E-ISSN: 2547 - 9431

BAGCILAR MEDICAL BULLETIN

Bağcılar Tıp Bülteni

Volume 7, Issue 2, June 2022

ORIGINAL RESEARCHES / ARAŞTIRMALAR

Periodical Publication of
Health Sciences University
Turkey, Bagcilar Training
and Research Hospital

BAGCILAR MEDICAL BULLETIN
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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: June 2022
E-ISSN: 2547-9431
International scientific journal published quarterly.

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Bagcilar Medical Bulletin (Bağcılar Tıp Bülteni) (BMB) is a periodical scientific publishing of Health Sciences University, İstanbul Bağcılar Training and Research Hospital. This editorially independent, unbiased, international journal periodically publishes peer-reviewed work in the all medical fields on an international scientific basis. Publication language is English for full text and Turkish and English for abstracts. The journal has been published in English since December issue of 2016 as an e-journal.

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

English Title: Bagcilar Medical Bulletin

Turkish title: Bağcılar Tıp Bülteni

Official abbreviation: Bagcilar Med Bull

E-ISSN: 2547-9431

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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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Official abbreviation: Bagcilar Med Bull

E-ISSN: 2547-9431

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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.

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Dergi Adı (İngilizce): Bagcilar Medical Bulletin

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

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Description

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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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- Case reports,
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- Letters to the Editor

The journal gives high priority to original studies in publication because of aims to add the findings of searches in Turkey to international scientific knowledge, to share them within the international science milieu and to constitute the introduction of Turkish scientists. The review articles to be published in the journal are authorized by the editor to the relevant authors working on the subject.

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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.

•All helpful things for editorial ship should be stated: The comments of previous editor/reviewers and the response of authors should be added if the manuscript has been sent to another journal for consideration, previously. The editor requested this information to accelerate the publication process.

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

- Reviewing the statistical design of the research article

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Copyright Transfer Form

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-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 Bagcilar Medical Bulletin uses plagiarism screening service to verify the originality of content submitted before publication. This journal does not accept articles that indicate a similarity rate of more than 15%, according to iThenticate reports.

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Duplication: Using data from another publication; this includes republishing an article in different languages.

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

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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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Bagcilar Med Bull 2022;7(2):85-89
DOI: 10.4274/BMB.galenos.2022.2022-03-027

Physiology of Exercise and Its Importance During COVID-19 Pandemic

COVID-19 Salgını Sırasında Egzersiz Fizyolojisi ve Önemi

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Abstract

Physical activity is important in the prevention and treatment of Coronavirus disease-2019 (COVID-19). There is a strong relationship between increased physical activity and improved general health during COVID-19 pandemic. Moderate aerobic exercises may be more beneficial than the exhausting exercises due to the post-COVID-19 syndromes or long-COVID. Regular program of aerobic exercise for 20-60 minutes in the form of cycling or walking with an intensity of moderate in repeated 2-3 sessions/week could safely enhance immune functions. The aim of this review is to highlight the recommendation to support exercise activities in the post COVID-19 period.

Keywords: Aerobic exercise, COVID-19 pandemic, health, physiology

Öz

Koronavirüs hastalığı-2019'un (COVID-19) önlenmesi ve tedavisinde fiziksel aktivite önemlidir. COVID-19 salgını sırasında fiziksel aktivite ile genel sağlığın iyileşmesi arasında güçlü bir ilişki vardır. COVID-19 sonrası veya uzun süreli COVID-19 sendromlarında orta düzeyde aerobik egzersizler yorucu egzersizlerden daha faydalıdır. Haftada 2-3 kere tekrarlanan, orta düzeyde, bisiklet veya yürüyüş şeklinde 20-60 dakikalık düzenli aerobik egzersiz programı bağışıklık fonksiyonlarını güvenli bir şekilde iyileştirebilir. Bu derlemenin amacı, COVID-19 sonrası dönemde egzersiz aktivitelerinin desteklenmesi önerisini vurgulamaktır.

Anahtar kelimeler: Aerobik egzersiz, COVID-19 salgını, fizyoloji, sağlık

Introduction

One of the most common challenges to body homeostasis is not a disease but an everyday activity: Exercise. Exercise comes in two major forms: Dynamic endurance exercises, which are distance running and cycling, and resistance training, which are weightlifting and strength training (1). These types of exercises have many different effects on body systems, especially immune system, cardiovascular-respiratory system, and muscle system.

Unidentified viral pneumonia cases were announced in December 2019, in the city of Wuhan, Hubei province, China (2). This unidentified virus extended all over the world in the following weeks. It was announced that viral pneumonia was a novel coronavirus [severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2)] by a research center in China, on January 7, 2020, later named Coronavirus disease-2019 (COVID-19) by the World Health Organization (WHO) (3). The COVID-19 pandemic has changed the living conditions of people and has had an unfavorable effect on many sectors

***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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Cite this article as: Kılıç A, Erkalp K, Darıyerli N. Physiology of Exercise and Its Importance During COVID-19 Pandemic. Bagcilar Med Bull 2022;7(2):85-89

in the economic, social, and commercial fields in many fields such as health, education, industry, transportation, tourism, and sports around the world. While COVID-19 may cause asymptomatic or mild infection with rapid recovery, acute and permanent complications may occur in some cases. Severe COVID-19 can potentially lead to an extensive diversity of clinical disorders containing various body systems, such as ongoing shortness of breath, heart damage, pulmonary fibrosis, or embolism. Recovery may be prolonged for survivors and some patients have a long-term and debilitating illness, which lasts for up to 4 weeks. Quarantine and sedentary lifestyle has affected the individual's quality of life during the COVID-19 pandemic. It is stated that the quarantine processes lead to a decrease in individual's physical activity and increase in unhealthy nutrition. Supporting this information, many studies have demonstrated that the physical activity levels of individuals significantly decrease during the quarantine period, which causes many health problems including cardiovascular, respiratory neuromuscular function and depression. Studies have shown that there is a strong relationship between increased physical activity and improved general health during COVID-19 pandemic (4).

Factors Causing Exercise Restrictions in COVID-19 Patients

COVID-19, immune responses and exercise: The effects of exercise on the immune system have been extensively studied in recent years. It is the main subject of research whether exercise increases the resistance to infections by improving the immune system, or whether it makes it easier to catch infections by suppressing the immune system. Different effects may occur in both innate and acquired immunity. The effect of exercise on immune system functions depends on many variables such as the intensity, duration, severity of exercise and the physical fitness level of the individual (5,6). The studies have suggested that regular moderate-intensity exercise reduces the incidence of infections such as common cold, while intense exercise increases the ratio of upper respiratory tract infections, and the severity of exercise increases the risk of upper respiratory tract infections. In addition, regular moderate-intensity exercise increases the resistance against upper respiratory tract infections (7). While the immune system functions increase with mild and moderate exercise, strenuous exercise is one of the strongest types of stress that suppresses the immune response. The immune system is suppressed following intense prolonged exercise. Since exhausting exercises will increase the secretion of cortisol from the hypothalamus-pituitary-adrenocortical axis, they may have a suppressive effect on the immune system and make the individual temporarily susceptible to infections (8).

During aerobic exercises, there is an increase in the number and functions of natural killer (NK) cells in our body (9). However, immediately after a single acute short-term and high-intensity exercise, the leukocyte concentration increases, and this increase is mostly carried out by neutrophils (10). The increase in the number of neutrophils progresses after exercise. The increase in lymphocyte concentration following prolonged exercise is almost twice that after short-term exercise (11). NK cells and B-cells are also suppressed after a single acute short-term and high-intensity exercise. Moreover, vigorous exercise causes an increase in circulating levels of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (12).

In severe forms of COVID-19, diffuse alveolar and interstitial inflammation occurs (13). While the rapid immune response represents the defense of first line against infection with the virus, the excessive inflammatory response of innate immunity can lead to systemic tissue damage. The infected immune system responds with a cytokine storm and hyperinflammation which itself leads to further multi-organ damage and even death. In other words, the immune-mediated damage developed in these patients is more harmful than the damage caused by the virus (14). Laboratory findings of COVID-19 patients are decreased or normal number of leukocytes and decreased lymphocyte count (15). Coronavirus triggers the release of a significant number of cytokines, which cause the activation of the immune system, especially IL-6 and other acute phase reactants (16). IL-6 receptors are expressed by almost all immune cells and have a major role in the proliferation and differentiation of immune cells. IL-6 is produced by the stimulation of SARS-CoV-2 itself or other immune cells. IL-6 is an important indicator of lung injury and was significantly associated with an increase in C-reactive protein, lactate dehydrogenase, ferritin and D-dimer levels. There is a relationship between the levels of IL-6 and the severity of COVID-19. The decrease in IL-6 level was related to the effectiveness of the treatment and the improvement of the disease, while the increase in IL-6 was associated with the progression of the disease and worsening of the clinical picture (17,18). Therefore, IL-6 level can be used as an important biomarker for the monitoring of the disease in severe COVID-19 cases. In a study, it was demonstrated that the higher levels of IL-6 and systemic inflammation markers

was associated with a poor prognosis and contributed to mortality (19).

Exercise is also thought to stimulate the mitochondrial biogenesis, thereby preventing severe forms of COVID-19 (20). Mitochondrial biogenesis is defined as the development of existing mitochondria that responds to metabolic, mechanical, and hypoxic stresses occurring in myocytes and the adaptation of skeletal muscle to exercise training. It has been suggested that muscle mitochondrial biogenesis increases with regular exercise, and this adaptation increases endurance performance in individuals. Mitochondrial biogenesis, and the amount and activity of oxidative proteins in mitochondria can be reduced as a result of mitochondrial dysfunction (21). As the infection progresses, redox-sensitive or redox-active intracellular pathways triggered by SARS-CoV-2 can put the reductive cycle into a process that makes it impossible to continue at physiological levels, in this case, the cells remain in an irreversible pathway, that is, in the oxidation clamp characterized by destruction (22). Advanced inflammation further provokes redox imbalance in favor of oxidation, and all components of the cardiovascular system collapse (23).

COVID-19, cardiovascular responses and exercise: Many studies have demonstrated the relationship between cardiovascular diseases and exercise (24,25). Research has shown that exercise has many benefits. These benefits comprising raising plasma high-density lipoprotein (HDL) cholesterol levels, decreasing plasma triglyceride levels, and lowering blood pressure (26). High blood pressure is a main risk factor for strokes, while elevated triglycerides and low HDL-cholesterol levels are linked with the development of atherosclerosis and increased risk of heart attack. It has been shown that regular aerobic exercises also reduce hypertension, which is one of the leading problems in the world. Studies have demonstrated that regular exercise lowers blood pressure in mild to moderate hypertension (27). It has also been revealed that moderate-intensity exercise can lower blood pressure more efficaciously than high-intensity exercise (28).

COVID-19 infection can lead to cardiac arrhythmias, myocarditis, and other cardiovascular complications, with potentially fatal consequences. Pathophysiological mechanisms of cardiac injury may include T-cell and cytokine-mediated hyperinflammatory reaction, or direct myocardial cell infection (29). Cardiac involvement may also be associated with high expression of angiotensin converting enzyme-2 (ACE-2). ACE-2 is a membrane glycoprotein found in epithelial cells of many organs in the body, mainly in the heart, lungs, and kidneys, and is a homolog of ACE. It catalyzes the conversion of angiotensin (ANG)-2 to ANG-1-9 and ANG-1-7, respectively. Since the SARS-CoV-2 spike protein binds to ACE-2 and enters the cell, ACE-2 expression and/or polymorphism has been shown to have an impact on susceptibility to SARS-CoV-2 infection and outcomes of COVID-19 disease (30,31). The ACE-2 protein is a component of the renin-angiotensin-system (RAS) as well as being a transmembrane receptor for the virus. In a study, it was revealed that the binding of SARS-CoV-2 to ACE-2 receptor decreased the immunity and the anti-inflammatory action exerted by mitochondria (20). Besides this information, many studies demonstrated the relationship between ACE-2 levels and training. In a study, it was suggested that high intensity interval exercise increased plasma ACE-2 levels, while moderate intensity continuous exercise increased the urinary concentration of ACE-2 (32). Klöting et al. (33) suggested that intensive physical exercise induced ACE-2 expression in skeletal muscle but led to lower circulating ACE-2 levels. That may be due to the fact that intensive physical exercise caused hypoxia in skeletal tissue and was involved in increased tissue ACE-2 expression. Although its underlying mechanism is still unclear, it is thought that high-intensity exercises increase tissue ACE-2 levels which inhibits mitochondrial anti-inflammatory function, while moderate-intensity exercises increase plasma ACE-2 levels which prevent infection (20).

Exercise Recommendations for COVID-19 Patients

According to the WHO, a sedentary lifestyle is among the main risk factors for deaths occurring all over the world. In addition, it has been revealed that 150 minutes of physical activity per week in adults and even individuals with chronic diseases reduce the risk of ischemic heart disease by 30%, the risk of type II diabetes by 27%, and the risk of breast and colon cancer by 20-25% (34). However, moderate aerobic exercises may be more beneficial than the exhausting exercises due to the post-COVID-19 syndromes or long-COVID (35). Microorganisms, especially viruses, can enter the body and cause infections when immunity is weakened after high-intensity exercise (11). Therefore, light, and moderate intensity exercise should be chosen especially during this period. Even in recovering cases, a return to vigorous physical exercise can develop heart damage and suppress immune system, which can pose a health risk (36).

If there is not any structural damage and symptoms of COVID-19, it is possible to return to exercise. Employees in jobs that require intense physical activity should be alert to the risks of cardiovascular and other complications

from COVID-19 and provide specific inquiry for COVID-19 complications during return-to-work fitness assessments (37).

Conclusion

Regular exercise can reduce the dose of the drug used in chronic diseases or eliminate the need for the drug. It reduces the risk of heart disease and other chronic diseases. It strengthens the immune system, reduces stress, helps to lose weight, and strengthens the muscle and bone structure. It increases one's self-confidence. As a result of all these, it increases the life span and quality of life of the individual. Physical activity is important in the prevention and treatment of COVID-19. For the post COVID-19 patients, it may be beneficial to evaluate exercise capacity and it should be supported to start previous exercise activities under the control of sports physicians. In post COVID-19 period, patients may follow a regular program of aerobic exercise for 20-60 minutes in the form of cycling or walking with an intensity of moderate, may be repeated 2-3 sessions/week. Thus, it could safely enhance immune functions.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., K.E., N.D., Design: A.K., K.E., N.D., Data Collection or Processing: A.K., K.E., N.D., Analysis or Interpretation: A.K., K.E., N.D., Literature Search: A.K., K.E., N.D., Writing: A.K., K.E., N.D.

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

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

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REVIEW

Bagcilar Med Bull 2022;7(2):90-101
DOI: 10.4274/BMB.galenos.2022.2022-04-032

DcR3 in All Its Aspects

Tüm Yönleriyle DcR3

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Abstract

Decoy receptor 3 (DcR3) is a supermember of tumor necrosis receptor (TNF) factor. DcR3 acts as a binding partner in multiple apoptotic ligands that inhibit apoptosis. TNF-associated apoptosis-inducing ligand (TRAIL)-induced apoptosis has been demonstrated to be sensitized by DcR3. DcR3 has been found to be a "pleiotropic" soluble factor with "decoy" and "non-decoy" activities that control cell functions. The connection between Fas and FasL can be inhibited by recombinant DcR3 coupled with an IgG1 Fc domain. TNF superfamily FasL can inhibit apoptosis and increase angiogenesis through neutralizing members of LIGHT and TL1A. DcR3 serum level is almost undetectable in most normal individuals without inflammatory diseases and cancer. According to several research, the level of DcR3 in the blood is linked to cancer stage in cancer patients. High DcR3 levels in serum or tissues have been found to be associated with poor prognosis and/or resistance to therapy in some cancer patients. As a result, identifying the cut-off value of the DcR3 serum level will provide to able to forecast the severity of disease in the future. While inhibiting DcR3 expression may slow tumor growth, improving DcR3-mediated effector functions could be a viable strategy for reducing autoimmunity and promoting tissue healing. Thus, recombinant DcR3 is a promising immunotherapeutic agent; yet, in the malignant environment, turning off DcR3 expression may improve cancer therapy success. The purpose of this review is to provide clinical convenience by collecting the findings of studies on DcR3 so far. These discoveries could help with cancer diagnosis, differentiation, metastasis, and stage detection. Furthermore, these may provide new therapeutic approaches to target carcinomas in the future.

Keywords: Biomarker, DcR3, DcR3 and cancer

Öz

Decoy reseptörü 3 (DcR3), tümör nekroz reseptörü (TNF) faktörünün bir üst üyesidir. DcR3, apoptozu inhibe eden çoklu apoptotik ligandlarda bağlayıcı bir ortak olarak görev yapar. TNF ile ilişkili apoptozu indükleyen ligand (TRAIL) ile indüklenen apoptozun DcR3 tarafından duyarlı hale getirildiği gösterilmiştir. DcR3'ün, hücre fonksiyonlarını kontrol eden "tuzak" ve "tuzak olmayan"" aktiviteleri olan bir "pleiotropik" çözünür faktör olduğu bulunmuştur. Fas ve FasL arasındaki bağlantı, bir IgG1 Fc alanı ile birleştirilmiş rekombinant DcR3 tarafından engellenebilir. TNF süper ailesi FasL, LIGHT ve TL1A üyelerini nötralize ederek apoptozu inhibe edebilir ve anjiyogenezi artırabilir. DcR3 serum seviyesi, enflamatuvar hastalıkları ve kanseri olmayan çoğu normal bireyde neredeyse saptanamaz düzeydedir. Birkaç araştırmaya göre, kandaki DcR3 seviyesi kanser hastalarında kanser evresi ile bağlantılıdır. Serum veya dokulardaki yüksek DcR3 seviyelerinin, bazı kanser hastalarında kötü prognoz ve/veya tedaviye direnç ile ilişkili olduğu bulunmuştur. Sonuç olarak, DcR3 serum seviyesinin eşik değerinin belirlenmesi, gelecekte hastalığın ciddiyetini tahmin ettirebilecektir. DcR3 ekspresyonunun inhibe edilmesi tümör büyümesini yavaşlatabilirken, DcR3 aracılı efektör fonksiyonların iyileştirilmesi, otoimmüniteyi azaltmak ve doku iyileşmesini desteklemek için uygun bir strateji olabilir. Bu nedenle, rekombinant DcR3 umut verici bir immünoterapi ajanıdır; yine de malign ortamda DcR3 ekspresyonunun önlenmesi kanser tedavisi başarısını artırabilir. Bu derlemenin amacı, şimdiye kadar DcR3 ile ilgili çalışmaların bulgularını toplayarak klinik kolaylık sağlamaktır. Bu keşifler kanser teşhisi, farklılaşma, metastaz ve evre tespiti konusunda yardımcı olabilir. Ayrıca, bunlar gelecekte karsinomları hedeflemek için yeni terapötik yaklaşımlar sağlayabilir.

Anahtar kelimeler: Biyobelirteç, DcR3, DcR3 ve kanser

Introduction

Decoy receptor 3 (DcR3/TNFRSF6B) is a receptor affiliated with the tumor necrosis factor receptor (TNFR) superfamily. Dissimilar to most members of the TNFR superfamily, the *DcR3* gene is not a cytoplasmic or transmembrane region, but encodes 300 amino acids with 29 residual signal sequences. The death ligament is

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Cite this article as: Helvacı N, Çağlar HG, Kural A. DcR3 in All Its Aspects. Bagcilar Med Bull 2022;7(2):90-101

a soluble receptor for three different TNF ligands (FasL, TL1A and LIGHT) that inactivate it by connecting to cd95L and is capable of neutralizing these ligands (1-5). The array resemblance between FasL, LIGHT, and TL1A is moderate (~30% identification) and each binds to different receptors eliciting different responses (5). There are studies showing that members of the TNFR superfamily can induce reverse signals after interacting with surface receptors (2).

The human *DcR3* gene is chromosomally mapped to 20q13.3 and this region is associated with many diseases (6). DcR3 mRNA is phrased in SW480 in lung tissues and colon adenocarcinoma (1). Recently, it has been reported that the C-terminal territory of DcR3, located except the TNF ligand-binding area, binds heparan sulfate proteoglycans (HSPGs) and triggers reverse signaling in antigen-presenting cells (APC) (5). There is a solid argument for overexposure of DcR3 in a variety of tumors such as lung, colon and pancreatic cancers, gastrointestinal tumors, malignant gliomas, virus-associated lymphomas, and tissues affected by autoimmune disease (7,8). Besides, excessive DcR3 expression was observed in cases of systemic lupus erythematosus or silicosis (9,10). DcR3 can act as a decoy or non-decoy receptor. In many cancer patients, DcR3 overexpression is associated with a worse prognosis of the disease. This proposes that excessive expression of DcR3 may breed some advantages for tumor growth and survival (2,6-8,11).

DcR3 and Its Functions

In their study, Yu et al. (1) used histidine-labeled recombinant DcR3 to scan soluble forms of TNF-ligand proteins with immunosuppressives. As a result, DcR3 was shown to bind especially to LIGHT and Fas ligand. While DcR3 prevents LIGHT-induced cytotoxicity in HT29 cells, LIGHT induces apoptosis of HT29 cells and various tumor cells. Data from the study showed that DcR3 suppressed LIGHT-mediated HT29 cell death by preventing the interaction of LIGHT with HVEM/TR2 and LTβR. It is therefore thought that DcR3, FasL and LIGHT may play a regulatory role in suppressing cell death (1).

Tang et al. (3) produced transgenic mice that over-expressed DcR3 in order to better understand DcR3's role in bone formation *in vivo*. Transgenic mice were compared with controls for bone mineral content (BMC) and total bone mineral density (BMD), resulting in much lower BMC and BMD in transgenic mice. After comparing DcR3 transgenic mice and control mice for BMD and BMC, there was a 35.7% reduction in trabecular bone volume in DcR3 transgenic mice. According to the study data, the number of osteoclasts incremented in DcR3 transgenic mice. However, regional administration of DcR3 to the tibial metaphysis significantly reduced the bone volume, BMC and BMD ratio of secondary spongiosis. Local injection of DcR3 has also been shown to increment the number of osteoclasts around the trabecular bone in the tibia. In an osteoclast activity experiment on substrate plates, it was stated that DcR3 remarkably incremented the absorption action of mature osteoclasts. High concentration DcR3 treatment slightly enhances nodule development and alkaline phosphatase action of primary cultured osteoblasts. From these results, it can be extracted that DcR3 induces the formation of osteoclasts from a bone stromal marrow cells, monocyte and, macrophage and this indicates that DcR3 may be critical in bone diseases and osteoporosis (3).

DcR3 is found in both rheumatoid arthritis (RA) and osteoarthritis (OA) fibroblast-like synoviocytes (FLS), according to the study by Hayashi et al. (12) DcR3-Fc protein inhibits Fas-source apoptosis in FLS, and DcR3 has been shown to increase down- regulation by siRNA and Fas-source apoptosis. In RA FLS, TNFa boosted DcR3 expression and prevented Fas-source apoptosis, but this was not the case in OA FLS (12).

To investigate autoimmune diseases, transgenic mice were generated by actin promoter-driven expression of human DcR3. While T-cell immune responses were suppressed in young DcR3-transgenic mice, the transgenic mice developed a systemic lupus erythematosus-like illness with distinct symptoms and produced autoantibodies against double helix DNA after 5-6 months. Proteinuria, leukocyturia, and hematuria were present in the kidneys, indicating accumulation of IgG, glomerular nephritis, and C3. Mice developed lymphocyte infiltration in their livers, skin lesions, as well as leukopenia, thrombocytopenia, anemia, similar to older transgenic mice. SLE-like syndrome was seen in approximately 60% of female transgenic mice versus 20% of males and was shown to be sex-related. Endogenous DcR3 and exogenous recombinant DcR3 (produced by transgenic T-cells) were shown to effectively protect T-cells against activation-induced apoptosis *in vitro*. Six months later, CD4 cells were increased in transgenic mice (13).

DcR3 makes cells of hematopoietic origin susceptible to TRAIL-induced apoptosis. DcR3 decreased host immunity by causing immune cell death, which You et al. (14) investigated. They showed that DcR3 induced dendritic cell (DC) apoptosis by activating PKC-δ and JNK to regulate DR5 upward by taking the Fas-related mortality area (FADD) to

spread apoptotic signals. The relationship of FADD with DR5 is that it activates the downstream apoptotic signaling cascade, causing the formation of the signaling complex (DISC) that leads to death. PKC-δ is activated (on DCs) by cross-linking heparan sulfate proteoglycan (HSPG) as the HBD. Fc fusion protein can trigger DC apoptosis. The results show the existence of a novel DcR3-mediated immunosuppressive mechanism (14).

Serum DcR3 levels in people with systemic lupus erythematosus were studied, and serum DcR3 levels in SLE patients were shown to be quite high. Also, when active SLE patients were compared with inactive SLE patients, the mean serum DcR3 level was found to be significantly higher in active patients. Soluble DcR3-Fc both reduced cell death induced by T-cells activated by FasL neutralization and, increased IL-2, T-cell proliferation and interferon-gamma production through co-stimulation of T-cells. In addition, lymphocytes taken from patients with SLE showed increased T-cell reactivity to common stimulation induced by DcR3, implying that elevated serum DcR3 was linked to heightened T-cell activation *in vivo*. The obtained information shows that serum DcR3 may be a guide in the pathogenesis of SLE (15).

Renal cell carcinoma tumor tissue samples and normal tissue samples from patients with renal cell carcinoma were compared for DcR3 expression. As a result of the study, high level of DcR3 expression was observed in renal cell carcinomas. Lymph node metastasis and the incision of distant metastasis were directly correlated with DcR3 expression, and metastases were found to be higher in the group with higher expression. DcR3 expression showed negative correlation with disease-specific survival ($p<0.001$) and non-progressive survival ($p<0.001$) in single-variable analyses. Patients with high-stage renal cell carcinoma expressing DcR3 had a 25% chance of 2-year survival, while patients with DcR3 negative tumors had a 65% chance of survival. DcR3 serum levels were also observed to be considerably greater in patients with advanced localized cancer and metastatic cancer (4).

Using human pancreatic cancer cells, high levels of DcR3 protein were shown in AsPC-1 cells through immunosuppression and ELISA method, while the presence of DcR3 in PANC-1 cells was not seen. Treatment with LY294002, wortmannin, Herbicide A, pyrrolidine dithiocarbamate or AG1024 has been shown to reduce endogenous DcR3 levels in AsPC-1 cells significantly. Also, transfection of AsPC-1 cells with IkappaBalpha or Akt dominant-negative plasmids lowered DcR3 levels considerably. DcR3 expression was enhanced in PANC-1 cells after a 48-hour transfection with a structurally active Akt (16).

The development of Crohn's disease is influenced by immune cell apoptosis resistance and epithelial barrier dysfunction. DcR3 neutralizes CD95L and thus displays an anti-apoptotic effect. The effect of DcR3 in Crohn's disease via CD95L was examined in one study. According to the results of the methods studied, DcR3 was found to be overexpressed in both actively inflamed and inactive regions of the epithelial layer of ileum samples in patients with Crohn's disease. People with Crohn's disease (active and inactive) had higher DcR3 expression levels compared to healthy people. TNF-α induces the expression of DcR3 in intestinal epithelial cells. The activation of nuclear factor kappa B (NF-kappaB) and the enhanced expression of DcR3 have been linked. As a result, it prevents CD95L-induced apoptosis in T-cells in the lamina propria and in intestinal epithelial cells. DcR3 can help with Crohn's disease inflammation by reducing CD95L-induced immune cell death and epithelial cell death and increasing NF-kappaB activation (17).

A study by Liang et al. (18) investigated the expression of survivin and DcR3 in colorectal carcinoma. Survivin mRNA and DcR3 mRNA levels in colorectal cancer tissues were shown to be greater than in surrounding tissues, according to RT-PCR data. Survivin protein and DcR3 protein expression levels in tumor tissues were considerably greater than levels in non-cancerous tissues according to western blotting data. In the immunohistochemical streptavidin-peroxidase (SP) method, DcR3 and survivin were positively correlated. They were more highly expressed in cancerous tissues (DcR3; 67.0% and survivin; 58.0%) compared to non-cancerous tissues (DcR3; 18.0% and survivin; 3.0%). According to the findings, DcR3 and survivin differentiation of colorectal cancer cells, as well as positive relationships with lymph node metastases and pathological stage, was found. DcR3 and survivin expression show a positive correlation with clinicopathological parameters of colorectal carcinoma (18).

The majority of follicles in mammalian ovaries experience atresia during the follicular development phase. Apoptotic cell death in granulosa cells is one of the features of this process. Fas ligand (FasL) and Fas, among other receptors and death bonds, were found in ovarian follicles, subsequently found to induce apoptosis in follicular cells. In light of this information, the expression of the default pig DcR3 mRNA in pig ovarian follicles was examined. The

nucleic acid sequence was found to have 80% homology compared to human DcR3, while the amino acid sequence was found to be 73% identical. According to the results of RT-PCR study, pDcR3 mRNA expression in granulosa cells from atretic follicles is weaker than in cells from healthy follicles. The individual layer cells, on the other hand, did not change significantly. While DcR3 regulates apoptosis in granulose cells during atresia, this is not the case in individual layer cells, according to these findings (19).

Yang et al. (20) investigated the concentration and clinical importance of DcR3 in serums of hepatocellular carcinoma (HCC) patients. According to the findings, serum DcR3 concentrations in patients with cirrhosis or HCC were considerably greater than in healthy people. Serum DcR3 levels in HCC patients were correlated with some factors such as TNM stage, metastasis, disease recurrence or para-cirrhosis. Protein expression and DcR3 serum levels had a positive connection in HCC tissues. Significantly elevated serum DcR3 levels, according to the findings, may have a role in the genesis, metastasis, and progression of HCC (20).

DcR3 was expressed in both osteoarthritis and normal chondrocytes in a study to investigate its roles on osteoarthritis chondrocytes. DcR3-Fc has been found to protect chondrocytes against apoptosis caused by Fas. DcR3-Fc boosted chondrocyte proliferation and selectively activated ERK phosphorylation. Chondrocyte proliferation induced by DcR3 is inhibited by blocking of the Fas-L antibody or pre-incubation of PD098059. DcR3 regulates chondrocyte proliferation in osteoarthritis chondrocytes via the ERK signaling pathway and Fas-source apoptosis (21).

The most prevalent kind of primary glomerulonephritis in the kidney is IgA nephropathy (IgAN), which affects mostly macrophages and T-cells. The theory that DcR3 can inhibit IgAN development, renal apoptosis, macrophage infiltration and T-cell activation was investigated in a study. A progressive IgAN (Prg-IgAN) model was used in mice with B cell deficiency. A short-term gene therapy was applied to mice with DcR3 plasmids through hydrodynamic-based gene transfer. When euthanasia was applied on the 21st day, compared to Prg-IgAN mice treated with empty vectors, they found systemic inhibition in T-cell proliferation and activation as a result of DcR3 gene therapy. Pro-inflammatory cytokines also have low serum levels. They found that progressive proteinuria, kidney function and kidney pathology decreased the rate of apoptosis in the kidney by suppressing macrophage and T-cell infiltration. DcR3 may be therapeutically beneficial in reducing IgAN development according to these data (22).

Yoo et al. (23) studied the expression of DcR3 in human endothelial cells and the effect of this expression in the early stages of Kaposi's sarcoma-associated herpes virus (KSHV). Infected cells were treated with recombinant human TL1A or anti-DcR3 antibody to assess cell proliferation and apoptosis. In the early stages of infection, DcR3 expression is upregulated. In the early phases of KSHV infection, DcR3 expression is critical for avoiding apoptosis in HUVECs, allowing for the effective formation and management of viral infection (23).

Pancreatic carcinomas and non-cancerous tissues were compared for DcR3 expression level, with the result that the ratio between tissues differed statistically significantly. DcR3 expression was shown to be associated with tumor size in the study. The preoperative pancreatic carcinoma resection group had a considerably higher level of DcR3 in their serum than the gallbladder carcinoma or benign pancreatic tumor groups. As a result, DcR3 is particularly effective in clinical-pathological factors in pancreatic carcinoma tissues that reflect tumor progression (24).

According to a study, DcR3 suppresses MHC II expression in TAMs via epigenetic regulation. Following this research, CT26-DcR3 stable transfects were developed to see if DcR3 promoted tumor growth. DcR3 transfections grew quicker than the vector control clone and led to TAM penetration. To evaluate tumor growth *in vivo*, CD68 promoter-guided DcR3 transgenic (Tg) mice were created. Macrophages from DcR3-Tg mice were compared with wild-type mice, resulting in higher levels of Ym1, arginase activity, IL-10, and IL-1ra, while MHC II, IL-12, IL-6, TNF-a, and NO were regulated downstream. A significant increase in tumor growth and spread was seen in DcR3-Tg mice. Tumor growth was eliminated with the histone deacetylase inhibitor sodium valproate and the arginase inhibitor N-ω-hydroxy-1-norargine. The results show that TAM activation is important for the effect of DcR3 in tumor development (6).

In the treatment of epithelial ovarian cancer, overcoming platinum resistance is a serious challenge. A study by Connor et al. (25) found that DcR3 was associated with platinum resistance. In a subsequent study, the effects of DcR3 on cellular interaction with epithelial ovarian cancer and platinum response were investigated. Women with epithelial ovarian cancer, who had high DcR3 levels in their peritoneal cavity, had a considerably shorter period until their first recurrence after platinum-based treatment. DcR3 is produced by non-malignant peritoneal cells. Despite not secreting DcR3, the cells investigated bind exogenous DcR3. This shows that cells can be affected by

DcR3 through external factors. All cells express CD44v3 and DcR3 binding heparan sulfate proteoglycans (HSPGs) Syndecans-2; however, DcR3s protein binding partners are poorly expressed or absent. Heparin and heparinase both block DcR3 binding. OVCAR-3 and SKOV-3 became more resistant to platinum (15% more) due to cell survival after exposure to DcR3, whereas CaOV3 became more vulnerable to platinum due to increased cell death (20-25%). According to the PCR results, BRCA1 mRNA expression increased in OVCAR-3 and SKOV-3 with DcR3 exposure, and BRCA1 expression decreased in CaOV-3. DcR3 easily binds to epithelial ovarian cancer cells through HSPGs and alters responses to platinum chemotherapy (25).

In one study, the DcR3 level was evaluated for early diagnosis of sepsis. A comparison was made by measuring the changes in plasma DcR3, IL-6, CRP and PCT levels of normal adults, SIRS and sepsis patients. As a result of the comparison, high DcR3 levels were observed in the majority of sepsis patients. For sepsis diagnosis, sensitivity was 97.69% and specificity was 98.04%. DcR3 density and sepsis level were positively correlated. In patients who died from sepsis, DcR3 levels increased in the blood culture 1-2 days before and reached the highest level on the 3rd day after blood culture was taken. In 13% of sepsis patients, PCT remained normal while DcR3 levels remained high. Based on these results, it is thought that DcR3 will assist in the follow-up of patients with sepsis (26).

According to a study conducted to understand the mechanism of DcR3 in gastric cancer, DcR3 increases migration, invasion, and proliferation and supports the epithelial-mesenchymal transition (EMT) of gastric cancer cells. It has also boosted the expression levels of DcR3, p-GSK-3β, β-catenin, GSK-3β and p-AKT, which are all components of the β-catenin/AKT/PI3K/GSK-3β signaling pathway. It also boosted vimentin and N-cadherin expression while decreasing E-cadherin expression. These findings showed that DcR3 played an important role in invasion of β-catenin/AKT/PI3K/GSK-3β and cell proliferation during gastric cancer progression. As a result, DcR3 is considered to be at an important point for the treatment of gastric cancer (27).

A study by Wei et al. (28) examined the function of DcR3 in liver cancer. As a result of the research, they found that DcR3 was regulated upwards in liver cancer tissues and serum. High levels of DcR3 were linked to aggressive clinicopathological features and a bad prognosis. While DcR3 increased invasion and cell migration *in vitro*, it directed tumor growth *in vitro* and *in vivo*. Furthermore, DcR3 resulted in a significant upregulation of interferon regulatory factor 1 (IRF1). In addition, DcR3 also supported cell adhesion molecule 1 (CEACAM1) expression associated with carcinoembryonic antigen through activated IRF1. The findings add to our understanding of DcR3's function and mechanism in liver cancer etiology (28).

In a study, DcR3 expression was suppressed in HepG2 cells to examine the effect of FasL on liver cancer HepG2 cells. In the investigation, FasL (10 ng/mL) was utilized to treat wild-type HepG2 cells (WT), DcR3 empty plasmid control HepG2 cells, and DcR3 siRNA knockout HepG2 cells (KD). After the treatment, when the WT cells in the G2/M phase were compared with the KD cells, it was seen that the KD cells decreased. FasL-induced apoptosis was more likely in KD cells. While the activity and migration of KD cells decreased with treatment, the expression of MMP9, VEGF-D, and VEGF-C also decreased. DcR3 was also implicated in the invasion and proliferation of HepG2 cells, a mechanism that could be linked to the regulatory influence of VEGF-D, VEGF-C, and MMP9 expression. Following DcR3 knockdown, FasL-mediated apoptosis was enhanced in HepG2 cells. As a result, FasL-coupled DcR3 may offer hope for treatment in liver cancer (29).

In a study by Zhu et al. (30), the relationship between hepatocellular carcinoma and DcR3 was examined. In this study, the TGFβ3-Smad-Sp1 signaling pathway was discovered to be responsible for the overexpression of DcR3 in hepatocellular carcinoma. DcR3 overexpression was associated with tumor invasion and metastasis in hepatocellular carcinoma tissues. While DcR3 inhibited the secretion and differentiation of Th1 cells, it significantly promoted the secretion and differentiation and of Th2 and Treg cells. In contrast, knocking down DcR3 expression in hepatocellular carcinoma dramatically improved CD4+ T-cell immunity. Finally, inhibiting DcR3 expression may provide a new immunotherapeutic treatment for HCC patients (30).

In one study, DcR3 was silenced to examine the susceptibility of HCC cells to TRAIL. In comparison to the LO-2, DcR3 was strongly expressed in Huh-7, HepG2, Hep3B, BEL-7402, SMCC7721, and MHCC97H cell lines. BEL-7402 and HepG2 were found to be tolerant to TRAIL-mediated apoptosis, which negatively correlated with DcR3 expression. In HepG2 and BEL-7402, shRNA-mediated silencing of DcR3 and treatment with TRAIL resulted in severe apoptosis, whereas more cancer cells were identified in the G1 phase. SiDcR3 can activate caspase-8, -9, and -3 when paired with TRAIL, increasing the expression of the protein Bax

while reducing the expression of non-apoptotic proteins. According to the findings, decreased concentration of DcR3 may promote apoptosis via TRAIL in hepatocellular carcinoma (31).

In another study, individuals with various malignancies and healthy individuals were evaluated in terms of DcR3 serum levels. Patients with breast cancer, lymphoma, and stomach malignancies had considerably greater DcR3 levels in their serum. DcR3 was also found to be linked with platelet distribution width (PDW) in metastatic malignancies. Based on this result, serum DcR3 together with hematocrit (Hct), hemoglobin (Hb) and PDW may be helpful in tracking the formation of cancer metastases. According to the findings, DcR3 can be used in early diagnosis for gastric cancer detection and metastasis when evaluated with hematological features (32).

In a study by Safaya et al. (33), DcR3 levels were examined in sickle cell anemia. Peripheral blood mononuclear cells (PBMC) were extracted from the blood of healthy controls and sickle cell anemia patients for research purposes. For real-time (RT) gene expression of DcR3/DR3/TL1A, RNA extracted from PBMC was employed. Within SCA patients with alpha-globin gene deletions or co-hereditary fetal Hb (HbF), gene expression was examined in subgroups. According to the study, they found that DcR3 and TL1A expression increased, while DR3 expression decreased in PBMC of sickle cell anemia subjects compared to normal control PBMC. While TL1A/DcR3 expression was lower in sickle cell anemia subjects with HbF>10%, DcR3/TL1A expression was higher in subjects with HbF<10%. Furthermore, patients with HbF greater than 10% had considerably fewer pain episodes than those with HbF less than 10%. The levels of DR3, DcR3 and TL1A circulating in the plasma of sickle cell anemia patients were found to be considerably higher. HbF above 10% moderates TL1A elevation, while HbF below 10% exacerbates TL1A/DcR3 reactions. Based on the findings, it is possible that increased DcR3 and TL1A expression in sickle cell anemia participants' PBMC during painful vasoocclusive crisis contributes to the pathogenesis of vasoocclusive crisis in sickle cell anemia with altered TL1A expression (33).

A study was conducted by Yang et al. (34) to examine the anticancer effects of triptolidine (TPL) on DcR3 in preclinical patient-derived tumor xenograft (PDTX) models of oral squamous cell carcinoma. The effects of TPL on cell proliferation and DcR3 expression in PDTX models and oral squamous cell carcinoma cell lines were examined as part of the study. Excess TPL therapy dramatically slowed tumor growth, while DcR3 expression was related to tumor size and survival. In *in vitro*, *in vivo*, and in PDTX models, TPL inhibited the synthesis of metastasis-associated protein 1 (MTA1), a transcription factor for DcR3. As a result, TPL was demonstrated to have anticancer properties in *in vitro*, *in vivo*, and in PDTX models via inhibiting DcR3 and MTA1 (34).

In a study by Zhang et al. (35), DcR3 levels were investigated in patients with lung cancer. For the study, DcR3 protein expression in normal lung tissues and lung cancer was compared. In addition, using the Cancer Genome Atlas database, the diagnostic and clinicopathological significance of DcR3 mRNA in lung cancer patients was investigated. DcR3 expression was found to be quite high in lung cancer tissues. In comparison to normal lung tissues, DcR3 was overexpressed in adenocarcinoma tissues and squamous cell carcinoma. In addition, DcR3 expression was found to correlate with tumor stage, tumor diameter, overall survival of lung adenocarcinoma and disease-free survival (35).

A study investigated the impact of tumor necrosis factor-derived protein-8 (TIPE) on DcR3 expression in colorectal cancer. TIPE and DcR3 were both highly expressed in colorectal cancer patients, and their levels were also positively associated. DcR3 and TIPE expression in HCT116 cells was verified to be high. TIPE overexpression boosted the DcR3 promoter's transcriptional activity. In conclusion, in addition to being significantly expressed in DcR3 and TIPE colorectal cancer, they are associated with a poor prognosis. TIPE regulates DcR3 expression and reduces apoptosis in colorectal cancer cells by stimulating the AKT/PI3K signaling pathway (36).

In another study, serum DcR3 levels were evaluated in 85 bronchial asthma patients. According to the results, serum DcR3 levels of asthmatic patients were found to be higher than those of healthy controls. Serum DcR3 levels were found to be inversely linked to the asthma control test score in patients with atopic asthma. DcR3 has the feature of being a good biomarker for atopic asthma, especially in children (37).

One study compared *in vivo* and *in vitro* studies to investigate DcR3 levels in kidney disease. Elevated serum DcR3 correlated positively with inflammatory indicators such as IL-6, adhesion molecules and high-sensitivity C-reactive protein in maintenance hemodialysis (HD) patients. DcR3 expression was originally thought to be connected to a 2-fold increase in blood creatinine or kidney

allograft failure. DcR3 protects renal myofibroblasts from Fas-induced apoptosis and causes renal fibrosis as a result. DcR3, which is expressed locally in renal tubular epithelial cells (RTECs), has been shown to decrease FasL-Fas-mediated T-cell apoptosis and produce an increase in allo-reactive T-cells. Cytomegalovirus promoter-driven human DcR3 plasmid and recombinant DcR3.Fc have been found to affect the activation and differentiation of dendritic cells and macrophages by ''non-decoy'' activity in addition to traditional biological roles. After hydrodynamic-based gene delivery of the DcR3 plasmid, both autoimmune crescentic glomerulonephritis and progressive IgA nephropathy in mice can be inhibited. *In vitro* study of overexpressing DcR3 or adding recombinant DcR3.Fc can be utilized to evaluate DcR3-mediated effects, whereas systemic effects *in vivo* can be investigated using CD68-driven DcR3 transgenic mice. Inhibiting DcR3 expression in humans could be a promising way to investigate pathogenic mechanisms (38).

HCC has been linked to chronic hepatitis B (CHB). DcR3 expression was investigated during hepatitis B virus (HBV) infection by Liang et al. (39). The researchers discovered that DcR3 was overexpressed in CHB patients, DcR3 overexpression was linked to HBV DNA burden and liver injury. They discovered that hepatitis B virus X protein (HBx) increased DcR3 expression, but that NF-kB inhibitors inhibited this rise. By attaching NF-kB subunits to the p65 and p50 DcR3 promoters, HBx also activated NF-kB and elevated DcR3. PI3K inhibition reduced DcR3 expression and prevented NF-kB from binding to DcR3 promoters. According to the findings, HBx stimulates DcR3 expression via the NF-kB/PI3K pathway. This pathway was assumed to play a role in the progression of HBV-mediated hepatocellular carcinoma (39).

In a study, DcR3 expression level and clinical significance were investigated in patients with acute chronic liver failure. The levels of serum DcR3 in individuals with acute chronic liver failure and patients with chronic liver disease who did not have acute failure were compared. Acute chronic liver failure patients have considerably greater serum DcR3 levels than non-acute chronic liver failure patients. International standardized ratio, aspartate aminotransferase, and prothrombin time were all favorably connected with neutrophilic granulocytes, while serum albumin and platelets were negatively correlated. While DcR3 level in the early stage of acute chronic liver failure disease did not differ much between survivors and non-survivors, DcR3 level increased in the late stage non-survivor group and gradually decreased in the survivor group. The findings imply that DcR3 may play a significant role in the prognosis of acute chronic liver failure patients (40).

Endometriosis is a multifactorial inflammatory illness in which the nuclear factor-κB (NF-κB) signaling pathway is persistently activated. The aberrant adherence of the endometrium is the first step in the evolution of endometriosis. DcR3 appears to be able to increase cell adhesion via activating focal adhesion kinase. They discovered that activation of the Akt-NF-κB signaling pathway elevated DcR3 in human ectopic endometrial cells, and that its expression was positively linked with intercellular adhesion molecule 1 (ICAM-1) and target cell adhesion molecule (HCAM; CD44). Knockdown of DcR3 reduced HCAM and ICAM-1 expression and also reduced cell migration and adhesion. The finginds support that DcR3 plays an important role in the pathophysiology of endometriosis and suggest that inhibiting DcR3 expression could be a promising therapy option for endometriosis (41).

Serum DcR3 level is elevated in chronic inflammatory diseases. In one study, IL-6 and DcR3 levels were measured in chronic obstructive pulmonary disease (COPD) patients and control subjects, and then correlation with airflow limitation by COPD stage was evaluated. The patient group consisted of patients with stable COPD (SCOD) and acute COPD exacerbation (AECOPD). Both IL-6 and DcR3 levels were increased ($p<0.01$ to 0.001), positively correlated with increased airflow limitation in the AECOPD and SCOPD groups. In addition, DcR3 and IL-6 levels were positively correlated with smoking history (annual). The serum DcR3 level rose with the severity of the increasing airway limitation, particularly during the acute exacerbation period in male COPD patients, according to the findings. These findings imply that DcR3 is linked to the underlying pathophysiology of COPD in male (42).

In a study, the mechanism of DcR3 in osteoclastogenesis induced by interleukin-1α (IL-1α) was investigated. IL-1α is a potent cytokine involved in bone loss and inflammatory arthritis. Considering the results, DcR3 inhibited bone resorption and suppressed IL-1α-induced osteoclastogenesis in RAW264.7 cells and primary murine bone marrow-derived macrophages (BMM). Expressing DcR3, IL-1a, secretory IL-1ra (sIL-1ra), intracellular IL-1ra (icIL-1ra), reactive oxygen species (ROS) and activating interleukin-1 receptor-associated kinase 4 (IRAK4) induced osteoclast precursor cells treated with RANKL. The abundance of buildup of ROS, expression of Fas ligand and IL-1ra secretion in apoptotic osteoclast precursor cells are

hypothesized to be responsible for the inhibition of DcR3 during IL-1 or RANKL induced osteoclastogenesis. It was discovered that DcR3 inhibited osteoclastogenesis through increasing ROS levels and the expression of ROS-induced Fas ligands, IL-1ra and IL-1a. According to the findings, increased DcR3 in preosteoclasts could be a viable target for therapy in inflammatory IL-1-induced bone resorption (43).

In the study by Chang et al. (44), the role of DcR3 in lung cancer was investigated. Within the scope of the research, DcR3 expression was examined in 461 lung adenocarcinomas. DcR3 was more expressed in acinar patterns, micropapillary, solid, as well as tumors with wild-type EGFR status, according to the findings. Furthermore, the disease-free survival rate for stage I patients was shown to be lower, which was linked to DcR3 expression level. Lung cancer differentiation and development are hypothesized to be influenced by DcR3 expression. DcR3 is also useful in the clinical setting of tumor growth for stage I in lung adenocarcinoma (44).

The effect of DcR3 on breast cancer prognosis was examined by Ge et al. (45). The study investigated the expression of DcR3 in MDA-MB-231 and MCF7 cell lines and used 115 breast tissue samples. While evaluating the results, patient groups were formed as those with good and with bad prognosis. When DcR3 expression in the patient groups was evaluated, the expression level in the bad prognosis group was found to be considerably higher than in the good prognosis group. DcR3 transcripts in stage 2 cancers, compared to stage 1 cancers, were found to increase significantly. DcR3 improves the ability of breast cancer cells to invade and plays a significant role in breast cancer metastasis according to the findings (45).

A study looked into the clinical implications of DcR3 overexpression in people with hepatic fibrosis and chronic hepatitis B. The study comprised 128 participants who had been clinically diagnosed with chronic hepatitis B and had their livers biopsied. The levels of DcR3, type III procollagen, hyaluronic acid (HA), laminin protein, and type IV collagen (IV-C), expression were all measured. DcR3 levels were observed to be considerably greater in chronic hepatitis B patients (especially in active disease). Patients with liver fibrosis and chronic hepatitis B with liver cirrhosis had higher DcR3 expression than patients with chronic hepatitis B without liver fibrosis. DcR3 is a marker for liver fibrosis in people with hepatitis B infection according to the findings. The use of DcR3 in conjunction with HA and IV-C may enhance the diagnostic value of DcR3 in the diagnosis of liver fibrosis (46).

Chen et al. (47) examined serum DcR3 levels in patients with atopic and non-atopic asthma. The serum DcR3 levels of asthmatics and healthy people were compared as part of the study. According to the presence or lack of allergen-specific immunoglobulin E (IgE), asthma patients were categorized into two subgroups: Non-atopic and atopic. In asthma patients, the average serum DcR3 level was considerably greater than in healthy controls. There was no noticeable difference in DcR3 levels between atopy patients and those who did not have atopy. However, total eosinophil count was favorably linked with serum DcR3 level. DcR3 blood levels were associated with illness severity in non-atopic asthma patients, suggesting that DcR3 could be a feasible biomarker for predicting non-atopic asthma severity (47).

In a study, DcR3 levels were examined in patients with severe burns. Within the scope of the study, the patient group (n=10) with severe burns was followed up in terms of PCT, DcR3, IL6, CRP, SOFA score, thrombocyte and white blood cell (WBC). DcR3 level increased on the first day. DcR3 levels were comparatively low in survivors, but they were consistently high in non-survivors. Continuously increasing DcR3 levels were observed in three patients, and these patients subsequently died. In the other two patients who did not survive, the DcR3 level peaked and decreased before death. A good correlation was observed between DcR3 and PCT, while DcR3 showed less correlation with platelet, CRP, WBC, SOFA score and IL6. DcR3 levels were discovered to be a valuable biomarker for understanding the clinical severity of severe burns and monitoring a mortality prediction as a result of the research (48).

Bou-Dargham et al. (49) conducted research on the mechanisms of immune avoidance (IEM) in prostate cancer. IEMs are used in various combinations in prostate cancers. Increased DcR3, cytotoxic T lymphocyte-associated protein 4 (CTLA4) and immunological ignorance were found in the majority of prostate cancer patients (51.6%). Some of the immunologically deficient patients had increased DcR3 expression, some up-regulated CTLA4, and some had all three pathways up-regulated. These data show that most human prostate cancer specimens are immunologically cold tumors that are resistant to mono-immunotherapy. These biomarkers can better understand a patient's immune-avoidance processes so that definitive treatment plans can be created to increase therapeutic efficacy (49).

In a study, it was investigated whether DcR3 and tumor necrosis factor (TNF)-like cytokine 1A (TL1A) played a role in promoting atherosclerosis. Plasma TL1A and DcR3 levels were compared in patients without coronary artery

disease and in patients with coronary artery disease who underwent coronary artery bypass grafting. The relationship between SYNTAX and coronary artery disease scores was also investigated. The coronary artery disease group had considerably greater plasma levels of DcR3 and TL1A than the non-coronary artery disease group. TL1A and DcR3 were found to be substantially linked with the existence of coronary artery disease in multivariate analysis. Furthermore, in coronary artery disease patients, TL1A was found to be positively and strongly linked with the SYNTAX score. Both DcR3 and TL1A levels are higher in coronary artery disease patients who require coronary artery bypass grafting, suggesting that they could be valuable biomarkers for detecting severe coronary artery disease. Furthermore, TL1A levels are related to the SYNTAX score, suggesting that it could be employed as a coronary artery disease severity indicator (50).

One study evaluated the levels of DcR3 in the blood of people who had coronary heart disease. In C57BL/6 mice with coronary heart disease, the effects of DcR3 on apoptosis and inflammation were investigated. In mice with coronary heart disease, DcR3 plasma concentrations were observed to be reduced. When DcR3 injection was given to mice with coronary heart disease, it was seen that the symptoms of the disease were reduced, while it was seen that it increased survival time by reducing inflammatory responses and myocardial cell death. DcR3 concentrations in the blood can be used to predict the risk and prognosis of the disease. DcR3 has also been shown to regulate the protein kinase B (AKT)/PI3K signaling pathway, which limits the production of inflammatory factors. The amount of DcR3 in circulation seems to be linked to the severity of the condition. The modulation of DcR3 in the AKT/PI3K signaling pathway has been suggested as a potential treatment for coronary heart disease (51).

The goal of one study was to use immune-related gene expression to classify different forms of breast cancer. Bou-Dargham et al. (49) identified 7 clusters on the Cancer Genome Atlas RNA-seq breast cancer data using the sequential binary clustering method. They found that 34.3% of the deaths were caused by Programmed cell death-1 (PD-1). DcR3 and TGF-β have been identified as new therapeutic targets for the treatment of breast cancer. Because 57.7% of patients overexpress TGF-β and DcR3, targeting these two molecules could be a powerful technique for breast cancer treatment. It was also observed that triple-negative breast cancer (TNBC) patients were equally clustered into two subgroups. The first had a problem with antigen presentation, whereas the second had four separate hijacking mechanisms as well as a high leukocyte uptake. As a result, various immunotherapy techniques can be used to treat different TNBC patients. These findings aid researchers in better understanding how patients respond to immunotherapies and shed information on the rational development of new combination treatments (52).

Gout is an inflammatory disease caused by the accumulation of monosodium urate (MSU) crystals in the joints. It stimulates macrophages to a proinflammatory state and induces neutrophil recruitment by triggering NLRP3-dependent production of interleukin-1β (IL-1β). DcR3 and its non-decoy action motif, the heparin sulfate proteoglycan (HSPG) binding domain (HBD), were studied in macrophages and mice to see how they affected MSU crystal-induced NLRP3 inflammatory activation. Both HBD.Fc and DcR3.Fc inhibited MSU crystal-induced IL-1β secretion and NLRP3 activation in THP-1, U937 cells, and bone marrow-derived macrophages, according to the findings. In DcR3-transgenic mice expressing DcR3 in myeloid cells, MSU was found to cause less IL-1β and chemokine release, an enhanced M2/M1 macrophage ratio, and reduced neutrophil recruitment in the air sac mouse model of gout. In addition, less inflammatory response was observed in mice treated intravenously with HBD.Fc or DcR3.Fc. The data show that by modulating lysosomal and mitochondrial processes, HBD of DcR3 can attenuate MSU crystal-induced NLRP3 inflammatory activation (53).

It was investigated if DcR3 might ameliorate neuroinflammation and Alzheimer's disease-like impairments in the central nervous system based on its immunosuppressive effect in a study. Human APP transgenic mice (J20 line) were crossed with human DcR3 transgenic mice to generate DcR3, APP, APP/DcR3 and wild-type mice for analysis. As a result of the study, it was observed that DcR3 reduced amyloid plaque accumulation and ameliorated hippocampus-related memory deficits in APP transgenic mice. DcR3's protective mechanism interacts with heparan sulfate proteoglycans and activates IL-4^{+}YM1^{+} M2a-like microglia, reducing Aβ-induced proinflammatory cytokines and enhancing microglia's phagocytosis capabilities. According to the findings, upregulation of DcR3 expression in the brain could be a viable treatment method for Alzheimer's disease (54).

The MAPK kinase/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)

signaling pathway controls DcR3 expression. In 30 patients with stage III gastric adenocarcinoma, researchers looked for expression of TIPE (α-induced protein 8), DcR3 and ERK in normal gastric tissues and pathological tissues. DcR3, TYPE and ERK1/2 expression in tumor tissues was significantly increased when tumor tissues of gastric cancer were compared with paracarcinoma tissues. However, TIPE expression was positively correlated with ERK1and DcR3 levels. Based on the findings, TIPE can be linked to the expression of ERK1/2 and DcR3, which may be implicated in gactric cancer cell death, and could be considered as a new biomarker for gastric cancer (55).

In one study, the cellularity of the downregulated sample of DcR3 in the cholangiocarcinoma cell line TFK-1 was examined on cell apoptosis and cell uptake. For this study, three distinct cell lines were grown. For investigation, the cholangiocarcinoma cell line with the greatest DcR3 expression was chosen. Expression of DcR3 was silenced in the selected cell line by transfection with DcR3-siRNA. Various biological phenotypic parameters, including cell cycle, cell viability and apoptosis, were found. TFK-1 was selected by measuring the protein levels and mRNA of DcR3 in three cell lines. After 48 hours of treatment with DcR3-siRNA, DcR3 mRNA, G0/G1 ratio increased and the G2/M ratio decreased in the treatment group. These findings point to the necessity for more research into the molecular mechanisms that regulate DcR3 expression in cholangiocarcinoma (56).

Conclusion

DcR3's potential in cancer, particularly as an anti-tumor target, is yet unknown. In summary and importantly, the differential expression and function of DcR3 has been highly implicated in cancer studies. DcR3 is associated with several ligands capable of influencing apoptosis, angiogenesis, and immune escape of tumors. DcR3 can both be considered a positive and negative regulator during cancer development and progression according to research. While increasing DcR3 expression is beneficial for the treatment of inflammatory diseases and enhances tissue repair, inhibiting DcR3 expression increases tumor apoptosis and suppresses tumor growth *in vivo*. Based on these findings, DcR3 can now be regarded a possible target for cancer gene therapy as well as an anticipating marker for malignant tumors.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Drafting Manuscript: N.H., H.G.Ç., A.K., Critical Revisation of Manuscript: N.H., H.G.Ç., A.K., Final Approval and Accountability: N.H., H.G.Ç., A.K.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):102-109
DOI: 10.4274/BMB.galenos.2022.2022-01-06

Could Asymmetric Dimethylarginine Have a Role in COVID-19 Cases?

Asimetrik Dimetilarjininin COVID-19'daki Rolü

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) is a disease with respiratory involvement and the virus-induced endothelial dysfunction is pronounced in the clinical course. In COVID-19 patients, to analyze the laboratory findings and the associations may help to better understand the pathophysiology of this disease.

Method: We analyzed the laboratory markers including white blood cell, platelet, mean platelet volume, red cell distribution width (RDW), lactate dehydrogenase, procalcitonin, arterial blood gas values and asymmetric dimethylarginine (ADMA) levels of 83 hospitalized COVID-19 patients with pneumonia. Thirty healthy individuals were enrolled as a control group and their laboratory findings were compared.

Results: No significant difference of ADMA levels (median value 225.6 μg/L vs 225.6 μg/L) was noted between COVID-19 patients and the control group (p=0.771). ADMA had an inverse correlation with RDW (r=-0.391, p<0.001). C-reactive protein (CRP) was the significant variable when patients were compared to the healthy group (p=0.002).

Conclusion: ADMA levels do not increase at the beginning of COVID-19 clinical course. CRP, as an established inflammation marker, has an imperative role in the clinical spectrum of this coronavirus infection.

Keywords: ADMA, COVID-19, infection

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) solunum tutulumu olan bir hastalıktır ve virüs kaynaklı endotelyal disfonksiyon klinik seyirde belirgindir. COVID-19 hastalarında laboratuvar bulgularının ve birlikteliklerin analiz edilmesi bu hastalığın patofizyolojisinin daha iyi anlaşılmasına yardımcı olabilir.

Yöntem: Hastaneye yatırılan 83 pnömonili COVID-19 hastasının beyaz kan hücresi, trombosit, ortalama trombosit hacmi, kırmızı hücre dağıtım genişliği (RDW), laktat dehidrogenaz, prokalsitonin, arter kan gazı değerleri ve asimetrik dimetilarginin (ADMA) düzeylerini içeren laboratuvar belirteçleri incelendi. Kontrol grubu olarak 30 sağlıklı kişi alındı ve laboratuvar bulguları karşılaştırıldı.

Bulgular: COVID-19 hastaları ve kontrol grubu arasında ADMA seviyelerinde (ortanca değer 225,6 μg/L'ye karşı 225,6 μg/L'ye karşı) anlamlı bir fark görülmedi (p=0,771). ADMA, RDW ile ters bir korelasyona sahipti (r=-0,391, p<0,001). Hastalar sağlıklı grupla karşılaştırıldığında C-reaktif protein (CRP) anlamlı bir değişkendi (p=0,002).

Sonuç: ADMA seviyeleri COVID-19 klinik seyrinin başlangıcında artmamaktadır. Yerleşik bir enflamasyon belirteci olarak CRP, bu koronavirüs enfeksiyonunun klinik spektrumunda zorunlu bir role sahiptir.

Anahtar kelimeler: ADMA, COVID-19, enfeksiyon

Introduction

Coronavirus disease-2019 (COVID-19) has been a global challenge since 2019. The World Health Organization (WHO) declared it as a pandemic in early 2020 (1). It is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and it has a variable clinical course from asymptomatic patients or mild respiratory symptoms to critical illness and death. Despite the extensive vaccination campaigns, third and fourth waves of the disease are challenging for the World. SARS-CoV-2 infects the host

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Cite this article as: Özkarafakılı MA, Yalçınkaya ZM, Bardakçı Mİ, Kibar Akıllı I. Could Asymmetric Dimethylarginine Have a Role in COVID-19 Cases?. Bagcilar Med Bull 2022;7(2):102-109

cells via binding angiotensin-converting enzyme 2 (ACE_2) receptors, which are expressed in the lungs, heart, kidney, gut and endothelium (2). Several studies including autopsy series show viral inclusion bodies which are found in endothelial cells and directly infected by SARS-CoV-2 (3,4). ACE_2 receptor also regulates the vascular functions via nitric oxide (NO) release, the molecule which plays a key role in endothelial inflammation and dysfunction (5,6). NO is involved in a broad spectrum of processes: It stimulates vasodilatory and bronchodilator effects in the lungs, and may help preventing pulmonary infections by producing antimicrobial effects (7). During the SARS outbreak in 2002-2003, also caused by another coronavirus infection, some studies demonstrated NO's antiviral effect (8). It is achieved by inhibiting viral replication of SARS-CoV or by reduction of expression of the spike (S) protein and the fusion of S protein-ACE_2 receptor (8). Inhaled NO was tested in some SARS patients and some beneficial effects, such as the improvement of arterial oxygenation and reduced spread of lung infiltrates, were noted (9). Stemming from these preliminary studies, some scientists recommend using inhaled NO in the management of severe hypoxia due to COVID-19 (10). NO is synthesized from its precursor L-arginine by endothelial nitric oxide synthetase (NOS) (11). Asymmetric dimethylarginine (ADMA) is a competitive inhibitor of NOS and accumulation of ADMA reduces NO levels. ADMA levels are increased in cardiovascular disease, renal failure, and diabetes (12,13). The role of ADMA, as a predictor of cardiovascular events or death in critically ill patients with sepsis, has been reported previously (14,15). Rising data suggest that COVID-19 is a vascular and thrombotic disease with the phenomenon of endothelial dysfunction, which particularly effects the patients with cardiometabolic disorders like hypertension, diabetes, and obesity (3). However, the underlying mechanisms are still not completely understood (16). C-reactive protein (CRP) is shown to be discriminative marker for the severity of COVID-19 from the early days of the pandemic (17). We need novel biomarkers which will help to understand these viral pathogenetic mechanisms and to find appropriate clinical approach for COVID-19 treatment. In this study, we analyze the plasma concentration of ADMA, an indirect marker of endothelial dysfunction (18), and its association with other inflammation markers like white blood cell (WBC), red cell distribution width (RDW), platelet count, mean platelet volume (MPV), CRP, lactate dehydrogenase (LDH), procalcitonin, and parameters of arterial blood gases [partial oxygen pressure ($P0_2$), partial carbon dioxide pressure (PCO_2), oxygen saturation percentage (SO_2%)].

Materials and Methods

The study was conducted in a tertiary care center after Institutional Ethics Committee approved the research plan on April 22, 2020 (no: 2737) and performed in accordance with the principles of Declaration of Helsinki. Written informed consents were taken from the participants. This study included 83 consecutive, laboratory-confirmed COVID-19 patients (48 male, 35 female; age 65±16.3 years) followed in pandemic wards between May and July 2020. COVID-19 patients who had pneumonia based on chest computed tomography findings and respiratory symptoms, without hypoxia, categorized as "moderate COVID-19 cases'' according to WHO case definitions were included in this study (1). Patients under the age of 18 years, those who were pregnant and who were transferred to intensive care unit or who passed away during follow-up were excluded from the study. Thirty gender-matched healthy individuals (15 male, 15 female; age 58.2±11.0 years) acted as the control group. Basic demographic data and comorbidities were recorded. Serum ADMA levels were measured together with other laboratory markers [WBC, RDW, platelet, MPV, CRP, LDH, procalcitonin, arterial blood gas analysis: ($P0_2$), PCO_2 SO_2% oxygen saturation percentage]. Patients were included only if the blood samples were obtained on the first day of admission, biomarker analysis was available and samples were stored under standardized conditions. For measuring ADMA, fasting blood samples were taken into vacuum tubes (BD, Plymouth, England). After keeping the samples at room temperature for 2 hours, they were centrifuged at + 4 °C at 1.000 x g for separating serum. Separated serums were kept at -80 °C until the analysis. Serum ADMA levels were analyzed by enzyme linked immunosorbent assay method using Elabscience Pharmaceuticals kit, (Houston, Texas, USA). The measurable range was 15.63-1.000 ng/mL, sensitivity was <9.38 ng/mL, and coefficient of variation was <10%.

Statistical Analysis

Descriptive statistics were given as mean ± standard deviation and median with minimum-maximum for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. Normality of the numerical variables was analyzed by the Kolmogorov-Smirnov test and checked by Q-Q plots and histograms.

Based on the distribution of sex and comorbid diseases, the Mann-Whitney U test was applied for variables without normal distribution. The Kruskal-Wallis test was

used to compare the platelet count and ADMA values. The Spearman Rho correlation coefficient was used to analyze the associations between ADMA and age and other numerical variables.

Demographic variables differing between the groups were controlled using the analysis of co-variance. The sm.ancova package in R software was used for non-parametric tests.

For statistical analysis and figures, Jamovi project (2020), Jamovi version 1.6.3 [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (version 0.13.1) (Retrieved from https://jasp-stats.org) were used. The significance level (p-value) was set at 0.05 in all statistical analyses.

Results

Plasma ADMA concentrations, and laboratory findings of 83 hospitalized COVID-19 patients were analyzed. In Table 1, demographic and clinical characteristics and laboratory features of the study group are summarized. The enrollees consisted of 48 (57.8%) male and 35 female (42.2%) patients with a mean age of 65±16.3 years. Forty-seven patients (56.6%) of all patients had at least one comorbid disease. Hypertension was the most common comorbidity seen in 29 patients (34.9%).

Among the inflammation markers, the mean WBC count was 8.4±4.0 (x109/L), whereas the mean values of CRP and procalcitonin were measured as 51.8±57.9 mg/L and 1.5±6.1 ng/mL, respectively. In the analysis of arterial blood gas, PO_2 and SO_2 were detected as 65.8±15.1 mm Hg and 90.5±5.2%, while PCO_2 was 37.01±4.3. The mean ADMA value was found as 360±420.8 µg/L with the minimum and maximum values of 58.6 and 2684.5 µg/L.

The median ADMA value was 196.9 µg/L in males, whereas 292.22 µg/L in females. There was no significant difference between male and female patients (p=0.166). There was also no significant difference found in serum ADMA concentrations of the patients with or without comorbidities (p=0.869) (Table 2).

We detected a significant inverse correlation between ADMA and RDW (r=-0.391, p<0.001) (Figure 1).

However, there were no significant correlations found between ADMA and age, WBC, platelet count, CRP, LDH, procalcitonin, PO_2, PCO_2 and SO_2% (p>0.05 for all) (Table 3).

In Table 4, the association of ADMA with the groupings based on upper and lower laboratory ranges of platelet count, CRP and procalcitonin is given. Although the median ADMA levels in patients with CRP <5 mg/L were higher than the levels in patients with CRP ≥5 mg/L, the difference was statistically insignificant (p=0.061). There was no significant association in the serum ADMA levels of the patients when grouped based on the higher and lower values of platelet count and procalcitonin (p=0.739 and p=0.942).

Table 1. Demographic and clinical characteristics and laboratory features of the study group

	Value	Min-max
Age (year)†	65±16.3	64.0 (26.0-94.0)
Sex‡		
Male	48 (57.8%)	
Female	35 (42.2%)	
Comorbid disease, yes‡	47 (56.6%)	
Hypertension	29 (34.9%)	
Diabetes mellitus	18 (21.7%)	
Chronic renal failure	8 (9.6%)	
Cerebrovascular accident	5 (6.0%)	
Atrial fibrillation	1 (1.2%)	
Malignancy	2 (2.4%)	
WBC count (x10⁹/L)†	8.4±4.0	7.3 (2.2-19.0)
RDW (%)†	14.3±1.7	14.0 (12.0-21.1)
Platelet count (x10³/L)†	219.8±76.2	212.0 (41.0-410.0)
MPV (fL)†	9.4±1.1	9.3 (7.4-13.4)
CRP (mg/L)†	51.8±57.9	27.8 (0.6-246.7)
LDH (U/L)†	278.6±98.4	254.0 (141.0-594.0)
Procalcitonin (ng/mL)†	1.5±6.1	0.2 (0.1-53.0)
PO_2 (mmHg)†	65.8±15.1	63.9 (41.9-99.7)
PCO_2 (mmHg)	37.01±4.3	36.7 (30.0-47.0)
SO_2 (%)†	90.5±5.2	90.8 (79.1-98.8)
ADMA (µg/L)†	360±420.8	225.6 (58.6-2684.5)

†: Mean ± SD, ‡: n (%). SD: Standard deviation, WBC: White blood cell, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PO_2: Partial pressure of oxygen, PCO_2: Partial pressure of carbon dioxide, $SO_{2\,\%}$: Oxygen saturation percentage, ADMA: Asymmetric dimethylarginine

Table 2. Distribution of serum ADMA according to sex and presence of comorbid diseases

	ADMA (µg/L)β	p
Sex		
Male (n=48)	196.9 (58.64-2684.5)	0.166
Female (n=35)	292.22 (64.4-2096)	
Comorbid disease		
Absent (n=36)	221.5 (64.4-1445.2)	0.869
Present (n=47)	237.7 (58.64-2684.5)	

β: Median (min-max), Mann-Whitney U test, ADMA: Asymmetric dimethylarginine

Table 3. Correlation of ADMA with numerical variables

			Spearman's rho	p
ADMA	-	**Age**	0.095	0.416
ADMA	-	**WBC count**	-0.132	0.261
ADMA	-	**RDW**	-0.391	**<0.001**
ADMA	-	**Platelet count**	-0.178	0.127
ADMA	-	**MPV**	0.182	0.121
ADMA	-	**CRP**	-0.133	0.257
ADMA	-	**LDH**	-0.196	0.092
ADMA	-	**Procalcitonin**	-0.172	0.141
ADMA	-	**PO_2**	-0.007	0.952
ADMA	-	**PCO_2**	0.028	0.809
ADMA	-	**SO_2%**	0.045	0.703

Spearman Rho correlation coefficient, ADMA: Asymmetric dimethylarginine, WBC: White blood cell, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PO_2: Partial pressure of oxygen, PCO_2: Partial pressure of carbon dioxide, SO_2 %: Oxygen saturation percentage

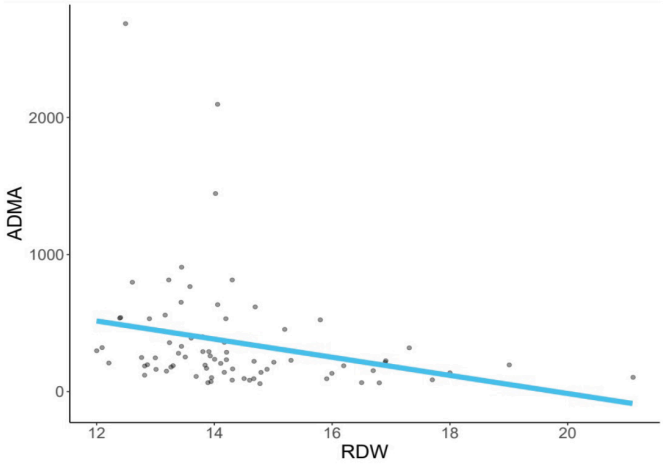

Figure 1. Correlation of ADMA with RDW (p<0.001)
ADMA: Asymmetric dimethylarginine, RDW: Red cell distribution width

Table 5 summarizes the comparison of the two groups as patients (n=83) and controls (n=30). Gender distribution was similar in both groups (p=0.599). The mean age of the patients was 65.0±16.3 years, whereas the age of the participants in the control group was significantly lower (58.2±11.0 years, p=0.013).

There were significant differences between the two groups in terms of erythrocyte distribution width (RDW), platelet count, CRP, LDH, procalcitonin, and O_2% (p<0.001 for all). When age was analyzed as a co-variance factor, CRP remained the only significant variable between the two groups (p=0.002).

Table 4. Association of ADMA with the groups according to upper and lower laboratory ranges of platelet count, CRP and procalcitonin

	ADMA	p
Platelet count (x10³/L)		
<4.5	305.86 (94.46- 652.06)	0.739
4.5-10.5	225.6 (58.64- 2684.5)	
>10.5	207.57 (65.62- 2096)	
CRP (mg/L)		
<5	509.7 (94.9- 907.9)	0.061
≥5	214.68 (58.64-2684.5)	
Procalcitonin (ng/mL)		
<0.12	204.78 (84.48-2684.5)	0.942
≥0.12	225.6 (58.64-2096)	

ADMA: Asymmetric dimethylarginine, CRP: C-reactive protein

The median value of ADMA was 225.6 µg/L in the patient group and 225.6 µg/L in the control group. There was no significant difference noted between the patient and control groups considering the ADMA values (p=0.771). WBC, MPV, PO_2 and PCO_2 were similar between the patients and controls (p>0.05).

Discussion

ADMA is a methylated product of L-arginine and an endogenous inhibitor of NOS, which is a known risk marker for cardiovascular disorders, end-stage renal disease, liver insufficiency and sepsis survival (19-21). ADMA is formed through protein arginine methyltransferase enzyme reaction (PRMT), which occurs in response to hypoxia in the airways (22). Previous studies suggested that elevated levels of ADMA were due to the upregulation of PRMT expression under chronic hypoxia in different clinical issues (23).

The aim of our study was to determine whether plasma concentrations of ADMA were elevated in moderate COVID-19 patients who were followed up in the pandemic wards and whether it could be useful markers in means of helping new treatment approaches. We found no difference in serum ADMA levels between COVID-19 patients and healthy control group. There was no statistically significant correlation observed between ADMA levels and basic inflammation markers (WBC, CRP, LDH, procalcitonin) or arterial blood oxygenation also.

NO maintains endothelial integrity by mediating host defense, contributing to pathogen elimination and vascular tone, which is formed in the endothelium by the activity of NOS. NO is a reactive free radical in the body and is involved in the respiratory disease pathophysiology (6). ADMA levels

Table 5. Comparison of demographic characteristics and laboratory parameters between the groups

	Groups			Covariants age
	Patient (n=83)	**Control (n=30)**	**p**	**p**
Sex‡				
Male	48 (57.8)	15 (50.0)	0.599	-
Female	35 (42.2)	15 (50.0)		
Age (year)†	65.0±16.3	58.2±11.0	**0.013**	-
WBC (x10^9/L)$^\beta$	7.3 (5.4-10.5)	7.8 (5.9-8.7)	0.528	-
RDW (%)†	14.3±1.7	12.8±1.2	**<0.001**	0.739
Platelet count (x10^3/L)†	219.8±76.2	327.8±92.6	**<0.001**	0.545
MPV (fL)†	9.4±1.1	9.2±1.5	0.693	-
CRP (mg/L)$^\beta$	27.8 (12.4-70.8)	3.5 (2.1-4.7)	**<0.001**	**0.002**
LDH†	278.6±98.4	181.4±40.1	**<0.001**	0.091
Procalcitonin (ng/mL)$^\beta$	0.2 (0.1-0.3)	0.0 (0.0-0.1)	**<0.001**	0.444
PO_2 (mmHg)†	65.8±15.1	65.8±6.8	0.976	-
PCO_2 (mmHg)†	37.0±4.3	36.9±3.3	0.884	-
SO_2 (%)†	90.5±5.2	96.0±1.7	**<0.001**	0.137
ADMA (μg/L)$^\beta$	225.6 (145.5-396.0)	243.4 (191.6-352.4)	0.771	-

Independent samples t-test or Mann-Whitney U test. Co-variate analysis for age, †: Mean ± SD, ‡: n (%), $^\beta$: Median (min-max), SD: Standard deviation, WBC: White blood cell, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PO_2: Partial pressure of oxygen, PCO_2: Partial pressure of carbon dioxide, SO_2 %: Oxygen saturation percentage, ADMA: Asymmetric dimethylarginine

have been shown to impair NO generation and to induce endothelial dysfunction (12). SARS-CoV-2 infection may be regarded as a vascular disease targeting endothelial cells throughout the body (3). The cardiovascular disorders, hypertension, obesity, and diabetes are the most common pre-existing morbidities in COVID-19 in which the main driver is endothelial dysfunction (3). Endothelial damage makes some COVID-19 patients prone to worse clinical outcomes characterized by thrombotic episodes (24). CRP, as a prototypic marker of inflammation, has been shown to cause downregulation of NOS activity and NO bioavailability in endothelial cells in previous studies (25). As ADMA, CRP has an important role in endothelial dysfunction (26). During the course of bacterial infection, procalcitonin, as a cytokine, amplifies NO production via the expression of inducible NOS (27). In earlier studies conducted by the administration of *Escherichia coli* endotoxin in healthy men, it was hypothesized that ADMA was essential in limiting cytokine-stimulated NO synthesis by iNOS, but it was not proven (28).

To date, less is known about the pathophysiology of SARS-CoV-2 infection, but it resembles that of SARS-CoV infection, with inflammatory responses damaging the airways (29). Although most of the patients do not progress beyond the phase of upper respiratory tract infection, COVID-19 has two major complications: Pneumonia and acute respiratory distress syndrome. The severity of the disease is both due to viral infection itself and host response. Initially, the patients presenting to emergency departments are categorized as “mild”, “moderate”, and “severe” according to symptoms and laboratory findings. During the SARS outbreak in 2003, improvement in lung function was reported in limited patients for whom inhaled NO was used in a pilot study (8). Martel et al. (30), inspired by this experience, provided a comprehensive study to increase airway NO for the prevention and treatment of COVID-19. Their study has stemmed from the hypothesis that NO deficiency is the cornerstone which results from endothelial dysfunction and contributes to thrombus formation, because of the endothelial cell tropism of SARS-CoV-2 virus (31). However, the role of NO in acute infection and inflammation still remains controversial. Nowadays, although many SARS-CoV-2 vaccines have been carried out worldwide, ongoing viral evolution and the substantial mortality due to COVID-19 have caused concern. This prompted an increased interest of scientists for an effective biomarker research. Hannemann et al. (32) analyzed ADMA in hospitalized, critically-ill COVID-19 patients to predict in-hospital mortality. In principal, their study group differed from ours. They included patients who had respiratory failure and global hypoxemia, and they had

shown high ADMA serum concentrations as a predictive biomarker for COVID-19 survival in these patients. They marked this finding in line with aforementioned studies reporting successfully administered inhaled NO in severe COVID-19 treatment.

Increased levels of ADMA were observed in previous studies of patients with sepsis, who were under treatment in intensive care unit (20,21). During this current research, which was performed to identify COVID-19 patients with high mortality risk, elevated levels of ADMA were also reported similarly (32).

They suggest that ADMA accumulation and improper function of endothelial NO synthase and multi-organ failure in critically-ill COVID-19 patients may explain the underlying mechanisms. It is noteworthy that our study setting is different from severe septicemic or critically-ill patients as they have organ-failure, and ADMA rises due to decreased hepatic turnover. The infection resolved in our patient group and no in-hospital death was registered.

Another group, different from our study, found higher ADMA concentrations in COVID-19 patients with lung involvement than in those who had not and in the healthy control group (33).

ADMA response in acute infectious diseases is a subject of debate. NOS is known to produce peroxynitrite, a strong oxidant, which causes organ damage in response to acute infections (34). The role of NO in underlying biochemical mechanisms of infection/inflammation is uncertain. On the one hand it has anti-inflammatory effects on host defense, but on the other hand it may have negative haemodynamic effects.

Zoccali et al. (18) coincidentally found increased serum concentrations of ADMA during the resolution of inflammation when the inflammation markers like CRP declined, but not changed in acute phase of bacterial infection. They suggested that the suppression of ADMA served to raise NO synthesis rather than a decrease, as NO's defensive, anti-microbial protective properties influenced acute phase of infections. Furthermore, cytokines like CRP stimulates the enzyme dimethylarginine dimethylaminohydrolase activity, which metabolizes ADMA, ensuing in suppression of ADMA levels. These findings are in line with our observations. We found no elevated levels of ADMA but found increased levels of CRP as a discriminative predictor in early days of COVID-19 patients. We may speculate that ADMA modulates NO/NOS production in favor of host defense actions versus peroxynitrite-dependent oxidative-stress.

Priorly, the increase of CRP levels was attributed to mostly bacterial infections but high levels were also reported in H1N1 influenza and SARS-CoV-2 infections (35,36). Elevated levels of CRP, as an indicator of deterioration, in hospitalized COVID-19 patients have been associated with cardiovascular complications, which are demonstrated in several studies from the early days of global pandemic (17).

Study Limitations

The study has several limitations. Firstly, it was a single-center study with a small number of patients. The individuals in the healthy control group we selected were younger than the COVID-19 patients, the main reason for which was the curfew for >65 year-old individuals. As we performed statistical analysis of covariance for age, no difference was found in ADMA levels according to age for the groups. We could have measured ADMA levels after infection subsided and note the interchange of this molecule. RDW, platelet count, CRP, LDH, procalcitonin and oxygen saturation % levels of the patient group were higher than those of the control group ($p<0.001$). However, only CRP was found to be the significant variable for COVID-19 patients after the analysis of covariance ($p=0.002$). This accentuates the value of CRP in SARS-CoV-2 infection in line with the literature. No association was shown between ADMA and commonly used parameters, except an inverse correlation with RDW ($p<0.001$).

Conclusion

Our data imply that ADMA concentrations do not rise in the acute setting of moderate COVID-19 patients. This may be attributed to its effect on NO synthesis, as NO has antimicrobial properties in host defense. CRP reflects the inflammatory response in patients with COVID-19, the disease in which pathogenesis is still incompletely understood. Future observations may shed light on the novel biomarkers which could help possible treatments for this lethal disease.

Ethics

Ethics Committee Approval: The study was conducted in a tertiary care center after Institutional Ethics Committee approved the research plan on April 22, 2020 (no: 2737) and performed in accordance with the principles of Declaration of Helsinki.

Informed Consent: Written informed consents were taken from the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.A.Ö., Design: M.A.Ö., Data Collection or Processing: M.A.Ö., Z.M.Y., Analysis or Interpretation: M.A.Ö., M.İ.B., I.K.A., Drafting Manuscript: M.A.Ö., Z.M.Y., I.K.A., Critical Revisation of Manuscript: M.A.Ö., M.İ.B., Z.M.Y., Technical or Material Support: M.A.Ö., M.İ.B., I.K.A.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):110-115
DOI: 10.4274/BMB.galenos.2022.2022-02-024

The Value of a Single Measurement of Calculus Density by Computed Tomography in Predicting the Composition of Stones and Its Use in Practice in Patients with Urolithiasis

Ürolitiazisli Hastalarda Bilgisayarlı Tomografiyle Kalkül Dansitesinin Tek Bir Ölçümünün Taş Bileşimi Öngörüsündeki Değeri ve Pratikte Kullanımı

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Abstract

Objective: Urinary tract stones consist of many subtypes. Prior knowledge of the chemical composition of stones is a key factor in determining the fragility of the stone and determining the treatment and prophylactic approach to be applied to the patient. In this way, the group of patients who can receive medical treatment can be determined, this group of patients can be kept away from repetitive imaging procedures and the cost to be made by reimbursement institutions can be reduced. In this study, it is aimed to predict the stone type according to Hounsfield unite (HU) values.

Method: One hundred-six patients between the ages of 18-70 who were diagnosed with urolithiasis and underwent biochemical analysis for these stones between 2013 and 2017 were included in the study. Non-contrast computed tomography images of the patients were analyzed retrospectively. While measuring the density of the stones, 3 region of interest (ROIs) were placed in different parts of the stones. The value with the highest Hounsfield unite (HU) value was determined as the density of the stone.

Results: According to the stone analysis results, 11 calcium phosphate, 18 calcium oxalate monohydrate-dihydrate, 42 calcium oxalate monohydrate, 10 cystine, 12 struvite, 13 uric acid stones were found. According to the measurement results, the density difference between the 6 stone groups was statistically significant (p=0.0001). No statistically significant difference was observed between the mean age of the stone type groups and the distribution of the sides (right-left) (p=0.284,

Öz

Amaç: Üriner sistem taşları pek çok subtipten oluşmaktadır. Taşların kimyasal bileşiminin önceden bilinmesi, taşın kırılganlığının saptanması ve hastaya uygulanacak tedavinin ve profilaktik yaklaşımın belirlenmesinde anahtar faktördür. Bu sayede medikal tedavi alabilecek hasta grubu belirlenebilmekte ve bu hasta grubunun tekrarlayan görüntüleme işlemlerinden uzak durması ve geri ödeme kurumları tarafından yapılacak maliyetin azaltılması sağlanabilmektedir. Bu çalışma ile Hounsfield unite değerlerine göre taş tipinin öngürülmesi amaçlanmaktadır.

Yöntem: 2013-2017 yılları arasında ürolitiazis saptanan ve bu taşlara yönelik biyokimyasal analiz geçiren 18-70 yaşları arasında 106 hasta çalışmaya dahil edildi. Hastaların kontrastsız bilgisayarlı tomografi görüntüleri retrospektif olarak incelendi. İş istasyonunda bilgisayarlı tomografi görüntülerindeki kalküllerin dansite ölçümleri, kemik pencere ön ayarında, standart büyütme altında, kalkülün en dens yerinden yapıldı. Dansite ölçümü dışında, taş lokalizasyonu, en büyük çapı da belirlendi. Ölçülen değerler ile kalkülün kimyasal analiz sonuçları karşılaştırıldı.

Bulgular: Taş analizi sonuçlarına göre 11 kalsiyum fosfat, 18 kalsiyum oksalat monohidrat-dihidrat, 42 kalsiyum oksalat monohidrat, 10 sistin, 12 strüvit, 13 ürik asit taşı bulundu. Ölçüm sonuçlarına göre 6 taş grubu arasında dansite farkı istatistiksel olarak anlamlı anlamlıydı (p=0,0001). Taş tipi gruplarının yaş ortalamaları ve taraf dağılımları (sağ-sol) arasında istatistiksel olarak anlamlı farklılık gözlenmedi (p=0,284, p=0,747). Taş tipi gruplarının cinsiyet dağılımları arasında istatistiksel olarak anlamlı farklılık

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Cite this article as: Sarıkaya E, Öncü S, Öncü M, Cimilli AT. The Value of a Single Measurement of Calculus Density by Computed Tomography in Predicting the Composition of Stones and Its Use in Practice in Patients with Urolithiasis. Bagcilar Med Bull 2022;7(2):110-115

Abstract

p=0.747). A statistically significant difference was observed between the gender distributions of the stone type groups (p=0.037). There was a statistically significant difference between the distribution of stone sizes and types (p=0.0001).

Conclusion: Density measurements of urinary tract stones in non-contrast computed tomography are useful in recognizing their subtypes. Thus, uric acid stones can be determined and the patient can be referred to oral chemolysis treatment. This may enable the patient to avoid repetitive imaging procedures and interventional treatments.

Keywords: Computed tomography, kidney, oral chemolysis, uric acid stone, urolithiasis

Öz

saptandı (p=0,037). Taş boyutlarının ve tiplerinin dağılımları arasında istatistiksel olarak anlamlı farklılık gözlendi (p=0,0001).

Sonuç: Kontrastsız bilgisayarlı tomografide üriner sistem taşlarının dansite ölçümlerinin yapılması subtiplerinin tanınmasında faydalıdır. Bu sayede ürik asit taşları belirlenebilir ve hasta oral kemoliz tedavisine yönlendirilebilir. Bu da hastanın tekrarlayan görüntüleme işlemlerinden ve girişimsel tedavilerden kaçınmasını sağlayabilir.

Anahtar kelimeler: Bilgisayarlı tomografi, böbrek, oral kemoliz, ürik asit taşı, ürolitiazis

Introduction

In addition to being a common disease, urinary system stone disease is an important reason for admission to the emergency department. According to a study conducted in the United States of America, although it varies according to age, race and gender, it is seen at a rate of 12% in men and 6% in women. A moderate increase of prevalence was observed in the second half of the twentieth century (1). Especially people with chronic stone disease receive various medical and surgical treatments in the long term. The choice of treatment methods is made by looking at factors such as the size of the stone, its localization, and its location, and its chemical composition is also very important at this stage. Oral chemolysis is a treatment method based on the medical dissolution of the stone and can only be applied to uric acid stones (1). Predicting that the stone is a uric acid stone allows the urologist to try medical treatment for the patient before surgical treatment methods.

Our aim in this study was to predict the chemical composition of the stones in the non-contrast computed tomography (CT) examination taken in almost all patients with suspected urolithiasis, to identify uric acid stones and to indicate this in our report, to guide the clinician in treatment, and as a result, to reduce the morbidity caused by surgical treatments in patients with chronic kidney stones. The aim is to reduce the radiation exposure and the financial burden on the health system as a result of repetitive imaging methods.

Materials and Methods

General Data

In this retrospective study, 106 urolithiasis patients (47 F, 59 M) aged between 18 and 70 years, who applied to the Urology Clinic of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between 2013 and 2017, were included. Stone composition analysis was performed on the calculi obtained as a result of percutaneous nephrolithotomy or ureterorenoscopy in all patients. Patients younger than 18 years of age, with mixed type calculi and calculi smaller than 5 mm in size were excluded from the study.

Ethics committee approval dated 08/12/2017 and numbered 2017.12.1.08.024 was obtained from University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Ethics Committee before the study.

CT Protocol and Evaluation of Images

The non-contrast CT images were obtained on the 64 detector Philips Brilliance device using the following parameters: Fixed noise index of 30.9; 0.625-mm collimation; reconstruction slice thickness of 2 mm 120 kVp; variable milliamperage determined by x-, y-, and z-axis dose modulation; gantry rotation time of 0.5 seconds; and 40% adaptive statistical iterative reconstruction (ASIR). All scans were applied spirally from the upper poles of the kidney to the base of the bladder in the urinary system for stone disease. While measuring the density of the stones, 3 region of interest (ROIs) were placed in different parts of the stones. The value with the highest Hounsfield unite (HU) value was determined as the density of the stone.

Statistical Analysis

In the evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation), One-Way analysis of variance was used in intergroup comparisons, the Tukey multiple comparison test was used in subgroup comparisons, and the chi-square test was used in

comparisons of qualitative data. The results were evaluated at the significance level of p<0.05.

Results

Applications for screening were evaluated due to the presence of flank pain, dysuria, and a family history of stones. All patients included in the study had laboratory stone composition analyses of calculi obtained as a result of percutaneous nephrolithotomy or ureterorenoscopy. The sizes of the stones varied between 3 and 50 mm, with an average of 20.6 mm. The distribution of stones according to their sizes is shown in Table 1.

A statistically significant difference was observed between the sizes of calcium phosphate, calcium oxalate monohydrate-dihydrate, calcium oxalate monohydrate, cystine, struvite and uric acid stone types (p=0.0001). While calcium oxalate monohydrate-dihydrate and calcium oxalate monohydrate were high in the group smaller than 10 mm, calcium oxalate monohydrate was found to be higher in the 10-30 mm group, and calcium phosphate and struvite were found to be higher in the group larger than 30 mm (Table 1).

A statistically significant difference was observed between the gender distributions and stone types (p=0.037). While struvite and uric acid were found to be high in women, calcium phosphate, calcium oxalate monohydrate-dihydrate and calcium oxalate monohydrate were found to be high in men (Table 2).

A statistically significant difference was observed between the appearances of calcium phosphate, calcium oxalate monohydrate-dihydrate, calcium oxalate monohydrate, cystine, struvite and uric acid stone types groups (p=0.0001). Calcium oxalate monohydrate-dihydrate, calcium oxalate monohydrate, cystine and uric acid were higher in the homogeneous group, while calcium phosphate and struvite were higher in the heterogeneous group (Table 3).

A statistically significant difference was observed between the mean density of calcium phosphate, calcium oxalate monohydrate-dihydrate, calcium oxalate monohydrate, cystine, struvite and uric acid stone subtypes (p=0.0001). The mean density of the uric acid stone subtype was statistically significantly lower than the other stone subtypes (p=0.0001). A statistical relationship between the densities of stone subtypes is shown in detail in Tables 4 and 5.

The appearance of uric acid and calcium phosphate stones and HU measurement are shown in the CT images below (Figures 1 and 2).

Discussion

Urinary system stone disease is the third most common pathology after urinary infections and prostate pathologies (2). The approach to stone disease begins with a detailed medical history and continues with physical examination, laboratory and imaging tests. Laboratory tests consist of blood and urine analysis and chemical analysis of the extracted stone. Laboratory analysis of stone composition cannot be performed in many centers, and it is an expensive and time-consuming method (3).

Table 2. Comparison of stone type groups by gender

	Gender			
	Male		Female	
Calcium phosphate	8	13.56%	3	6.38%
Calcium oxalate monohydrate-dihydrate	12	20.34%	6	12.77%
Calcium oxalate monohydrate	26	44.07%	16	34.04%
Cystine	6	10.17%	4	8.51%
Struvite	2	3.39%	10	21.28%
Uric acid	5	8.47%	8	17.02%
	p=0.037			

chi-square test

Table 1. Distribution of stone type groups by size

	Stone size					
	<10 mm		10-30 mm		>30 mm	
Calcium phosphate	0	0.00%	4	5.56%	7	36.84%
Calcium oxalate monohydrate-dihydrate	5	33.33%	13	18.06%	0	0.00%
Calcium oxalate monohydrate	6	40.00%	32	44.44%	4	21.05%
Cystine	0	0.00%	9	12.50%	1	5.26%
Struvite	0	0.00%	6	8.33%	6	31.58%
Uric acid	4	26.67%	8	11.11%	1	5.26%
	p=0.0001					

chi-square test

Table 3. Comparison of stone type groups by appearance

	Stone appearance			
	Homogeneous		Heterogenous	
Calcium phosphate	0	0.00%	11	28.21%
Calcium oxalate monohydrate-dihydrate	14	20.90%	4	10.26%
Calcium oxalate monohydrate	30	44.78%	12	30.77%
Cystine	9	13.43%	1	2.56%
Struvite	3	4.48%	9	23.08%
Uric acid	11	16.42%	2	5.13%
	p=0.0001			

chi-square test

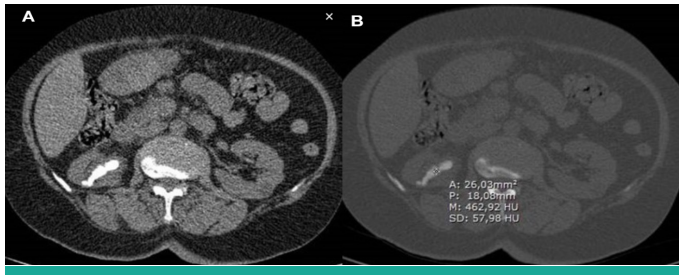

Figure 1. A 42-year-old female patient has calculus in the lower pole of the right kidney (A). Stone analysis was reported as uric acid. The average HU value taken from the densest region of the calculus is 462.92 HU (B)

HU: Hounsfield unite

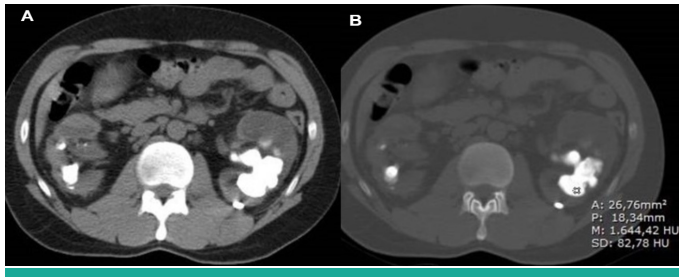

Figure 2. A 33-year-old male patient has calculi in the bilateral pelvicalyceal system (A). Stone analysis for calculus in the left kidney pelvicalyceal system was reported as calcium phosphate. The mean HU value taken from the densest region of the calculus is 1644.42 HU (B)

HU: Hounsfield unite

Imaging methods are the best problem solvers in stone disease. The location of the stone, its dimensions, whether it is single or more than one, whether there are underlying factors that may cause stone formation, whether the stone obstructs the urinary tract, and the condition of the other kidney are important in planning the treatment. Non-contrast CT plays an important role in detecting urinary system calculus, distinguishing calculus from other anomalies (such as stricture, neoplasia), and determining non-urological causes of flank pain (4).

Table 4. Comparison of densities of stone subtypes

	n	Stone density
Calcium phosphate	11	1406.45±187.71
Calcium oxalate monohydrate-dihydrate	18	1224.94±213.33
Calcium oxalate monohydrate	42	1313.31±210.53
Cystine	10	762.00±66.97
Struvite	12	749.00±126.57
Uric acid	13	413.00±60.27
		p=0.0001

One-Way Analysis of Variance

Table 5. Comparison of densities of stone subtypes

Tukey multiple comparison test	p
Calcium phosphate/calcium oxalate monohydrate-dihydrate	0.095
Calcium phosphate/calcium oxalate monohydrate	0.642
Calcium phosphate/cystine	**0.0001**
Calcium phosphate/struvite	**0.0001**
Calcium phosphate/uric acid	**0.0001**
Calcium oxalate monohydrate-dihydrate/calcium oxalate monohydrate	0.501
Calcium oxalate monohydrate-dihydrate/cystine	**0.0001**
Calcium oxalate monohydrate-dihydrate/struvite	**0.0001**
Calcium oxalate monohydrate-dihydrate/uric acid	**0.0001**
Calcium oxalate monohydrate/cystine	**0.0001**
Calcium oxalate monohydrate/struvite	**0.0001**
Calcium oxalate monohydrate/uric acid	**0.0001**
Cystine/struvite	0.999
Cystine/uric acid	**0.0001**
Struvite/uric acid	**0.0001**

Singh et al. (5), in their study with 100 patients in 2020, found high sensitivity and specificity in the detection of stone subgroups by dual-energy CT. The sensitivity and specificity of dual-energy computed tomography (DECT) for hydroxyapatite, uric acid, cysteine, oxalic acid, and mixed types were 89.6% and 88.5%, 82.6% and 97.5%, 86.7% and 96.5%, 80% and 98.9%, and 88.9% and 98.9%, respectively (5). Erdogan et al. (6), on the other hand, conducted a study involving 373 patients using dual-energy CT in 2019. *In vitro* analysis of stones was performed in 35 patients, and 8 hydroxyapatite, 18 calcium oxalate, 6 uric acid and 3 cystine stones were detected. In DECT analysis results compared with the results of *in vitro* analysis, the correct type of stone was detected in 32 (91.4%) patients and the wrong type of stone in 3 (8.6%) patients. All uric acid and cystine stones were detected correctly, especially

with DECT (6). With advanced post-procedure analysis methods, DECT can analyze urinary stones. DECT has been found to be superior, especially in the detection of uric acid and cystine stones. It also has a high success rate in detecting hydroxyapatite and calcium oxalate stones.

There are *in vivo* and *in vitro* studies on stone analysis in the literature. From *in vitro* studies, Mostafavi et al. (7) distinguished the chemical content of pure stones as uric acid, struvite and calcium oxalate stones in CT taken with 120 kV. They also stated in their studies that stones of similar density such as cystine, brushite and calcium oxalate could be distinguished by using dual energy (7). Saw et al. (8) scanned 127 stones using 1 mm, 3 mm, and 10 mm collimation and stated that they could distinguish stones other than brushite from hydroxyapatite at 1 mm collimation. From *in vivo* studies, Nakada et al. (9) showed that there was a statistically significant difference between the densities of stones containing uric acid and calcium in a study on 129 patients.

In the results of our study, a statistical difference was observed in terms of the average density of stone subtypes (p=0.0001). The mean density of calcium phosphate and calcium oxalate monohydrate-dihydrate subtypes was statistically significantly higher than the mean density of cystine, struvite and uric acid stone subtypes (p=0.0001). In addition, the mean density of the uric acid subtype was found to be statistically significantly lower than the mean density of cystine and struvite stone type groups (p=0.0001). In our study, it was concluded that the density values of the calcium-containing stones were found to be significantly higher than the other groups, but they could not be distinguished between themselves only by the non-contrast CT method.

In the study of Patel et al. (10), 100 stones were analyzed. Considering HUs, calcium phosphate stones (brushite and apatite) have the highest density (1.123±254, 844±346 HU). There is a significant difference between HU values of all calcium stones and HU values of uric acid stones (10). Similarly, there was a significant difference in HU values between calcium stone groups and uric acid, cystine and struvite stones in our study. However, in our study, there was no significant difference between the calcium-containing stone subtypes in terms of HU values.

In the study of Spettel et al. (11), 235 stone analyses were performed. The average density of uric acid stones was 484±44 HU, the average density of calcium-weighted stones was 890±20, and the difference between them was statistically significant. When these results were evaluated together with the urine pH results, the sensitivity of detecting uric acid stones was 100% and the specificity was 80% (11).

When we compare the *in vivo* and *in vitro* studies in the literature, it is seen that the density of stone types in *in vivo* studies is lower than those stated in *in vitro* studies. This is most likely due to the volume average effect of adjacent soft tissue and the use of smaller collimation size in *in vitro* studies. As the collimation decreases, the volume average artifacts will decrease and thus the attenuation-size measurement will be better.

Study Limitations

Our study had some limitations. Urinary system stones can be better shown using dual-energy tomography. In the following years, images obtained using dual-energy CT can be studied in a larger patient group.

Conclusion

Our main goal in our study is to show the detectability of uric acid stones, one of the urinary system stones, by non-contrast tomography, as well as to draw attention to its use in clinical practice. When we examined the patient histories retrospectively, it was seen that repetitive CT, IVP and anterograde pyelography examinations were applied to the patients more than once. This means unnecessary radiation dose is given to patients with a history of chronic kidney stones. In the treatment of urinary system stones, oral chemolysis treatment, other than interventional procedures, is a method that can only be applied to uric acid stones, with a lower cost and less patient morbidity. Indicating the localization and size of the stone as well as the calculus density value in radiology reports may save the patient from unnecessary interventional treatment methods and reduce morbidity.

Ethics

Ethics Committee Approval: Ethics committee approval dated 08/12/2017 and numbered 2017.12.1.08.024 was obtained from University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Ethics Committee before the study.

Informed Consent: The study was conducted retrospectively, because of that we did not obtain consent of patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.S., M.Ö., Design: E.S., M.Ö., Data Collection or Processing: S.Ö., A.T.C., Analysis or Interpretation: E.S., S.Ö., Drafting Manuscript: E.S., S.Ö., Critical Revisation of Manuscript: M.Ö., A.T.C., Final Approval and Accountability: E.S., S.Ö., M.Ö., A.T.C.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):116-123
DOI: 10.4274/BMB.galenos.2022.2022-02-017

Acute Rhabdomyolysis in the Pediatric Intensive Care Unit: Etiology, Clinical Features, Treatment, and Prognosis

Çocuk Yoğun Bakım Ünitesinde Akut Rabdomiyoliz: Etiyoloji, Klinik Özellikler, Tedavi ve Prognoz

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Abstract

Objective: This study was designed to identify the underlying etiology, evaluate the treatment methods, and determine the incidence of acute kidney injury (AKI), and to establish the predictive laboratory values for kidney failure and the factors associated with mortality in critically ill children with a diagnosis of rhabdomyolysis and high creatine kinase (CK) levels.

Method: Twenty-three patients who were diagnosed with acute rhabdomyolysis in the first 48 hours in the pediatric intensive care unit between January 2011 and January 2021 and whose CK levels were found to be ≥50.000 IU/L in follow-up were included in the study. The ages of the patients ranged from 1 month to 18 years. Patients with muscular diseases, postoperative patients, and chronic renal failure patients were not included.

Results: The median age of the patients was 71 months (41-141 months). The three most common causes were infection (n=11, 47%), intoxication (n=5, 21.7%), and metabolic disease (n=4, 17.3%). While the mean CK value of the patients at admission was 53.570±32.37 IU/L, the peak CK value was 88.936 IU/L (60.558-122.962). Eleven patients (47.8%) developed AKI. Continuous renal replacement therapy (CRRT) was performed for six patients (26%). Between those who developed kidney failure and those who did not, the differences between the pediatric risk of mortality scores, blood urea nitrogen, creatinine, uric acid, and calcium measured during hospitalization were significant, while the difference in CK values was not.

Öz

Amaç: Rabdomiyoliz tanısı konulan ve kreatin kinaz (CK) düzeyi yüksek olan kritik çocuk hastalarda, altta yatan etiyolojiyi saptamak, tedavi yöntemlerini değerlendirmek, akut böbrek yetmezliği (ABY) görülme sıklığını ve böbrek yetmezliği için prediktif laboratuvar değerlerini saptamak ve mortalite ile ilişkili faktörleri belirlemektir.

Yöntem: Çalışmaya Ocak 2011-Ocak 2021 arasında çocuk yoğun bakım ünitesinde ilk 48 saatte akut rabdomiyoliz tanısı konulan ve izlemde CK düzeyi 50,000 IU/L ve üzerinde tespit edilen 23 hasta dahil edildi. Hastaların yaşları 1 ay-18 yaş arasındaydı. Kas hastalığı bulunanlar, postoperatif hastalar ve kronik böbrek yetmezliği hastaları dahil edilmedi.

Bulgular: Hastaların yaş ortancası 71 ay (41-141 ay) idi. En sık üç neden enfeksiyon (n=11, %47), zehirlenme (n=5, %21,7) ve metabolik hastalık (n=4, %17,3) idi. Hastaların yatış ortalama CK değeri 53,570±32.371 IU/L iken, pik CK değeri 88,936 IU/L (60,558-122,962) idi. On bir hastada (%47,8) ABY gelişti. Altı hastaya (%26) sürekli renal replasman tedavisi (SRRT) uygulandı. Böbrek yetmezliği gelişenler ile gelişmeyenler arasında; pediatrik ölüm riski skorları, yatış sırasında bakılan BUN, kreatinin, ürik asit ve kalsiyum değerleri arasındaki farklılık anlamlı iken, CK değerlerindeki farklılık anlamlı değildi. Mekanik ventilatör, inotrop, ekstrakorporeal tedavi ihtiyacı olanlar ile üç ve üzerinde organ yetmezliği gelişen hastalarda böbrek yetmezliği görülme sıklığı anlamlı derecede yüksekti. İnotrop ihtiyacı olan, SRRT tedavisine ihtiyaç duyan, üç ve üzerinde organ yetmezliği olan ve evre 3 böbrek yetmezliği gelişen hastaların mortalitesi anlamlı düzeyde yüksekti. Sağ kalan hastaların hiçbirinde son dönem

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Cite this article as: Azapağası E, Akkaya B, Onguner S, Yazıcı Uysal M, Öztürk Z. Acute Rhabdomyolysis in the Pediatric Intensive Care Unit: Etiology, Clinical Features, Treatment, and Prognosis. Bagcilar Med Bull 2022;7(2):116-123

Abstract

The incidence of kidney failure was significantly higher in patients who needed mechanical ventilation, inotrope administration, or extracorporeal therapy and in patients with three or more organ failures. Mortality was significantly higher in patients who needed inotropes or CRRT, had three or more organ failures, or developed stage 3 kidney failure. End-stage kidney failure was not observed in any of the surviving patients. Four patients (17.4%) included in the study died. The relationship between mortality and peak CK elevation was not significant.

Conclusion: The prognosis of rhabdomyolysis is related to the underlying etiology and comorbid conditions. Early aggressive fluid therapy positively affects the course of the disease.

Keywords: Acute kidney injury, creatinine kinase, mortality, pediatric intensive care, prognosis, rhabdomyolysis

Öz

böbrek yetmezliği görülmedi. Çalışmaya dahil edilen dört hasta (%17,4) öldü. Mortalite ile pCK yüksekliği arasındaki ilişki anlamlı değildi.

Sonuç: Rabdomiyolizin prognozu altta yatan etiyoloji ve komorbid durumlar ile ilişkilidir. Erken agresif sıvı tedavisi hastalığın seyrini olumlu yönde etkilemektedir.

Anahtar kelimeler: Akut böbrek yetmezliği, çocuk yoğun bakım, kreatinin kinaz, mortalite, prognoz, rabdomiyoliz

Introduction

Rhabdomyolysis is a condition that occurs when creatine kinase (CK) and myoglobin are released into the circulation as a result of damage to the skeletal muscle by traumatic or non-traumatic biological, physical, and toxic causes (1). Myoglobin toxicity can cause tubular damage (2,3). The most common causes of rhabdomyolysis in children are viral myositis and trauma, while less common causes include neonatal metabolic diseases, drug toxicity, and inflammatory conditions (2). While the disease may be asymptomatic, it may also cause consequences of varying severity ranging from myoglobinuria to acute kidney injury (AKI) (4). While the incidence of AKI is 10-50%, the mortality rate has been reported as 7-80% (3).

In the diagnosis of rhabdomyolysis, the absence of erythrocytes in the urine despite darkening of the urine color, CK levels at least five times normal, hyperphosphatemia, hyperkalemia, and hypocalcemia are important criteria (4).

This study aimed to identify the underlying etiology, evaluate the treatment modalities, and determine the incidence of AKI and predictive laboratory values for kidney failure as well as to determine the factors associated with mortality in critically ill patients who were hospitalized in the pediatric intensive care unit with a diagnosis of acute rhabdomyolysis and CK level of ≥50.000 IU/L in follow-up.

Materials and Methods

Twenty-three patients, who were diagnosed with acute rhabdomyolysis in the first 48 hours in the pediatric intensive care unit between January 2011 and January 2021 and whose CK levels were found to be ≥50.000 IU/L in follow-up, were included in the study. The ages of the patients ranged from 1 month to 18 years. The study was designed as a retrospective study.

We obtained Ethics Committee approval from our hospital's Medical Specialization Education Board for the study (number: 2020-KAEK-141/264, protocol no: E-21/12-257).

Rhabdomyolysis was diagnosed based on medical history and laboratory findings including elevated serum CK levels of >1000 IU/L.

Age, sex, laboratory parameters, underlying etiologies, presence of chronic diseases, inotrope and mechanical ventilation needs, treatment method, extracorporeal treatments, renal replacement therapies, length of stay in the intensive care unit and the hospital, pediatric risk of mortality (PRISM) score, organ failure, survival, and prognosis were recorded for all patients included in the study.

Extracorporeal treatments included extracorporeal membrane oxygenation (ECMO), therapeutic plasma exchange (TPE), and renal replacement therapy.

Renal replacement therapies were classified as peritoneal dialysis, hemodialysis, and continuous renal replacement therapy (CRRT).

Laboratory parameters including serum blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), uric acid, sodium (Na), potassium (K), calcium (Ca), phosphorus (P), urine microscopy, metabolic tests, pH and bicarbonate values, and CK levels were recorded at the time of diagnosis and during the peak time.

Serum and urinary myoglobin are not routinely assessed at our hospital.

AKI was defined as an increase in creatinine clearance of 50% or more within 7 days, or an increase of 0.3 g/dL in

serum creatinine in 2 days, or patients becoming oliguric for more than 6 hours (5). The kidney disease: Improving Global Outcomes (KDIGO) guidelines were used to define the stages of AKI (6). The KDIGO stages are shown in Table 1.

Metabolic acidosis was defined as having a pH level below 7.25 while partial CO_2 pressure was 35-45 mmHg. Applied medical treatments were recorded.

Since our hospital is not a trauma center, only patients with elevated CK levels due to non-traumatic reasons were included in the study.

Patients with muscular diseases such as muscular dystrophy, postoperative patients, patients with chronic kidney failure, and patients whose files could not be accessed were not included in the study.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics 22.0. In the evaluation of the data, frequencies and percentages were given for qualitative data. For quantitative data, descriptive statistical methods were applied to obtain an arithmetic mean for data with normal distribution and a median (25^{th}-75^{th} percentile) for those without standard deviation. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to identify normally distributed data. The chi-square test or Fisher's Exact test was employed to compare qualitative data between the groups. In comparisons between two independent groups, the Student's t-test (paired samples) was used for data with normal distribution and the Mann-Whitney U test was used for data with non-normal distribution. Degrees of relationship between variables were evaluated with the Spearman correlation analysis. All statistical calculations were evaluated at 95% confidence intervals and at a significance level of $p<0.05$.

Table 1. Proposed KDIGO staging of AKI (6)

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline or ≥0.3 mg/dL (≥26.5 µmol/L) increase	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dL(≥353.6 µmol/L) increase or initiation of RRT or in patients<18 years a decrease in GFR <35 mL/min/1.73 m²	<0.3 mL/kg/h for ≥24 h or anuria ≥12 h

KDIGO: Kidney disease: Improving global outcomes, AKI: Acute kidney injury, RRT: Renal replacement therapy, GFR: Glomerular filtration rate

Results

Twenty-three patients were included in the study and 47.8% (n=11) of the patients were female. The median age of the patients was 71 months (41-141 months) and the mean PRISM score was 16.50±10.6.

The most important underlying cause was infection. Eleven patients had symptoms and signs of viral or bacterial infection before the diagnosis of rhabdomyolysis. The detected viral agents were adenovirus, influenza, and bocavirus. Four patients were admitted to the intensive care unit with severe septic shock. Gram-negative agents were shown in two of these cases, while agents could not be identified in the other two cases.

Five patients had acute rhabdomyolysis due to intoxication. While drug poisoning was the cause in four cases of patients hospitalized for this reason, the cause was mushroom poisoning in one case. Drugs causing rhabdomyolysis by intoxication were metformin, selective serotonin reuptake inhibitor, Ca channel blocker, and weight loss pills taken together with a salbutamol inhaler capsule. The patient taking metformin was also in a state of diabetic ketoacidosis. Carnitine palmitoyl transferase II deficiency (CPT II) was detected in three cases and very long-chain fatty acid dehydrogenase deficiency (VLCAD) was found in one case. The three patients' underlying causes were status epilepticus, out-of-hospital cardiac arrest, and hypokalemia secondary to Bartter syndrome.

Thirteen patients (56.5%) needed mechanical ventilation. The median duration of mechanical ventilator was 2 days (0-20 days).

Demographic information, clinical features, renal findings, and hospital details of the patients are summarized in Table 2.

While the mean CK value of the patients at admission was 53.570±32.371 IU/L, the peak CK value was 88.936 IU/L (60.558-122.962). While CK values peaked on day 2 (1-3) of hospitalization, they returned to normal in 13.60±5.38 days.

CK levels at the diagnosis and at the peak time are shown in Table 3.

Fourteen (60.8%) patients had black/tea-colored urine. No erythrocytes were detected in the microscopy results of the patients who had a positive blood reaction in urinalysis.

Table 2. Demographic, clinical, renal, and hospital data of patients

Parameters	n	%
Demographic information		
Number of patients	23	
Female	11	47.8
Age (at diagnosis), months	70 (41-141)	
Underlying disease	11	47.8
Primary diagnosis		
Intoxication	5	21.7
Infection	11	47.8
Metabolic disease	4	17.4
Other		
Bartter syndrome-hypokalemia	1	4.3
Status epilepticus	1	4.3
Out-of-hospital arrest	1	4.3
Clinical details		
Inotrope/vasoactive agent	10	43.5
2 or more organ failures	14	60.9
Dark urine	14	60.9
Mechanical ventilation	13	56.5
Extracorporeal therapy		
ECMO	1	4.3
Therapeutic plasma exchange	4	17.3
Renal findings		
Acute kidney injury		
Stage 1	0	0
Stage 2	2	8.7
Stage 3	9	39.1
Continuous renal replacement therapy	6	26
Chronic kidney disease	0	0
Hospital details		
Intensive care unit stay, days	6* (3-25)	
Hospital stay, days	13* (8-42)	
Mortality	4	17.3

ECMO: Extracorporeal membrane oxygenation, * 25th percentile-75th percentile

A statistically significant and moderate positive correlation was found between creatinine values at the time of hospitalization and creatinine value at the peak CK time (r=0.565, p<0.05). However, no statistically significant relationship was found between peak CK and organ failure, need for inotropes, need for CRRT, or mortality.

Eleven patients (47.8%) developed AKI. Only two patients (18.1%) were experiencing stage 2 renal failure, while the remaining nine patients (29.7%) were in stage 3 renal failure. Six patients (26%) needed CRRT.

Table 3. Laboratory parameters of all patients at hospitalization and pCK

During diagnosis During pCK	Result
CK (IU/L)	53570.91±32371.10
pCK (IU/L)	88936 (60558-122962)
Creatinine (mg/dL)	0.76 (0.56-1.51)
pCK creatinine (mg/dL)	0.72 (0.50-1.20)
AST(IU/L)	1334.26±1234.55
pCK AST (IU/L)	2651.78±1590.11
ALT(IU/L)	314 (78-701)
pCK ALT (IU/L)	802 (431-1386)
BUN (mg/dL)	16 (11-44)
pCK BUN (mg/dL)	16 (11-34)
Sodium	141.61±7.27
pCK sodium	140 (137-148)
Potassium	4.49±1.23
pCK potassium	3.90 (3.38-4.30)
Calcium	8.23±1.08
pCK calcium	8.36±1.15
Phosphorus	5.54±2.64
pCK phosphorus	4.40 (3.00-5.10)
Uric acid (mg/dL)	6.40 (3.50-13.70)
pCK peak uric acid (mg/dL)	4.10 (2.80-9.50)
pH	7.29±0.18
Bicarbonate (mEq/L)	19.06±6.95

CK: Creatinine kinase, pCK: Peak creatinine kinase, BUN: Blood urea nitrogen, AST: Aspartate amino transferase, ALT: Alanine amino transferase, data are presented as mean ± standard deviation

While the differences between PRISM scores and BUN, creatinine, uric acid, and Ca values measured during hospitalization between patients with and without kidney failure were statistically significant (p<0.05), the difference in CK values was not statistically significant (p>0.05). The incidence of renal failure was significantly higher in patients who needed mechanical ventilation, inotrope administration, and extracorporeal treatments and in patients with three or more organ failures compared to the other group (p<0.05).

The clinical and laboratory findings of patients with and without renal failure are shown in Table 4, 5.

The routine treatment protocol was 2500-3000 mL/m^2 of intravenous hydration (crystalloid solution), sodium bicarbonate treatment of more than 40 mEq/L in solution, diuretics for patients with low urine output, and CRRT for patients with oliguria or hypervolemia. The targeted urine output was 3-4 mL/kg/h. Electrolyte and acid-base

Table 4. Comparisons of laboratory findings, age, hospital data, and PRISM between AKI and non-AKI groups

Parameters	Non-AKI (n=12)	AKI (n=11)	t/Standardized test statistic	p
Age	88.67±67.46*	93.82±62.76	0.189	0.852
PRISM	9.22±8.07*	23.78±8.26	3.781	**0.002*** **
Diagnosis CK (IU/L)	61653.50±35188.42*	44753.55±27917.58	-1.268	0.219
Peak CK (IU/L)	87138.00 (65591.00-11383.50)**	93105.00 (60558.00-154200.00)	-0.677	0.525
Diagnosis BUN (mg/dL)	12.67±4.27*	40.45±23.18	3.915	**0.003*** **
Diagnosis creatinine (mg/dL)	0.60±0.14*	2.20±1.59	3.328	**0.007*** **
Diagnosis uric acid (mg/dL)	3.60±1.64*	13.65±4.20	7.380	**<0.001*** **
Diagnosis AST (IU/L)	1806.42±1224.10*	819.18±1070.25	-2.051	0.053
Diagnosis ALT (IU/L)	474.00 (250.00-872.50)	103.00 (26.00-445.00)	1.969	0.051
Diagnosis sodium (mEq/L)	138.83±5.97*	144.64±7.61	2.045	0.054
Diagnosis potassium (mEq/L)	4.15±0.86*	4.87±1.49	1.434	0.166
Diagnosis phosphorus (mg/dL)	4.64±2.07*	6.34±2.94	1.436	0.169
Diagnosis calcium (mg/dL)	8.67±1.06*	7.75±0.93	-2.189	**0.040*** **
Intensive care stay duration	5.00 (3.00-15.00)**	13.00 (4.00-42.00)	-1.174	0.260
Hospital stay duration	9.50 (8.00-20.00)**	25.00 (7.00-42.00)	-0.955	0.347

AKI: Acute kidney injury, CK: Creatinine kinase, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine amino transferase, PRISM: Pediatric risk of mortality score, *data are presented as mean ± standard deviation or median (25^{th}-75^{th} percentile), continuous variables were compared with a student t-test. **Data are presented as median (25^{th} and 75^{th} percentiles). Continuous variables were compared with the Mann-Whitney U test. ***Statistically significant values (p<0.05)

disturbances were treated. None of the patients underwent hemodialysis or peritoneal dialysis.

End-stage renal disease was not observed in any of the surviving patients.

Four patients (17.4%) included in the study died. The relationship between mortality and peak CK elevation was not statistically significant (p>0.05). However, the mortality rates among patients who needed inotropes, needed CRRT, had three or more organ failures, or developed stage 3 renal failure were statistically significantly higher (p<0.05) (Table 6).

Discussion

Rhabdomyolysis is a syndrome that occurs due to skeletal muscle damage that disrupts the integrity of the sarcolemma (3). An increase in serum CK level is the most typical indicator of muscle damage (7).

Pediatric studies show that not only trauma but also infections are a common cause of rhabdomyolysis. A previous report found that infections accounted for 59.5% of the causes of pediatric rhabdomyolysis (8). Wu et al. (9) reported that viral myositis accounted for more than half of all cases of pediatric rhabdomyolysis, and physical exertion and seizure were the second and third most common reasons, respectively. Kim et al. (10) reported that respiratory tract infection and seizure were the most common causes of rhabdomyolysis. Trauma patients were not included in our study and the three most common causes were infection (n=11, 47%), intoxication (n=5, 21.7%), and metabolic disease (n=4, 17.3%), respectively.

In the diagnosis of rhabdomyolysis, myoglobin elevation is helpful. However, the diagnostic necessity of measuring myoglobin levels in the urine and serum is controversial because although myoglobin rises before the CK level, its half-life is quite short (1-3 hours). Therefore, it is likely to give false negatives (11). Although the blood reaction is positive in urinalysis, the absence of erythrocytes in microscopy supports myoglobinuria (11). The urine and serum myoglobin levels could not be studied in the present study. However, the absence of erythrocytes in the microscopy of patients with black urine output and positive urine blood reaction were accepted as supporting findings for myoglobinuria.

The CK level begins to rise within 12 hours after the initial injury, reaches its peak in about 2 days, and usually returns to normal within 6-10 days in most cases (11). In the present study, the peak value of CK was obtained on the 2^{nd} day and returned to normal in approximately 14 days.

Table 5. Comparison of risk factors for groups with and without kidney injury

Parameters	No kidney injury (n=12)		Kidney injury (n=11)		X^2	p
	n	(%)	n	(%)		
Sex					3.569	0.059
Female	8	(66.7)	3	(27.3)		
Male	4	(33.3)	8	(72.7)		
Diagnosis					4.455	0.238
Intoxication	2	(16.7)	3	(27.3)		
Metabolic disease	4	(33.3)	-	-		
Infectious (viral-bacterial)	5	(41.7)	6	(54.5)		
Other	1	(8.3)	2	(18.2)		
Underlying disease					0.048	0.827
Yes	6	(50.0)	5	(45.5)		
No	6	(50.0)	6	(54.5)		
MV					5.490	**0.036**
Yes	4	(33.3)	9	(81.8)		
No	8	(66.7)	2	(18.2)		
Inotropes					7.340	**0.012**
Yes	2	(16.7)	8	(72.7)		
No	10	(83.3)	3	(27.3)		
Extracorporeal therapy					10.977	**0.001**
Yes	-	-	7	(63.6)		
No	12	(100.0)	4	(36.4)		
Extracorporeal therapy method					-	-
CRRT	-	-	2	(28.6)		
Plasma exchange	-	-	1	(14.3)		
ECMO	-	-	-	-		
Multiple	-	-	4	(57.1)		
CRRT					8.856	**0.005**
Yes	-	-	6	(54.5)		
No	12	(100.0)	5	(45.5)		
End-stage kidney injury in surviving patients						**<0.001**
Yes	-	-	-	-		
No	12	(100.0)	7	(100.0)		
Number of organ failures					15.653	**<0.001**
No organ failure	7	(58.3)	-	-		
1 organ failure	1	(8.3)	1	(9.1)		
2 organ failures	4	(33.3)	2	(18.2)		
3 or more organ failures	-	-	8	(72.7)		
Mortality					5.282	**0.037**
No	12	(100.0)	7	(63.6)		
Yes	-	-	4	(36.4)		

MV: Mechanical ventilation, CRRT: Continuous renal replacement therapy, ECMO: Extracorporeal membrane oxygenation. Categorical variables were compared using the Pearson's chi-square test or Fisher's Exact test

AKI is a common and serious complication of rhabdomyolysis. Its incidence is reported to vary within a wide range of 5-50% (8,12,13). Different values such as 5%, 8.7%, and 35.9% have been reported in retrospective studies (8,10). In the present study, the incidence of AKI was 47.8%, which is quite high. Although the high CK levels (median values of 88.936 IU/L) were thought to be the reason for the very high incidence of kidney injury, the relationship

Table 6. Comparison of risk factors for surviving and non-surviving patients

Parameters	Mortality (-) (n=19)		Mortality (+) (n=4)		X^2	p
	n	(%)	n	(%)		
MV					3.725	0.104
Yes	9	(47.4)	4	(100.0)		
No	10	(52.6)	-	-		
Inotropes					6.295	**0.024**
Yes	6	(31.6)	4	(100.0)		
No	13	(68.4)	-	-		
Extracorporeal therapy					4.542	0.067
Yes	4	(21.1)	3	(75.0)		
No	15	(78.9)	1	(25.0)		
Extracorporeal therapy method					3.937	0.257
CRRT	-	-	2	(66.7)		
Plasma exchange	1	(25.0)	-	-		
ECMO	-	-	-	-		
Multiple	3	(75.0)	1	(33.3)		
CRRT					6.008	**0.040**
Yes	3	(15.8)	3	(75.0)		
No	16	(84.2)	1	(25.0)		
Stage of kidney injury					7.532	**0.038**
No kidney injury	12	(63.2)	-	-		
Stage 1 AKI	-	-	-	-		
Stage 2 AKI	2	(10.5)	-	-		
Stage 3 AKI	5	(26.3)	4	(100.0)		
End-stage kidney injury in surviving patients						
Yes	-	-	-	-	-	-
No	19	(100.0)	-	-		
Number of organ failures					6.613	**0.049**
No organ failure	7	(36.8)	-	-		
1 organ failure	2	(10.5)	-	-		
2 organ failures	6	(31.6)	-	-		
3 or more organ failures	4	(21.1)	4	(100.0)		

MV: Mechanical ventilation, CRRT: Continuous renal replacement therapy, ECMO: Extracorporeal membrane oxygenation, AKI: Acute kidney injury, categorical variables were compared using the Pearson's chi-square test or Fisher's Exact test

between CK values and kidney injury was not statistically significant in this study. Studies evaluating CK elevation as a predictive value for AKI have presented varying results. While a few studies carried out with adults (7,14) and one conducted with children (9) indicated a relationship between high CK levels and the development of AKI, other studies did not support that view (8,11,15). In the present study, there was no statistically significant relationship between very high CK levels and the development of AKI.

Watanabe (13) reported that AKI develops more frequently in children with dehydration, metabolic acidosis, severe muscle damage, and multiple organ failure. Studies carried out with adults showed that creatinine value was a predictive factor. However, this was not the case in studies with children (7,8,16,17). In the present study, high BUN, creatinine, uric acid, and PRISM score values were statistically significantly more common in patients with kidney injury than in patients who did not develop kidney injury. Ca level was found to be significantly lower among patients with AKI. The incidence of kidney failure was significantly higher in patients who needed mechanical ventilation, inotrope administration, or extracorporeal therapy and in patients with three or more organ failures compared to the other group. Therefore, this study suggests that kidney failure is associated with underlying diseases and multiple-organ failure rather than CK level.

Early recognition is essential to prevent AKI, and the basis of treatment is aggressive intravenous fluid resuscitation with correction of electrolyte abnormalities. Adjunctive therapies including the alkalization of urine, diuretics, and CRRT have been applied; however, there is controversy regarding the benefits of these treatment modalities (8). High-alkaline intravenous hydration therapy, diuretic therapy, and, when necessary, CRRT were applied for patients in the present study. The patients' responses to treatment were good. None of the surviving patients developed end-stage renal disease. In the literature, it is stated that aggressive fluid therapy, mainly when applied in the early period, has positive effects on the prognosis of the patients (8,17,18).

In a previous study, the degree of elevation of the CK level was not shown to predict mortality. Chronic kidney disease was found to be a rare complication of rhabdomyolysis in children requiring intensive care (3). Children's reported mortality rates were 7% to 10%, but all died secondarily to their underlying etiology and not due to rhabdomyolysis (11). Similar to the literature, no statistically significant correlation was found between high CK value and mortality in the present study. As in the literature, none of the patients developed chronic renal failure. However, when the patients who died are taken into consideration, it is seen that these patients needed inotropic and extracorporeal therapy and had stage 3 kidney failure. They also had three or more organ failures. The underlying cause of mortality for two of these patients was drug intoxication. These two patients, who were admitted after consuming serotonin reuptake inhibitor and Ca channel blocker, were brought

to the hospital in the final stage. One patient died due to severe septic shock, and the other due to to out-of-hospital cardiac arrest. Therefore, the causes of deaths of these patients were not acute rhabdomyolysis but rather underlying secondary causes.

A study conducted with critically ill children stated that peak CK level was not associated with mortality but that these patients needed more intensive care resources. In the same study, the development of chronic kidney disease was not common in this patient group (3).

In this study, no statistical relationship could be demonstrated between high CK values and AKI development. This may be related to the small sample size. We think a study with a larger number of patients who have lower CK values may reflect more objective results.

Although the incidence of AKI and peak CK values were high in this study, chronic kidney disease was not observed in any surviving patients. This may be related to early and aggressive fluid therapy and CRRT administered to patients.

Study Limitations

This was a single-center retrospective study with a small group of patients.

Conclusion

This study showed that the prognosis of rhabdomyolysis is related to the underlying etiology and comorbid conditions. Aggressive fluid therapy applied in the early period positively affects the course of the disease.

Ethics

Ethics Committee Approval: We obtained Ethics Committee approval from our hospital's Medical Specialization Education Board for the study (number: 2020-KAEK-141/264, protocol no: E-21/12-257).

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

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.A., B.A., S.O., M.U.Y., Z.Ö., Design: E.A., B.A., S.O., M.U.Y., Z.Ö., Analysis or Interpretation: S.O., B.A., Writing: E.A., Z.Ö., Manuscript Review and Revisation: E.A., B.A., S.O., M.U.Y., Z.Ö.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):124-129
DOI: 10.4274/BMB.galenos.2022.2021-12-122

Down Syndrome Patients in the Pediatric Emergency Department

Çocuk Acil Serviste Down Sendromlu Hastalar

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Abstract

Objective: The purpose of this study was to evaluate Down syndrome (DS) cases presenting to the pediatric emergency department and to compare them with DS cases with clinical presentations for routine check-ups.

Method: DS patients presenting to the pediatric emergency department of a tertiary hospital between 01.10.2018 and 31.03.2019 (group 1) and DS patients presenting for routine clinical check-ups (group 2) were included in the study. Patients' demographic data (age and gender), weight, height ad head circumference measurements, and data for general health were examined.

Results: Forty-one patients (13 girls, 28 boys) with a mean age of 50.24±48.4 (1-163) months were enrolled in group 1, and 49 cases (17 girls, 32 boys) with a mean age of 52.94±50.1 (1-168) months in group 2. Cases in group 1 had higher rates of heart disease (p=0.004), drug use for heart disease (p=0.038), thyroid disease (0.001), and drug use for thyroid disease (p=0.001) compared to group 2, while engagement in sporting activity was significantly higher among cases in group 2 (p=0.32) than in group 1. There was no difference between the groups in terms of anthropometric measurements.

Conclusion: DS cases presenting to the pediatric emergency department differ from DS cases presenting for routine check-ups in terms of general health status and accompanying diseases. Pediatric practitioners can be more knowledgeable about cases with DS who are admitted to the emergency department.

Keywords: Down syndrome, fever, health, pediatric emergency medicine

Öz

Amaç: Bu çalışmada çocuk acil servise başvuran Down sendromlu (DS) olguların değerlendirilmesi ve rutin kontrol amacı ile poliklinik başvurusu yapan DS olgularla karşılaştırılması amaçlandı.

Yöntem: 01.10.2018-31.03.2019 tarihleri arasında, üçüncü basamak bir üniversite hastanesi çocuk acil servisine herhangi bir nedenle başvuran DS hastalar (grup 1) ile, çocuk polikliniğine rutin kontrol amacıyla başvuran DS hastalar (grup 2) çalışmaya alındı. Hastalara ait demografik veriler (yaş, cinsiyet), ağırlık, boy ve baş çevresi ölçümleri, genel sağlık durumlarına ait veriler incelendi. Grup 1'deki olguların çocuk acil servis başvuru şikayeti, fizik muayene bulguları, laboratuvar tetkikleri, görüntüleme yöntemleri ve hastanın sonlanımı değerlendirildi.

Bulgular: Grup 1'de ortalama yaşları 50,24±48,4 (1-163) ay olan 41 olgu (13 kız, 28 erkek), grup 2'de ortalama yaşları 52,94±50,1 (1-168) ay olan 49 olgu (17 kız, 32 erkek) çalışmaya alındı. Grup 1'deki olguların grup 2'ye göre kalp hastalığı (p=0,004), kalp hastalığı için ilaç kullanma (p=0,038), tiroid hastalığı (p=0,001) ve tiroid hastalığı için ilaç kullanma (p=0,001) oranı daha yüksek iken grup 2'deki olguların grup 1'e göre spor yapma (p=0,032) durumu istatistiksel olarak anlamlı yüksek idi. Gruplar arasında antropometrik ölçümler açısından fark yoktu.

Sonuç: Dezavantajlı hasta gruplarının genel sağlık durumlarının bilinmesi onlara daha iyi sağlık hizmeti sunumuna imkan verecektir. Çocuk acil servise başvuran DS olgular genel sağlık durumu ve eşlik eden hastalıklar açısından rutin kontrol amaçlı polikliniğe başvuran DS olgulardan farklı özellik sergilemektedir.

Anahtar kelimeler: Down sendromu, ateş, sağlık, çocuk acil tıp

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Cite this article as: Bucak İH, Aydın H, Geyik M, Tanrıverdi H, Kılıç FE. Down Syndrome Patients in the Pediatric Emergency Department. Bagcilar Med Bull 2022;7(2):124-129

Introduction

Down syndrome (DS) is the most common genetic disease. The reported incidence is 1/600-1/800 live births (1-3). Studies examining the general health of DS patients have reported mental retardation, loss of hearing, obstructive sleep apnea syndrome, ophthalmological diseases (such as cataract and vision problems), congenital heart diseases (such as atrioventricular septal defect, and ventricular septal defect), gastrointestinal system diseases [such as celiac disease (CD) and Hirschprung disease], thyroid diseases, hematological diseases, and infections such as otitis media (1,2,4-8).

Life expectancy in DS patients ranges between 43 and 55 years (9). The main factors reported in this reduced life expectancy are respiratory system diseases (pneumonia, respiratory failure, and acute respiratory distress syndrome), congenital heart diseases, and dementia (9-11). Length of hospital stay is longer in DS patients than in the general pediatric population, and intensive care requirements are greater (12). Although DS cases in the childhood age group present to the pediatric emergency department with symptoms related to the diseases listed above, no previous studies have evaluated DS cases in the pediatric emergency department and outpatient clinic.

The purpose of this prospective study was to examine the clinical findings and general health status of DS patients presenting to the pediatric emergency department of a tertiary university hospital and to compare these with those of DS cases presenting for routine clinical check-ups.

Materials and Methods

The study was planned prospectively in the pediatric emergency department and outpatient clinic of a tertiary university hospital in Turkey. DS patients presenting to the pediatric emergency department (group 1) for any reason or to the outpatient clinic (group 2) for routine examination between 01.10.2018 and 31.03.2019 were enrolled. Non-DS patients were excluded. In addition, in the event of repeat presentations by DS patients during the study period, the first presentation was evaluated.

Demographic data (age and sex), month of presentation, presentation symptoms to the pediatric emergency department, weight, height and head circumference measurements were recorded for patients in group 1 and 2. Laboratory tests (complete blood count, blood gas analysis, biochemical parameters, and C-reactive protein), imaging methods (direct X-ray, computed tomography, ultrasonography, and magnetic resonance imaging), and outcomes (discharge, or admission to the ward or intensive care) were recorded for group 1. Reference ranges for Turkish children with DS were used in the interpretation of anthropometric measurements (13).

Information concerning whether or not patients received special education, involvement in any sporting activities, hearing problems and hearing aid use, heart disease or drug use in association with heart disease, history of heart surgery and/or angiography, presence of gastrointestinal disease, vison problems or use of visual aids, thyroid disease and use of drugs associated with thyroid disease, presence of snoring/sleep apnea, hematological disease, and whether patients had been investigated for CD and the results if applicable was recorded in order to determine the general health of the DS patients included in the study.

Statistical Analysis

The data obtained were analyzed on SPSS software (IBM, version 24.0, Chicago, IL, USA). Categorical data were expressed as number and percentage, and constant variables as mean plus standard deviation. The test of normality was evaluated with the Shapiro-Wilk test. The chi-square test was used to compare non-parametric categoric variables, independent sample t-test in the comparison of normally distributed variables.

The study was performed in compliance with the Declaration of Helsinki for human research and was approved by the Institutional Ethics Committee (no: 2018/6-5). Written informed consent was obtained from the patients' parents for their anonymized information to be published in this article.

Results

Forty-one DS patients, with a mean age of 50.24±48.4 (1-163) months, 13 girls (31.7%) and 28 boys (68.3%), presented to the pediatric emergency department during the six-month study period (group 1). Forty-nine DS cases, 17 (34.7%) girls and 32 (65.3%) boys with a mean age of 52.94±50.1 (1-168) months presented to the pediatric outpatient clinic for routine examinations during the same period (group 2). No statistically significant difference was determined between group 1 and group 2 in terms of age [(p=0.957), independent sample t-test] or gender (p=0.471). The most frequent month of presentation in group 1 was October (36.6%), followed in decreasing order by November (24.4%), December (14.6%), January (9.8%), February (9.8%), and March (4.9%). In group 2, presentations were most frequent in October (28.6 %) followed by November

(18.4%) and December (18.4%), January (16.3%), February (10.2%), and March (8.2%). No significant difference was determined between the groups in terms of months of presentation (p=0.835).

The most common presentation symptoms among the cases in group 1 were fever and respiratory difficulty. The most common physical examination finding at time of presentation in group 1 involved the lower respiratory system (Table 1).

The mean weight in group 1 was 17.7±22.3 (2.1-130) kg, and the mean height was 88.3±27.3 (47-148) cm. The mean weight and height values in group 2 were 18.2±15.6 (2.75-64) kg and 88.9±29.15 (46-159) cm. No statistically significant difference was observed between the groups in terms of weight [(p=0.886), independent sample t-test] or height [(p=0.67), independent sample t-test]. The mean head circumference in the 22 cases aged less than 36 months in group 1 was 40.9±3.4 (33-46) cm, and while that of the 25 cases aged under 36 months in group 2 was 41±4 (33-47) cm [(p=0.238), independent sample t-test]. Cases' weight, height, and cranial circumference percentiles for age are shown in Table 2. No significant differences were observed between the groups in terms of weight percentiles [(p=0.629), chi-square test] height percentiles [(p=0.21), chi-square test] and head circumference percentiles [(0.336), chi-square test].

Analysis of laboratory tests and imaging techniques performed in the emergency department revealed that complete blood count and biochemical tests were studied in 30 (73.2%) of the 41 cases, blood gas analysis was performed in 15 (36.6%), X-ray in 29 (707), and computed tomography in one (2.4%). Twenty-three (56.1%) of the 41 cases were discharged without admission to hospital, while 13 (31.7%) were admitted to the pediatric ward, and five (12.2%) to the pediatric intensive care unit. The total rate of admission to hospital from the pediatric emergency department during the study department was 4.3%.

Comparison of group 1 and group 2 in terms of general health status revealed statistically significant differences in terms of heart disease (p=0.004)* and drug use for heart disease (p=0.038)*, engagement in sporting activity (p=0.032)*, thyroid disease (p=0.001)*, and drug use for thyroid disease (p=0.001)* [*chi-square test]. CD was investigated in eight (18.9%) of the cases in group 1 and six (12.2%) of those in group 2, and only one case from each group was diagnosed with the disease. Drugs used, comorbidities and general health status of the subjects included in the study are shown in Table 3.

Table 1. DS cases' emergency department presentation symptoms and physical examination findings

Symptoms		**n (%)**
Fever		11 (22)
Respiratory difficulty		11 (22)
Cough		10 (20)
Vomiting		6 (12)
Diarrhea		6 (12)
Abdominal pain		2 (4)
Constipation		1 (2)
Foreign body aspiration		1 (2)
Rash		1 (2)
Seizure		1 (2)
Physical examination findings		n (%)
Lower respiratory tract (n=31)	Wheezing	17 (20)
	Prolonged expirium	12 (13.8)
	Rhoncus	6 (6.9)
	Rales	4 (4.5)
	Nasal discharge	7 (8)
Upper respiratory tract (n=10)	Tonsillar hyperemia	5 (5.7)
	Tonsillar crypt	2 (2.2)
	Tonsillar hypertrophy	8 (9.1)
	Increased bowel sounds	2 (2.2)
Gastrointestinal system (n=4)	Defense	1 (1.1)
	Abdominal tenderness	2 (2.2)
	Decreased skin turgor and prolonged capillary refilling	2 (2.2)
General findings (n=21)	Urticarial eruption	1 (1.1)
	Cardiac murmur	18 (21)
	Wheezing	17 (20)

DS: Down syndrome

Table 2. DS cases' weight, height, and head circumference percentiles

	Weight		**Height**		**Head circumference**	
	Group 1 n (%)	**Group 2 n (%)**	**Group 1 n (%)**	**Group 2 n (%)**	**Group 1 n (%)**	**Group 2 n (%)**
<3p	12 (29.2)	6 (12.2)	10 (24.4)	8 (16.3)	10 (24.4)	7 (28)
3-10p	4 (9.7)	4 (8.2)	4 (9.8)	6 (12.2)	4 (9.8)	2 (8)
10-25p	6 (14.6)	7 (14.3)	8 (19.5)	9 (18.4)	4 (9.8)	3 (12)
25-50p	7 (17)	12 (24.5)	9 (22)	11 (22.4)	1 (2.4)	5 (20)
50-75p	6 (14.6)	9 (18.4)	3 (7.3)	12 (24.5)	1 (2.4)	5 (20)
75-90p	3 (7.3)	7 (14.3)	3 (7.3)	3 (6.1)	1 (2.4)	2 (8)
90-97p	1 (2.4)	2 (4.1)	2 (4.9)	-	-	1 (4)
>97p	2 (4.8)	2 (4.1)	2 (4.9)	-	1 (2.4)	-
p*	0.629		0.21		0.336	

*chi square test, DS: Down syndrome

Table 3. Drugs used, comorbidities and general health status of the subjects included in the study

		Group 1 n (%)	Group 2 n (%)	p*
Special education	Yes	22 (53.7)	24 (49)	0.678
	No	19 (46.3)	25 (51)	
Taking part in sporting activity	Yes	2 (4.8)	11 (22.4)	**0.032**
	No	39 (95.2)	38 (77.6)	
Hearing problems	Yes	8 (19.5)	10 (20.4)	0.565
	No	33 (80.5)	39 (79.6)	
Use of hearing aid	Yes	4 (9.8)	4 (8.2)	0.539
	No	37 (90.2)	45 (91.8)	
Heart disease	Yes	22 (53.6)	12 (24.5)	**0.004**
	No	19 (46.4)	37 (75.5)	
Drug use for heart disease	Yes	11 (26.7)	5 (10.2)	**0.038**
	No	30 (73.2)	44 (88.8)	
History of heart surgery and/or angiography for heart disease	Yes	10 (24.4)	4 (8.2)	0.065
	No	31 (75.6)	45 (91.8)	
Gastrointestinal system disease	Yes	10 (24.4)	7 (14.3)	0.279
	No	31 (75.6)	42 (85.7)	
Vision problems	Yes	2 (4.9)	3 (6.1)	0.585
	No	39 (95.1)	46 (93.9)	
Using spectacles	Yes	1 (2.4)	1 (2)	0.706
	No	40 (97.6)	48 (98)	
Thyroid disease	Hypothyroidism	15 (36.6)	4 (8.2)	**0.001**
	No	26 (63.4)	45 (91.8)	
Drug use for thyroid disease	Yes	12 (29.3)	2 (4.1)	**0.001**
	No	29 (70.7)	47 (95.9)	
Snoring/sleep apnea	Yes	8 (19.5)	9 (18.4)	0.550
	No	33 (80.5)	49 (81.6)	
Musculoskeletal system disease	Yes	2 (4.9)	3 (6.1)	0.585
	No	39 (95.1)	46 (93.9)	
Hematological disease	Yes	8 (19.5)	7 (14.3)	0.351
	No	33 (80.5)	42 (85.7)	
Investigated for celiac disease	Yes	8 (19.5)	6 (12.2)	0.256
	No	33 (80.5)	43 (87.8)	

*chi-square test

Discussion

Although there have been several studies involving DS, to the best of our knowledge, no previous research has examined DS cases in the emergency department and compared these with DS cases presenting for routine check-ups. The most common presentation symptoms in our DS cases were fever and respiratory difficulty. Physical examination findings supported the presentation symptoms, with lower respiratory system findings being most frequent. Diseases of the lower respiratory system in DS cases are more commonly seen as a result of structural pulmonary development anomalies accompanying congenital heart diseases and particularly prolonged ventilator requirements following cardiac surgery (3,14,15). Immune system components are also known to involve more abnormal parameters in DS cases compared to the healthy population (2). Additionally, swallowing dysfunction and gastroesophageal reflux have also been proved to exacerbate lower respiratory system infection findings (2,16). Several studies have identified lower respiratory system infections as the most common cause of admission to hospital in DS cases (16,17). Pneumonia/aspiration has also been reported as the most

common cause of admission in adult DS cases (18). Our study is consistent with the existing literature. Analysis of admission rates from the pediatric emergency department shows an approximately 10-fold greater hospitalization requirement in DS cases compared to non-DS cases. Our study data show that physicians must exhibit greater care in terms of lower respiratory system infections and hospitalization when DS cases present to the pediatric emergency department.

DS cases present more frequently to hospital due to accompanying comorbid conditions. Congenital heart diseases are an important disease group in determining the general health status of patients with DS. The incidence of congenital heart disease in group 1 (53.6%) was consistent with the previous literature. However, the incidence of heart disease was significantly higher in group 1 compared to group 2 [(p=0.004), chi-square test]. We think that there is now a need for further studies investigating the potential effects (such as the likelihood of admission to hospital) of this higher incidence of heart disease in DS cases presenting to the pediatric emergency department. The incidence of thyroid gland diseases in DS cases ranges between 4% and 8% (19). Our data indicate the presence of thyroid gland disease in 36.6% of cases in group 1 and 8.2% of cases in group 2 [(p=0.001), chi-square test]. The significantly higher incidences of thyroid disease and heart disease in group 1 compared to group 2 suggest that the presence of additional chronic disease for DS cases presenting to the emergency department increases the numbers of such presentations.

Bermudez et al. (20) investigated 1,027 DS patients and determined gastrointestinal system symptoms and diseases in 50.7% of them, the most common of which was chronic intestinal constipation. In addition, one meta-analysis reported a comorbidity rate of 5.8% for biopsy-confirmed CD and DS (21). CD was investigated in eight (19.5%) cases in group 1 and six (12.2%) in group 2 but was only diagnosed in one case from each group. Although co-existence of CD and DS has been described in the literature, the presence of CD was investigated at lower rates in both groups than in the previous literature. This indicates that awareness of CD needs to be increased among physicians planning follow-up and treatment of cases of DS.

The prevalence of obstructive sleep apnea syndrome (OSAS) in several studies ranged between 24% and 95% (22). The prevalence of OSAS and/or snoring was lower in the present study. Hematological abnormalities (such as transient neonatal myelopoiesis, and acute myeloid leukemia) have previously been reported in DS cases (23). The reported prevalence of iron deficiency anemia in DS is 2.6% (24). No statistically significant difference was observed between the two groups in terms of hematological diseases.

Although the incidences of some chronic diseases were similar between group 1 and 2, comorbid diseases that were not similar in DS cases presenting to the emergency department and in other DS cases (such as heart disease and thyroid disease) need to be determined. If a disease accompanying cases of DS presenting to the emergency department is identified, we think that health workers' accumulated knowledge will expand, and that the quality of the health service provided for patients will improve.

Various problems concerning growth are encountered in anthropometric measurements of DS cases. Obesity is one noteworthy problem in addition to retardation in weight, height, and cranial circumference (25,26). Gastrointestinal system problems such as absorption, chewing and swallowing disorders result in inadequate calorie intake, leading to subsequent short stature. Approximately 25% of the DS cases presenting to the pediatric emergency department in our study exhibited retardation in weight, height and head circumference compared to their peers, but there was no statistically significant difference between the groups. Weight and height retardation may be expected to result in DS patients falling ill more frequently and presenting to emergency departments. The number of obese DS cases was quite low, at approximately 5% in both groups.

Participation in case-specific sporting activities is recommended to increase DS patients' social adaptation and skills (27). A sedentary life is known to lead to health problems in all age groups. Mentally deficient individuals have been reported to be at greater risk of low physical activity (28). The fact that only two (4.8%) of the DS cases in group 1 took part in sporting activities, a figure significantly lower compared to group 2 [(p=0.032), chi-square test], was interpreted as showing that their general health status was not conducive to sporting activity.

Conclusion

This is the first study to compare general health status and accompanying diseases in cases of DS presenting to the pediatric emergency department with those of DS cases presenting for routine clinical examination. A good knowledge of the general health status of disadvantaged patient groups will make it possible to provide better health services for them.

Ethics

Ethics Committee Approval: The study was performed in compliance with the Declaration of Helsinki for human research and was approved by the Adıyaman University Institutional Ethics Committee (no: 2018/6-5).

Informed Consent: Written informed consent was obtained from the patients' parents for their anonymized information to be published in this article.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: İ.H.B., H.A., M.G., Design: İ.H.B., H.A., M.G., Data Collection or Processing: M.G., H.T., Analysis or Interpretation: İ.H.B., H.A., F.E.K., Critical Revision of Manuscript: H.A., M.G., Final Approval and Accountability: İ.H.B., H.A., M.G., H.T., F.E.K., Technical or Material Support: İ.H.B., H.A., M.G., Supervision: H.T., F.E.K.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):130-136
DOI: 10.4274/BMB.galenos.2022.2021-09-098

Predictive Factors of Complete Tumor Response to First Line Chemotherapy in Patients with Extensive-stage Small Cell Lung Cancer

Yaygın Evreli Küçük Hücreli Akciğer Kanseri Tanılı Hastalarda İlk Kemoterapiye Tam Yanıtı Etkileyen Faktörler

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Abstract

Objective: We aimed to investigate the factors affecting the complete response (CR) rate and the effect of treatment response on survival in patients with extensive stage-small cell lung cancer (ES-SCLC) who received a combination of cisplatin and etoposide as first-line therapy.

Method: This retrospective analysis included 140 ES-SCLC patients, who were followed in an oncology clinic. Patients were divided into two groups as CR and non-CR according to radiological evaluation after first line chemotherapy. Clinical and demographic characteristics and pre-treatment hemogram parameters were obtained from electronic medical record system.

Results: While CR was seen in 34 (24.3%) of all patients after the first line chemotherapy, 106 (75.7%) patients were in the non-CR group. On univariate analysis, predictors for CR to treatment were the absence of brain metastasis, receiving 6 chemotherapy cycles and good performance status (p<0.001; p=0.020; p=0.001, respectively). In multivariate analysis, the absence of brain metastasis and good performance status were independent predictive factors for CR (p=0.033; p=0.019, respectively). Better treatment response rate to first-line chemotherapy was found to be associated with improved disease-free survival, and overall survival (log-rank p<0.001; log-rank p<0.001, respectively).

Conclusion: Good performance status and the absence of brain metastases were identified as independent predictive factors for CR in ES-SCLC patients at the time of diagnosis. Patients who achieved CR had a significantly longer survival rate than patients with lower treatment response.

Keywords: Chemotherapy, complete response, small cell lung cancer, survival prognosis

Öz

Amaç: Yaygın evre-küçük hücreli akciğer kanseri (ES-SCLC) tanılı olup, ilk basamakta sisplatin ve etoposid kombinasyon kemoterapisi alan hastalarda tedaviye tam yanıtı (CR) etkileyen faktörleri ve tedaviye yanıt düzeyinin sağkalıma etkisini araştırdık.

Yöntem: Bu retrospektif çalışmada ES-SCLC tanılı 140 hasta incelendi. İlk basamak kemoterapi sonrası radyolojik yanıt değerlendirmesine göre CR ve CR olmayan (non-CR) olarak iki grup belirlendi. Klinik, demografik hasta özellikleri ve tedavi öncesi hemogram parametreleri arşivden elde edildi.

Bulgular: Hastaların 34'ü (%24,3) CR, 106 (%75,7) hasta non-CR grubunda yer aldı. Yapılan tek değişkenli analizde tanı anında beyin metastazı yokluğu, 6 kemoterapi siklusu alma ve iyi performans durumu CR için öngörücü faktörler olarak bulundu (sırasıyla p<0,001; p=0,020; p=0,001). Çok değişkenli analizde ise beyin metastaz yokluğu ve iyi performans durumu CR için bağımsız prediktif faktörler olarak saptandı (sırasıyla p=0,033; p=0,019). Ayrıca birinci basamak kemoterapiye verilen yanıt arttıkça hastalıksız sağkalım süresi ve genel sağkalım süresinin uzadığı tespit edildi (sırasıyla log-rank p<0,001; log-rank p<0,001).

Sonuç: Tanı anında beyin metastaz yokluğu ve iyi performans durumu birinci basamak tedaviye tam yanıt için bağımsız prediktif faktörlerdir. Tam yanıta ulaşan hastalar, daha düşük tedavi yanıtına göre önemli ölçüde daha uzun sağkalıma sahiptir.

Anahtar kelimeler: Kemoterapi, küçük hücreli akciğer kanseri, sağkalım, tam yanıt

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Cite this article as: Çavdar E, İriağaç Y, Sakin A, Şeber ES. Predictive Factors of Complete Tumor Response to First Line Chemotherapy in Patients with Extensive-stage Small Cell Lung Cancer. Bagcilar Med Bull 2022;7(2):130-136

Introduction

According to 2021 data, lung cancer is the leading cause of cancer deaths worldwide (1). Despite the advancing medical science, its high mortality continues (2). Small cell lung cancer (SCLC), an aggressive subtype of lung cancer, is a neuroendocrine cancer and accounts for approximately 15% of lung cancers. Up to 60-70% of them are extensive stage-small cell lung cancer (ES-SCLC) at the time of diagnosis (3,4).

There are limited treatment options beneficial for survival in ES-SCLC. The combination of platinum (cisplatin or carboplatin) and etoposide continues to be the standard in initial treatment for SCLC, while the median overall survival (mOS) with this treatment is around 8-13 months (5,6). ES-SCLC patients have been reported to have an objective response rate up to 80% to chemotherapy while 20-30% of patients have a complete response (CR); however, the median response time is short and the 2-year survival rate is less than 10% (7-9). In addition, immunotherapy, PCI, and thoracic radiotherapy are known to prolong survival. Immunotherapies have not yet become a standard in many countries due to the fact that immunotherapies are expensive and therefore difficult to access (10). In treatment guidelines, prophylactic cranial irradiation (PCI) and thoracic radiotherapy are recommended as standard treatment approaches only in patients with a good response to chemotherapy (2,11,12).

In this study, we aimed to examine the factors affecting the treatment response in patients receiving cisplatin and etoposide, the most common regimen used as the first line treatment in ES-SCLC patients, and to evaluate the relationship between treatment response and survival.

Materials and Methods

Patients

In our study, medical records of 140 consecutive patients with ES-SCLC at the time of diagnosis between the years of 2015 and 2020, who were treated in Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Oncology, were analyzed retrospectively. Patients who received either etoposide (100 mg/m^2; day 1-3) and cisplatin (75 mg/m^2; day 1 or 25 mg/m^2; day 1-3) combination every 3 weeks chemotherapy were included in the study. The following were used as exclusion criteria: The presence of a different concomitant solid or hematological malignancy, acute infection, no evidence of extensive stage disease according to European Society for Medical Oncology guideline, being under 18 years of age, having an autoimmune disease and a history of immunosuppressive drug use (2). In the staging of the patients, pre-treatment computed tomography, fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography and brain magnetic resonance imaging were used.

Data Collection

Eastern cooperative oncology group (ECOG) performance score, age, gender, smoking status, body mass index (BMI), site of metastasis, presence of superior vena cava syndrome (SVCS), status of receiving PCI, local radiotherapy, number of chemotherapy cycles received, laboratory parameters before initiation of the treatment (neutrophil count, thrombocyte count, hemoglobin value) obtained from blood serum samples were recorded from archive files. Performance scores of the patients were recorded as ECOG 0-1 and 2-3, and their use of cigarette pack/year was separated as over 50 pack/year and below 50 pack/year.

Treatment responses of the patients were determined from their imaging after the chemotherapy regimen was completed. Treatment response was evaluated with computed tomography imaging. As per the RECIST version 1.1, the best response after first-line chemotherapy was categorized as CR, partial response (PR), stable disease (SD) and progressive disease (PD). Intergroup evaluation was done by dividing into two groups as CR and non-CR (partial, stable or progression). Disease-free survival duration (DFS) was considered as the time from onset of disease to the date of radiological progression (according to modified RECIST version 1.1). mOS was calculated as the time from disease diagnosis to the date of death.

Statistical Analysis

SPSS 22.0 for Windows software was used for the statistical analysis. The Fisher's Exact test and the chi-square test for trend were used to assess the association between categorical or ordinal variables and the presence of CR. Univariate and multivariate analyses were performed using the logistic regression model. Survival analysis was done by the Kaplan-Meier method.

Ethical Approval

Ethics approval to carry out the study was provided by Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (date: 27.04.2021, no: 2021.117.04.12).

Results

One-hundred forty patients with ES-SCLC diagnosed according to the criteria included in the study were

included, 109 (77.7%) were male and 31 (22.1%) were female. The median age was 59 years (range: 25-81). Thirty-four (24.3%) of patients achieved a CR to the first line of treatment, 104 (75.7%) patients were in the non-CR group. A total of 54 (41.2) patients received second line of treatment. One-hundred ten (78.6%) of entire patient population died during the study period completed (Table 1).

In the univariate analysis performed, patients without brain metastases, with an ECOG performance score of 0-1 at the time of diagnosis, and who received 6 chemotherapy cycles had a significantly higher CR response (p=0.001, p=0.018, p=0.020, respectively). Besides, the rate of progression seen after first-line chemotherapy, second-line treatment status and the rate of patients who died were higher in patients with non-CR treatment response (p<0.001, p<0.001, respectively). There was no relationship between age, gender, BMI, smoking history, presence of SVCS, extra-brain metastasis area, primary mass location (right/left) and hemoglobin value, platelet value and NLR (neutrophil-lymphocyte ratio) and treatment response to first chemotherapy (p>0.05) (Table 2).

Multivariate analysis of significant factors provided from univariate analyses showed that patients with 0-1 ECOG performance score at the time of diagnosis and those without brain metastases were frequently in the CR group (p=0.019, p=0.033, respectively) (Table 3).

We examined the relationship between the treatment response of the patients to the first chemotherapy and DFS and OS. We divided the initial treatment response into CR, PR, SD and PD. According to the Kaplan-Meier analysis, initial treatment response median DFS (mDFS) was 14.8 months [95% confidence interval (CI) 12.7-15.2], 7 months (95% CI 6.1-7.8), 4 months (95% CI 3.5-4.4), and 1 month, respectively (95% CI 0.6-1.3). There was a statistically significant difference between the groups for mDFS (log-rank p<0.001) (Figure 1). Patients' mOS were 20 months (95% CI 16.6-23.3), 11 months (95% CI 9.1-12.8), 6 months (95% CI 4.8-7.) for the CR, PR, SD and PD groups, respectively and 2 months ((95% CI 1.2-2.7). There was a statistically significant difference between the groups for mOS (long-rank p<0.001) (Figure 2).

Discussion

One-hundred fourty patients diagnosed with ES-SCLC were examined in our study. The aim of this study was to evaluate the relationship between treatment response and survival after first-line chemotherapy in ES-SCLC

Table 1. Patients' characteristics

Characteristic		n	%
Gender	**Female**	**31**	**22.1**
	Male	**109**	**77.9**
Age	**Median (min-max)**	59 (25-81)	
Smoking	**No**	4	2.9
	Yes	136	97.1
Cigarettes package/year	**Over 50**	70	50.0
	Below 50	70	50.0
BMI	**Mean-SD**	24.0±4.5	
ECOG group	**0-1**	105	75.0
	2-3	35	25.0
Localization	**Right**	77	55.0
	Left	63	45.0
SVCS	**No**	131	93.6
	Yes	9	6.4
Brain met	**No**	114	81.4
	Yes	26	18.6
Pleura met	**No**	109	77.9
	Yes	31	22.1
Contra-lung met	**No**	115	82.1
	Yes	25	17.9
Liver met	**No**	102	72.9
	Yes	38	27.1
Adrenal met	**No**	102	72.9
	Yes	38	27.1
Bone met	**No**	69	49.3
	Yes	71	50.7
#Of CT cycles	**Median (min-max)**	6 (1-6)	
Hb (g/dL)	**Mean-SD**	12.6-1.7	
PLT (10^3/uL)	**Mean-SD**	306.2±121.9	
NLR	**Mean-SD**	4.3±3.0	
Response after first series	**CR**	34	24.3
	PR	68	48.6
	SD	15	10.7
	PD	23	16.4
Local RT	**Not received**	112	80.0
	Received	28	20.0
Prophylactic cranial irradiation (PCI)	**Not received**	118	84.3
	Received	22	15.7
Second series treatment	**No**	77	58.8
	Yes	54	41.2
First series treatment	**No**	7	5.0
	Yes	133	95.0
Final status	**Alive**	30	21.4
	Exitus	110	78.6

BMI: Body mass index, ECOG: Eastern cooperative oncology group, SVCS: Superior vena cava syndrome, CT: Chemotherapy, Hb: Hemoglobin, PLT: Levels of platelet, NLR: Neutrophil-to-lymphocyte ratio, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, RT: Radiotherapy

Table 2. Patients' characteristics according to treatment groups

Characteristics*		Complete		Non-complete		p
		n	%	n	%	
Gender	Female	9	26.9	22	20.8	0.485
	Male	25	73.1	84	79.2	
Age	Median (min-max)	58 (25-74)		60 (41-81)		0.798
Smoking	No	0	0.0	4	3.8	0.576
	Yes	34	100.0	102	96.2	
Cigarettes package/ year	Over 50	18	52.9	52	49.1	0.693
	Below 50	16	47.1	54	50.9	
BMI	Mean-SD	24.9±4.1		23.6±4.6		0.935
ECOG group	0-1	33	97.1	72	67.9	**0.001**
	2-3	1	2.9	34	32.1	
Localization	Right	20	58.8	57	53.8	0.607
	Left	14	41.2	49	46.2	
SVCS	No	31	91.2	100	94.3	0.454
	Yes	3	8.8	6	5.7	
Brain met	No	30	88.2	84	79.2	**<0.001**
	Yes	4	11.8	22	20.8	
Pleura met	No	27	79.4	82	77.4	0.802
	Yes	7	20.6	24	22.6	
Contra-lung met	No	30	88.2	85	80.2	0.286
	Yes	4	11.8	21	19.8	
Liver met	No	25	73.0	77	72.6	0.919
	Yes	9	26.0	29	27.4	
Adrenal met	No	26	76.0	76	71.7	0.586
	Yes	8	23.0	30	28.3	
Bone met	No	20	58.8	49	46.2	0.201
	Yes	14	41.2	57	53.8	
#Of CT cycles	Median (min-max)	6 (4-6)		5 (1-6)		0.020
Hb (g/dL)	Mean ± SD	12.8±1.7		12.5±1.7		0.536
PLT (10^3/uL)	Mean ± SD	322-125.6		299.7 (121.1)		0.409
NLR	Mean ± SD	4.2±3.6		4.4±2.7		
Response after first series	CR	34	100.0	0	0.0	**<0.001**
	PR	0	0.0	68	64.2	
	SD	0	0.0	15	14.2	
	PD	0	0.0	23	21.7	
First series treatment	No	7	20.6	0	0.0	**<0.001**
	Yes	27	79.4	106	100.0	
Second series treatment	No	10	29.4	67	68.4	**<0.001**
	Yes	24	70.6	31	31.6	
Final status	Alive	15	44.1	15	14.2	**<0.001**
	Exitus	19	55.9	91	85.8	

*Important values are shown in bold. BMI: Body mass index, ECOG: Eastern cooperative oncology group, SVCS: Superior vena cava syndrome, CT: Chemotherapy, Hb: Hemoglobin, PLT: Levels of platelet, NLR: Neutrophil-to-lymphocyte ratio, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 3. Multivariate analysis for complete response

Characteristics		OR	95% CI for OR		p
ECOG performance score	2-3 vs 0-1	11.670	1.493	91.197	**0.019**
#Of CT cycles received		0.776	0.583	1.033	0.082
Presence of brain metastasis	Yes vs no	2.631	1.082	6.395	**0.033**

Important values are shown in bold. ECOG: Eastern cooperative oncology group, CT: Chemotherapy, CI: Confidence interval, OR: Odds ratio

patients and to evaluate predictive factors for CR. Similar to previous studies, the rate of patients with CR in our study was 24.3% (7-9,13). A significant relationship was found between first-line treatment response (CR, PR, SD or PD) and median OS (mOS) and median DFS (mDFS). One of the main findings was that the more patients responded to the first treatment, the longer they had survival duration. CR treatment response was higher in those with 0-1 ECOG performance score, those without brain metastases at the time of diagnosis, and those who received more first-line chemotherapy cycles. Good performance status and absence of brain metastases were found to be independent predictors for CR in multivariate analysis.

The disadvantage of the performance score is that it can be affected by many acute events during the disease process, but it is known in studies conducted since 1970 that this score is an important prognostic factor in SCLC patients (14-19). However, there are limited studies in the literature comparing the relationship between chemotherapy response and performance status. Tummarello et al. (20) and de Wet et al. (21) showed that performance status was related to treatment response. Consistently, in our study, good performance status was determined as a predictive factor for CR to treatment (20,21). In our study, it was seen that those with better ECOG performance score had significantly more CR to first line chemotherapy than those with poor performance.

In our study, those who received a median of 6 cycles of chemotherapy achieved a higher CR response than those who received a median of 5 cycles of chemotherapy. In previous studies, a comparison of 4-6 cycles was performed and no difference was reported for CR (22,23). The reason for achieving meaningful results in our study may be due to the fact that all patients in the CR group received at least 4 cycles of chemotherapy. This result is consistent with the literature and international guidelines (2,24-27). Nevertheless, the fact that the number of chemotherapy cycles seen as predictive in the univariate analysis was not

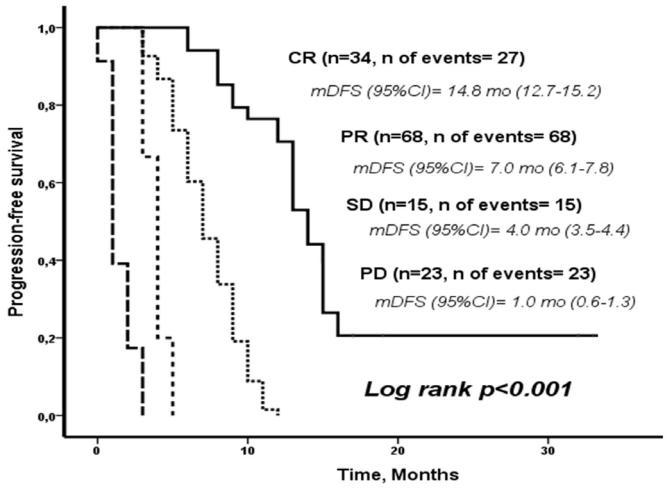

Figure 1. Kaplan-Meier curves displaying the estimated disease free survival probability for 4 different groups of treatment response in ED-SCLC patients receiving cisplatin etoposide combination in the first line therapy

mDFS: Median free survival, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

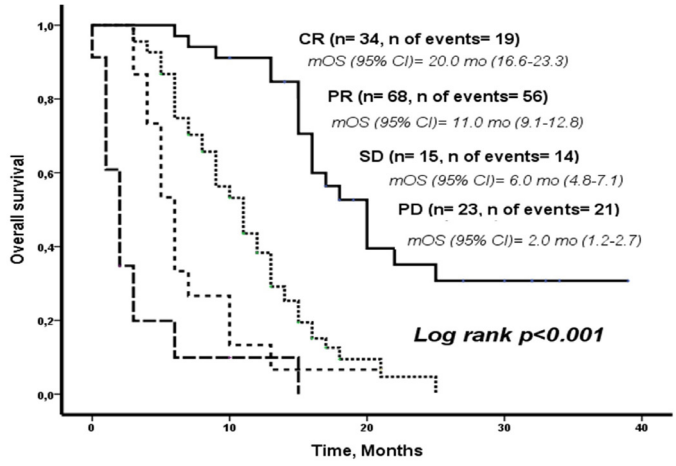

Figure 2. Kaplan-Meier curves displaying the estimated overall survival probability for 4 different groups of Treatment Response in ED-SCLC patients receiving cisplatin etoposide combination in the first line therapy

mDFS: Median free survival, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

found as an independent predictive factor in the multivariate analysis and this may be due to its high correlation with the ECOG, in which the number of chemotherapy cycles received is analyzed together.

In the studies of Bremnes et al. (28), Früh et al. (24), and Gerdan et al. (29), the presence of brain metastasis was reported as an important prognostic factor for ES-SCLC. In our study, the presence of brain metastases at the time of diagnosis predicted poor response to first-line treatment response. This may be due to the low chemotherapy efficacy in the treatment of brain metastases due to the blood-brain barrier, and therefore not to show its maximum effect or from the effect of brain metastasis on performance and treatment compliance (30).

In previous studies, there are consistent results with higher treatment response and better survival of patients (27,31-33). However, there are also reports on that the first line treatment response does not benefit survival in this disease with rapid recurrence (34,35). In our study, it was observed that as the first line treatment response increased, the patients reached better mOS and mDFS times. Accordingly, the highest mOS and mDFS were observed in patients with CR response, while the lowest survival durations were found in patients with PD responses. There is no consensus on this issue in the literature and it still remains controversial. This situation may depend on the characteristic of the tumor, the characteristics of the selected patients or the status of receiving advanced chemotherapy and the chemotherapy regimens chosen.

There are many studies in the literature reporting that NLR and PLR, which are considered systemic inflammatory markers, are prognostic for ES-SCLC (14,19,36,37). In the studies of Torres-Durán et al. (38) and Huang and Shi (39), smoking status has been reported as a poor prognostic factor. In addition, there are several studies reporting the prognostic role of bone, liver and other organ metastasis (28,40). In our study, these factors were also included in our comprehensive analysis; however, they were not found to be independent predictive factors for CR.

Study Limitations

Some factors that were previously determined to be prognostic and predictive could not be examined (e.g. uric acid, neuron-specific enolase, weight loss, alkaline phosphatase, lactate dehydrogenase), which is among the limiting factors of our study, because it was a single-center and retrospective study. However, our study analyzed patient and treatment characteristics more comprehensively than previous studies. In addition, detailed analysis of treatment groups and sole inclusion of patients receiving cisplatin and etoposide combination therapy for survival analysis evaluation increased the sensitivity of our evaluation.

Conclusion

This study demonstrated that better performance score and brain metastasis status at the time of diagnosis are independent predictive factors for CR, which is the main

treatment goal in ES-SCLC patients. Prognostic factor analysis and investigation of effective treatments are needed, as overall survival times are short even if patients diagnosed with ES-SCLC are treated. Finding predictive markers with such studies may be useful both for patient classification in future studies and for patient-specific treatment and follow-up decisions.

Ethics

Ethics Committee Approval: Ethics approval to carry out the study was provided by Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (date: 27.04.2021, no: 2021.117.04.12).

Informed Consent: Patient consent was not required for this study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.Ç., E.S.Ş., Design: E.Ç., Y.İ., A.S., Data Collection or Processing: E.Ç., A.S., Y.İ., Analysis or Interpretation: E.Ç., Y.İ., E.S.Ş., Literature Search: E.Ç., A.S., Writing: E.Ç., E.S.Ş., Manuscript Review and Revisation: E.Ç., Y.İ., A.S., E.Ş.S.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):137-143
DOI: 10.4274/BMB.galenos.2022.2022-01-09

The Effect of MAR Technique on Image Quality of the Anorectal Region in Pelvic CT in Patients with Metallic Hip Prostheses

Metalik Kalça Protezli Hastalarda Pelvik BT'de MAR Tekniğinin Anorektal Bölgenin Görüntü Kalitesine Etkisi

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Abstract

Objective: In this study, we aimed to compare the effects of using the iterative reconstruction (IR) method alone and together with metallic artifact reduction (MAR) on the image quality in computed tomography (CT) imaging of the anorectal region in patients with a metallic hip prosthesis, and to evaluate the contribution of IR+MAR approach to radiological evaluation.

Method: In 22 patients carrying hip prosthesis, as subjective criteria, the degree of metal artifact visualization and critical anatomical structures as the anal canal (AC), inferior rectum (InR), mesorectum (MsR), perianal fat tissue (PFT), and levator ani muscle (LAM) were evaluated in the images of pelvic CT with IR and MAR reconstructions, using only IR technique and IR+MAR approach. As objective criteria, most pronounced hypodense artifacts obscuring the pelvic soft tissue and hyperdense artifacts were measured in the images with MAR and without MAR technique.

Results: It was found that the use of the MAR technique for common metal artifacts observed after CT imaging significantly increased the diagnostic value on AC, InR, MsR, PFT, and LAM radiologically. It was determined that the method provided a significant increase in the visualization of the pelvic bone and muscle tissues and the quality of diagnosis. The differences between hypodense artifact measurements and hyperdense artifact measurements were statistically significant.

Conclusion: Performing IR+MAR reconstruction on pelvic CT in patients with a metallic hip prosthesis improves image quality and the diagnostic value of CT. It can be used in the imaging of anorectal pathologies in patients who cannot undergo magnetic resonance imaging.

Keywords: Anorectal pathologies, hip prosthesis, iterative reconstruction, MAR technique

Öz

Amaç: Bu çalışmada metalik kalça protezi olan hastalarda anorektal bölgenin bilgisayarlı tomografi (BT) görüntülemesinde yinelemeli rekonstrüksiyon (IR) yönteminin tek başına ve metalik artefakt azaltma (MAR) ile kullanılmasının görüntü kalitesi üzerindeki etkilerini karşılaştırmayı ve IR+MAR yaklaşımının radyolojik değerlendirmeye katkısını değerlendirmeyi amaçladık.

Yöntem: Kalça protezi taşıyan 22 hastada, sübjektif kriterler olarak metal artefakt görselleştirme derecesi ve anal kanal (AK), alt rektum (InR), mezorektum (MsR), perianal yağ dokusu (PFT) ve levator ani kası (LAM) gibi kritik anatomik yapılar, sadece IR tekniği ve IR+MAR yaklaşımı kullanılarak IR ve MAR rekonstrüksiyonları ile pelvik BT görüntüleri değerlendirildi. Objektif kriterler olarak, MAR tekniği ve MAR tekniği uygulanmayan görüntülerde pelvik yumuşak dokuyu kapatan en belirgin hipodens artefaktlar ve hiperdens artefaktlar ölçüldü.

Bulgular: BT görüntüleme sonrası gözlenen yaygın metal artefaktları için MAR tekniğinin kullanılmasının radyolojik olarak AC, InR, MsR, PFT ve LAM'de tanısal değeri önemli ölçüde artırdığı bulundu. Yöntemin pelvik kemik ve kas dokularının görüntülenmesinde ve tanı kalitesinde belirgin bir artış sağladığı belirlendi. Hipodens artefakt ölçümleri ile hiperdens artefakt ölçümleri arasındaki farklar istatistiksel olarak anlamlıydı.

Sonuç: Metalik kalça protezi olan hastalarda pelvik BT'de IR+MAR rekonstrüksiyonu yapılması görüntü kalitesini ve BT'nin tanısal değerini iyileştirmektedir. Manyetik rezonans görüntüleme yapamayan hastalarda anorektal patolojilerin görüntülenmesinde kullanılabilir.

Anahtar kelimeler: Anorektal patolojiler, iteratif rekonstrüksiyon, kalça protezi, MAR tekniği

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Cite this article as: Baş S, Zarbaliyev E. The Effect of MAR Technique on Image Quality of the Anorectal Region in Pelvic CT in Patients with Metallic Hip Prostheses. Bagcilar Med Bull 2022;7(2):137-143

Introduction

Many radiological methods are used in the evaluation of soft tissue pathologies located in the pelvic region. For this purpose, the use of pelvic magnetic resonance imaging (MRI) becomes more widespread (1-3). The superiority of pelvic MRI in the evaluation of malignant and non-malignant diseases of rectal, perirectal, and perianal regions has been demonstrated in many studies (1,2). However, some factors such as claustrophobia, pacemaker, and eye prosthesis may be present in patients, which limits MRI scanning (4). Therefore, other radiological methods are preferred. Computed tomography (CT) is recommended as the other non-invasive and most frequently used radiological method in these patients (5). The presence of hip and femoral head prostheses, the use of which is increasing day by day, especially in the elderly population, makes it almost impossible to evaluate the pelvic region. The presence of metal artifacts in standard CT scans also limits the evaluation of organs and soft tissues in the pelvic region and may cause existing pathologies to be overlooked. Different methods have been tried to improve these images and reduce possible artifacts. Metal artifact reduction techniques (MAR), which have been used in recent years, stand out as the most effective method (6). In this study, we aimed to investigate the effectiveness of the IR+MAR technique compared to the use of IR alone in eliminating the image disorders arising from the artifacts caused by a metal prosthesis in CT scans in patients with hip implants.

Materials and Methods

Formal Aspects

All procedures performed in studies 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. Approval was granted by the Local Ethics Committee (date: 05.04.2021/no: 2021/04-653). Informed consent was obtained from all individual participants included in the study.

Patients

We retrospectively reviewed our PACS database for medical records from May 2020 to April 2021. Patients who met the inclusion criteria were those who were scanned with a pelvic CT, having uni or bilateral hip prostheses. We evaluated the metal artifact reduction technique in patients without contrast alone. IV, oral, and rectal contrast used patients were excluded so that the study could be performed in a homogeneous group.

CT Examination Protocol

All patients underwent a pelvic CT without contrast medium, using a 160 mm, 3rd generation MDCT scanner (Revolution CT, GE Healthcare, Milwaukee, WI, USA). Pelvic CT scanning mode had the following parameters: tube voltages were 120 kV; Assist mode, 80-120; tube current, SmartmA mode 100-400 mA; detector width, 80 mm; helical pitch, 0.992:1; rotation time, 0.60s; slice thickness, 1.5 mm and slice interval, 1.5 mm. CT reconstructions were made by using 40% adaptive statistical iterative reconstruction (ASIR) alone and with both smart metal artifact reduction (SMAR) algorithm and 40% ASIR.

Image Reconstruction and Analysis

CT images were reconstructed by using ASIR and prototype SMAR algorithm (abdominal parameters). SMAR was performed by using a vendor-specified ''ABDOMEN'' setting, which entails predetermined SMAR reconstruction parameters appropriate for pelvic anatomy and hardware.

Each study was evaluated by viewing ASIR and SMAR with ASIR images side-by-side, with soft tissue settings [400 Hounsfield units (HU) window width and 40 HU window level]. Images were only evaluated in the axial plane without multiplanar reformations. After reconstructions, images were loaded onto Advantage Windows Workstation 4.7 (GE Healthcare, Milwaukee, Wisconsin/USA) for viewing.

Subjective Evaluation Criteria and Image Analysis

Qualitative image analyses and evaluations were performed in consensus by two radiologists with 16 years and 10 years of experience. In the first session, they graded the degree of metal artifacts and visualization of critical anatomical structures in images reconstructed with ASIR and SMAR and with ASIR alone. As the study was limited to the hip prosthesis in the pelvic region, critical anatomical structures were defined as the anal canal (AC), inferior rectum (InR), mesorectum (MsR), perirectal fat tissue (PFT), and elevator ani muscle (LAM) (7,8). Two radiologists concurrently evaluated the image quality of critical anatomical structures using a 5-point image quality scale for soft tissue (400/40 HU) on ASIR reconstructed and SMAR with ASIR reconstructed CT images. The scale was rated as follows (9,10): 1) Severe artifacts with the invisibility of surrounding structures, 2) Obvious artifacts with significant distortion and insufficient identification of surrounding structures, 3) Moderate artifacts that allow identification of surrounding structures, 4) Mild artifacts with the blurring of surrounding structures, 5) No artifacts. A total of 12 separate scorings was made by assessing the

soft tissue window settings for the ASIR images and SMAR with ASIR images of critical anatomical structures.

Objective Image Analysis

Quantitative analyses were performed according to previous studies (10-12). Regions of interest (ROI) were placed in the same axial slice close to the metal implant, medially in the most pronounced hypodense artifacts obscuring the pelvic soft tissue, laterally in the most pronounced hyperdense artifacts. Furthermore, ROIs were placed in the acetabulum, the gluteus maximus muscle, subcutaneous fat, not affected by the artifacts, as well as in the urine-filled bladder. ROIs were placed in the soft tissue window [width: 400 Hounsfield Units (HU), level: 40 HU]. The sizes of ROIs were only adjusted to prevent the inclusion of tissues not affected by the artifacts. The mean attenuation values [± standard deviations (SD)] of these structures were recorded. The SD of the CT number (expressed in HU) was used to measure image noise (Figure 1).

Statistical Analysis

The Wilcoxon signed-rank test was performed by comparing the categorical scores provided by the radiologists for the degree of visualization of metal artifacts and critical anatomical structures as AC, InR, MsR, PFT, and LAM, using ASIR and SMAR with ASIR in soft-tissue images, depending on the image quality and the ability to evaluate. Paired t-test was used to compare noise, hypodense, and hyperdense artifacts on ASIR and SMAR images with ASIR images, as the data were normally distributed (SPSS 13.0, SPSS Inc., Chicago, IL). For all comparisons, statistical significance was defined as $p<0.05$.

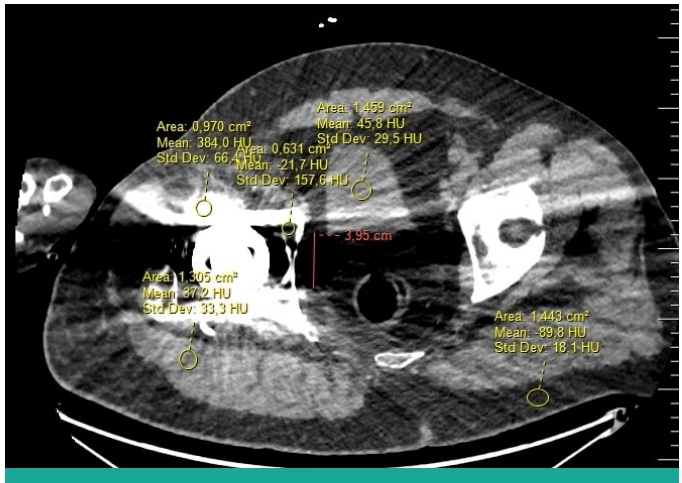

Figure 1. Quantitative assessment of image quality, regions of interest (ROI) were placed on soft tissue window (width 400, length 40). Furthermore, ROI was placed close to metal prosthesis, superiorly in the most pronounced hyperdense artifact. Additionally, ROIs were placed in the subcutaneous adipose tissue, adjacent bone (acetabulum), muscle (gluteus maximus muscle), and the urine filled bladder. The width of most pronounced hypodense artifact was measured

Results

A total of 22 patients, including 10 female and 12 male, met the inclusion criteria (mean patient age=66 years; range=26-93 years). Of these patients, 20 had unilateral hip prostheses (13 left prostheses and 7 right prostheses) and 2 had a bilateral hip prosthesis. This study was carried out completely retrospectively on the films of patients with metallic hip prostheses, who had pelvic CT for other indications (Figure 2 a, 2 b). No CT scan was performed on

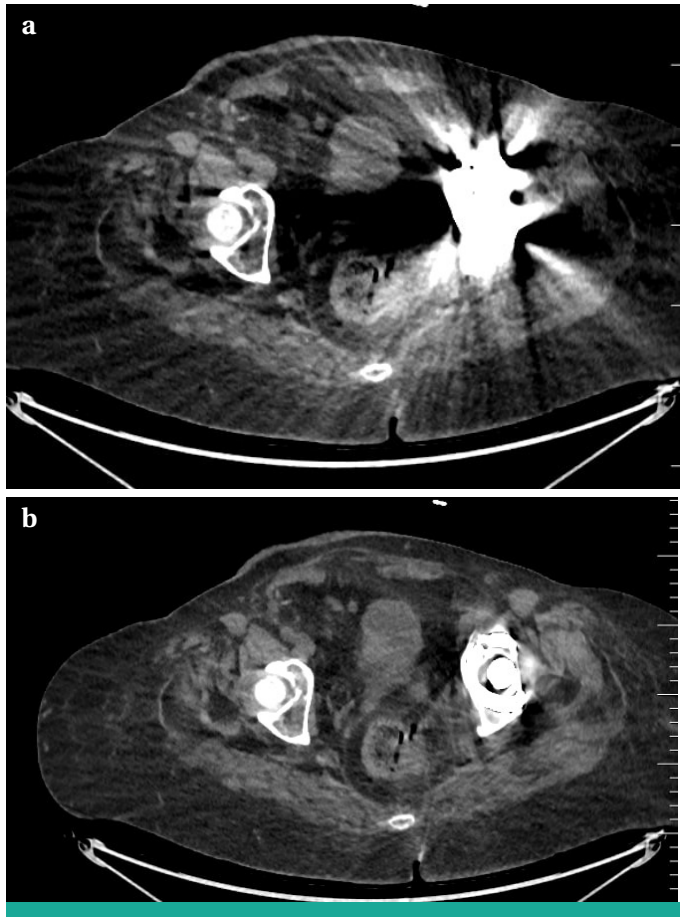

Figure 2. Forty-five-year-old man with trauma, who was checked for abdominal and pelvic hematoma. a) Axial computed tomography (CT) image reconstructed with iterative reconstruction (IR) technique (ASIR, General Electric Healthcare) without iterative metal artifact reduction shows wide beam hardening artifacts accompanied by low-attenuation and high-attenuation streak artifacts that obscure pelvic structures. b) Axial CT image reconstructed with both IR technique and smart metal artifact reduction technique (SMAR, General Electric Healthcare) are reduced. Pelvic regions were better visualized

the patients for the study. The indications for CT included the evaluation of trauma (n=10), bone metastasis (n=4), urinary system calculi (n=3), acute appendicitis (n=3), acute diverticulitis (n=1), and spontaneous rectus sheath hematoma (n=1) (Table 1).

In IR and IR+SMAR images, the scores of critical anatomical structures and metal artifact visualization degrees (as median, minimum, and maximum) for subjective evaluation are given in Table 2. Soft tissue visualization scores (median) of critical anatomical structures were 4 and 4 for AC (Z=-3.557, p<0.001), 3 and 4 for InR (Z=-3.666, p<0.001), 3 and 5 for MsR (Z=-3.482, p<0.001), 3 and 5 for PFT (Z=-3.493, p<0.001), 3 and 5 for LAM (Z=-3.461, p=0.001) in IR and IR+SMAR imaging, respectively. Metal artifact visualization degrees were found to be 2 and 4 (Z=-4.200, p<0.001), in IR and IR+SMAR imaging, respectively. All the differences were statistically significant.

Table 1. Demographic data and prosthetic sideness

Age (year)	66±19.6 (26-93)
Gender	**n**
Female	10
Male	12
Hip prothesis	
Bilateral	2
Unilateral right	7
Unilateral left	13

In addition, as objective criteria, the measurements of hypodense (in mm) and hyperdense (in HU) artifacts and noise values obtained from bone and muscle tissue adjacent to the prostheses, distant fat tissue, and bladder are presented in Table 2.

The differences between hypodense artifact (mm) measurements and hyperdense artifact (HU) measurements on ASIR and ASIR+MAR images were statistically significant (p<0.001). Although the differences about bone and muscle and bladder values in proximity were statistically significant (p<0.001) in noise measurements, the values of distant subcutaneous adipose values were not statistically significant (p=0.028).

Discussion

Although MRI is a priority in the diagnostic evaluation of pelvic and proctological pathologies, this is not possible in some patients. Different recommendations have been presented in the evaluation of pelvic pathologies, especially in patients who cannot undergo MRI due to claustrophobia, cardiac pacemakers, and metallic implants in critical regions such as the eye (13). On the other hand, MRI is also not preferred in patients with pelvic trauma because of the long scan time. As a matter of fact, in some studies, perineal ultrasound (USG) and rectal USG, which are invasive procedures, have been recommended in such cases (14). However, the diagnostic value of perineal USG is low especially in perirectal/perianal inflammatory diseases,

Table 2. ASIR only and SMAR with ASIR, subjective and objective analysis results

	ASIR (min-max)					**ASIR + SMAR (min-max)**					**p**
Subjective (median)	AC	InR	MsR	PFT	LAM	AC	InR	MsR	PFT	LAM	
Soft-tissue visualization score	4 (2-4)	3 (2-4)	3 (2-5)	3 (2-5)	3* (1-5)	4 (4-5)	4 (4-5)	5 (4-5)	5 (4-5)	5* (4-5)	p<0.001 p=0.001*
Degree of visualization metal artifact	2 (1-4)					4 (4-5)					p<0.001
Objective (mean)											
Width of hypodense artifact (mm)	33 (10-68)					4.5 (0-20)					p<0.001
Attenuation of hyperdense artifact (HU)	576 (183-995)					221 (36-664)					p<0.001
Noise (HU)											
Bone	129					59					p<0.001
Muscle	38					26					p<0.001
Subcutaneous fat	23					21					**p=0.028**
Bladder	27					24					p<0.001

AC: Anal canal, InR: Inferior rectum, MsR: Mesorectum, PFT: Perirectal fat tissue, LAM: Levator ani muscle, HU: Hounsfield units, ASIR: Adaptive statistical iterative reconstruction, SMAR: Smart metal artifact reduction. As a statistical test, the Wilcoxon signed-rank test is used for subjective evaluations and paired t-test is used for objective evaluations

and it is very difficult to perform these examinations in emergency services in patients with rectal trauma (15). CT is widely used for pelvic and anorectal imaging in patients with contraindications for MRI and trauma. However, the use of CT is limited in patients with hip prostheses due to severe metal artifacts in the pelvic and perianal region (16). Pelvic CT scans of patients with hip prostheses show a significant decrease in the quality of images of the AC, distal rectum, perirectal adipose tissue, and middle and lower segments of the rectum due to the metal artifacts (17). On the other hand, with the use of the MAR technique, a significant increase in the quality of images of the same regions and significant improvements in subjective and objective evaluation parameters are observed. In their experimental study, Morsbach et al. (16) reported that the image quality was improved using the MAR technique and it was especially useful in determining HU values in soft tissue. In our study, after a statistically significant decrease in the noise values obtained from the bone and muscle structures in proximity and the bladder using IR together with the MAR technique, it was observed that there was a significant improvement in the image quality of all pelvic organs. It was observed that there was no significant difference in the noise values obtained only from the distal subcutaneous adipose tissue. Accordingly, it was observed that the use of the IR+MAR approach did not affect the quality of the image of the distal subcutaneous adipose tissue.

The use of CT in the evaluation of infected perianal fistulas and abscesses has recently become widespread. Perineal USG and endorectal USG are frequently used in the evaluation of these patients admitted to the emergency services, but these procedures are not preferred since they are too painful. On the other hand, long MRI scan time in painful patients can be a difficult process for the patient to endure. Khati et al. (5) showed that CT could be an alternative in this patient group. However, the presence of hip prostheses is a hindering factor because of impairing the imaging of perianal tissues in these patients due to the artifacts (7). On the other hand, the use of the MAR technique makes it possible for these patients to be scanned with pelvic CT and increases the diagnostic value of CT by increasing the image quality.

The role of CT in the local staging of rectal cancers is very limited and has an accuracy of 70% (17). Therefore, pelvic MRI is more recommended among the non-invasive procedures (8,18). Maizlin et al. (19) showed the superiority of pelvic MRI over CT in local staging of rectal tumors. Tan and Iyer (20) demonstrated the superiority of MRI in showing local staging, lymph node involvement, mesorectal fascia, and surrounding tissue invasion. However, the inability to evaluate these patients, who cannot undergo MRI for various reasons and who have extensive artifact formation on conventional CT due to hip prosthesis, creates a major handicap. As a result, it is not possible to make an optimal radiological evaluation with MRI and conventional CT in this patient group. In this case, the CT scan using the MAR technique allows radiological evaluation. On the other hand, studies showing artifact reduction by using MAR technique in hip MRI have been published in the literature in recent years (21). Delli Pizzi et al. (4) reported that they could not evaluate patients with hip replacement in their MRI-supported study to evaluate the response to treatment in rectal tumors as well. Therefore, Liang et al. (8) recommended pelvic CT as a non-invasive procedure in this patient group. On the other hand, Ippolito et al. (22) reported that these patients who underwent pelvic CT could not be evaluated due to metal artifacts. CT using the MAR technique is also useful in these patients.

Especially with the aging of the population, the number of patients having rectal cancer with hip replacement is increasing (23). Non-invasive methods are required for local staging and postoperative follow-up in these patients (13,24,25). In cases where pelvic MRI cannot be performed and CT is taken, metal artifact distortions related to the prosthesis seen on CT can be eliminated by MAR methods and the diagnostic value of CT can be increased. Today, CT has been used more frequently in the postoperative follow-up of local recurrences and the radiological detection of anastomotic leaks (26,27). Widespread use of the MAR technique will further increase this frequency. Thus, a scan with CT has become possible not only in patients who cannot undergo MRI but also in other conditions demonstrated by the American College of Radiology where pelvic CT is indicated, including hip replacements (27).

In our study, we investigated whether there is a significant difference in image quality in terms of radiological evaluation by using the MAR technique in patients who underwent pelvic CT for other reasons and had hip prostheses. For this reason, none of our patients had rectal pathology. In the subjective evaluation made in our study, it was observed that the MAR technique provided powerful improvements in image quality in all AC, InR, MsR, PFT, and LAM examinations. It was observed that the average of the metal artifact visualization grade increased from 2 to 4. In the objective criteria evaluation, a significant decrease was observed in hypodense and hyperdense artifacts. It

was determined that there was a statistically significant decrease in noise values obtained from bone and soft tissue close to the prosthesis. Only the noise value measured from the subcutaneous adipose tissue, which is the furthest from the prosthesis, did not show a statistically significant difference.

Study Limitations

First, our study followed a retrospective study design with a small number of patients. Second, we did not use dual-energy CT for the examinations. Several studies have shown that metal artifact reduction with dual-energy CT is affected by the composition of the material used for prosthesis. In routine clinical practice, it is difficult to know the composition of the material. Third, the performance of various metal artifact reduction algorithms from different CT manufacturers may differ. Comparative studies analyzing these various algorithms may be needed. Finally, we evaluated the effect of MAR only in cases without pathology in the anorectal region. We believe that our study will be an inspiration and a cornerstone for prospective studies with larger series on the ability of MAR to evaluate pathological conditions and especially comparative prospective studies with MRI.

Conclusion

In pelvic CT using MAR, image quality and radiological evaluation efficiency are significantly increased compared to CT without MAR. CT together with MAR can be considered as an alternative approach in patients with hip prosthesis and anorectal pathologies, who cannot undergo pelvic MRI for various reasons. Therefore, it can be used as a non-invasive and effective method in the preoperative local staging of rectal cancers, in the diagnosis of inflammatory diseases, in the detection of localized fistulas in the pelvic region, in the follow-up of local recurrence and anastomotic leakage in patients with hip replacement surgery for rectal cancer.

Ethics

Ethics Committee Approval: All procedures performed in studies 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. Approval was granted by the Local Ethics Committee (date: 05.04.2021/no: 2021/04-653).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):144-149
DOI: 10.4274/BMB.galenos.2022.2022-02-015

Clinicopathological Features and Prognostic Factors in Patients with Small Bowel Adenocarcinoma

İnce Bağırsak Adenokarsinomlu Hastalarda Klinikopatolojik Özellikler ve Prognostik Faktörler

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Abstract

Objective: Small bowel adenocarcinoma is a rare tumor, and data on prognosis are limited. We aimed to evaluate the clinicopathological features and prognostic factors in small bowel adenocarcinoma in this study.

Method: Twenty-two patients were evaluated. Clinicopathological features and treatment approaches were retrospectively recorded. The Kaplan-Meier and Cox regression analyses were used to assess overall survival and prognostic factors.

Results: The origin sites of the tumor were the duodenum (50%), jejunum (31.8%), and ileum (18.2%), respectively. The number of *de novo* metastatic patients was 11 (50%). The most common metastatic sites were the peritoneum (%45), liver (%41), and lymph nodes (18%). The median overall survival was 19.9 months (7.3-32.5). One- and two-year survival ratios were 65.9% and 39%, respectively. The response ratio (complete or partial) of first-line chemotherapy in metastatic patients was determined as 46.2%. In multivariate analysis, surgery (p=0.024) and age at diagnosis (p=0.017) were statistically significant prognostic factors for overall survival. However, the site of the tumor (p=0.106), *de novo* metastatic disease (p=0.323), and the number of metastatic sites (p=0.086) were not.

Conclusion: Patients with small bowel adenocarcinoma were diagnosed in advanced stages, and the prognosis of the disease was poor. We observed that removing the primary tumor improved survival, and being older than 60 years was a negative prognostic factor.

Keywords: Chemotherapy, prognosis, small bowel adenocarcinoma

Öz

Amaç: İnce bağırsak adenokarsinomu nadir görülen bir tümördür ve prognozu ile ilgili veriler sınırlıdır. Bu çalışmada ince bağırsak adenokarsinomlu hastalarda klinikopatolojik özellikleri ve prognostik faktörleri değerlendirmeyi amaçladık.

Yöntem: Yirmi iki hasta değerlendirildi. Klinikopatolojik özellikler ve tedavi yaklaşımları retrospektif olarak kaydedildi. Genel sağkalımı ve prognostik faktörleri değerlendirmek için Kaplan-Meier ve Cox regresyon analizleri kullanıldı.

Bulgular: Tümörün primer çıkış yerleri sırası ile duodenum (%50), jejunum (%31,8) ve ileum (%18,2) idi. *De novo* metastatik hasta sayısı 11 (%50) idi. En sık metastatik bölgeler sırası ile periton (%45), karaciğer (%41) ve lenf düğümleri (%18) idi. Medyan genel sağkalım süresi 19,9 aydı (7,3-32,5) idi. Bir ve iki yıllık sağkalım oranları sırasıyla %65,9 ve %39 olarak bulundu. Metastatik hastalarda birinci basamak kemoterapinin yanıt oranı (tam veya kısmi yanıt) %46,2 olarak tespit edildi. Çok değişkenli analizde cerrahi (p=0,024) ve tanı yaşı (p=0,017) genel sağkalım için istatistiksel olarak anlamlı prognostik faktörler olarak tespit edildi. Ancak primer tümör bölgesi (p=0,106), *de novo* metastatik hastalık (p=0,323) ve metastatik bölge sayısı (p=0,086) istatistiksel olarak anlamlı değildi.

Sonuç: İnce bağırsak adenokarsinomlu hastalara sıklıkla ilerlemiş hastalık ile tanı konulmuştu ve hastalığın prognozu kötüydü. Primer tümörün çıkarılmasının sağkalımı iyileştirdiğini ve tanı sırasında 60 yaşından büyük olmanın olumsuz bir prognostik faktör olduğunu tespit ettik.

Anahtar kelimeler: İnce bağırsak adenokarsinomu, kemoterapi, prognoz

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Cite this article as: Doğan İ, Taştekin D. Clinicopathological Features and Prognostic Factors in Patients with Small Bowel Adenocarcinoma. Bagcilar Med Bull 2022;7(2):144-149

Introduction

Small bowel tumors are rare and account for less than 1% of all cancers and approximately 2% of gastrointestinal tract tumors (1,2). Several theories have been proposed to explain the rarity of small bowel tumors. The small intestines have more fluid content and are exposed to less irritants, the bacterial load is less, and the protective effect of the lymphatic tissue may be one of the reasons for this less frequent tumor development (3-5). It can be seen with a large number of different types of tumors, including benign and malignant, in the small intestines. Malignant tumors of the small intestine are frequently adenocarcinoma, neuroendocrine tumors, and lymphomas. While adenocarcinoma is observed more frequently in the duodenum and jejunum, neuroendocrine tumors are more commonly diagnosed in the ileum (6). Due to its rarity, it was obtained from risk factors and registry analyses in patients with small bowel cancer. It has been stated that alcohol consumption, smoking, dietary characteristics, and Celiac disease pose a risk for the development of small bowel cancer (7-9). Small bowel cancers can present with very variable non-specific symptoms at diagnosis. Therefore, there is often a delay in its diagnosis. Abdominal pain, nausea, vomiting, weight loss, dyspepsia, and anemia-related symptoms may be associated with small bowel cancer. Moreover, patients may appear with intestinal obstruction and bowel perforation due to the difficulties and delay in diagnosis.

Surgery is the primary treatment for small bowel adenocarcinoma (SBA). Adjuvant or neoadjuvant treatments have not been clearly defined. For this reason, it is usually treated similarly to colon cancer. In this perspective, if there is lymph node positivity or T3 and T4 in tumors that have been surgically removed, adjuvant therapy is often given in routine practice. In metastatic disease, fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and irinotecan can be used in different combinations. There are insufficient data on the efficacy and safety of anti-EGFR (cetuximab or panitumumab) and anti-VEGF (bevacizumab and others) agents. Data on the efficacy and safety of immunotherapies have only just begun to be determined. Pembrolizumab was found to be ineffective in a phase 2 study that included previously treated patients with progressive SBA (10). Patients with SBA have a worse prognosis compared to patients with colon cancer. In this study, we aimed to examine the clinicopathological features and prognosis of patients with SBA followed in our clinic.

Materials and Methods

Patients and Data Collection

The data of patients diagnosed and treated in the single tertiary medical oncology outpatient clinic between 2015 and 2019 were reviewed retrospectively. Approval was obtained from the Local Ethics Committee at the İstanbul University, İstanbul Faculty of Medicine before the study (number: 232479). Patients were identified through the hospital information system. All patients with sufficient data were included in the study. Symptoms at the time of diagnosis, clinical (age, gender, stage, metastasis regions, etc.), pathological (tumor region, tumor type, grade, etc.), and treatment characteristics (type of surgery, adjuvant chemotherapy and radiotherapy, metastatic treatment regimens, responses, and adverse events) were recorded from patient files and hospital database. Tumor staging was performed according to the eighth TNM tumor staging system. According to the Eastern Cooperative Oncology Group system, the patient's performance status was determined.

Metastatic patients received different chemotherapy regimens for treatment in the first series. In the FOLFOX regimen, 5-fluorouracil 2.400 mg/m^2, oxaliplatin 85 mg/m^2 and calcium folinate 400 mg/m^2 were administered every two weeks. In the FOLFIRI regimen, 5-fluorouracil 2,400 mg/m^2, irinotecan 180 mg/m^2 and calcium folinate 400 mg/m^2 were administered every two weeks. In the XELOX, XELIRI regimen, capecitabine was administered at a dose of 1,000 mg/m^2 in the morning and evening for 14 days for a 21-day cycle, instead of the 5-fluorouracil. In addition, capecitabine was administered alone at a dose of 1,000 mg/m^2 for a period of 14 days and a 21-day cycle interval. Gemcitabine was given at a dose of 1,000 mg/m^2 on the 1st and 8th days of the 21-day cycle. In the FOLFOX + bevacizumab regimen, bevacizumab was administered at 5 mg/kg dose every 14 days. Treatment response evaluations were performed according to the response evaluation criteria in solid tumors (RECIST). The Common Terminology Criteria for Adverse Events Version 5.0 was used for treatment-related toxicity assessment. Univariate analysis was performed to evaluate the survival effect for all clinicopathological characteristics of the patients. Multivariate analysis was performed for prognostic variables that were found to be

statistically significant in univariate analysis or statistically significant in the literature.

Statistical Analysis

SPSS 25 (IBM, USA) was used for statistical analysis. Descriptive analysis was performed for all variables. For continuous variables, minimum and maximum values were specified, along with the median value. Categorical variables were indicated by numbers and percentages. A log-rank test was performed for survival analysis, and the Kaplan-Meier curve was drawn. The Cox-regression model was applied for univariate and multivariate analysis.

Results

Clinicopathological Features and Treatment Data

Twenty-two patients with small bowel cancer were included in the study. All patients were in the adenocarcinoma histological subtype. The median age was 57 years (27-80). The ratio of males/females was 1.45. The most common symptom in the presentation was pain (50%), and 18% of the patients had ileus. The origin sites of the tumor were the duodenum (50%), jejunum (31.8%), and ileum (18.2%). The number of *de novo* metastatic patients was 11 (50%). Sixteen (72.7%) of the patients underwent surgery. The most common metastatic site was the peritoneum (45%). Clinicopathological characteristics of the patients are presented in Table 1.

Metastatic disease developed in five patients during follow-up, and a total of 16 (72.7%) patients were evaluated for metastatic treatment.

The most commonly used chemotherapy combinations were FOLFOX or XELOX (37.6%), and the second most commonly used regimens were FOLFIRI or XELIRI (12.6%). The disease control rate (complete response, partial response, and stable disease) was determined as 53.8%. Table 2 presents the treatment approach of the patients. The most common hematological side effects included anemia and thrombocytopenia. Non-hematological side effects were nausea and fatigue.

Survival Outcomes and Prognosis

The median follow-up was 14.7 (0.4-72.3) months, and the median overall survival (OS) was defined as 19.9 (7.3-32.5) months. One- and two-year survival ratios were 65.9% and 39%, respectively (Figure 1). In multivariate analysis, surgery (no vs. yes) [p=0.024, hazard ratio: 0.14, 95% confidence interval (CI)] and age at diagnosis (<60 vs. ≥60) (p=0.017, hazard ratio: 11.2, 95% CI) were statistically significant prognostic factors for OS. However, the site of the tumor (p=0.106), *de novo* metastatic disease (p=0.323), and the number of metastatic sites (p=0.086) were not. Table 3 shows the results of univariate and multivariate analyses.

Discussion

In this study, we showed the clinicopathological features of the patients and parameters affecting the prognosis in patients with SBA. Considering data of our study, we found that SBA was seen around the age of 60 years. In our patients, adenocarcinoma of the small intestine was most frequently detected in the duodenum (50%). In a retrospective analysis conducted by Halfdanarson et al. (11), the patient characteristics were similar to our study. The median age of the patients was 62 years, and the tumor localization was in the duodenum, jejunum, and ileum at the rates of 57%, 29%, and 10%, respectively (11). In another study published by Dabaja et al. (12), which included a large number of patients, the median age was 52 years, the most common tumor localization was the duodenum (52%), and 35% of the patients had metastatic disease at diagnosis.

Table 1. Clinicopathological characteristics of the patients

	Number of patients Total number: 22	%
Gender		
Male	13	59
Female	9	41
Tumor localization		
Duodenum	11	50
Jejunum	7	31.8
Ileum	4	18.2
Stage at diagnosis		
Stage 1	1	4.5
Stage 2	3	13.7
Stage 3	7	31.8
Stage 4	11	50
Surgery (primary or palliative) at diagnosis	16	72.7
Yes	6	27.3
No		
Adjuvant chemotherapy after primary surgery		
Yes	11	11
No	11	11
Recurrence after primary surgery		
Yes	6	55
No	5	45
Metastatic sites		
Peritoneum	10	45.5
Liver	9	41
Lymphadenopathy	4	18
Other sites	2	9.1

Table 2. Treatment features of the metastatic patients

	Number of patients (Total number: 16)	%
The first-line chemotherapy regimen		
FOLFOX or XELOX	6	37.6
FOLFIRI or XELIRI	2	12.6
FOLFOX + bevacizumab	1	6.2
FOLFOXURI	1	6.2
Gemsitabin + capecitabine	1	6.2
Gemcitabine	1	6.2
Capecitabine	1	6.2
No therapy	3	18.8
Response ratios of first-line chemotherapy		
Complete response	2	15.3
Partial response	4	30.8
Stable disease	1	7.7
Progression	6	46.2
Grade 1-2 toxicity		
Yes	10	76.9
No	3	23.1
Grade 3-4 toxicity		
Yes	2	15.4
No	11	84.6

Table 3. Univariate and multivariate analyses of prognostic factors for overall survival

	Univariate analysis	Multivariate analysis	
	p	p	Hazard ratio 95% CI
Age (year) <60 vs. ≥60	0.226	0.017	11.2 (1.5-81.8)
Gender Male vs. female	0.784		
Ileus at diagnosis Yes vs. no	0.367		
Primary tumor localization	0.202	0.106	
Tumor grade	0.537		
***De novo* metastatic disease** Yes vs. no	0.328	0.323	
Surgery at diagnosis No vs. yes	0.023	**0.024**	**0.14 (0-0.57)**
Number of metastatic sites	0.982	0.086	

Multivariate analysis p-value: 0.03, CI: Confidence interval

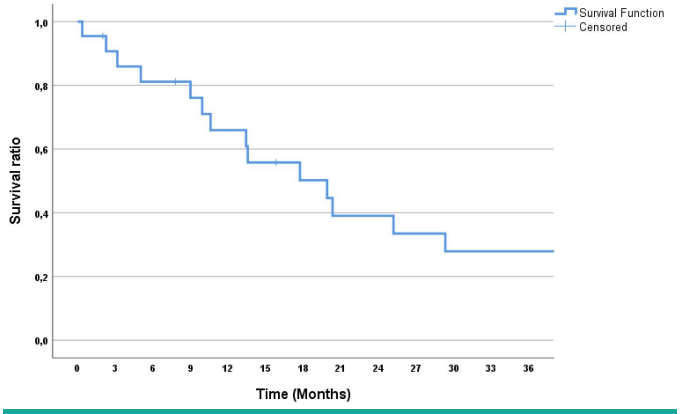

Figure 1. Kaplan-Meier curve for overall survival

Since there is no randomized study for treating patients with SBA, fluoropyrimidine-based therapies are frequently used in the treatment, similar to colon cancer. A phase 2 study published by Xiang et al. (13) showed that the FOLFOX regimen was effective and well-tolerated in patients with advanced SBA. Our patients received more frequently oxaliplatin or irinotecan regimens combined with fluoropyrimidine as chemotherapy. In a multicenter study published by Tsushima et al. (14), in which 132 patients with unresectable SBA were included, the combination of oxaliplatin and fluoropyrimidine was found to be the most promising first-line chemotherapy regimen compared to other chemotherapy regimens. In a multicenter study that included 93 patients published by Zaanan et al. (15), the FOLFOX regimen was found to be more effective than the combination of fluorouracil and cisplatin. In addition, patients' baseline performance scores, CEA, and CA19-9 levels were determined as independent predictive factors for disease-free survival and OS (15). The addition of bevacizumab to the XELOX regimen was found to be effective in a phase 2 study conducted by Gulhati et al. (16), which included 30 patients. However, in a multicenter study of 28 patients published by Aydin et al. (17), adding bevacizumab to the FOLFOX or FOLFIRI regimens did not provide a benefit in terms of disease prognosis.

Patients with SBA have a poor prognosis. Due to delays in diagnosis, most of the patients present in the metastatic stage. Half of the patients had metastatic disease at the time of diagnosis in our study. The median OS was less than two years in the patients. Few studies have examined the prognostic factors in patients with SBA. In our study, patients over the age of 60 years were found to have a higher risk in terms of OS than those younger than 60 years. In addition, patients who did not undergo surgery (primary or palliative) at the time of diagnosis were found to have a poor prognosis. In a study by Aparicio et al. (18), including patients nationwide, the median OS

time of patients with metastatic SBA was found to be 12.7 months, and tumor grade and T-stage were determined as prognostic factors. A retrospective analysis that included a large number of patients by Halfdanarson et al. (11) showed that older age, advanced tumor stage, and a lymph node positivity ratio of 50% or greater were statistically significant factors affecting survival. In a retrospective study including 78 patients, postoperative margin positivity was identified as an independent prognostic factor, and the benefit of adjuvant therapy was not found (19). Contrary to this study, in a study published by Akce et al. (20), it was found that adjuvant chemotherapy improved OS. In another study published by Sakae et al. (21), the presence of symptoms at the time of diagnosis, poor performance status, low albumin level, high CEA level, and LDH level were defined to be poor prognostic factors.

Study Limitations

There were some limitations in our study. Our study was retrospective and included a heterogeneous patient group. The number of patients was small because it is a rare tumor.

Conclusion

Due to the delay in diagnosis, the patients were diagnosed in advanced stages, and the disease was showed a poor prognosis. We observed that removing the primary tumor improved survival, and being older than 60 years was a negative prognostic factor. Also, we detected that tumor localization and *de novo* metastatic disease did not affect OS. To the best of our knowledge, our study is a rare study to describe the characteristics and treatment features of patients with SBA in the Turkish population. It contains essential information about the treatment processes and prognoses of patients with SBA, which seems to be rare. To diagnose and treat SBA more effectively, multicenter randomized controlled studies with large numbers of patients are needed in the future.

Ethics

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee at the İstanbul University, İstanbul Faculty of Medicine before the study (number: 232479).

Informed Consent: For this type of research, informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.D., D.T., Design: İ.D., D.T., Data Collection or Processing: İ.D., D.T., Analysis or Interpretation: İ.D., D.T., Writing: İ.D., D.T.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):150-157
DOI: 10.4274/BMB.galenos.2022.2022-04-035

Our Anesthesia Experience in Catheterization and Angiography Procedures in the Cardiac Catheterization Laboratory in Pediatric Patients with Congenital Heart Disease: Single Center 360 Cases

Konjenital Kalp Hastalığı Olan Pediyatrik Olgularda Kardiyak Kateterizasyon Laboratuvarında Kateterizasyon ve Anjiyografi İşlemlerinde Anestezi Deneyimlerimiz: Tek Merkez 360 Olgu

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Abstract

Objective: Pediatric cardiac catheterization and angiography are two of the methods used in the diagnosis and treatment of patients with congenital heart disease. Anesthesia approaches in these patients are special and come with many anesthetic challenges. In this framework, the objective of this study is to evaluate our anesthesia experience and complications in catheterization procedures performed in the pediatric angiography laboratory.

Method: This study was conducted with patients who underwent diagnostic or interventional catheterization in the pediatric angiography laboratory, between August 1st, 2020, and December 31st, 2021. Demographic and clinical characteristics of these patients, including their cardiac diagnosis, gender, weight, procedural characteristics, and anesthesia management principles employed during the procedure and complications, were evaluated.

Results: A total of 390 procedures were applied to 360 patients during the period covered by the study. The median age and weight of these patients were three months [interquartile range (IQR) 20 days-7 years)] and 7 kg (IQR 3.4-24), respectively. Of these patients, 51% were male, and 49% were female. Of the 390 procedures, 134 were performed diagnostically, and 256 were performed invasively. The median duration of the procedure was 35 minutes (IQR 25-60). The catheterization procedure was performed under general anesthesia in 33% of the cases. A total of 52 (13.3%) complications were observed during the procedures. During

Öz

Amaç: Pediyatrik kardiyak kateterizasyon ve anjiyografi konjenital kalp hastalıklı olgularda tanı ve tedavi amacıyla kullanılan yöntemlerden ikisidir. Bu olgularda anestezi yönetimi özeldir ve pek çok anestezik zorluklarla birliktedir. Bu çalışmada, konjenital kalp hastalığı tanısı almış pediyatrik olgularda kateterizasyon işlemlerinde anestezi yönetim deneyimlerimizin ve komplikasyonların değerlendirilmesi amaçlandı.

Yöntem: Çalışma 1 Ağustos 2020-31 Aralık 2021 tarihleri arasında pediyatrik anjiyografi laboratuvarımızda tanısal veya girişimsel amaçlı kateterizasyon işlemi yapılan olgular üzerinde gerçekleştirildi. Olguların kardiyak tanısı, cinsiyet, ağırlık, işlem özellikleri, işlem sırasındaki anestezi yönetim ilkeleri ve gerçekleşen komplikasyonları incelendi.

Bulgular: Çalışma döneminde 360 olguya 390 işlem uygulandı. Olguların medyan yaşı 3 ay [çeyrekler arası aralık (ÇAA) 20 gün -7 yıl] ve medyan ağırlığı 7 kg (ÇAA 3,4-24) idi. Olguların %51'i erkek ve %49'u kızdı. Üç yüz doksan prosedürün 134'ü tanısal olarak ve 256'sı invaziv olarak gerçekleştirildi. Medyan işlem süresi 35 dakika (ÇAA 25-60) idi. Kateter işlemleri olguların %33'ünde genel anestezi altında gerçekleştirildi. İşlemler sırasında toplam 52 (%13,3) komplikasyon gözlendi. Anestezi yönetimi sırasında 17 olguda hipotansiyon, 10 olguda desatürasyon, 7 olguda ritim bozukluğu gelişti. İşlem sırasında iki hastada ekstrakorporeal membran oksijenasyonu desteğine ihtiyaç duyuldu. Dört hasta acilen ameliyat edildi. İşlem nedeniyle hiçbir hasta kaybedilmedi.

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Cite this article as: Özcanoğlu HD, Gümüş Özcan F. Our Anesthesia Experience in Catheterization and Angiography Procedures in the Cardiac Catheterization Laboratory in Pediatric Patients with Congenital Heart Disease: Single Center 360 Cases. Bagcilar Med Bull 2022;7(2):150-157

Abstract

the anesthesia management, hypotension was observed in 17 patients, desaturation in 10 patients, and rhythm disturbances in 7 patients. Two patients needed extracorporeal membrane oxygenation support during the procedure. Four patients had to be operated on urgently. No patient was lost due to the procedure.

Conclusion: Anesthesia management is characteristic during the catheterization procedure in pediatric cases with congenital heart disease. A case-specific anesthesia approach should be preferred, taking into account factors such as the type of cardiac pathology, hemodynamic characteristics, and type of procedure.

Keywords: Anesthesia, cardiac catheterization, child, complication

Öz

Sonuç: Konjenital kalp hastalıklı pediyatrik olgularda kateterizasyon işlemleri anestezi yönetimi özellik gösterir. Kardiyak patolojinin türü, hemodinamik karakteristikler, prosedür şekli gibi faktörler göz önünde bulundurularak olguya özel anestezi yaklaşımı tercih edilmelidir.

Anahtar kelimeler: Anestezi, çocuk, kalp kateterizasyonu, komplikasyon

Introduction

Congenital heart diseases refer to a group of heterogeneous diseases featuring various pathologies and subgroups and are among the primary causes of mortality and morbidity in pediatric cases. Timely and accurate diagnosis and appropriate treatment approaches are critical in order to increase the chance of survival in these cases (1,2).

Electrocardiography (ECG) and echocardiography (ECHO) are the most frequently used diagnostic methods in the evaluation of cardiac diseases in children. In cases where these methods do not produce satisfactory results, cardiac catheterization and angiography may be performed for diagnostic or interventional purposes (3). However, given that the heart's anatomy may be evaluated with high sensitivity and specificity also by other methods such as computed tomography (CT) and magnetic resonance imaging in pediatric cases, catheterization procedures are performed more frequently for interventional purposes than for diagnostic purposes. Interventional procedures include many different techniques such as the closure of defects, electrophysiological studies and ablation, balloon atrial septostomy, percutaneous pulmonary valve replacement, balloon valvuloplasty (aortic or pulmonary), and stent placement in the patent ductus arteriosus (3,4).

The goals of anesthetic management during pediatric cardiac catheterization include to provide adequate sedation, analgesia, immobility, and hemodynamic stability. Cardiac catheterization in children with congenital heart disease can be performed under general anesthesia or through the administration of sedoanalgesia with oxygen support. Many factors, such as the characteristics of pediatric patients and the variety of procedures to be performed, affect anesthesia management. Furthermore, the choice of various anesthetic agents according to the nature of the procedure and the type of primary cardiac pathology creates additional difficulties (5).

The objective of this study is to evaluate our experience in anesthesia management and complications in catheterization procedures performed in the pediatric angiography laboratory context of pediatric patients diagnosed with congenital heart disease.

Materials and Methods

Population and Sample

The population of this retrospective study consisted of patients with congenital heart disease younger than 18 years of age who underwent cardiac catheterization and angiography in the pediatric angiography laboratory between August 1st, 2020 and December 31st, 2021. Prematurely born patients, patients older than eighteen years old, those who underwent angiography due to electrophysiological studies, those whose records could not be accessed, and those who were initially operated under extracorporeal membrane oxygenation (ECMO) were excluded from the study. The study protocol was approved by the Local Ethics Committee and carried out in accordance with the principles outlined in the Declaration of Helsinki (University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital 2022.03.84).

The decision for cardiac catheterization and angiography was taken upon the evaluation of the results of detailed physical examination and cardiac examinations (ECG, teleradiography, ECHO) of each hospitalized patient by the pediatric cardiologist. All patients were evaluated preoperatively by a pediatric cardiac anesthetist. Patients' legal guardians were informed in detail about the advantages and disadvantages of the procedure and the complications that might be encountered. One unit

of erythrocyte suspension was prepared for use in cases deemed necessary.

Anesthetic Approach and Procedural Characteristics

All procedures were carried out in the pediatric angiography laboratory, under sterile conditions, using the Philips Biplane Azurion 7 B12/12 (Philips Medical Systems International B.V., Best, Netherlands) image-guided therapy system. The procedure was performed with appropriate positioning under sterile conditions and general anesthesia (laryngeal mask or intubation) or sedoanalgesia and with sheaths and catheters of appropriate size for the planned procedure. The percutaneous technique was used for the intervention. Right heart catheterization was performed via the femoral vein, and left heart catheterization was performed via the femoral artery. Sometimes other axillary carotids, umbilical artery, or vein routes were preferred according to the technique used to perform the procedure. In all cases except the cases under two months old, punctures were performed with the support of ultrasonography.

All patients were monitored with ECG, peripheral oxygen saturation, arterial blood pressure, temperature, and urine analysis during the procedure. In addition, near-infrared spectroscopy monitoring of regional cerebral oxygenation was performed in all newborn cases. Advanced life support devices (ECMO), and necessary vasoactive inotropic medications, infusion pumps were on standby in the operating room. All patients were premedicated using diphenhydramine and dexamethasone after establishing vascular access in order to prevent possible allergic reactions due to the contrast agent. Oxygen was provided via mask as 2-4 liters/minute. All patients were actively heated to prevent hypothermia. General anesthesia was administered to patients who were to undergo interventional procedures such as pulmonary valve replacement, patent ductus arteriosus (PDA) stent, atrial septal defect (ASD), and ventricular septal defect (VSD) closure. General anesthesia was induced with hypnotic agents combination, usually composed of 0.1 mg/kg midazolam, 1-2 mg/kg ketamine, 0.5-3 mg/kg propofol and neuromuscular blocking agent esmeron 0.6 mg/kg. Sevoflurane 1-2% was used for anesthesia maintenance. Sedoanalgesia was preferred in diagnostic cases where general anesthesia was not required. Sedoanalgesia was induced either by bolus injection or infusion of 0.1 mg/kg midazolam, 1-2 mg/kg ketamine and 0.5-3 mg/kg propofol or 0.05 mcg/kg/min remifentanil combination. Targeted sedation level for the procedures was considered according to the Ramsay sedation score (RSS) 4 (6); 1-Patient is anxious, agitated, or restless. 2. Patient is co-operative, oriented, and calm. 3. Patient is responsive to verbal command only. 4. Patient exhibiting brisk response to light glabellar tap or to an auditory stimulus. 5. Patient exhibiting a sluggish response to light glabellar tap or to an auditory stimulus. 6. No response to any of these stimulation). Airway security was provided by orotracheal intubation or laryngeal mask if targeted sedation level was not satisfactory.

Definitions

A data form was created and then filled out for each patient using their data available in the hospital data system, including age, gender, weight, diagnosis, type of procedure performed, American Society of Anesthesiology risk score (ASA), Catheterization Risks in Pediatrics (CRISP) score (7), procedural data, anesthetic approaches, agents used, and anesthetic complications observed during the procedure.

Life-threatening complications such as death, permanent rhythm problems, bleeding requiring blood transfusion, desaturation or respiratory arrest, presence of hypotension requiring the use of inotropes, cardiac perforation, stent embolization, complications requiring rushing into surgery were categorized as major complications, and complications requiring switching to ECMO support and non-life-threatening complications such as transient rhythm disturbance, hypotension not requiring the use of inotropes, laryngospasm, and allergic reactions were categorized as minor complications. Any death that occurred within the first 24 hours after the completion of cardiac catheterization and angiography was deemed procedurerelated death.

Desaturation was defined as having more than a 10% decrease compared to the baseline SpO_2 (peripheral capillary oxygen saturation) value, whereas hypotension was defined as having more than a 20% decrease compared to the baseline blood pressure. The arrhythmias were categorized as asystole, sinus bradycardia, conduction abnormalities (complete atrioventricular block), supraventricular arrhythmias (supraventricular tachycardia, atrial fibrillation, atrial flutter, or focal atrial tachycardia), and ventricular tachycardia, or ventricular fibrillation (8,9).

Statistical Analysis

The distribution of the research data was classified in the computer environment, and descriptive values were

obtained using the SPSS (Statistical Package for the Social Sciences for Windows) software package. Results were expressed as median [(interquartile range (IQR)] and percentage-percentile values.

Results

Cardiac catheterization and angiography were performed in 360 patients (45 emergent cases), of whom 184 were male and 176 were female, during the period covered by the study. The median age and weight of these patients were three months (IQR 20 days-7 years) and 7 kg (IQR 3.4-24), respectively. According to ASA scoring, 12% of the patients were in ASA II, 36% in ASA III, and 52% in the ASA IV category. Two percent of the patients had a history of allergy.

The most common diagnoses were pulmonary artery atresia (PAA) (n=78), tetralogy of Fallot (TOF) (n=44), PDA (n=36), and hypoplastic left heart syndrome (HLHS) (n=34). Detailed information about patient diagnoses is given in Table 1. Of the 390 procedures evaluated within the scope of this study, 256 (65.6%) were interventional, and 134 (34.3%) were diagnostic procedures. The most common interventional procedures were PDA stent placement and PDA closure. Evaluation of the pulmonary artery and its branches due to TOF was the most common reason for performing the diagnostic cardiac catheterization procedures. The list of diagnostic and interventional procedures performed is given in detail in Table 2.

Table 1. Diagnoses of the patients who underwent cardiac catheterization

	n	%
Tetralogy of fallot	44	12.2
Complex pathologies	18	5
Atrial septal defect	28	7.7
Patent ductus arteriosus	36	10
Ventricular septal defect	10	2.7
Double outlet right ventricle	21	5.8
Pulmonary atresia	78	21.6
VSD-PA	36	10
Tricuspit atresia-PA	4	1.1
IVS-PA	6	1.6
With complex pathologies	32	8.8
HLHS	34	9.4
TAPVR	8	2.2
Pulmonary stenosis	25	6.9
Tetralogy of fallot-absence of pulmonary valve	3	0.8
Coarctation of aorta	12	3.3
Interrupted aortic arch	8	2.2
Aortic stenosis	3	0.8
Shone-aortic stenosis	4	1.1
TGA or taussig bing anomaly	16	4.4
Total	360	100

VSD-PA: Ventricular septal defect pulmonary atresia, IVS-PA: Pulmonary atresia with intact ventricular septum, HLHS: Hypoplastic left heart syndrome, TGA: Transposition of great arteries, TAPVR: Total anomalous pulmonary venous return

Anesthesia Methods

Cardiac catheterization was performed under general anesthesia in 33% of cases (n=119). Orotracheal intubation and LMA were preferred for airway in 12% and 21% of cases, respectively. Sedoanalgesia was used in 67% of cases (n=241). The most common drug combination for sedoanalgesia was midazolam and remifentanil. Anesthetic methods and agents are shown in Table 3.

Twenty-seven cases had a genetic syndrome. Six cases experienced difficult intubation even they were intubated without complication. Invasive arterial monitorization was performed in 32 cases (9%). In 51 cases (14%), the CRISP score category was >3.

Table 2. List of the procedures performed on the cases

Procedure	n	%
Diagnostic	134	34.3
Interventional	256	65.6
ASD closure	28	7.1
PDA closure + MAPCA closure	1	0.2
PDA closure	35	8.9
VSD closure	3	0.6
PDA stenting	66	16.9
Balloon atrial septostomy	16	4.1
Balloon atrial septoplasty and PDA stenting	8	2
Pulmonary balloon valvuloplasty	24	6.1
Aortic balloon valvuloplasty	3	0.7
Aortic arch stenting	1	0.2
Balloon coarctation angioplasty	10	2.5
Stenting of coarctation of the aorta	4	1
Pulmonary balloon angioplasty + PDA stenting	1	0.2
Percutaneous pulmonary valve implantation	9	2.3
RVOT stenting in infants	11	2.8
Sequestering artery/MAPCA closure	7	1.8
Other procedures	29	7.4
TOTAL	390	100

ASD: Atrial septal defect, RVOT: Right ventricular outflow tract, PDA: Patent ductus arteriosus, MAPCA: Major aortopulmonary collateral arteries, VSD: Ventricular septal defect

Complications

A total of 45 (11.5%) complications were observed during the procedures. Of these complications, 29 (7.4%) were classified as major, and 23 (5.9%) were classified as minor complications. Two neonatal patients received ECMO support during the procedure. One of these patients was the patient whose PDA was closed during PDA stenting due to VSD-pulmonary atresia, and the other was the patient who was followed up with the diagnosis of HLHS and developed ventricular fibrillation and cardiac arrest during balloon atrial septostomy.

Four patients developed complications during the procedure, requiring them to be rushed into surgery. Two of these patients had hypoxic spells due to TOF, and the other two required an emergency shunt surgery due to PAA. During the anesthesia management, hypotension was observed in 17 patients, 9 of whom required the administration of inotropes, low saturation was observed in 10 patients, and rhythm disturbances were observed in 7 patients. No patient died during the procedure and within the first 24 hours after the procedure. The major and minor complications the patients developed during the procedure are summarized in Table 4.

Table 3. Anesthesia management in catheterization procedures

Local anesthesia + sedation	241 (67)
General anesthesia	119 (33)
Endotracheal intubation	43 (12)
Laryngeal mask airway	76 (21)
Genetic syndrome	27 (7)
Difficult intubation	6
Sedo-analgesic medications	
Midazolam-propofol	41 (17)
Midazolam-ketamine	52 (22)
Remifentanil-midazolam	107 (44)
Dexmedetomidine	18 (7)
Ketamine-propofol	23 (10)
Invasive artery monitoring	32 (9)
CRISP score category >3	51 (14)
Urgent procedure	45 (13)
Total fluid volume (mL)	60 (40-90)
Transfer to pediatric cardiac intensive care unite	70 (19)

n (%) or median interquartile range

Discussion

In this study, we aimed to share our experiences and complications by evaluating our anesthesia management approaches in 360 pediatric patients with congenital heart disease where diagnostic and interventional cardiac catheterization procedures were performed. In this retrospective study, we observed that general anesthesia and sedoanalgesia approaches could be applied safely

Table 4. Complications, treatments and clinical outcomes

MAJOR	n	TREATMENT	OUTCOME
Stent embolization	8	The stent of 1 patient was snared and removed, then the procedure continued.	Discharged
		2 patients underwent emergency surgery.	Discharged
		The stents of 4 patients were fixed with a second stent or a balloon.	Discharged
		1 patient supported with ECMO	Discharged
Spell	2	Underwent emergency surgery.	Discharged
	2	Transferred to the ICU.	Discharged
Arrhythmia	2	1 patient received CPR.	Discharged
		1 patient supported with ECMO	25th day exitus (HLHS)
Anemia due to excessive bleeding	2	ES transfused.	
Hypotension	9	Inotropic support was increased	
Desaturation	4	Endotracheal intubation and increased oxygen supply	
MINOR			
Hypotension	8		
Vascular complications	7	Heparin infusion was initiated.	
Desaturation	2	Corrected after stenting or balloon.	
Arrhythmia	5	Corrected by catheter manipulation.	
Allergy	1	Corrected with diphenhydramine and dexamethasone.	

CPR: Cardiopulmonary resuscitation, ECMO: Extracorporeal membrane oxygenator, HLHS: Hypoplastic left heart syndrome

in selected patients and procedures by using appropriate anesthetic agent combinations. It was determined that most cardiac catheterization and angiography procedures were performed for interventional purposes with acceptable complication rates. This study is one of the few studies conducted in Turkey, which has investigated the anesthesia management efficiency in the context of pediatric patients with congenital heart disease.

Several factors should be considered in the perioperative anesthetic management of the catheterization procedure in pediatric cases with congenital heart diseases. For this reason, patients' detailed history, cardiac pathology, genetic syndromes, allergy and bronchospasm history should be obtained. Also, cyanotic seizures should be questioned. Subsequently, anesthetic approach should be determined according to the physiological and anatomical characteristics of heart disease. In addition, it is necessary to have sufficient information about the pharmacodynamic and pharmacokinetic aspects of the medications used by the patients or to be used during the procedure (5).

Congenital heart diseases have increased risks during anesthesia. Myocardial ischemia and cardiac arrest can occur suddenly in patients with single ventricle physiology even after anesthesia induction and positive pressure ventilation. We have not experienced cardiac arrest after anesthesia induction and positive pressure ventilation.

Positive pressure ventilation under general anesthesia provides airway safety and control of $PaCO_2$, but increased intrathoracic pressure may alter hemodynamic stability. Spontaneous ventilation mimics natural intrathoracic physiology and, consequently, may result in more stable hemodynamic data. However, oversedation can cause airway obstruction, hypoventilation and subsequent respiratory acidosis. These factors increase pulmonary vascular resistance and might alter shunt physiology and affect hemodynamic measurements. Although general anesthesia and sedation protocols were applied at different rates in the studies, there is a tendency toward sedoanalgesia. Tokel et al. (10) reported general anesthesia as low as 2% in their study. Similarly, in the studies of İyilikçi et al. (11), they applied sedoanalgesia in more than half of the cases. In comparison, in this study, the rate of general anesthesia was reported to be as high as 33%. Our study's high rate of general anesthesia, compared to other studies, is probably related to high intervention rates. The recent technological developments have allowed performing many diagnostic or interventional procedures on pediatric cases with a variety of heart diseases. In parallel, the percentage of cardiac catheterization and angiography procedures performed due to interventional purposes has started to increase due to the developments in non-invasive imaging methods such as ECHO, CT, and magnetic resonance angiography. As a matter of fact, compared to the rates of interventional procedures reported by Tokel et al. (10) and Shim et al. (12), which are 30% and 50%, respectively, the rate of interventional procedures was found as 65.6% in this study.

Interventional procedures have significant advantages such as less invasiveness, shortened length of hospital stay, re-applicability, and provision of both palliation and cure (3,13). Among the procedures applied for therapeutic purposes in pediatric cases reported in the literature are balloon atrial septostomy, aortic coarctation balloon angioplasty, pulmonary and aortic valve valvuloplasty, stenting of the PDA, radiofrequency pulmonary valve perforation, right ventricular outflow tract velocity stent ASD closure, PDA closure and VSD closure (3,11-19). In comparison, in this study, interventional procedures were most commonly performed for stenting of the PDA. This finding can be attributed to the fact that the patients followed up in the cardiovascular surgery center, where this study was conducted, were predominantly those diagnosed with PAA or HLHS.

Different sedative and analgesic medications are preferred during catheterization. Ketamine, dexmedetomidine, propofol, midazolam, and fentanyl are the most commonly used agents. A case-based approach is recommended in the selection of medications. Senzaki et al. (20) have stated that dexmedetomidine is a better option in cardiac patients (especially infants) who have hypercyanotic seizures. Benzodiazepines may produce dose-related respiratory depression. This effect may be more pronounced in patients with congenital heart disease and when benzodiazepines are used in combination with opioids. Choice of medication should be made considering all these effects. Oklu et al. (21) compared propofol and ketamine infusion for cardiac catheterization. They reported no change with the use of ketamine, whereas a decrease in systemic vascular resistance resulted in increased right-to-left shunting with the use of propofol. Additionally, Akin et al. (22) stated that they could manage catheterization procedures with minimal side effects when they used ketamine and propofol in combination. Similar to the relevant studies available in the literature, the method of anesthesia management was decided based on a case-based approach in our study. Accordingly, midazolam-propofol, midazolam-

ketamine, remifentanil-midazolam, and dexmedetomidine and ketamine-propofol combinations were preferred considering the clinical and cardiac problems of the patient and the type of procedure to be performed.

Hypovolemia might be present at the initiation of the catheterization, particularly in small infants and children, secondary to dehydration after prolonged periods of preoperative fasting. Hypovolemia is particularly important in newborns and patients with cyanosis or shunt-dependent lesions. In our study, considering these factors, necessary fluid infusion was done and hypovolemia was tried to be prevented (9).

Complication rates in pediatric cardiac catheterization and angiography depend on patients' diagnosis and procedure itself. Demographic and clinical characteristics such as age, weight, clinical condition at the time of the intervention, the type of underlying disease, whether the catheter procedure is diagnostic or interventional, anesthesia management, and the skill and experience of the cardiologist are factors in complication risks (11-13). Complications range from minor complications to complications requiring emergency open-heart surgery, complications leading to persistent severe sequelae, or even death. The catheterization-related complication rates in pediatric patients reported in the literature range from 2% to 40% (15). In a study, it was stated that the most common complication in the general population was vascular problems and that the vascular problems were even more pronounced in the neonatal age group (16). Kaya et al. (17) reported the complication rate as 5.8% in their series of 120 cases, whereas Bergensen et al. (18) reported complication rates between 7% and 25% in their prospective multicenter study. In comparison, in this study, the overall complication rate was determined as 13.3%. No patient died during or within the first 24 hours after the procedure.

Complications due to sedation and anesthesia or unexpected complications can be seen in catheterization procedures. Lin et al. (19) reported hypotension, which was seen in 0.68% of their cases, as the most critical complication of anesthesia management in their series. There are also studies in which hypotension has been described as a low-risk, self-correcting condition with no permanent consequences (19). Along these lines, Tokel et al. (10) reported anesthesia-related complications, which were seen in 6% of the 2.662 catheterization procedures evaluated within the scope of their study, as the most critical complication. They attributed this result to the very low rates of general anesthesia in their cases. In the series of 1535 cases by İyilikçi et al. (11), the rate of anesthesia-related complications, which primarily consisted of laryngospasm (n=3), desaturation (n=18), transition to general anesthesia (n=5), and hypotension (n=19), was reported as 2.9% (n=45). In comparison, the primary anesthesia-related complications in this study were hypotension and desaturation, which were observed in 4.3% and 2.5% of the cases, respectively. Apart from this, there was no major complication related to anesthesia.

Study Limitations

The study's primary limitation is that it was carried out as a retrospective and single-center study and with a limited number of patients. Another limitation is that different methods have been adopted in the anesthesia management of patients due to the complexity of cardiac pathologies.

Conclusion

Anesthesia management is an essential part of the catheterization procedure in pediatric patients with congenital heart disease. General anesthesia and sedoanalgesia can be safely applied using an appropriate combination of meticulously titrated anesthetics. A case-specific anesthesia approach should be preferred, considering the type of cardiac pathology, hemodynamic characteristics, and type of procedure. Ensuring ideal anesthesia management led by the cardiac anesthesiologist and adopting a multidisciplinary approach under adequate monitoring will help to reduce pediatric cases' catheterization-related morbidity and mortality rates.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee and carried out in accordance with the principles outlined in the Declaration of Helsinki (University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital 2022.03.84).

Informed Consent: All patients were evaluated preoperatively by a pediatric cardiac anesthetist. Patients' legal guardians were informed in detail about the advantages and disadvantages of the procedure and the complications that might be encountered.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: H.D.Ö., F.G.Ö., Design: H.D.Ö., F.G.Ö., Data Collection or Processing: H.D.Ö., Analysis or Interpretation: H.D.Ö., F.G.Ö., Drafting Manuscript: H.D.Ö., F.G.Ö., Critical

Revision of Manuscript: F.G.Ö., Final Approval and Accountability: H.D.Ö., F.G.Ö.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):158-164
DOI: 10.4274/BMB.galenos.2022.2022-05-039

Determining the Factors Affecting the Development of Perioperative Complications According to Aging Stages

Yaşlılık Evrelerine Göre Perioperatif Komplikasyon Gelişimine Etki Eden Faktörlerin Belirlenmesi

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Abstract

Objective: This study aimed to examine perioperative complication risks in elderly patients stratified by age.

Method: Elderly patients (youngest-old, ages 65 to 74 years; middle-old, 75 to 84 years; and oldest-old, ≥85 years) and controls (20-30 years) who underwent surgical intervention under general anesthesia were included in this prospective observational study.

Results: Two-hundred-sixty patients were included. Different age subgroups showed a different course in terms of perioperative complications. For any combined end-point of any perioperative complication, having a body mass index>28 [odds ratio (OR): 2.4; 95% confidence interval (CI): 1.2-4.6; p=0.012] and being on multi-pharmacy regimen at baseline (OR: 1.9; 95% CI: 1.1-3.5; p=0.029) emerged as significant independent predictors. In reference to controls, each elderly age group emerged as a significant independent predictor: youngest-olds (OR: 4.9; 95% CI: 2.2-10.8; p<0.001); middle-olds (OR: 2.5; 95% CI: 1.1-5.4; p=0.025); oldest-olds, (OR: 5.6; 95% CI: 2.5-12.6; p<0.001).

Conclusion: Elderly patients appear to have higher risk for intraoperative and postoperative complications when compared to the young patients, and each age group appears to have increased risk for different type of complications.

Keywords: Complications, elderly, middle-old, surgery, oldest-old, youngest-old

Öz

Amaç: Bu çalışma yaşa göre katmanlara ayrılmış yaşlı hastalarda perioperatif komplikasyon risklerini incelemeyi amaçlamıştır.

Yöntem: Bu prospektif gözlemsel çalışmaya, genel anestezi altında cerrahi girişim yapılan yaşlı hastalar (yaşlı hastalar, 65-74 yaş; ileri yaşlı hastalar, 75-84 yaş; ve çok ileri yaşlı hastalar, ≥85 yaş) ve kontrol grubu (20-30 yaş) dahil edilmiştir.

Bulgular: İki yüz altmış hasta çalışmaya dahil edilmiştir. Farklı yaş alt grupları perioperatif komplikasyonlar açısından farklı seyir göstermiştir. Herhangi bir komplikasyon olması şeklindeki kombine sonlanım noktası için, vücut kitle indeksi>28 olması [olasılık oranı (OO): 2,4; %95 güven aralığı (GA): 1,2-4,6; p=0,012] ve başlangıçta çoklu ilaç kullanıyor olmak (OO: 1,9; %95 GA: 1,1-3,5; p=0,029) anlamlı bağımsız belirleyiciler olarak bulunmuştur. Kontrollere göre, her bir yaşlı alt grubunda bulunmak anlamlı bağımsız belirleyici olarak saptanmıştır: Yaşlılar (OO: 4,9; %95 GA: 2,2-10,8; p<0,001); ileri yaşlılar (OO: 2,5; %95 GA: 1,1-5,4; p=0,025); çok ileri yaşlılar (OO: 5,6; %95 GA: 2,5-12,6; p<0,001).

Sonuç: Genç hastalarla karşılaştırıldığında, yaşlı hastalar intraoperatif ve postoperatif komplikasyonlar açısından yüksek risk altında görünmektedir ve her bir yaş grubunun farklı tip komplikasyonlar için riski artmıştır.

Anahtar kelimeler: Cerrahi, çok ileri yaşlı, ileri yaşlı, komplikasyonlar, yaşlı, yaşlılar

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Cite this article as: Orhon Ergün M, Ülgen Zengin S, Çorman Dinçer P, Umuroğlu T, Aykaç Z. Determining the Factors Affecting the Development of Perioperative Complications According to Aging Stages. Bagcilar Med Bull 2022;7(2):158-164

Introduction

World population is becoming gradually older (1), and proportion of elderly people is expected to double by 2050 (2). Advanced medical technologies and better healthcare facilities together with improved living conditions seem to be the main causes of such increase. Population aging is associated with increases in the prevalence of chronic diseases and complex medical conditions; therefore, healthcare systems need to respond and adapt such demands for specialized care (1).

Owing to the overall aging of the population, gradually more elderly become candidates for surgical interventions (3,4). Older individuals more frequently utilize healthcare facilities, and they have higher rates for inpatient and outpatient surgical and non-surgical procedures (5-8). In England, people who underwent surgery almost doubled between the years of 2004 and 2007 and the years of 2014 and 2015, and nearly one-third of these patients are older than 85 years (9).

Old age is commonly considered a risk factor for anesthesia and surgery and has been included as a scoring item in most known risk stratification tools (10,11), although frailty rather than chronological age may also be considered to estimate risks associated with cumulative age-related decline in physiological systems (9,12,13). In general, elderly require higher level of perioperative care when compared to the younger patients since they are prone to develop postoperative complications, functional impairment, and dependency (3).

To date, several studies have examined the complication rates in different old age groups, but with particular emphasis on postoperative complications (14-18). Due to structural and functional deterioration of physiological systems, elderly is not only prone to postoperative surgical complications, but also intraoperative problems as well. Identifying age-related perioperative risks before a surgical intervention would aid to provide better intraoperative management and postoperative care; thus, would improve surgical outcomes and consequent healthcare costs.

This study aimed to examine the intraoperative as well as postoperative risks in elderly patients stratified by age (youngest-old, middle-old, oldest-old), in comparison with young adults.

Materials and Methods

Patients

Elderly patients and controls who underwent surgical intervention under general anesthesia were included in this prospective observational study. Three groups of elderly patients stratified for age (youngest-old, ages 65 to 74 years; middle-old, 75 to 84 years; and oldest-old, ≥85 years) and young controls (20 to 30 years old) comprised the study groups. Sixty-five consecutive eligible patients were included into each group. Patients who underwent a surgical intervention shorter than two hours were excluded. The study protocol was approved by the Local Ethics Committee (Marmara University Medical Faculty Ethics Committee for Clinical Research, no: 09.2016.438; date: 15.07.2016) and the study was conducted in accordance with the Declaration of Helsinki.

Anesthesia Management

Anesthesia was induced by 1.5-2 mg/kg propofol and 0.6 mg/kg rocuronium and maintained by desflurane or sevoflurane, depending on the decision of the anesthesiologist. The dose of inhalational anesthetic was adjusted to keep bispectral index between 35 and 45.

Perioperative Assessments

Besides body mass index (BMI), operation type and number of medications were recorded for each patient. Intraoperatively, heart rate (HR), mean arterial pressure (MAP), body temperature (TEMP), bispectral index (BIS), and train of four (TOF) were continuously monitored throughout the operation and were recorded every 30 minutes. HR and MAP were measured non-invasively. Body temperature was measured using forehead skin probe. Depth of anesthesia was monitored using BIS (Aspect Medical Systems, Natick, Mass, ABD). Train of four measurements were done using a muscle-nerve stimulator. Two electrodes were placed over the region innervated by the ulnar nerve in the arm just above the wrist (negative electrode distally, positive electrode proximally). Movement sensor and temperature probe were placed on the thumb and hypothenar region of the hand, respectively. A 2 Hz stimulation was administered every 0.5 seconds. Basal train-of-four value provided by the device was recorded and this value was monitored throughout the operation; in addition, this value aided in the intubation and extubation of the patient.

In addition, duration of anesthesia/surgery and intraoperative complications as well as ephedrine, atropine,

norepinephrine, and glyceryl trinitrate use were recorded. Postoperatively, post-anesthesia care unit (PACU) stay time, delayed awakening, intensive care unit (ICU) admission, nausea/vomiting, and postoperative complications were recorded. Patients were asked to self-evaluate their pain using 10-point visual analogue scale (VAS) (0, no pain; 10, worst imaginable pain) at the time of awakening. In addition, the groups were compared for the combined end-point of any perioperative complication or death defined as follows (some are intraoperative untoward events): Atelectasis, bronchospasm, re-intubation, bradycardia, hypotension, desaturation, hypertension, hyperglycemia, hyponatremia, tachycardia, bleeding, laryngospasm, subcutaneous emphysema, or mortality (within 30 days after or during the operation).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21.0 was used for data analysis. Graphical methods and hypothesis tests were used to test the normality of continuous variables. For intergroup comparisons of continuous data, the One-Way ANOVA or Kruskal-Wallis test was employed, where appropriate; and for pairwise comparisons, the Tukey HSD, Games-Howell, or built in post-hoc test of Kruskal-Wallis was used. For intergroup comparisons of categorical data, the Pearson's chi-square test was utilized, and Bonferroni correction was performed for pairwise comparisons of the groups. To compare the groups in terms of changes in intraoperative measurements (HR, MAP, TEMP, BIS, TOP), Two-Way ANOVA for repeated measurements was used and for pairwise comparisons of the groups, LSD test was preferred. Logistic regression was used for multivariate analysis of potential predictors of any perioperative complication. Receiver operating characteristic curves were evaluated to identify optimal cut-off values for continuous variables to be incorporated in multivariate analysis. A p-value <0.05 was considered an indication of statistical significance.

Results

A total of 260 patients equally distributed to four study groups were included in the study. Distribution of surgery types was as follows: General surgery operations (n=134, 51.5%), orthopedic surgery (n=53, 20.4%), eye surgery (n=36, 13.8%), and others (n=37, 14.2%) (neurosurgery, plastic and reconstructive surgery, urology, thoracic and cardiovascular surgery, obstetrics surgery). Anesthetic type was desflurane and sevoflurane in 137 (52.7%) and 123 (47.3%) patients, respectively. The study groups did not differ regarding BMI (p=0.206), but number of medications was significantly higher in elderly patient groups when compared to controls (Table 1).

Comparison of Perioperative Parameters

Table 1 shows comparisons of intra- and post-operative characteristics of the four groups. Although differences in duration of anesthesia did not reach statistical significance on pairwise comparisons, duration of surgery was significantly longer in the oldest-old group when compared to the youngest-old group. The groups did not differ regarding atropine and nitroglycerine need; however, vasopressor (ephedrine, norepinephrine) need was higher in all elderly groups when compared to controls.

Delayed awakening was more common among the middle old and oldest-old groups and PACU stay time was longer in all elderly groups. ICU admission was more common among the oldest-old group, when compared to controls only. In contrast, the middle-old and oldest-old groups had lower VAS score when awakening, compared to controls and youngest-olds. None of the groups emerged as significantly different from others in terms of nausea/vomiting and mortality.

Comparison of the Groups in Terms of Perioperative Complications

All three elderly groups [youngest-olds, odds ratio (OR): 5.6 (95% confidence interval (CI): 2.6-12.0, p<0.001; middle-olds, OR: 2.8 [95% CI: 1.3-5.9], p=0.007; oldest-olds, OR: 6.0 [95% CI: 2.8-12.8], p<0.001] had significantly higher perioperative complication rate when compared to controls, without any difference between each elderly group (Table 1).

Predictors of Any Perioperative Complication

On multivariate analysis, age groups, a BMI>28 (OR: 2.4; 95% CI: 1.2-4.6; p=0.012), and being on multi-pharmacy regimen at baseline (OR: 1.9; 95% CI: 1.1-3.5; p=0.029) emerged as significant independent predictors of any perioperative complication. In reference to controls, each elderly age group emerged as a significant independent predictor: youngest-olds (OR: 4.9; 95% CI: 2.2-10.8; p<0.001); middle-olds (OR: 2.5; 95% CI: 1.1-5.4; p=0.025); oldest-olds, (OR: 5.6; 95% CI: 2.5-12.6; p<0.001).

Changes in Intraoperative Parameters Over Time

Figure 1 shows intraoperative changes in HR, MAP, body temperature, BIS, and TOF of the four groups. The groups did not differ in terms of changes in HR (p<0.076); on the other hand, they differed in terms of changes in other

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

	Youngest-old (65-74 y)	Middle-old (75-84 y)	Oldest-old (≥85 y)	Controls (20-30 y)	p
Clinical characteristics					
BMI, kg/m^2	25.4±3.5	24.9±3.8	23.9±3.8	24.7±4.6	0.206
No. of medications	1.4±1.1†	1.3±1.3†	1.5±1.0†	0.49±0.7	<0.001
Intraoperative parameters					
Duration of anesthesia, min	169.4±49.6	151.2±31.1	158.3±30.2	153.9±38.2	0.043*
Duration of surgery, min	147.4±36.2	131.3±21.5	132.5±30.5‡	138.5±31.9	0.022
Atropine need	4 (6.2%)	6 (9.2%)	7 (10.8%)	2 (3.1%)	0.341
Nitroglycerine need	4 (6.2%)	2 (3.1%)	2 (3.1%)	0 (0.0%)	0.248
Vasopressor need	34 (13.8%)†	27 (52.3%)†	28 (41.5%)†	9 (43.1%)	<0.001
Postoperative characteristics					
Delayed awakening	8 (12.3%)	16 (24.6%)†	25 (38.5%)†,‡	3 (4.6%)	<0.001
PACU stay time, min	19.8±8.1†,‡,§	23.2±7.2†	26.4±8.3†	11.5±2.6	<0.001
Awakening VAS>3	44 (67.7%)	1 (1.5%)†,‡	0 (0.0%)†,‡	42 (64.6%)	<0.001
ICU admission	6 (9.2%)	10 (15.4%)	14 (21.5%)†	2 (3.1%)	0.010
Nausea-vomiting	20 (30.8%)	13 (20.0%)	10 (15.4%)	10 (15.4%)	0.097
Mortality	1 (1.5%)	3 (4.6%)	6 (9.2%)	0 (0.0%)	0.003*
Primary endpoint					
Any complication or mortality†	42 (64.6%)†	31 (47.7%)†	43 (66.2%)†	16 (24.6%)	<0.001

Following were the perioperative untoward events classified as a complication (some are intraoperative untoward events): Atelectasis, bronchospasm, re-intubation, bradycardia, hypotension, desaturation, hypertension, hyperglycemia, hyponatremia, tachycardia, bleeding, laryngospasm, subcutaneous emphysema, or mortality (within 30 days after or during the operation).

†: Significantly different than controls, ‡: Significantly different than the youngest-old group, §: Significantly different than the middle-old group, *: Pairwise comparisons with correction did not reveal any significant difference between the groups, VAS: Visual analogue scale, BMI: Body mass index, PACU: Post-anesthesia care unit, ICU: Intensive care unit

parameters (p=0.002, p<0.001, p<0.001, and p<0.001, for MAP, TEMP, BIS, and TOR, respectively).

Pairwise comparisons revealed overall mean differences between groups regarding the course throughout the operation. Overall, in controls, MAP was significantly lower than in the youngest-old and middle-old groups (p=0.003 and p=0.033, respectively), but higher than in the oldest-old group (p=0.018). The oldest-old group had significantly lower MAP when compared to the youngest-old and middle-old groups (p<0.001 for both). Body temperature was the highest among controls and significantly and gradually decreased by increasing age (p<0.005 for all comparisons). Although anesthesia depth was adjusted using BIS scores, the youngest-old group had the highest BIS scores (p<0.05 for all), and the oldest-old group had the lowest BIS scores when compared to other groups (p<0.05 for all) throughout the operation. Controls had the lowest TOF scores when compared to all other groups (p<0.01 for all), and the middle-old and oldest old groups had the highest TOF scores (p<0.05 for all); however, no difference was evident between the two latter groups (p=0.158).

Discussion

Findings of this study suggest that there may be unique perioperative course characteristics for individual elderly patient groups. Increased vasopressor need, longer PACU stay time, higher postoperative complication rate, and low body temperature were evident for all elderly patient groups. Delayed awakening, higher intraoperative blood pressure, and higher TOF scores were the issues seen in the youngest-old and middle-old groups. Increased pain on awakening and higher BIS scores seem to be concerns for youngest-olds, whereas surgery time was longer in oldest-olds. Although several studies have so far tested postoperative complication rates among individual age groups of elderly patients, the present study not only focuses on postoperative course, but also on intraoperative and immediately postoperative course.

This study found higher complication rates in all elderly groups when compared to younger patients (<65 years). This is in line with previous observations indicating that age is a risk factor for surgical complications and other unwanted events, even after adjustment for preoperative

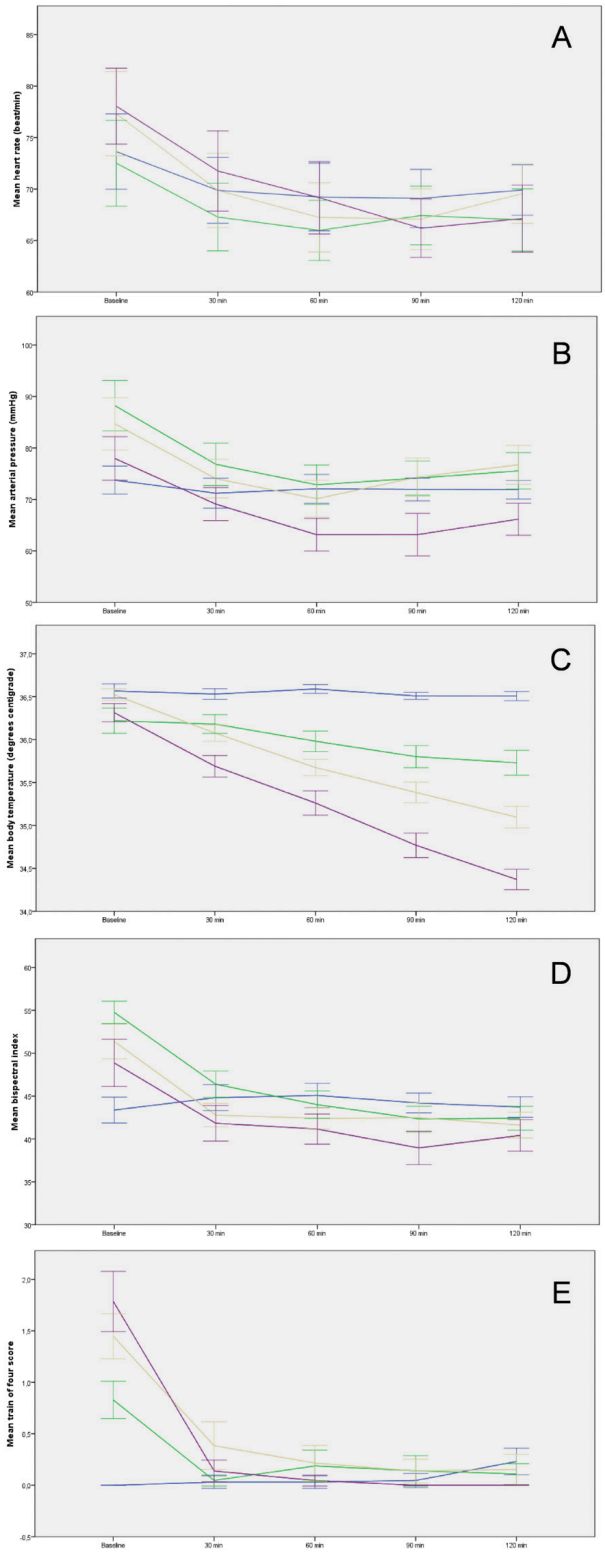

Figure 1. Changes in mean heart rate (A), arterial pressure (B), body temperature (C), bispectral index (D), and train of four score (E) over time during the operation. Error bars indicate 95% confidence intervals. Line colors for each group: Controls (20-30 y), blue; youngest-old group (65-74 y), green; middle-old group (75-84 y), gray; oldest-old group (≥85 y) violet

co-morbidities (19-21). Age has been found to be an independent predictor for postoperative complications after rectal and colon cancer (21).

To date, several studies have compared different elderly age sub-groups mainly in terms of postoperative complications. A 2014 study compared postoperative complication rates in two elderly groups, which correspond to middle-old and oldest-old patients in the present study, who underwent radical cystectomy (14). In line with our findings, that study did not find any difference between the two groups in terms of any complication rate as well as duration of hospital stay, major complication rate or 3-year survival, although 90-day mortality was higher in the oldest-old group. However, it is of note to mention that the study focused on postoperative complications. The present study, on the other hand, also included intraoperative complications into the analysis.

A recent study compared three different elderly patient groups and young patients who underwent percutaneous nephrolithotomy in terms of surgical outcomes and complications (15). Age stratification was slightly different than the present study: Young patients (18-64 years), 65-69 years, 70-79 years, and 80+ years. No significant difference was found between young patients and elderly patients (≥65 years) in terms of duration of hospitalization, duration of hospitalization, blood transfusion, any complication, major complication, or urinary tract infection rates. In addition, elderly subgroups did not differ in terms of these parameters.

Another study examining the predictors of postoperative complications in two elderly patient groups (75-84 and ≥85 years) who underwent surgery for gastric cancer did not find any difference in terms of postoperative complications (16).

A recent Japanese study compared complication rates in younger adults and three age groups of elderly patients after spine surgery for spinal stenosis. In that study, an increase in total and medical complications were evident with increasing age; however, such a relationship was not found for surgical complications (17).

On the other hand, a study including a large series of cases (more than 25.000 women) who underwent surgery for endometrial cancer found differences between old age groups in terms of complications (18). In that study, where five different elderly age groups were examined, women at their sixties were more likely to have perioperative surgical complications as well as postoperative medical complications when compared to oldest olds (≥85 years).

In addition, relatively younger old age was associated with longer hospital stay, more frequent transfusion requirement, and increased mortality. Increased morbidity of older age persisted even after adjustment for medical co-morbidities.

Relatively few studies examining the effect of elderly age group on surgical complications mainly focused on postoperative complications. However, the present study also included intraoperative complication into the analyses, considering that elderly people would be rather fragile under general anesthesia and period of surgery would also pose risks for that particular age group.

An important implication of our findings is the predominance of particular complications in each elderly age group. Although subgroups of elderly were not different in terms of the combined endpoint (any complication), several complication types appeared to be unique for particular age groups. Therefore, we believe that each elderly patient should be considered individually for operative risks through the evaluation of the functional status of the organ systems as well as by taking into account the particular age subgroup of the patient.

Study Limitations

Lack of any cognitive evaluation may be considered as a limitation of the present study since any cognitive impairment after surgery would be regarded as a surgical complication.

Conclusion

The elderly patients appear to have higher risk for perioperative and postoperative complications when compared to the young patients. However, although individual elderly age groups do not differ in terms of overall complication rate, each group appears to have increased risk for different type of complications. Larger studies are warranted to shed light on the individual age related perioperative and postoperative risks for the elderly patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee (Marmara University Medical Faculty Ethics Committee for Clinical Research, no: 09.2016.438; date: 15.07.2016) and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Elderly patients and controls who underwent surgical intervention under general anesthesia were included in this prospective observational study. Three groups of elderly patients stratified for age (youngest-old, ages 65 to 74 years; middle-old, 75 to 84 years; and oldest-old, ≥85 years) and young controls (20 to 30 years old) comprised the study groups. Sixty-five consecutive eligible patients were included into each group. Patients who underwent a surgical intervention shorter than two hours were excluded.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.O.E., S.Ü.Z., P.Ç.D., Concept: M.O.E., S.Ü.Z., Design: M.O.E., Data Collection or Processing: M.O.E., Analysis or Interpretation: M.O.E., S.Ü.Z., P.Ç.D., T.U., Z.A., Literature Search: M.O.E., P.Ç.D., T.U., Z.A., Writing: M.O.E., S.Ü.Z.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):165-173
DOI: 10.4274/BMB.galenos.2022.2022-03-031

The Relationship Between KRAS Mutation and ^{18}F-FDG Uptake Parameters in Colorectal Cancer

Kolorektal Karsinomda KRAS Mutasyonu ve ^{18}F-FDG Tutulum Parametreleri Arasındaki İlişki

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Abstract

Objective: Our purpose in this study was to evaluate whether Kirsten rat sarcoma viral oncogene (KRAS) exon-2 mutation affected ^{18}F-fluorodeoxyglucose (FDG) accumulation patterns, total lesion glycolysis and metabolic tumor volume in colorectal cancer.

Method: This retrospective study included 52 colorectal cancer patients. Dual-time ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) parameters such as the maximum standardized uptake values (SUV_{max}), tumor-to-liver parenchyma SUV_{max} ratios (TLR), retention index (RI), metabolic tumor volumes (MTV), total lesion glycolysis (TLG) and glucose corrected-TLGs were measured.

Results: There were no statistical differences in PET/CT imaging parameters between mutated and wild-type colon cancer, but RI and RI (TLR) values were statically higher in wild-type than in mutated-type. KRAS exon-2 wild-type rectal cancer patients had low MTV (p=0.044). KRAS mutation status was correlated with MTV (r=-0.277, p=0.048). ROC curves analysis showed that MTV and MTV (%) predicted KRAS exon-2 mutation status accurately.

Conclusion: Although we did not find a relationship between KRAS exon-2 mutation status and increased ^{18}F-FDG uptake in both colon and rectal cancer patients in our study, KRAS exon-2 wild-type colon cancer patients showed interestingly increased uptake of ^{18}F-FDG in time. Even if we find a correlation between KRAS exon-2 mutation status and MTV, it was not very strong.

Keywords: Colorectal neoplasms, fluorodeoxyglucose F18, KRAS protein, human, positron emission tomography

Öz

Amaç: Bu çalışmadaki amacımız, kolorektal kanserde Kirsten sıçan sarkom viral onkogeni (KRAS) ekson-2 mutasyonunun ^{18}F-florodeoksiglukoz (FDG) tutulum paternlerini, toplam lezyon glikolizini ve metabolik tümör hacmini etkileyip etkilemediğini değerlendirmektir.

Yöntem: Bu retrospektif çalışmaya 52 kolorektal kanserli hasta dahil edildi. Maksimum standartlaştırılmış uptake değerleri (SUD_{maks}), tümör-karaciğer parankim SUV_{maks} oranları (TKO), retansiyon indeksi (RI), metabolik tümör hacimleri (MTV), toplam lezyon glikoliz (TLG) ve glukozla düzeltilmiş TLG'ler gibi çift zamanlı ^{18}F-FDG pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) parametreleri ölçüldü.

Bulgular: Mutasyona uğramış ve vahşi tip kolon kanseri arasında PET/BT görüntüleme parametrelerinde istatistiksel fark yoktu, ancak RI ve RI (TKO) değerleri vahşi tipte mutasyona uğramış tipten istatiksel olarak daha yüksekti. KRAS ekson-2 vahşi tip rektum kanseri hastalarında düşük MTV vardı (p=0,044). KRAS mutasyon durumu MTV ile korele idi (r=-0,277, p=0,048). ROC eğrileri analizi, MTV ve MTV'nin (%) KRAS ekson-2 mutasyon durumunu doğru bir şekilde öngördüğünü gösterdi.

Sonuç: Çalışmamızda hem kolon hem de rektum kanserli hastalarda KRAS ekson-2 mutasyon durumu ile artmış ^{18}F-FDG tutulumu arasında bir ilişki bulamasak da, KRAS ekson-2 vahşi tip kolon kanserli hastalarda ilginç bir şekilde zamanla artan ^{18}F-FDG tutulumu görülmüştür. KRAS ekson-2 mutasyon durumu ile MTV arasında bir korelasyon bulsak bile, bu çok güçlü değildi.

Anahtar kelimeler: Florodeoksiglukoz F18, insan, KRAS proteini, kolorektal neoplazmalar, pozitron emisyon tomografi

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Cite this article as: Özen A, Menekşe S, Namal E, Kahraman Akkalp A, Tokoçin M, Vartanoğlu T, Gökmen E, Çelebi F. The Relationship Between KRAS Mutation and 18F-FDG Uptake Parameters in Colorectal Cancer. Bagcilar Med Bull 2022;7(2):165-173

Introduction

The colorectal cancer (CRC) is one of the most common cancer types worldwide (1). By rising developments in diagnostic imaging modalities and optimization of surgical, neoadjuvant and palliative therapies, the mortality rate of CRC has decreased by more than 20% in the last 10 years. Pathogenesis of CRC is still not clear. Initially, it was thought that genetic mutations and chronic inflammation played the key role in its pathogenesis. Approximately 35-40% of CRC exhibits a mutation in the V-KI-RAS2 Kirsten rat sarcoma viral oncogene (KRAS) that involved codons 12 and 13 in more than 90% of cases. Although testing for mutations in KRAS exon 2 containing codons 12 and 13 was recommended previously, the current guidelines recommend to analyze not only KRAS exon-2 but also KRAS exons-3, containing codons 59 and 61 and exon-4, containing codons 117 and 146, NRAS exons-2, containing codons 12 and 13, exons-3, containing codons 59 and 61, and exons-4, containing codons 117 and 146 (2). Clinical significance of RAS mutation is associated with resistance to drugs targeting the epidermal growth factor receptor (EGFR), which is linked to cell survival, motility, proliferation, angiogenesis and metastasis. Currently, anti-EGFR drugs are recommended for wild-type KRAS metastatic CRC patients.

Molecular imaging has gained wide acceptance in many clinical oncology practices as a less invasive diagnostic technique. For this purpose, imaging is performed with positron emission tomography combined with computed tomography (PET/CT), in which tumor-seeking agents are used. It allows molecular and morphologic evaluation at the same time and displays a powerful tool within one imaging modality for whole body staging, restaging, and evaluation of therapy. The radiopharmaceutical commonly used in clinical routine for PET/CT scans is ^{18}F-fluorodeoxyglucose (FDG), which is an analog of glucose. Thus, glucose metabolism is measured *in vivo* by uptake of ^{18}F-FDG. Likewise, in glucose metabolism, it is taken into the cell via glucose transporters (GLUT) and then phosphorylated to FDG-6-phosphate by hexokinases and trapped inside the cell. Using delayed or dual-time PET/CT scans in molecular imaging has been suggested by some researchers because uptake of ^{18}F-FDG uptake increases markedly in malignant cells over time. Semi-quantitative parameters calculated on ^{18}F-FDG PET/CT scans are standardized uptake value (SUV), reflecting ^{18}F-FDG accumulation, metabolic tumor volume (MTV), and total lesion glycolysis (TLG). There are some human studies demonstrating the relationship between SUV and KRAS mutational status (3-9). However, in most of these studies, FDG accumulation pattern in dual-time imaging, glucose corrected-TLG (cor-TLG) and also MTV and TLG were not studied. The aim in this study was to analyze whether KRAS exon-2 mutation affected ^{18}F-FDG accumulation patterns in dual-time PET/CT imaging, MTV, TLG, and cor-TLG in CRC.

Materials and Methods

We retrospectively reviewed the medical records of all CRC patients who underwent ^{18}F-FDG PET/CT scan as a part of a staging work-up before treatment at our institution between February 2010 and August 2015. We enrolled 52 patients (mean age: 59.65±14.053 years, 23 female and 29 male) with CRC who had KRAS exon-2 gene mutation analysis and underwent preoperative ^{18}F-FDG PET/CT scan before resection or neoadjuvant treatment. CRC was diagnosed by colonoscopical biopsy in all patients before ^{18}F-FDG PET/CT imaging. Local ethics committee approved this retrospective study. Due to the retrospective design of this study, the requirement for informed consent was not deemed necessary.

PET/CT scans were achieved with a Gemini GXL PET/CT scanner (Philips Healthcare, Cleveland, Ohio, USA) after intravenous 354.31±56.5 MBq (9.57±1.53 mCi) ^{18}F-FDG injection when patients were fasted for at least six hours prior to injection. Also, blood glucose levels were checked just prior to injection. An oral contrast agent was used for each patient. After injection, all patients were rested in a quiet room for a good FDG distribution during the waiting period. They emptied their bladder before scanning. Whole body ^{18}F-FDG PET/CT imaging at 1 hour was acquired from the skull base to the mid thighs in supine position. A CT image was achieved firstly from the integrated PET/CT scanner with the use of a standardized protocol. This involved a section thickness of 3.3 mm, 120 kV, automatically calculated mA·s for the patient's weight, a tube rotation time of 0.75 s per rotation, and a pitch of 0.85. Afterwards, PET images were acquired immediately and reconstructed using CT data for attenuation correction with iterative reconstruction. In 37 (71.15%) of the patients, delayed imaging was performed to better localize suspicious or primary lesions after 104.31±34.11 minutes from whole body scan.

For quantitative assessment, nuclear medicine specialist with ten years of experience evaluated the images of ^{18}F-FDG PET/CT with visual inspection in transaxial, coronal and sagittal planes using a commercial workstation

(IntelliSpace Portal; Philips Healthcare, USA). The regions of interest were drawn over the tumor. The maximum SUV (SUV_{max}) at whole body image (SUV1) and delayed spot image (SUV2) were automatically calculated with polygonal free-hand regions of interest in all patients. Furthermore, SUV_{max} was measured from the normal liver parenchyma with circular regions of interest at dual-time ($SUV1_{liver}$ and $SUV2_{liver}$). Non-tumor regions of interest were drawn larger than 1 cm. For tumor-to-liver SUV_{max} ratio calculation (TLR), SUV_{max} of primary tumor was divided to liver SUV_{max} as follows:

$TLR1 = SUV1/SUV1_{liver}$

$TLR2 = SUV2/SUV2_{liver}$

The retention index (RI) from SUV_{max} and TLR values, obtained dual-time images, was calculated via the formula below:

$RI = (SUV2 - SUV1) \times 100/(SUV1)$

$RI\ (TLR) = (TLR2-TLR1) \times 100/(TLR1)$

Additionally, MTV was automatically calculated from primary lesions on whole body PET/CT images with two different methods (Figure 1). The drawn regions of interest that protrudes the lesion in each section were checked. The first method described as MTV was that the contouring margins around the tumor were defined using a fixed SUV_{max} cut-off level, 2.5 or greater. Another method described as MTV (%) was that contouring margins were defined using a relative threshold with 40% or greater of SUV_{max}.

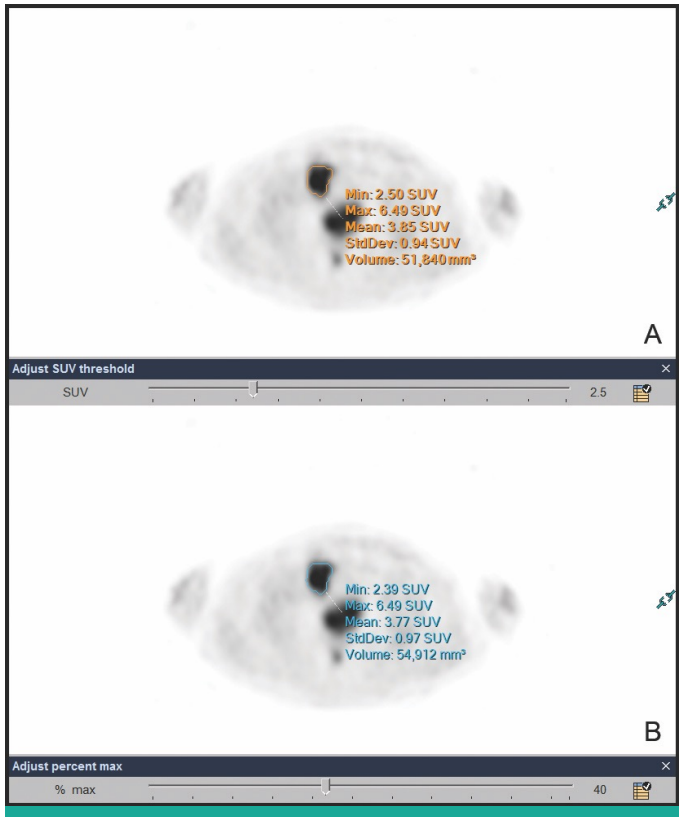

Figure 1. Calculation of metabolic tumor volume. The contouring margins around the tumor were defined using A) A fixed SUV cut-off level, 2.5 or greater and B) A relative threshold with 40% or greater of SUV_{max}

TLG values, considering both the metabolic activity and tumor burden, were calculated from primary lesion mean SUVs (SUV_{mean}) and MTVs (10) with this formula;

$TLG = SUV_{mean} \times MTV$.

In addition, SUV_{mean} corrected for the blood glucose level was calculated as (SUV_{mean}) × (blood glucose level)/100 (11), and then glucose corrected TLGs (cor-TLG) were also calculated from attenuation-corrected ^{18}F-FDG PET/CT images. Furthermore, values at two different methods such as TLG, TLG (%), cor-TLG, and cor-TLG (%) were defined depending on different MTV measurement methods, which is one parameter in TLG formula.

In 38 of 52 (73.1%) patients with metastasis at the diagnosis, KRAS gene mutation testing was conducted immediately. In the remaining 14 (26.9%), KRAS mutation gene testing was studied after detecting metastasis during follow-up. For KRAS mutation analysis, genomic deoxyribonucleic acid was extracted from formalin-fixed paraffin-embedded tumor tissue sections by using microdissection method. Pathologists experienced in gastrointestinal tumors, utilizing real-time polymerase chain reaction and pyrosequencing method, analyzed for the mutations specific for codons 12, 13, 61, and 146 of *KRAS* gene, and only exon-2 mutations were included in this study. Also, NRAS mutation status was not studied in all patients.

Statistical Analysis

Statistical calculations were carried out using the NCSS Statistical Software version 2007 (Kaysville, UT, USA). Quantitative parameters were analyzed by mean and standard deviation. Qualitative parameters were analyzed by percentage and frequencies. In case, the KRAS mutation status groups were classified as KRAS exon-2 mutated or KRAS exon-2 wild-type. The Mann-Whitney U test for variables was used. The Spearman correlation test among all parameters was performed. The analyses to compare the predictive ability were tested by receiver operating characteristic curve analysis. Values of p less than 0.05 were considered as significant.

Results

Thirty-one (59.6%) of the 52 patients had colon and 21 (40.4%) had rectal cancer. KRAS mutation status was KRAS exon-2 mutated in 14 (26.9%; 11 colon and 3 rectal cancer) patients and KRAS exon-2 wild-type in 38 (73.1%; 20 colon and 18 rectal cancer) patients. According to the KRAS status of patients, their descriptive statistics are presented in Table 1.

In ^{18}F-FDG PET/CT evaluations, the metastasis was detected in the liver in 30 patients, at the non-regional lymphatic station in the abdomen in 6 patients, and in the lung in 5 patients. 3 of patients had bone metastasis and 3 of them had peritoneal implants. The mean blood glucose level during ^{18}F-FDG injections was 107.38±19.748 mg/dL. Although there were no statistical differences in whole body PET/CT imaging parameters between mutated and wild-type colon cancer, RI and RI (TLR) values, reflecting gradually increasing glucose uptake, were higher in wild-type colon cancer than mutated patients (Figure 2). In rectal cancer, KRAS exon-2 wild-type patients had low MTV than mutated cases (Table 2).

Table 1. Descriptive statistics of patients

Characteristics	KRAS exon-2 mutated	KRAS exon-2 wild-type
n	14	38
Age (years)		
Mean ± SD*	61.5±12.72	58.97±14.62
Sex		
Female	8 (57.1%)	15 (39.5%)
Male	6 (42.9%)	23 (60.5%)
Blood glucose		
Mean ± SD*	109.43±25.157	106.63±17.692
CEA		
<5.0	2 (14.3%)	12 (31.6%)
≥5.0	12 (85.7%)	26 (68.4%)
Tumor localization		
Colon	11 (78.6%)	20 (52.6%)
Rectum	3 (21.4%)	18 (47.4%)
Metastases at diagnosis		
Yes	10 (71.4%)	28 (73.7%)
No	4 (28.6%)	10 (26.3%)
Tumor type		
Adenocarcinoma	12 (85.7%)	32 (84.2%)
Adenocarcinoma with mucinous differentiation	1 (7.1%)	4 (10.5%)
Signet ring cell adenocarcinoma	1(7.1%)	2 (5.3%)

* p-value>0.05, SD: Standard deviation, KRAS: Kirsten rat sarcoma viral oncogene

In correlation analyses, KRAS exon-2 mutation status was only correlated with MTV (%) (r=-0.277, p=0.048). SUV1 and SUV2 were strongly correlated with MTVs, TLGs, and cor-TLGs (Table 3 and Figure 3). The strong positive correlations were found between MTVs and TLGs because of the TLG derived from MTV. When receiver operating characteristic curves were analyzed to compare the efficacy of various parameters, the results showed that MTV and MTV (%) most accurately predicted the KRAS exon-2 mutated state (Figure 4). The areas under the curve were 0.722 [95% confidence interval (CI)=0.394-1] and 0.806 [95% CI=0.537-1], respectively. We then sought to determine optimal cut-off to distinguish between KRAS exon-2 mutated and wild-type patients. Receiver operating characteristic curve analysis showed cut-off value of 62.144 mm^3 for MTV with 63.64% sensitivity and 69.23% specificity (positive predictive value=46.7%, negative predictive value=81.8%, likelihood ratio=2.07). The cut-off value for MTV (%) was 31.616 mm^3 with 85.71% sensitivity and 60.53% specificity (positive predictive value=44.4%, negative predictive value=92%, likelihood ratio=2.17).

Discussion

The *RAS* gene family is a proto-oncogene that includes the oncogenes KRAS, HRAS, and NRAS. They have similar structure and function. When they become active, they begin to function as oncogenes and play an important role in the pathogenesis of cancer. RAS is involved in processes such as signal transduction, proliferation, mutation, adhesion, apoptosis and migration of cells. When RAS and RAS-associated proteins are increased, they often lead to the formation of cancers by increasing invasion and metastasis and reducing apoptosis (12). Many human malignancies, including lung cancer, pancreatic cancer, and particularly CRC, show (13,14). Overexpressions of KRAS mutations at codons 12, 13, 59, 61, 117, and 146 have been shown to induce RAS protein activation. The mutations of KRAS in CRC occur in codons 12 and 13 with approximately rate of 97%, while other mutations such as codons 61 and 146 are less frequent (15). KRAS exon-2 mutations are commonly observed in approximately 35-40% of patients with CRC, while the frequency is 10-15% for other RAS mutations (16). Clinical significance of KRAS mutations is due to its effect on treatment selection.

Uptake of ^{18}F-FDG into cancer cells is complex. It is affected by tumor-related factors such as histological type, differentiation, hypoxia, tumor size and nontumor-related factors like diabetes mellitus. This radiopharmaceutical

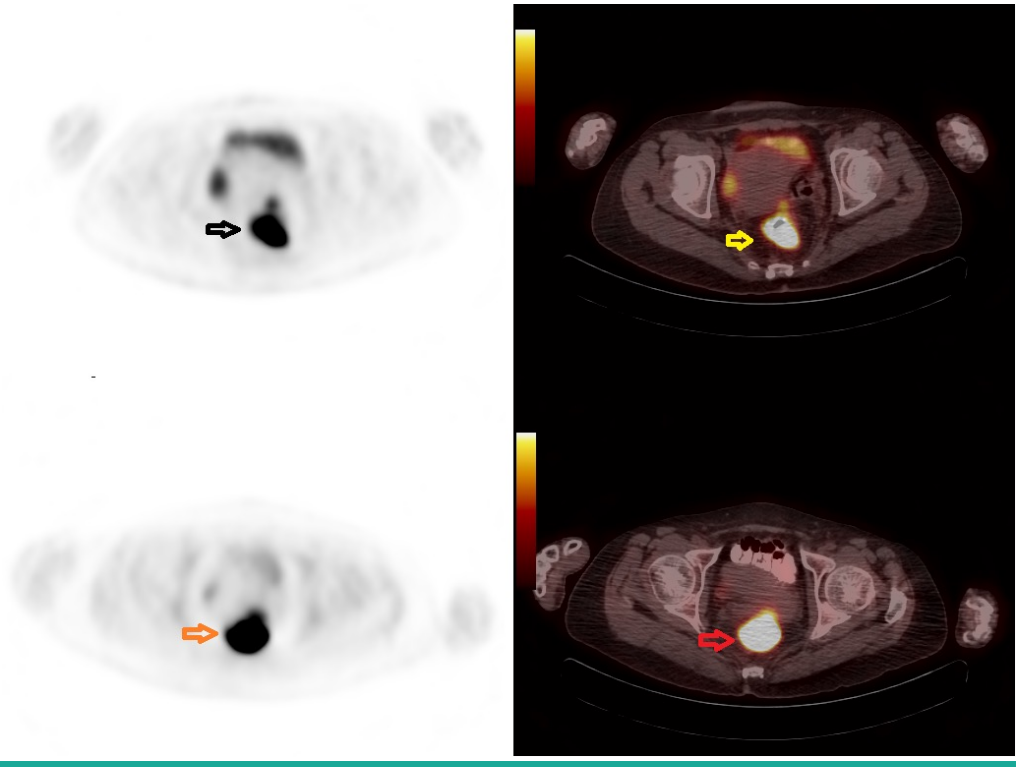

Figure 2. A 47-year-old female patient, KRAS wild type, rectal grade 2 adenocarcinoma. Early PET (black arrow) and fusion (yellow arrow) images in the upper row, late PET (orange arrow) and fusion (red arrow) images in the lower row. SUV_{max} values measured from the rectum were 28.5 and 37.1 for early and late images, respectively. In mutant type KRAS patients, there was no such difference for SUV_{max} values

PET: Positron emission tomography, KRAS: Kirsten rat sarcoma viral oncogene

Table 2. The Mann-Whitney U test for parameters of glucose metabolism from ^{18}F-FDG PET/CT scans according to KRAS exon-2 mutation status

	Colon cancer			Rectal cancer		
	Mutated	Wild		Mutated	Wild	
	Mean ± SD (n)	Mean ± SD (n)	p	Mean ± SD (n)	Mean ± SD (n)	p
Whole body imaging parameters						
SUV1	12.90±7.18 (11)	13.03±7.85 (20)	>0.05	17.18±6.76 (3)	14.17±6.07 (18)	>0.05
TLR1	6.05±3.31 (11)	5.51±3.303 (19)	>0.05	11.51±10.24 (3)	6.34±2.716 (18)	>0.05
MTV (mm^3)	91.537±86.596 (11)	77.722±96.798 (20)	>0.05	111.467±33.166 (3)	56.825±58.990 (18)	0.044
TLG	589.18±555.11 (11)	519.27±868.36 (20)	>0.05	689.00±253.73 (3)	396.93±484.73 (18)	>0.05
cor-TLG	686.28±700.65 (11)	619.44±1177.70 (20)	>0.05	693.11±170.45 (3)	425.53±515.23 (18)	>0.05
MTV (%) (mm^3)	73.117±60.994 (11)	55.066±64.531 (20)	>0.05	57.493±17.615 (3)	41.407±42.203 (18)	>0.05
TLG (%)	524.07±469.37 (11)	411.60±650.26 (20)	>0.05	465.27±66.38 (3)	329.37±400.46 (18)	>0.05
cor-TLG (%)	595.89±546.52 (11)	488.86±877.54 (20)	>0.05	477.04±52.15 (3)	351.03±421.69 (18)	>0.05
Delayed spot imaging parameters						
SUV2	15.79±10.059 (8)	21.02±11.67 (14)	>0.05	N/A	18.08±7.53 (14)	N/A
TLR2	7.86±4.44 (8)	9.98±5.57 (13)	>0.05	N/A	8.98±4.02 (14)	N/A
RI	24.09±10.51 (8)	40.15±16.29 (14)	0.017	N/A	32.64±33.27 (14)	N/A
RI (TLR)	31.89±13.93 (8)	57.78±33.34 (13)	0.030	N/A	45.38±41.74 (14)	N/A

SD: Standard deviation, KRAS: Kirsten rat sarcoma viral oncogene, MTV: Metabolic tumor volumes, TLG: Total lesion glycolysis, FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

Table 3. The Spearman correlation test of ^{18}F-FDG PET/CT parameters

		SUV1	SUV2	TLR1	TLR2
MTV	r	0.535	0.519	0.457	0.440
	p	0.000	0.001	0.001	0.007
TLG	r	0.665	0.625	0.570	0.521
	p	0.000	0.000	0.000	0.001
cor-TLG	r	0.665	0.633	0.561	0.522
	p	0.000	0.000	0.000	0.001
MTV (%)	r	0.321	0.292	0.273	0.214
	p	0.020	0.080	0.053	0.210
TLG (%)	r	0.591	0.550	0.498	0.451
	p	0.000	0.000	0.000	0.006
cor-TLG (%)	r	0.585	0.551	0.488	0.452
	p	0.000	0.000	0.000	0.006

r: Correlation coefficient, FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, MTV: Metabolic tumor volumes, TLG: Total lesion glycolysis

is transported into the cell through GLUTs. On the other hand, uptake of ^{18}F-FDG can also be seen in inflammatory processes. Depending on the different levels and degrees of GLUT and hexokinase expressions, there are profile differences in inflammatory lesions and cancer. For this purpose, dual-time imaging can be used for the differential diagnosis. Several studies have recently reported that the most essential factor for ^{18}F-FDG uptake in CRC is increased GLUT1 expression (5,17). Accumulation of ^{18}F-FDG in colon carcinoma can predict the underlying tumor biology in terms of forecasting of malignancy potential and prognosis (17). Furthermore, colon may occasionally demonstrate high ^{18}F-FDG uptake. Moreover, dual-time imaging is also useful in distinguishing tumors from normal tissues seen with high ^{18}F-FDG uptake. However, focal intense hypermetabolism is highly suggestive in neoplasm (18). Due to the fact that subcentimetric lesions may cause false negative results in ^{18}F-FDG PET/CT scanning, we perform

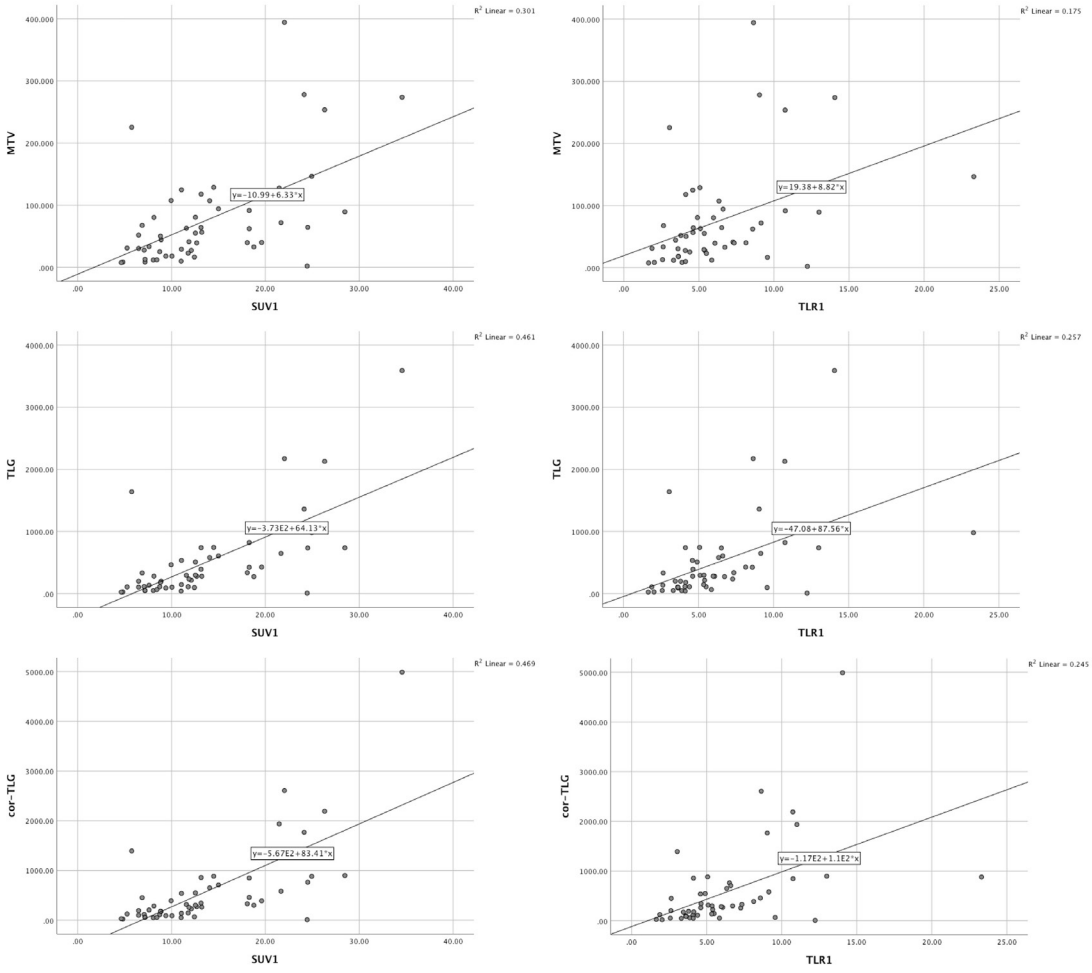

Figure 3. Correlation graphs of ^{18}F-FDG parameters
FDG: Fluorodeoxyglucose

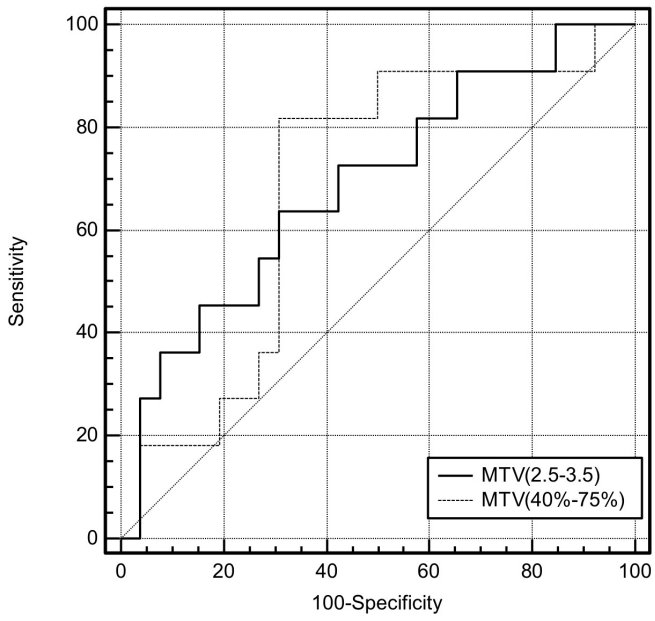

Figure 4. Receiver operating characteristic curve analysis of different MTV measurement methods to compare their diagnostic performance in detecting KRAS mutation status

KRAS: Kirsten rat sarcoma viral oncogene, MTV: Metabolic tumor volumes

^{18}F-FDG PET/CT imaging for patients with lesion size larger than 1 cm to avoid partial volume effect in our institution.

Interestingly, some studies have found that mutant KRAS or BRAF alleles have always higher GLUT1 transcript expression times compared to wild type, ranging from 3- to 22- fold (5,19,20). These CRC cells are thus able to survive under low glucose conditions with increased GLUT1 expression (20). At this point, more ^{18}F-FDG uptakes can be expected in patients with KRAS-mutant. Some studies in the CRC have examined this hypothesis in the literature (3-9). Firstly, Kawada et al. (5) investigated the relationship between ^{18}F-FDG accumulations of KRAS/BRAF mutations in 51 CRC patients. They calculated SUV_{max} for primary tumor and TLR, as well as evaluated GLUT1 and hexokinase type-II levels. They found that both SUV_{max} and TLR were significantly higher in the mutant group. Afterwards, Miles et al. (9) found that KRAS mutants with high SUV_{max} had a significantly increased likelihood of expressing hypoxia-inducible factor-1, while KRAS mutants with low SUV_{max} expressed minichromosome maintenance protein 2 in 33 CRC patients. In a study comparing KRAS exon-2 mutational status and SUV_{max} at the metastatic lesions of 44 CRC patients, they expressed no statistically significant correlation between SUV_{max} and KRAS mutation status in liver metastasis (7). A recent study by Chen et al. (3) in 121 CRC patients revealed that KRAS-mutated tumor exhibited higher SUV_{max}. In addition, researchers found that SUV_{max} and PET-based maximal tumor width with a 40% threshold of SUV_{max} were two predictors of KRAS mutations. In this study, MTVs and TLGs with different thresholds, such as 2.5 or 3.0 SUV_{max}, and volume greater than 20%, 30%, 40%, 50% of SUV_{max}, were calculated and no significant difference was found for *KRAS* gene mutation. In another study, researchers demonstrated that GLUT1 protein expression was about 2.5-3.0-fold in higher KRAS mutant in paired isogenic human CRC cell lines, and hexokinase 2 protein expression was also dramatically higher in the mutant KRAS cells than in wild-type cells. Under hypoxic situations, the researchers showed that KRAS mutated CRC cells show increased ^{18}F-FDG accumulations depending on the hypoxia-inducible factor 1κ pathway, whereas the enhanced uptake of ^{18}F-FDG in hypoxic wild-type CRC cells was independent of the hypoxia-inducible factor 1κ pathway (19). In a recent study, Chen et al. (4) found that SUV_{max}, various thresholds of MTV, TLG and tumor width on PET/CT yielded similar results for KRAS in 103 CRC patients as in other studies. In a second study of Kawada et al. (6) analyzing 55 tumors, they found no significant relationship between SUV_{max} and KRAS status including tumor size below 10 mm. Excluding cases with a small tumor size to minimize the bias of the partial volume effect, the researchers found higher SUV_{max} values in mutant KRAS patients than wild-type with 71.4% accuracy when the SUV_{max} cut-off value was 6.0. In a recently published study involving 179 CRC patients, researchers examined the value of PET/CT parameters such as SUV^{max}, SUV_{peak}, MTV, and TLG for the prediction of KRAS mutation and investigated their variability depending on C-reactive protein levels (8). They found higher accumulations of ^{18}F-FDG in CRC patients with KRAS mutations, and SUV_{max} and SUV_{peak} were independent predictors of KRAS mutation with positive LN metastasis. Also, the association changed with higher CRP levels.

In this study, we hypothesized that KRAS mutations would increase ^{18}F-FDG uptake especially in SUV2 and RI in dual-time imaging, and also affect the TLGs in CRC. With this aspect, our study is the first to evaluate delayed imaging findings and also to correct glucose-TLG values. We did not find a relationship between KRAS status and SUV_{max} of the primary lesion. This seems to be contrary to other publications in literature. However, in a meta-analysis, ^{18}F-FDG PET was shown to have low sensitivity and specificity for the prediction of KRAS mutation in CRC patients (21). On the other hand, we found higher levels

for RI and RI (TLR) parameters obtained from dual-time imaging in KRAS exon-2 wild-type colon cancer patients. However, we could not determine a cut-off value for RI and RI(TLR) in this study. Low MTV level was found in KRAS exon-2 wild-type rectal cancers. Beside TLGs, neither difference nor relationship was detected for cor-TLGs. The reason of discrepancy with literature for SUV_{max} was thought to be the performance of KRAS mutational analysis not only on the pathology specimens but also on samples of biopsy in our study as possible causes of discordance. In our study, KRAS mutation analysis was performed only in 73.1% of patients at the time of diagnosis. The remaining patients were examined for their metastatic lesions during their follow-up. Therefore, the KRAS mutation analyses of the patients were not homogeneous in terms of the samples examined. For this reason, the relationship between ^{18}F-FDG parameters according to KRAS sampling method was not evaluated in this study. However, Baas et al. (22) showed that tumor tissue had a high agreement of over 97% from endoscopic biopsies and matched resected specimens in the determination of RAS mutation status. Beside this, in different anatomical regions of the same patient, as an indicator of cancer, heterogeneity of KRAS mutational status can be determined as a molecular discordance (23-25). In addition, poor DNA quality in the tissue sample is seen in approximately 6% and 9% of cases, as a defect in determining KRAS mutation status (26).

Study Limitations

There are several limitations in our study. First of all, the greatest bias of this work derives from the retrospective nature of the study itself. Also, the number of patients was few in this study. The effects on ^{18}F-FDG accumulations of mutations of exon-3, 4 and also *NRAS* gene could not be assessed. While KRAS exon-2 mutation status was studied following tumor resection in a minority of patients, it was observed from biopsy specimen in others. Finally, the analysis of the mutational status of all patients was performed in a different laboratory.

Conclusion

As a result, although we did not find a relationship in our study between KRAS exon-2 mutation status and increased ^{18}F-FDG uptake in both colon and rectal cancer patients, which was previously expressed in literature, KRAS exon-2 wild-type colon cancer patients showed interestingly increased uptake of ^{18}F-FDG in time. Even if we were to find a correlation between KRAS exon-2 mutation status and MTV, it would not be very strong.. Therefore, we believe that further studies that examine subgroups for mutations and larger series are needed to clarify our hypothesis.

Acknowledgements

The authors would like to thank Rana Konyalıoğlu for her assistance with biostatistics that greatly improved the manuscript.

Ethics

Ethics Committee Approval: This study was approved by Non-invasive Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (GOKAEK/2016-432).

Informed Consent: Due to the retrospective design of this study, the requirement for informed consent was not deemed necessary.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Conception/Design of Study: A.Ö., S.M., E.N., Data Acquisition: A.Ö., M.T., T.V., E.G., A.K.A, Data Analysis or Interpretation: A.Ö., A.K.A., F.Ç., Drafting Manuscript:A.Ö., M.T., T.V., E.G., Critical Revision of Manuscript: S.M., E.N., F.Ç., A.K.A., Final Approval and Accountability: A.Ö, S.M., E.N., A.K.A., M.T., T.V., E.G., F.Ç., Technical or Material Support: A.K.A., M.T., T.V., E.G., Supervision: A.Ö, S.M., E.N., F.Ç.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):174-179
DOI: 10.4274/BMB.galenos.2022.2022-04-033

Incidence of Fentanyl-induced Cough and Effect of Dose: Randomized Placebo-controlled Trial

Fentanilin İndüklediği Öksürük İnsidansı ve Dozun Etkisi: Randomize Plasebo Kontrollü Çalışma

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University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Abstract

Objective: Fentanyl is one of the opioids commonly used in the induction of general anesthesia and can cause coughing. The cough that occurs can be a problem in patients for whom it is necessary to avoid pressure increase. This study aimed to determine the incidence of fentanyl-induced cough (FIC) and the difference between the doses used.

Method: This prospective randomized placebo-controlled trial included 750 ASA I-II patients aged 18-65 years who underwent elective surgery under general anesthesia. The patients were randomly divided into three groups. 1 μg kg^{-1} fentanyl was used to induce the patients in group 1, and 2 μg kg^{-1} fentanyl was used for the induction of the patients in group 2. In the installation of patients in group K, the control group, fentanyl was not used, and a placebo was administered. All patients were observed for 60 seconds after fentanyl injection. The cough severity (mild: 1-2, moderate: 3-4, severe: >5 times), time of cough and demographic data of the patients were recorded and compared.

Results: Demographic data were similar among the groups. Cough was observed in 15 patients (6%) in group 1 and 80 patients (32%) in group 2. Incidences of FIC were 6%, 32%, and 0% in groups 1, 2, and K, respectively. While all of group 1 was mild, 82% of the cough observed in group 2 was mild, and 18% was moderate. The incidence and severity of cough in group 2 were significantly higher than in group 1 (p<0.001).

Conclusion: Reducing the dose of fentanyl significantly decreases the severity and incidence of cough. We recommend reducing the induction dose to avoid undesirable pressure increases such as intracranial and intraocular surgeries.

Keywords: Cough, fentanyl, general anesthesia

Öz

Amaç: Fentanil, genel anestezi indüksiyonunda yaygın olarak kullanılan ve öksürüğe sebep olabilen opioidlerdendir. Meydana gelen öksürük basınç artışından kaçınmanın gerekli olduğu hastalarda problem oluşturabilmektedir. Bu çalışmanın amacı, fentanilin indüklediği öksürük (FİÖ) insidansını belirlemek ve kullanılan dozlar arasındaki farkı saptamaktır.

Yöntem: Prospektif randomize plasebo kontrollü bu çalışmaya genel anestezi altında elektif operasyona alınan 18-65 yaş arası, ASA I-II 750 hasta dahil edildi. Hastalar randomize olarak üç gruba ayrıldı. Grup 1'deki hastaların indüksiyonunda 1 μg kg^{-1}, grup 2'deki hastaların indüksiyonunda 2 μg kg^{-1} fentanil kullanıldı. Kontrol grubu olan grup K'daki hastaların indüksiyonunda fentanil kullanılmayıp plasebo uygulandı. Fentanil enjeksiyonu sonrası tüm hastalar 60 sn gözlendi. Hastaların öksürük şiddeti (hafif: 1-2, orta: 3-4, şiddetli: >5 adet) ve zamanı ile demografik verileri kaydedilerek karşılaştırıldı.

Bulgular: Demografik veriler gruplar arasında benzerdi. Grup 1'de 15 hastada (%6) ve grup 2'de 80 hastada (%32) öksürük gözlendi. FİÖ insidansı grup 1, 2 ve 3 için sırasıyla %6, %32 ve %0 bulundu. Grup 1'deki öksürüğün tamamı hafif şiddetteyken grup 2'de gözlenen öksürüğün %82'si hafif ve %18'i orta şiddetteydi. Grup 2'deki öksürük insidansı ve şiddeti grup 1'e göre anlamlı olarak yüksek bulundu (p<0,001).

Sonuç: Fentanil dozunun azaltılması, öksürük şiddeti ve insidansını anlamlı olarak azaltmaktadır. İntrakraniyal ve intraoküler cerrahiler gibi istenmeyen basınç artışlarından kaçınmak için indüksiyon dozunun azaltılmasını öneriyoruz.

Anahtar kelimeler: Fentanil, genel anestezi, öksürük

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Cite this article as: Arslan K, Şahin AS. Incidence of Fentanyl-induced Cough and Effect of Dose: Randomized Placebo-controlled Trial. Bagcilar Med Bull 2022;7(2):174-179

Introduction

Fentanyl is one of the synthetic opioids widely used in the induction of general anesthesia due to its rapid onset of action, strong analgesic effect, and cardiovascular stability. Although opioids generally have antitussive effects, paradoxically, intravenous (iv) administration of fentanyl can cause coughing. This condition is known as fentanyl-induced cough (FIC) (1-3).

It is precisely unknown by which mechanism the cough during anesthesia induction occurs. In the suggested opinions, it has been stated that sudden adduction and supraglottic obstruction due to opioid administration may be the cause (4). Although this situation is temporary and self-limiting in most patients, it can lead to dangerous results in some cases.

Life-threatening airway obstructions and aspiration pneumonia secondary to severe FIC have been reported (5). FIC causes an increase in intracranial, intraocular, and intraabdominal pressures. Open eye injury, pneumothorax, cerebral aneurysm, intracerebral hernia, and dissection may cause problems in patients with aneurysms. Premedication with drugs and various methods have been tried to prevent this situation (1-9). Although there are not enough incidence studies in our country, when the literature is examined, the incidence varies in a wide range between 3% and 80% in studies conducted with different doses (10).

This study aims to determine the incidence of cough caused by fentanyl, which is frequently used in anesthesia induction, and to determine the effect of two different induction doses.

Materials and Methods

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: 07.07.2021 number: 223). An informed consent form was obtained from the patients participating in the study. The principles of the Declaration of Helsinki complied with the investigation.

Patients between the ages of 18 and 65 years, who underwent elective surgery under general anesthesia by general surgery, urology, gynecology, and orthopedics and who underwent elective surgery from the ASA I-II Physical status, were included in the study. As exclusion criteria, patients with a history of chronic obstructive pulmonary disease, asthma or upper respiratory tract infection, those smoking, those having angiotensin-converting enzyme inhibitors in the previous two weeks and having chronic cough, those who could not be observed for 60 seconds for cough due to hemodynamic or respiratory problems and high intracranial pressure, intraocular or intra-abdominal pressure were excluded from the study. Patients were randomized into three groups by choosing opaque envelopes extended to them. 1 μg kg^{-1} fentanyl was used to induce the patients in group 1, and 2 μg kg^{-1} fentanyl was used for the induction of the patients in group 2. In the installation of patients in group K, the control group, fentanyl was not used, and a placebo was administered (Figure 1). After a routine electrocardiogram, non-invasive blood pressure, pulse oximetry monitoring, and 20 Gauge iv vascular access, the balanced crystalloid infusion was started in the patients taken to the operation room. No premedication was applied to all three groups. Patients in group 1 were injected intravenously with 1 μg kg^{-1} fentanyl in 2 seconds, patients in group 2 were injected with 2 μg kg^{-1} fentanyl in 2 seconds, and patients in group K were injected with placebo saline in 2 seconds. All patients were observed for 60 seconds by the same anesthesia technician who was blinded to the study. The cough, severity, and time of occurrence were recorded in patients with cough. When assessing the severity of cough, it was classified as mild: 1-2, moderate: 3-4, and severe: >5. Based on the duration of the cough, it was classified as first 5 seconds, 6-10 seconds, 11-30 seconds, and 31-60 seconds. Evaluating the frequency and severity of cough, Zhou et al.'s (1) study was taken as a reference.

After all, patients were observed for 60 seconds, and the study was terminated to determine the cough's presence, severity, and duration. For induction, 0.03 mg kg^{-1} midazolam and 2-3 mg kg^{-1} propofol were used. 1-2 μg kg^{-1} fentanyl was administered to the control group, and surgery was started after endotracheal intubation using 0.6 mg kg^{-1} rocuronium as a neuromuscular blocker.

Hung et al. (7) took their work as a reference in calculating the sample size. In their pilot study, the incidence of cough was determined as 20% due to bolus administration of 150 μg IV fentanyl. At least 199 in each group were required to achieve α:0.05 and 80% power (β:0.2) (7). The sample size was kept more extensive than the reference study, as 750, with 250 patients in each group.

Statistical Analysis

SPSS Inc., Chicago, USA (SPSS v22.0) program was used for statistical analysis. The conformity of the variables to the

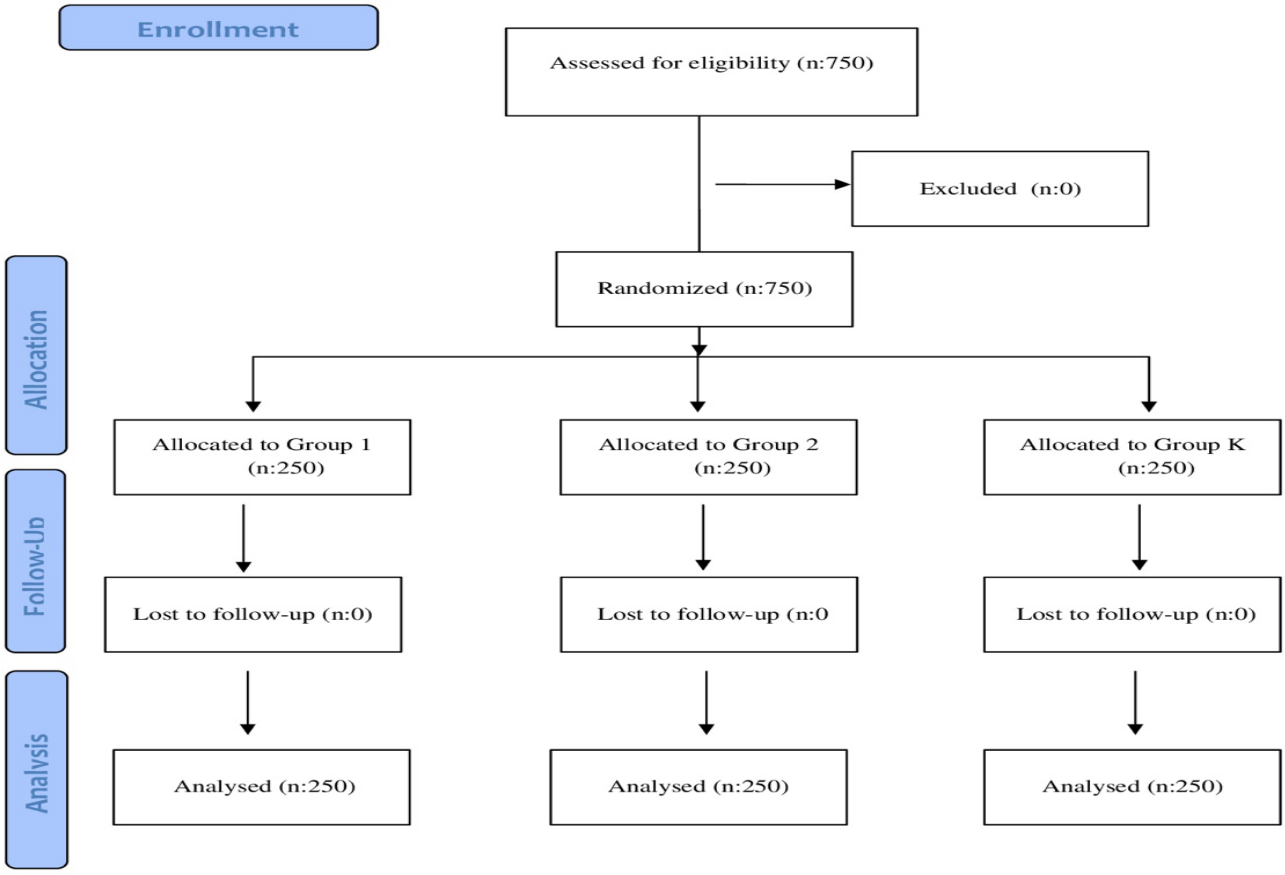

Figure 1. Consort flow chart of the study

normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). The chi-square test was used in the evaluation of qualitative data. The Kruskal-Wallis test was used to analyze quantitative data that did not have a normal distribution. The statistical significance limit was accepted as $p<0.05$.

Results

There was no significant difference between the groups regarding age, body mass index, and gender distribution of the patients. Demographic data of the groups are shown in Table 1. All patients were observed for 60 seconds after iv injection and the study was terminated. None of the patients had hemodynamic instability and oxygen desaturation (SpO_2< 92%) that required termination of the study. Cough was detected in 95 (12.6%) of the patients. While it was observed in 15 patients in group 1 and 80 patients in group 2, the cough was not observed in group K. In both groups, the cough was mainly mild (1-2 times). The incidence was determined as 6% for group 1, 32% for group 2, and 0% for group K. While all of the coughs in group 1 were mild, it was mild in 66 (82%) patients and moderate in 14 (18%) patients in group 2. Severe cough was not observed in either group. Coughing in group 1 was significantly higher than in the control group ($p<0.001$).

Table 1. Demographic data of the groups

	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
Gender (F/M) (n)	130/120	104/146	120/130	0.06
Age (years)	44.8±14.2	43.8±15.4	45.8±12.5	0.61
Body mass index (kg/m²)	26.2±3.0	25.9±3.3	26.2±2.7	0.21

Values are the number of patients (n), mean ± standard deviation

Cough severity and incidence (32%) in group 2 were significantly higher than in group 1 (6%) ($p<0.001$). In Table 2, cough severity according to the groups is shown. Cough occurred in the first 5 seconds after fentanyl injection in 83% of patients for groups 1 and 2. Cough was observed in the first 10 seconds in 94.7% of the patients. No cough was observed after 30 seconds in any of the patients. In the comparison between the groups, the duration of cough was significantly different for both the first 5 seconds and 6-10 seconds ($p<0.001$). The cough occurrence times of the groups are shown in Table 3 and Figure 2.

Discussion

Our study determined that cough induced by fentanyl administered at a dose of 2 μg kg^{-1} iv was significantly higher in the group administered at a dose of 1 μg kg^{-1} than in the control group. The incidence of cough was 32% in group 2, and decreased to 6% in group 1.

It has not been determined precisely how FIC occurs. There are various hypotheses put forward in this regard. In studies, the cough has generally been attributed to a reflection of muscle rigidity and consequent sudden adduction of the vocal folds or supraglottic obstruction of soft tissues.

Table 2. Cough frequency and severity of the groups

	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
Coughing patient (n)	15	80	0	<0.001
Mild cough (1-2 times) (n)	15	66	0	<0.001
Moderate cough (3-5 times) (n)	0	14	0	<0.001
Severe cough (>5 times) (n)	0	0	0	-

Values are given as the number of patients

Table 3. Distribution of patients according to the time of cough after fentanyl injection

	Group 1 (n=250)	Group 2 (n=250)	Group K (n=250)	p
First 5 seconds (n)	13	66	0	<0.001
6-10 seconds (n)	1	10	0	<0.001
11-30 seconds (n)	1	4	0	0.99
31-60 seconds (n)	0	0	0	-

Values are given as the number of patients

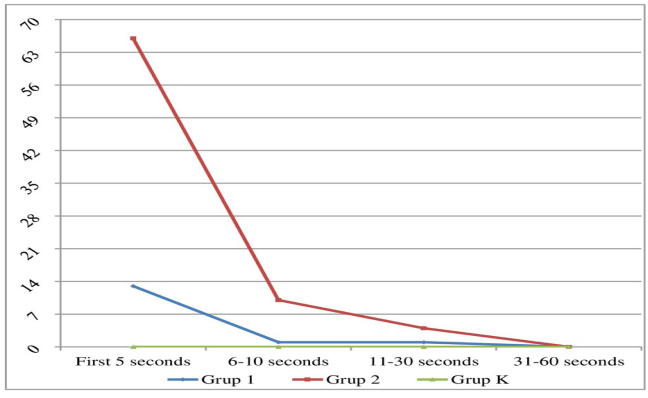

Figure 2. Distribution of patients according to the time of cough after fentanyl injection

Figure 2. Distribution of patients according to the time of cough after fentanyl injection

According to other hypotheses, cough is due to the release of histamine by iv administered fentanyl or the secretion of tachykinin by stimulating the pulmonary C-fibers of the citrate. Cough occurs by causing bronchoconstriction in tracheal smooth muscle cells (10). In general, in controlled studies with 9% NaCl, it was reported that cough was higher in the fentanyl group. However, there are also studies reporting that the incidence of cough observed in the placebo group was not different from the fentanyl group. The injection site, administration from angiocath or central venous catheter, genetic factors, and comorbidities may play a role in the emergence of this situation (11). In our study, 9% NaCl was used in the control group, and cough was not detected in any patients.

Cough has also been reported after iv injection of remifentanil, sufentanil, and alfentanil from the same family (12). In studies, the incidence of cough has been reported in a wide range between 3% and 80% (9). Our study found that the average incidence of cough was 12.6%. The literature investigated the effects of the applied dose, administration time, diluting of the fentanyl dose, lowering the concentration, various premedication agents, and methods on the cough (13,14). He et al. (14) investigated the effect of 1 μg kg^{-1} dexmedetomidine in their studies using fentanyl at a dose of 4 μg kg^{-1}. The incidence, 60% in the control group, decreased to 18% in the treated group (14). Hung et al. (7) reported that preemptive administration of a small dose (25 μg) of fentanyl used in induction in their studies resulted in a significant decrease in the incidence of cough compared to the group given a total dose (2 μg kg^{-1}).

Uvelin and Rakic (15) recommended guidelines to prevent the harmful effects of coughing in high-risk patients. Studies have reported that genetic factors may also be influential on fentanyl cough. The incidence, which can reach 80% in the Far East and Asian countries, decreases to 3% in European countries (16,17). The incidence detected in our study is similar to the studies reported in European countries.

Lin et al. (18) reported that age was also influential on fentanyl cough. They attributed the higher incidence in the young than the elderly to the higher irritant receptor activity in the young. Although the mean age of the patients in all three groups was similar in our study, the relationship between age and the presence of cough was not examined. Pandey et al. (13) used 3 μg kg^{-1} fentanyl in their studies and reported the frequency of mild cough as 70% and moderate cough as 30%. In our study, mild cough was detected in 81% and moderate cough in 19%, while severe cough was not

observed. Cough severity was significantly higher in group 2 than in group 1, which is consistent with the literature.

When the literature is examined, there is no consensus on the duration of FIC. Hung et al. (7) proposed the hypothesis that the rate of iv injection created a particular blood concentration in cough formation. Yakıcı et al. (10), in their study examining the effect of iv injection speed of fentanyl, divided the patients into two groups and administered 2 μg kg^{-1} fentanyl in 5 and 30 seconds. In both groups, the cough was observed within the first 10 seconds in more than half of the cases (10). In our study, the FIC was observed within the first 5 seconds in 83% of the patients and within the first 10 seconds in 94% of the patients. No cough was observed 30 seconds after IV administration.

Study Limitations

The limitation of our study is that it was single-centered and it did not analyzed according to age groups. The incidence of FIC can be high in young people.

Conclusion

In our study, the incidence was determined as 6% for group 1, 32% for group 2, and 0% for group K. The mean incidence in patients was 12.6%. There is a significant relationship between fentanyl dose and the incidence and severity of the cough. We recommend reducing the amount of fentanyl used in induction to avoid cough in cases where local pressure increases may be problematic, such as intracranial or intraocular surgery.

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: 07.07.2021 number: 223).

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

Peer-review: Internally and externally peer-reviewed.

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.

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

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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(2):180-188
DOI: 10.4274/BMB.galenos.2022.2022-02-020

A Multicenter Evaluation of the Temporal and Clinical Differences of COVID-19 in Two Different Regions in Turkey: Comparison of İstanbul and Diyarbakır

Türkiye'de İki Farklı Bölgede COVID-19'un Zamansal ve Klinik Farklılıklarının Çok Merkezli Bir Değerlendirmesi: İstanbul ve Diyarbakır'ın Karşılaştırılması

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Abstract

Objective: This study compared the temporal course of virulence and symptomatology of severe coronavirus-19 (COVID-19) infection in two metropolitan cities with different geographic features. The study aimed to shed light on the possible etiology of the differences observed between two regions.

Method: We retrospectively reviewed polymerase chain reaction confirmed COVID-19 cases for the period of March-June 2020 in two different cities (İstanbul and Diyarbakır) located in northern and southern parts of Turkey, respectively. Data on demographic features, presenting symptoms, clinical history, radiological findings, laboratory parameters, and mean hospitalization duration were collected. Additionally, meteorological data including daily temperature, diurnal temperature variation, relative humidity, wind speed, mean rainfall, ultraviolet index, altitude, and latitude were retrieved for the study period.

Results: Total case number was higher in İstanbul during March and April, whereas it was higher in Diyarbakır during May and June (p=0.001). During the study period, daily temperature, diurnal temperature variation, and ultraviolet index were higher in Diyarbakır, whereas relative humidity, wind speed, and mean rainfall was higher in İstanbul (p=0.001). In Diyarbakır, patients presented with a predominance of dyspnea, whereas there was a predominance of fever and cough in İstanbul. Patients in

Öz

Amaç: Bu çalışmada, farklı coğrafi özelliklere sahip iki büyükşehirde şiddetli koronavirüs-19 (COVİD-19) enfeksiyonunun virülansının zamansal seyri ve semptomatolojisi karşılaştırıldı. Çalışmada, iki bölge arasında gözlenen farklılıkların olası etiyolojisine ışık tutulması amaçlandı.

Yöntem: Mart-Haziran 2020 döneminde Türkiye'nin kuzey ve güney kesimlerinde bulunan iki farklı şehirde (İstanbul ve Diyarbakır) polimeraz zincir reaksiyonu ile doğrulanmış COVİD-19 olgularını geriye dönük olarak inceledik. Demografik özellikler, başvuru semptomları, geçmiş klinik öykü, radyolojik bulgular, laboratuvar parametreleri ve ortalama hastanede yatış süresi kaydedildi. Ayrıca çalışma dönemi için günlük sıcaklık, günlük sıcaklık değişimi, bağıl nem, rüzgar hızı, ortalama yağış, ultraviyole indeksi, yükseklik ve enlem gibi meteorolojik veriler de elde edildi.

Bulgular: Toplam olgu sayısı İstanbul'da Mart ve Nisan aylarında daha yüksek iken, Diyarbakır'da Mayıs ve Haziran aylarında daha yüksekti (p=0,001). Çalışma süresi boyunca Diyarbakır'da günlük sıcaklık, günlük sıcaklık değişimi ve ultraviyole indeksi daha yüksek iken, İstanbul'da bağıl nem, rüzgar hızı, ortalama yağış miktarı daha yüksek bulundu (p=0,001). Diyarbakır'da hastalar daha çok nefes darlığı ile başvururken, İstanbul'da ise ateş, öksürük hakimdi. Diyarbakır'daki hastaların nötrofil, nötrofil/lenfosit oranı, D-dimer, laktat dehidrogenaz, ferritin ve C-reaktif protein

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Cite this article as: Vuran Ö, Tekcan Şanlı DE, Şanlı AN, Altundağ A. A Multicenter Evaluation of the Temporal and Clinical Differences of COVID-19 in Two Different Regions in Turkey: Comparison of İstanbul and Diyarbakır. Bagcilar Med Bull 2022;7(2):180-188

Abstract

Diyarbakır had significantly elevated neutrophil, neutrophil/lymphocyte ratio, D-dimer, lactate dehydrogenase, ferritin and C-reactive protein values compared to patients in İstanbul (p=0.018; p=0.006; p=0.001, p=0.001; p=0.001, p=0.001 respectively). The predominant computed tomography infiltration was multicentric and bilateral crazy-paving pattern in Diyarbakır, whereas unilateral ground-glass opacity was the dominant pattern in İstanbul.

Conclusion: The socio-cultural and genetic factors may affect the epidemiological, clinical and imaging features of COVID-19 more than meteorological variations.

Keywords: COVID-19, etiology, geographic features

Öz

değerleri İstanbul'daki hastalara göre anlamlı olarak yüksekti (p=0,018; p=0,006; p=0,001, p=0,001; p=0,001, p=0,001 sırasıyla). Diyarbakır'da baskın bilgisayarlı tomografi infiltrasyonu multisentrik ve bilateral crazy paving paterni iken, İstanbul'da tek taraflı buzlu cam opasitesi baskın paterndi.

Sonuç: Sosyo-kültürel ve genetik faktörler, COVİD-19'un epidemiyolojik, klinik ve görüntüleme özelliklerini meteorolojik varyasyonlardan daha fazla etkileyebilir.

Anahtar kelimeler: Coğrafi özellikler, COVID-19, etiyoloji

Introduction

Initial detection and peaking of Coronavirus disease-2019 (COVID-19) cases in Turkey were seen relatively later compared to the rest of the European countries. The first COVID-19 case in Turkey was confirmed on March 11, 2020 in İstanbul according to the data published by the Turkish Ministry of Health. In the upcoming weeks, İstanbul, which is a cosmopolitan city with a population of 15 million (constituting 20% of Turkey's population) and a high density national and international city hub, became the epicenter of the disease. The peak period was seen within 2 months with a subsequent plateau phase, similar to other countries. On the other hand, Diyarbakır and other cities located in the Southeastern Turkey did have limited case numbers in the initial phase of infection with a later peak period in 3-4 months. Additionally, hospitalized cases in these southeastern cities had more severe clinical and radiological courses.

Host-related genetic factors may affect infectivity, disease course, and mortality (1). Human genetics have a high similarity ratio; however, *HLA* genes which constitute the pillars of human immune system and immune response to an infectious or allergic factor show considerable variation (2,3). The main entry mechanism of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is via ACE-2 receptors (4,5). Increased ACE-2 expression by host cells may increase viral pathogenicity, replication, and cellular damage (6,7). Several studies have shown a correlation between host ACE-2 receptor numbers and viral load and disease severity (8). On the other hand, mounted immune response is the most important factor in infection control and determines the disease severity, complication, and mortality.

COVID-19 may have variable clinical course ranging from asymptomatic carrier state to a fatal outcome. 18-30% of cases can be asymptomatic or mildly symptomatic, with higher complication and mortality rates seen in elderly males with comorbidities (9-13). In addition to more severe disease course, this susceptible population has higher hospitalization and intensive care unit admission rates. Younger adults usually have milder or even asymptomatic form of the disease; however, even immunocompetent healthy young adults with no risk factors or comorbidities may have severe disease course. There are numerous studies investigating the relationship between the disease course and viral (viral load, pathogenicity, viral genetic subtype/mutation analysis), host (age, sex, ACE-2 receptor status/polymorphism, immune status, comorbidities), environmental (temperature, humidity, rainfall, wind speed), and socio-economic factors (ethnicity, culture, lifestyle, abiding/adapting to isolation and disinfection measures). However, no ground truth could be established to predict transmission dynamics and disease course.

In this study, we assessed the temporal course of clinical and radiological findings of COVID-19 cases in two hospitals from different regions of Turkey. Our aim was to evaluate the relationship between clinical/radiological findings and meteorological, socio-economic, ethnic and genetic variables.

Materials and Methods

Study Population

This study was approved by the Local Ethics Committee (date: 11.06.2020 number: 2020/12). We retrospectively reviewed polymerase chain reaction confirmed COVID-19 cases from two hospitals, Acıbadem Kozyatağı Hospital and Diyarbakir Selahaddin Eyyubi State Hospital, in two different cities in Turkey for the period of March-June 2020. Demographic features, presenting symptoms, clinical history, radiological findings [typical vs atypical lung computed tomography (CT) features, infiltration pattern, and distribution], laboratory parameters [(C-reactive

protein (CRP), leukocyte, neutrophil, lymphocyte counts, hemoglobin, thrombocyte, D-dimer, lactate dehydrogenase (LDH) levels], and mean hospitalization duration were collected.

Meteorological Parameters

Monthly meteorological data including daily temperature, diurnal temperature variation, relative humidity, wind speed, mean rainfall, ultraviolet index, altitude, and latitude were retrieved for the study period. Also, air pollution quality index was recorded.

Radiological Assessment

Chest CT scans were acquired with Siemens Somatom Sensation-Syngo CT and GE Optima 660 in İstanbul and Diyarbakır, respectively. A single radiologist with 10 years of experience in thorax radiology assessed all CT images from two centers based on the Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19 (14). CT images were reviewed for typical/atypical disease patterns, dominant infiltration patterns (ground-glass, crazy-paving, consolidation), and distribution of parenchymal involvement (unilateral/bilateral involvement, lower/upper lobe predominance, diffuse/peripheral/central/mixed). Additionally, changes at follow-up chest CT scans were assessed.

Statistical Analysis

All statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. The Shapiro-Wilk test was used to determine whether the data showed normal distribution. The Student's t-test and Mann-Whitney U test were used for parametric and non-parametric data, respectively. For categorical variables, the chi-square, Fisher's Exact and Fisher-Freeman-Halton Exact tests were used. The Spearman test was used for correlation. A p-value of <0.05 was considered statistically significant.

Results

A total of 429 cases from two cities (Acıbadem Kozyatağı Hospital in İstanbul, Gaziantep Selahaddin Eyyubi State Hospital in Diyarbakır) with a slight male dominance (209 (48.7%) female, 220 (51.3%) male patients) were included in the study. The mean age of the study population was 50.43±16.72 years (5-93). There was a female predominance with a slightly older population (52.06±17.73 years) in patients recruited from Diyarbakır (p=0.049) (Table 1) (Figure 1).

The total case number was higher in İstanbul during March and April, whereas it was higher in Diyarbakır during May and June (p=0.001) (Figure 1). The interval between symptom onset and presentation to the hospital was significantly higher in Diyarbakır (5.34±3.12/3.27±1.26, p=0.001). There was a significantly higher hospitalization rate among presenting patients in Diyarbakır (99.5%/47.8%, p=0.001) with no significant difference in the duration of hospitalization (5.59±3.43/5.85±3.71, p=0.595) (Table 1).

There was no significant difference in comorbidity rates between the two cities. In Diyarbakır, patients presented with a predominance of dyspnea, and myalgia whereas there was a predominance of fever, cough, headache, sore throat, and loss of appetite in İstanbul (Table 1).

Though patients in Diyarbakır had lower white blood cell values compared to İstanbul cases, this difference did not reach a statistical significance (p=0.057). Patients in Diyarbakır had significantly elevated neutrophil, neutrophil/lymphocyte ratio, D-dimer, LDH, ferritin and CRP values compared to those in İstanbul (p=0.018; p=0.006; p=0.001, p=0.001; p=0.001, p=0.001, respectively) (Table 2).

There were significant differences in abnormal chest CT findings according to the number of lesions between the two cities (p=0.001). There was a significant tendency for multiple and bilateral infiltration patterns in Diyarbakır compared to İstanbul (p=0.001). A total of 19% cases had normal CT findings in İstanbul whereas this rate was 4.3% in Diyarbakır. 50% of cases in İstanbul had a typical COVID-19 infiltration pattern whereas 88% of cases in Diyarbakır had the typical COVID-19 infiltration pattern. The predominant CT infiltration was a crazy-paving pattern in Diyarbakır whereas unilateral, solitary ground-glass opacity was the dominant pattern in Istanbul (Tables 3 and 4).

During the study period, daily temperature, diurnal temperature variation, and the ultraviolet index were significantly higher in Diyarbakır compared to İstanbul (p=0.001) (Figure 1). Similarly, the UV index was significantly higher in Diyarbakır compared to İstanbul whereas relative humidity, wind speed, and mean rainfall were higher in İstanbul (p=0.001) (Tables 5 and 6) (Figure 1). The mean air pollution index was 87 (moderate) in Diyarbakır and 101

Table 1. Evaluation of descriptive characteristics by city

			City		
		Total (n=429)	İstanbul (n=224)	Diyarbakır (n=205)	p
Age	**Min-max (median)**	5-93 (49)	5-93 (47)	17-87 (53)	[a]**0.054**
	Mean ± SD	50.43±16.72	48.94±15.64	52.06±17.73	
Gender	**Female**	209 (48.7)	99 (44.2)	110 (53.7)	[b]**0.049***
	Male	220 (51.3)	125 (55.8)	95 (46.3)	
Hospitalization	**No**	118 (27.5)	117 (52.2)	1 (0.5)	[b]**0.001****
	Yes	331 (72.5)	107 (47.8)	204 (99.5)	
Average hospitalization time	Min-max (median)	1-34 (5)	1-20 (5)	1-34 (5)	[c]**0.595**
	Mean ± SD	5.68±3.53	5.85±3.71	5.59±3.43	
Interval between symptom onset to the hospital	Min-max (median)	1-15 (3)	1-8 (3)	1-15 (4)	[c]**0.001****
	Mean ± SD	4.26±2.55	3.27±1.26	5.34±3.12	
Month	**March**	101 (23.5)	89 (39.7)	12 (5.9)	[b]**0.001****
	April	183 (42.7)	117 (52.2)	66 (32.2)	[b]**0.001****
	May	54 (12.6)	16 (7.2)	38 (18.5)	[b]**0.001****
	June	91 (21.2)	2 (0.9)	89 (43.4)	[b]**0.001****
Comorbidities		76 (17.7)	38 (17.0)	38 (18.5)	[b]**0.670**
Complaints	**Headache**	88 (20.5)	59 (26.3)	29 (14.1)	[b]**0.002****
	Anorexia	84 (19.6)	62 (27.7)	22 (10.7)	[b]**0.001****
	Cough	230 (53.6)	133 (59.4)	97 (47.3)	[b]**0.012***
	Shortness of breath	125 (29.1)	48 (21.4)	77 (37.6)	[b]**0.001****
	Weakness	137 (31.9)	43 (19.2)	94 (45.9)	[b]**0.001****
	Sore throat	54 (12.6)	36 (16.1)	18 (8.8)	[b]**0.023***
	Fever	181 (42.2)	129 (57.6)	52 (25.4)	[b]**0.001****

[a]: Student's t-test, [b]: Pearson's chi-square test, [c]: Mann-Whitney U test, *p<0.05, **p<0.01, SD: Standard deviation

(unhealthy for sensitive groups) in İstanbul between March and June 2020.

Discussion

Some of the most intriguing points about the COVID-19 pandemic are variability in transmission rates, clinical course and mortality rates among different countries and regions. Differences in national healthcare policies, type and amount of testing, isolation and treatment protocols might be some of the underlying factors (15). Additionally, variability in climate conditions might affect the virus pathogenicity (16,17). Ma et al. (16), in a study investigating the effects of temperature, humidity and diurnal temperature variation on COVID-19 mortality, reported a negative correlation with temperature and humidity and a positive correlation with diurnal temperature variation (18,19). Additionally, studies reported the effects of other different meteorological parameters like ultraviolet index and wind speed on virulence and transmission rates (16,20,21). However, the results of our study showed a later peak and more severe disease course in Diyarbakır despite higher temperature and ultraviolet index, suggesting

Figure 1. Temporal differences of Diyarbakır and İstanbul according to their geographical locations

COVID-19: Coronavirus disease

Table 2. Evaluation of laboratory findings by city

			City		
		Total (n=429)	İstanbul (n=224)	Diyarbakır (n=205)	p
WBC	Min-max (median)	2.5-23.1 (7)	2.5-20 (7)	2.6-23.1 (6.84)	[c]**0.057**
	Mean ± SD	7.83±3.41	8.01±3.24	7.64±3.58	
NEU (%)	Min-max (median)	0-93.6 (66.1)	0-92.4 (62.7)	35.9-93.6 (70.1)	[a]**0.001****
	Mean ± SD	65.52±13.95	61.93±14.69	69.22±12.12	
LYMP (%)	Min-max (median)	2.5-75.2 (23.4)	2.5-75.2 (24)	3-54.8 (22.1)	[a]**0.031***
	Mean ± SD	24.27±11.31	25.45±11.98	23.06±10.48	
NEU	Min-max (median)	1.1-18.41 (4.43)	1.1-14.3 (4.08)	1.1-18.41 (4.58)	[c]**0.018***
	Mean ± SD	5.09±2.84	4.77±2.65	5.42±3.00	
LYMP	Min-max (median)	0.27-8.56 (1.49)	0.27-8.56 (1.57)	0.3-7.52 (1.44)	[c]**0.236**
	Mean ± SD	1.68±0.97	1.72±0.98	1.63±0.96	
N/L	Min-max (median)	0.2-37.3 (2.85)	0.2-37.3 (2.65)	0.7-30.8 (3.16)	[c]**0.006****
	Mean ± SD	4.14±4.51	3.92±4.83	4.36±4.15	
D-dimer	n	342	150	192	[c]**0.001****
	Min-max (median)	0-1210 (25.3)	0-138 (19)	1.5-1210 (54.5)	
	Mean ± SD	4.9±10.65	1.5±18	8.73±130	
HGB	n	413	210	203	[a]**0.680**
	Min-max (median)	5.4-17.3 (13.7)	9.1-17.3 (13.7)	5.4-17 (13.7)	
	Mean ± SD	13.48±1.83	13.52±1.75	13.45±1.92	
PLT	n	413	209	204	[a]**0.880**
	Min-max (median)	12.2-562 (208)	12.2-562 (209)	80-466 (207.5)	
	Mean ± SD	216.74±74.38	216.19±75.6	217.3±73.3	
LDH	n	262	129	133	[c]**0.001****
	Min-max (median)	81-649 (221.5)	81-489 (181)	132-649 (255)	
	Mean ± SD	246.4±103.78	201.23±72.4	290.21±110.83	
Ferritin	n	138	38	100	[c]**0.001****
	Min-max (median)	0-1588 (107.1)	0-1002 (88)	5.4-1588 (259.55)	
	Mean ± SD	229.13±285.3	21±41	316.12±291.34	
CRP	n	301	97	204	[c]**0.001****
	Min-max (median)	0-350 (8.5)	0-17 (0.71)	1.5-350 (24.5)	
	Mean ± SD	35.95±58.14	2.08±3.18	52.05±64.67	

[a]: Student's t-test, [c]: Mann-Whitney U test, *p<0.05, **p<0.01, SD: Standard deviation, CRP: C-reactive protein, LDH: Lactate dehydrogenase, PLT: Platelet count, HGB: Hemoglobin, WBC: White blood cell, NEU: Neutrophil, LYMP: Lymphocyte

that the effect of meteorological variations on disease virulence and transmission rates might be limited. Patients in İstanbul generally had a milder COVID-19 infection, similar to other viral upper respiratory tract infections. We think that these parameters may be an important factor for the virus to remain as an upper respiratory tract infection without descending to the lower respiratory tract.

Cultural differences affect the social life and behavior. Consequently, this might influence the dynamics of infectious disease like transmission rates and isolation control. Since the main transmission route is respiratory droplets, increased population density and high population mobility may account for higher transmission rates and increased case numbers in crowded cities like İstanbul. Southeastern cities like Diyarbakır have extended family structure with a much higher rate of social interaction. Traditional wedding ceremonies and funeral services with limited social isolation practice might account for high number of cases in relatively less densely populated cities like Diyarbakır. Additionally, lower educational levels in Diyarbakır may have led to lower rates of personal protective equipment utilization. We think that higher rates encountered in Diyarbakır might be related to differences in socio-cultural and educational differences. In support of this hypothesis, a study from Brazil reported varying mortality rates across different regions and ethnicities and suggested that this regional difference might be related to socio-economic factors (22). According to the results of our study, we think that sociocultural characteristics are more effective in the spread of the disease.

Table 3. Evaluation of radiological findings by city

		City			p
		Total	İstanbul	Diyarbakır	
		n (%)	n (%)	n (%)	
CT	**▪Normal**	52	43	9	[b]**0.468**
	Typical	293 (77.7)	113 (62.4)	180 (91.8)	
	Atypical	84 (22.3)	68 (37.6)	16 (8.2)	
	▪Normal	52	43	9	[b]**0.001****
	Single	180 (47.7)	145 (80.1)	35 (17.9)	
	Multiple	197 (52.3)	36 (19.9)	161 (82.1)	
Percentage of parenchyma in the progression phase	**1**	195 (51.7)	60 (33.1)	135 (68.9)	[d]**0.001****
	2	163 (43.2)	121 (66.9)	42 (21.4)	
	3	15 (4.0)	0 (0.0)	15 (7.7)	
	4	4 (1.1)	0 (0.0)	4 (2.0)	
Side	**Unilateral**	79 (21.0)	60 (33.1)	19 (9.7)	[b]**0.001****
	Bilateral	298 (79.0)	121 (66.9)	177 (90.3)	
Dominant infiltration pattern	**Ground glass**	184 (49.3)	102 (57.6)	82 (41.8)	[b]**0.001****
	Crazy-paving	133 (35.7)	43 (24.3)	90 (45.9)	
	Consolidation	56 (15.0)	32 (18.1)	24 (12.2)	
Dominant distribution	**Lower lobe**	224 (59.9)	115 (64.6)	109 (55.6)	[b]**0.083**
	Upper lobe	59 (15.8)	29 (16.3)	30 (15.3)	
	Common	91 (24.3)	34 (19.1)	57 (29.1)	
Distribution	**Basal/peripheral**	238 (63.1)	103 (56.9)	135 (68.9)	[b]**0.001****
	Central	55 (14.6)	41 (22.7)	14 (7.1)	
	Common	84 (22.3)	37 (20.4)	47 (24.0)	
Largest lesion diameter	n	259	131	128	[c]**0.425**
	Min-max (Median)	1-20 (3)	1-20 (3)	1-15 (3)	
	Mean ± SD	4.16±2.84	4.47±3.40	3.84±2.10	
Pleural effusion		42 (11.1)	22 (12.2)	20 (10.2)	[b]**0.548**
Pleural thickening		135 (35.8)	65 (35.9)	70 (35.7)	[b]**0.968**
Fibrotic band		101 (26.8)	73 (40.3)	28 (14.3)	[b]**0.001****
Stage of the disease in the first CT	**Early**	116 (39.6)	59 (52.2)	57 (31.7)	[b]**0.001****
	Consolidation	162 (55.3)	47 (41.6)	115 (63.9)	
	Dissolution	15 (5.1)	7 (6.2)	8 (4.4)	

[b]: Pearson's chi-square test, [c]: Mann-Whitney U test, [d]: Fisher-Freeman-Halton test, **p<0.01, ▪not included in the comparison, CT: Computed tomography, SD: Standard deviation

In addition to regional differences across countries, differences in temporal course, infectivity and pathogenicity have been reported in different districts of the same city. A study evaluating the effect of ethnicity, socio-economic and educational status on hospitalization and mortality rates in different districts of New York reported worse outcomes in Bronx, which have a higher ratio of African American young adult population (23). This supports the hypothesis that lower socio-economic and educational status and ethnicity may affect mortality rate more than patient's age.

Viral and host-related genetic variations have been extensively studied for their effects on infectivity, disease severity and mortality. Variations in viral structure may account for the differences seen in disease severity and mortality across different nations. Karacan et al. (24) isolated 3 different viral strains in a patient population with different clinical course (mild-moderate-severe).

In the present study, hospitalization rates were significantly higher for Diyarbakır. It is possible to explain this situation with the fact that, first, the patients in Diyarbakır had a more severe disease; secondly, those who applied to the hospital in Diyarbakır were most seriously ill; and mild-moderate patients were not admitted to the hospital. On the contrary, in İstanbul, even mild to moderate patients were admitted to the hospital and were hospitalized for different indications.

Table 4. Evaluation of radiological findings of patients with typical CT results by city

CT: Typical		City		p
		İstanbul	Diyarbakır	
		n (%)	n (%)	
	Single	87 (77.0)	30 (16.7)	[b]0.001**
	Multiple	26 (23.0)	150 (83.3)	
Percentage of parenchyma in the progression phase	1	30 (26.5)	124 (68.9)	[d]0.001**
	2	83 (73.5)	39 (21.7)	
	3	0 (0.0)	13 (7.2)	
	4	0 (0.0)	4 (2.2)	
Side	Unilateral	30 (26.5)	17 (9.4)	[b]0.001**
	Bilateral	83 (73.5)	163 (90.6)	
Dominant infiltration pattern	Ground glass	63 (55.8)	73 (40.6)	[b]0.033*
	Crazy-paving	37 (32.7)	84 (46.7)	
	Consolidation	13 (11.5)	23 (12.8)	
Dominant distribution	Lower lobe	68 (60.2)	100 (55.6)	[b]0.738
	Upper lobe	15 (13.3)	27 (15.0)	
	Common	30 (26.5)	53 (29.4)	
Distribution	Basal/peripheral	57 (50.4)	128 (71.1)	[b]0.001**
	Central	25 (22.1)	11 (6.1)	
	Common	31 (27.4)	41 (22.8)	
Largest lesion diameter	n	99	124	[c]0.486
	Min-max (median)	1-20 (3)	1-15 (3)	
	Mean ± SD	4.30±3.19	3.77±2.03	
Pleural effusion		10 (8.8)	20 (11.1)	[b]0.534
Pleural thickening		39 (34.5)	68 (37.8)	[b]0.572
Fibrotic band		47 (41.6)	27 (15.0)	[b]0.001**

[b]: Pearson's chi-square test, [c]:Mann-Whitney U test, [d]: Fisher-Freeman-Halton test, **p<0.01, SD: Standard deviation, CT: Computed tomography

Table 5. Evaluation of climatic conditions by city

			City		
		Total (n=429)	İstanbul (n=224)	Diyarbakır (n=205)	p
Daytime air temperature	Min-max (median)	11.5-31.9 (16)	11.5-25 (16)	13.3-31.9 (24.5)	[c]0.001**
	Mean ± SD	19.71±7.20	14.65±2.88	25.24±6.39	
Night air temperature	Min-max (median)	8.6-29.6 (11.9)	8.6-20.2 (11.9)	9.3-26.9 (18.9)	[c]0.001**
	Mean ± SD	15.48±6.54	10.97±2.31	20.42±6.08	
Temperature difference	Min-max (median)	2.9-5.58 (4.13)	2.9-4.8 (4.13)	4-5.58 (5)	[c]0.001**
	Mean ± SD	4.23±0.80	3.68±0.62	4.82±0.50	
Humidity	Min-max (median)	29-69 (62)	59-69 (62)	29-63 (46)	[c]0.001**
	Mean ± SD	54.05±14.28	64.61±3.62	42.51±12.53	
Wind speed	Min-max (median)	9-16 (14)	14-16 (15)	9-12 (10)	[c]0.001**
	Mean ± SD	13.01±2.63	15.32±0.62	10.49±1.37	
Rainfall	Min-max (median)	4-63 (41)	31-63 (41)	4-56 (35)	[c]0.001**
	Mean ± SD	39.67±20.75	49.00±11.67	29.47±23.55	
UV angle	Min-max (median)	4-10 (5)	4-8 (5)	5-10 (9)	[c]0.001**
	Mean ± SD	6.58±2.27	4.77±0.85	8.56±1.57	

[c]: Mann-Whitney U test, **p<0.01, SD: Standard deviation

Table 6. Evaluation of radiological findings by cities in patients with atypical CT findings

CT: Atypical		City		p
		İstanbul	Diyarbakır	
		n (%)	n (%)	
	Single	58 (85.3)	5 (31.3)	[e]0.001**
	Multiple	10 (14.7)	11 (68.8)	
Percentage of parenchyma in the progression phase	1	30 (44.1)	11 (68.8)	[d]0.003**
	2	38 (55.9)	3 (18.8)	
	3	0 (0.0)	2 (12.5)	
Side	Unilateral	30 (44.1)	2 (12.5)	[b]0.019*
	Bilateral	38 (55.9)	14 (87.5)	
Dominant infiltration pattern	Ground glass	39 (60.9)	9 (56.25)	[d]0.010*
	Crazy-paving	6 (9.4)	6 (37.50)	
	Consolidation	19 (29.7)	1 (6.25)	
Dominant distribution	Lower lobe	50 (73.5)	9 (56.3)	[d]0.74
	Upper lobe	14 (20.6)	3 (18.8)	
	Common	4 (5.9)	4 (25.0)	
Distribution	Basal/peripheral	43 (66.2)	7 (43.8)	[d]0.028*
	Central	16 (24.6)	3 (18.8)	
	Common	6 (9.2)	6 (37.5)	
Largest lesion diameter	n	32	4	[c]0.416
	Min-max (median)	1-20 (5)	2-10 (6)	
	Mean ± SD	5.00±3.98	6.00±3.27	
Pleural effusion		12 (17.6)	0 (0.0)	[e]0.111
Pleural thickening		26 (38.2)	2 (12.5)	[b]0.049*
Fibrotic band		26 (38.2)	1 (6.3)	[b]0.014*

[b]: Pearson's chi-square test, [c]: Mann-Whitney U test, [d]: Fisher-Freeman-Halton test, [e]: Fisher's Exact test, **p<0.01, SD: Standard devaition, CT: Computed tomography

Study Limitations

This study, in which we compared the temporal course of virulence and symptomatology of SARS-CoV-2 infection in two different cities, despite being a multicenter study, is still limited by lack of multiple centers from the same city. Additionally, we did not have access to regional Turkish Ministry of Health data for these two cities, which limited the assessment of actual infectivity and mortality rate for these two cities in total. We could not obtain genetic analysis due to limited funding, which renders the genetic differences between patient populations an assumption at best.

Conclusion

COVID-19 infectivity, pathogenicity, clinical course and mortality rates show variation across nations, cities and individuals. In addition to age, sex and comorbidities, environmental, meteorological, socio-economical, and racial factors might account for some of these variations.

Main points

1. The clinical course of COVID-19 varies according to host-related factors (age, sex, race, ACE-2 receptor status/polymorphism, immune status, comorbidities).

2. Environmental parameters such as temperature, humidity, rainfall, and wind speed can affect COVID-19 virulence.

3. Socio-economic status and cultural characteristics affect the spread of the disease.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (date: 11.06.2020 number: 2020/12). We retrospectively reviewed polymerase chain reaction confirmed COVID-19 cases from two hospitals, Acıbadem Kozyatağı Hospital and Diyarbakir Selahaddin Eyyubi State Hospital, in two different cities in Turkey for the period of March-June 2020.

Informed Consent: Written informed consent for publication was not necessary because no identifying patient data have been included in this manuscript.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: Ö.V., D.E.T.Ş., A.A., Design: Ö.V., D.E.T.Ş., A.A., Data Collection or Processing: Ö.V., D.E.T.Ş., Analysis or Interpretation: D.E.T.Ş., A.N.Ş., A.A., Drafting Manuscript: Ö.V., D.E.T.Ş., A.N.Ş., Critical Revisation of Manuscript: D.E.T.Ş., A.N.Ş., A.A., Final Approval and Accountability: Ö.V., D.E.T.Ş., A.N.Ş., A.A.

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

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

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CASE REPORT

Bagcilar Med Bull 2022;7(2):189-191
DOI: 10.4274/BMB.galenos.2022.2022-02-023

A Common But Usually Overlooked Cause of Fever of Unknown Origin: Still's Disease

Nedeni Bilinmeyen Ateşin Sık Fakat Genellikle Gözden Kaçan Bir Nedeni: Still Hastalığı

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Abstract

A wide variety of causes, ranging from bacterial or viral infections to malignancies, may be responsible from the development of fever of unknown origin (FUO). However, rheumatologic disorders are usually overlooked in the differential diagnosis of FUO. The diagnosis of adult Still's disease depends on the exclusion of other possible causes, which is the main challenge. In this case report, we present a twenty-three-year-old male patient who was followed up with FUO and diagnosed with Still's disease.

Keywords: Arthritis, fever of unknown origin, Still's disease

Öz

Bakteriyel ve viral enfeksiyonlardan malignitelere varan birçok farklı faktör, nedeni bilinmeyen ateş gelişiminden (NBA) sorumlu olabilmektedir. NBA ayırıcı tanısında romatolojik hastalıklar genellikle gözden kaçırılmaktadır. Still hastalığı tanısında ana zorluk diğer hastalıkların dışlanmasıyla konulmasıdır. Bu olgu sunumunda yirmi üç yaşında, NBA ile takip edilip Still hastalığı tanısı konan bir olguyu sunmaktayız.

Anahtar kelimeler: Artrit, nedeni bilinmeyen ateş, Still hastalığı

Introduction

Fever of unknown origin (FUO was first defined by Petersdorf and Beeson (1), as fever higher than 38.3 °C on at least 3 occasions over a period of three weeks with one week of hospitalization. The term ''unknown'' is used to emphasize the difficulty in diagnosing the underlying disease. The disorder is not uncommon in internal medicine practice with an incidence of 3% of all hospital admissions and it is associated with a mortality rate of 12-35% (2).

More than 200 causes of FUO, which can be divided into 4 main categories as infections, malignancies, non-infectious inflammatory disease, and extremely rare causes, have been identified (3). Non-infectious inflammatory diseases include autoimmune and rheumatic diseases such as vasculitis, granulomatous disease and arthritis. Infections with atypic viral and bacterial agents such as parvovirus, herpesvirus, tuberculosis, toxoplasmosis, and yerisinosis may mimic the symptoms and signs of Still's disease. Moreover, cancers like lymphoid tumors or kidney and colon cancers as well as rare disorders, namely Castleman disease or Kikuchi-Fujimoto disease, may complicate the diagnosis (4). On the other hand, despite the improvements in the laboratory and radiologic techniques, a remarkable proportion of cases (10-50%) remains undiagnosed, even that some patients may undergone to surgery (5).

The main presenting feature of Still's disease is polyarthritis accompanied by fever and macular rash, which was defined by Still (6). However, patients may be admitted with a

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Cite this article as: arhan C, Solmaz İ, Özçaylak S, Kutlu Z, Anık E, Atay AE. A Common But Usually Overlooked Cause of Fever of Unknown Origin: Still's Disease. Bagcilar Med Bull 2022;7(2):189-191

variety of different symptoms. Because the symptoms may mimic many infectious and rheumatologic diseases, the diagnosis may usually take weeks.

Here, we present a case of Still's disease in a young male who presented with FUO.

Case Report

A 23-year-old male with chronic hepatitis B was admitted with polyarthritis, fever, and sore throat. He had no history of chronic drug use, smoking or addiction. His polymerase chain reaction for severe acute respiratory syndrome-coronavirus-2 was negative in two occasions. On physical examination, no abnormal medical finding including lymphadenopathy, skin rash or icterus was observed. He was hospitalized to the internal medicine inpatient service.

His blood, urine and pharyngeal cultures were received at the time whenever fever exceeded 38 °C. During his follow-ups, migratory swelling in the upper and lower extremity joints was observed. His laboratory examination including TORCH panel, VDRL and TPHA for syphilis, thick-drop smear for plasmodium, brucella agglutination and PPD for tuberculosis on two occasions were negative. Except elevated serum ferritin (1614 ng/mL; normal range: 30-400 ng/mL), C-reactive protein (CRP) (241 mg/L; normal range: 0-5 mg/L) and sedimentation rate (64 mm; normal range: 0-20 mm), all biochemical, hormonal and hemogram parameters were within normal range. Furthermore, autoantibodies such as anti-nuclear antibody, anti-ds DNA, anti-CCP and also c-ANCA and p-ANCA were negative.

On ultrasonographic examination, there were two reactive right supraclavicular lymphadenopathies that were approximately 1.5x5 mm each, and hepatomegaly (160 mm) and splenomegaly (125 mm). Echocardiographic, thyroid ultrasonographic and carotid and vertebral artery Doppler ultrasonographic examinations of the patient were uneventful. Positron emission tomography-computed tomography examination performed to investigate an occult malignancy was also normal.

As his bone marrow examination and acid-resistant bacteria examination of bone marrow were found negative, he was consulted to rheumatology department. After excluding other causes of arthritis by the observation of clinical course and involvement of joints and because the autoantibodies, which are the markers of vasculitis and the other rheumatologic causes of arthritis, were negative, he was diagnosed with Still's disease. Because he had chronic hepatitis B, steroid replacement accompanied by antiviral therapy with lamivudin 100 mg/day was initiated. Subsequent to the resolution of his symptoms including fever and arthralgia and improvement in laboratory parameters such as ferritin, CRP and sedimentation rate, he was discharged with the recommendation of rheumatology outpatient visits.

Discussion

Diagnostic workup of FUO should contain the investigation of medical history, detailed physical examination and laboratory analysis including aerobic and anaerobic blood cultures. Classifying the causes into infections, malignancies, inflammatory disorders and miscellaneous causes may help to diminish the number of probable conditions. However, a remarkable proportion of the cases still remains undiagnosed. While the percentage of unresolved cases was 7% in 1961, it accounted slightly more than half of the cases in 2007 (6).

The essential presenting symptom of Still's disease is fever, which usually varies between 38'' and 40'' °C and spikes generally in the afternoon and evening, followed by resolution in the other times of the day. Sore throat is another common symptom in the early course of the disorder. However, physicians frequently fail to culture a specific pathogen, unless an overlapping bacterial infection occurs. Rash is another manifestation of the disease which usually accompanies to fever, and may disappear after the resolution of the fever. Mild arthralgia may persist for weeks and well-responds to anti-inflammatory drugs or corticosteroids. Splenomegaly may be observed between 15% and 60% of all patients (7). Other less common symptoms may range from pleuritis and myocarditis to nervous system involvement and psychiatric problems. The presenting case exhibited no radiologic or echocardiographic sign of respiratory or cardiovascular involvement.

Despite the attempts to establish a diagnosis, there is no clear and standardized laboratory test to distinguish Still's disease from other possible causes of FUO. Because Still's disease is a type of rheumatoid arthritis, patients may require synovial fluid examination which shows inflammatory synovitis (8). The arthritis may affect any joint, but most common sites are knees and wrists. Anemia and high sedimentation rate are observed during the active disease.

Early administration of steroids is not recommended due to the fact that it may camouflage signs and symptoms and may cause delay in the diagnosis as well as may complicate

the progress of the situation (9). Steroid replacement is a kind of diagnostic challenge in the differential diagnosis, especially when it indicates the probability of a rheumatologic disorder. Similarly, as the possibility of an infection was unlikely and the risk of hepatitis flare was decreased by concomitant use of antiviral therapy, our patient received steroid administration that immediately provided resolution in the symptoms.

Prognosis of Still's disease is usually well, with minor complications. Vast majority of the patients remain clinically inactive, but a negligible proportion may suffer from recurrent arthritis requiring short-term corticosteroid administration (10). However, physicians should be aware of the development of amyloidosis, which is manifested with unexplained anemia, persistent proteinuria and splenomegaly. Diagnosis of amyloidosis can be confirmed by histopathologic examination of rectal or renal biopsy (11).

In conclusion, Still's disease is a common but generally overlooked cause of FUO. Although there are published algorithms for solving FUO cases, it is reasonable to individualize the diagnostic approaches according to manifestations. With regard to Still's disease, fever, arthritis and cutaneous rash are the most common presenting symptoms. At the onset of disease, arthritis may not be evident, which may cause a delay in the diagnosis. However, because a number of disorders varying from viral infections to malignancies may mimic Still's disease, physicians should consider Still's disease in patients admitted with FUO and arthritis after excluding all other possible diagnoses.

Ethics

Informed Consent: Written informed consent received from the patient.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Follow-up of the Case: C.V., İ.S., S.Ö., Z.K., E.A., Literature Search: C.V., A.E.A., S.Ö., Z.K., E.A., Writing: C.V., A.E.A., İ.S., Z.K., Manuscript Review and Revisation: S.Ö., İ.S., E.A., A.E.A.

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

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

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