1%)	36 (17.3%)	7 (5.9%)	**0.003**
Anemia and leucopenia	25 (7.6%)	24 (11.5%)	1 (0.8%)	**<0.001**
Anemia and thrombocytopenia	12 (3.7%)	10 (4.8%)	2 (1.7%)	0.223
Thrombocytopenia and leucopenia	6 (1.8%)	2 (0.9%)	4 (3.7%)	0.195
Isolated anemia	99 (30.3%)	77 (37.1%)	22 (18.4%)	**<0.001**
Isolated leucopenia	12 (3.7%)	7 (3.7%)	5 (4.2%)	0.763
Isolated thrombocytopenia	15 (4.5%)	7 (3.7%)	8 (6.7%)	0.163

Leucopenia (WBC <4x10^9/L) was found in 15.9% (n=52) of the study participants. The overall prevalence of leucopenia was 20.1% and 8.4% among Somalian and Turkish patients, respectively. Leucopenia was statistically significantly more common in the Somalian patient group (p=0.005).

The mean ± SD absolute lymphocyte count for all study population was 1.856±1.020×10^9 (range 0.200-6.740)/L. Lymphopenia (lymphocyte count <1x10^9/L) was found in 18.4% (n=60) of the participants, the prevalence was 22.6% (47/208) and 10.9% (13/119) for Somalian and Turkish patients, respectively (p=0.009). Neutropenia was present in 18/327 patients (5.6%) and no patient had severe neutropenia.

The cytopenias in treatment-naive HIV positive patients in both Somalian and Turkish groups is given in Table 3. Cytopenia was detected in 178/327 (54.4%) of patients in our cohort, of which 126 (38.5%) patients had unicytopenia, 43 (13.1%) had bicytopenia, and 9 (2.8%) had pancytopenia. Isolated anemia was the most common unicytopenia in this study. Among the unicytopenia cases, 99 (30.3%) patients had isolated anemia, 12 (3.7%) had isolated leukopenia, and 15 (4.5%) had isolated thrombocytopenia. The anemia and leucopenia combination was the most frequent bicytopenia (7.6%, n=25). This was followed by anemia and thrombocytopenia combination at the rate of 3.7% (n=12). Leukopenia and thrombocytopenia combination was seen rarely 1.8% (n=6). The prevalence of cytopenia/s was higher in Somalian patients compared to Turkish patients (65.4% vs 35.3%) and the difference was statistically significant (p<0.001). The distribution of cytopenia is shown in Table 3.

Discussion

Anemia was the most common hematological abnormality which was followed by leucopenia and then thrombocytopenia in the study. Anemia was more frequent among Somalian patients compared to Turkish patients. All of the patients with severe anemia were Somalian patients.

To our knowledge, our study is the first study from Turkey, comparing hematological findings in HIV-positive treatment-naive individuals with those in other countries.

Hematological abnormalities, such as cytopenias, are a major problem in HIV-positive individuals, especially in those who are not on antiretroviral therapy or in uncontrolled ones. HIV-induced impaired hematopoiesis, drug side effects, and several other factors may lead to cytopenias (3).

Anemia has been shown to influence the progression of HIV disease by accelerating and increasing mortality. There are many reports suggesting that anemic HIV patients have faster disease progression, higher morbidity and mortality rate than non-anemic ones (27,36-38). In our study, the anemia prevalence among treatment-naive Somalian HIV patients was similar to results of studies from different countries in Africa, such as Ghana (64%) (39), Ethiopia (52%) (40), South Africa (60%) (19), Uganda (48%) (8), and Tanzania (77%) (41). In Nigeria, Erhabor et al. (42) and Kagu et al. (43) reported a very high anemia prevalence of 80% and 90%, respectively. Daka et al. (44) reported an anemia prevalence of 86% among treatment-naive HIV positive patients in Ethiopia. In the present study, the prevalence of anemia among Turkish patients was lower than these values. The differences in anemia rates of Somalian and Turkish patients can be explained by the differences in socio-economic conditions, levels of poverty and malnutrition. A similar result was shown in another study, showing the high prevalence of anemia in poorer countries compared to resource-rich countries (45). In another study conducted in Africa and Haiti, the authors emphasized that

the cause of anemia might be related to the levels of poverty, low income and nutritional deficiency in these areas of the world (17). On the other hand, Mata-Marin et al. (13), Akinbami et al. (46) and Enawgaw et al. (25) reported the prevalence of anemia as 20% in Mexico, 24.2% in Nigeria and 29.7% in Ethiopia, respectively, among treatment-naive HIV-positive patients, which was similar to Turkish patients in our study. The difference between our finding and others can be explained by the differences in study populations, race/ethnicity, socio-demographic profile, geographical location, variability in the study design, and definition of anemia used in each study.

In the study, anemia frequency was higher in HIV infected females compared to males. This was also documented in different studies (17,47). The reason for the difference in anemia between the Somalian and Turkish patients may be due to the difference in gender distribution between the two groups since the proportion of female patients was very small in Turkish patients than in Somalian patients. However, this is not valid for the present study. In the comparison of only male patients, the frequency of anemia was detected to be 53% in Somalian male patients and 20% in Turkish male patients.

The anemia associated with HIV is characteristically a normochromic, normocytic anemia, yet the HIV-positive patients can also present with a hypochromic microcytic anemia. Macrocytosis is also infrequent (18,21,23). Similarly, in the present study, we found the normocytic normochromic as the most common morphologic type of anemia in patients without antiretroviral treatment, and it was followed by microcytic hypochromic and macrocytic anemia. This finding is supported by the other studies in which normocytic normochromic anemia is the major type of anemia in HIV infected treatment-naive patients (7,18,23,25,42,48).

Thrombocytopenia may be the first clinical manifestation in asymptomatic HIV infected patients. The degree of thrombocytopenia is generally mild to moderate in treatment-naive HIV infected patients. Thrombocytopenia is correlated with low levels of CD4+ cell and older age (8,23,25,30,49). The possible mechanisms that may be responsible for the development of thrombocytopenia include increased autoimmune-mediated destruction of thrombocytes due to the presence of anti-platelet antibodies, and ineffective platelet production by direct infection of megakaryocytes with HIV (25,50).

The frequency of thrombocytopenia was similar in both Somalian and Turkish patients in the present study. Different studies conducted in Ethiopia, Uganda, Tanzania, Nigeria, Rwanda, and Iran reported that the prevalence of thrombocytopenia was 18.7%, 17.8%, 14.4%, 16.1%, 13.5%, and 20%, respectively, among antiretroviral treatment-naive patients (23,29,51-53). In some African countries such as Ethiopia and Uganda, the frequency of thrombocytopenia has been found to be lower (9% and 8.3%, respectively) in treatment-naive HIV-positive patients (8,25). In another study from Turkey, the frequency of thrombocytopenia was 23.1%, which is higher compared to our results (54).

The prevalence of leucopenia in our study group was 15.9%. This rate was 20.1% in Somalian patients, which is similar with studies from Nigeria (26.8%), Uganda (24.3%), Tanzania (23.7%) and Ethiopia (16.6%) (8,23,25,53). A study conducted among adult HIV infected Zimbabweans showed that the prevalence of leukopenia was 1.7% (55). The prevalence of leucopenia was much lower in the Turkish patient group (8.4%).

In this study, we found that unicytopenia was the most common type of cytopenia and it was followed by bicytopenia and pancytopenia. At least one form of cytopenia was present in half of the participants, but cytopenia was found twice as much in Somalian patients compared to Turkish patients. The anemia was the most common type of cytopenia among unicytopenias, and it was followed by leucopenia and thrombocytopenia. While anemia and leucopenia were the most common bicytopenias in Somalian patients, thrombocytopenia and leukopenia were the most common bicytopenias in Turkish patients.

Prior studies reported different rates of HIV associated cytopenias among treatment-naive individuals. Studies conducted in Uganda, Ethiopia, South Africa and Nigeria reported that 65%, 63.4%, 63.2%, and 59.8% of the participants had at least one form of blood cytopenias, respectively (8,19,51,56). The prevalence of cytopenia in Somalian patients was in agreement with these studies. On the other hand, the prevalence of cytopenia in Turkish patients was found to be lower compared to studies conducted in African countries, which was higher than the rates reported in studies conducted in China (19.1%) and South Korea (11.2%) (57,58).

Study Limitations

To our knowledge, this is the first study from Turkey, which compares hematological parameters among groups of HIV-positive treatment-naive patients between two different

countries with different geographic location, ethnic and socio-economic conditions. Yet, there are some limitations in our study. First, our study was a cross-sectional study and there was no follow-up period. Second, there were very few female patients in the Turkish patient group.

Conclusion

The most common cytopenia in this study was anemia and the most frequent form was normocytic normochromic anemia. Anemia was significantly more common in Somalia patients than in Turkish patients. Leukopenia was the second most common hematological abnormality in Somalian patients, while thrombocytopenia was the second most common hematological abnormality in Turkish patients. Leucopenia was rare in Turkish patients. These findings have implications for the selection of antiretroviral drugs and other agents in HIV-positive individuals and also in monitoring the development of side effects. It should also be also kept in mind that these results vary between countries with socio-economic and geographical differences.

Ethics

Ethics Committee Approval: Ethics committee permission was obtained from Recep Tayyip Erdoğan Training and Research Hospital for this study (date: 25.11.2019, no: 153).

Informed Consent: Written informed consent was taken from all the participants.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.S., S.T., Ü.Ü., M.K., Concept: Ö.S., Design: Ö.S., Data Collection or Processing: Ö.S., S.T., M.K., Analysis or Interpretation: Ö.S., Ü.Ü., S.T., Literature Search: Ö.S., M.K., S.T., Writing: Ö.S., S.T., Ü.Ü., M.K.

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CASE REPORT

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Abnormal Uterine Bleeding Associated with Bupropion: A Case Report

Bupropion ile İlişkili Anormal Uterin Kanama: Olgu Sunumu

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Abstract

In the literature, many cases of abnormal uterine bleeding associated with selective serotonin reuptake inhibitors have been reported as a side effect of antidepressant treatment. However, abnormal uterine bleeding associated with bupropion, a norepinephrine-dopamine reuptake inhibitor, has been reported in only two case studies to date. A 28-year-old, oligomenorrheic female patient was admitted to the psychiatry department with the symptoms of depression. The patient was diagnosed with major depression and bupropion 150 mg/day was prescribed. After the initiation of the treatment, the patient experienced mild-to-moderate uterine bleeding, which was resolved with the discontinuation of the drug. In the patient's anamnesis, it was learned that the same side effect had developed with the previous bupropion treatment. A comprehensive examination of the patient suggested that this adverse effect could strongly be associated with bupropion. This case supports the view that antidepressants can cause bleeding abnormalities, in particular vaginal bleeding caused by bupropion usage. Physicians who prescribe bupropion should carefully follow up their patients to identify such adverse effects.

Keywords: Abnormal uterine bleeding, adverse effect, bupropion, case reports

Öz

Literatürde, antidepresan tedavisi yan etkisi olarak selektif serotonin reuptake inhibitörleri ile ilişkili çok sayıda anormal uterin kanama olgusu bildirilmiştir. Bir norepinefrin-dopamin geri alım inhibitörü olan bupropion ile ilişkili anormal uterin kanama bu tarihe kadar sadece iki olgu sunumunda bildirilmiştir. Yirmi sekiz yaşında, oligomenoreik kadın hasta, depresyon belirtileri ile kliniğimize başvurdu. Hastaya majör depresyon tanısı konuldu ve bupropion 150 mg/gün reçete edildi. Tedavinin başlamasından sonra hastada, ilacın kesilmesi ile düzelen hafif-orta derecede düzensiz uterin kanama gelişti. Hastanın anamnezinde daha önceki bupropion tedavisi ile de aynı yan etkinin gelişmiş olduğu bilgisi edinildi. Kapsamlı bir inceleme sonrasında, bu yan etkinin bupropion ile güçlü bir şekilde ilişkili olabileceği düşünüldü. Bu olgu, antidepresanların kanama anormalliklerine, özellikle bupropion kullanımına bağlı vajinal kanamalara neden olabileceği görüşünü desteklemektedir. Bupropion reçetesi yazan doktorlar, bu tür yan etkileri belirlemek için hastalarını dikkatle izlemelidirler.

Anahtar kelimeler: Anormal uterin kanama, bupropion, olgu sunumu, yan etki

Introduction

An increasing number of studies and case reports are involved in the literature associated with abnormal uterine bleeding (AUB) after treatment with various antidepressants. Most of these cases are associated with selective serotonin reuptake inhibitors (SSRIs) (1). A few cases of AUB have also been reported due to the use of venlafaxine, a serotonin norepinephrine reuptake inhibitor (2). To date, a case series of two patients with AUB associated with bupropion, a norepinephrine dopamine reuptake inhibitor, has been found in the literature. In this case series, it was reported that bupropion caused irregular and increased menstrual bleeding in one patient, and shortened cycles and secondary amenorrhea in the other patient (3). In this article, a patient who was treated with

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bupropion for depression and developed AUB as a side effect is presented.

Case Report

A 28-year-old woman was presented to our psychiatry clinic with the symptoms of depression, including feeling down, aversion, nervous temperaments, obliviousness, pessimistic thoughts and reluctance to social interaction. The patient was diagnosed with major depression. Her Beck depression scale (BDS) score was 24. In her anamnesis, it was learned that she had applied to a psychiatrist with the diagnosis of depressive disorder one year ago, and 150 mg/day bupropion treatment had been started, which had been increased to 300 mg/day at the 2nd month. The patient stated that she had AUB that had lasted for 15-20 days, except for menstrual bleeding, during the entire treatment, but she had not told her doctor about this. Within the sixth month of the treatment, the patient had stopped taking the medication due to the increased amount and duration of the bleeding. Fifteen days later, the patient's AUB had been resolved. She had had regular menstrual periods for the following 1 year. The patient, whose depressive symptoms had recurred after a one-year drug-free period, was admitted to the psychiatry clinic of our hospital this time. Based on her history, the patient was evaluated by the gynecology clinic of our hospital. No pathology was observed in the gynecological examination. We prescribed bupropion 150 mg/day. At the one-month visit after the initiation of the treatment, there was a reduction in her depressive symptoms and BDS score was fourteen. She also reported that, apart from normal menstrual bleeding, she had vaginal bleeding that lasted for four days. At the end of the third month, her depressive symptoms disappeared and she noted that the duration and intensity of her vaginal bleeding were the same as in the first month. Thereupon, the patient was evaluated gynecologically again. Her coagulation parameters and serum hormone levels were found to be normal. No pathology was observed as a result of the endometrial sampling performed under office hysteroscopy. After the fourth month, the patient discontinued her treatment because she thought she got better. Although we informed the patient on the potential risks of quitting the medication and strongly advised her to continue the treatment, she refused to receive it. We followed the patient for the next six months for depression and menstrual cycles. During this period, we observed that the patient's depression symptoms and AUB did not recur.

Discussion

Numerous mechanisms about how antidepressants can cause bleeding abnormalities have been suggested in previous research. Serotonin (5-HT) is important in platelet aggregation and the modulation of vascular tone. SSRIs block platelet uptake and endothelial metabolism of serotonin and use of these agents may result in bleeding and vasospastic complications (4). Serotonin is found in the reproductive tract of female mammals, including the ovaries, follicular fluid, mature oocytes, and cumulus cells, and its concentration changes during the menstrual cycle and it is involved in the modulation of follicular maturation (5). Antidepressants with serotonergic effects may cause vaginal bleeding due to their effects on gonadal hormones (1). With respect to this case, the above-mentioned case raises the question whether bupropion exhibits any serotonergic activities. A study with rats has provided evidence that all neurotransmitter levels (dopamine, norepinephrine, and serotonin) have significantly increased after bupropion injection (6). Medications that influence the dopaminergic and norepinephrinergic systems can presumably increase 5-HT transmission (7). These findings favor the notion that bupropion can demonstrate serotonergic effects and may cause bleeding abnormalities through modulation of gonadal hormones. We also explored the relationship between dopamine and norepinephrine reuptake and vaginal bleeding. An *in vitro* study demonstrates that the therapeutic concentration of the selective norepinephrine reuptake inhibitor desipramine inhibits serotonin uptake in platelets and that the 5-HT content in platelets is reduced by 38% compared to pretreatment levels in depressed patients (8). It has also been found that increasing dopaminergic neurotransmission can impair platelet functions, although the mechanism has not been clarified (9).

We have concluded that the AUB that developed in the patient might be related to the use of bupropion because, without an underlying organic reason, vaginal bleeding started after each bupropion use and was resolved after the discontinuation of the drug. More research is needed to fully understand how antidepressants cause bleeding abnormalities, and patients using bupropion should be carefully monitored for such side effects.

Ethics

Informed Consent: Informed consent form was signed by the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K.V., E.E.K., Design: M.K.V., E.E.K., Data Collection or Processing: M.K.V., E.E.K., Analysis or Interpretation: M.K.V., E.E.K., Literature Search: M.K.V., E.E.K., Writing: M.K.V., E.E.K.

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