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Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin (BTB), 2016'dan beri 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.

Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin, yazıların İngilizce dilinde, yazıların özetlerinin Türkçe ve İngilizce dillerinde online olarak yayınlandığı bir dergidir.

Derginin Sahibi

T.C.Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi adına Başhekim Doç. Dr. Ozan Beytemür. (Türkiye Cumhuriyeti Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Ortopedi ve Travmatoloji Kliniği, İstanbul, Türkiye).

Dergi Adı (İngilizce): Bagcilar Medical Bulletin

Dergi Adı (Türkçe): Bağcılar Tıp Bülteni

Resmi Kısaltma: Bagcilar Med Bull

E-ISSN: 2547-9431

Yayın Politikası

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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, DOAJ, ProQuest, J-Gate** and **ScopeMed.**

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English Title: Bagcilar Medical Bulletin

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AMAÇ VE KAPSAM

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

Dergi Adı (Türkçe): Bağcılar Tıp Bülteni

Resmi Kısaltma: Bagcilar Med Bull

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Açık Erişim Politikası

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

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Description

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- Original researches,
- Brief researches,
- Case reports,
- Reviews,
- Letters to the Editor

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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.

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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.

Materials 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.

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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.

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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.

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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.

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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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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.

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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.

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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.

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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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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.

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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:

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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.

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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

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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:

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

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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.

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-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.

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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

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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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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, reklam 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 verilmelidir.

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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.

YAZARLARA BİLGİ

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.

Yazarların makalelerini göndermeden önce bir eksiklik olmadığından emin olmalarını sağlamak için bir kontrol listesi bulunmaktadır. Yazarlar derginin kontrol listesini kullanıp gönderilerini kontrol etmeli ve makaleleri ile birlikte bu formu göndermelidirler.

YAZARLARA BİLGİ

SON KONTROL LİSTESİ

• Editöre sunum sayfası

- Makalenin kategorisi

- Başka bir dergiye gönderilmemiş olduğu bilgisi

- Sponsor veya ticari bir firma ile ilişkisi (varsa belirtiniz)

- İstatistik kontrolünün yapıldığı (araştırma makaleleri için)

- İngilizce yönünden kontrolünün yapıldığı

- Telif Hakkı Devir Formu

- Yazar Katkı Formu

- ICMJE Potansiyel Çıkar Çatışması Beyan Formu

• Daha önce basılmış materyal (yazı-resim-tablo) kullanılmış ise izin belgesi

• İnsan öğesi bulunan çalışmalarda "gereç ve yöntemler" bölümünde Helsinki Deklarasyonu prensiplerine uygunluk, kendi kurumlarından alınan etik kurul onayının ve hastalardan "bilgilendirilmiş olur (rıza)" alındığının belirtilmesi

• Hayvan öğesi kullanılmış ise "gereç ve yöntemler" bölümünde "Guide for the Care and Use of Laboratory Animals" prensiplerine uygunluğunun belirtilmesi

• Kapak sayfası

- Makalenin Türkçe ve İngilizce başlığı (tercihen birer satır)

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BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

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REVIEW

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The Strategic Role of Paediatricians in Protecting Children's Oral and Dental Health

Çocuklarda Ağız ve Diş Sağlığının Korunmasında Çocuk Doktorlarının Stratejik Rolü

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Abstract

Dental caries and oral health problems are a major public health concern in our country and around the world. Society needs to improve tooth brushing habits, reduce sugar and carbohydrate intake and provide adequate fluoride to achieve dental and oral health goals. Additionally, we must reach out to disadvantaged and socio-culturally backward populations. Although scans that detect the issue could be significant, tooth brushing sessions with role models who turn behavioral changes into habits are even more crucial in solving the problem. Families should be taught the triangle of brushing teeth, reading books and then sleeping.

Keywords: Children, dental caries, tooth brushing, oral health

Öz

Diş çürükleri ve ağız sağlığı problemleri ülkemizde ve dünyada bir global halk sağlığı sorunu olarak kendini göstermektedir. Diş ve ağız sağlığı hedefleri, toplum çapında diş fırçalama alışkanlığının geliştirilmesi, şeker ve karbonhidrat ağırlıklı beslenmenin azaltılması ve gerekli flor desteği ile sağlamak mümkündür. Bunun yanında dez avantajlı sosyo-kültürel olarak geri kalmış kitlelere de mutlaka ulaşılmalıdır. Sorunu tespit eden taramalar önemli olmakla beraber sorunu çözüme kavuşturan davranış değişikliklerini alışkanlığa dönüştüren rol modellerle diş fırçalama seansları daha bir önem arz eder. Ailelere sırasıyla diş fırçalama, kitap okuma ve sonrasında uyku üçgeni öğretilmelidir.

Anahtar kelimeler: Ağız sağlığı, çocuk, diş çürükleri, diş fırçalama

Introduction

Oral and dental health are critical components of overall health and can have a significant impact on quality of life and health outcomes. Therefore, it is important to consider oral and dental health as an integral part of the overall health evaluation. Maintaining and preserving oral and dental health, as the gateway to our digestive system, can ensure protection of overall body health. Many common oral health issues, including dental caries, malocclusion, and fluorosis, often first appear during childhood. Effective prevention of these problems can be achieved through regular preventive dental care and counselling (1,2).

Providing preventive dental care and counselling during regularly scheduled routine screenings is very important for achieving dental health goals. Since paediatricians and family physicians are the first physicians to encounter children, being competent in good counselling will be an important component of preventive health services. Patients should be referred to dentists when necessary. The purpose of this review is to examine the risk factors for oral and dental health in children from the perspective of the pediatrician's consultancy and strategic role. We will emphasise the precautions and protective factors that should be taken to ensure an optimal oral health outcome.

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Epidemiology

Although dental caries prevalence has decreased since the 1970s, it remains a pervasive chronic disease among children of all ages. In 2017, untreated caries' global age-standardized prevalence was about 8% in primary teeth and 29% in permanent (3). In a meta-analysis conducted by Kazeminia et al. (4), 164 articles from various countries were analyzed to determine the prevalence rates of dental caries in deciduous and permanent teeth. The findings revealed the rates to be 46.2% and 53.8% respectively (4). Similarly, Şengül et al. (5) determined the prevalence of early childhood caries to be 73.3% in a study involving 1156 preschool children. This study highlights the severity of the situation in our country (5). Unfortunately, dental caries in children are rising in developing countries where preventive health services and educational programs are not implemented (6).

Risk Factors

Risk factors associated with poor oral and dental health comprise of low income, cultural disparities in nutrition, infrequent dental appointments, lower parental education levels, insufficient, oral and dental health knowledge among parents and their children, ineffective oral hygiene practices, and a high-calorie diet (1,2,7). In addition, parents and children may lack knowledge of effective preventive measures, misunderstand the relationship between diet and oral health, and prefer to eat a high calorie diet. The correlation between access to dental practitioners and dental health is not considered to be significant. Therefore, more attention should be given to knowledge and attitude in addressing the issue of dental caries. It is crucial to implement interventions aimed at changing lifestyle practices and conduct, through education and awareness programs. Systematic data related to oral health behavior must be utilized for the planning and assessment of oral health education (8). Children should be referred to a dentist for early assessment, preventive care and counselling if the risk factors listed in Table 1 are present (9,10).

Strategies to Protect Dental Health

Specific education or counselling interventions can globally reduce dental caries. If education, the provision of toothbrushes and toothpaste, and additional training of primary health care providers are combined, the incidence of dental caries may decrease in high-risk children under five years old (11-14). Pediatricians need to analyze the etiology of dental caries and the risk factors that cause and promote dental caries to guide future, preventive and protective interventions. Since the causative factors of dental caries in patients are multifactorial, the suggested guidance also ought to be multifactorial and wide-ranging. In order to ensure optimal health and development, it is important to consider the following recommendations for parents (15-18).

Table 1. Risk factors for early referral to the dentist

A caregiver or mother who has tooth decay is present
low socio-economic standing
Breast-feed or bottle-fed for children over 12 months
Frequent sugary drinks and snacking
Extended use of a training cup throughout the day
Use of a bottle before going to bed, especially with drinks containing sugar
More than three weeks' use of liquid medicines
Passive smoking exposure
Children with special medical needs
Inadequate fluoride exposure
Visible plaque on the upper front teeth
Pits or defects in the enamel

Dietary guidance

1- The baby should be exclusively breast-fed for the first 6 months and then can be fed for up to 1 year or more depending on mother-baby co-operation (up to 2 years).

2- Avoid letting the child fall asleep with a bottle to prevent dental decay.

3- Develop a daily routine for dental health like triangle B (brush, book, bed).

4- After the age of one, it is recommended that the bottle is discontinued.

5- The consumption of sugary foods and drinks should be restricted to mealtimes.

6- Carbonated, sugary drinks and fruit juice drinks that are not 100% fruit juice should be avoided.

7- Fluorine-containing water is sufficient during meals (about 2 tea cups), drinks with 100% fruit juice can also be taken 30 mL 4-6 times a day (about 30 mL 4-6 times a day).

8- Traditional home cooking is preferable to processed foods.

A) Maintaining Oral Hygiene

1- Parents/carers should be encouraged to model and maintain good oral hygiene and a relationship with their dental provider.

2- Parents or carers with significant tooth decay should avoid mouth contact with children's belongings.

3- The child's teeth should be brushed twice a day as soon as they erupt. A grain of fluoride the size of a grain of rice is sufficient. From the age of three, it can be the size of a pea. Until the age of eight, the family should help with tooth brushing.

B) Fluoride Use and Other Precautions

1- Fluoride toothpaste decrease the likelihood of tooth decay.

2- If there is adequate fluorine present in the drinking source or drinking water, additional fluorine supplementation is unnecessary.

3- Fluoride varnish is a sticky resin with a high fluoride concentration. It is applied professionally, and two or more applications per year can prevent tooth decay in high-risk children of all ages. In certain countries, paediatricians administer this treatment.

4- In the first few months of life, the pacifier should only be used during sleep, as it provides a protective effect against sudden infant death syndrome.

5- Finger sucking and the use of pacifiers should be stopped before the age of three to prevent the development of oral and dental structural problems.

6- Dental injuries in school-age children and toddlers can affect almost a quarter of children. It's particularly important to cover sharp objects and not to take children in cars without a proper car seat. Pediatricians should encourage the use of mouth guards during children's sports activities.

7- In the first year, all children should be examined by a dentist.

In order for these preventive strategies to be effective, it is necessary to establish collaborative relationships between physicians and dentists at the community level and to protect oral and general health by increasing access to dental care for all children. There is a one-to-one connection between oral hygiene and diseases. Therefore, the department of paediatrics should have the necessary competencies in oral hygiene and should work in coordination with dentistry. Dental health should be given due importance in education programs and speciality training. Dental rotations of paediatric residents and family physicians should be extended throughout the country. Preventing tooth loss before caries is both more cost-effective and more rational.

The protection of oral and general health of children and the entire population cannot be achieved solely through the efforts of physicians and families. It is also necessary to establish the necessary legal regulations to deal with sugary, carbonated drinks and fast foods that are easily sold everywhere with the intense effect of advertisements with technological developments. Unfortunately, school canteens are not under the supervision of physicians. Local administrations should establish the necessary legislation in this regard. On the other hand, low-income families who do not have access to adequate nutrition eat a carbohydrate-based diet. These families and children should receive more social assistance in favour of children.

In addition to all these, therapies focused on changing behavior (cognitive therapies) can be applied to families with poor oral hygiene and poor tooth brushing habits despite having all kinds of opportunities. Although there are not enough studies, we think that collective tooth brushing sessions with role models in places such as schools, prisons and military barracks may be useful in terms of changing behaviors into habits. The crucial role of paediatricians in protecting and promoting oral and dental health, both globally and in our own country, cannot be understated. While Hippocrates famously said, "All diseases start in the gut", we propose an addition: "All diseases begin in the mouth…" By recognising this, we can cultivate psychologically, physically, and socially healthy future generations.

Highlight Key Points

- Unfortunately, oral and dental health is far from the desired level in our country.
- Pediatricians can have a strategic role in maintaining oral and dental health.

It is important that pediatricians work in coordination with dentists.

- Dental and oral health should be given more place in pediatric specialty training.
- Tooth brushing, reading, and a sleep routine (triangle BBB: Brush, book, bed) should be taught from childhood.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

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

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REVIEW

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Comparative Evaluation of Lactulose and Bisacodyl in the Management of Chronic Constipation: Efficacy, Safety, and Patient Preferences

Kronik Kabızlık Yönetiminde Laktüloz ve Bisakodilin Karşılaştırmalı Değerlendirmesi: Etkinlik, Güvenlik ve Hasta Tercihleri

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Abstract

Chronic constipation is a common gastrointestinal disorder, and its management often requires long-term use of laxatives. This review addresses the differences between two commonly used laxatives, lactulose and bisacodyl. The efficacy, side effect profiles, tolerance development, use in special populations, drug interactions, contraindications, and impacts on patient compliance and quality of life of these two laxatives are compared. Both lactulose and bisacodyl are effective in improving bowel movements and are widely used in clinical practice. However, lactulose might present a more favorable profile for certain patient populations when considering factors such as side effect profile, patient compliance, quality of life, and cost-effectiveness. Primary care physicians should consider these aspects when choosing the most appropriate treatment option for their patients, always considering individual patient characteristics and preferences.

Keywords: Bisacodyl, constipation, lactulose, laxative, osmotic, purgative, stimulant

Öz

Kronik kabızlık, yaygın bir gastrointestinal bozukluktur ve yönetimi genellikle laksatiflerin uzun süreli kullanımını gerektirir. Bu derlemede, yaygın olarak kullanılan iki laksatif olan laktüloz ve bisakodil arasındaki farklılıklar ele alınmıştır. Her iki laksatif etkinlik, yan etki profili, tolerans gelişimi, özel popülasyonlarda kullanım, ilaç etkileşimleri ve kontrendikasyonları, hasta uyumu ve yaşam kalitesi üzerindeki etkileri yönünden var olan kanıtlar ışığından karşılaştırılmıştır. Hem laktüloz hem de bisakodil, bağırsak hareketlerini iyileştirmede etkili olup klinik uygulamada yaygın olarak kullanılırlar. Ancak, yan etki profili, hasta uyumu, yaşam kalitesi ve maliyet-etkinlik gibi faktörler göz önüne alındığında, laktüloz belirli hasta popülasyonları için daha olumlu bir profil sunabilir. Aile hekimleri, hastaları için en uygun tedavi seçeneğini seçerken bu yönleri göz önünde bulundurmalı ve her zaman bireysel hasta özelliklerini ve tercihlerini dikkate almalıdırlar.

Anahtar kelimeler: Bisakodil, kabızlık, laksatif, laktüloz, müshil, osmotik, uyarıcı

Introduction

Constipation is a common condition encountered in primary care, with a reported prevalence of up to 27% in North America and Europe (1). It is characterized by infrequent bowel movements, hard stool consistency, and difficulty or straining during defecation. Chronic constipation can significantly impair the quality of life, posing both a physical and psychological burden on patients (2).

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The management of constipation often includes lifestyle modifications such as increased dietary fiber and fluid intake, regular exercise, and over-the-counter laxatives. Among these, lactulose and bisacodyl are two widely prescribed laxatives. Lactulose is an osmotic laxative that draws water into the colon to soften stools and stimulate bowel movements (3). Bisacodyl, on the other hand, is a stimulant laxative that promotes intestinal motility by directly stimulating the enteric nerves of the colon (4).

Despite their everyday use, there remains a need for more consensus in primary care regarding the optimal laxative for treating constipation. This narrative review aims to compare lactulose and bisacodyl regarding efficacy, safety, patient preference, and cost-effectiveness, focusing on evidence from clinical studies published in medical journals.

Pharmacological Overview

Lactulose and bisacodyl represent two distinct classes of laxatives: osmotic and stimulant laxatives. These two types of laxatives operate through different mechanisms within the gastrointestinal tract.

Lactulose is a synthetic disaccharide not absorbed in the small intestine due to the lack of appropriate enzymes. Upon reaching the colon, it is metabolized by bacterial flora into low molecular weight organic acids, primarily lactic acid and small amounts of formic and acetic acids (5). This metabolic process increases the osmotic pressure within the bowel, leading to an influx of water that softens the stool and promotes peristalsis (6). The acidification of the colonic contents also stimulates the growth of beneficial, acid-loving bacteria while inhibiting the growth of potentially pathogenic, ammonia-producing bacteria. This makes lactulose particularly beneficial for patients with hepatic encephalopathy, where it is used to reduce blood ammonia levels (7).

Bisacodyl is a diphenylmethane derivative and functions as a stimulant laxative. It works locally on the colon to stimulate peristalsis and the accumulation of water and electrolytes within the intestinal lumen (8). After oral administration, bisacodyl is metabolized in the small intestine and colon to form the active compound bis-(p-hydroxyphenyl)-pyridyl-2 methane, which stimulates the nerves of the colonic wall, increasing the movement of the intestines (4). Bisacodyl is known for its rapid onset of action, often producing a bowel movement within 6 to 12 hours of administration (9).

While bisacodyl is effective in stimulating bowel movements, its mechanism of action can cause cramping and discomfort due to increased peristalsis. Additionally, it can affect electrolyte balance within the colon, leading to potential electrolyte imbalances if used excessively (9). In contrast, lactulose's osmotic action offers a gentler, more physiologic method for promoting bowel movements. While it may take longer to produce a bowel movement than bisacodyl, its side effect profile is generally milder and includes less risk of causing electrolyte imbalances (10).

It's crucial to note that while lactulose and bisacodyl are effective for relieving constipation, their different mechanisms of action may be more suitable for different types of patients or specific clinical scenarios. The choice between lactulose and bisacodyl will ultimately depend on individual patient factors, the specific clinical scenario, and the overall treatment goals. The following sections will provide a more in-depth look at their comparative efficacy, safety, and patient preferences.

Clinical Efficacy and Side Effect Profile

The clinical efficacy of a laxative is generally assessed based on its ability to improve bowel movement frequency, ease of defecation, and stool consistency. Both lactulose and bisacodyl have demonstrated efficacy, but several studies suggest differences in their performance and applicability to specific patient groups. Side effects play a substantial role in patient adherence to treatment, especially when dealing with chronic conditions like constipation. Both lactulose and bisacodyl have distinct side effect profiles that should be considered.

Lactulose, as an osmotic laxative, has long been studied in extensive trials in adults and children and has consistently been shown to alleviate constipation symptoms (3). Lactulose is exceptionally well tolerated. Nearly no absorption from the intestines and the rapid excretion of the absorbed portion from the kidneys results in almost all reported side effects being mild and limited to the gastrointestinal system (11). These effects include bloating, gas, and, less frequently, nausea and diarrhea (3). It has been shown that these effects decrease as the body adapts to the medication with continued use (5). No clinically significant lactulose toxicity has been reported, and no evidence of toxicity has been found in animal studies. Warnings exist about rare allergic reactions in those with milk allergy and the potential triggering of lithium toxicity through dehydration in psychiatric patients taking lithium (11). A randomized controlled trial comparing lactulose

with a senna-fiber combination in elderly patients with long-standing chronic constipation demonstrated that lactulose was as effective as the senna-fiber combination in increasing bowel movement frequency and improving stool consistency but with fewer side effects (10). Due to this efficacy, it should be considered in the third-line treatment after lifestyle changes and increased fiber intake, especially in patients with chronic constipation (12). One of its most important effects is its use as a cornerstone in treating nearly hepatic encephalopathy due to reducing ammonia absorption via several different mechanisms (11). It decreases the formation of cholesterol stones by speeding up transit time. Recent studies have reported that lactulose exhibits anti-cancer effects by binding to galectins, carbohydrate-binding proteins known to play a role in tumor progression (13).

Bisacodyl, as a stimulant laxative, typically acts faster than lactulose, but on the other hand, has a different set of potential side effects due to its stimulant nature. A study by Kienzle-Horn et al. (4) demonstrated that bisacodyl produced a bowel movement within 6 to 12 hours of administration, indicating its particular utility for patients requiring quick relief. However, the same study also showed that bisacodyl was associated with severe abdominal cramps in some patients, which limits its acceptability and long-term use. Other side effects include diarrhea and electrolyte imbalance, which is mainly a problem in the elderly with excessive use (8). Kamm et al. (14) conducted a randomized, double-blind, parallel-group study at 27 centers in the US to compare bisacodyl with placebo. They thoroughly examined its efficacy as well as its side effect profile (14). Of the patients in the bisacodyl group, 17.8% (n=44/247) could not continue the study due to various side effects, primarily diarrhea, upper abdominal pain, and headache. Half of the patients reported good tolerance of bisacodyl (14). According to a report prepared in 2005 by the American College of Gastroenterology Association Chronic Constipation Task Force, which has not yet been updated, there is not enough evidence of sufficient strength to support the use of stimulant laxatives like bisacodyl, stool softeners, herbal supports, and lubricants, while there is A-level evidence for the efficacy of osmotic laxatives like lactulose, polyethylene glycol, and tegaserod (15). Effects shown in animal studies, such as the damage to the myenteric plexus and smooth muscle, and colon dilation caused by the chronic use of stimulant laxatives, and triggering transitional cell carcinoma in the bladder epithelium of mice have not been demonstrated in humans (16). A limited number of publications related to its association with complications such as salt loading, hypokalemia, and protein-losing enteropathy (17). In chronic use, high dosage results in severe diarrhea and toxicity due to electrolyte disorders, including hypokalemia, hypocalcemia, metabolic acidosis, or alkalosis. It has also been reported to cause renal calculus formation at levels that block double-J stents in overdose (16). Due to the unclear long-term effects of bisacodyl and the potential carcinogenic risks of stimulant laxatives, avoiding use for more than four weeks is recommended until these points are clarified with epidemiological studies (18).

Both lactulose and bisacodyl have minimal drug interactions. However, lactulose may reduce the absorption of other oral drugs when taken concurrently due to its effect on bowel motility (19). Lactulose is contraindicated in patients with galactosemia. On the other hand, bisacodyl may enhance the effects of diuretics and corticosteroids, leading to an increased risk of electrolyte imbalance (20). Both drugs should not be used in patients with ileus, acute surgical abdomen, or severe dehydration(20).

In summary, while both lactulose and bisacodyl generally have well-tolerated side effect profiles, the milder side effect profile of lactulose, lower risk of diarrhea, lower risk of electrolyte imbalance, proven efficacy and safety in long-term treatment mainly make lactulose a more appropriate choice in patients with chronic constipation, candidates for long-term use, elderly, and those with comorbidities.

Tolerance Development

Tolerance development to medications is a crucial factor, especially for conditions requiring long-term management, such as chronic constipation.

Lactulose is a non-stimulant laxative, and it has been demonstrated in multiple studies that patients do not develop tolerance to lactulose with long-term use. Its effectiveness remains consistent over time, even with continuous use (21).

In contrast, the available literature suggests that with long-term use, some patients may develop a tolerance to bisacodyl and other stimulant laxatives. This tolerance could necessitate higher doses to achieve the same effect, potentially increasing the risk of side effects such as abdominal discomfort and electrolyte imbalances (8). However, it's worth noting that this effect is not seen in all patients and can vary significantly.

Therefore, when considering treatment for long-term use in managing chronic constipation, lactulose may

offer advantages in terms of consistent efficacy without developing tolerance.

Use in Special Populations

Special populations such as the elderly, children, and pregnant women often require careful consideration when prescribing medication.

Lactulose has been widely used across all age groups, including children and the elderly, and is generally considered safe during pregnancy (22). Its sweet taste and the availability of a liquid formulation may be particularly appealing to the pediatric patient population. It is also appropriate for patients with renal impairment as it does not contribute to electrolyte imbalances (22). According to a review by Mulhem et al. (23) lactulose is recommended as a second-line treatment after polyethylene glycol for children with constipation. The European and North American Societies for pediatric gastroenterology, hepatology, and nutrition recommend lactulose as a first-line maintenance treatment for pediatric patients with chronic constipation if polyethylene glycol is not available (24).

Constipation is one of the most significant gastrointestinal complications in pregnant women (25). Li et al. (25) conducted a randomized controlled trial in 2020 on 113 pregnant patients with constipation, comparing the effects of taking 10 g of polyethylene glycol twice daily with 15 mL of lactulose twice daily. After a 3-week treatment period, no side effects were observed in either group, and both groups showed statistically and clinically significant improvements in Wexner constipation scores, with no significant difference found between the two groups (25).

Bisacodyl, while generally safe in most populations, should be used cautiously due to the potential risk of electrolyte imbalances, particularly in those with renal impairment or diuretics (4). It is contraindicated in pediatric patients under the age of 10 and has not been approved for use in pediatric patients by the FDA (20). Its safety during pregnancy has not been definitively established, and it should be used only when the potential benefits outweigh the risks (26).

Use in Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)

Both lactulose and bisacodyl may have roles in managing bowel-related symptoms in patients with IBD and IBS. However, they are not primary treatments for these conditions. Recent research suggests that restoring balance to the gut microbiota could be a practical treatment approach in IBD and IBS (27). Prebiotics are indigestible food components that can stimulate the growth and activity of beneficial bacteria in the gut, and lactulose also has these prebiotic properties.

IBD: In patients with IBD, constipation can occur as a symptom, particularly in those with Crohn's disease affecting the colon or as a side effect of certain medications used to treat IBD. Lactulose has been used to manage constipation in IBD patients due to its mild osmotic action and good tolerance. It also has a potential role in reducing ammonia production, which can benefit patients with hepatic encephalopathy. This complication can occur in IBD patients with liver involvement. In addition to these effects, it has been found that lactulose as a prebiotic induces the growth of host microflora of a specific type that may help enhance the function of the gut. Furthermore, the demonstration that lactulose and other prebiotics have anti-inflammatory effects suggests potential additional benefits in managing diseases such as IBD (27). On the other hand, bisacodyl, due to its stimulant effect, should not be used as it may worsen IBD symptoms, particularly abdominal pain and diarrhea (20).

IBS: IBS is a functional bowel disorder characterized by chronic abdominal pain and altered bowel habits, including constipation (IBS-C), diarrhea (IBS-D), or both (IBS-M). In IBS-C, lactulose can soften stools and promote regular bowel movements. However, it may cause bloating and flatulence, which are often significant symptoms in IBS patients (28). Bisacodyl is also generally not recommended as a first-line treatment for IBS-C due to its potential to cause abdominal cramping. However, it may be used in patients who do not respond to other treatments (29).

Patient Compliance and Quality of Life

Patient compliance with treatment and the subsequent impact on quality of life are crucial considerations in managing constipation. Both lactulose and bisacodyl have unique characteristics that can influence these aspects.

Lactulose, due to its generally mild side effect profile and non-stimulant mechanism of action, may be better tolerated by some patients, promoting long-term compliance. In a study comparing lactulose with polyethylene glycol, both treatments were effective, but patient preference was significantly higher for lactulose due to its better taste (5). Another study on 112 children between 10 months and 15 years old showed that only two refused lactulose due to its taste (30). The fact that the side effects of lactulose, which

are mentioned in detail above, are milder and can be easily taken even by children contributes to patient compliance in long-term use.

With its faster onset of action, bisacodyl may be preferred by patients requiring rapid relief. However, the potential for abdominal cramping and electrolyte imbalances may limit its long-term use and patient compliance (4). Furthermore, the need for dose timing (usually recommended at bedtime to produce a morning bowel movement) may not suit all lifestyle patterns and could impact compliance (31).

In terms of quality of life, effective management of constipation can significantly improve patients' overall well-being and daily functioning (32). Given that lactulose and bisacodyl have demonstrated efficacy in relieving constipation, both can contribute positively to quality of life. However, the choice of laxative should consider individual patient factors such as tolerance of side effects, lifestyle, and personal preference to ensure optimal compliance and quality of life improvement.

Conclusion

The management of chronic constipation often requires long-term use of laxatives. Both lactulose and bisacodyl have shown efficacy in improving bowel movements and are widely used in clinical practice. However, lactulose might present a more favorable profile for certain patient populations when considering factors such as side effect profile, patient compliance, quality of life, and cost-effectiveness. Primary care physicians should consider these aspects when choosing the most appropriate treatment option for their patients, always considering individual patient characteristics and preferences.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH

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Impact of Nosocomial COVID-19 Infection Among Hospitalized Patients with Respiratory Diseases

Solunum Hastalığı Nedeniyle Hastanede Yatan Hastalarda Nozokomial COVID-19 Hastalığının Etkisi

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Abstract

Objective: There are very few studies concerning the frequency and course of nosocomial Coronavirus disease-2019 (COVID-19) infection among patients hospitalized having diseases other than COVID-19. In our study, patients who were admitted to the pulmonology inpatient clinic from the emergency room due to non-COVID-19 diseases and later diagnosed with COVID-19 (index cases) and the nosocomial transmission caused by these patients and the clinical outcomes were analyzed.

Method: This study was carried out on 44 inpatients without COVID-19 at a pulmonology inpatient clinic during the first wave of COVID-19 pandemic. Oro-nasopharyngeal swab samples were taken at the time of hospitalization to detect COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) test. The test results of four patients were found to be positive. Due to the risk of nosocomial transmission, the remaining patients were re-evaluated for COVID-19 disease by clinical, radiological, and RT-PCR tests (1 to 3 times, and/or if symptoms developed). All patients were followed up for 30 days after discharge.

Results: Thirty-six males (81%) and 8 females (19%) with a mean age of 65.6±13.6 (31-93) years were included in the study. Twenty-five of these patients had cancer, six had chronic obstructive pulmonary disease exacerbation, four had an aggravation of idiopathic pulmonary fibrosis, three had infected bronchiectasis, two had pulmonary embolisms, and four had other disorders. The RT-PCR test results were found positive in 4 patients. In about two weeks, COVID-19 infection emerged in 16 of the remaining 40 patients, and 10 of them (63% of the infected) died. The RT-PCR test results of patients with COVID-19 infection were found to be positive on day 8.2 averagely (6-13).

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu dışı hastalıklar nedeniyle hastanede yatan hastalar arasında nozokomiyal COVID-19 olgu sıklığı ve seyri ile ilgili az sayıda çalışma mevcuttur. Çalışmamızda COVID-19 dışı hastalık nedeni ile acil servisten göğüs hastalıkları servisine yatırılan ve yatıştan sonra COVID-19 enfeksiyonu saptanan hastalar (indeks olgu) ve bu hastaların neden olduğu nozokomiyal bulaşma seyri ve sonuçları incelendi.

Yöntem: Çalışmaya, COVID-19 pandemisinin birinci dalgası sırasında göğüs hastalıkları servisinde akciğer hastalığı tanısı ile yatan 44 hasta dahil edildi. Hastaneye yatış sırasında tüm hastalardan COVID-19 ters transkripsiyon-polimeraz zincir reaksiyonu (RT-PCR) testi için oro-nazofaringeal sürüntü örneği alındı. COVID-19 RT-PCR testi dört hastada pozitif bulundu. Test sonuçları negatif bulunan hastalar nozokomiyal bulaş riski nedeni ile klinik, radyolojik olarak ve RT-PCR testi (1-3 kez, ve/veya semptom geliştiğinde) ile COVID-19 açısından yeniden değerlendirildi. Hastaların tümü taburculuk sonrası 30 gün süreyle takip edildi.

Bulgular: Çalışmaya dahil edilen hastaların %81'i (36) erkek, %19'u (8) kadın ve yaş ortalamaları 65,6±13,6 (31-93) yıl olarak bulundu. Hastaların 25'inde malignite, altısında kronik obstrüktif akciğer hastalığı alevlenmesi, dördünde idiyopatik pulmoner fibrozis alevlenmesi, üçünde enfekte bronşektazi, ikisinde pulmoner emboli ve dördünde farklı akciğer hastalıkları bulunmaktaydı. Dört hastanın COVID-19 RT-PCR testi sonucu pozitif bulundu. Yaklaşık iki hafta içinde 40 hastanın 16'sında COVID-19 enfeksiyonu gelişti ve bu hastaların onu (enfekte olanların %63'ü) hayatını kaybetti. COVID-19 enfeksiyonu gelişen hastaların RT-PCR test sonuçlarının ortalama 8.2. (6-13) günde pozitifleştiği saptandı.

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Abstract

Conclusion: Nosocomial transmission of COVID-19 may create a risk of severe illness and death among vulnerable patients. It is crucial to take necessary measures in order to reduce the risk of COVID-19 transmission in hospitals.

Keywords: COVID-19, hospitalized patients, mortality, nosocomial infection, pulmonary disease

Öz

Sonuç: Akciğer hastalığı bulunan hastalarda nozokomiyal COVID-19 enfeksiyonu gelişimi ağır hastalık ve ölüm için ciddi bir risk oluşturmaktadır. Sağlık kurumlarında COVID-19 enfeksiyonu bulaşma riskini azaltmak için gerekli önlemler alınmalıdır.

Anahtar kelimeler: Akciğer hastalığı, COVID-19, hastanede yatan hastalar, mortalite, nozokomial enfeksiyon

Introduction

The pandemic started in Wuhan, China, at the end of 2019 and spread rapidly worldwide; its cause was identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and the disease was named Coronavirus disease-2019 (COVID-19) (1). Over 750 million confirmed cases and over 6.8 million deaths have been reported globally by the second month of 2023 (2). Although the COVID-19 pandemic has reduced its effect at present, it still shows a fluctuating course worldwide and continues to be a potential risk for public health.

SARS-CoV-2 is found in the respiratory secretions and the main route of SARS-CoV-2 transmission is through exposure to respiratory particles carrying the virus. Other modes of transmission are direct contact like shaking hands and airborne transmission of the virus that linger in the air over long periods of time. It can also infect people via contact with contaminated surfaces (3,4). Although studies have shown that SARS-CoV-2 virus maintains its viability on inanimate surfaces for a long time, it has been reported that contamination from surfaces is very rare (5,6). The virus can also be transmitted from asymptomatic carriers or individuals whose symptoms have not yet started (7,8).

With the normalization process, the number of hospitals and clinics accepting patients with non-COVID diseases has increased. When patients with unidentified COVID-19 infection are admitted to these clinics, the risk of nosocomial infection rises. Since COVID-19 infection is not considered in these patients in the first place, the prevention measures against COVID-19 may not be taken adequately (9-11).

There are few studies on the frequency and course of nosocomial COVID-19 cases. In the first weeks of the pandemic in Belgium, it was shown that patients hospitalized for other reasons were infected with the virus; also it was reported that the management of these patients was quite complex during the pandemic (12). In another study evaluating 138 COVID-19 cases hospitalized in Wuhan, it was reported that 12% of these were hospitalized for non-COVID-19 reasons and subsequently diagnosed with nosocomial COVID-19 infection. In this series, while the need for an intensive care unit (ICU) admission was needed by 22% in all COVID-19 patients, 53% of patients with nosocomial transmission required an intensive care unit admission (13). In France, cases of COVID-19 were also reported among patients in the geriatric ward who accepted only non-COVID-19 patients with reverse transcription-polymerase chain reaction (RT-PCR) negativity, and it was emphasized that the virus spreads very rapidly (14). Regarding the 435 COVID-19 cases at a center in the United Kingdom, 11% (n=47) were reported to be definitely, and 4% (n=19) were probably nosocomially transmitted COVID-19 patients. Patients with nosocomial transmission were older and had a high mortality rate (15). Another study reported that nosocomial infections were higher in older and more vulnerable individuals but had no effect on disease severity (16). In our country, there is no study on this subject.

University of Health Sciences Turkey, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital also serves the patients with respiratory diseases requiring hospitalization other than COVID-19. In cases requiring urgent hospitalization, COVID-19 is first eliminated by patient history and clinical and radiological findings. The nasopharyngeal swabs of the patients are taken either at the time of administrations or after hospitalization, and the results are obtained later.

This study focuses on patients, transferred from the emergency room to be hospitalized for non-COVID-19 diseases, and later who were diagnosed with COVID-19. A nosocomial transmission is highly suspected and results of these inectionsare examined. It was determined that nosocomial transmission originated from these patients and its clinical results were evaluated.

Materials and Methods

Patients hospitalized at the pulmonology inpatient clinic for examination and treatment of non-COVID-19 diseases

during the first wave of COVID-19 pandemic were included in this cross-sectional retrospective study. The clinical information and data for the patients were reviewed retrospectively. These patients stayed in single or two beded rooms (separated by curtains) and shared the same bathroom and toilet.

Of the 46 patients hospitalised within this period two of them (having pulmonary embolism and thymoma) were not taken nasopharyngeal swabs thus excluded from the study. The Oro-nasopharyngeal swabs taken from the remaining 44 patients were placed in viral transport media, and tested for COVID-19 via RT-PCR. Routine blood tests (complete blood count, biochemistry, serology, and coagulation tests) were performed at the time of hospitalization and upon hospitalization chest radiographs and thorax computerized tomography (CT) scans were taken from all of the patients. The diagnosis of COVID-19 was made depending on positive SARS-CoV-2 PCR test results (17). Four patients whose RT-PCR tests were positive were referred to the services where the treatment and follow-up of COVID-19 patients were carried out. Remainder of the patients were followed up clinically, radiologically, and also with RT-PCR tests. Patients were continued to be followed up for a period of 30 days after their discharge from the hospital.

Definition of nosocomial infection: The cases, where the infection occurred at least 5 days after patients had been admitted to the hospital and confirmed via positive RT-PCR test results.

Definition of nosocomial COVİD-19 outbreak: It was defined as the detection of three or more COVID-19 cases likely connected to one another (18).

Ethical Approval

The study was approved by the Ethical Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (ID: 2419) and the Ministry of Health of the Republic of Turkey (T14-49-25), and it was also conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using the SPSS 27.0 program. All categorical variables are shown as percentages. Variables are given as mean with standard deviation; continuous variables are shown as median and range. Student's t-test and chi-square tests were used to make comparisons between groups. A p-value <0.05 was accepted as significant.

Results

The mean age of the patients was 65.6±13.6 (31-93), and 36 (82%) of the patients were male and 8 (18%) were female. Of the 44 patients included in the study, 25 had malignancies (23 primary lung cancers, one lung metastasis spread from colorectal cancer, one mesothelioma), six had chronic obstructive pulmonary disease (COPD) exacerbations, four had aggravations of idiopathic pulmonary fibrosis (IPF), three had infected bronchiectasis, two had pulmonary embolism (PE) and four had other disorders and 31 (70%) of these patients had comorbidities of which 15 with multiple comorbidities. The most common comorbidity observed in 24 patients [hypertension 20, ischemic heart disease (IHD) 11, congestive heart failure 5), was cardiovascular system diseases, followed by COPD (7 patients), type 2 diabetes

Table 1. Demographic characteristics and comorbidities of patients

Characteristics	Number of patients (n=44)
Gender, n (%)	
Female	8 (19%)
Male	36 (81%)
Age	
Mean ± SD, (min-max)	65.6 ±13.6 (31-93)
Diagnosis, n (%)	
Cancer*	25 (56%)
COPD exacerbation	6 (13%)
Interstitial pulmonary fibrosis	4 (9%)
Pneumonia	2 (4%)
Bronchiectasis	3 (6%)
Other**	4 (9%)
Comorbidities, n (%)	
None	13 (29%)
Various	31 (71%)
Comorbidities by distribution, n (%)	
Hypertension	20 (45%)
Ischemic heart disease	11 (25%)
Congestive heart failure	5 (11%)
COPD	7 (15%)
DM	4 (9%)
Chronic renal failure	3 (6%)
Pulmonary embolism	2 (4%)
Cerebrovascular disease	2 (4%)

SD: Standard deviation, COPD: Chronic obstructive lung disease, DM, Diabetes mellitus, Cancer*, Metastatic lung cancer (1 patient), mesothelioma (1 patient); other**, benign tracheal stenosis (1 patient), tuberculosis (1 patient), heart failure (1 patient), pulmonary embolism (1 patient)

mellitus (DM) (4 patients), PE (2 patients), and previous cerebral vascular disease (2 patients)]. The demographic characteristics of the patients are shown in Table 1.

The clinical characteristics and length of stay of four patients who were RT-PCR positive for COVID-19 at the time of admission were examined. Also, thorax CT scans of the patients were reviewed retrospectively. Due to radiological abnormalities related to patients' primary diseases, lesions suggestive of a suspected COVID-19 infection were easily omissible (19).

The clinical characteristics, radiological findings, length of stay, physical conditions, and outcomes of the patients who were COVID-19 positive were summarized below (Figure 1).

Case 1: A 69-year-old male patient was hospitalized with the diagnosis of lobar pneumonia. He also had DM, IHD, and COPD. Complaints of progressive dyspnea, cough, and sputum production were present. His thorax CT scan revealed, consolidation in the right lower lobe. He stayed in a single room for 48 hours, used a shared toilet, then was transferred to the COVID service when RT-PCR was positive, and discharged after recovery.

Case 2: An 81-year-old male patient with IHD was hospitalized with shortness of breath and hypoxia. Bilateral pleural effusion and ground-glass appearance in the base of the lungs were observed in his thorax CT scan. Transudate pleural fluid was taken by a thoracentesis. Like Case 1, he stayed in a single room for 48 hours, used a shared toilet, transferred to the COVID-19 service when RT-PCR was positive, and discharged after recovery.

Case 3: A 75-year-old male patient having IHD and COPD, diagnosed with squamous cell lung cancer a year ago presenting with blood-tinged sputum, showing signs of weakness, and deterioration of general condition was hospitalized. On thorax CT, there was a mass appearance of lung cancer on the right, which was also present in the previous CT scan, and newly emerged peripheral ground glass images on the left. The patient stayed in a double room for 48 hours with another patient and shared a toilet. Then he was followed in the COVID-19 service, recovered, and discharged.

Case 4: A 75-year-old female patient was hospitalized due to worsening dyspnea and respiratory failure. She was diagnosed with non-specific interstitial pneumonia three years ago and was still using corticosteroids 20 mg/day and long-term oxygen therapy. During the hospitalization period, thorax CT scan showed a progression of a bilateral infiltration compared to the CT scan of two months before, and new ground-glass appearances emerged on the left as well. She stayed in a double room for 48 hours in the service and used shared toilets. The patient was transferred to the COVID-19 service and then transferred to the intensive care unit 5 days later, and then died after three days.

Sixteen (40%) of the remaining 40 patients in the clinic were found to be RT-PCR (+) after an average of 8.2 (6-13) days. Comparison of laboratory results of the patients who developed and did not develop COVID-19 showed no statistical difference (Table 2).

Four index cases (Group 1), 16 nosocomial COVID-19 patients (Group 2), and 24 non-infected patients (Group 3) were followed during hospitalization and in the first month after discharge. One of the index cases died in the intensive care unit (Case 4). Nine of the 16 patients with nosocomial COVID-19 died in hospital and one within 1 month after discharge. Of the 24 patients who were not infected with COVID-19, five died during hospitalization, and seven

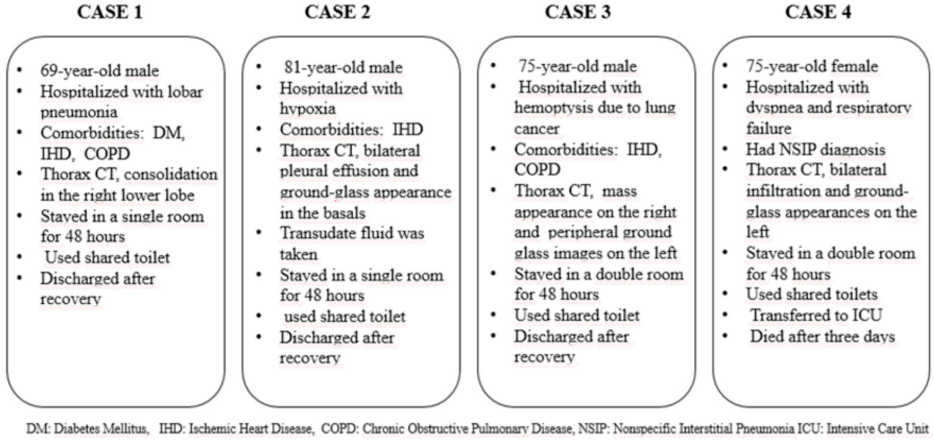

Figure 1. Clinical characteristic features of four index cases

died within one month after discharge probably due to their underlying primary diseases (Table 3). Mortality was observed to be as 25% (one case) in index cases, 21% (five cases) in non-infected, and 56% (nine cases) in nosocomial COVID-19 cases. A significant relationship was found between CVD/DM and mortality in patients with and without nosocomial COVID-19 infection (p=0.023, p=0.037, p<0.05, respectively) (Table 4).

Table 2. Comparison of demographic characteristics and laboratory results of the patients

	Normal values	Hospitalized COVID-19 (n=4)	Nosocomial COVID-19 (n=16)	Non-infected (n=24)	p
WBC x10^9	4-10	13.0±9.1	10.9±4.7	13.4±5.7	0.151
RBC x10^9	3.6-5.5	4.6±0.6	3.9±0.6	4.3±0.1	0.099
PLT count x10^9	150-450	336.3±271.9	297.3±102.9	285.1±148.1	0.776
Lymphocyte count x10^9	0.8-4	1.1±0.5	1.2±0.6	1.5±1	0.358
Lymphocyte %	10-50	11.8±7.1	11.9±6.1	13.2±11.6	0.679
Fibrinogen, mg/dL	180-350	431.7±39.1	524.4±238.8	468.7±194.1	0.862
Ferritin, ng/dL	23.9-336.2	393.0±258.3	462.9±433.2	350.7±411.5	0.779
D-dimer, mg/dL	0-0.60	2.0±3.1	2.3±1.9	5.2±9.4	0.438
LDH, U/L	<247	305.5±74.9	347.2±151.2	431.5±238.8	0.438
CRP, mg/L	0-5	140.2±112.7	107±75.9	102.7±97.0	0.882
ESR, mm/h	0-30	81.7±44.1	85.7±47.3	64.5±36.8	0.202
Procalcitonin, ng/mL	<0.5	0.1±0.02	0.7±1.02	0.3±0.3	0.091
Age		75±4.89	66.8±12.3	63.3±12.3	0.423
Gender F/M		1/3	1/15	6/18	0.114

COVID-19: Coronavirus disease-2019, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table 3. Comparison of death rates by groups

	Group 1 hospitalized COVID-19 (index cases) (n=4)	Group 2 nosocomial COVID-19 (n=16)	Group 3 non-infected (n=24)	Overall (n=44)
Alive, n (%)	3 (75%)	6 (37%)	12 (50%)	21 (47.7%)
Death in hospital, n (%)	1 (25%)	9 (56%)	5 (21%)	15 (34.1%)
Death in the first month, n (%)	0 (0%)	1 (6%)	7 (29%)	8 (18.2%)

COVID-19: Coronavirus disease-2019

Table 4. Comparison of mortality by comorbidities in deceased patients during hospitalization

n (%)	Nosocomial COVID-19 n=16		Non-infected n=24		p value
	Died n (%)	Alive n (%)	Died n (%)	Alive n (%)	
Comorbidities	6 (66.7)	5 (71.4)	5 (100)	10 (52.9)	0.076
Cardiovascular disease	6 (66.7)	4 (57.1)	5 (100)	6 (31.6)	**0.023**
COPD	2 (22.2)	1 (14.3)	1 (20)	3 (15.8)	0.122
DM	2 (22.2)	0 (0)	1 (20)	0 (0)	**0.037**
Cerebrovascular disease	0 (0)	0 (0)	1 (20)	1 (5.3)	0.122
PE	0 (0)	1 (14.3)	1 (20)	1 (5.3)	0.224
CRF	0 (0)	1 (14.3)	1 (20)	1 (5.3)	0.224

COVID-19: Coronavirus disease-2019, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, PE: Pulmonary embolism, CRF: Chronic renal failure. *p<0.05. Bold indicates statistical significance

Discussion

COVID-19 pandemic showed vulnerabilities and the importance of response capacity for preventing avoidable losses and quickly spiraling costs. Hospitalized patients constitute the most vulnerable group of patients due to the environment's proneness to infection and lack of adequate, established measures during the start of any epidemic (14,20). Our study therefore serves to guide the management of hospitalizations during periods of high levels of contingencies and unknowns. Both loss of life and public costs of health crisis could be controlled better by taking adequate measures and precautions at the very beginning of an epidemic/pandemic. Similar to previous studies, our study reveals that screening of the pandemic is crucial since nosocomial COVID-19 infection is highly contagious and mortal in patients with underlying disease who are hospitalized for non-COVID-19 disease (15,21).

Nosocomial COVID-19 infection directly affects patients' life quality and is reflected in the costs of hospitals as an extra burden. It has been shown that COVID-19 is transmitted through close, unprotected contact with infected patients. Moreover, current preventive and containment measures tend to overlook asymptomatic individuals and super spreaders whose nasopharyngeal swabs were not taken because they were not thought to be sick (10).

Moreover, COVID-19 patients exhibiting atypical clinical features such as gastrointestinal symptoms and fever were misclassified and hospitalized in non-COVID-19 clinics where different infection control protocols are applied. This situation was reported to lead to the spread of nosocomial COVID-19 (13,22). In our study, the clinical and radiological findings of 4 cases were hidden or masked the findings of COVID-19. These 4 index cases caused the nosocomial spread of COVID-19 and resulted in a mortality rate of 63% among infected patients.

Read et al. (22) drew attention to nosocomial COVID-19 infection in the first wave of the pandemic in England. They stated that there was a significant heterogeneity in nosocomial infection rates regarding the services provided by hospitals. The nosocomial infection rate was 9.7% in hospitals providing emergency and general care, whereas it was reported as 61.9-67.5% in community care hospitals and mental health hospitals (22). The rate of nosocomial infections in our clinic almost as high as that seen in nursing homes, led to the review of in-service infection control measures. Rooms were reallocated to serve for single occupancy. Visits of the patient's relatives were restricted. Limits were also put on the mobilization of the patients within the service area. Daily training was conducted on mask use and hand hygiene, and inspections were carried out to assure compliance. Afterward, no in-service contamination was observed. Another research reported that out of 662 inpatients with COVID-19, 45 (6.8%) were likely to have nosocomial COVID-19 and forty (88.9%) of them had previously shared a ward with a confirmed COVID-19 case (11).

COVID-19 is transmitted rapidly from person to person and the incubation period is relatively short. Average incubation period was found to be 4.5 days and the time to onset of disease symptoms was determined to be 5.2+3.2 days in 35 healthcare workers and their family members studied due to a hospital pandemic in Wuhan (23). In the meantime, recently published a meta-analysis of 142 studies involving 8.112 patients reported that the pooled incubation period was 6.57 days and ranged from 1.80 to 18.87 days (24). COVID-19 can be transmitted rapidly from person to person, even in asymptomatic situations, both in the hospital environment and in social activities. Practical measures, including public health services, isolation of cases, monitoring of close contacts, and containment of severe outbreak areas, may stop the spread (9,23).

Hospitalized patients upon health problems are usually older, have comorbidities, and are more susceptible and vulnerable to COVID-19 infection (15). In a cohort study relating to susceptible patients reported that one dayin the same ward with another patient with hospital-acquired COVID-19 was associated with an additional eight infections per 1.000 susceptible patients per day (25).

At the beginning of the pandemic, doctors working in hospitals that provided the National Health Service in England drew attention to the risk of nosocomial infection (25). They emphasized that this infection could lead to death, especially in the sensitive patient group. They recommended that some measures be taken such as separating patients, social distancing, accelerating the process of obtaining test results, and creating different areas based on swab results (26). Moreover there are suggestions for designing non-COVID services (27,28). It is essential that sufficient personal protective equipment is used and strict hand hygiene protocols are implemented (29).

It was reported that COVID-19 showed rapid nosocomial spread in the French geriatric unit, the infection rate was 20%, and the mortality rate was 28.6% in a 24-bed ward. They underlined the strict implementation of infection control

guidelines in geriatric units where the risk of morbidity and mortality is high (14). In the multicenter nosocomial COVID-19 study of COPE (COVID-19 in older people) from England and Italy, the mortality rate was reported as 27.0%. The average age of the patients was seventy-four. Older age, high CRP levels, impaired kidney function, coronary artery disease, and high clinical frailty were identified as risk factors for mortality (21).

In their study from Canada, which covers a similar period, Elkrief et al. (20) reported the incidence of nosocomial COVID-19 infection among patients with cancer and COVID-19 as 19%. The mortality rate due to COVID-19 in all cancer patients was 28%. Regarding the mode of transmission, the mortality rate was 47% in nosocomial COVID-19 patients and 24% in community-infected COVID-19 patients. Older age, poor Eastern Cooperative Oncology Group performance status, and another severe disease have been identified as independent risk factors for a short life span in patients with cancer and nosocomial COVID-19 (20,30).

In our study, the mortality rate of nosocomial COVID-19 cases was higher than the studies mentioned above. It was found that mortality was linked with the CVD/DM in patients with and without nosocomial COVID-19 infection as reported previously in the literature (13,21).

During the first wave, when the health system got blocked almost all over the world, only patients with serious illnesses requiring hospital care were admitted to the hospital. The mortality rate during hospitalization and 30-day follow-up was 50% in the non-COVID-19 patient group, indicating an undesirable delay in accessing health services for those with non-COVID-19 disease. In the early phase of the pandemic, false-negative rates of up to 33% have been reported for RT-PCT tests (31). The failure to diagnose COVID-19 in some patients in this group may also have contributed to this high rate.

Study Limitations

The limitations of our study are the failure to monitor the chain of infection and traceability of infectivity due to the lack of complete genomic sequences of coronavirus strains; the failure to test the nasopharyngeal swab of the patients' family members and contacts during hospitalization. However, this study is important to draw attention to making the necessary arrangements in the health system for the treatment and care of this patient group these days, when we cannot predict the future of the pandemic. It would not be wrong to predict that humanity will face similar or different infectious diseases such as COVID-19 in the future.

Conclusion

We conclude that, nosocomial COVID-19 in hospitalized patients is associated with high mortality. Taking all the deaths into consideration, the devastating effect of the pandemic on the elderly and patients with comorbidities is obviously remarkable. Therefore, utmost attention should be paid to the prevention of nosocomial infections.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Board of University of Health Sciences Turkey, İstanbul Training and Research Hospital (ID: 2419) and the Ministry of Health of the Republic of Turkey (T14-49-25).

Informed Consent: Cross-sectional retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: M.G.O., Design: M.G.O., Data Collection or Processing: M.G.O., B.A.B., S.T.O., T.Ö., F.T.A., E.S.A.K., I.K.A., Analysis or Interpretation: M.G.O., B.A.B., S.T.O., T.Ö., F.T.A., E.S.A.K., I.K.A., Literature Search: M.G.O., Writing: M.G.O.

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ORIGINAL RESEARCH

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Serum Vitamin B12 Level of Children and Its Clinical Relationship with Febrile Seizures

Çocuklarda Vitamin B12 Kan Düzeyi ve Ateşli Nöbetlerle Klinik İlişkisi

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Abstract

Objective: In the present study, our aim was to investigate the correlation between vitamin B12 levels and febrile seizures (FS) in the pediatric population.

Method: The study included a total of 104 patients, comprising 50 children who were admitted with FS and 54 healthy children who served as the control group. Demographic characteristics, seizure types, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers (C-reactive protein, procalcitonin) and the serum levels of vitamin B12 in the patients were retrospectively examined by reviewing the records in the hospital database.

Results: Demographic parameters were similar between groups. The median age of the children in the FS group was 21.6±11.6 months. The mean temperature of the patients measured by tympanic thermometer during the seizure was 38.3±0.29, 76% of the patients presented with simple FS, 22% with complex FS. In the etiology, upper respiratory tract infections was defined as the most common (72%) cause. The serum vitamin B12, sodium, potassium, calcium, magnesium, phosphorus and platelet values of the febrile convulsion group were statistically lower than the control group.

Conclusion: In the course of our research, we observed a significant decrease in vitamin B12 levels among the FS group compared to the control group. These findings suggest that low levels of vitamin B12 may contribute to an elevated risk of FS.

Keywords: Child, febrile seizures, vitamin B12

Öz

Amaç: Çalışmamızda çocuklarda febril konvülziyon (FK) ile vitamin B12 düzeyleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntem: Çalışmaya FK ile başvuran 50 çocuk ve kontrol grubu olarak 54 sağlıklı çocuk olmak üzere 104 hasta dahil edildi. Hastaların demografik özellikleri, nöbet tipleri, biyokimyasal parametreler (glikoz, Na, K, Ca, Mg, P), enfeksiyon belirteçleri (C-reaktif protein, prokalsitonin) ve serum vitamin B12 düzeyleri hastane veri tabanından retrospektif olarak incelendi.

Bulgular: Demografik parametreler gruplar arasında benzerdi. FK grubunda ortanca yaş 21,6±11,6 aydı. Hastaların nöbet sırasında timpanik termometre ile ölçülen ortalama ateşi 38,3±0,29 olup, hastaların %76'sı basit FK, %22'si kompleks FK ile başvurdu. Etiyolojide en sık (%72) üst solunum yolu enfeksiyonu olarak tanımlandı. FK geçiren grubun serum vitamin B12, sodyum, potasyum, kalsiyum, magnezyum, fosfor ve trombosit değerleri kontrol grubuna göre istatistiksel olarak düşüktü.

Sonuç: Yaptığımız çalışmada, FK grubunda vitamin B12 düzeyleri, kontrol grubuna göre anlamlı olarak düşük bulunmuştur. Düşük B12 vitamini düzeylerinin artmış FK riskine katkıda bulunabileceğini düşünüyoruz.

Anahtar kelimeler: Çocuk, febril konvülziyon, vitamin B12

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

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Introduction

According to the International League Against Epilepsy (ILAE), febrile seizure (FS) is defined as a seizure associated with a febrile illness without the presence of central nervous system (CNS) infection or a specific cause (such as acute electrolyte imbalance, metabolic disorder, trauma, intoxication) in children aged 6 months to 5 years who have not experienced prior afebrile seizures (1-3). FSs are acknowledged the most prevalent neurological disorder in the pediatric population (3,4). The frequency and occurrence of FS demonstrate heterogeneity, contingent upon geographical, socio-economic, and genetic factors. In studies conducted internationally, it has been reported that around 2-5% of neurologically healthy children experience at least one FS during their childhood (1,5,6). In a study conducted in our country, FS rate was reported as between 2.6% and 5.8% (4). FSs are observed to be more frequent in boys compared to girls, and they are most commonly observed between the ages of 12 and 18 months (1,4).

FSs may be classified according to their physical characteristics, duration (simple or complex), and their recurrence rate (1). FSs can be categorized into three groups: simple FS, complex FS, and febrile status epilepticus. A simple FS is characterized by a generalized, typically tonic-clonic, seizure that is induced by fever and lasts for a maximum of 15 minutes. It does not recur within 24 hours. A complex FS is a seizure lasting longer than 15 minutes which is focal and/or recurrent within 24 hours. Febrile status epilepticus is defined as a prolonged febrile seizure lasting for more than 30 minutes, or recurring within 30 minutes without the return of consciousness (1,7). Viral infections account for approximately 80% of the cases of fever that lead to FS (7,8). Roseola infantum (exanthem subitum), influenza A and human coronavirus HKU1 have been identified as the most significant viral infections associated with an increased risk of FS. These viralinfections play a notable role in triggering FS in susceptible individuals, particularly young children (1,5,9). In addition it has been documented that the incidence of FS exhibits a transient elevation within a few days following the administration of specific vaccines; namely combined diphtheria-tetanus toxoids-whole cell pertussis and measles vaccines (1,10). Other significant etiologies of FS include viral upper respiratory tract infections (URTIs), pharyngitis, otitis media, and gastroenteritis (1,5). Moreover, research findings have indicated that deficiencies in vitamin B12, folic acid, selenium, calcium, and magnesium have been associated with an elevated risk of febrile seizures (11-15).

Vitamin B12 plays a vital role in neural myelination, synaptogenesis, and neurotransmitter synthesis, all of which have potential implications for cognitive development (14-16). Vitamin B12 deficiency in early childhood has been associated with many factors that negatively affect the child's neurological development, including impaired cognitive development (14). Absolutely, apart from its role in neural myelination, synaptogenesis, and neurotransmitter synthesis, vitamin B12 also plays a crucial role in various other biological processes. These include DNA synthesis, where it is essential for the formation of nucleotides, and methylation reactions, which are vital for regulating gene expression and other cellular functions (16,17). Studies on FS have reported that children with FS have lower serum vitamin B12 levels and lower folic acid levels may lead to recurrence of FSs (13,18). In the present study, our main objective was to explore whether there is an association between low serum vitamin B12 levels and FS in children who were referred to the pediatric outpatient clinic for this condition. Additionally, we aimed to determine if the serum vitamin B12 level can be considered a potential risk factor for the occurrence of FSs in this particular population.

Materials and Methods

Between January 2021 and December 2021, a total of 50 pediatric patients with a recent history of FS who presented at the Pediatric Outpatient Clinic of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, were enrolled in the study, along with 54 healthy children who had no previous history of FS and attended the pediatric outpatient clinic for routine check-ups. Between January 2021 and December 2021, 50 pediatric patients with a history of FS who applied to the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Pediatric Outpatient Clinic and 54 healthy children who had no history of FS before and applied to the Pediatric outpatient clinic for routine control were included in the study. Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (dated: 04/10/2021, number: E-10840098-772.02-4983). Our study was carried out in accordance with the Helsinki criteria. While the accepted reference value for serum vitamin B12 level is 180-1165 pg/dL (13), the observed vitamin B12 levels in our patients were notably higher at 400 pg/dL. However, intriguingly, within the FS subgroup, the serum vitamin B12 levels were found to be significantly lower compared to the control group.

The patients included in the study were between 6 months and 5 years old. The patients were grouped according to their gender as boys and girls. Simple FS was defined as primary generalized, tonic-clonic seizures lasting less than 15 minutes and not recurring within 24 hours. Sizures with focal onset, lasting longer than 15 minutes or recurring within 24 hours, with at least one of the following features were defined as complex FS. Febrile status epilepticus is defined as a prolonged febrile seizure lasting for more than 30 minutes, or recurring within 30 minutes without the return of consciousness (1,7,19). Patients with CNS infection or chronic neurological disease, electrolyte imbalance, metabolic disorder, intoxication or trauma and patients who received vitamin B12 supplements were excluded from the study.

According to these criteria, 104 patients, including 50 children admitted with FS and 54 children without any seizure in the similar age group were included in our study. Demographic characteristics, seizure types, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers [C-reactive protein (CRP), procalcitonin (PCT)] and serum vitamin B12 levels of the patients were retrospectively scanned from the hospital database and recorded in an Excel file.

Serum glucose, sodium, potassium, magnesium, phosphorus, calcium and vitamin B12 levels were determined using the Hitachi 7600-020 automatic biochemical analyzer. Serum PCT was determined with the Swiss Roche Cobas E601 electrochemiluminescence immunoassay analyzer. Calibration solution, reagents and quality control products were all supplied by Roche.

Statistical Analysis

The data were evaluated in the statistical package program of IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were expressed as number of units (n), percent (%), mean ± standard deviation, median (M), minimum, maximum and interquartile range. The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk normality test. Comparisons of the two groups for numerical variables were made with the t-test for independent samples if the data were normally distributed, and with the Mann-Whitney U test if they were non-normally distributed. Focus of fever between groups was compared by using One-Way Analysis of Variance if the data were normally distributed, and Kruskal-Wallis analysis if the data were non-normally distributed. In case the One-Way Analysis of Variance result was found to be significant, Tukey test was used as a (post-hoc) multiple comparison test. Pearson chi-square and Fisher's Exact tests were used to compare the groups according to gender. A p-value of <0.05 was considered statistically significant.

Results

Based on the data presented in Table 1, the study comprised a total of 104 patients, with 50 patients included in the FS group and 54 patients in the control group. In the FS group, the number of male patients was 36, accounting for 72.0% of the group. In contrast, the control group had 30 male patients, representing 55.6% of the group. The difference in the proportion of male patients between the two groups was not statistically significant (p>0.05). The median age was 21.6±11.6 months in the febrile convulsion group and 20.5±11.2 months in the control group. There is no statistical difference between the study population and control group regarding age of the subjects (p>0.05).

Considering the descriptive characteristics of the patients presenting with FS according to Table 2, 76% (n=38) of the patients presented with simple FS, 22% (n=11) with complex FS, and 1 patient corresponding to 2% with febrile status epilepticus. When the focus of fever was examined, URTIs was determined in 72% (n=36), acute gastroenteritis in 14% (n=7), and other causes of fever in 12% (n=6) of the patients.

Table 3 presents the means of various blood indices, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers (CRP, PCT) and serum vitamin B12 levels for the FS group, along with a comparison to the corresponding means of the control group.

According to the table, there was no significant difference observed between the hemoglobin (Hb) values of the FS

Table 1. Comparison of descriptive characteristics of the groups

	Groups		Test statistics	
	Febrile convulsion n=50	Control n=54	Test value	p-value
Gender, n (%)			3.028†	0.104
Male	36 (72.0)	30 (55.6)		
Female	14 (28.0)	24 (44.4)		
Age, (years)			0.765&	0.444
Mean ± SD	21.6±11.6	20.5±11.2		
M (min-max)	17.5 (8-58)	17.0 (8-51)		

SD: Standard deviation, M: Median, †: Chi-square test, &: Mann-Whitney U test

and control groups (p>0.05). However, the leukocyte [white blood cell (WBC)] count showed a statistically significant difference, with higher values in the FS group compared to the control group (p<0.05). Moreover, the infection markers, CRP, PCT, and glucose levels in the FS grou pwere significantly higher than those in the control group (p<0.001).

The vitamin B12 (p<0.05), sodium, potassium, calcium, magnesium, phosphorus and PLT values of the FS group were statistically lower than the control group (Table 3).

According to Table 4, there is no statistical difference between the descriptive features and laboratory values of the simple and complex FS groups (p>0.05).

Discussion

FS is a convulsive disorder that is common in childhood and its underlying causes have not been fully explained. It is defined as a convulsion occurring during a febrile illness in patients without neurological infection, metabolic disorder or a history of FSs (2,20). Studies on FS have emphasized that children with FSs have lower serum vitamin B12 levels (13). In our research, we observed that the vitamin B12 levels were notably lower in the FS group when compared to the control group.

In the current investigation, we found no statistically significant difference in terms of gender and age distribution between the FS group and the control group.

Table 2. Descriptive characteristics of febrile convulsion group (n=50)

Gender, n (%)	
Male	36 (72.0)
Female	14 (28.0)
Age, (years)	
Mean ± SD	21.6±11.6
M (min-max)	17.5 (8-58)
Fever, (celcius)	
Mean ± SD	38.30±0.29
M (min-max)	38.30 (38.00-39.80)
Seizure classification, n (%)	
Simple	38 (76.0)
Complex	11 (22.0)
Status	1 (2.0)
Focus of fever, n (%)	
AGE	7 (14.0)
URTI	36 (72.0)
Teething	6 (12.0)

Sd: Standard deviation, M: Median

In the FS group, there were 36 male patients, accounting for 72% of the group and 14 female patients, representing 28% of the group. In concordance with our study, male predominance was reported in other studies (21,22).

Table 3. Comparison of laboratory values between groups

	Groups		Test statistics	
	Febrile seizures n=50	**Control n=54**	**Test value**	**p-value**
Hb	11.46±1.05	11.27±1.03	0.914†	0.363
Sodium	134.92±2.54	137.85±1.82	6.701†	**<0.001**
Potassium	4.41±0.46	4.60±0.36	2.389†	**0.019**
Calcium	9.41±0.51	10.03±0.45	6.619†	**<0.001**
Magnesium	2.026±0.150	2.116±0.194	2.623†	**0.010**
Phosphorus	5.13±0.58	5.36±0.51	2.092†	**0.039**
WBC	10.560 (6.437)	8.945 (4.665)	2.394	**0.017**
PLT (x10³)	280.5 (135.2)	318.0 (132.0)	2.189	**0.029**
CRP	4.85 (15.93)	0.43 (1.53)	5.264	**<0.001**
Procalcitonin	0.14 (0.17)	0.05 (0.09)	4.934	**<0.001**
Glucose	111.5 (31.0)	84.5 (9.2)	6.607	**<0.001**
Vitamin B12	401 (175)	441 (228)	1041&	**0.044**

Data are expressed as mean ± standard deviation or median (interquartile range) values. †: Independent samples t-test, &: Mann-Whitney U test, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, Normal ranges: Vitamin B12 180-1165 pg/mL (13)

Table 4. Comparison of descriptive characteristics and laboratory values according to seizure classification

	Groups		Test statistics	
	Simple n=38	**Complex n=11**	**Test value**	**p-value**
Gender, n (%) Male Female	 28 (73.7) 10 (26.3)	 8 (72.7) 3 (27.3)	 0.004	 >0.999
Age	17.0 (10.5)	18.0 (12.0)	0.552&	0.581
Hb	11.45±0.83	11.49±1.71	0.089†	0.929
Na	134.84±2.72	135.00±2.00	0.179†	0.859
K	4.36±0.42	4.40±0.27	0.288†	0.775
Ca	9.34±0.51	9.54±0.31	1.197†	0.237
Mg	2.03±0.14	1.98±0.16	0.948†	0.348
Phosphorus	5.11±0.54	5.07±0.55	0.190†	0.850
WBC	10.560 (6.325)	10.030 (8.272)	0.264&	0.792
PLT (x10³)	289 (124.5)	280 (185.2)	0.048&	0.962
CRP	4.47 (17.08)	3.78 (12.18)	0.383&	0.701
Procalcitonin	0.12 (0.25)	0.23 (0.14)	0.336&	0.737
Glucose	112.0 (29.0)	115.5 (39.0)	0.647&	0.517
B12	425±158	335±120	1.75†	0.087

Data are expressed as mean ± standard deviation or median (interquartile range) values. †: Independent samples t-test, &: Mann-Whitney U test, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein

In our research, we observed that the median age of patients referred to the pediatric emergency department with FS was 21.6±11.6 months, which aligns with the findings reported in the existing literature (1,4,7,12). Indeed the accepted body temperature threshold for FS has been reported as 38 °C in certain studies, while in others, it is considered to be 38.5 °C and above (4). In the study of Sfaihi et al. (23) on 482 cases, he stated that the mean body temperature was above 39 °C when the patients with FS referred to the hospital. In a study of 457 cases by Canpolat et al. (4) in our country, the body temperature was below 39 °C in 24.7% of the cases and above 39 °C in 75.3% of the cases. In our study, the mean fever value in patients with FS was 38.3 °C (38.00-39.80 °C) (4). In accordance with our study 80-85% of cases referring to the emergency department with FS have simple FS and 10-15% have complicated FS (4,24,25). FSs are associated with viral infections in around 80% of patients who experience them. Additionally, certain infections, such as URTIs, pharyngitis, acute otitis media, lower respiratory tract infection, urinary tract infection, and acute gastroenteritis, have been identified as potential precipitating factors for FS. These infections can trigger the onset of FS in susceptible individuals, especially in young children (24,26,27). Consistent with the literature, URTIs were in the first place in our study (n=36, 72%), followed by acute gastroenteritis (n=7, 14%), urinary tract infections (n=1, 2%) and other factors (teething..) (n=6, 12%) (1,4,13,28).

Upon comparison of the laboratory parameters between the FS group and thecontrol group, no statistically significant difference was found in terms of Hb values. Similarly to ourstudy in two studies conducted in our country, no difference was found in Hb values between the groups (13,22).

WBC, CRP, PCT and glucose values of the group referring with FS were statistically higher than the control group. It was thought that the increase in glucose level compared to the control group may be due to stress, and the results were found to be similar with other studies (29,30). However, sodium, potassium, calcium, magnesium, phosphorus and PLT values were statistically lower than the control group. In parallel with our study, low platelet levels were found in children referring with FS elsewhere (8). In addition, studies have emphasized low electrolyte values in children referring with FS, and it has been reported that low levels of sodium, calcium, and magnesium may be encountered, similar to our study (11,12).

Vitamin B12 is vital for humans, especially for the central nervous system. Vitamin B12 deficiency in early childhood has been associated with many factors that negatively affect the child's neurological development, including impaired cognitive development (14). In our study, vitamin B12 values were statistically lower in patients who referred to the pediatric outpatien tclinic with FS compared to the control group. Similarly in the studies performed, vitamin B12 levels were found to be lower than the control group in patients presenting with FS and the study suggested that low vitamin B12 levels might be involved in the etiopathogenesis of FS (13,22).

In this present study, there is no statistical difference between the descriptive features and laboratory values of the simple FS and complex FS groups. In a study conducted in our country with a small sample size, it was stated that there were differences in Hb between the groups, while no statistical difference was found in our study (31).

Study Limitations

The limitations of our study are it is being retrospective, single-center and the number of patients is small. In addition, because it is retrospective, the family history of the patients and the causes that may increase the risk of recurrence could not be fully questioned. There is a need for multicenter, larger studies on the precise role of B12 deficiency in febrile seizures.

Conclusion

76% of our patients were simple FS and 22% were complicated FS. URTIs were the most common underlying cause. The observation that vitamin B12 levels were significantly lower in the group presenting with FS compared to the control group suggest that low vitamin B12 levels may play a role in the increased risk of FS.

Ethics

Ethics Committee Approval: Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (dated: 04/10/2021, number: E-10840098-772.02-4983).

Informed Consent: Informed consent was obtained

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: O.Y., M.T.K., M.E., A.Ö., Design: O.Y., M.T.K., M.E., H.S.S., Ö.B., Data Collection or Processing: O.Y., H.S.S., A.Ö.,

Ö.B., Analysis or Interpretation: O.Y., M.T.K., M.E., A.Ö., Ö.B., Literature Search: O.Y., M.T.K., H.S.S., Ö.B., Writing: O.Y., M.E.

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ORIGINAL RESEARCH

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Clinical Utility of Hepassocin and TXNDC5 in Patients with Non-alcoholic Fatty Liver Disease and/or Type 2 Diabetes

Alkolik Olmayan Yağlı Karaciğer Hastalığı ve/veya Tip 2 Diyabet Hastalarında Hepassosin ve TXNDC5'in Klinik Yararı

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Abstract

Objective: The prevalence of non-alcoholic fatty liver disease (NAFLD) is high both in the general population and in people with type 2 diabetes mellitus (T2DM), while studies on its etiopathogenesis are still ongoing. The aim of this study is to investigate the association between the ultrasound grade of liver steatosis and serum levels of hepassocin (HPS) and thioredoxin domain-containing protein 5 (TXNDC5) in patients with T2DM.

Method: The cross-sectional study included 156 participants who were divided into four groups: isolated NAFLD, isolated T2DM, both NAFLD and T2DM, and healthy controls. The demographic data as well as the physical characteristics, laboratory findings, and ultrasonographic grades of liver steatosis of the participants were evaluated between all groups.

Results: According to ultrasound examinations, HPS values were significantly higher in patients with grade 1 and 2 liver steatosis than in patients without liver steatosis. HPS levels were significantly higher in the vast majority of participants, including healthy controls than in those with isolated T2DM. No significant differences were found between HPS and diabetes. There was no significant correlation between TXNDC5 serum levels and ultrasound results in all groups.

Conclusion: In the present study, our results show that serum HPS levels were higher in individuals with liver steatosis than in individuals without liver steatosis. These results provide further evidence for the association

Öz

Amaç: Alkolik olmayan yağlı karaciğer hastalığının (NAFLD) prevalansı hem genel popülasyonda hem de tip 2 diyabeti (T2DM) olan kişilerde yüksek olmakla birlikte; etiyopatogenezi üzerine çalışmalar halen devam etmektedir. Çalışmamızın amacı, T2DM'li hastalarda karaciğer yağlanmasının ultrasonografik derecesi ile hepassosin (HPS) ve tiyoredoksin domain içeren protein 5 (TXNDC5) serum düzeyleri arasındaki ilişkiyi araştırmaktır.

Yöntem: Bu kesitsel çalışmaya 156 katılımcı dahil edilmiş ve izole NAFLD, izole T2DM, hem NAFLD hem de T2DM ve sağlıklı kontrol olmak üzere dört grup oluşturulmuştur. Katılımcıların demografik verilerinin yanı sıra fiziksel özellikleri, laboratuvar bulguları ve karaciğer yağlanmasının ultrasonografik dereceleri tüm gruplar arasında değerlendirilmiştir.

Bulgular: Ultrasonografik incelemeye göre, 1. ve 2. derece karaciğer yağlanması olan hastalarda HPS seviyeleri, karaciğer yağlanması olmayanlara göre anlamlı derecede yüksekti. HPS seviyeleri, sağlıklı kontroller de dahil olmak üzere katılımcıların büyük çoğunluğunda izole T2DM'li olanlardan anlamlı derecede yüksekti. HPS ile diyabet arasında önemli farklılıklar bulunmamıştır. Ayrıca, tüm gruplarda serum TXNDC5 düzeyleri ile ultrason sonuçları arasında anlamlı bir ilişki bulunmamıştır.

Sonuç: Bu çalışmada, bulgularımız karaciğer yağlanması olanlarda serum HPS düzeylerinin karaciğer yağlanması olmayanlara göre daha yüksek olduğunu göstermektedir. Bu sonuçlar, HPS'nin NAFLD ile

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Abstract

of HPS with NAFLD and expand our understanding of its potential role in the pathogenesis of NAFLD. In addition, our study can be considered one of the first studies in the literature to investigate the association between ultrasonographic hepatic steatosis and serum HPS levels.

Keywords: Hepassocin, non-alcoholic fatty liver disease, TXNDC5, type 2 diabetes mellitus, ultrasonography

Öz

ilişkisi için daha fazla kanıt sağlamakta ve NAFLD patogenezindeki olası rolü hakkındaki anlayışımızı genişletmektedir. Ayrıca, çalışmamız ultrasonografik karaciğer yağlanması ile serum HPS düzeyleri arasındaki ilişkiye dair literatürdeki ilk araştırmalardan biri olarak kabul edilebilir.

Anahtar kelimeler: Alkolik olmayan yağlı karaciğer hastalığı, hepassosin, tip 2 diyabet, TXNDC5, ultrasonografi

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver disease in the world population. NAFLD encompasses a range of damage, from a mildly abnormal accumulation of liver triglycerides to non-alcoholic steatohepatitis (NASH), which can lead to fibrosis and potentially irreversible cirrhosis (1,2). NAFLD is a growing health problem in Western countries, the most common form of liver disease, and the leading cause of end-stage liver disease (3).

NAFLD is associated with various metabolic disorders such as hyperlipidemia, visceral obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM), and hypertension and is thought to be a manifestation of metabolic syndrome in the liver (4). The study by Chiloiro et al. (5) showed that fatty liver is associated with metabolic syndrome in overweight and obese patients. As a result of these studies, the Asia-Pacific consensus report by Eslam et al. (6) suggested updating the nomenclature from NAFLD to metabolic (dysfunction) associated fatty liver disease. Excessive adiposity is associated with *de novo* lipogenesis in the liver leading to accumulation of triglycerides in the liver and increased lipid flux to the liver (7). NAFLD is also cited as a significant factor in the onset and development of cardiovascular disease and as the first marker for atherosclerosis, particularly in patients with T2DM (8).

The prevalence of T2DM in patients with NAFLD has been reported to be as high as 70%, as T2DM makes the development of NAFLD more likely (9). Since oxidative stress (OS) is critical to the pathogenesis of diabetes and liver disease (10), methods to reduce the effects of OS (11) have been shown to be effective in preserving liver function in diabetes (12). OS and lipotoxicity-induced endoplasmic reticulum (ER) stress are the main causes of liver damage in NAFLD (13). Studies have shown that ER stress is involved in the pathogenesis of various liver diseases such as NAFLD, viral hepatitis, and cirrhosis (14).

Hepassocin (HPS), also called hepatocyte-derived fibrinogen-related protein and fibrinogen-like 1, is a hepatokine and a liver-specific expression gene that has DNA synthesis-stimulating activity in hepatocytes and plays an important role in the regulation of hepatocyte proliferation (15,16). HPS has been shown to be a strong regulator of liver cell growth not only in rats but also in humans (15). HPS expression is reduced in patients with hepatocellular carcinoma (17). A recent study has revealed a causal relationship between HPS and NAFLD. According to this study, HPS plays a crucial role in NAFLD and causes the accumulation of liver lipids via an ERK1/2-dependent pathway (18). Although the functions of HPS have been established in patients with liver failure and hepatocellular carcinoma, its role in NAFLD is still unknown and several clinical studies are needed.

Thioredoxin domain holding protein 5 (TXNDC5), also called resident endoplasmic reticulum 46 (Erp46), 15th member of protein disulfide isomerase family A, thioredoxin-related protein in the cytoplasm or endo-PDI, is a protein disulfide isomerase (19). TXNDC5, which is affected by liver fat and associated with the regulation of ER stress, is thought to contribute significantly to the control of apolipoprotein B and the development of steatosis (20). Under these conditions, high fatty acid levels, calcium deficiency, and IR have been observed to cause damage to ER homeostasis through improperly packaged proteins and OS (20). There is ample evidence that dysregulation of its expression can cause cell aging, oxidative stress, and many pathological conditions such as arthritis, cancer, diabetes, vitiligo, and viral infections. Altered expression in pancreatic cells could alter insulin folding and adiponectin response, which could be a new etiology of diabetes (19).

In the present study, we investigated serum levels of HPS and TXNDC5 in patients with isolated NAFLD, with isolated diabetes, and with NAFLD and T2DM compared to healthy controls. A further aim was to compare the levels of these markers with biochemical, metabolic, and anthropometric

parameters associated with NAFLD and T2DM and with the ultrasonographic grade of liver steatosis.

Materials and Methods

Patients and Study Design

In our study, patients were selected in the following order: To determine whether liver fat was present, a hepatobiliary ultrasound was performed to identify those who were admitted to the radiology department for various reasons. Subsequently, patients with and without hepatic steatosis, patients previously diagnosed with T2DM, and those found to be at risk of T2DM were referred to the internal medicine and diabetes outpatient clinic to be screened for the study. Eligible participants were screened for T2DM according to the American Diabetes Association diagnostic criteria (fasting blood glucose ≥126 mg/dL, 2-hour postprandial glucose ≥200 mg/dL after the 75 g oral glucose tolerance test, or HbA1c ≥6.5%) (21). All participants read and signed a written informed consent, which was added to the study.

The age of the study participants was between 18 to 65 years, with no ethnic difference between the patients and the control group. Physical examination findings, age, gender, and anthropometric measurements [body mass index (BMI), waist circumference (WC), hip circumference (HC)]; cardiovascular risk factors including family history, hypertension, dyslipidemia, diabetes, hyperuricemia, and ongoing medication use were recorded.

The inclusion criteria and the division of the groups were defined as follows: Group 1, patients with isolated NAFLD; Group 2, patients with isolated T2DM without liver steatosis; Group 3, patients with both NAFLD and T2DM; and Group 4, healthy controls. Patients with one or more of the following conditions that may affect metabolic parameters were excluded from the study: Hyper-hypothyroidism, renal failure, hepatic failure, heart failure, alcoholism, malignancies, pregnancy, pancreatic disease, and medications associated with steatohepatitis (corticosteroids, valproic acid, amiodarone, estrogen, tamoxifen, diltiazem, etc.). Serologic tests showed that the patients had no active or chronic viral hepatitis.

Laboratory Measurement

Serum concentrations of HPS/FGL1 and TXNDC5 were assayed in duplicate using enzyme-linked immunoassay kits (Hepassocin: catalog no: SED022Hu, Cloud-Clone Corp., TX, USA; TXNDC5, catalog no: SRB-T-86174, Shanghai Sunred Biological Technology Co., Ltd., PRC) according to the manufacturer's protocol. The intra- and inter-assay coefficients of variation were <10% and <12% for HPS (detection range 0.156-10 ng/mL and sensitivity 0.071 ng/mL), respectively. The intra- and inter-assay coefficients of variation were <10% and <12%, respectively, for TXNDC5 (detection range 0.2-30 ng/mL and sensitivity 0.136 ng/mL). To obtain a standard optical density (OD) curve for the concentration of both markers (HPS and TXNDC5), we introduced samples, standard samples, and biotin-labeled antibodies into micropores pre-coated with both marker antibodies. Subsequently, the OD values of the standard samples and samples were measured using a microplate spectrophotometer (Smart Microplate Reader; USCN KIT INC.) at a wavelength of 450 nm. The concentrations of HPS and TXNDC5 were then determined by comparing the OD values of the samples with the standard curve.

Radiological Measurement

The same radiologist at the hospital's radiology clinic performed the hepatobiliary ultrasound examination of the patients using a grayscale ultrasound machine (Mindray DC-7) and a convex multihertz probe that can vary between 3.3-5 mHz. The grade of liver steatosis in all participants was determined after 10 hours of fasting based on the increase in echo in the liver parenchyma and the ultrasound image of liver fat infiltration. The degree of ultrasonographic adiposity was classified as follows: Grade 0: patients without adiposity; Grade 1: minimal diffuse increase in liver echogenicity (mild adiposity); Grade 2: moderate increase in liver echogenicity (moderate adiposity); Grade 3: significant increase (severe) in liver echogenicity as inability of sound to penetrate the posterior part of the right lobe of the liver or inability to see hepatic vessels and diaphragm (severe adiposity).

Ethics Issues

Before to conducting the study, ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital with protocol number date: IRB number: 2019.03.3.05.034 (March 29, 2019). All participants acknowledged and signed their written informed consent. The authors declare that there are no potential conflicts of interest relevant to this article.

Statistical Analysis

Number Cruncher Statistical System 2007 (Kaysville, UT, USA) was preferred for the statistical analysis. Descriptive statistical methods and the data distribution were analyzed using the Shapiro-Wilk test. The Kruskal-Wallis test was used to compare the quantitative data of more than two

groups, and the Mann-Whitney U test was preferred to compare two groups. The chi-square test was used to determine the relationship between qualitative data. Evaluation of the significance was carried out at the levels of p<0.01 and p<0.05.

Results

Participants' Characteristics

One hundred fifty-six participants were included in the study [48.7% (n=76) male and 51.3% (n=80) female]. The distribution of the study groups was determined as 24.4% (n=38) Group 1; 25% (n=39) Group 2; 25.6% (n=40) Group 3 and 25% (n=39) Group 4. According to ultrasound findings were found to have 50% (n=78) no liver steatosis (grade 0) (39 from group 2 and 37 from group 4), 26.9% (n=42) mild liver steatosis (grade 1) (25 from group 1 and 17 from group 3) and 23.1% (n=36) moderate liver steatosis (grade 2) (13 from group 1 and 23 from group 3) (Table 1). There was no patient with grade 3 ultrasonographic liver steatosis.

Comparison of Demographic Features, Anthropometric Measurements, and Physical Examination Findings

When comparing the age distribution of the study groups, the mean age of the controls was lower than the other groups (p=0.001) (Table 2).

The BMI, WC, HC, and WC/HC ratio (WHR) values in the control group were found to be significantly lower than all other groups (p=0.001), while the BMI, WC, and HC values of group 3 were significantly higher than those of group 1 and group 2 (p=0.001) (Table 2). In terms of systolic blood pressure values, the values of the control group were significantly lower than those of Group 2 and Group 3, and the values of Group 1 were lower than those of Group 2 (p=0.001).

Comparison of Laboratory Findings

Serum HPS levels of the groups showed statistically significant differences (p=0.001). The HPS levels of group 1, group 3, and group 4 were higher than those of group 2 (p=0.001). There was no significant difference in TXNDC5 serum levels between the groups (p=0.109) (Table 3).

The liver-related enzymes [aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), except alkaline phosphatase (ALP)] of the groups containing NAFLD were significantly higher than those without it, and co-existing diabetes increased this (p=0.002, p=0.001, p=0.001 and p=0.507; respectively). The AST/ALT ratio of the control group was higher than that of all other groups (p=0.001) (Table 3).

Comparison of the Patient Groups in Terms of the Use of Antidiabetic Drugs

A significant relationship was detected between the use of antidiabetic drugs in the study groups (p=0.001). Besides, the antidiabetic drug users were found to be statistically significantly lower than the non-users in group 3 (p=0.001). It also indicated to be statistically significant that the

Table 1. Distribution of participants according to ultrasonographic grades of the liver steatosis

	Isolated NAFLD (Group 1)	Isolated T2DM (Group 2)	NAFLD + T2DM (Group 3)	Controls (Group 4)
Grade 0 (n=78)	0	39	0	37
Grade 1 (n=42)	25	0	17	0
Grade 2 (n=36)	13	0	23	0

NAFLD: Non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus

Table 2. Comparison of age and anthropometric measurements according to study groups

	Isolated NAFLD (Group 1) n=38	Isolated T2DM (Group 2) n=39	NAFLD + T2DM (Group 3) n=40	Controls (Group 4) n=39	p
			Mean ± SD		
Age	38.82±11.3	50.18±9.08	47.83±9.43	30.38±9.5	**0.001****
BMI	31.68±6.02	28.36±4.53	33.18±4.58	26.12±4.98	**0.001****
WC	94.42±10.52	94.48±9.03	98.69±8.04	82.08±12.38	**0.001****
HP	105.42±13.43	100.48±9.18	108.74±8.15	96.44±10.5	**0.001****
WHR	0.9±0.08	0.95±0.1	0.91±0.07	0.85±0.09	**0.001****

SD: Standard deviation, NAFLD: Non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus, BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WHR: Waist/hip ratio, ANOVA test, *p<0.05, **p<0.01

antidiabetic drug users were higher than non-users in Group 2 (p=0.001) (Table 4).

Comparison of Anthropometric Measurements According to the Ultrasound Results

As the grade of liver steatosis increased, the BMI, WC, and HC values also significantly increased (p=0.001). In line with the ultrasound results, age was not significantly different within all ultrasound patterns (p=0.314) (Table 5).

Comparison of Laboratory Findings Based on the Ultrasound Results

According to the ultrasound results, serum HPS levels demonstrated a significant difference (p=0.002). The serum HPS levels of those without liver steatosis (grade 0) were significantly lower than those with grades 1 and 2 liver steatosis (p=0.001). In line with the ultrasound results, serum TXNDC5 levels were not significantly different within all ultrasound patterns (p=0.154) (Table 6).

In patients with liver steatosis (grade 1-2), serum levels of AST, ALT, and AST/ALT ratio were significantly higher than those without it (p=0.001, p=0.001, and p=0.018; respectively) (Table 6).

Discussion

In the present study, we found that HPS levels are significantly higher in patients with fatty liver. There was no significant difference in TXNDC5 serum levels between the ultrasound groups. The liver-related enzymes (AST, ALT, GGT), BMI, WC and HC levels of the groups with hepatic

Table 3. Comparison of laboratory measurements by study groups

	Isolated NAFLD (Group 1) n=38	Isolated T2DM (Group 2) n=39	NAFLD + T2DM (Group 3) n=40	Controls (Group 4) n=39	p
			Min-max (median) or mean ± SD		
Hepassocin	0.79-4.91 (2.09)	0.16-8.99 (1.18)	0.42-9.85 (2.08)	0.16-4.01 (1.69)	**0.001**[a]
TXNDC5	0.63-18.09 (0.79)	0.54-16.82 (0.88)	0.43-16 (0.77)	0.4-15.9 (1.44)	0.109[a]
AST	12-50 (23)	9-75 (18)	12-52 (23)	13-61 (20)	**0.002**[a]
ALT	7-100 (27)	9-109 (17)	11-72 (26)	7-67 (17)	**0.001**[a]
AST/ALT ratio	0.97±0.38	0.95±0.46	0.88±0.36	1.26±0.5	**0.001**[b]
ALP	73.74±18.83	83±39.63	79.78±25.49	77.68±16.86	0.507[b]

NAFLD: Non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus, TXNDC5: Thioredoxin domain containing protein 5, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation, ALP: Alkaline phosphatase, [a]Kruskall-Wallis test (min-max/median), [b]ANOVA test (mean ± SD), *p<0.05, **p<0.01

Table 4. Comparison of the use of antidiabetic drugs according to study groups

	Isolated NAFLD (Group 1) n=38	Isolated T2DM (Group 2) n=39	NAFLD + T2DM (Group 3) n=40	Controls (Group 4) n=39	p
Antidiabetic drug use					
Yes	0	23 (59%)	15 (37.5%)	0	**0.001****
No	38 (100%)	16 (41%)	25 (62.5%)	39 (100%)	

Chi-square test, **p<0.01, NAFLD: Non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus

Table 5. Comparison of age and anthropometric measurements according to the ultrasonographic grades of the liver steatosis

	Grade 0 liver steatosis n=78	Grade 1 liver steatosis n=42	Grade 2 liver steatosis n=36	p
		Mean ± SD		
Age	40.28±13.58	43±10.57	43.94±12.16	0.314
BMI	27.24±4.85	31.01±5.02	33.82±5.47	**0.001****
WC	87.82±12.53	94.29±9.96	99.57±8.11	**0.001****
HP	98.31±10.04	105.18±10.47	109.6±11.49	**0.001****
WHR	0.89±0.11	0.9±0.08	0.91±0.08	0.700

BMI: Body mass index, SD: Standard deviation, WC: Waist circumference, HC: Hip circumference, WHR: Waist/hip ratio, ANOVA test, *p<0.05, **p<0.01

Table 6. Comparison of laboratory measurements according to the ultrasonographic grades of the liver steatosis

	Grade 0 liver steatosis n=78	Grade 1 liver steatosis n=42	Grade 2 liver steatosis n=36	p
	Min-max (median) or mean ± SD			
Hepassocin	0.16-8.99 (1.4)	0.79-9.85 (2.23)	0.42-6.19 (2)	**0.002**[a]
TXNDC5	0.4-16.82 (0.91)	0.5-18.09 (0.78)	0.43-16.34 (0.81)	0.154[a]
AST	9-75 (19)	12-50 (21)	12-52 (24)	**0.001**[a]
ALT	7-109 (17)	7-98 (25)	11-100 (28.5)	**0.001**[a]
AST/ALT ratio	1.1±0.5	0.98±0.4	0.85±0.31	**0.018***[b]
ALP	80.19±29.73	77.38±21.51	75.85±23.64	0.736[b]

NAFLD: Non-alcoholic fatty liver disease, T2DM: Type 2 diabetes mellitus, TXNDC5: Thioredoxin domain containing protein 5, SD: Standard deviation, AST: Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase, [a]Kruskall-Wallis test (min-max/median), [b]ANOVA test (mean ± SD), *p<0.05, **p<0.01

steatosis were significantly higher than those without hepatic steatosis.

NAFLD is strongly associated with T2DM and IR. According to the study by Xie et al. (22), hepatic steatosis is an independent determinant of increased IR and is associated with increased insulin secretion. In T2DM patients without liver steatosis detected by ultrasound, ALT and AST are associated with hyperinsulinemia and IR in the study by Esteghamati et al. (23). In the literature, results show that HPS induces hepatic lipid accumulation in NAFLD (18), may be involved in the development of NAFLD (24), and may facilitate the accumulation of elevated hepatic lipids in NAFLD and T2DM (25). Our results are in line with the consensus in the literature on the interaction between HPS and NAFLD. First, as the most important finding of our study, when evaluated between study groups, those with the healthy control group, those with both NAFLD and T2DM, and those with isolated NAFLD had higher serum HPS levels than those with isolated T2DM. In other words, those with isolated T2DM had the lowest serum HPS levels compared to the other groups. Second, when evaluated according to the extent of ultrasound fatty liver, serum HPS levels were found to be higher in steatosis. Importantly, the results show that this study is the first to demonstrate an incremental relationship between HPS and ultrasonographic hepatic steatosis. This finding suggests that HPS levels can predict ultrasonographic steatosis. Through a more comprehensive planned study with defined HPS cut-off points, the ultrasonographic degree of liver steatosis can be estimated based on HPS values. Although the results of the study contribute to the literature, prospective research is needed to prove the association between HPS and NAFLD.

An interesting aspect that emerged from the current analysis was that the HPS scores of the groups with isolated T2DM were the lowest compared to the other groups, including the control group. The results, which differ from those of the researchers (26), suggest that elevated HPS levels may be a risk factor for the development of diabetes and IR and that HPS could also be used as a biomarker for the diagnosis of prediabetes. Few studies have examined the causal relationship of HPS with IR, obesity, and diabetes (25-29), and the current study partially contradicted them with respect to diabetes. The contradiction revealed by the current study on diabetes and HPS might be due to confounding factors highlighted by Giorda et al. (3). To summarize these proposed reasons: a reasonable proportion of patients recovered from fatty liver disease, while lower IR (less abdominal obesity, dyslipidemia, hypertension, renal damage) facilitated this; older patients with higher LDL and HbA1c levels had a lower likelihood of resolving NAFLD status; pharmacological treatment of diabetes has been shown to be a notable probable factor for progression or regression of NAFLD. The fact that the diabetic patients in our study received different diabetes treatments was considered an important factor among all these proposed reasons. The HPS score may have been lower because those with isolated T2DM were taking more diabetes medications than others.

Although there was an indication that TXNDC5 contributes to the development of steatosis and seems to be a marker for hepatic steatosis in the absence of apoE (20), there were not enough studies aimed at this, so no association was found in our study either. Many studies have reported that ER stress is involved in the pathophysiologic development of NAFLD. In a study aimed at this, glucagon-like peptide-1 (GLP-1) was shown to ameliorate NAFLD by reducing hepatic ER stress and subsequent apoptosis, and that treatment with GLP-1 analogs may contribute significantly to the maintenance of NAFLD (30). In the same study,

it was suggested that the anti-lipotoxic effect of GLP-1 might have an impact on the activation of the Erp46 (TXNDC5) signaling pathway. However, the link between T2DM and TXNDC5 could not be established in this study. In this regard, our study showed no association between TXNDC5 and diabetes. The association between serum levels of TXNDC5 and the parameters of the current study was not statistically significant in all analyzes.

Study Limitations

The limitations of our study, the use of antidiabetic drugs and the different age distribution between the groups proved to be possible confounding factors. In addition, the fact that the study was conducted in a tertiary care hospital prevents generalization of the results. There is a need for studies that include newly diagnosed diabetics who have not yet received antidiabetic medication and the age differences between the groups that comprise the entire population. The study cohort is limited by the absence of grade 3 steatosis, which limits the availability of data for the worst grade of steatosis with hepassocin.

Conclusion

Our study has shown the association of HPS with NAFLD, confirming previous studies and contributing to the literature on its involvement in the pathogenesis of NAFLD. Our study is originally based on the fact that it is the first study to demonstrate the association between HPS and ultrasonographic grade of liver steatosis. No comparable association was demonstrated between HPS and T2DM and, as an additional finding, no significant association was found between TXNDC5 and NAFLD and T2DM, either individually or together. More comprehensive prospective research is needed to confirm the results of the current study, taking into account potential limitations.

Ethics

Ethics Committee Approval: Before to conducting the study, ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital with protocol number date: IRB number: 2019.03.3.05.034 (March 29, 2019).

Informed Consent: All participants acknowledged and signed their written informed consent.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.D., E.S., İ.D., Design: E.D., E.S., İ.D., Data Collection or Processing: E.D., E.S., M.D., Analysis or Interpretation: İ.D., M.D., Ş.A., Drafting Manuscript: E.D., E.S., İ.D., Ş.A., Critical Revision of Manuscript: E.D., E.S., M.D., Final Approval and Accountability: E.D., E.S., İ.D., M.D., Ş.A., Technical or Material Support: E.D., E.S., İ.D., Supervision: E.D., E.S., Writing: E.D., E.S., İ.D., M.D., Ş.A.

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ORIGINAL RESEARCH

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Evaluation of Hepatitis C in 20 Years: A Turkish Experience

Hepatit C'nin 20 Yıllık Değerlendirilmesi: Bir Türkiye Deneyimi

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Abstract

Objective: Hepatitis C virus (HCV) infection still maintains its importance since it is one of the most important causes of liver cirrhosis and hepatocellular carcinoma. Our hospital, located in İstanbul, which is the 10th most crowded city in the world, has a patient cohort where epidemiological change can be observed due to its deep-rooted history and serving people of different nations in terms of settlement. Main aim in this study is to evaluate the change in HCV epidemiology in our country over the years.

Methods: Patients who were at the age of 18 and above and whose HCV-RNA was positive between January 2001 and January 2021 were evaluated.

Results: 1.166 patients whose HCV genotype was determined were evaluated. The mean age of the population is 52±14.75 years, 83.53% of all patients was infected with genotype 1 (GT1), 8.23% with GT3, 5.83% with GT2, 2.23% with GT4 and 0.17% of them with GT5. While the GT1 rate decreased in patients over the years, an increase was found in other GTs. GT1 and GT2 were more common in females (p<0.001); GT3 and GT4 were more dominant in males (p<0.001). The mean age of females was high in all genotypes. The mean age of GT3 was significantly lower than the other groups (p<0.001).

Conclusion: Although GT1 is still dominant in our country, GT3 and GT4 have been increasingly seen over the years, suggesting that the genotype distribution may change in the coming years due to uncontrolled migration and effective direct-acting antivirals.

Keywords: Distribution, genotype, hepatitis C, migration

Öz

Amaç: Hepatit C virüs (HCV) enfeksiyonu, karaciğer sirozu ve hepatoselüler karsinomun en önemli nedenlerinden biri olması nedeniyle önemini halen korumaktadır. Dünyanın en kalabalık 10. şehri olan İstanbul'da bulunan hastanemiz, köklü geçmişi ve yerleşim açısından farklı milletlerden insanlara hizmet vermesi nedeniyle epidemiyolojik değişimin gözlenebildiği bir hasta kohortuna sahiptir. Bu çalışmada temel amaç ülkemizde HCV epidemiyolojisinin yıllar içindeki değişimini değerlendirmektir.

Yöntem: Ocak 2001 ile Ocak 2021 tarihleri arasında HCV-RNA'sı pozitif olan 18 yaş ve üstü hastalar değerlendirildi.

Bulgular: HCV genotipi belirlenen 1,166 hasta değerlendirildi. Nüfusun ortalama yaşı 52±14,75 olup, tüm hastaların %83,53'ü genotip 1 (GT1), %8,23'ü GT3, %5,83'ü GT2, %2,23'ü GT4 ve %0,17'si GT5 ile enfekte olmuştu. Yıllar içinde hastalarda GT1 oranı azalırken, diğer GT'lerde artış saptandı. GT1 ve GT2 kadınlarda daha yaygındı (p<0,001); GT3 ve GT4 erkeklerde daha baskındı (p<0,001). Kadınların ortalama yaşı tüm genotiplerde yüksekti. GT3'ün ortalama yaşı diğer gruplara göre anlamlı derecede düşüktü (p<0,001).

Sonuç: Ülkemizde GT1 hala baskın olmasına rağmen, GT3 ve GT4'ün yıllar geçtikçe artan bir şekilde görülmesi, kontrolsüz göç ve etkili direkt etkili antiviraller nedeniyle genotip dağılımının önümüzdeki yıllarda değişebileceğini düşündürmektedir.

Anahtar kelimeler: Dağılım, genotip, göç, hepatit C

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Introduction

Hepatitis C virus (HCV) infection still maintains its importance since it is one of the most important causes of liver cirrhosis and hepatocellular carcinoma, and there is limited access to effective treatment options (1). According to the 2016 global report of the World Health Organization (WHO), it has been reported that 71 million people worldwide are infected with HCV, causing 400,000 deaths annually (2). Although its incidence rate is decreasing in developed countries, a decrease in deaths due to liver disease is expected only in the next 20 years (3,4). Again, in this report, WHO has targeted the eradication of HCV and hepatitis B virus (HBV) until 2030.

Although the seroprevalence of HCV in Turkey is in the range of 0.6-1.6%; it is responsible for 25% of all liver cirrhosis, 25-30% of hepatocellular carcinoma and also 50% of liver transplantation cases (5-7).

HCV is a single strand RNA virus from the *Flaviviridae* family. There are regions in the genome structure that are both very well preserved and highly variable. According to sequencing, it has been found that there are 7 main genotypes and nearly 67 related subtypes (3). It is important to determine the genotype in collecting epidemiological data of HCV, shaping antiviral treatment, and predicting prognosis.

The distribution of HCV genotypes varies also geographically. Genotype 1 (GT1), genotype 2 (GT2) and genotype 3 (GT3), subgroup 1a, 1b, 2a and 3a are the most common ones worldwide. These genotypes are considered as infections acquired before safe blood transfusion and epidemic subtypes thought to be spread by IV drug users. Other species (GT4-GT7) are classified as endemic and are distributed in restricted areas (3,8,9).

In our globalizing world, changes are observed in the epidemiology of infectious diseases due to the changing conditions. Our hospital, located in Istanbul, which is the 10th most crowded city in the world, has a patient cohort where epidemiological change can be observed due to its deep-rooted history and serving people of different nations in terms of settlement. Our aim in this study is to evaluate the change in HCV epidemiology in our country over the years.

Materials and Methods

In this retrospective, single-center observational study, patients who were at the age of 18 and above and admitted to the University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2001 and January 2021 and whose HCV-RNA was positive were evaluated were evaluated. The demographic characteristics, admission dates, race and HCV genotypes of the patients were obtained through the hospital information system and recorded in the prepared forms.

Inclusion Criteria

1. Patients diagnosed with HCV between January 2001 and January 2021,

2. Patients who were at the age of 18 and above,

3. Patients whose initial HCV RNA level was measured and genotype was studied were included in the study.

Exclusion Criteria

1. Patients who were under the age of 18,

2. Patients with undetectable initial HCV RNA or genotype, or both, for any kind of reason.

For HCV genotype determination, the Innolipa HCV II kit (Bayer Diagnostics, USA) was used between 2000-2010, and the HCV Genotype Plus Real-TM (Sacace Biotechnologies-Italy) kit between 2011-2020.

Statistical Analysis

Statistical analysis was performed using Software SPSS 21 (SPSS Inc., Chicago, Illinois, USA). Chi-squared and Fisher's Exact tests were used for qualitative variables. The Mann-Whitney U test was used for variables with non-normal distribution, which was determined by the Kolmogorov-Smirnov test. Comparison of HCV RNA levels among genotypes was performed by Kruskal-Wallis test. $p<0.001$ was considered as statistically significant.

Our study was conducted in accordance with the Helsinki Declaration Principles and the Ethics Committee Approval of the University of Health Sciences Turkey, İstanbul Training Research Hospital Clinical Research Ethics Committee on 19.03.2021-with the number 2776.

Results

Between January 2001 and January 2021, 1.166 patients whose HCV genotype was determined were evaluated. The mean age of the population is 52±14.75 years. When the general genotype distribution is examined, 83.53% (n=974) of all patients was infected with GT1, 8.23% (n=96) with GT3, 5.83% (n=68) with GT2, 2.23% (n=26) with GT4 and 0.17% (n=2) of them with GT5. In GT1 subgroup, 8.42% of patients

was infected with undetermined subtype, 13.04% with GT1a and 78.54% with GT1b. In GT2 subgroup, 76.47% of patients was infected with undetermined subtype, 17.65% with GT2a and 5.88% with GT2c. In GT3 subtype, 62.5% of patients was infected with undetermined subtype, 36.46% with GT3a and 1.04% of them was infected with GT3b. GT5 was detected in 2 cases, all of them were subtyped as 5a. Evaluation of demographic and genotype distributions of our patients is shown in Table 1. While the GT1 rate decreased in our patients over the years, an increase was found in other GTs. Genotype distribution percentages over the years are shown in Graphic 1, and the distribution of genotypes by years is shown in Graphic 2. GT6 and GT7 were not detected in the study group. The infection caused by more than one genotype at a time was not detected in 2 people (1b/4 and 1b/2a). These cases were Syrian.

The study population consisted of 611 (52.4%) females, 555 (47.6%) males. There was a significant difference in the distribution of genotypes by gender. While GT1 and GT2 were more common in females ($p<0.001$), GT3 and GT4 were more dominant in males ($p<0.001$) (Table 2). The mean age of the population was 52±14.75 years, while the mean age of females was 54.2±4.07 years and the mean age of males was 48.55±6.42 years. The mean age of females was high in all genotypes. The mean age of GT3 was significantly lower than the other groups ($p<0.001$) (Table 2).

Discussion

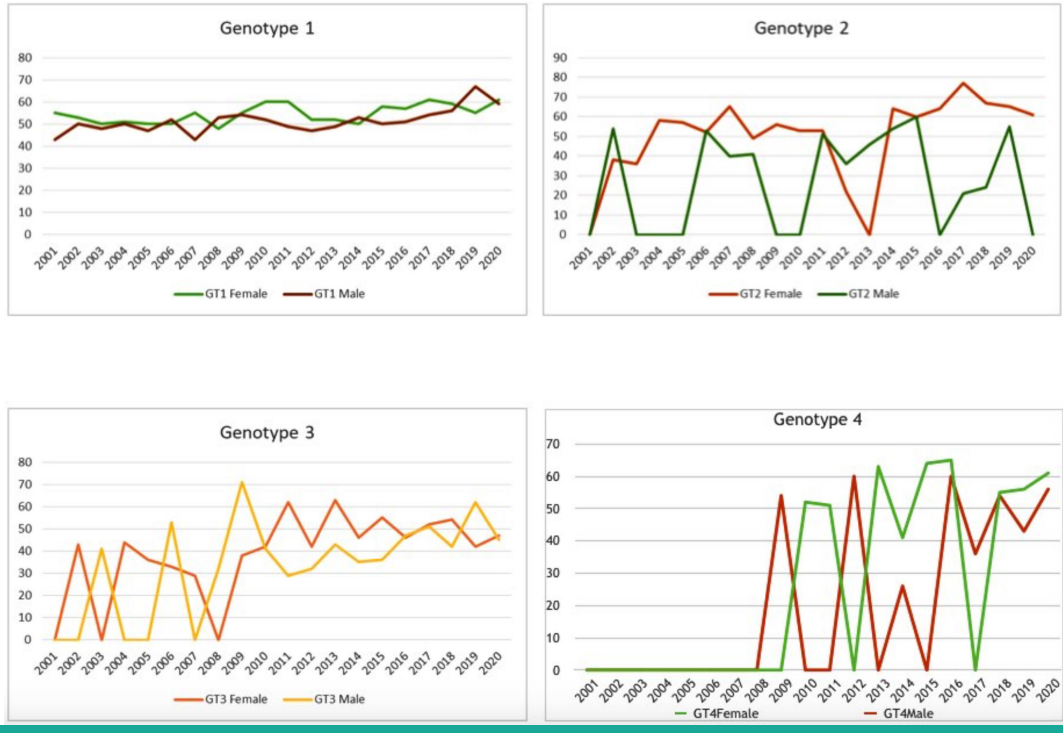
Transfusion of uncontrolled blood and blood products, invasive procedures and intravenous (IV) drug use are effective in the transmission of HCV. In developed countries, after safe transfusion procedures, its incidence is increasing in IV drug users, even if it incidence is decreasing in overall. In a multi-center study from 2013, it was reported that the incidence of HCV infection gradually decreased with the transition to safe blood transfusion practices and the number of new cases remained constant due to the low rate of IV drug users in our society. Consistent with this high incidence before 1992, a higher prevalence of HCV has been reported in patients over 50 years of age. In our study, the mean age was 52 years old (4).

The distribution of HCV genotypes varies worldwide. It is responsible for 49.1% of GT1 adult infections worldwide. It

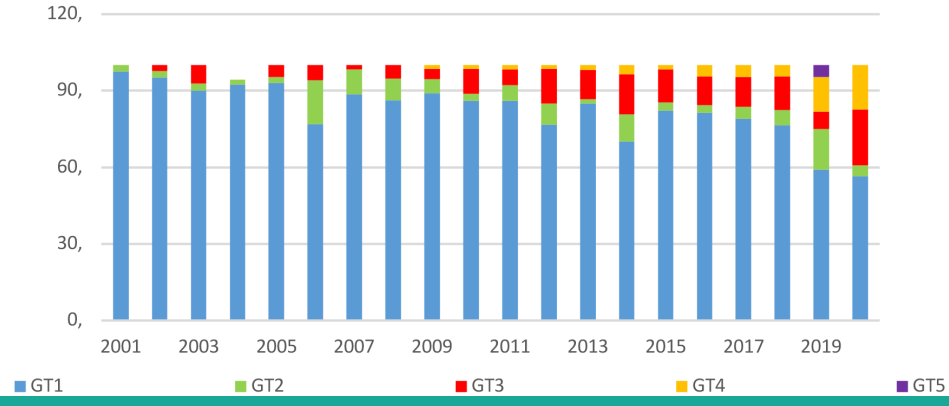
Table 1. Evaluation of demographic and genotype distributions of our patients with HCV

	Genotype 1							Genotype 2					Genotype 3					Genotype 4				
	N_t	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m
2001	39	51	38	28	55	10	43	1	1	38	0	0	0	0	0	0	0	0	0	0	0	0
2002	85	51	81	48	53	33	50	2	1	38	1	54	2	2	43	0	0	0	0	0	0	0
2003	70	49	63	35	50	28	48	2	2	36	0	0	5	0	0	5	41	0	0	0	0	0
2004	53	51	49	25	51	24	50	1	1	58	0	0	3	3	44	0	0	0	0	0	0	0
2005	44	49	41	28	50	13	47	1	1	57	0	0	2	2	36	0	0	0	0	0	0	0
2006	52	51	40	26	50	14	52	9	7	52	2	53	3	1	33	2	53	0	0	0	0	0
2007	62	50	55	27	55	28	43	6	5	65	1	40	1	1	29	0	0	0	0	0	0	0
2008	58	49	50	22	48	28	53	5	2	49	3	41	3	0	0	3	32	0	0	0	0	0
2009	73	55	65	38	55	27	54	4	4	56	0	0	3	2	38	1	71	1	0	0	1	54
2010	72	55	62	33	60	29	52	2	2	53	0	0	7	1	42	6	41	1	1	52	0	0
2011	65	55	56	35	60	21	49	4	3	53	1	51	4	2	62	2	29	1	1	51	0	0
2012	73	46	56	24	52	32	47	6	1	22	5	36	10	4	42	6	32	1	0	0	1	60
2013	53	50	45	21	52	24	49	1	0	0	1	46	6	1	63	5	43	1	1	63	0	0
2014	57	50	40	16	50	24	53	6	4	64	2	54	9	2	46	7	35	2	1	41	1	26
2015	62	62	51	34	58	17	50	2	1	60	1	60	8	1	55	7	36	1	1	64	0	0
2016	70	53	57	23	57	34	51	2	2	64	0	0	8	3	46	5	47	3	2	65	1	60
2017	43	55	34	17	61	17	54	2	1	77	1	21	5	1	52	4	51	2	0	0	2	36
2018	68	56	52	24	59	28	56	4	3	67	1	24	9	3	54	6	42	3	1	55	2	54
2019	44	58	26	11	55	15	67	7	3	65	4	55	3	2	42	3	62	6	3	56	3	43
2020	23	52	13	7	61	6	59	1	1	61	0	0	5	2	47	3	45	4	1	61	3	56

N_t: Total number, N_f: Total number of females, N_m: Total number of males, Age_m: Age values were given as mean, HCV: Hepatitis C virus



Graphic 1. Genotype distribution percentages over the years



Graphic 2. The distribution of genotypes by years Graphic 2. The distribution of genotypes by years

is followed by GT3 (17.9%), GT4 (16.8), GT2 (11%), GT5 (2%) and GT6 (1.4%) (3).

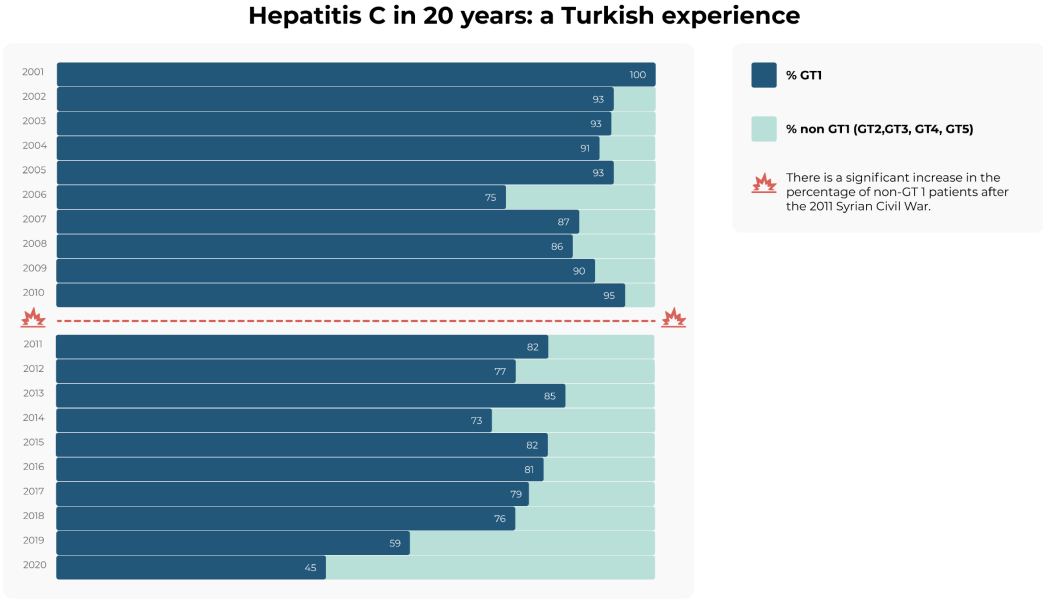
GT1, the most prevalent genotype in developed countries, is also the most prevalent worldwide and respond well to the second generation direct-acting antiviral (DAA) therapies with the viral eradication rates of >0% (10). In our study, the dominant genotype was GT1 (83.53%), followed by GT 3 (8.23%) and GT2 (5.83%). GT1 prevalence were reported between 62.4-95.3% in studies conducted in different regions of Turkey (11,12). The prevalence of GT1b, which is the most frequently observed genotype of the world (23.2-92.6%), was reported in Turkey with regional differences between 17.7% to 87%. Our study supports the general trend with a rate of 78.54% (10,11-13). Identifying previously unreported genotype "GT5" and showing relative increase of GT4 were probably caused by immigrants involved in our study group (Graphic 3).

It is known that social events such as wars and migrations play an important role in the epidemiological change of infectious diseases. GT3 is the second most common genotype, and it is the genotype that has spread among IV drug users, especially in Europe. In our previous study conducted between 2012-2019, the prevalence was 11.86% for GT3. In this study, the prevalence of GT3 was 8.23%, and two of our patients were IV drug user. In studies conducted in our country, the prevalence has been reported to be

Table 2. Difference in the distribution of genotypes by gender and age

	GT1		GT2		GT3		GT4		GT5	
	n	%	n	%	n	%	n	%	n	%
2001	38	(97.44)	1	(2.56)	0	(.00)	0	(0.00)	0	(0.00)
2002	81	(95.29)	2	(2.35)	2	(2.35)	0	(0.00)	0	(0.00)
2003	63	(90.00)	2	(2.86)	5	(7.14)	0	(0.00)	0	(0.00)
2004	49	(92.45)	1	(1.89)	3	(5.66)	0	(0.00)	0	(0.00)
2005	41	(93.18)	1	(2.27)	2	(4.55)	0	(0.00)	0	(0.00)
2006	40	(76.92)	9	(17.31)	3	(5.77)	0	(0.00)	0	(0.00)
2007	55	(88.71)	6	(9.68)	1	(1.61)	0	(0.00)	0	(0.00)
2008	50	(86.21)	5	(8.62)	3	(5.17)	0	(0.00)	0	(0.00)
2009	65	(89.04)	4	(5.48)	3	(4.11)	1	(1.37)	0	(0.00)
2010	62	(86.11)	2	(2.78)	7	(9.72)	1	(1.39)	0	(0.00)
2011	56	(86.15)	4	(6.15)	4	(6.15)	1	(1.54)	0	(0.00)
2012	56	(76.71)	6	(8.22)	10	(13.70)	1	(1.37)	0	(0.00)
2013	45	(84.91)	1	(1.89)	6	(11.32)	1	(1.89)	0	(0.00)
2014	40	(70.18)	6	(10.53)	9	(15.79)	2	(3.51)	0	(0.00)
2015	51	(82.26)	2	(3.23)	8	(12.90)	1	(1.61)	0	(0.00)
2016	57	(81.43)	2	(2.86)	8	(11.43)	3	(4.29)	0	(0.00)
2017	34	(79.07)	2	(4.65)	5	(11.63)	2	(4.65)	0	(0.00)
2018	52	(76.47)	4	(5.88)	9	(13.24)	3	(4.41)	0	(0.00)
2019	26	(59.09)	7	(15.91)	3	(6.82)	6	(13.64)	2	(4.55)
2020	13	(56.52)	1	(4.35)	5	(21.74)	4	(17.39)	0	(0.00)
Male[1]	453	(81.62)	23	(4.14)	64	(11.53)	14	(2.52)	1	(0.18)
Female[1]	521	(85.27)	45	(7.36)	32	(5.24)	12	(1.96)	1	(0.16)
Ages[2]	52.79±13.99		52.91±15.85		42.46±12.16		52.27±14.16		53.00±19.80	

[1] Chi-squared test (p<0.001) [2]Kruskal-Wallis test (p<0.001)



Graphic 3. Graphical course of hepatitis C after the 2011 Syrian Civil War

between 1.1-46%, and 0.6-71.6% from different regions in the world (10,11,14,15).

GT2 and GT4 are genotypes of African origin, and GT4 is thought to have spread iatrogenically, especially during the schistosomiasis vaccination applied in Egypt in the past, and spread to Europe due to the political relations of the countries and through frequent travels (16). In our country, it is known that it increased with the refugees coming after the Syrian civil war. In the study of Cirit et al. (17) evaluated the GTs of Syrian refugees, GT4 was found to be 48.2%. In our study, GT4 has been detected since 2009 at a rate of 2.23%. While the prevalence of GT2 is between 0.1% and 24.5% in the world, it is between 1.4-14.5% in studies conducted in our country and in our study, the prevalence was found to be 5.83% (13,18).

In the study, the low number of cases in 2020 is thought to be due to the low number of patients admitted due to the Coronavirus disease-2019 outbreak. It was observed that age and gender were effective in genotype distribution. While GT1 and GT2 were more common in females, GT3 was observed more frequently in males. In the study conducted by Karabulut et al. (19), GT1 and GT2 were observed with a higher rate in females (20).

In the GEHEP 2005 study conducted in Spain, while male gender is dominant over GT3 and GT4; female gender is dominant in GT1 and GT2 (21). Similar results were obtained in a study in which Western Europe, Russia and Israel regions were evaluated. It is thought that the prevalence in female gender is due to the fact that they are more exposed to childbirth and related invasive procedures and blood transfusion practices.

Study Limitations

Our study had limitations. Because of its retrospective nature, transmission routes, nationality, and diagnostic method (screening, presence of clinical findings), which could lead epidemiologically could not be obtained. In addition, DAAs, which were included in the scope of payment by the Social Security Institution in June 2016 in our country, are out of the scope for asylum seekers and foreign nationals, and these antivirals are not sold freely, but are distributed by the state. Since this patient group does not have a treatment opportunity, it is possible that their application will be reduced.

Conclusion

Although GT1 is still dominant in our country, GT3 and GT4 have been increasingly seen over the years, suggesting that the genotype distribution may change in the coming years due to uncontrolled migration and effective DAAs.

Ethics

Ethics Committee Approval: Our study was conducted in accordance with the Helsinki Declaration Principles and the ethics committee approval of the University of Health Sciences Turkey, İstanbul Training Research Hospital Clinical Research Ethics Committee on 19.03.2021-with the number 2776.

Informed Consent: An informed consent obtained as written forms from all of our patients to publish.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: N.D.S., İ.S., Design: N.D.S., İ.S., Data Collection or Processing: N.D.S., İ.S., Analysis or Interpretation: N.D.S., İ.S., Drafting Manuscript: N.D.S., İ.S., S.B., Critical Revision of Manuscript: N.D.S., İ.S., S.B., Final Approval and Accountability: N.D.S., İ.S., S.B., Technical and Material Support: N.D.S., S.B., Supervision: N.D.S., S.B., Writing: N.D.S., İ.S., S.B.

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ORIGINAL RESEARCH

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Predictors of No-reflow Phenomenon Development in Patients Presenting with ST Segment Elevated Myocardial Infarction and Treated with Primary Percutaneous Coronary Intervention

Birincil Perkütan Koroner Girişim Uygulanan ST Segment Yükselmeli Miyokart İnfarktüsü Hastalarında Akımsızlık Fenomeni Gelişimi Öngördürücüleri

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Abstract

Objective: No-reflow phenomenon is one of well-known complications of percutaneous coronary intervention (PCI). The rate of no-reflow phenomenon was reported between 2-44% differing on the accompanying situations and more frequent in acute myocardial infarction. Predictive factors for no-reflow phenomenon have not been clearly defined. We aimed to define predictive factors for no-reflow development in patients who presented with ST-segment elevation MI (STEMI) and treated with primary (PPCI).

Method: Patients who underwent PPCI between 2017 and 2021 in our clinic were included retrospectively. Demographic, clinical and laboratory findings were recorded. Two groups generated according to no-reflow development: no-reflow (+) and (-).

Results: Six hundred eighty-nine patients were included. Mean age was 55.9±8.7 years and 71.8% were male. 107 patients (15.5%) were formed no-reflow (+) group and 582 patients were formed no-reflow (-) group. Left ventricular ejection fraction, troponin, fasting blood glucose, TIMI thrombus grade and TIMI thrombus category were determined as independent predictors of no-reflow development.

Conclusion: Considering the relationship between no-reflow development and adverse outcomes such as in-hospital adverse cardiac events, left ventricular remodeling, malignant ventricular arrhythmia, or

Öz

Amaç: Koroner anjiyografide (KAG) mekanik tıkanıklık olmamasına ve sorumlu koroner arterde yeterli açıklık sağlanmasına rağmen ilgili myokard segmentinde perfüzyonun sağlanamamasına no-reflow (akımsızlık) fenomeni denir. No-reflow fenomeninin akut myokard infarktüsü (MI) hastalarında daha sık olduğu ve tekrarlayan MI, hastane içi istenmeyen kardiyak olaylar, sol ventrikül yeniden yapılanması, malign ventriküler aritmi ve uzun dönemde kalp yetersizliği gelişimi ile ilişkili olduğu son yapılan çalışmalarda gösterilmiştir. No-reflow fenomenini öngördürücü faktörler net olarak tanımlanamamıştır. Biz bu çalışmamızda, kliniğimize ST segment yükselmeli MI (STSYMI) ile başvuran hastalarda no-reflow gelişimi ile ilgili öngördürücü faktörleri tanımlamayı amaçladık.

Yöntem: Kliniğimize 2017-2021 tarihleri arasında STYMI tanısı ile primer perkütan koroner girişim (PPKG) uygulanan hastalar geriye dönük dahil edildi. Demografik, klinik ve laboratuvar bulguları hastane veri tabanı taranarak elde edildi. KAG'de sorumlu epikardiyal koroner arterde yeterli açıklık sağlanmasına ve spazm, diseksiyon olmamasına rağmen TIMI ≤2 akım olan hastalar no-reflow gelişen gruba dahil edildi. No-reflow fenomeni gelişimini öngördürebilecek demografik, klinik, laboratuvar ve anjiyografik parametrelerin tanımlanması planlandı.

Bulgular: Çalışmamıza toplam 689 hasta dahil edildi. Yaş ortalaması 55,9±8,7 olup hastaların %71,8'i erkekti. No-reflow gelişimine göre 2

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Abstract

heart failure, it may help to identify the factors that predict the risk of no-reflow and take preventive measures to improve the long-term outcome.

Keywords: No-reflow, ST elevation myocardial infarction, TIMI thrombus grade

Öz

grup oluşturulduğunda 107 hastada (%15,5) no-reflow geliştiği gözlendi. Lojistik regresyon analizinde sol ventrikül ejeksiyon fraksiyonu, troponin, açlık kan şekeri, TIMI trombüs yükü ve TIMI trombüs yükünün derecesi no-reflow gelişiminin bağımsız öngördürücüleri olarak saptandı.

Sonuç: Hastane içi istenmeyen kardiyak olaylar, sol ventrikül yeniden şekillenmesi, malign ventriküler aritmi ve kalp yetmezliği sıklığının no-reflow fenomeni gelişen hastalarda fazla olduğu göz önünde bulundurulduğunda, no-reflow riskinin öngördürücü faktörlerinin belirlenmesi uzun vadeli sonucu iyileştirmek için önleyici tedbirler alınmasına yardımcı olabilir.

Anahtar kelimeler: No-reflow, ST segment yükselmeli miyokard infarktüsü, TIMI trombüs derecesi

Introduction

Percutaneous coronary intervention (PCI) is a widely used treatment regimen in cardiology era and is the main treatment for patients with presenting with ST segment elevation myocardial infarction (STEMI) (1,2). No-reflow phenomenon is an extreme form of coronary slow flow (3) and one of the well-known complications of PCI (4,5). Inadequate myocardial perfusion despite lack of angiographic epicardial vessel dissection, obstruction or spasm is called the "no-reflow" phenomenon (6). The rate of no-reflow phenomenon was reported between 2-44% differing on the accompanying situations (4,7). It is known to be more frequent in patients presenting with acute myocardial infarction (8,9). Considering the relation between short and long-term adverse cardiovascular events (10), defining related risk factors and patients under risk may help to take precautions to decrease the no-reflow development and improve outcomes.

In this study, we aimed to define the predictive factors for the development of no-reflow in patients presenting with STEMI and treated with primary PCI (PPCI).

Materials and Methods

All STEMI patients who underwent PPCI between 2017-2021 in our center were included in this retrospective single center study. Local hospital electronic database and patients' files were screened to for demographic, clinical and laboratory data. ST elevation myocardial infarction diagnosis was based on recent guidelines (1). Patients who did not undergo stent implantation due to unsuitable anatomy or decided to be treated by emergent surgery were excluded. Additionally, patients presenting after 12 hours from the symptom onset, underwent rescue PCI and those with spontaneous or procedure related coronary dissection were excluded. Coronary flow was defined according to Thrombolysis in Myocardial Infarction (TIMI) score and no-reflow was defined as TIMI flow grade ≤2 (11).

Congestive heart failure (CHF) (12), hypertension (HT) (13), stroke (14), transient ischemic attack (TIA) (15), diabetes mellitus (DM) (16) was defined according to recent guidelines. Simpson's method was applied to measure left ventricular ejection fraction (EF) by transthoracic echocardiography (Vivid S70; GE Medical System, Herten, Norway).

Coronary angiography views were reviewed to define culprit vessel and lesion localization, TIMI flow and thrombus grades on admission. Thrombus burden was classified based on TIMI thrombus grade (TTG); values >3 indicating high and ≤3 indicating low TTG (17). Coronary artery stenosis was defined at least 70% decrease in the internal diameter of the left anterior descending or circumflex or right coronary artery and their major branches or a 50% decrease in internal diameter of left main coronary artery (18). Stent type (bare metal or drug eluting), stent size (length, diameter), the type and dose of anticoagulant, antiaggregant agents were documented. Two groups were created according to no-reflow development as no-reflow (+) and (-) group. No-reflow phenomena development is accepted as the primary endpoint of the study. Human Studies and Research Committee of our institution approved the study and patient consent was waived accordingly. (Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital date: 16/11/2022; decision number: 2022/11/07/028). Patient consent was waived due to retrospective design of the study.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA). Categorical data are stated as number (n) and percentages (%) and continuous variables are stated as mean ± standard deviation. Differences in categorical variables were analyzed with chi-square test. Student's t-test or Mann-Whitney U test was used to compare unpaired samples. Independent variables of no-reflow development were identified by using univariate and multivariate logistic regression analyses. In order to find a cut-off value for the laboratory parameters receiver operating characteristic (ROC) curves were acquired and the ideal values with the greatest total sensitivity and specificity in the prediction of no-reflow were selected. Groups were compared for all parameters with regards to no-reflow occurrence. A 2-sided p<0.05 was assumed as statistically significant.

Results

Seven hundred and fifty-seven patients were evaluated. After exclusion of patients as defined in methodology and those with lack of data, finally 689 patients were included in this retrospective study (Figure 1). The mean age was 55.9±8.7 and 70.1% were male. When patients were grouped according to no-reflow development as no-reflow (+) an (-); 107 (15.5%) patients formed the no-reflow (+) whereas 582 (84.5%) patients formed no-reflow (-) group. Both groups were similar in terms of age, gender, body mass index, incidence of hyperlipidemia, history of myocardial infarction and coronary artery bypass surgery. However, smoking status (62.6% vs. 55.7%; p=0.036), incidence of HT (57.1% vs. 38.8%: p=0.001) and DM (46.7% vs. 31.6%; p=0.002), patients with a history of stroke (11.2% vs. 2.4%; p<0.0001), and CHF (20.6% vs. 10.9%; p=0.006) were significantly higher in no-reflow (+) group. In terms of laboratory markers; NT pro-BNP [1350 (62-3500) vs.1056 (50-35000); p=0.012], troponin (114.2±26.4 vs. 56.6±11.6; p<0.0001), fasting blood glucose (166.3±68.3 vs. 131.3±38.7; p<0.0001) were significantly higher and albumin (3.9±0.6 vs. 4.2±0.6; p=0.043), left ventricular EF (51.2±11.3 vs. 56.1±9.5; p<0.0001) levels were significantly lower in no-reflow (+) group. Furthermore, when angiographic findings were evaluated stent length (33.5±6.3 vs. 23.3±5.2; p<0.0001), TTG [2.9 (0-5) vs. 1.6 (0-5); p<0.0001)], volume of contrast media (166±22 vs. 101±15; p<0.0001) and GENSINI score (21.8±9.2 vs. 19.9±8.5; p=0.032) were significantly higher in no-reflow (+) group. Moreover 30-day cardiovascular mortality (13.1% vs. 3.6%; p<0.0001) was significantly higher in no-reflow (+) group (Table 1).

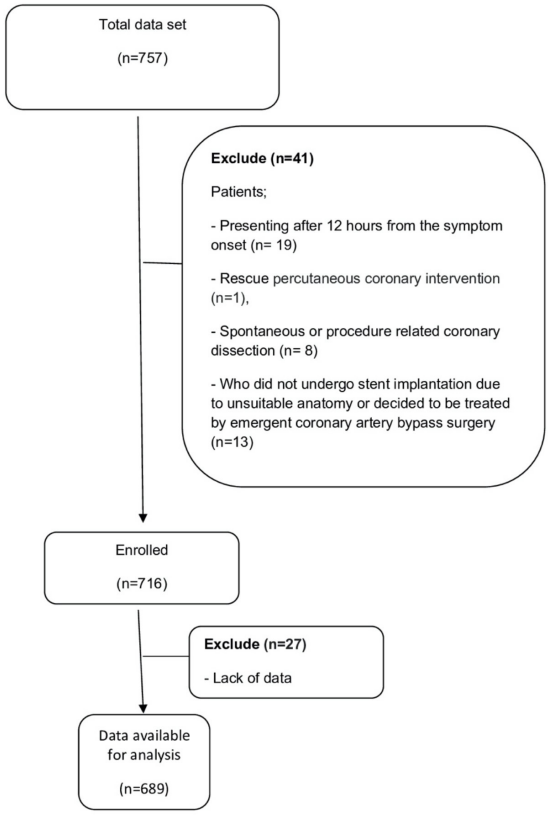

Figure 1. Selection of the study population

To further evaluate individual risk factors for no-reflow development, univariate logistic regression analysis was performed for smoking, DM, HT, history of stroke, and CHF, volume of contrast media used, left ventricular EF, NT pro-BNP, troponin, fasting blood glucose, albumin, GENSINI score, TTG, TTG class and stent length, respectively. By univariate logistic regression analysis, smoking, presence of DM, HT, history of stroke, left ventricular EF, troponin, fasting blood glucose, GENSINI score, TTG and TTG class were correlated with no-reflow development. These variables were assessed in the multivariate logistic regression model. Left ventricular EF [p=0.046, β: 0.952, OR (95% CI): 0.907-0.999], troponin [p<0.0001, β: 1.177, OR (95% CI): 1.131-1.226], fasting blood glucose [p=0.032, β: 1.010, OR (95% CI): 1.001-1.018], TTG [p=0.035, β: 1.834, OR (95% CI): 1.043-3.226] and TTG class [p=0.016, β: 2.788, OR (95% CI): 1.162-5.762] were revealed as independent risk factors associated with no-reflow development by multivariate logistic regression analyses (Table 2). ROC curve analysis was performed to identify the optimal cut-off value and area under the curve (AUC) for troponin, glucose and TTG. ROC curve for accuracy of troponin,

Table 1. Clinical, demographic, laboratory and angiographic data

Variables	All n=689	Group 1 No-reflow (+) n=107	Group 2 No-reflow (-) n=582	p
Clinical Characteristics and Comorbidities				
Age (years)	55.9±8.7	56.7±8.8	55.7±8.6	0.308
Male, n (%)	495 (71.8)	75 (70.1)	420 (72.2)	0.661
Body mass index, (kg/m²)	27.4±4.4	27.9±5.1	27.4±4.3	0.723
Smoking, n (%)	391 (56.7)	67 (62.6)	324 (55.7)	**0.036**
Hypertension, n (%)	287 (41.7)	61 (57.1)	226 (38.8)	**0.001**
Hyperlipidemia, n (%)	249 (36.1)	44 (41.1)	205 (35.2)	0.243
Diabetes mellitus, n (%)	234 (34.0)	50 (46.7)	184 (31.6)	0.002
Previous myocardial infarction, n (%)	117 (16.9)	18 (16.8)	99 (17.1)	0.428
Previous CABG, n (%)	77 (11.2)	12 (11.2)	65 (11.1)	0.546
Previous stroke, n (%)	26 (3.8)	12 (11.2)	14 (2.4)	**<0.0001**
Previous CHF, n (%)	86 (12.5)	20 (20.6)	64 (10.9)	**0.006**
Left ventricular ejection fraction, %	55.3±9.9	51.2±11.3	56.1±9.5	**<0.0001**
Laboratory Parameters				
Urea, mg/dL	34.1±13.5	34.4±13.5	33.9±13.5	0.831
Creatinine, mg/dL	0.9±0.6	0.9±0.2	0.9±0.5	0.979
Hemoglobin, g/dL	14.1±1.7	14.2±1.7	14.1±1.6	0.709
Hematocrit, (%)	42.3±5.2	42.8±5.1	42.2±5.3	0.352
WBC x10³/μL	9.7±4.3	9.7±5.2	8.9±4.6	0.289
Platelet counts 10³/μL	236.6±67.6	245.1±63.6	234.9±68.3	0.246
Albumin, g/dL	4.0±0.4	3.9±0.6	4.2±0.6	**0.043**
CRP, mg/L	0.9 (0.1-9.4)	1.2 (0.16-5.08)	1.6 (0.1-9.4)	0.783
NT pro-BNP, pg/mL	737 (50-35000)	1350 (62-3500)	1056 (50-35000)	**0.012**
Troponin, ng/mL	65.5±25.6	114.2±26.4	56.6±11.6	**<0.0001**
Fasting blood glucose, mg/dL	136.7±46.3	166.3±68.3	131.3±38.7	**<0.0001**
Total cholesterol, mg/dL	181.6±41.5	182.5±38.9	176.7±53.3	0.344
Triglycerides, mg/dL	159.7±63.2	167.7±61.4	158.2±63.5	0.306
LDL cholesterol, mg/dL	123.2±34.8	123.9±34.7	119.5±35.5	0.386
HDL cholesterol, mg/dL	38.5±10.3	38.1±14.8	40.2±9.1	0.172
Angiographic findings				
Stent length, mm	26.2±5.4	33.5±6.3	23.3±5.2	**<0.0001**
Stent diameter, mm	2.9±0.4	2.9±0.5	2.9±0.4	0.947
TTG	1 (0-5)	2.9 (0-5)	1.6 (0-5)	**<0.0001**
TTG category, n (%)				
≤3	500 (72.6)	62 (57.9)	438 (75.3)	
>3	189 (27.4)	45 (42.1)	144 (24.7)	**<0.0001**
Volume of contrast media, (mL)	137±51	166±22	101±15	**<0.0001**
GENSINI score	20.2±2.1	21.8±9.2	19.9±8.5	**0.032**
Mortality, n (%)	35 (5.1)	14 (13.1)	21 (3.6)	**<0.0001**

CABG: Coronary artery bypass graft, CHF: Congestive heart failure, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, NT-proBNP: N terminal peptide brain natriuretic peptide, TTG: TIMI thrombus grade, WBC: White blood cell

glucose and TTG for predicting no-reflow development in STEMI patients is shown in Figure 2. The AUC for troponin was 0.984 (95% CI: 0.976-0.993). A cut-off value of 77.5 for troponin was associated with 92.5% sensitivity and 91.8% specificity in prediction of no-reflow development. Additionally, the AUC for glucose was 0.659 (95% CI: 0.596-0.721) and a cut-off value of 139.5 for glucose was associated with 66.4% sensitivity and 62.7% specificity in prediction of no-reflow development. Moreover, AUC for TTG was 0.680 (95% CI: 0.633-0.727) and a cut-off value of 3.0 for TTG was associated with 68.2% sensitivity and 66.7% specificity in prediction of no-reflow development.

Discussion

In this study we sought to assess predictive factors for no-reflow development in patients presenting with STEMI and treated with PPCI. Consequently, reduced left ventricular EF, higher troponin and fasting blood glucose levels on admission, TTG and TTG class were revealed as independent risk factors associated with no-reflow

Table 2. Univariate and multivariate logistic regression analysis for predictors of no-reflow development

	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
Smoking	0.080	0.004-0.115	**0.028**	0.580	0.206-1.629	0.301
Diabetes mellitus	0.116	0.031-0.145	**0.002**	0.715	0.239-2.141	0.548
Hypertension	0.134	0.044-0.153	**<0.0001**	1.020	0.360-2.886	0.971
Previous CHF	0.715	0.033-1.196	0.132			
Previous stroke	0.318	0.178-0.459	**<0.0001**	0.339	0.019-6.165	0.465
Left ventricular ejection fraction	0.516	0.365-0.667	**<0.0001**	0.952	0.907-0.999	**0.046**
NT pro-BNP	0.456	0.239-1.098	0.078			
Troponin	0.600	0.557-0.643	**<0.0001**	1.177	1.131-1.226	**<0.0001**
Fasting blood glucose	0.138	0.056-0.219	**0.001**	1.010	1.001-1.018	**0.032**
Albumin	0.924	0.808-1.109	0.749			
GENSINI score	1.026	1.002-1.050	**0.033**	0.978	0.902-1062	0.601
TTG	1.322	1.199-1.459	**<0.0001**	1.834	1.043-3.226	**0.035**
TTG class	0.453	0.295-0.695	**<0.0001**	2.788	1.162-5.762	**0.016**
Volume of contrast media	0.981	0.556-1.731	0.947			
Stent length	1.008	0.970-1.046	0.699			

CHF: Congestive heart failure, NT-proBNP: N terminal peptide brain natriuretic peptide, TTG: TIMI thrombus grade, CI: Confidence interval, OR: Odds ratio

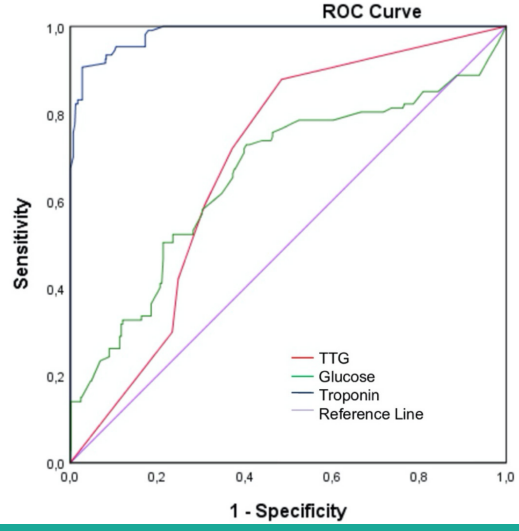

Figure 2. ROC curve for accuracy of troponin, glucose and TIMI thrombus grade for predicting no-reflow development in patients presenting with ST segment elevated myocardial infarction and treated with primary percutaneous coronary intervention

ROC: Receiver operating characteristic, TIMI: Thrombolysis in myocardial infarction

development. Therefore TTG ≥3, increased troponin and fasting blood glucose levels on admission can be used in conjunction with reduced left ventricular EF in order to stratify patients under risk of no-reflow development with a diagnosis of STEMI and treated with PPCI.

Previous studies have stated that lack of reflow may be associated with some clinical determinants. A relationship between delayed reperfusion and no-reflow phenomenon has been demonstrated (19,20). In our study, troponin values were higher in patients with no-reflow compared to those with normal flow, which may be related to prolonged symptoms and time to reperfusion. Also, recent studies have shown a higher incidence of no-reflow in patients with reduced left ventricular EF (19,21). Reduced microvascular perfusion in conjunction with reduced EF may one of the underlying pathophysiological mechanisms. In addition, increased left ventricular end-diastolic pressure and impaired coronary perfusion may trigger no-reflow development (8,22,23). In our study, we revealed decreased left ventricular EF as an independent predictor of no-reflow development. However, the relation between hyperglycemia and no-reflow has been shown and it was thought to be linked with microvascular dysfunction. This leads to larger infarct size and worse functional recovery (24,25). In the present study, high fasting blood glucose levels on admission was detected as an independent predictor of no-reflow development.

Implanted stent length and diameter were reported as predictors of no-reflow development previously (26). Although, there were no difference regarding stent diameter, stent length was higher in no-reflow (+) group in our study. However, stent length was not found as an independent predictor for no-reflow development in further analysis.

Various clinical, laboratory and angiographic parameters were defined as predictors for no-reflow development previously. Age, male gender, smoking, DM, HT and the Killip class were reported to be related with increased risk of no-reflow development in a metanalysis (27). One of the underlying mechanisms is thought to be endothelial dysfunction, and it has been shown that advanced age, DM, HT and male gender are also associated with endothelial dysfunction (28-31). Impaired coronary flow reserve and increased vulnerability of the myocardium might be the other underlying mechanisms in conjunction with endothelial dysfunction. Moreover, preexisting microvascular dysfunction which was thought to be associated with these risk factors might be the facilitating mechanism (32). According to our results, groups were familiar regarding age and sex; whereas DM, HT and smoking were found to be higher in no-reflow (+) group, however those were not found independent predictors of no-reflow development. High serum glucose levels on admission, TTG and TTG class were independent predictors associated with no-reflow development according to our results.

Distal embolization of plaque and/or thrombus may result with no-reflow. Plaque volume was evaluated with intravascular ultrasound after primary PCI and decrease in plaque volume was observed more obvious those with inadequate flow (33). Considering the high prevalence of thrombus burden in STEMI patients, distal embolization is one of the possible mechanisms. However, we did not perform intravascular imaging. Additionally, increased alpha adrenergic tone, thromboxane A2 and serotonin levels may end up with exaggerated vasoconstriction and no-reflow. These pathophysiological mechanisms should not be ignored, but in this article, we aimed to define clinical risk factors and raise clinical suspicion.

Single-center and retrospective design with a relatively small patient population were the main limitations of the study. The time interval from symptom onset to CAG of each patient and no-reflow may be reasons for increased mortality in STEMI patients. Our results were based on CAG findings; however, advanced imaging options (intravenous ultrasound and optical coherence tomography) may provide crucial information such as thrombus and plaque burden and erosions which may augment no-reflow phenomena development. Definitely, larger and prospectively designed further studies are needed to demonstrate the relationship between predictive factors for the development of no-reflow in patients presenting with STEMI. Our study showed that no-reflow during PPCI is associated with 30-day mortality.

Conclusion

TIMI thrombus grade ≥3, higher levels of troponin and fasting blood glucose on admission can be used in conjunction with reduced left ventricular ejection fraction in order to stratify patients for high risk of no-reflow development presenting with STEMI and treated with PPCI. The incidence of in-hospital adverse cardiac events, left ventricular remodeling, malignant ventricular arrhythmia, and long-term development of heart failure, were increased in patients with no-reflow phenomenon. Thus, identifying predictive factors for no-reflow development may help to take precautions to decrease the no-reflow incidence and improve long-term results. Prospective studies, evaluating

the effect of protective measures and strengthen with the intravascular imaging modalities to define the underlying mechanism in patient basis would give more reliable evidence.

Ethics

Ethics Committee Approval: Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital date: 16/11/2022; decision number: 2022/11/07/028.

Informed Consent: Informed consent waived due to retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.D., S.Ö., İ.Ş., E.O., Design: E.D., S.Ö., İ.Ş., E.O., Data Collection or Processing: E.D., S.Ö., Analysis or Interpretation: E.D., S.Ö., Drafting Manuscript: E.D., S.Ö., Critical Revision of Manuscript: E.D., S.Ö., İ.Ş., E.O., Final Approval and Accountability: E.D., S.Ö., İ.Ş., E.O., Technical of Material Support: İ.Ş., E.O., Writing: E.D., S.Ö., İ.Ş., E.O.

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

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ORIGINAL RESEARCH

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Plasma Fibrinogen to Albumin Ratio as an Indicator of Endothelial Dysfunction in Smoking

Sigara Kullanımında Endotel Fonksiyon Bozukluğu Göstergesi Olarak Plazma Fibrinojen Albumin Oranı

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Abstract

Objective: Smoking causes endothelial dysfunction by causing systemic inflammation. Our aim is to investigate the predictive role of fibrinogen albumin ratio (FAR), neutrophil lymphocyte ratio, platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR), monocyte high-density lipoprotein ratio (MHR), mean platelet volume (MPV), systemic immune inflammatory index (SII) and systemic inflammatory response index (SIRI) which are the newest markers of systemic inflammation, in smoking.

Method: The study was planned as a single-center, prospective case-control study. People aged between 20-45 years [n=76; female/male (n)=37/39] who met the inclusion criteria were included. Two groups consisting of smokers (n=38) and non-smokers (n=38) were compared according to demographic data and biochemical values. p-value was accepted as <0.05 in terms of statistical significance.

Results: The proportion of men in the study group was 51.3% [total n=76; mean age 30.18±5.75 years; female/male (n):37/39]. There was no significant difference between the two groups of smokers (n=38) and non-smokers (n=38) in terms of gender and age (p=0.386, p=0.296, respectively). The average amount of smoking was 22.84±11.48 packs/year and 29.73±9.94 packs/day. FAR, MPV, MHR, MLR and SIRI were significantly higher and PLR was significantly lower in the smokers than the other group (p<0.05). According to the ROC analysis, the areas under the curve of FAR, MHR, MLR, SIRI, MPV and PLR were determined as 0.70, 0.90, 0.83, 0.80, 0.69 and 0.66, respectively (p<0.001). The variants with the highest sensitivity were monocytes and MPV, and the variant with the highest specificity was monocytes. FAR was positively correlated with MHR, MLR, SIRI (p=0.00, r=0.34; p=0.05, r=0.2; p=0.03, r=0.24, respectively).

Öz

Amaç: Endotel disfonksiyonu, nitrik oksit (NO) sentezinde azalmayla beraber endotelin gevşeme ve kasılma fonksiyonlarının bozulmasıdır. Sigaranın sistemik enflamasyona yol açarak endotel disfonksiyonu yaptığı bilinmektedir. Yeni enflamasyon belirteçleri olan fibrinojen albumin oranını (FAR) sigara kullanımında oluşan sistemik enflamasyonun göstergesi olarak araştırdık. Beraberinde nötrofil lenfosit oranını (NLR), trombosit lenfosit oranını (PLR), monosit lenfosit oranını (MLR), monosit yüksek dansiteli lipoprotein oranını (MHR), ortalama trombosit hacmini (MPV), sistemik immün enflamatuvar indeksini (SII) ve sistemik enflamatuvar yanıt indeksini (SIRI) araştırdık.

Yöntem: Bu çalışma tek merkezli, prospektif vaka-kontrol çalışması olarak planlanmış olup, çalışmaya başvuranlardan dahil edilme kriterlerine uygun olup, 20-45 yaş aralığında bilinen hiçbir hastalığı ve ilaç 3 kullanımı olmayan 76 kişi dahil edildi. Sigara kullanan (n=38) ve kullanmayan (n=38) bireylerden oluşturulan iki grup; yaş, boy, kilo, paket/yıl ve adet/gün olarak içilen sigara miktarı ve laboratuvar değerleri açısından karşılaştırıldı. p-değerinin 0,05'in altında olduğu durumlar istatistiksel olarak anlamlı sonuçlar şeklinde değerlendirildi.

Bulgular: Çalışma grubunun %51,3'ü erkekti [total n=76; yaş ort: 30,18±5,75 yıl; kadın/erkek (n): 37/39]. Sigara kullanan (n=38) ve kullanmayan (n=38) iki grup arasında cinsiyet ve yaş açısından anlamlı fark yoktu (sırasıyla p=0,386, p=0,296). Sigara kullanma miktarları ortalama 22,84±11,48 paket/yıl ve 29,73±9,94 adet/gün idi. İki grup karşılaştırıldığında, sigara içen grupta FAR, MPV, MHR, MLR ve SIRI anlamlı olarak yüksek, PLR ise anlamlı olarak düşük saptandı (p<0,05). ROC analizine göre FAR, MHR, MLR, SIRI, MPV ve PLR eğrisi altında kalan alanlar sırasıyla 0,70, 0,90, 0,83, 0,80, 0,69 ve 0,66 olarak belirlendi (p<0,001). ROC analizi sonucunda, duyarlılığı en yüksek olan değişkenler monosit ve MPV iken, özgüllüğü en yüksek olan değişken monosit olarak

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Abstract

Conclusion: Our study suggests that new inflammatory markers can be used to predict the inflammatory process in endothelial dysfunction caused by smoking. It may be beneficial to conduct new studies with larger number of participants to see whether these markers can also be predictors of other silent inflammatory processes in non-smokers.

Keywords: Endothelial dysfunction, fibrinogen albumin ratio, inflammation, monocyte, smoking

Öz

bulundu. FAR ile PLR negatif yönde korele iken MHR, MLR ve SIRI pozitif yönde korele bulundu (p=0.00, r=0.34; p=0.05, r=0.2; p=0.03, r=0.24, sırasıyla).

Sonuç: Çalışmamız sigaranın neden olduğu endotel disfonksiyonunda inflamatuar süreci öngörmek için yeni inflamatuvar belirteçlerin kullanılabileceğini düşündürmektedir. Bu belirteçlerin sigara içmeyenlerdeki diğer sessiz inflamatuvar süreçlerin habercisi olup olamayacağını görmek için daha fazla katılımcıyla yeni çalışmalar yapılması faydalı olabilir.

Anahtar kelimeler: Endotel disfonksiyonu, enflamasyon, fibrinojen albumin oranı, monosit, sigara

Introduction

Endothelial dysfunction is defined as decreased nitric oxide synthesis and impairment of relaxation-contraction functions (1). Cardiovascular risk factors such as smoking, diabetes, atherogenic dyslipidemia, abdominal obesity, hypertension and age initiate the inflammatory process by disrupting the endothelial structure (2,3). Atherosclerosis is a chronic and progressive disease characterized by endothelial dysfunction and inflammation. Deterioration of vascular tone, increased cytokine production, accumulation of inflammatory cells in the endothelium, and migration of smooth muscle cells to the damaged area cause atherosclerotic plaque formation (4).

Smoking causes disorders in the hemostatic system and lipid profile and endothelial dysfunction (5). It also predisposes the body to thrombosis and disrupts the procoagulant fibrinolytic activity of the endothelium (6). While smoking suppresses anti-inflammatory cytokines, it causes systemic inflammation in the body by using pro-inflammatory cytokines and acute phase proteins such as C-reactive protein (CRP) and fibrinogen (7).

The increase in plasma viscosity is associated with cardiovascular diseases because it leads to a procoagulant state. The main substances that increase viscosity are fibrinogen and lipoproteins. Fibrinogen may play a triggering role in cardiovascular diseases by increasing viscosity or by affecting the platelets and fibrin formation mechanism. Increased fibrinogen in chronic smokers contributes to the inflammatory and atherosclerotic basis (8). In a prospective study, it was shown that increased fibrinogen and CRP have an effect on the pathogenesis of cardiovascular diseases (9,10).

Normal albumin levels have antiatherogenic and anti-inflammatory effects in the body. Therefore, the decrease in albumin causes an increase in pro-inflammatory markers along with an increase in systemic inflammation in the body and is linked to oxidative stress (11). In a study, it was shown that serum albumin value varies in smokers and has an important role in the development of coronary artery disease in those people (12). In subsequent studies, serum albumin was shown to be a strong risk factor for MI when other risk factors were adjusted (13).

Studies have reported that high fibrinogen/albumin ratio (FAR) is an important marker for inflammation and atherosclerosis (9). Neutrophil/lymphocyte ratio (NLR) levels have been found to be quite high in diseases that cause endothelial damage, such as diabetes, myocardial infarction, atherosclerosis and hypertension, and are considered a poor prognostic factor (14). The diagnostic role of monocyte/lymphocyte ratio (MLR) in showing the level of inflammation in cardiovascular and autoimmune diseases has been proven (15). Monocyte/high-density lipoprotein (HDL) ratio (MHR) is emerging as a new prognostic indicator in predicting oxidative stress and systemic inflammation levels in the atherosclerosis process (16). Platelet/lymphocyte ratio (PLR), which is an important indicator of inflammation and thrombosis, is used in many diseases (17). Mean platelet volume (MPV) indicates platelet activation in vascular diseases (18). The role of inflammation in all stages of cancer has been proven, and the increase in systemic inflammatory response index (SIRI) levels, an important inflammatory marker, has been shown to be valuable in predicting survival in cancer patients (19). Systemic immune inflammatory index (SII), a new marker, shows the immune response and inflammation in the body more strongly than other markers (20).

In this study, we aimed to investigate FAR, a new inflammatory marker, as an indicator of endothelial dysfunction due to smoking. In addition, it is planned

to study MLR, NLR, PLR, MPV, MHR, SII and SIRI as inflammatory markers in smokers.

Materials and Methods

Study group

This study was planned as a single-center, prospective case-control study. Seventy-six participants aged 20-45 years, who applied to the outpatient clinics between November 2021 and April 2022, were included according to inclusion criteria. Individuals who had chronic lung, liver and kidney diseases, connective tissue diseases, acute or chronic infection, malignancy, metabolic syndrome, obesity, pregnancy status, menopause, chronic diseases such as hypertension and diabetes mellitus, severe trauma or surgery in the last 6 months, cardiac disease, any chronic medication, Coronavirus disease-2019 in the last 6 months and active alcohol users were excluded. Demographic data and biochemical values of the groups were compared among two groups as smokers (n=38) and non-smokers (n=38).

Ethics Committee Approval

This study was approved (dated: 06/03/2020 and numbered: 2213) by Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital. The expenses of the study were covered by University of Health Sciences Turkey, İstanbul Training and Research Hospital. All participants were informed about the study and their consent was obtained.

Sample Size

Cohen's d effect size was 0.80; α value 0.05; the power (1-β) value was taken as 0.80, and the minimum number of samples required for statistical comparison of two independent groups was calculated as n=30 participants for each group through the G*Power version 3.1.9.4 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Statistical Analysis

Statistical analyzes were performed with the help of SPSS version 28.0 program. To assess the normality of the data, Kolmogorov-Smirnov test was used. Mean, standard deviation and median values were used when presenting descriptive analyzes. Two-sample independent test was used for parametric variables and Mann-Whitney U test was used for non-parametric variables. Receiver operating characteristic (ROC) analysis was applied to evaluate the performance of the tests with diagnostic accuracy, sensitivity, specificity and area under the curve (AUC) values. Pearson Correlation test was used to evaluate the relationships between quantitative variables by accepting the variables that had a significant relationship with the FAR as independent variables. p-value was accepted as <0.05 in terms of statistical significance.

Results

Participants consisted of 37 women and 39 men. Two groups were formed as smokers (n=38) and non-smokers (n=38). The mean age was 29.78±5.75 years. The average height was 170.22±8.51 cm, the average weight was 69.44±12.62 kg and body mass index (BMI) were 23.86 kg/m^2. No statistically significant difference was found between the demographic data of the two groups (p>0.05) (Table 1). The smoking rates of the individuals were 22.84±11.48 pack/year and 29.73±9.94 pcs/day. No statistically significant difference was observed when smoking amounts of smokers were compared according to gender (p>0.05) (Table 2).

The levels of white blood cell (WBC), neutrophil, monocytes, lymphocyte, MPV, fibrinogen, MHR, MLR, SIRI and FAR were significantly higher in smokers compared to non-smokers (p<0.05). Albumin and PLR levels were found to be significantly lower in the smokers (p<0.05). HDL values were found to be significantly higher in non-smokers, while triglyceride (TG) and low-density lipoprotein (LDL) values were significantly higher in smokers (p<0.05) (Table 3).

Table 1. Comparison of demographic data of the participants

Mean ± SD	All participants	Non-smokers (n=38)	Smokers (n=38)	p-value
Age (years)	29.78±5.75	29.42±4.63	30.90±5.73	0.296
Gender, n (%)				
Female	37 (48.7%)	19 (50.00%)	18 (42.50%)	0.386
Male	39 (51.3%)	19 (50.00%)	20 (57.50%)	
Height (cm)	169.61±8.51	168.34±7.95	170.89±8.94	0.174
Weight (kg)	68.92±12.62	67.34±10.20	70.50±14.52	0.261[a]
Body mass index (kg/m^2)	23.86±2.54	23.87±2.16	23.85±2.91	0.175[a]

[a]Student's t-test, Mann-Whitney U test, SD: Standard deviation

Table 2. Comparison of participants' cigarette use by gender

Mean + SD	Female (n=18)	Male (n=20)	p-value
Pack/year	20.38±12.28	25.05±10.86	0.264
Pcs/day	27.94±9.02	31.40±10.46	0.573

Mann-Whitney U test, SD: Standard deviation

According to the ROC analysis, the AUC of FAR, MHR, MLR, SIRI, MPV and PLR were determined as 0.70, 0.90, 0.83, 0.80, 0.69 and 0.66, respectively (p<0.001) (Table 4). Monocyte had the highest sensitivity (90.48%) and specificity (92.30%) among all of the inflammatory markers when cut-off point was calculated as 0.50 10^9/L. The AUC for monocytes was 93.7% (95% confidence interval: 0.60-0.83) (p<0.001) (Table 4, Figure 1).

A significant positive correlation was found between FAR and the new inflammatory markers MHR, MLR and SIRI (p=0.00, r=0.34; p=0.05, r=0.22; p=0.03, r=0.24) (Table 5).

Table 3. Comparison of laboratory data of the groups

Mean ± SD	Non-smokers (n=38)	Smokers (n=38)	p-value
White blood cell (10^9/L)	6.73±1.51	8.47±2.22	**<0.001[a]**
Hemoglobin (g/dL)	13.85±1.34	14.05±2.18	0.150
Platelet (10^9/L)	256.67±57.69	258.92±50.17	0.912[a]
Neutrophil (10^9/L)	3.98±1.08	5.07±1.86	**<0.001**
Monocyte (10^9/L)	0.38±0.12	0.66±0.18	**<0.001[a]**
Lymphocyte (10^9/L)	2.19±0.60	2.47±0.76	**0.027**
MPV (fL)	9.86±1.02	10.48±0.78	**0.005[a]**
Fibrinogen (mg/dL)	262.02±47.05	601.62±57.18	**0.002[a]**
Albumin (g/L)	48.52±2.15	46.85±4.30	**0.004[a]**
NLR	1.97±0.59	2.18±1.06	0.150
PLR	124.48±30.00	111.24±33.89	**0.013**
MHR	0.01±0.00	0.01±0.01	**<0.001[a]**
MLR	0.18±0.06	0.28±0.10	**<0.001**
SII	499.81±163.43	565.49±284.65	0.231
SIRI	0.77±0.33	1.52±0.95	**<0.001**
FAR	5.41±1.01	6.47±1.27	**<0.001[a]**
Cholesterol (mg/dL)	174.87±32.28	186.1±43.37	0.112[a]
LDL (mg/dL)	96.90±32.10	111.92±40.07	**0.042[a]**
TG (mg/dL)	92.66±46.61	124.44±70.33	**0.007[a]**
HDL (mg/dL)	59.20±18.46	49.89±11.52	**0.004**

[a]Student's t-test, Mann-Whitney U test, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, MHR: Monocyte/high-density lipoprotein ratio, MLR: Monocyte/lymphocyte ratio, SII: Systemic immune inflammatory index, SIRI: Systemic inflammatory response index, FAR: Fibrinogen/albumin ratio, LDL: Low-density lipoprotein, TG: Triglyceride, HDL: Monocyte/high-density lipoprotein

Table 4. Receiver-operator curve analysis of novel inflammatory markers

	Area under the curve	Cut-off	Sensitivity	Specificity
Monocyte (10^9/L)	0.93	>0.50	90.48%	92.30%
MPV (fL)	0.69	>9.55	90.48%	41.10%
PLR	0.66	≤100.56	54.76%	82.50%
MHR	0.90	>0.09	85.71%	84.60%
MLR	0.83	>0.20	80.95%	79.50%
SIRI	0.80	>0.86	80.95%	84.60%
FAR	0.70	>5.35	83.33%	53.80%

FAR: Fibrinogen/albumin ratio, MPV: Mean platelet volume, SIRI: Systemic inflammatory response index, MLR: Monocyte/lymphocyte ratio, MHR: Monocyte/high-density ratio, PLR: Platelet/lymphocyte ratio

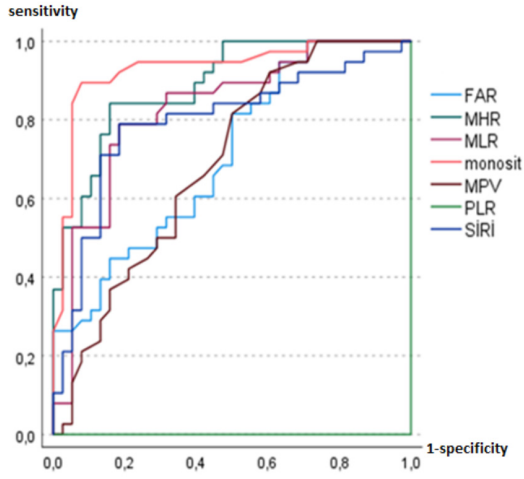

Figure 1. Receiver operator curve analysis graphic

FAR: Fibrinogen/albumin ratio, SIRI: Systemic inflammatory response index, PLR: Platelet/lymphocyte ratio, MHR: Monocyte/high-density ratio, MLR: Monocyte/lymphocyte ratio, MPV: Mean platelet volume

Table 5. Correlation assessment between of fibrinogen to albumin ratio and other measurements

(n=76)	Correlation coefficient (r)	p-value
Age (year)	0.22	**0.05**
Height (cm)	-0.17	0.13
Weight (kg)	-0.05	0.69
Pack/year	0.37	**0.02**
Pcs/day	0.08	0.62
White blood cell (10^9/L)	0.35	**0.00**
Hemoglobin (g/dL)	-0.09	0.40
Platelet (10^9/L)	0.21	0.06
Neutrophil (10^9/L)	0.27	0.01
Monocyte (10^9/L)	0.40	**0.00**
Lymphocyte (10^9/L)	0.27	**0.01**
MPV (fL)	-0.02	0.90
NLR	0.04	0.75
PLR	-0.13	0.26
MHR	0.34	**0.00**
MLR	0.22	**0.05**
SII	0.13	0.23
SIRI	0.24	**0.03**
Cholesterol (mg/dL)	0.39	**0.00**
LDL (mg/dL)	0.45	**0.00**
TG (mg/dL)	0.11	0.34
HDL (mg/dL)	-0.09	0.44

Pearson Correlation. MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MHR: Monocyte/high-density ratio, MLR: Monocyte/lymphocyte ratio, SII: Systemic immune inflammatory index, SIRI: Systemic inflammatory response index, LDL: Low-density lipoprotein, TG: Triglyceride, HDL: Monocyte/high-density lipoprotein

Discussion

It is known that fibrinogen is one of the most important factors determining plasma viscosity. As fibrinogen levels increases, flow of blood cells slows down, they tend to stick together and viscosity increases. These events cause atherosclerotic changes in vessels. As a result, it has been shown that the increase in plasma fibrinogen levels is effective in the process starting with endothelial dysfunction and progressing to atherosclerosis (21-23). Albumin is decreased in inflammation and is associated with high mortality in cardiovascular diseases (24). In the British Regional Heart Study, it was found that low albumin levels were associated with smoking (25). Karahan et al. (26) found FAR levels more sensitive compared to fibrinogen or albumin values alone in predicting venous insufficiency. In another study, FAR was found to be high in patients with stable angina pectoris, which was associated with lower mortality (27).

In our study, in accordance with the literature, fibrinogen levels were found to be high and albumin levels were low in smokers (25). FAR, one of the markers we used to predict endothelial dysfunction in smoking, was found to be high in the smoking group. The early stage of atherosclerosis is endothelial dysfunction, and previous studies have shown that FAR is high in atherosclerosis. In conclusion, our study suggests that high FAR may indicate endothelial dysfunction.

In a study, WBC, neutrophil and lymphocyte counts were found to be high in smokers (28). Similar effects of smoking were revealed in the study of Gumus et al. (29). In the study of Kutlu and Demirbas (30) MPV was found to be significantly higher in smoking individuals while no significant difference was found in platelet count. In our study, WBC, neutrophil, lymphocyte, monocytes and MPV levels were found to be significantly higher in the smokers group. It is well known that platelets are involved in the atherosclerotic process and MPV shows the platelet activation. In our study, platelet count not statistically significant difference between groups. But MPV levels were found to be significantly higher in smokers, similar to the studies that examining the hemogram parameters of smokers (18). When we evaluated the parameters that increase with smoking, MPV was found to be one of the parameters with the highest sensitivity. Our study suggests that high MPV levels predict endothelial dysfunction in smokers.

NLR is a biomarker that has gained importance in showing morbidity and mortality in the atherosclerotic process (14). In the study by Çekici et al. (31), when two groups consisting of smokers and non-smokers were compared, the NLR value was found to be higher in the smokers group. In our study, NLR levels were found to be higher in smokers compared to the other group, but this elevation was not statistically significant. As reported above, our study group consisted of people without any comorbidities and lower mean age unlike other studies. Besides, few number of participants of our study may have caused this difference.

PLR is an indicator of inflammation in endothelial dysfunction and is also used as a marker for atherosclerosis and cardiovascular disease (17). In our study, PLR values of the two groups were compared and it was found to be significantly lower in the smoking group consistent with the study of Gumus et al. (29).

Demirbaş et al. (32), analyzed MHR, MLR and PLR as new inflammatory markers showing inflammation and oxidative stress in vitiligo and found them significantly higher in vitiligo patients than controls. Therefore these parameters were suggested as new indicators of inflammation in vitiligo patients (32). Many studies have investigated MHR in various diseases. MHR has gained importance in demonstrating systemic inflammation. High MHR is an increased risk for cardiovascular diseases (33). It has been shown that, in atherosclerosis the number of monocytes increase whereas HDL level remains low. We showed that the number of monocytes was significantly higher in the smoking group ($p<0.05$). According to ROC analysis, the sensitivity and specificity of monocyte was found to be the highest variable among the parameters increasing due to smoking. It is known that monocytes play a role in the first step of the atherosclerotic process and the number of monocytes increase in cardiovascular diseases (15,16). As the levels of MHR and MLR which are suggested as new inflammatory markers are evaluated, both were found to be significantly higher in the smokers group ($p<0.05$). The cut-off value we obtained in the ROC analysis was calculated as 0.09 for MHR and 0.20 for MLR. According to the results, we think that these two markers may be stimulatory and/or predictive in endothelial dysfunction due to smoking.

In a study, it was found that SIRI values of 285 patients with nasopharyngeal cancer were more significant in predicting the survival of patients compared to cancer staging (34). In another study, SIRI values were found to be an important predictor of survival in patients with pancreatic cancer (35). When other inflammation markers were examined, it was observed that they were not as strong as SIRI (36). This marker has been mostly investigated to determine the prognosis of cancer patients. The relationship between smoking and SIRI has not been investigated before, and our study shows the relationship between SIRI and smoking-induced inflammation.

Studies have shown that systemic inflammation has a very important role in the formation of cancer cells (37). SII has been found to be a strong predictor of survival for patients diagnosed with colorectal cancer. It was even found important in distinguishing high-risk among patients with the same cancer stage. In this study, SII was found to be more valuable when compared to other inflammation markers (38). In another study, many parameters were examined and NLR, PLR and SII were found to be significantly higher in patients with kerataconus. Here, the reason for the high SII was thought to be the role of endothelial dysfunction rather than chronic inflammation (39). In our study, SII was found to be high in smokers, but high SII was not statistically significant in demonstrating smoking-related endothelial dysfunction.

We think that this issue should be examined with more number of participants and comprehensive studies.

Conclusion

We showed that biomarkers such as FAR, MPV, PLR, MHR, MLR and SIRI may predict endothelial damage caused by smoking. Our study may inspire new and exhaustive ones investigating new inflammatory markers to predict silent inflammatory processes in healthy individuals.

Ethics

Ethics Committee Approval: This study was approved (dated: 06/03/2020 and numbered: 2213) by Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital.

Informed Consent: All participants were informed about the study and their consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ş.A., H.F.A., Z.A.S., Design: Ş.A., H.F.A., Z.A.S., Data Collection or Processing: Ş.A., H.F.A., Analysis or Interpretation: Ş.A., H.F.A., Z.A.S., Drafting Manuscript: Ş.A., H.F.A., Critical Revision of Manuscript: Ş.A., H.F.A., Z.A.S., Final Approval and Accountability: Ş.A., H.F.A., Z.A.S., Supervision: Ş.A., H.F.A., Z.A.S., Writing: Ş.A., H.F.A., Z.A.S.

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CASE REPORT

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Simultaneous Tubal Heterotopic Pregnancy with Acute Appendicitis: A Case Report and Literature Review of 5 Cases

Akut Apandisit ile Eş Zamanlı Tubal Heterotopik Gebelik: Bir Olgu Sunumu ve 5 Olgunun Literatür Taraması

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Abstract

Heterotopic pregnancy (HP) is a serious obstetrics phenomenon that occurs when both intrauterine and ectopic pregnancies exist simultaneously. It is an extremely rare condition with potentially life-threatening outcomes. The incidence of acute appendicitis in pregnancy is generally less common compared to the non-gravid population, and its coexistence with HP is exceedingly rare. Herein, we report a case of HP complicated with appendicitis that occurred in a 32-year-old G2P1 female presenting at 12 weeks of gestation with acute severe right lower abdominal pain. She denied any history of assisted reproductive technology or risk factors for ectopic pregnancy. On examination, the patient was conscious, oriented, afebrile, and hemodynamically stable. The abdomen was distended and tender on palpation. Pelvic ultrasonography demonstrated viable intrauterine pregnancy with a heterogenous mass within the right uterine wall with surrounding peripheral vascularity. Fluid collections were also visible in the intraperitoneal cavity. The patient underwent emergency laparotomy with right salpingectomy and appendectomy. Early diagnosis and treatment are correlated with favourable obstetrics outcomes and long-term prognosis. A surgical approach with either laparoscopy or laparotomy is more appropriate compared to medical or conservative management.

Keywords: Appendectomy, appendicitis, ectopic pregnancy, heterotopic pregnancy, salpingectomy

Öz

Heterotopik gebelik (HP), hem intrauterin hem de ektopik gebeliklerin aynı anda var olduğu durumlarda ortaya çıkan ciddi bir obstetrik fenomendir. Potansiyel olarak yaşamı tehdit eden sonuçları olan son derece nadir bir durumdur. Gebelikte akut apandisit insidansı genellikle gebe olmayan popülasyona göre daha az görülür ve HP ile birlikteliği son derece nadirdir. Burada, gebeliğin 12. haftasında akut şiddetli sağ alt karın ağrısı ile başvuran 32 yaşında G2P1 bir kadında ortaya çıkan apandisit ile komplike bir HP olgusu sunuyoruz. Herhangi bir yardımcı üreme teknolojisi öyküsünü veya ektopik gebelik için risk faktörlerini reddetti. Muayenede hastanın bilinci açık, oryante, ateşsiz ve hemodinamik olarak stabildi. Karın palpasyonla şişmiş ve hassastı. Pelvik ultrasonografi, sağ uterus duvarında çevreleyen periferik vaskülarite ile heterojen bir kitle ile canlı intrauterin gebelik gösterdi. İntraperitoneal boşlukta sıvı koleksiyonları da görüldü. Hastaya sağ salpenjektomi ve apendektomi ile acil laparotomi uygulandı. Erken tanı ve tedavi, olumlu obstetrik sonuçlar ve uzun vadeli prognoz ile ilişkilidir. Laparoskopi veya laparotomi ile cerrahi bir yaklaşım, tıbbi veya konservatif tedaviye kıyasla daha uygundur.

Anahtar kelimeler: Apandisit, apendektomi, ektopik gebelik, heterotopik gebelik, salpenjektomi

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Introduction

Heterotopic pregnancy (HP) is a condition characterized by the coexistence of intrauterine pregnancy (IUP) with ectopic pregnancy (EP). Acute appendicitis, although relatively uncommon during pregnancy, is the most common non-obstetrics cause of acute abdomen in a pregnant woman. The simultaneous occurrence of HP with acute appendicitis poses an extremely difficult diagnostic challenge as both conditions are rare in the pregnancy setting. Delayed diagnosis and management can result in dreaded complications, including intraperitoneal hemorrhage, peritonitis, sepsis, shock, and death. Similar to EP, the majority of HPs occur in the fallopian tube. There is growing evidence of the rise in the incidence of HP with the widespread use of assisted reproductive technology (ART). Its application also increases the risk for more atypical sites and the complexity of the condition (1). Radiological studies have become increasingly reliable in accurately diagnosing HP (2,3). The aim of the management of HPs with concurrent acute appendicitis is to resolve the pathology of the appendix and EP while attempting to preserve the IUP. Our center experienced a rare case of HPs with concurrent acute appendicitis in a 32-year-old G2P1, presenting at 12 weeks of gestation with severe recurrent abdominal pain, nausea, and vomiting. Radiological studies with transabdominal pelvic ultrasonography (TAUS) confirmed the diagnosis of HP while acute appendicitis was found to be inflamed during laparotomy. Subsequent management with appendectomy and right salpingectomy was performed and the patient was able to continue her pregnancy with routine antenatal follow-up.

Case Report

We present the case of a 32-year-old G2P1 female at 12 weeks of gestation. She was a known case of spontaneous conception without prior ART. Her last pregnancy was 11 years ago and was delivered via vaginal delivery. She presented to the emergency department (ED) with a 1-day history of severe lower abdominal pain. The abdominal pain started abruptly and was described as stabbing pain in the right iliac fossa (RIF). The pain has progressively worsened since the onset. The pain was associated with nausea and several bouts of non-bilious vomiting. She denied the presence of urinary symptoms and vaginal spotting. The past medical history includes a history of irritable bowel syndrome.

She has had 2 previous hospital admissions since the start of her pregnancy. Her initial admission was 7.5 weeks ago for evaluation of pregnancy of unknown location. Her initial β-hCG was 5.851 mIU/mL 48 hours before admission, with a follow-up β-hCG of 7.622 mIU/mL. The patient strictly refused transvaginal pelvic ultrasonography (TVUS). A TAUS was then performed, revealing a normal uterus size and a small echo lucent area in the endometrial cavity that could indicate an early intrauterine gestational sac (IUGS). The fetal pole could not be visualized, and the right and left ovaries were normal in size. There was no visible free fluid in the pelvic cavity. The plan was for an outpatient department (OPD) antenatal follow-up after 4 weeks.

The patient presented to the ED 3 days prior to her OPD appointment with lower abdominal pain and vaginal spotting. A bedside US showed a single viable fetus consistent with 10 weeks of gestation and positive fetal cardiac activity (FCA). The patient was diagnosed with threatened abortion and was discharged on analgesics and progesterone support. One week later, she presented again to the ED with severe lower abdominal pain and worsening dizziness. Laboratory investigation showed anemia and normal leukocyte counts. Initial TAUS showed moderate fluid collection seen in Morison's pouch and left splenorenal region (Figure 1). She was admitted for further investigation and observation. A subsequent follow-up TAUS revealed a localized tender oval-shaped heterogeneous soft tissue mass located adjacent to the right wall of the uterus. The mass could not be delineated from the right ovary, measuring 4.6x3.4x3.6 cm with mild peripheral vascularity. Additionally, the mass displayed neither demonstrable calcification nor mesenteric lymphadenopathy. An initial diagnosis of HP was confirmed. The decision was made by a multidisciplinary team for surgical management. However, the patient refused and insisted on non-surgical management. Consequently, the patient was treated conservatively with analgesics, hydration, broad-spectrum antibiotics, and observation with serial TAUS. She was eventually discharged after 9 days of conservative treatment.

On physical examination, the patient was conscious and oriented. The patient's vital signs were stable. She was afebrile. Abdominal examination revealed rebound tenderness over the RIF region and a moderately distended abdomen. Laboratory evaluation showed Hb of 11.3 g/dL, leukocytes of $9.8x10^3$/μL (n=4-10), and neutrophils of $7.9x10^3$/μL (n=2-7.5). TAUS revealed a single viable fetus with a crown-rump length consistent with $12^{3/7}$ weeks gestation. The previously seen heterogeneous mass was visible within the right uterine wall measuring 3.2x4.1 cm

with unclear peripheral vascularity (Figure 2). Severe fluid was detected in both sides of the pelvic cavity measuring 5.9x5.6x5 cm. Moderate fluid collections were also visible in Morison's pouch. Other abdominal structures, including the appendix, could not be visualized clearly. The scanning process was notably difficult due to obstructed fields by bowel, gas, and probe tenderness throughout the scanning examination.

The decision was made for emergency exploratory laparotomy with the attendance of a general surgeon. Informed consent was received from the patient. An infraumbilical midline skin incision was made. Ruptured right fallopian tubal pregnancy was confirmed Figure 3, and the appendix was found to be grossly inflamed. There was no active bleeding at the ruptured tube and sealed with a clot. The left fallopian tube was intact. Both the right and left ovaries looked intact. Hemoperitoneum was seen and evacuated by scooping and suction. Right salpingectomy and appendectomy were performed. The excised appendix and right fallopian tube were sent for histopathology. Hemostasis was secured and a drain was subsequently placed. Histopathology report of the appendix revealed lymphoid tissue hyperplasia, sheets of macrophages, and giant cells confirming acute appendicitis, whereas the right fallopian tube confirmed the diagnosis of tubal ectopic pregnancy.

Postoperatively, the patient made an excellent recovery. The drain was removed on postoperative day 2. The wound healed without any problem. The patient was discharged on postoperative day 4. OPD follow-up was scheduled after 10 days and she showed progressive recovery and reassuring IUP. The patient underwent routine antenatal checkups in our hospital until 41 weeks of gestation when she insisted to deliver at another hospital. Her delivery outcome is unknown.

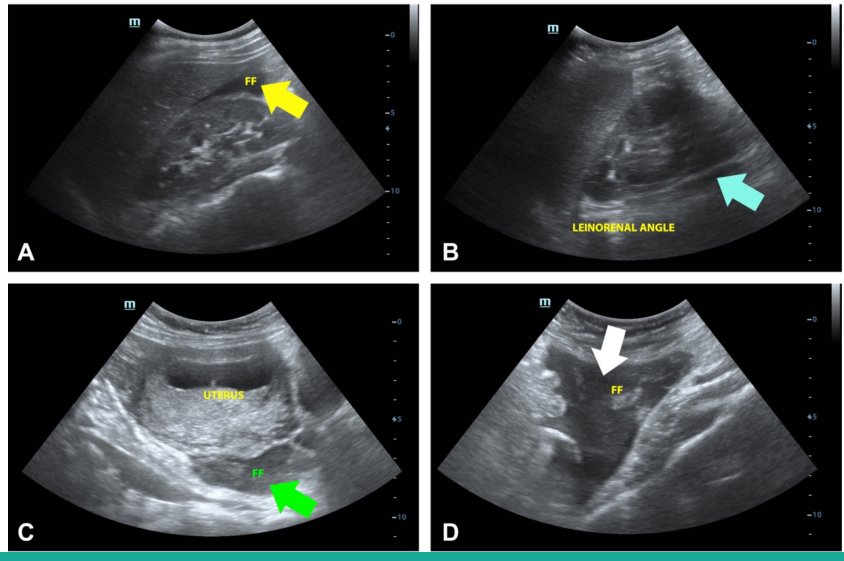

Figure 1. TAUS of the patient demonstrated moderate fluid collection in hepatorenal angle (**A**, yellow arrow), splenorenal angle (**B**, blue arrow), pouch of Douglas (**C**, green arrow), and Morison's pouch (**D**, white arrow)

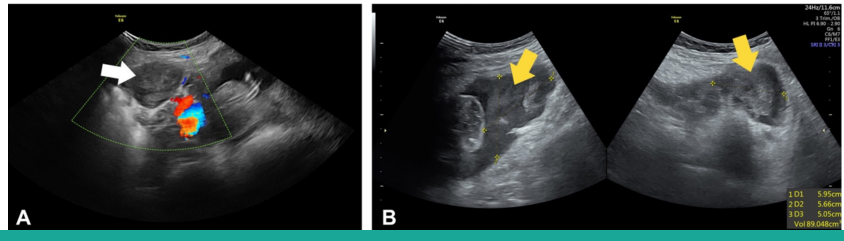

Figure 2. TAUS of the patient at $12^{3/7}$ weeks of gestation showed a heterogenous mass within the right uterine wall measuring 3.2x4.1 cm (**A**, white arrow) with peripheral vascularity observed around the mass. Severe fluid collections were visible on both sides of the pelvic cavity measuring approximately 5.9x5.6x5.0 cm (**B**, yellow arrows). Fluid collection was also observed in Morison's pouch and splenorenal recess

TAUS: Transabdominal pelvic ultrasonography

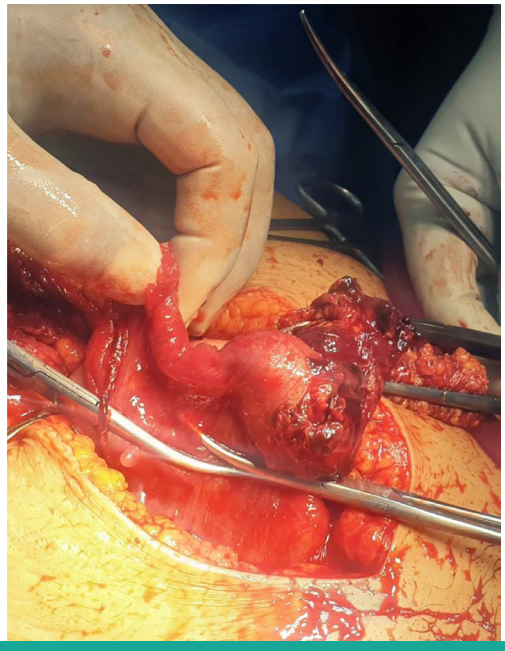

Figure 3. Intraoperative image of the ruptured ampullary part of the right Fallopian tube

Discussion

Here, we described the case of spontaneous HP with coexisting acute appendicitis. HP is exceedingly rare. Its incidence is approximated to be 1/30,000 spontaneous pregnancies (2). However, the risk increases in pregnant women following successful ART, with an estimated incidence of 0.1-1.0% (4). In addition, the incidence rate of acute appendicitis during pregnancy is reported to be between 1/1.250 and 1/1.500 (5). Currently, the incidence of concurrent appendicitis with HP is unknown, with only limited cases have been reported in the literature. We conducted a literature search on Medline/PubMed and Google Scholar using the following keywords: [heterotopic pregnancy (Title/Abstract)] AND [appendicitis (Title/Abstract)]. Our literature search as of February 2023 has yielded only 7 relevant available case reports. Two articles were excluded for unavailable full text. A literature review of the topic is summarized in Table 1. Our case report is also included in the analysis.

Table 1. Characteristics of the included case reports

Authors	Year	Country	Age/GP	GA (w)	PMH	Clinical presentation	Diagnosis confirmation/ Site of EP	Intervention	Obstetric outcome
Murewanhema et al. (6)	2020	Zimbabwe	34/ G3P2+0	11	No significant PMH/PSH	Abdominal pain, poorly localized vaginal bleeding backache WBC: 18.3	Radiological diagnosis (US) fallopian tube (left)	Laparotomy with midline incision appendectomy and left salpingectomy	Pregnancy continues Delivery outcome: N/A
Downes (7)	2015	Bahamas	36/G3P1+1	6	Unruptured ectopic pregnancy with salpingostomy	Abdominal pain, periumbilical migrating to RIF nausea, vomiting WBC: 17.1	Surgical diagnosis fallopian tube (right)	Single-port laparoscopy appendectomy and right salpingectomy	Pregnancy continues LSCS
Barnett et al. (8)	2009	UK	32/G1P0+0	9	Primary infertility due to tubal damage Prior IVF	Abdominal pain RIF vomiting, diarrhea WBC: 8.1	Surgical diagnosis fallopian tube (left)	Laparotomy Pfannenstiel's incision appendectomy and right salpingectomy	Twin pregnancy continues multiple admissions for HG CS at 37th week
Daponte et al. (9)	2006	Greece	31/G1P0+0	6	Prior IVF 6 times	Abdominal pain RIF nausea, anorexia WBC: 15.9	Radiological diagnosis (US) fallopian tube (right)	Laparotomy appendectomy and right salpingectomy	Pregnancy continues CS at 38th week
Radwan et al. (10)	2006	Poland	35/ G4P0+4	7	N/A	Lower abdominal pain	Radiological diagnosis (US) fallopian tube (right)	Laparoscopy appendectomy and right salpingectomy	Pregnancy continues delivery at 39th week

US: Ultrasonography, WBC: White blood cell, RIF: Right iliac fossa, EP: Ectopic pregnancy

The median age of the patients is 33 years (range between 31-36 years old). The majority of cases were diagnosed in the first trimester, with the median gestational age at the presentation of 8 weeks of gestation (range between 6-12 weeks). A total of 33.3% (2 in 6 women) were in their first pregnancy. In addition, as many as 50% of women have preceding risk factors for HP (2), including ART (33.3%), tubal damage including salpingostomy (33.3%), and a previous history of EP (16.7%). Our patient has no identifiable risk factor.

The diagnosis of HP is especially challenging and is sometimes missed due to the paradoxically reassuring presence of IUGS on the ultrasonography (US) (2). The presence of IUGS sometimes, and frequently, distracts physicians from the suspicion of possible extrauterine pregnancy. The clinical manifestations are generally non-specific and overlap with other more common obstetrics problems. In this review, all patients presented with abdominal pain, which is mostly right lower abdominal pain (66.7%). Nausea and vomiting are typical, occurring in 66.7% of women. Other symptoms include vaginal spotting, backache, and anorexia. Fever is unexpectedly not observed in any of the patients. This, compounded by low suspicion of intraabdominal non-obstetrics pathologies such as appendicitis, makes the diagnosis of concurrent HP with acute appendicitis frequently delayed. Delayed diagnosis may subsequently lead to complications such as rupture with peritonitis, intraperitoneal hemorrhage, sepsis, shock, and even death.

Historically, the majority of HPs were diagnosed surgically (3). However, the definitive diagnosis of HP has mostly shifted toward radiological diagnosis, mostly by US (2). This is primarily due to the improved quality of sonographic imaging in addition to the increased awareness following the rising popularity of ART in recent years. Importantly, TVUS is preferred since it provides better accuracy in diagnosing EP compared to TAUS and permits earlier detection. In this review, HP was diagnosed radiologically in 66.7% of cases. In the case of acute appendicitis in pregnancy, the diagnosis is particularly challenging, as clinical diagnosis using the Alvarado score may be unreliable during pregnancy (6). Many obstetrics conditions can also mimic acute appendicitis, such as miscarriage, ectopic pregnancy, round ligament pain, adnexal torsion, and placental abruption. Visualization of the appendix by the US, as in our case, can be difficult, especially when EP has ruptured and the view becomes obstructed by increased intraperitoneal and bowel gas.

Although the management of HP may include medical management by either methotrexate or US-guided potassium chloride injection, the management of HP with concurrent acute appendicitis should primarily be surgical (4). Methotrexate should not be used if IUP is viable and continuation of pregnancy is desirable. The surgical approach is generally preferable, with options being either laparoscopy or laparotomy. The laparoscopic approach is generally safe in pregnancy and is desirable in hemodynamically stable patients. Alternatively, laparotomy is frequently done in the emergency setting when the patient is hemodynamically unstable. Other indications may include the surgeon's expertise, preference, and available modalities. In this review, the majority of cases (66.7%) were managed by laparotomy with subsequent salpingectomy and appendectomy. The authors recommend against conservative management in the case of HP with concurrent acute appendicitis as it has proven ineffective to treat the patient's condition in our case.

Conclusion

HP is rare, and its coexistence with acute appendicitis is exceedingly uncommon. However, with the more widespread use of ART, the condition may become more frequently encountered in the clinical setting. Misdiagnosis can occur owing to its rarity, however delay in diagnosis may potentially be fatal. The presence of IUP doesn't exclude the possibility of coexisting EP. Therefore, a low threshold of suspicion for HP should be applied even in the presence of an established IUP. The clinicians should get detailed clues and focus on narrowing the possible differential diagnosis. In our case, there were no identifiable risk factors that could be obtained, therefore, a trained clinical judgment is necessary. Early surgical management with either laparotomy or laparoscopy is the mainstay of therapy and is associated with good outcomes.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: Y.B.A., M.C.J., T.D.I., M.A.A., Design: Y.B.A., M.C.J., T.D.I., M.A.A., Data Collection or Processing: Y.B.A., M.A.A., Analysis or Interpretation: M.C.J., T.D.I., Drafting Manuscript: M.C.J., T.D.I., Critical Revision of Manuscript: Y.B.A., M.C.J., T.D.I., M.A.A., Final Approval

and Accountability: Y.B.A., M.C.J., T.D.I., M.A.A., Technical or Material Support: Y.B.A., M.A.A., Writing: Y.B.A., M.C.J., T.D.I., M.A.A.

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CASE REPORT

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Late Diagnosis of Bladder Injury During Cesarean Section

Geç Tanı Konulan Sezaryen Mesane Yaralanması Olgusu

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Abstract

Intraoperative bladder injury in cesarean deliveries is an important complication that causes maternal morbidity. Bladder adhesions resulting from previous abdominal operations, cesarean section under emergency conditions, cesarean section after prolonged labor or in the second stage of labor are predisposing factors for bladder injury. In order to prevent bladder injury, it is important to be aware of bladder injury during peritoneal incision in risky cases, delivery of the baby, and hysterotomy and fascia closure. In this article, we present the diagnosis and treatment of a patient who was diagnosed with intraperitoneal bladder perforation, intra-abdominal abscess and peritonitis one week after cesarean section, in the light of current literature. In our case, intraoperative diagnosis could not be made, postoperative active hematuria was not observed, the focus was on the diagnosis of postoperative ileus, and intra-abdominal abscesses developed. A multidisciplinary team ensured success in the treatment.

Keywords: Abdominal abscesses, bladder injury, cesarean

Öz

Sezaryen doğumlarda intraoperatif mesane yaralanması maternal morbiditeye neden olan önemli bir komplikasyondur. Daha önce geçirilen batın operasyonlarından kaynaklanan mesane yapışıklıkları, acil şartlarda sezaryen yapma, uzamış doğum eylemi sonrası veya doğumun ikinci evresinde sezaryen uygulama, mesane yaralanması için predispozan faktörlerdir. Mesane yaralanmasını önlemek için riskli olgularda peritoneal insizyon yapılmasında, bebeğin doğumunda, histerotomi ve fasya kapanması sırasında mesane yaralanması farkındalığının olması önemlidir. Bu yazıda, sezaryenden bir hafta sonra intraperitoneal mesane perforasyonu, batın içi apse ve peritonit tanısı almış bir hastanın tanı ve tedavisini, güncel literatür eşliğinde sunuyoruz. Olgumuzda intraoperatif tanı konulamamış, postop aktif hematüri gözlenmemiş, postop ileus tanısı üzerine yoğunlaşılmış ve bu süreçte hastada batın içi apseler gelişmiştir. Operasyondan bir hafta sonra akut batın tablosuyla yatırılan hastanın preop-postop yönetiminde kadın doğum, genel cerrahi, üroloji, radyoloji, enfeksiyon hastalıkları, anestezi hekimlerinden oluşan multidisipliner ekip çalışması yapılmış olmasıyla tedavide başarılı olunmasını sağlanmıştır.

Anahtar kelimeler: Batın apseleri, mesane yaralanması, sezaryen

Introduction

Intraoperative bladder injury during cesarean delivery is an important complication that causes maternal morbidity. Bladder injury is approximately 0.2% during primary cesarean section and 0.6% during repeat cesarean section (1). Today, in increasing number of cases of placenta accreta spectrum (PAS), bladder injury is seen as 11.7% (2). Especially in risky cases, it should be carefully checked that there are no visceral structures around it when making a peritoneal incision. It is important to be aware of bladder injury during the delivery of the baby, repair of hysterotomy, creation of bladder flaps, and fascia closure. In suspicious cases, it is appropriate to check whether there is fluid leakage by performing retrograde bladder filling. The rate of return to normal urological functions is high in cases diagnosed and repaired intraoperatively. We aimed to discuss the diagnosis and treatment of a patient who was diagnosed with intraperitoneal bladder perforation, intra-

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abdominal abscess, and peritonitis 1 week after cesarean section, with regard to the current literature.

Case Report

It was learned from the history of a 32-year-old patient who had a previous cesarean section, that she gave birth by planned cesarean section 1 week ago in an external hospital, and that there was no macroscopic hematuria after delivery, and the catheter remained for 2 days. Pre-diagnosis was ileus for the patient whose abdominal pain complaints increased after catheter removal and the catheter was re-administered for 1 day. The patient, who had gaseous stool discharge, applied to our general surgery clinic 2 days after discharge, with the complaints of abdominal pain, vomiting and fever. On examination, the abdomen was tense and defensive. Gas stool output and spontaneous urine output were decreased. Vital parameters and laboratory results were as fever: 37.8, TA: 154/88, heart rate: 115 beat/min, SpO_2: 97, C-reactive protein: 161 mg/L, leuk: 10,400/mcL, hemoglobin: 12.6 g/dL, procalcitonin: 0.26 ng/mL, creatinine 0.99 mg/dL. Oral/intravenous (IV)/rectal contrast-enhanced upper abdomen and pelvic computed tomography (CT) results showed intense free acid containing free air in the abdomen, thickening of the peritoneal wall and suspected iatrogenic bladder wall damage (Figures 1, 2). She was urgently referred to our urology clinic with a preliminary diagnosis of intraperitoneal bladder perforation.

The decision of laparotomy was made. In the abdominal exploration, the entire abdomen was in abscess formation up to the liver and subspleen superiorly, and the Douglas cavity inferiorly (Figure 3). 2.300 cc of pus was drained. The uterine incision site was intact and regular. It was observed that the bladder was perforated 8 cm transversely from the dome in the inferoanterior of the uterus, the trigone and bilateral ureter and orifice regions were intact and there was no pathology. The perforation line was debrided and sutured continuously from mucosa to mucosa with 3/0 vicryl. The seromuscular 2nd layer was closed with 2/0 vicryl. The bladder was filled with 300 cc saline (SF) and tested. The general surgery consultation was needed peroperatively. The abscess areas were washed with SF, adhesiolysis was performed and drains were placed in 3 separate areas (subhepatic, subsplenic and retzius). Antibiotic (piperacillin + tazobactam) treatment was started. Foley catheter was kept for 10 days. Control retrograde cystography was performed on the 10th day for the patient who had no postoperative problems (Figure 4). No complication is observed.

Discussion

Knowledge of risk factors, increasing awareness of symptoms and planning their management are crucial to reduce the potential morbidity rate in this patient population. The most important risk factor for bladder injury in cesarean delivery is bladder adhesions resulting from previous abdominal operations (3,4). The incidence of bladder injury is 3 to 9 times higher in cases who have

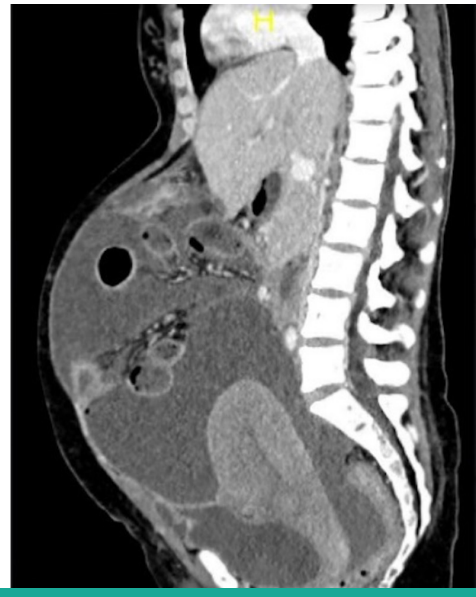

Figure 1. Bladder anterior perforation

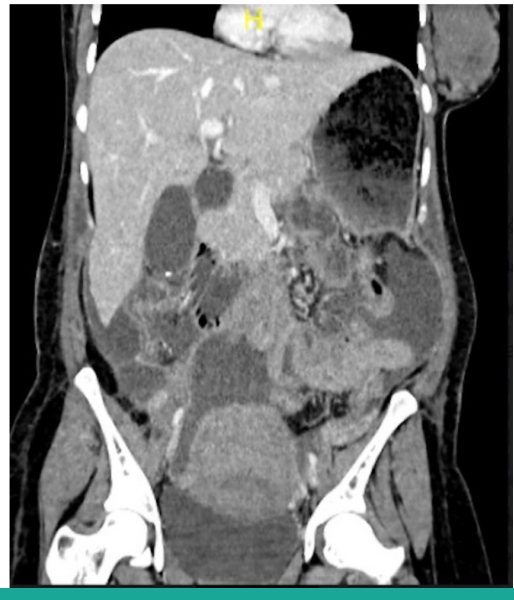

Figure 2. Subhepatic subsplenic abscess area

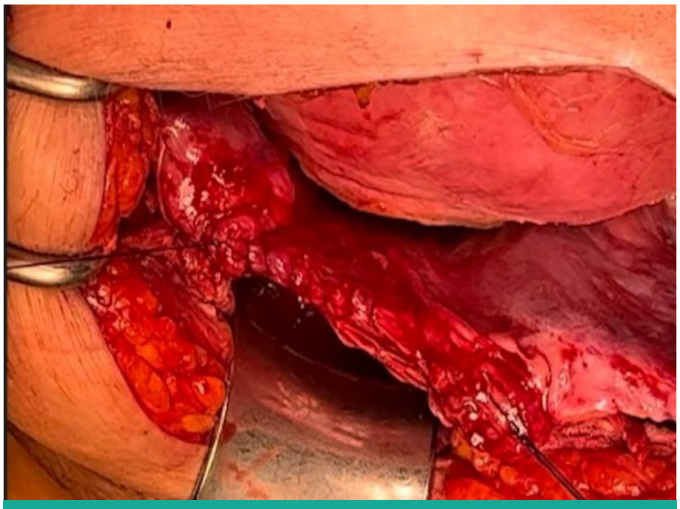

Figure 3. Intraoperative view

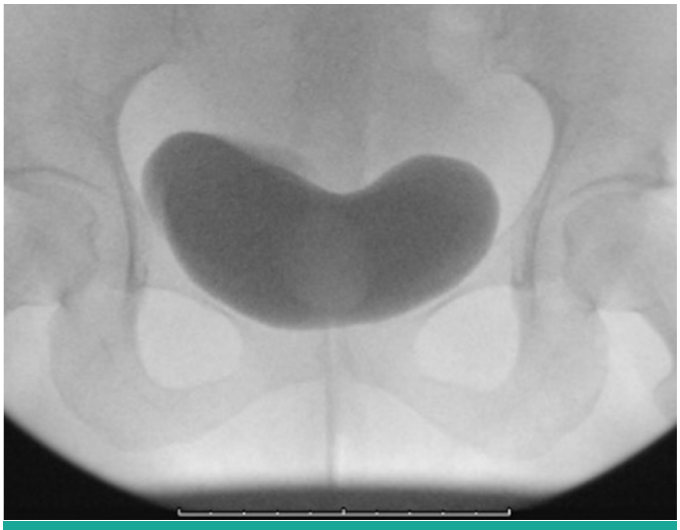

Figure 4. Cystogram image on postoperative day 19

given birth by cesarean section before (3). These rates were given as 0.09% for the second cesarean section, 0.28% for the third cesarean section, 1.17% for the fourth cesarean section, 1.94% for the fifth cesarean section, and 4.49% for the sixth cesarean section (5). In primary cesarean sections, giving birth by cesarean section in the second stage of labor (full cervical dilatation), having a cesarean section after a failed vacuum extraction attempt, and having an emergency cesarean section are the factors that increase the risk of bladder injury (6). Displacement or delivery of a baby entering the pelvis may cause surgical trauma around the bladder (7). Bladder injuries during cesarean section occur in 95% bladder domes, 5% in trigone region and average 1-10 cm in length. It has been shown that 43% of the injuries occur during the creation of the bladder flap, 33% during the opening of the peritoneal cavity, 24% during the uterine incision or after the lateral extension of the uterine incision (4). In our case, the length of the bladder injury was 8 cm transversely from the dome, suggesting that it was during the creation of the bladder flap or due to the traumatic effect of the retraction instruments. It should be checked that there are no visceral structures around the incision during the opening of the peritoneum or uterine incision while entering the abdominal cavity. In cases with dense adhesion, a sharp dissection should be preferred instead of a blunt dissection of the bladder with gauze (8). In morbidly adherent PAS cases, filling the bladder with 200 mL of saline before cesarean section will reduce bladder damage (9). Increasing awareness of the risk of intraoperative bladder injury, presence of urine leakage in the operation area, presence of foley catheter balloon, and detrusor muscle rupture allow us to diagnose. Hematuria may be present in 95% of the cases (10). If injury is suspected, retrograde bladder filling is performed via the Foley catheter. 62% of the injuries are detected during the delivery of the baby and repair of the hysterotomy, 21% during the creation of bladder flaps, 12% at the entrance to the peritoneal cavity, and 5% before the fascia is closed (3). As in our case, bladder dome injuries can usually be repaired with two or three-layer closure (8,11). After the repair, the retrograde bladder is filled with at least 300 mL of methylene blue or SF, and the integrity of the bladder is checked. Postop foley catheter is kept for 7-14 days. A closed suction drain can be kept in the perivesical space and pelvis to control urine leakage (12). Hematuria, oligouria, lower abdominal pain, ileus, ascites, peritonitis, sepsis, fistula, and increased urea nitrogen/creatinine ratio in the blood may suggest bladder injury, which may occur in the early postoperative period (13). Retrograde cystography is a useful diagnostic procedure for postoperative patients with suspected urological injury. Abdominal CT with cystography has a high diagnostic value in cases of acute abdomen. Diagnostic laparotomy should always be considered if intraperitoneal bladder injury is suspected (13). In our case, the absence of postoperative active hematuria, the insertion of an intermittent catheter, the fact that only a standing direct abdominal X-ray was taken in the early period, the focus on the diagnosis of ileus with surgical consultation, and the failure to consult the urology caused a delay in the diagnosis of actual bladder injury. Hence, intra-abdominal abscesses are developed. After the presence of acute abdomen 1 week after the operation, the diagnosis was made by performing upper abdomen and pelvic CT with oral/IV/rectal contrast. Multidisciplinary team has ensured success in the treatment.

Ethics

Informed Consent: The patient is informed about the publication process by the informed consent and written confirmation is provided to the journal.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: G.P., Design: G.P., Data Collection or Processing: G.P., G.Ç., V.G., Analysis or Interpretation: G.P., T.A., Drafting Manuscript: G.P., T.A., G.Ç., V.G., Critical Revision of Manuscript: T.A., Final Approval and Accountability: G.P., T.A., G.Ç., V.G., Supervision: T.A., Technical or Material Support: G.P., G.Ç., V.G., Writing: G.P., T.A., G.Ç., V.G.

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

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CASE REPORT

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Unusual Suspect After Spinal Anesthesia: Herpetic Encephalitis

Spinal Anestezi Sonrası Gelişen Olağan Dışı Şüpheli: Herpetik Ensefalit

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Abstract

Herpes simplex virus (HSV) is the most common cause of acute, sporadic viral encephalitis. Usually occurs with the activation of the latent virus. Sudden onset fever and especially temporal lobe involvement are typical clinical features of HSV encephalitis. In this article, we aimed to present a case of herpetic encephalitis, which is an unusual factor in meningitis after spinal anesthesia. Severe headache and convulsion developed at postoperatively. Body temperature of the patient was 38.3 °C and neck stiffness developed. The patient was diagnosed with herpes encephalitis by clinical, laboratory and cranial magnetic resonance, and acyclovir treatment was started immediately. The patient was discharged home with recovery on the 14th day. Loss of consciousness and convulsions with fever seen at the postoperative period after spinal anesthesia, may not always be due to bacterial meningitis but sometimes due to HSV-associated acute herpetic meningoencephalitis. Rapid diagnosis and treatment is life-saving.

Keywords: Acyclovir, encephalitis, herpes simplex, spinal anesthesia

Öz

Herpes simpleks virüsü (HSV) akut, sporadik viral ensefalitlerin en sık etkenidir. Genellikle latent virüsün aktivasyonu söz konusudur. Ani başlayan ateş ve özellikle temporal lob tutulumu HSV ensefalitinin tipik klinik özellikleridir. Bu yazımızda spinal anestezi sonrası meningoensefalitte, olağan dışı bir etken olan herpetik ensefalit olgusunu sunmayı amaçladık. Cerrahi sonrası 5. günde şiddetli baş ağrısı, konvülziyon gelişen hastanın vücut ısısı 38,3 °C ve ense sertliği geliştiği görüldü. Klinik, laboratuvar ve manyetik rezonans görüntüleme ile herpes ensefaliti tanısı konulan hastaya hızla asiklovir tedavisi başlandı. Hasta 14. gün şifa ile evine taburcu edildi. Spinal anestezi sonrası postoperatif dönemde görülen bilinç kaybı ve ateşli konvülsiyonlar her zaman bakteriyel menenjite bağlı olmayabilir, ancak bazen HSV ile ilişkili akut herpetik ensefalite bağlı olabilir. Hızlı teşhis ve tedavi hayat kurtarıcıdır.

Anahtar kelimeler: Asiklovir, ensefalit, herpes simpleks, spinal anestezi

Introduction

Encephalitis is characterized by the sudden onset of fever, headache, focal neurological signs, epileptic seizures, and impaired consciousness (1). The causes of meningoencephalitis may include infectious agents such as bacteria, viruses, parasites, and non-infectious factors (2). The most commonly encountered infectious agent is the herpes simplex virus (HSV type 1), which selectively affects the temporal and frontal lobes, leading to necrotizing encephalitis characterized by edema, necrosis, and hemorrhage (3). It is usually observed due to the acute exacerbation of the latent virus (3,4). Early diagnosis plays a crucial role in recovery without sequelae (5). In this case report, we aimed to present a case of herpetic encephalitis (HE) following ureterorenoscopy (URS) under spinal anesthesia.

Case Report

Informed consent was obtained from the patient and a 34-year-old male patient who underwent elective URS operation under spinal anesthesia developed

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severe headache, fever, nausea, and vomiting on the 5th postoperative day. The symptoms progressively worsened, and later the patient experienced delirium and a few minutes of generalized tonic-clonic convulsion. Upon initial examination, the patient's consciousness was confused and agitated, with impaired cooperation and nuchal rigidity. Heart rate was 120-130 beats/min, blood pressure 130/76 mmHg, respiratory rate 25/min, peripheral oxygen saturation 97%, and axillary body temperature 38.3 °C. According to the perioperative anesthesia records, spinal anesthesia was applied sitting at the lumbar 4-5 space, using 15 mg of heavy marcaine under sterile conditions, with no premedication. The patient received 400 mg of intravenous ciprofloxacin 2x1 in the postoperative period. The patient was admitted to our hospital's intensive care unit (ICU) for further investigation and treatment, suspecting meningitis based on the clinical presentation. Following admission to the ICU, blood tests revealed a leukocyte count of 20,000/mm^3, with no other pathology detected. Electroencephalography showed a slow-wave pattern. While cranial computed tomography was standard, hyperintense areas in the temporal lobe were observed on cranial magnetic resonance imaging (MRI) T2 sequence (Figure 1). Focal encephalitis in the temporal lobe and EEG findings suggested herpes encephalitis (1-6). Cerebrospinal fluid (CSF) microscopy showed 80.000 leukocytes/mm^3 (80% lymphocyte predominance), 56 erythrocytes/mm^3, and 96 mg/dL protein. CSF culture did not yield any bacterial growth. ELISA tests showed positive HSV-1 IgG and negative HSV-1 IgM, supporting the diagnosis, although polymerase chain reaction (PCR) could not be performed. The patient was diagnosed with HE and started on 30 mg/kg/day acyclovir. On the 2nd day of treatment, the patient began to cooperate, and by the 6th day, his general condition had improved, and he was transferred to the ward. The patient was discharged home on the 14th day of treatment, with complete recovery and no sequelae.

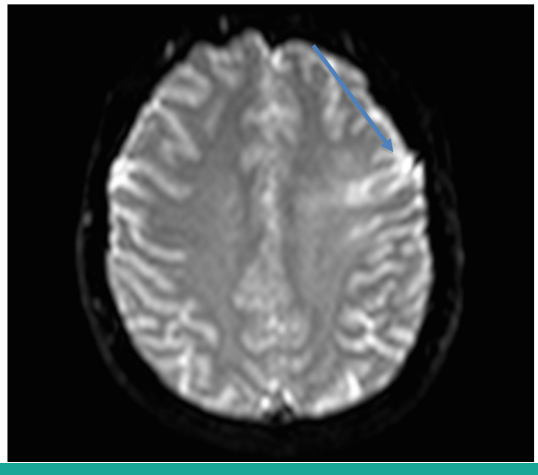

Figure 1. Hyperintense appearance in temporal region T2 sequence in cranial MRI

MRI: Magnetic resonance imaging

Discussion

HSV, whose only natural reservoir is human, is common worldwide.The virus spreads through body secretions and causes skin, eyes, and central nervous system infections, primarily around the mouth and genital regions (7). Following recovery, the virus can remain latent in neurons, leading to recurrent infections. However, the mechanism by which the virus becomes activated to cause encephalitis is unknown (8).

HE is the most common type in the general population and has a high mortality rate. HSV-1 has been reported as the causative agent in 0.8-30% of all encephalitis cases and 20-75% of necrotizing encephalitis cases (9). It predominantly affects the temporal and frontal lobes, causing focal encephalitis. The annual incidence ranges from 0.002-4% (5). It can cause infection in individuals of any age, gender, or demographic, independently of these factors. However, research has indicated that HE is more common in adult patients (7).

The disease can manifest in various clinical forms, ranging from high fever to loss of consciousness and convulsions (1-9). If left untreated, the mortality rate can reach 70%, and the resulting sequelae are often permanent (5-10). Conversely, if treatment is initiated early, before the development of consciousness loss, a 92% recovery rate without sequelae can be achieved (9-12). Therefore, early diagnosis is of great importance. The first symptom of the disease is a headache. Postspinal headache is the first consideration in cases of headache following spinal anesthesia. Thus, in our case, the developing headache was initially evaluated in this manner, and treatment was planned accordingly. However, this situation also delayed treatment for a potential case of meningitis. Therefore, clinical findings should be closely monitored in cases of postspinal headache, and meningitis should not be overlooked (13). Fever is an important finding but also a common postoperative symptom.

The sudden onset of fever, headache, focal neurological signs, epileptic seizures, and impaired consciousness characterizes Meningoencephalitis. The differential diagnosis should consider other causes of

meningoencephalitis (10,12,13). Bacterial meningitis is the most common cause following spinal anesthesia. In our patient, we initially suspected bacterial meningitis after observing fever, loss of consciousness, and convulsions.

Diagnosing herpes encephalitis based solely on clinical findings is challenging. Clinical data must be supported by laboratory and imaging results. However, laboratory findings are generally non-specific. Bacterial, viral, and fungal cultures obtained from blood and CSF samples usually do not yield any growth (9,12). Antibody titers for specific viral antigens typically only rise weeks after the onset of the disease (8-13). Detection of HSV-DNA in CSF using the PCR method is currently considered the "gold standard" for diagnosing HSV encephalitis. HSV-DNA in CSF can be detected by PCR from the first 24 hours of symptom onset up to one week after treatment initiation. However, HSV-DNA has been detected in only 1-19% of cases with suspected viral encephalitis. Studies have reported that PCR has a 98% sensitivity and 94-100% specificity for detecting HSV-DNA (9-12). PCR analysis is not accessible in every institution.

In cases of acute viral encephalitis, meningeal or parenchymal involvement can be reliably demonstrated in the early stages using MRI. In HE, it has been reported that hyperintense lesions characterized by localized edema, necrosis, and hemorrhage in the temporal and frontal lobes can be observed in T2 sequence examinations (6). This specific involvement in HE is essential as a distinguishing feature from other types of encephalitis (10). In healthcare institutions where PCR is unavailable or limited, diagnosis using MRI findings becomes critically important. Since the PCR method was unavailable in our center, the patient's diagnosis was made based on clinical results, CSF microscopy, and MRI findings specific to the disease (Figure 1).

The most effective agent for treatment is considered to be acyclovir (12). Studies have shown that mortality was 50-55% in patients treated with vidarabine, while in patients treated with acyclovir, mortality was 20-30% (8,13,14). It is widely accepted that the best treatment option for HE is intravenous acyclovir at a dose of 10 mg/kg every 8 hours for 14-21 days (14,15). In our case, the patient recovered without sequelae following a 21-day course of acyclovir treatment at a dose of 3x10 mg/kg/day. Anti-edema support therapy is also crucial in managing the disease (1,2,14,15).

In conclusion, bacterial meningitis is the first consideration in patients who develop meningitis symptoms after spinal anesthesia. However, as seen in this case, surgical stress may trigger latent HSV-1 by causing immunosuppression and leading to acute herpes encephalitis. This possibility should be kept in mind.

This case report demonstrates that viral encephalitis can also occur following surgery. Furthermore, as illustrated by this case, we would like to emphasize the importance of MRI imaging in healthcare institutions where PCR is unavailable.

Information: Our article was previously presented as an "e-poster" at the 56th National Congress of the Turkish Society of Anesthesiology and Reanimation.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.İ., R.G., Concept: R.G., B.K.U., Design: R.G., M.A.T., Data Collection or Processing: Y.İ., M.A.T., Analysis or Interpretation: Y.İ., B.K.U., Literature Search: Y.İ., M.A.T., B.K.U., Writing: Y.İ., R.G.

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

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LETTER TO THE EDITOR

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A Rare Cause of Acute Abdomen in Children: Heterotopic Gastric Mucosa Located in the Ileum Mimicking Intussusception

Çocuklarda Nadir Bir Akut Karın Nedeni: İleumda İnvajinasyonu Taklit Eden Heterotopik Gastrik Mukoza

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Dear Editor,

Heterotopic gastric mucosa (HGM) is usually a clinically asymptomatic benign lesion. The incidence of this lesion usually diagnosed incidentally is around 2%, and it is more common in the adult population. Congenital remnants of gastric mucosa can be seen anywhere in the gastrointestinal tract (such as the esophagus, duodenum, small intestine, and Meckel's diverticulum), but ileum localization is rare. HGM located in the ileum is usually in the form of a polypoid mass smaller than 1 cm, attached to the intestinal wall on the mesentery surface of the intestine (1).

Although HGM is seen mainly in the esophagus, duodenum, and Meckel's diverticulum, it is rarely in the jejunum and ileum. Most jejunal and ileal HGMs are diagnosed by samples of histological results after surgery. HGM is usually in the form of an entrance patch in the upper 1/3 of the esophagus; It is seen as nodular and jejunal masses in the duodenum and as polypoid masses in the ileum (2).

HGM may be congenital or acquired, but its formation is unknown. Acquired HGM occurs when gastric mucosa epithelium is affected by the effect of inflammatory or peptic processes. HGM is usually clinically silent and does not require treatment; however, surgical intervention may be required after complications such as bleeding and intestinal obstruction. Therefore, HGM of the ileum is extremely rare. Diagnosis of ileal polypoid lesions is important in affecting gastric mucosal epithelium (3).

In this study (patient informed consent form was obtained), a ten-year-old girl with complaints of abdominal pain and vomiting referred to our clinic with a preliminary diagnosis of intussusception as a result of ultrasonography (US) performed in a private medical center. When he applied to our clinic, the patient did not have acute abdomen findings in the examination and did not have a palpable mass. Her complaints of pain regressed and his vomiting stopped. In the standing direct abdominal X-ray (Figure 1), air-fluid levels, which is the radiological finding of intestinal obstruction, and on repeated US a 10 cm long intussusception image extending from the lower quadrant of the abdomen to the left upper side was observed. In the examination performed proximally from the ileocecal valve in the patient who was taken into surgery, no other obvious pathology was observed in the small bowel serosa.

The mucosal lesion in the sessile polyp structure was excised within the invaginated segment approximately

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40 cm proximal to the ileocecal valve, located on the mesenteric side and continuing for about 10 cm, leaving intact intestinal margins. Intestinal continuity was achieved with primary anastomosis. The patient, who was fed orally on the third postoperative day, was discharged on the fifth day. Its pathology was reported as polypoid gastric heterotopia (Figure 2). The patient is followed up in the 2nd postoperative month without any complaints.

In conclusion, although HGM is asymptomatic, they can sometimes present with symptoms suggestive of acute abdomen, as in our case. Although rare, HGM should be kept in mind in such cases. This case was diagnosed as "polypoid gastric heterotype" postoperatively and presented as a rare cause of acute abdomen.

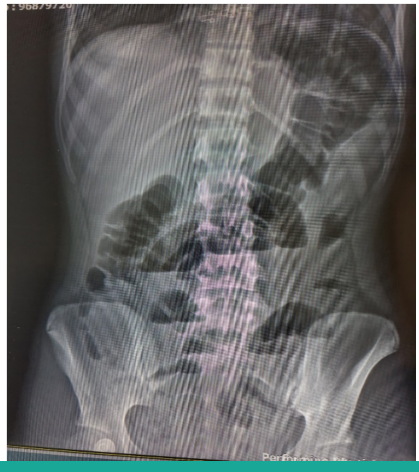

Figure 1. In the standind direct abdominal

X-ray, air-fluid levels, which is the radiological finding of ileus

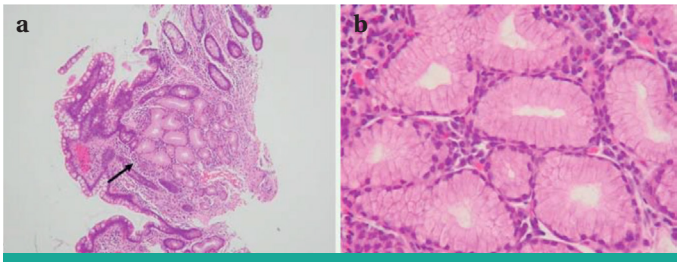

Figure 2. A heterotopic diagnosis. gastric mucosa of the ileum (HGM).

Lesions showing images obtained with hematoxylin and eosin of biopsy specimens from the polypoid a. Mucinous glands resembling pyloric glands in the lamina propria (arrow) stomach (original magnification X100); b. Higher power view of mucinous glands (original magnification X400)

Keywords: Acute abdomen, heterotopic gastric mucosa, intussusception

Anahtar kelimeler: Akut karın, heterotopik mide mukozası, invajinasyon

Ethics

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