E-ISSN: 2547 - 9431

BAGCILAR MEDICAL BULLETIN

Bağcılar Tıp Bülteni

Volume 6, Issue 3, September 2021

ORIGINAL RESEARCHES / ARAŞTIRMALAR

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

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: September 2021
E-ISSN: 2547-9431
International scientific journal published quarterly.

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About the Journal

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

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 branches will be accepted for evaluation in BMB.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2017, archived at http://www.icmje.org/) rules.

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

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T.C.Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi adına Hastane Yöneticisi Ahmet Yaser Müslümanoğlu, Prof. M.D (Türkiye Cumhuriyeti Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, İstanbul, Türkiye).

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Description

Bagcilar Medical Bulletin is a peer reviewed English journal aiming to publish original research, current review articles, case reports and letters related to all medical fields. The journal is currently published quarterly as online publication. The articles will become freely available to all readers in pdf format as soon as they have been accepted after peer review. Accepted articles will immediately appear as a part of the issue belonging to that publication period. The journal is currently published by Galenos Publishing House. The journal is using online manuscript submission, review and tracking systems.

Editorial Policies and Review Process

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Bagcilar Medical Bulletin considers for publication papers in the following categories:

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

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

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Papers that have not been published before or under evaluation by other publications are accepted for evaluation by the journal, if approved by each of the author. Publication board may amend manuscripts upon informed consent of authors. Editors and redactors are fully empowered to correct mistakes related to orthography, citation as given in National Library of Medicine MEDLINE/PubMed Resources.

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Biomedical Research-revised in 2006 http://www.wma.net/en/30publications/10policies/a18/

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

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

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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.

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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.

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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).

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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.

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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.

Preparation of Manuscripts

The "Bagcilar Medical Bulletin'' follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org/). 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) (http://www.consort-statement.org /),

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.) (http://www.prisma-statement.org /),

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.) (http://www.stard-statement.org /),

INSTRUCTIONS TO AUTHORS

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org /),

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.) (http://www.care-statement.org /

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

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

Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the National Library of Medicine for its databases. Authors should consult NLM’s Citing Medicine (http://www.nlm.nih.gov/bsd/uniform_requirements.html) 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. In addition the list should be obtained in the web address of http://www.nlm.nih.gov. Accuracy of citation is the author’s responsibility. All references should be cited in text. Type references in the style shown below. If there are more than 6 authors, list them followed by et al. Abbreviations of journal names should conform to the style used in National Library of Medicine. If a journal is not indexed in National Library of Medicine’s MEDLINE/PubMed, it should not be abbreviated.

Examples for References:

1. For articles in journals:

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

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

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

Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3(4):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.

INSTRUCTIONS TO AUTHORS

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:

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

For the citation from a translated book:

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

5. For the citation from thesis:

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. 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 2011, Antalya, 2011:102.

7. Online Article:

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

SUBMISSION TO JOURNAL

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

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

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

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

SUBMISSION CHECKLIST

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

Ensure that the following items are present:

- Cover letter to the editor
  - The category of the manuscript
  - Acknowledgement of "the paper is not under consideration for publication in another journal"
  - Disclosure of any commercial or financial involvement
  - Reviewing the statistical design of the research article
  - Last control for fluent English
- Copyright Transfer Form
- Author Contribution Form
- ICJME Form for Disclosure of Potential Conflicts of Interest
- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000.
- Statement that informed consent was obtained after the procedure(s) had been fully explained.
- Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
- Title page
  - The title of the manuscript both in Turkish and in English
  - All authors and their affiliations
  - All authors' e-mail address, full postal address, GSM phone, business telephone and fax numbers
- Abstracts (400-500 words) Both in Turkish and in English
- Key words: 3 to 10 words (in Turkish and in English)
- Body text
- Acknowledgement
- Reference
- All tables (including title, description, footnotes)

YAZARLARA BİLGİ

Derginin Tanımı

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.

Yazarların Sorumluluğu

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 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

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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 konusunda aşağıdaki kaynağa bakabilirsiniz; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/

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. Yayın etiği konusunda COPE kaynağına bakabilirsiniz. https://publicationethics.org/files/u7141/1999pdf13.pdf

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, Genel Yayın Yönetmeni'ne 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.

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 olarak COPE kaynağına bakabilirsiniz: http://publicationethics.org/files/Peer review guidelines.pdf

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 http://publicationethics.org/resources/flowcharts izlenir.

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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, 1975 Helsinki Deklarasyonu'nun 2004 yılında revize edilen Ethical Principles for Medical Research Involving Human Subjects'e http://www.wma.net/en/30publications/10policies/b3/index.html ve 2006 yılında revize edilen WMA Statement on Animal Use in Biomedical Research'e http://www.wma.net/en/30publications/10policies/a18/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.

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" (www.nap.edu/catalog/5140.html) doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadırlar. Hayvan deneyleri rapor edilirken yazarlar, laboratuvar hayvanlarının bakımı ve kullanımı ile ilgili kurumsal ve ulusal rehberlere uyup uymadıklarını yazılı olarak bildirmek zorundadırlar.

Editör ve yayıncı, reklâm amacı ile dergide yayınlanan ticari ürünlerin özellikleri ve açıklamaları konusunda hiçbir garanti vermemekte ve sorumluluk kabul etmemektedir. Eğer makalede doğrudan veya dolaylı ticarî bağlantı veya çalışma için maddî destek veren kurum mevcut ise yazarlar; kaynak sayfasında, kullanılan ticarî ürün, ilaç, ilaç firması v.b. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar) bildirmek zorundadır. Bağcılar Tıp Bülteni, WAME'nin çıkar çatışması tanımını benimser http://www.wame.org/about/wame-editorial-on-coi

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.

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 Formueklenerek gönderilmelidir. Yazıların alınmasının ardından yazarlara makalenin alındığı, bir makale numarası ile bildirilecektir. Tüm yazışmalarda bu makale numarası kullanılacaktır. Makaleler sayfanın her bir kenarından 2,5 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

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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. 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 http://www.bilimterimleri.com 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 (MedicalSubjectHeadings, 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 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

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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.

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.

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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. 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 sembollerde sadece standart kısaltmalar kullanılmalıdır, 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 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 - http://www.icmje.org/). Makalenin sunulması üzerine, yazarlar deneme/araştırma türünü belirtmeli ve uygun olduğunda aşağıdaki kuralların kontrol listesini sağlamalıdır:

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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.) (Http:// www.prisma-statement.org /),

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.) (http://www. stard-statement.org /),

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STROBE gözlemsel çalışma raporlarında yer alması gereken maddelerin kontrol listesi (http://www.strobe-statement.org /),

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).

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.) (Http://www.care-statement.org /

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.

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Tek tip kurallar esas olarak National Library of Medicine, tarafından uyarlanmış olan bir ANSI standart stilini kabul etmiştir. Kaynak atıfta bulunma örnekleri için yazarlar www.nlm.nih.gov/bsd/uniform_requirements.html sitesine başvurabilirler. Dergi isimleri National Library of Medicine kaynağında yer alan şekilleriyle kısaltılmalıdır.

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MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3(4):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).

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.

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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 2011, 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

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ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):220-228
DOI: 10.4274/BMB.galenos.2021.03.031

The Relationship Between Active and Passive Exposure to Cigarette Smoke and Severe Lumbar Intervertebral Disc Degeneration According to Demographic Data

Demografik Verilere Göre Sigara Dumanına Aktif ve Pasif Maruziyet ile Ciddi Lomber İntervertebral Disk Dejenerasyonu Arasındaki İlişki

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Abstract

Objective: To investigate the effect of current, former and passive smoking status on degeneration of lumbar intervertebral discs.

Method: Three hundred and sixty patients between the ages of 20 and 70 years, who underwent lumbar spinal magnetic resonance imaging, were included in the study. The patients were grouped according to their smoking status as current, former, passive smokers and non-smokers. The cumulative smoking dose for current and former smokers was calculated in terms of pack-years and categorized further into two subgroups: smoked ≤9 pack-years or >9 pack-years. Patients who had been exposed to cigarette smoke for more than one year and more than one hour a day were included in the passive smoker group. The lumbar intervertebral discs were evaluated by the Pfirrmann disc degeneration grading system using sagittal T2-weighted magnetic resonance images. Grades IV and V were considered as "severe disc degeneration".

Results: There was a statistically significant difference between smoking status and gender, age, body mass index and lumbar lordosis angle ($p<0.05$). There was a statistically significant difference between smoking status and the presence of severe disc degeneration at L1-2, L2-3, L5-S1 levels ($p<0.05$). The rate of severe intervertebral disc degeneration was low at L1-2 (15%) and gradually increased at other disc levels (L2-3: 20.3%, L3-4: 28.3%, L4-5: 47.2%, L5- S1: 53.6%). According to multivariate analysis, each unit increase in age was significantly associated with intervertebral disc degeneration at all levels ($p<0.05$). Passive smoking was found to be significantly associated with L2-3 and L3-4 disc degeneration; and >9 pack-years current smoking was found to be significantly associated with L5-S1 disc degeneration ($p<0.05$).

Öz

Amaç: Aktif, eski ve pasif sigara içme durumunun lomber intervertebral disklerin dejenerasyonuna etkisini araştırmaktır.

Yöntem: Çalışmaya lomber spinal manyetik rezonans görüntüleme yapılan 20-70 yaş aralığında olan 360 hasta dahil edildi. Hastalar sigara içme durumlarına göre aktif, eski, pasif içici ve içmeyen olarak gruplandırıldı. Aktif ve eski sigara içenler için kümülatif sigara dozu paket yılı cinsinden hesaplandı ve iki alt gruba ayrıldı: ≤9 paket-yıl veya >9 paket-yıl. Bir yıldan fazla ve günde bir saatten fazla sigara dumanına maruz kalan hastalar pasif içici grubuna dahil edildi. Lomber intervertebral diskler, sagital T2 ağırlıklı manyetik rezonans görüntüleri kullanılarak Pfirrmann disk dejenerasyon derecelendirme sistemi ile değerlendirildi. Grade IV ve V olarak tanımlanan diskler, "ciddi disk dejenerasyonu" olarak kabul edildi.

Bulgular: Sigara içme durumu ile cinsiyet, yaş, vücut kitle indeksi ve lomber lordoz açısı arasında istatistiksel olarak anlamlı bir fark vardı ($p<0,05$). Sigara içme durumu ile L1-2, L2-3, L5-S1 seviyelerinde ciddi disk dejenerasyonu varlığı arasında istatistiksel olarak anlamlı fark vardı ($p<0,05$). Ciddi intervertebral disk dejenerasyonu oranı L1-2'de (%15) düşüktü ve diğer disk seviyelerinde kademeli olarak arttı (L2-3: %20,3, L3-4: %28,3, L4-5: %47,2, L5- S1: %53,6). Çok değişkenli analize göre, yaştaki her bir birim artış tüm seviyelerde intervertebral disk dejenerasyonu ile anlamlı derecede ilişkiliydi ($p<0,05$). Pasif içicilik L2-3 ve L3-4 disk dejenerasyonu ile anlamlı derecede ilişkili bulunurken, >9 paket-yıl aktif sigara içimi L5-S1 disk dejenerasyonu ile anlamlı derecede ilişkili bulundu ($p<0,05$).

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Cite this article as: Bahadır Ülger FE. The Relationship Between Active and Passive Exposure to Cigarette Smoke and Severe Lumbar Intervertebral Disc Degeneration According to Demographic Data. Bagcilar Med Bull 2021;6(3):220-228

Abstract

Conclusion: There is a significant relationship between passive smoking and severe disc degeneration at upper lumbar levels. Also it was thought that quitting smoking could reverse some of the negative effects associated with smoking contributing to disc degeneration.

Keywords: Current smoker, former smoker, intervertebral disc degeneration, magnetic resonance imaging, passive smoker, smoking

Öz

Sonuç: Üst lomber seviyelerde pasif sigara içimi ile ciddi disk dejenerasyonu arasında anlamlı bir ilişki vardır. Ayrıca sigarayı bırakmanın, disk dejenerasyonuna katkıda bulunan bazı sigara ile ilgili olumsuz etkileri tersine çevirebileceği düşünülmüştür.

Anahtar kelimeler: Aktif sigara içen, eski sigara içen, intervertebral disk dejenerasyonu, manyetik rezonans görüntüleme, pasif içicilik, sigara içme

Introduction

Besides normal aging, genetic and environmental factors are important potential determinants of lumbar disc degeneration. The effect and importance of heredity on disc degeneration has been shown in some twin studies (1-3). Acquired factors such as obesity, diabetes mellitus, smoking, physical loading and bone mineral density were found to be associated with disc degeneration in the literature (4). There are also studies investigating the relationship between atherosclerosis and disc degeneration. Disruption of the blood supply due to atherosclerosis contributes to the degeneration process (5-7). The association between lumbar disc degeneration/herniation and cardiovascular risk factors was also investigated by Hangai et al. (4) and Jhawar et al. (8) considering the relationship between atherosclerosis and cardiovascular risk factors.

Smoking causes serious health problems, particularly lung and other cancers, heart disease and respiratory diseases, and is among the most common causes of death worldwide (9,10). These serious consequences of smoking affect not only smokers but also passive smokers (11). Besides these commonly known diseases related to smoking, numerous studies have shown that smoking has detrimental effects on the musculoskeletal system and worsens the prognosis and treatment of leukomotor diseases (12). Experimental studies investigating the association between smoking and disc degeneration have shown that the toxic effect of nicotine, increased degradation of collagen and disc malnutrition caused by decreased blood flow are the most accepted mechanisms explaining the disc degeneration process (12,13).

In the literature, there are clinical (surgical and imaging) and experimental studies examining the effect of smoking status on disc degeneration (13). In some of the imaging studies, smoking was associated with disc degeneration and herniation (14-18), but the others did not find any relation (4,19-21). Only current smoker, former smoker and non-smoker groups were included in these studies. To the best of our knowledge, the effect of passive smoking on intervertebral disc degeneration in humans has not been investigated in previous studies. The aim of the study was to investigate the effect of current, former and passive smoking status on degeneration of lumbar intervertebral discs.

Materials and Methods

This retrospective study was performed by obtaining medical records of patients who underwent lumbar spinal magnetic resonance imaging (MRI) between September 2019 and February 2020. Patients with a history of spinal surgery or instrumentation, spinal fracture, trauma, congenital or acquired spinal deformity tumor or infection and those whose MRI data were unavailable were excluded from the study. After the application of exclusion criteria, 955 patients were determined between the specified dates. These patients were called by phone to be questioned about their smoking status, demographic data (weight and height) and whether they were working in heavy work and whether they were athletes (22). Heavy workers and athletes were also excluded from the study and a total of 360 patients whose smoking status information could be obtained were included in the study. The patients were grouped according to their smoking status which was assessed by self-report using following questions: “Have you ever smoked?”, “Do you currently smoke?”, “Have you been exposed to cigarette smoke from other smokers?”. If a patient answered that he currently smoked, he was classified as “current smoker”. If a patient answered that he had a history of smoking but not smoking currently, he was classified as “former smoker”. If a patient answered that he did not currently smoke, did not have a history of smoking, and was not exposed to smoke, he was classified as “non-smoker”. If a patient never smoked and never had a history of smoking, but exposed to cigarette smoke due to a family member or a colleague to a minimum of one hour every day for more than one year, he was classified as “passive smoker” (11,23,24). The cumulative smoking dose for current and former smokers was calculated in terms of pack-years and categorized

further into two subgroups: smoked ≤9 pack-years or >9 pack-years (25). The number of pack-years was calculated by dividing the number of cigarettes consumed per day by 20 and multiplying by the years that the patient had smoked (19). Age and gender were recorded. Body mass index (BMI) was calculated as weight/(height)^2.

Lumbar spinal MRI was performed using a 1.5 Tesla imaging system (General Electric Healthcare, Milwaukee, WI), using the following settings: amplitude: 44 mT/m; slew rate gradient configuration: 200 T/m/s. MRI images were evaluated using a GE advantage workstation (GE Healthcare, Buc, France) and volume share software v.7.0. The lumbar lordosis angle was measured and the lumbar intervertebral discs were evaluated by the Pfirrmann disc degeneration grading system using sagittal T2-weighted MR images (TR/TE: 2500/85 ms, matrix: 320x224, slice thickness: 4 mm, FOV: 32) (26).

According to the Pfirrmann disc degeneration grading system, the degree of degeneration was classified into five grades. In accordance with the literature, grades IV and V were accepted as severe disc degeneration (4,27). In this classification, grade IV identification is used for discs with inhomogeneous structures, where nucleus and annulus distinction cannot be made, with intermediate to hypointense signal intensity, normal or slightly decreased height. Grade V identification is used for discs with inhomogeneous structures, where nucleus and annulus distinction cannot be made, with hypointense signal intensity, collapsed disc space (Figure 1). We accepted the dependent variable in logistic regression as patients with severe disc degeneration. When evaluating the factors affecting severe disc degeneration, the non-smoker group was considered as a reference and the effect of other smoking status on severe disc degeneration compared to non-smokers was examined.

MRI evaluations were made by the same experienced radiologist who was blinded to the smoking status of the participants. The Institutional Review Board approved the study protocol (24.02.2020-17073117-050.06-E.65) Informed consent for lumbar spinal MRI was obtained from all individual participants included in the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY, USA). Frequency and percentage for discrete data, mean ± standard deviation and median for continuous data were given as descriptive values. The ''ANOVA test'' was used for comparing the means between the groups and comparing the means of more than two groups. The ''Logistic Regression Analysis'' was used to evaluate the severe disc degeneration at each lumbar level. Results were considered statistically significant when p-value was less than 0.05.

Results

The mean age of the participants was 47.17±12.65 years (range: 20-70 years). Among the 360 participants, 134 were male (37.2%) and 226 were female (62.8%). The mean BMI of the participants was 27.40±4.92 kg/m^2 (range: 15.9-47.8 kg/m^2), and the mean lordosis angle of the participants was 42.69±12.90° (range: 9.8-82.5°). The rate of severe intervertebral disc degeneration was 15% at L1-2, 20.3% at L2-3, 28.3% at L3-4, 47.2% at L4-5, and 53.6% at L5-S1 disc level (Table 1).

Distributions of demographic variables according to smoking status are given in Table 2. There was a statistically significant difference between smoking status and gender, age, BMI and lumbar lordosis angle (p<0.05). The vast majority of passive smokers were women, and former smokers had the highest values in terms of age and BMI.

Distributions of severe disc degeneration at lumbar intervertebral disc levels according to smoking status

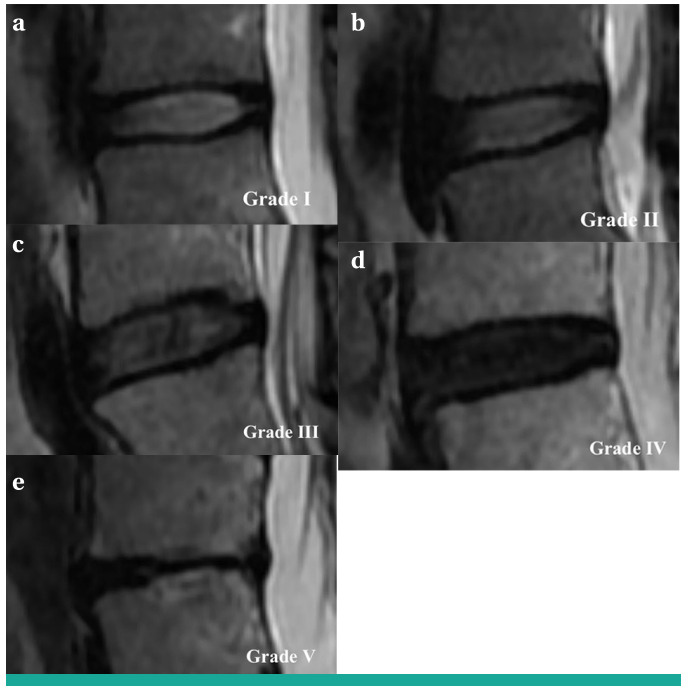

Figure 1. T2-weighted sagittal MR images of the lumbar intervertebral discs graded according to the Pfirrmann's classification (a-e). Grades IV and V were considered as "severe disc degeneration"

MR: Magnetic resonance

are given in Table 3. There was a statistically significant difference between smoking status and the presence of severe disc degeneration at L1-2, L2-3, L5-S1 levels (p<0.05). It was determined that severe disc degeneration at the L1-2 level was mostly in the passive and >9 pack/year former smoker groups. At the L2-3 level, severe disc degeneration was found mostly in the passive smoker group. At the L5-S1 level, the most severe disc degeneration was detected in the >9 pack/year current smoker group. There was no statistically significant difference between smoking status and the presence of severe disc degeneration at L3-4, L4-5 levels.

Table 1. Characteristics of participants

	Total			By category	
Variables	**N**	**Mean**	**SD**	**N**	**%**
Age	360	47.17	12.646	-	-
BMI	360	27.40	4.924	-	-
Gender	360	-	-	-	-
Male	-	-	-	134	37.2
Female	-	-	-	226	62.8
Smoking status	360	-	-		
Current smoker ≤9 pack/year	-	-	-	49	13.6
Current smoker >9 pack/year	-	-	-	79	21.9
Passive smoker	-	-	-	77	21.4
Non-smoker	-	-	-	96	26.7
Former smoker ≤9 pack/year	-	-	-	25	6.9
Former smoker >9 pack/year	-	-	-	34	9.4
Lordosis angle	360	42.69	12.897	-	-
L1-2	360	2.03	1.16	-	-
Severe disc degeneration (grade 4-5)	-	-	-	54	15
L2-3	360	2.26	1.244	-	-
Severe disc degeneration (grade 4-5)	-	-	-	73	20.3
L3-4	360	2.57	1.28	-	-
Severe disc degeneration (grade 4-5)	-	-	-	102	28.3
L4-5	360	3.14	1.234	-	-
Severe disc degeneration (grade 4-5)	-	-	-	170	47.2
L5-S1	360	3.34	1.325	-	-
Severe disc degeneration (grade 4-5)	-	-	-	193	53.6

BMI: Body mass index, SD: Standard deviation

The results of univariate and multivariate analysis examining the relationship between demographic data and smoking status in terms of severe lumbar disc degeneration are given in Table 4 and 5. In univariate analysis, age, BMI and >9 pack/year former smokers were found statistically significant in terms of disc degeneration at L1-2 and L4-5 disc levels; age, BMI, lordosis angle and passive smokers were found statistically significant in terms of disc degeneration at L2-3 and L3-4 disc levels; age, lordosis angle, >9 pack/year current smokers, ≤9 pack/year former smokers, and >9 pack/year former smokers were found statistically significant in terms of disc degeneration at L5-S1 disc level (p<0.05). For example, at L1-2 disc level for every 1 year increase in age, L1-2 disc degeneration increased 1.15 times, for every 1 unit change in BMI L1-2 disc degeneration increased 1.10 times, and former smokers had L1-2 disc degeneration 5.16 times more than non-smokers (Table 4).

According to multivariate analysis, age, and BMI were found statistically significant in terms of disc degeneration at L1-2 and L4-5 disc levels; age, and passive smokers were found statistically significant in terms of disc degeneration at L2-3 disc levels; age, BMI and passive smokers were found statistically significant in terms of disc degeneration at L3-4 disc levels; age, lordosis angle, and >9 pack/year current smokers were found statistically significant in terms of disc degeneration at L5-S1 disc levels (p<0.05). For instance, at L1-2 disc level for every 1 year increase in age, L1-2 disc degeneration increased 1.16 times, for every 1 unit change in BMI L1-2 disc degeneration increased 1.07 times. According to multivariate analysis gender, ≤9 pack/year current smoker, ≤9 pack/year former smoker and >9 pack/year former smoker were not associated with disc degeneration at any level (Table 5).

Discussion

In the present study, the rate of severe intervertebral disc degeneration was low at L1-2 (15%), and increased gradually at more inferior intervertebral disc levels (L2-3: 20.3%, L3-4: 28.3%, L4-5: 47.2%, L5-S1: 53.6%) (Table 1). The vast majority of passive smokers were women, and former smokers had the highest values in terms of age and BMI. According to multivariate analysis, each unit increase in age was significantly associated with intervertebral disc degeneration at all levels (p<0.05). Passive smoking was found to be significantly associated with L2-3 and L3-4 disc degeneration, and >9 pack-years current smoking was found to be significantly associated with L5-S1 disc degeneration (p<0.05) (Table 5).

Table 2. Distribution of demographic variables according to smoking status

	Smoking status							p
	Passive	Current ≤9 pack/year	Current >9 pack/year	Former smoker ≤9 pack/year	Former smoker >9 pack/year	Non-smoker	Total	
N (%)	77 (21.4)	49 (13.6)	79 (21.9)	25 (6.9)	34 (9.4)	96 (26.7)	360 (100)	
Females, n (%)	64 (83.1)	33 (67.3)	35 (44.3)	17 (68.0)	9 (26.5)	68 (70.8)	226 (62.8)	**<0.0001***
Age (years), mean ± SD	47.0±13.0	39.0±11.9	46.0±11.2	49.0±14.2	57.0±8.6	48.0±12.2	47.0±12.6	**<0.0001****
BMI (kg m^{-2}), mean ± SD	28.0±5.1	25.9±4.7	26.2±4.1	28.9±4.9	29.0±4.5	27.7±5.3	27.4±4.9	**0.003****
LLA (°), mean ± SD	42.5±13.6	42.3±13.6	39.8±12.5	39.3±12.9	44.9±12.6	45.5±11.8	42.7±12.9	**0.044****

BMI: Body mass index, LLA: Lumbar lordosis angle, SD: Standard deviation, *chi-square test, **ANOVA test

Table 3. Distribution of severe disc degeneration at lumbar intervertebral disc levels according to smoking status

	Smoking status							p*
Severe disc degeneration at lumbar disc levels	**Passive**	**Current ≤9 pack/year**	**Current >9 pack/year**	**Former smoker ≤9 pack/year**	**Former smoker >9 pack/year**	**Non- smoker**	**Total**	
P L1-2, n (%)	12 (22.2)	5 (9.3)	11 (20.4)	3 (5.6)	12 (22.2)	11 (20.4)	54 (100)	**0.023**
P L2-3, n (%)	24 (32.9)	5 (6.8)	12 (16.4)	6 (8.2)	10 (13.7)	16 (21.9)	73 (100)	**0.026**
P L3-4, n (%)	30 (29.4)	10 (9.8)	18 (17.6)	9 (8.8)	13 (12.7)	22 (21.6)	102 (100)	0.057
P L4-5, n (%)	42 (24.7)	21 (12.4)	35 (20.6)	14 (8.2)	20 (11.8)	38 (22.4)	170 (100)	0.209
P L5-S1, n (%)	40 (20.7)	23 (11.9)	51 (26.4)	16 (8.3)	22 (11.4)	41 (21.2)	193 (100)	**0.033**

P Pfirrmann grade, *chi-square test

Considering the socioeconomic burden caused by low back pain due to intervertebral disc degeneration in societies, it can be understood that a great interest was paid on the investigation of the factors in the etiology of disc degeneration (28). Various factors such as age, mechanical factors, genetics, nutrition, metabolic disorders, infection, and toxic factors like nicotine have been found to have detrimental effects on intervertebral discs (22).

In addition to the negative effects of smoking on the lung and cardiovascular system, the harmful effects of smoking on the musculoskeletal system have also been the subject of research (12,23). Studies on this issue have shown that smoking delays fracture healing, decreases bone mineral density, increases fracture risk, and causes bone graft non-union in spinal fusion surgeries (29). Another area of interest in this subject is the effect of smoking on intervertebral disc degeneration. Disc malnutrition, caused by both tobacco-induced anoxia and vascular disease and the direct effects of chemical substances on disc cell viability are the most accepted mechanisms that explain smoking related disc degeneration (13,28). In addition, chronic cough, which is common in smokers, can cause an increase in intradiscal pressure and mechanically induce degeneration negatively (30).

In the literature, there are studies showing the negative effect of smoking on lumbar disc degeneration, as well as others with different results. Battié et al. (14) found that smokers had 18% greater mean disc degeneration scores in the lumbar spine compared to non-smokers in a population consisting of identical twins. Jakoi et al. (28) reported a strong correlation between lumbar disc degenerative disease and tobacco use. They found a nearly 6-fold increase in the prevalence of smokers' lumbar disc degenerative disease compared to non-smokers. In a systematic review, Huang et al. (31) reported that current smokers showed a higher risk of developing lumbar disc herniation than former smokers and both male and female smokers had a similar risk of lumbar disc herniation. Schumann et al. (32) concluded that smoking 20-40 pack/years significantly increased the rate of lumbar disc herniation in men and smoking 8-20 packs/year increased the risk of lumbar disc herniation in women. Livshits et al. (15) found that smoking showed statistically significant relationships with risk of disc herniation. On the other hand, there have been studies that found opposing results. Hangai et al. (4) could not find a correlation between smoking and disc degeneration in their study. However, they thought that this might be due to the insufficient number of patients who actively smoked (4). Kuisma et al. (19) reported that smoking was not significantly associated

Table 4. Univariate analysis for severe disc degeneration at lumbar intervertebral disc levels

Univariate analysis*	P L1-2		P L2-3		P L3-4		P L4-5		P L5-S1	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	**1.15 (1.10-1.19)**	**<0.0001**	**1.15 (1.11-1.19)**	**<0.0001**	**1.12 (1.09-1.15)**	**<0.0001**	**1.08 (1.06-1.10)**	**<0.0001**	**1.07 (1.05-1.09)**	**<0.0001**
Female	1.01 (0.55-1.84)	0.976	1.75 (0.99-3.07)	0.054	1.34 (0.83-2.18)	0.230	1.42 (0.92-2.18)	0.113	1.11 (0.72-1.70)	0.637
BMI	**1.10 (1.04-1.16)**	**0.001**	**1.08 (1.03-1.14)**	**0.003**	**1.15 (1.09-1.21)**	**<0.0001**	**1.12 (1.06-1.17)**	**<0.0001**	1.02 (0.97-1.06)	0.368
LLA	1.02 (1.00-1.04)	0.116	**1.02 (1.00-1.04)**	**0.027**	**1.02 (1.0-1.04)**	**0.024**	1.01 (0.99-1.03)	0.140	**1.02 (1.01-1.04)**	**0.005**
Smoking status										
Non-smoker	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
Current ≤9	1.30 (0.38-4.22)	0.719	1.68 (0.58-4.90)	0.343	1.16 (0.49-2.83)	0.707	1.13 (0.56-2.29)	0.734	1.04 (0.51-2.10)	0.920
Current >9	1.21 (0.48-3.07)	0.687	1.15 (0.51-2.60)	0.737	1.02 (0.50-2.08)	0.956	1.16 (0.64-2.12)	0.625	**2.80 (1.51-5.18)**	**0.001**
Passive	1.93 (0.81-4.56)	0.136	**2.07 (1.01-4.24)**	**0.047**	**2.41 (1.25-4.63)**	**0.009**	1.68 (0.93-3.05)	0.087	1.54 (0.85-2.80)	0.152
Former ≤9	1.36 (0.34-5.41)	0.665	1.88 (0.64-5.53)	0.254	2.47 (0.93-6.58)	0.070	1.83 (0.72-4.66)	0.204	**3.00 (1.12-8.03)**	**0.029**
Former >9	**5.16 (1.96-13.61)**	**0.001**	2.27 (0.91-5.70)	0.080	2.14 (0.90-5.08)	0.084	**3.36 (1.43-7.87)**	**0.005**	**2.67 (1.16-6.16)**	**0.021**

BMI: Body mass index, LLA: Lumbar lordosis angle, P Pfirrman grade, *Logistic Regression Analysis, CI: Confidence interval, OR: Odds ratio

Table 5. Multivariate analysis for severe disc degeneration at lumbar intervertebral disc levels

Multivariate analysis*	P L1-2		P L2-3		P L3-4		P L4-5		P L5-S1	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	**1.16 (1.10-1.20)**	**<0.0001**	**1.17 (1.12-1.21)**	**<0.0001**	**1.13 (1.09-1.16)**	**<0.0001**	**1.08 (1.06-1.10)**	**<0.0001**	**1.09 (1.07-1.12)**	**<0.0001**
Female	1.16 (0.50-2.21)	0.704	2.14 (1.08-4.62)	0.043	1.12 (0.65-2.30)	0.719	1.55 (0.92-2.62)	0.099	1.40 (0.82-2.39)	0.219
BMI	**1.07 (0.99-1.14)**	**0.049**	1.03 (0.96-1.09)	0.454	**1.13 (1.05-1.19)**	**<0.0001**	**1.07 (1.02-1.13)**	**0.009**	1.02 (0.97-1.08)	0.481
LLA	1.01 (0.98-1.04)	0.613	1.01 (0.98-1.03)	0.656	1.01 (0.98-1.03)	0.813	1.01 (0.99-1.03)	0.504	**1.04 (1.03-1.07)**	**<0.0001**
Smoking status										
Non-smoker	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
Current ≤9	3.17 (0.75-13.51)	0.118	2.13 (0.55-8.22)	0.275	3.42 (1.15-10.14)	0.127	2.74 (1.19-6.29)	0.118	2.08 (0.89-4.83)	0.090
Current >9	2.19 (0.73-6.55)	0.163	1.45 (0.54-3.91)	0.463	1.87 (0.79-4.46)	0.156	1.65 (0.83-3.27)	0.154	**3.24 (1.59-6.57)**	**0.001**
Passive	2.35 (0.88-6.27)	0.088	**2.82 (1.17-6.80)**	**0.021**	**3.42 (1.53-7.67)**	**0.003**	1.81 (0.92-3.55)	0.087	1.54 (0.79-3.01)	0.210
Former ≤9	1.09 (0.23-5.24)	0.910	1.48 (0.40-5.59)	0.558	2.54 (0.74-8.70)	0.137	1.58 (0.55-4.51)	0.394	2.52 (0.86-7.41)	0.093
Former >9	3.01 (0.97-9.37)	0.057	1.33 (0.45-3.97)	0.605	1.01 (0.36-2.80)	0.982	2.13 (0.83-5.47)	0.115	1.46 (0.58-3.68)	0.423

BMI: Body mass index, LLA: Lumbar lordosis angle, P Pfirrman grade, *Logistic Regression Analysis, CI: Confidence interval, OR: Odds ratio

with severe disc degeneration in a population consisting of middle-aged male workers. Kanayama et al. (20) concluded that smoking status was not a significant risk factor for the prevalence of disc degeneration and herniation. Schistad et al. (33) found that smoking status had no significant impact on 5-year disc degeneration development.

As mentioned above, numerous studies in the literature have found results that current smokers and former smokers have increased the risk of intervertebral disc degeneration. The effect of passive smoking, another subgroup in terms of exposure to smoking, on disc degeneration has been investigated in experimental studies using animal models (34-36). However, as far as we know, there is no study investigating the relationship between passive smoking and intervertebral disc degeneration in humans.

Passive smoking poses a considerable risk of associated diseases compared to active smokers, and the serious consequences of smoking affect not only smokers but also passive smokers (37,38). Smoking is blamed for an estimated 480,320 deaths per year in the United States, of which 41.280 are due to lung cancer and coronary heart disease in individuals exposed to passive smoking (39). Considering the systemic proposed mechanisms of smoking on disc degeneration, the relationship between passive smoking and lumbar disc degeneration was also aimed to be investigated in this study.

Mechanical stress due to physical loading is expected to cause degeneration at lower lumbar levels (14). Since the effect of smoking is systemic, as previously described, it may cause higher degeneration grades in the upper and/or lower lumbar levels. Saberi et al. (17) found that after eliminating the effect of other factors, cigarette smoking was associated with nucleus pulposus dislodgement only in upper lumbar levels (p=0.038). According to the results of this study, the significant relationship between disc degeneration at the upper (L2-3 and L3-4) lumbar levels and passive smoking suggests that passive smoking may cause more degeneration in the upper lumbar levels than mechanical stress.

Another remarkable topic from the results of the studies in the literature is whether there is a change in the degeneration findings after quitting smoking. In a review by Huang et al. (31), it was found that current smokers had a higher risk of developing lumbar disc herniation compared to former smokers. In an experimental study, Nemoto et al. (34) found that intervertebral disc degeneration due to smoking could be repaired to some extent after quitting smoking. While investigating the relationship between smoking and surgical disc disease in their study, An et al. (40) stated that smoking cessation might have beneficial effects since there was no significant difference between former smokers and non-smokers. One of the results of the large-scale study by Knuttson et al. (41) was that quitting smoking reduced surgery. In the present study, when the current smokers and former smokers were compared in terms of severe disc degeneration, although current smoker's age and BMI were lower, >9 pack/year current smokers were found statistically significant in terms of disc degeneration at L5-S1 disc levels according to multivariate analysis. This result is thought to be a supportive finding that some of the negative effects of smoking may be reversed after quitting smoking.

Study Limitations

The present study has some limitations. Although those who did heavy physical work and athletes were excluded from the study, one of the limitations was that the subjects were not evaluated in terms of other risk factors that might cause lumbar disc degeneration, such as family history, daily physical activity and habits (long-term sitting, poor posture, alcohol use, etc.), diabetes and cardiovascular diseases, and musculoskeletal system diseases that increased the burden on the lumbar region. However, this was a retrospective study and it was not possible to retrospectively collect accurate information about the patient's daily activities and habits of previous days and other risk factors. Self-reporting on smoking status and smoking exposure may have led to misclassification of patients. However, self-questionnaire has been used in studies on this subject in the literature. Studies that are confident about the amount of exposure to smoking may only be available in experimental studies with animal models or in prospective studies.

Conclusion

Breathing cigarette smoke can systemically affect many organs/parts of the body negatively regardless of active smoking. Based on the significant relationship found between passive smoking and intervertebral disc degeneration at upper lumbar levels, which are less affected by mechanical factors, it has been considered as a finding supporting that cigarette smoke exposure may have an effect on disc degeneration. The study supports the view that some negative effects on disc degeneration may be reversible after smoking cessation. The longer we stay away from smoking or its smoke, the more we keep a preventable risk factor for disc degeneration away from our lives.

Acknowledgments

The author acknowledges Cem Sener for his support on statistical analysis.

Ethics

Ethics Committee Approval: The Institutional Review Board of Fatih Sultan Mehmet Training and Research Hospital, İstanbul, approved the study protocol on February 24, 2020.

Informed Consent: Informed consent for lumbar spinal MRI was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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

References

1. Battie MC, Videman T, Parent E. Lumbar disc degeneration: epidemiology and genetic influences. Spine 2004;29(23):2679-2690.
2. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. Spine 1995;20(24):2601-2612.
3. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. Arthritis Rheum 1999;42(2):366-372.
4. Hangai M, Kaneoka K, Kuno S, Hinotsu S, Sakane M, Mamizuka N, et al. Factors associated with lumbar intervertebral disc degeneration in the elderly. Spine J 2008;8(5):732-740.
5. Kauppila LI, McAlindon T, Evans S, Wilson PW, Kiel D, Felson DT. Disc degeneration/back pain and calcification of the abdominal aorta. A 25-year follow-up study in Framingham. Spine 1997;22:1642-1647; discussion 1648-1649.
6. Kauppila LI, Penttila A, Karhunen PJ, Lalu K, Hannikainen P. Lumbar disc degeneration and atherosclerosis of the abdominal aorta. Spine 1994;19(8):923-929.
7. Kurunlahti M, Kerttula L, Jauhiainen J, Karppinen J, Tervonen O. Correlation of diffusion in lumbar intervertebral disks with occlusion of lumbar arteries: a study in adult volunteers. Radiology 2001;221(3):779-786.
8. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Cardiovascular risk factors for physician-diagnosed lumbar disc herniation. Spine J 2006;6(6):684-691.
9. Elmasry S, Asfour S, de Rivero Vaccari JP, Travascio F. Effects of tobacco smoking on the degeneration of the intervertebral disc: a finite element study. PLoS One 2015;10(8):e0136137. doi:10.1371/journal.pone.0136137
10. WHO Report on the Global Tobacco Epidemic, 2017 external icon. Geneva: World Health Organization, 2017 Last Accessed Date: 31.01.2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/255874/9789241512824-eng.pdf?sequence=1
11. Nondahl DM, Cruickshanks KJ, Schubert CR. A questionnaire for assessing environmental tobacco smoke exposure. Environ Res 2005;97(1):76-82.
12. Abate M, Vanni D, Pantalone A, Salini V. Cigarette smoking and musculoskeletal disorders. Muscles Ligaments Tendons J 2013;3(2):63-69.
13. Jackson AR, Dhawale AA, Brown MD. Association between ıntervertebral disc degeneration and cigarette smoking: clinical and experimental findings. JBJS Rev 2015;3(3):01874474-201503030-00002. doi: 10.2106/JBJS.RVW.N.00057.
14. Battié MC, Videman T, Gill K, Moneta GB, Nyman R, Kaprio J, et al. 1991 Volvo Award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: an MRI study of identical twins. Spine (Phila Pa 1976) 1991;16(9):1015-1021.
15. Livshits G, Cohen Z, Higla O, Yakovenko K. Familial history, age and smoking are important risk factors for disc degeneration disease in Arabic pedigrees. Eur J Epidemiol 2001;17(7):643-651.
16. Videman T, Battié MC, Parent E, Gibbons LE, Vainio P, Kaprio J. Progression and determinants of quantitative magnetic resonance imaging measures of lumbar disc degeneration: a five-year follow-up of adult male monozygotic twins. Spine (Phila Pa 1976) 2008;33(13):1484-1490.
17. Saberi H, Rahimi L, Jahani L. A comparative MRI study of upper and lower lumbar motion segments in patients with low back pain. J Spinal Disord Tech 2009;22(7):507-510.
18. Matsumoto M, Okada E, Ichihara D, Watanabe K, Chiba K, Toyama Y, et al. Age-related changes of thoracic and cervical intervertebral discs in asymptomatic subjects. Spine (Phila Pa 1976) 2010;35(14):1359-1364.
19. Kuisma M, Karppinen J, Haapea M, Niinimäki J, Ojala R, Heliövaara M, et al. Are the determinants of vertebral endplate changes and severe disc degeneration in the lumbar spine the same? A magnetic resonance imaging study in middle-aged male workers. BMC Musculoskelet Disord 2008;9:51.
20. Kanayama M, Togawa D, Takahashi C, Terai T, Hashimoto T. Cross-sectional magnetic resonance imaging study of lumbar disc degeneration in 200 healthy individuals. J Neurosurg Spine 2009;11(4):501-507.
21. Okada E, Matsumoto M, Ichihara D, Chiba K, Toyama Y, Fujiwara H, et al. Aging of the cervical spine in healthy volunteers: a 10-year longitudinal magnetic resonance imaging study. Spine (Phila Pa 1976) 2009;34(7):706-712.
22. Sharma MK, Petrukhina E. Strong association of smoking with lumbar degenerative spine disease. Open Neurosurg J 2013;6:6-12.
23. Jhee JH, Joo YS, Kee YK, Jung SY, Park S, Yoon CY, et al. Secondhand Smoke and CKD. Clin J Am Soc Nephrol 2019;14(4):515-522.
24. Abrahamsen R, Fell AK, Svendsen MV, Andersson E, Torén K, Henneberger PK, et al. Association of respiratory symptoms and asthma with occupational exposures: findings from a population-based cross-sectional survey in Telemark, Norway. BMJ Open 2017;7(3):e014018. doi: 10.1136/bmjopen-2016-014018.
25. Kaila-Kangas L, Leino-Arjas P, Riihimäki H, Luukkonen R, Kirjonen J. Smoking and overweight as predictors of hospitalization for back disorders. Spine (Phila Pa 1976) 2003;28(16):1860-1868.
26. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976) 2001;26(17):1873-1878.

27. Teichtahl AJ, Urquhart DM, Wang Y, Wluka AE, O'Sullivan R, Jones G, et al. Lumbar disc degeneration is associated with modic change and high paraspinal fat content - a 3.0T magnetic resonance imaging study. BMC Musculoskelet Disord 2016;17(1):439.

28. Jakoi AM, Pannu G, D'Oro A, Buser Z, Pham MH, Patel NN, et al. The Clinical Correlations between Diabetes, Cigarette Smoking and Obesity on Intervertebral Degenerative Disc Disease of the Lumbar Spine. Asian Spine J 2017;11(3):337-347.

29. Sloan A, Hussain I, Maqsood M, Eremin O, El-Sheemy M. The effects of smoking on fracture healing. Surgeon 2010;8(2):111-116.

30. Frymoyer JW, Pope MH, Costanza MC, Rosen JC, Goggin JE, Wilder DG. Epidemiologic studies of low-back pain. Spine 1980;5:419-423.

31. Huang W, Qian Y, Zheng K, Yu L, Yu X. Is smoking a risk factor for lumbar disc herniation? Eur Spine J 2016;25:168-176.

32. Schumann B, Bolm-Audorff U, Bergmann A, Ellegast R, Elsner G, Grifka J, et al. Lifestyle factors and lumbar disc disease: results of a German multi-center case-control study (EPILIFT). Arthritis Res Ther 2010;12(5):R193. doi:10.1186/ar3164

33. Schistad EI, Bjorland S, Røe C, Gjerstad J, Vetti N, Myhre K, et al. Five-year development of lumbar disc degeneration-a prospective study. Skeletal Radiol 2019;48(6):871-879.

34. Nemoto Y, Matsuzaki H, Tokuhasi Y, Okawa A, Uematu Y, Nishimura T, et al. Histological changes in intervertebral discs after smoking and cessation: experimental study using a rat passive smoking model. J Orthop Sci 2006;11(2):191-197.

35. Nakahashi M, Esumi M, Tokuhashi Y. Detection of apoptosis and matrical degeneration within the intervertebral discs of rats due to passive cigarette smoking. PLoS One 2019;14(8):e0218298. doi:10.1371/journal.pone.0218298

36. Iwahashi M, Matsuzaki H, Tokuhashi Y, Wakabayashi K, Uematsu Y. Mechanism of intervertebral disc degeneration caused by nicotine in rabbits to explicate intervertebral disc disorders caused by smoking. Spine (Phila Pa 1976) 2002;27(13):1396-1401.

37. WHO global report on trends in tobacco smoking 2000-2025 - 1st edition. Available from: https://www.who.int/quantifying_ehimpacts/publications/SHS.pdf

38. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke nearly as large as smoking. Circulation 2005;111(20):2684-2698.

39. Reed RM, Dransfield MT, Eberlein M, Miller M, Netzer G, Pavlovich M, et al. Gender differences in first and secondhand smoke exposure, spirometric lung function and cardiometabolic health in the old order Amish: a novel population without female smoking. PLoS One 2017;12(3):e0174354. doi: 10.1371/journal.pone.0174354.

40. An HS, Silveri CP, Simpson JM, File P, Simmons C, Simeone FA, et al. Comparison of smoking habits between patients with surgically confirmed herniated lumbar and cervical disc disease and controls. J Spinal Disord 1994;7(5):369-373.

41. Knutsson B, Mukka S, Wahlström J, Järvholm B, Sayed-Noor AS. The association between tobacco smoking and surgical intervention for lumbar spinal stenosis: cohort study of 331,941 workers. Spine J 2018;18(8):1313-1317.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):229-233
DOI: 10.4274/BMB.galenos.2021.03.035

How Does Falling Relate to Fatigue, Fear of Falling, Mood and Quality of Life in Pregnancy?

Gebelerde Düşme ile Yorgunluk, Düşme Korkusu, Duygu Durumu ve Yaşam Kalitesi Arasındaki İlişki

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Abstract

Objective: There are many studies on the impact of physical changes on pregnancy falls. We conducted this study to investigate the effects of mental changes as well as physical changes on pregnancy fall. Therefore, we evaluated how people who fell during pregnancy were related to fatigue, fear of falling, mood and health-related quality of life.

Method: Pregnant women were divided into 2 groups as those who falled (group 1) and those who did not (group 2). Pregnant women in both groups were tested to stand on one leg, and the following forms were filled: fatigue severity scale (FSS), Beck depression inventory (BDI), falls efficacy scale international (FES), and Nottingham health profile (NHP). The groups were compared based on the data obtained.

Results: FSS (group 1: 4.9±1.6, group 2: 4.0±1.8, p=0.002), BDI (gsroup 1: 23.9±12.5, group 2: 10.8±7.3, p<0.001), FES (group 1: 39.5±10.5, group 2: 26.6±6.6, p<0.001), and NHP (group 1: 321.9±123.1, group 2: 189.4±96.1 p<0.001) were found to be significantly higher in group 1. FES was positively correlated with FSS, BDI and NHP, and significantly negatively correlated with the test of standing on one leg. The test of standing on one leg was negatively correlated with FES, FSS, BDI and NHP.

Conclusion: This study shows that mental changes as well as physical changes can have an impact on falls and balance in pregnant women.

Keywords: Depression, fall, fatigue, pregnancy, quality of life

Öz

Amaç: Fiziksel değişikliklerin hamilelik düşmeleri üzerindeki etkisi üzerine pek çok çalışma bulunmaktadır. Bu çalışma fiziksel değişikliklerin yanı sıra zihinsel değişikliklerin de gebelikte düşme üzerindeki etkilerini araştırmak için yapıldı. Bu amaçla hamilelik sırasında düşen kişilerin yorgunluk, düşme korkusu, ruh hali ve sağlıkla ilişkili yaşam kalitesi ile nasıl ilişkili olduğunu değerlendirdik.

Yöntem: Gebe kadınlar düşenler (grup 1) ve düşmeyenler (grup 2) olarak iki gruba ayrıldı. Her iki gruptaki gebelere tek ayak üzerinde durma testi yapılarak ve yorgunluk şiddet ölçeği (FSS), Beck depresyon envanteri (BDE), uluslararası düşme etkinlik ölçeği (FES), Nottingham sağlık profile (NSP) formları dolduruldu. Elde edilen veriler gruplar arasında karşılaştırıldı.

Bulgular: FSS (grup 1: 4,9±1,6, grup 2: 4,0±1,8, p=0,002), BDE (grup 1: 23,9±12,5, grup 2: 10,8±7,3, p<0,001), FES (grup 1: 39,5±10,5, grup 2: 26,6±6,6, p<0,001), NSP (grup 1: 321,9±123,1, grup 2: 189,4±96,1, p<0,001) skorları grup 1'de anlamlı yüksek bulundu. Korelasyon analizinde FES ile, FSS, BDE ve NSP arasında pozitif yönde ve tek ayakta durma testi arasında negatif yönde anlamlı ilişki vardı. Tek ayak üstünde durma testi ile FES, FSS, BDE ve NSP arasındaki negatif yönde ilişki anlamlı idi.

Sonuç: Bu çalışma, fiziksel değişikliklerin yanı sıra zihinsel değişikliklerin hamile kadınlarda düşme ve denge üzerinde etkili olabileceğini göstermektedir.

Anahtar kelimeler: Depresyon, düşme, gebelik, yaşam kalitesi yorgunluk

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Cite this article as: Can İ, Keyif B. How Does Falling Relate to Fatigue, Fear of Falling, Mood and Quality of Life in Pregnancy? Bagcilar Med Bull 2021;6(3):229-233

Introduction

Adaptive changes occur in the musculoskeletal system as well as in many tissues and organs during pregnancy, depending on the increasing metabolic needs of the fetus and mother. Increased weight of the fetus and its posture cause excessive loading of the lumbar spine and abdominal muscles. This changes the body's center of gravity, resulting in an increase in the posterior direction of the position of the pregnant woman's head, anterior pelvic tilting and lumbar lordosis (1,2). In addition to changes in posture, weight gain, memory difficulties and concentration problems, increased laxity in ligaments, swelling in the hands and feet, reduced neuromuscular control, and changes in body biomechanics due to adaptations in soft tissues and joints may affect the balance in pregnant women and cause them to fall (3). Studies have reported that about 25-26% of pregnant women fall at least once during pregnancy, and this happens most frequently in the third trimester (4,5). Pregnant women have a higher risk of falling and injury than non-pregnant women. Falling during pregnancy has a broad spectrum of effects ranging from simple results such as joint sprains and muscle injuries to bone fractures, head traumas, visceral organs ruptures, internal bleeding, premature birth, sudden placental and uterine ruptures, early rupture of membranes, and maternal and fetal death (1,2).

There may be changes in physical and mental health that can reduce the quality of life in pregnant women. Pregnant women may experience hormonal changes triggering symptoms of nausea and vomiting, sleep disturbances, anxiety, depression, low energy and fatigue (6). Such situations can act as a trigger for falls by affecting the sensory motor organization needed for the postural balance (7).

In our study, we aimed to assess how falling was related to fatigue, fear of falling, mood and health-related quality of life of people falling during pregnancy.

Materials and Methods

After the approval of the local ethics committee (ethics committee no: 2019/01), 130 pregnant women who presented to the gynecology outpatient clinic between February and June 2019 were included in our study.

The study included 18-45-year-old women pregnant with a single baby in the third trimester, who did not have a risky pregnancy or any neurological conditions that had an effect on balance. Those who had fallen at least once during their pregnancy were assigned into the first group and those who had never fallen into the second group. Pregnant women who had not fallen in the second group were followed until the end of pregnancy, and 2 people who fell during the study were assigned into the group of people who had fallen. The study was concluded with 67 patients in group 1 and 63 patients in group 2.

All pregnant women were tested for standing on one leg (8). The fatigue severity scale (FSS) was filled to assess the level of fatigue, the Beck depression inventory (BDI) to assess mood, the falls efficacy scale (FES) to assess the fear of falling, and the Nottingham health profile (NHP) to assess the quality of life, all of which had been tested for validity and reliability in Turkish (9-12).

Test of standing on one leg: This is a test that assesses the balance and risk of falling of patients. Patients are told to maintain their balance by standing up while lifting one leg up, keeping their hip in neutral position and their knee at 90-degree flexion. The upper limit in the test is accepted to be 30 seconds, and the test is terminated for of pregnant women who complete this period. Those who complete the test under 10 seconds have balance disorder, and those who complete the test in less than 5 seconds are at risk of falling.

FSS: This is a scale that measures people's level of fatigue. People specify how much they consent to each item by choosing a number from 1 to 7. The score range of the scale consisting of a total of 9 questions is from 9 to 63. A score of 36 or higher shows severe fatigue (9).

BDI: The BDI is made up of 21 questions. Each question is scored between 0 and 3. A score of 21 or higher is considered as a diagnosis of clinical depression (10).

FES: This is a test consisting of 16 questions that measure people's fear of falling. People are asked how safe they feel when performing simple daily living activities and are asked to mark it on paper from 1 to 10 (1 is completely unsafe, 10 is extremely safe). A score between 0 and 100 in total is obtained to assess their fear of falling (11).

NHP: This is a general health survey of 38 items that assess the quality of life. Six sub-parameters made up of energy level, emotional reactions, physical activity (PA9, pain, sleep and social isolation and total points are assessed. The answers to the questions are marked as "yes" or "no." The total score ranges from 0 to 600, and a high health-related quality of life perception is inversely proportional to the score obtained (12).

The specified tests and scales were administered to both groups, and the groups were compared based on the data obtained.

Statistical Analysis

SPSS (Statistical Package for Social Science) program version 22.0.0 was used for statistical analysis. Confidence interval was accepted as 95%. The normality of the data was analyzed using the Kolmogorov-Smirnov test. The Levene's test was used to determine the homogeneity and equality of variances. The Student's t-test and the Mann-Whitney U test were used when comparing the groups in terms of quantitative data. The Pearson's chi-square test was used when comparing the groups in terms of qualitative data. Correlation analysis was conducted using the Pearson correlation method. The statistical significance level was accepted as $p<0.05$. Results were presented as mean ± standard deviation.

Results

There was no significant difference between the groups in terms of average age, body mass index, gestational week and demographic data. Group 1 showed significantly worse performance in the test of standing on one leg compared to group 2, while they had significantly higher scores on the FSS, BDI, and the FES. On the other hand, they had significantly higher scores on the NHP, which is inversely proportional to the score of perception of high quality of life related to health (Table 1).

FES was positively correlated with FSS, BDI and NHP, and significantly negatively correlated with the test of standing on one leg. The test of standing on one leg was correlated negatively with FES, FSS, BDI and NHP (Table 2).

Table 1. Comparison between the pregnant women who had fallen and who had not

	Group 1 (n=67)	Group 2 (n=63)
Weight	70.5±12.4	71.6±9.5
Height	158.5±6.6	160.8±5.6
BMI	28.0±4.4	27.6±3.2
Age	27.0±6.5	26.6±6.5
Gestational week	29.8±7.8	31.1±6.8
FES	39.5±10.5**	26.6±6.6**
FSS	4.9±1.6*	4.0±1.8*
BDI	23.9±12.5**	10.8±7.3**
NHP	321.9±123.1**	189.4±96.1**
Test of standing on one leg	15.7±12.1**	22.7±8.6**

Results are presented as mean ± standard deviation, *p<0.05, **p<0.01, BMI: Body mass index, FSS: Fatigue severity scale, BDI: Beck depression inventory, NHP: Nottingham health profile, FES: Falls efficacy scale international

Table 2. Correlation analysis results

	FES	FSS	BDI	NHP	Test of standing on one leg
FES	1	0.442**	0.738**	0.713**	-0.355**
FSS	0.442**	1	0.511**	0.480**	-0.298**
BDI	0.738**	0.511**	1	0.705**	-0.257**
NHP	0.713**	0.480**	0.705**	1	-0.368**
Test of standing on one leg	-0.355**	-0.298**	-0.257**	-0.368**	1

FSS: Fatigue severity scale, BDI: Beck depression inventory, NHP: Nottingham health profile, FES: Falls efficacy scale international, **p<0.01

Discussion

Our study is a study the argues that psycho-social changes in pregnancy, as well as physical changes, may have an impact on falls. In this context, we examined how falling was related to fatigue, depression, fear of falling and quality of life. First of all, pregnant women who had fallen performed significantly worse in the test of standing on one leg. This is the expected outcome considering the impact on balance of physical changes in pregnancy. Second, fatigue, depression and fear of falling among the pregnant women who had fallen were significantly higher. Moreover, the health-related quality of life was lower.

Postural balance is a complex process generated by the coordination of vestibular, somato-sensory and visual inputs at the central nervous system level (13). All these systems need to work in coordination to achieve balance. In addition to physical changes in pregnancy, somato-sensory and psychosomatic changes may also play a role in balance and falls. Previous studies have shown that anxiety may be associated with balance disorders. Wada et al. (14) reported in their study on anxiety levels on college students that the degree of anxiety affected anteroposterior oscillation while eyes were open. Nagai et al. (15) showed that high anxiety during pregnancy caused imbalance while standing with eyes open. This decreased when the eyes were closed. In this study, it was emphasized that the pregnant women balanced current physical difficulties using somato-sensory cues and achieved their balance thus. In our study, we found higher scores of fatigue, depression and fear of falling among the pregnant women who had fallen. The health-related quality of life of these people was also worse. According to these results, we can say that pregnant women who are psychosomatically affected and have a poorer sense of quality of life are more prone to falling.

While there are few studies assessing the impact of psychosomatic processes on balance, the relationship between psychological processes and balance remains unclear. In the study of Bolmont et al. (16), healthy male students were subjected to a 12-day balance test program while their daily mood and anxiety levels were examined. The study also involved an investigation of how balance was related to emotions such as depression, fatigue, vitality, confusion, and anger/aggressiveness, in addition to anxiety. The Global Sensory Organization test, which demonstrated the ability to use inputs from the sensory system, was found to have a positive correlation with anxiety, depression and anger scores. A negative correlation was found between the ability to evaluate somato-sensory inputs and anxiety, between the ability to evaluate visual inputs and depression and anger/aggressiveness, between the ability to evaluate vestibular inputs and anxiety, depression and anger/aggressiveness. There was a positive correlation between vitality and the ability to evaluate vestibular inputs. Motor control test performances showed a negative correlation with fatigue and tension. This study has shown that they can influence the ability to use data from the somato-sensory visual or vestibular system to maintain balance. It has also shown that low mood can change balance performance, causing falls. Similarly, higher levels of fatigue, depression and fear of falling were observed in our study, too, while the quality of life was significantly lower among the pregnant women who had fallen. The correlation analysis showed that the test of standing on one leg had a significant and negative correlation with the fear of falling, fatigue, depression and NHP.

Although many studies have been carried out on postpartum depression, research associated with pregnancy depression is limited. The incidence of depression in pregnancy is between 25% and 30% on average in these studies (17). Anxiety and depression have been shown to occur more prominently in the first and third trimesters of pregnancy compared to the second trimester (17). During pregnancy, sleep and appetite changes, fluctuations in conditions of sensation and anxiety, excessive fatigue, loss of libido, and difficulty in concentration may be observed. These negative changes can have a negative effect on the processing of somato-sensory inputs in the pregnant woman, which can cause falls. In our study, we found that depression scores were significantly higher among the pregnant group who had fallen. Moreover, we found that depression was positively correlated with fear of falling, fatigue, and poor quality of life.

A number of studies have investigated the relationship between changes in postural stability and disorders occurring during pregnancy (17-20). It has been observed that pregnant women with morning sickness reduce body oscillation in order to control dizziness and other symptoms (18). Deterioration in postural stability and the risk of falling have also been reported to be increased in pregnant women diagnosed with hyperemesis gravidarum, which is a heavier form of morning sickness (20). A vast majority of pregnant women (87.2-96.5%) complain of fatigue and exhaustion (21). More pronounced fatigue occurs at night. Fatigue begins in weeks 11 and 12 and reaches the highest levels in the third trimester. Prenatal fatigue has also been found to be related to depression, anxiety and premature birth (21). In other words, maternal stress and fatigue have a similar effect on pregnant women's well-being. The level of fatigue in our study was higher in the group of pregnant women who had fallen. Fatigue can impair somato-sensory inputs as well as reducing physical performance, causing falls.

Memory loss and attention issues are two physiological changes that arise during pregnancy, along with fatigue (22). A reduction in visuospatial working memory and executive functions has also been linked to maternal depression and anxiety (23). The importance of a decrease in visuospatial memory is not only related to spatial skills, but it may also cause the mother to fall by affecting her ability to perceive and respond to changes in the environment quickly. There is a need for extensive studies in this regard.

Study Limitations

This is a cross-sectional study, and all patients were selected from among patients at a single center, who were in their 3rd trimester. The sample size can be increased. Notwithstanding these limitations, our study is important to show that somato-sensory inputs can impact falls in pregnancy.

Conclusion

We have presented the first study exploring how falling in pregnancy is related to depression, fatigue, fear of falling, and changes in quality of life. These parameters can affect the somato-sensory organization of balance in pregnant women, which can increase the frequency of falls. Simple tests can easily identify patients who may have a low quality of life, excessive fatigue, or depression. In these patients, both the level of depression and fatigue can be reduced, and the quality of life is improved through psychotherapeutic

interventions, by arranging exercise programs such as pregnancy Pilates, balance and resistance exercises, aerobic exercises, yoga, and tai chi to improve balance. All of these interventions can help pregnant women avoid falling. Further studies on this issue involving larger samples and longer follow-up periods are needed.

Ethics

Ethics Committee Approval: Van Regional Training and Research Hospital received ethical approval from the Non-Interventional Research Ethics Committee on 3.1.2019, numbered 2019/01.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.C., Design: İ.C., Data Collection or Processing: B.K., Analysis or Interpretation: İ.C., Drafting Manuscript: İ.C., B.K., Supervision: İ.C., B.K., Writing: İ.C.

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

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

References

1. Çakmak B, Ribeiro AP, İnanir A. Postural balance and the risk of falling during pregnancy. J Matern Fetal Neonatal Med 2016;29(10):1623-1625.
2. Bertuit J, Leyh C, Rooze M, Feipe V. Pregnancy-related changes in center of pressure during gait. Acta Bioeng Biomech 2017;19(4):95-102.
3. McCrory JL, Chambers AJ, Daftary A. Redfern MS. Dynamic postural stability in pregnant fallers and non-fallers. BJOG 2010;117(8):954-962.
4. Dunning K, Le Masters G, Bhattacharya A. A major public health issue: the high incidence of falls during pregnancy. Matern Child Health J 2010;14(5):720-725.
5. Danna-Dos-Santos A, Magalhães AT, Silva BA, Duarte BS, Barros G, Silva MDFC, et al. Upright balance control strategies during pregnancy. Gait Posture 2018;66:7-12.
6. O'Connor PJ, Poudevigne MS, Johnson KE, Araujo JB, Ward-Ritacco CL. Effects of resistance training on fatigue-related domains of quality of life and mood during pregnancy: a randomized trial in pregnant women with back pain. Psychosom Med 2018;80(3):327-332.
7. Bolmont B, Gangloff P, Vouriot A, Perrin PP. Moodstates and anxiety influence abilities to maintain balance control in healthy human subjects, Neurosci Lett 2002;329(1):96-100.
8. Vellas BJ, Wayne SJ, Romero L, Baumgartner RN, Rubenstein LZ, Garry PJ. One-leg balance is an important predicotr of injurious falls in older persons. J Am Geriatr Soc 1997;45(6):735-758.
9. Armutlu K, Korkmaz NÇ, Keser İ, Sumbuloglu V, Akbiyik İD, Guney Z, et al. The validity and reliability of the Fatique Severity Scale in Turkish multiple sclerosis patients. Inter J Rehab Res 2007;30(1):81-85.
10. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliliği ve güvenirliliği. Psikoloji Dergisi 1989;7(23):3-13.
11. Ulus Y, Durmus D, Akyol Y, Terzi Y, Bilgici A, Kuru O. Reliability and validity of the Turkish version of the Falls Efficacy Scale International (FES-I) in community-dwelling older persons. Arch Gerontol Geriatr 2012;54(3):429-433.
12. Kücükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, Arasil T. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res 2000;23(1):31-38.
13. Paulus W, Straube A, Brandt T. Visual postural performance after loss of somatosensory and vestibular function. J Neurol Neurosurg Psychiatry 1987;50(11):1542-1545.
14. Wada M, Sunaga N, Nagai M, Anxiety affects the postural sway of the antero-posterior axis in college students. Neurosci Lett 2001;302(2-3):157-159.
15. Nagai M, Isida M, Saitoh J, Hirata Y, Natori H, Wada M. Characteristics of the control of standing posture during pregnancy. Neurosci Lett 2009;462(2):130-134.
16. Bolmont P, Gangloff A, Vouriot PP. Perrin, mood states and anxiety influence abilities to maintain balance control in healthy human subjects. Neurosci Lett 2002;329(1):96-100.
17. Schetter CD, Tanner L. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr Opin Psychiatry 2012;25(2):141-148.
18. Yu Y, Chung HC, Hemingway L, Stoffregen TA. Standing body sway in females with and without morning sickness in pregnancy. Gait Posture 2013;37(1):103-107.
19. Workman JL, Barha CK, Galea LAM. Endocrine substrates of cognitive and affective changes during pregnancy and postpartum. Behav Neurosci 2012;126(1):54-72.
20. Çakmak B, Inanir A, Nacar MC. Postural balance in pregnancies complicated by hyperemesis gravidarum. J Matern Fetal Neonatal Med 2015;28(7):819-22.
21. Cheng CY, Pickler RH. Perinatal stress, fatigue, depressive symptoms, and immune modulation in late pregnancy and one month postpartum. Scientific World Journal 2014;2014:652630. doi: 10.1155/2014/652630.
22. Logan DM, Hill KR, Jones R, Holt-Lunstad J, Larson MJ. How do memory and attention change with pregnancy and childbirth? A controlled longitudinal examination of neuropsychological functioning in pregnant and postpartum women. J Clin Exp Neuropsychol 2014;36(5):528-539.
23. Kataja EL, Karlsson L, Huizink AC, Tolvanen M, Parsons C, Nolvi S, et al. Pregnancy-related anxiety and depressive symptoms are associated with visuospatial working memory errors during pregnancy. J Affect Disord 2017;218:66-74.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):234-241
DOI: 10.4274/BMB.galenos.2021.02.022

The Performance Analysis of the Thyroid Nodule Size to Predict the Coexistence of Micropapillary Carcinoma

Mikropapiller Karsinom Birlikteliğini Tahmin Etmekte; Tiroid Nodül Boyutu Performans Analizi

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Abstract

Objective: Incidental micropapillary carcinoma (IMC) is the most common variant of thyroid malignancies. There are unmet needs regarding the efficacy of nodule size in the prediction of the coexistence of IMC. We aimed to measure the effect of nodule size on the prediction of the coexistence of IMC.

Method: The data of 194 patients who underwent biopsy for fine-needle aspiration cytology and subsequent thyroidectomy in a research and training hospital between January 2017 and February 2020 were analyzed retrospectively. The patients were divided into three groups according to the sizes of thyroid nodules as 0-10 mm, 11-20 mm, and >20 mm. Logistic regression analysis was performed.

Results: The patients with nodule size between 0 mm and 10 mm mostly showed hypothyroidism (51.0% vs. 28.8% vs. 41.8%) while patients with size between 11 mm and 20 mm mostly had euthyroidism (44.2% vs. 45.1% vs. 41.8%, p=0.0175). Both malignancy (51.9% vs. 49.0% vs. 42.9%, p=0.544) and IMC (65.4% vs. 51.0% vs. 56.0%, p=0.32) were observed more likely in patients with moderate size (11-20 mm). We found the following variables to be predictors for the coexistence of IMC: absence of halo [odds ratio (OR): 4.50, 95% confidence interval (CI): 1.61-14.71, p=0.007], and interestingly decrease in vascularity [OR: 0.33, 95% CI: 0.12-0.87, p=0.030], and total thyroidectomy, [OR: 4.55, 95% CI: 2.30- 9.56, p<0.001].

Conclusion: With increased nodule size (>2 cm), we reported more IMC inside the thyroid gland. However, the nodule size has the low performance to be a predictor for the coexistence of IMC in the thyroid gland.

Keywords: Malignancy, nodule size, thyroidectomy

Öz

Amaç: İnsidental mikropapiller karsinom (İMK), tiroid malignitelerinin en yaygın mikropapiller varyantıdır ve son on yılda insidansı artmaktadır. Tiroid bezinde İMK varlığını tahmin etmede nodül boyutunun etkinliğine ilişkin veriler yeterli değildir. Bu retrospektif çalışmada nodül boyutunun, İMK'lerin tiroid bezinde diğer lezyonlarla bir arada bulunmasının öngörülmesine etkisini araştırdık.

Yöntem: Ocak 2017-Şubat 2020 tarihleri arasında ince iğne aspirasyon sitolojisi ve ardından tiroidektomi için biyopsi yapılan 194 hastanın verileri retrospektif olarak incelendi. Hastalar tiroid nodüllerinin boyutlarına göre 0-10 mm, 11-20 mm ve >20 mm olarak üç gruba ayrıldı.

Bulgular: Nodül boyutu 0-10 mm arasında olan hastalarda en çok hipotiroidizm (%51,0, %28,8 ve %41,8) görülürken, boyutu 11-20 mm arasındaki hastalarda en çok ötiroidizm görüldü (%44,2, %45,1 ve %41,8, p=0,0175). Hem malignitenin (%51,9, %49,0 ve %42,9, p=0,544) hem de İMK'nin (%65,4, %51,0 ve %56,0, p=0,32), orta büyüklükte (11-20 mm) nodül boyutu olan hastalarda görülme olasılığı yüksekti. Aşağıdaki değişkenlerin İMK'nin görülmesini daha fazla etkilediğini bulduk: halo yokluğu [olasılık oranı (OO): 4,50, %95 güven aralığı (GA): 1,61-14,71, p=0,007], vasküleritede azalma [OO: 0,33, %95 GA: 0,12-0,87, p=0,030] ve total tiroidektomi [OO: 4,55, %95 GA: 2,30-9,56, p<0,001].

Sonuç: Nodül boyutunda artışla (>2 cm) birlikte tiroid bezi içinde daha fazla İMK'ye rastlanmıştır. Bununla birlikte, nodül boyutunun tiroid bezinde İMK bulunma riski için prediktif bir faktör olma potansiyeli düşüktür.

Anahtar kelimeler: Malignite, nodül boyutu, tiroidektomi

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Cite this article as: Hacım NA, Ercan G, Ülgen Y, Vartanoğlu Aktokmakyan T, Tokoçin M, Meriç S, Velimirovic M, Erçetin C, Akbaş A, Altınel Y. The Performance Analysis of the Thyroid Nodule Size to Predict the Coexistence of Micropapillary Carcinoma. Bagcilar Med Bull 2021;6(3):234-241

Introduction

Thyroid nodules are typically benign lesions with a prevalence of 2-6% with palpation, 19-35% with routine ultrasound imaging (USG), and 8-65% in biopsy (1). The incidental malignant tumors of the thyroid gland can be detected by postoperative examination because of benign lesions. Additionally, incidental thyroid carcinoma is the most common pathological type with an incidence ranging from 3% to 20.3% (2,3). Incidental micropapillary carcinoma (IMC) is the most common micropapillary variant (3), with an increasing incidence in the past decades, due to developments and much use of diagnostic procedures, which enable the detection of smaller tumors, particularly IMC in the nodules of a diameter smaller than 10 mm according to the World Health Organization classification system (4). It is controversial whether or not the size of the thyroid nodule is correlated with the presence of IMC and other clinicopathological features of patients (5,6). Despite the fact that the prognostic advantage of IMCs has been an issue of debate in recent studies (6-8), there is a lack of information about the predictive value of the size of thyroid nodules in the risk and early diagnosis of IMC among thyroid cancers (9-11). Although most IMCs were discovered incidentally on Fine Needle Aspiration Cytology (FNAC) during the pathological examination of benign lesions, there are unmet needs regarding the efficacy of nodule size in the prediction of the presence of IMCs in the thyroid gland. We investigated the effect of the nodule size on the prediction of the association of IMCs in the thyroid gland with ultrasonographical non-visualized adjacent malignancies. Our retrospective study is a good clinical tool to consider the nodule size as a predictive factor for the presence of IMC in the thyroid gland. It is important to consider the thyroid nodule size during outpatient follow-up to suspect the further association of IMC in the thyroid gland.

Materials and Methods

A retrospective review of the data of 194 patients who underwent FNA biopsy and subsequent thyroidectomy in the General Surgery Department of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between January 2017 and February 2020 was performed. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (no: 2020.02.1.03.021, date: 07/02/2020). All procedures were consistent with the principles of the Helsinki Declaration. The patient consent could not be received from the patients due to the retrospective design of the study.

Patients

The selection criteria of the patients were based on the FNA biopsy and subsequent thyroidectomy, including all data of demographics and clinical features. The patients with incomplete data were excluded from the study. The data of patients including the demographic features were about sex, age, radiation history, family history of thyroid diseases, type of surgery, and the diameter of the nodule (mm). As clinical indications, FNA, nodule size, compression/cosmetics, Grave's disease, toxic goiter, and coexisting hyperparathyroidism were recorded. The diagnoses with thyroid function tests, including hypothyroidism, euthyroidism, or hyperthyroidism, were recorded. Lymphadenectomy was performed as central, regional, or central with regional levels. FNA cytology (FNAC) findings were determined by the Bethesda category, and an overall histopathological diagnosis (benign or malignant) was recorded according to the pathology reports. All data were analyzed by comparing the outcomes with the nodule size and IMC. The sizes of thyroid nodules were determined according to the recent ATA guidelines and the patients were divided accordingly into three groups as 0-10 mm, 11-20 mm, and >20 mm (12). IMC was determined as a well-differentiated single tumor or multiple tumors smaller than 1 cm, diagnosed incidentally in intra- or extranodular region, inside or outside the same lobe with a benign or malignant lesion. IMC was also confirmed by immunohistochemically positive staining for thyroglobulin, showing a follicular differentiation. We included IMC in intranodular region and inside the same lobe with a benign or malignant lesion.

USG

Ultrasound (US) imaging of the thyroid was performed by the Esaote Color Doppler US (MAG Technology Co, Ltd. Model: 796FDII Yung-ho City, Taipei, Taiwan). Radiological findings recorded for each nodule included the echogenicity (hypoechoic or hyper- and isoechoic), margin (irregular or well-bordered), microcalcifications (absent or present), the peripheral halo (absent or present), increased vascularity (absent or present), and cervical lymph nodes (13).

FNAC

All cytological and pathological examinations of thyroid samples were performed by an experienced cytopathologist. FNA biopsy was performed by the guidance of General Electric Logiq pro 200 US (Model number 2270968; GE Healthcare Korea, Seongnam SI, Gyean GGI-DO, Korea).

The aspiration samples were evaluated by May-Grunwald-Giemsa for cytological examination. The Bethesda System for Reporting Thyroid Cytopathology system was used to analyze FNAC samples described in the literature (14).

Statistical Analysis

The categorical variables were reported as percentages and also continuous variables as mean with standard deviation for descriptive statistics. The chi-square test for categorical variables and t-test for continuous variables were performed by univariate analysis comparing patients with the coexistence of IMC. The dataset was diverged arbitrarily into two cohorts: 75% of patients were used in a training set, and the remaining 25% were used as a test set. A clinically applicable prediction model for the coexistence of IMC was created by a selection-based analysis ($p<0.05$ in univariate analyses of the unadjusted covariates based on the per-operative assessment). The determination of predictive variables for the coexistence of IMC to control potential confounders was utilized by multivariable logistic regression. The test set identified the sensitivity, specificity and receiver-operating characteristic curve (receiver operating characteristic curve) of each model. The bootstrapping to generate a 95% confidence interval of the sensitivity and specificity was performed. Significance was the level of $p<0.05$. R software version 3.4.2. was used for analysis.

Results

Outcomes Regarding Nodule Size

A comparison of patient characteristics based on the increase in nodule size was evaluated (Table 1). The total number of patients was 194, 75.3% of these patients were female, and 24.7% were male. The mean age of all patients was 46.6±13.1 years (18-89 years). Only one patient having a nodule size larger than 20 mm (0.52%) had radiation therapy on the neck, and three patients (1.55%) had a family history of thyroid carcinoma. The mean diameter of nodules was found as 22.2±14.8 mm. Euthyroidism was diagnosed in 84 patients (43.3%). Hyperthyroidism was the rarest status of thyroid function among all patients (15.5%). The patients with nodule size between 0 mm and 10 mm mostly showed hypothyroidism (51.0% vs. 28.8% vs. 41.8%, p=0.0175) while patients with size between 11 mm and 20 mm mostly had euthyroidism (44.2% vs. 45.1% vs. 41.8%, p=0.0175). The ratio of overall benign pathology (53.1%) was higher than that of malignancies (46.9%) among all patients. Lastly, 57.2% of all patients were diagnosed as IMC, without any difference among the groups. Both a malignancy (49.0% vs. 51.9% vs. 42.9%, p=0.544) and IMC (51.0% vs. 65.4% vs. 56.0%, p=0.32) were observed more likely in the patients with a moderate nodule size (11-20 mm). Especially, malignancy was observed in the nodules less than 2 cm (Table 1, 2).

Outcomes Regarding IMC

We reported, based on univariate regression (Table 3), that thyroid function status (euthyroidism, hyperthyroidism), absence of halo, and total thyroidectomy in the intraoperative features emerged to be associated with the coexistence of IMC. Increase in nodule size did not seem to predict eventual coexistence of IMC [odds ratio (OR): 1.066, 95% confidence interval (CI): 0.757-1.501, p=0.712], (Table 2).

In our latest multivariable prediction model, there were 6 variables, which were identified according to either they were statistically significant on the univariate analysis or they had been formerly mentioned in the literature as potential predictors for the coexistence of IMC: thyroid function status (euthyroidism, hyperthyroidism), radiological absence of halo radiological vascularity, and surgery (total thyroidectomy), overall malignant pathology and pathological differentiation (nodular goiter, etc.). Briefly, we reported some of the findings to be a predictor for the coexistence of IMC: absence of halo (OR: 4.50 95% CI: 1.61-14.71, p=0.007), and interestingly decrease in vascularity (OR: 0.33, 95% CI: 0.12-0.87, p=0.030), and total thyroidectomy, (OR: 4.55, 95% CI: 2.30-9.56, p<0.001), (Figure 1).

The area under curve of the test set was 0.72 (95% CI: 0.61-0.78), sensitivity and specificity were 0.56 (95% CI: 0.38-0.72) and 0.79 (95% CI: 0.64-0.92), respectively (Figure 2). Our model was pretty good at detecting the true negatives of IMC, but average at detecting true positives of IMC.

Discussion

Thyroid nodules are clinically indicated for thyroid dysfunction and compressive symptoms; however, they are mostly critical in the diagnosis of thyroid malignancies. The ratio of malignancy in thyroid nodules diagnosed by biopsy has been reported between 4.0% and 6.5% and generally unconventional of the nodule size (15,16). However, IMCs which are incidentally diagnosed at the time of thyroidectomy are much more common than the overall malignancies (up to 36%) (17). Consistent with our findings, malignancy was observed

Table 1. Demographic and clinical features of the patients in comparison to the nodule size

Variables		Total n=194	Nodule size			p
			0-10 mm n=51	11-20 mm n=52	>20 mm n=91	
Sex, n (%)	Female	146 (75.3)	44 (86.3)	39 (75)	63 (69.2)	0.078
	Male	48 (24.7)	7 (13.7)	13 (25)	28 (30.8)	
Age (year)	Mean ± SD	46.6±13.1	48.6±13.6	47.2±12.3	45.1±13.1	0.276
	Min-max	(18-89)	(22-74)	(21-78)	(18-80)	
Radiation history	n (%)	1 (0.52)	0 (0)	0 (0)	1 (1.1)	0.566
Family history	n (%)	3 (1.55)	0 (0)	0 (0)	3 (3.3)	0.178
Status of thyroid function n (%)	Hypothyroidism	78 (40.2)	26 (51.0)	15 (28.8)	38 (41.8)	**0.0175**
	Euthyroidism	84 (43.3)	23 (45.1)	23 (44.2)	38 (41.8)	
	Hyperthyroidism	30 (15.5)	2 (3.9)	14 (26.9)	14 (15.4)	
Type of surgery n (%)	Lobectomy	19 (9.8)	8 (15.7)	4 (7.7)	7 (7.7)	0.257
	Total thyroidectomy	175 (90.2)	43 (84.3)	48 (92.3)	84 (92.3)	
Diameter of nodule (mm)	Mean ± SD	22.2±14.8	7.05±2.1	15.0±2.3	34.9±11.8	**<0.0001**
	Min-max	(3-70)	(3-10)	(11-20)	(21-70)	
Radiological findings n (%)	Hypo echogenicity	119 (61.3)	38 (74.5)	33 (63.5)	49 (53.8)	-
	Irregular margin	47 (24.2)	19 (37.3)	7 (13.5)	21 (23.1)	-
	Microcalcifications	51 (26.3)	19 (37.3)	10 (19.2)	22 (24.2)	0.214
	Loss of halo	29 (14.9)	8 (15.7)	6 (11.5)	15 (16.5)	-
	Increased vascularity	26 (13.4)	4 (7.8)	5 (9.6)	17 (18.7)	-
	Cervical lymph nodes	73 (37.6)	24 (47.1)	23 (44.2)	26 (28.6)	-
Pathology (%)	Toxic nodular goiter	43 (22.1)	6 (11.8)	10 (19.2)	27 (29.7)	0.058
	MNG	60 (30.9)	20 (39.2)	15 (28.8)	25 (27.5)	-
	Papillary carcinoma	81 (41.7)	25 (49.0)	24 (46.2)	32 (35.2)	-
	Hurthle cell carcinoma	10 (5.3)	0 (0.0)	3 (5.8)	7 (7.7)	-
FNAC findings n (%)	Non-diagnostic/insufficient	20 (10.3)	8 (15.7)	1 (1.9)	11 (12.1)	0.065
	Benign	34 (17.5)	10 (19.6)	7 (13.5)	17 (18.7)	
	AUS/FLUS	41 (21.1)	9 (17.6)	9 (17.3)	23 (25.3)	
	Follicular neoplasm	12 (6.2)	0 (0)	6 (11.5)	6 (6.6)	
	Cancer suspicious	58 (29.9)	15 (29.4)	22 (42.3)	21 (23.1)	
	Cancer	28 (14.4)	9 (17.6)	7 (13.5)	12 (13.2)	
Overall pathology n (%)	Benign	103 (53.1)	26 (51.0)	25 (48.1)	52 (57.1)	0.544
	Malignant	91 (46.9)	25 (49.0)	27 (51.9)	39 (42.9)	
IMC	n (%)	111 (57.2)	26 (51.0)	34 (65.4)	51 (56.0)	0.320

SD: Standard deviation, FNAC: Fine needle aspiration cytology, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance, IMC: Incidental micropapillary carcinoma, MNG: Multinodular goiter

at the rate of 36% in patients with IMC (p=0.0008). Although the prognostics of IMC are controversial, early diagnosis and treatment of IMC are still crucial since the small size alone does not lower the risk of incidental thyroid malignancies (3,6,18,19). Consistent with our study, overall malignancy was reported more likely in the nodules less than 2 cm (49% vs. 51.9% vs. 42.9%, p=0.544). Additionally, the diameter of nodule size has no impact to induce the coexistence of IMC (51% vs. 65.4% vs. 56%, p=0.32). Since this risk of malignancy is high, such nodules including IMCs require urgent examination and diagnosis. Therefore, we investigated the effect of the nodule size on the prediction of the association of IMCs in patients' pathological specimen with ultrasonographical non-visualized adjacent malignancies. We found that an increase in nodule size did not seem to predict the eventual coexistence of IMC (OR: 1.066, 95% CI: 0.757-1.501, p=0.712).

In current literature, it was shown that high TSH level prior to surgery was shown with a higher risk of differentiated

Table 2. Demographic and clinical features of the patients in comparison to the presence of IMC

Variables		Total n=194	IMC		p
			Absent n=83	Present n=111	
Sex, n (%)	Female	146 (75.3)	60 (72.3)	86 (77.5)	0.509
	Male	48 (24.7)	23 (27.7)	25 (22.5)	
Age (year)	Mean ± SD	46.6±13.1	45.6±13.2	47.4±13.0	0.343
	Min-max	(18-89)	(18-78)	(18-80)	
Status of thyroid function n (%)	Hypothyroidism	78 (40.2)	41 (49.4)	38 (34.2)	0.078
	Euthyroidism	84 (43.3)	33 (39.8)	51 (45.9)	
	Hyperthyroidism	30 (15.5)	9 (10.8)	21 (18.9)	
Type of surgery n (%)	Lobectomy	19 (9.8)	15 (18.1)	4 (3.6)	**0.0019**
	Total thyroidectomy	175 (90.2)	68 (81.9)	107 (96.4)	
Diameter of nodule (mm)	Mean ± SD	22.2±14.8	22.7±16.0	21.8±13.8	0.988
	Min-max		(3-70)	(4-65)	
Radiological findings n (%)	Hypo echogenicity	119 (61.3)	52 (62.7)	68 (61.3)	-
	Irregular margin	47 (24.2)	20 (24.1)	27 (24.3)	-
	Microcalcifications	51 (26.3)	25 (30.1)	26 (23.4)	0.356
	Loss of halo	29 (14.9)	7 (8.4)	22 (19.8)	-
	Increased vascularity	26 (13.4)	13 (15.7)	13 (11.7)	-
	Cervical lymph nodes	73 (37.6)	32 (38.6)	41 (36.9)	-
FNAC findings n (%)	Non-diagnostic/insufficient	20 (10.3)	7 (8.4)	13 (11.7)	0.598
	Benign	34 (17.5)	13 (15.7)	21 (18.9)	
	AUS/FLUS	41 (21.1)	17 (20.5)	24 (21.6)	
	Follicular neoplasm	12 (6.2)	3 (3.6)	9 (8.1)	
	Cancer suspicious	58 (29.9)	28 (33.7)	30 (27.0)	
	Cancer	28 (14.4)	14 (16.9)	14 (12.6)	
Overall pathology n (%)	Benign	103 (53.1)	32 (38.6)	71 (64.0)	**0.0008**
	Malign	91 (46.9)	51 (61.4)	40 (36.0)	

SD: Standard deviation, FNAC: Fine needle aspiration cytology, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance, IMC: Incidental micropapillary carcinoma

thyroid carcinoma while hyperfunctioning was not considered as a protective factor. Also, incidental thyroid carcinoma is found to be more in euthyroid patients. (4,20). We reported that the patients diagnosed with IMC more likely showed euthyroidism, suggesting that the preoperative status of thyroid function might induce the coexistence of IMC in the thyroid gland.

It might be considered that TSH concentration is promptly related to the size of the malignant nodule, regardless of the other kind of nodule. Furthermore, TSH concentrations were found to be increased with differentiated thyroid carcinoma inside the dominant nodule in these patients compared to those with a benign dominant nodule (4,20). Consistently, we found that the nodule size between 0 mm and 10 mm was mostly indicative of hypothyroidism while the size between 11 mm and 20 mm was mostly indicative of euthyroidism. The nodule size larger than 20 mm showed similar rates of hypothyroidism and euthyroidism among patients. The rates of hyperthyroidism among patients with middle and large size nodules were significantly larger than those among patients with a smaller size, suggesting that TSH concentrations might be correlated with the coexistence of IMC regarding the increase in nodule size.

In some studies, it has been reported that nodule size has a low potential impact on the presence of malignancy regardless of the diameter such as a nodule smaller than 1 cm or larger in the presence of doubtful ultrasonographic findings (21). Small nodules are suggested to be biopsied only if there is more than one suspicious ultrasonographic feature, extracapsular growth, abnormal cervical lymph nodes, or high-risk history. Likewise, a diameter of 1 cm can be utilized for solid nodules that have only one doubtful ultrasonographic finding, such as microcalcifications or hypo echogenicity (22), which is consistent with our findings

including irregular margins in the nodule size less than 1 cm. In addition, we especially reported a correlation with the coexistence of IMC between the decreased vascularity (OR: 0.33, 95% CI: 0.12-0.87, p=0.030) and loss of halo (OR: 4.50, 95% CI: 1.61-14.71, p=0.007) in thyroid tissue.

Table 3. Unadjusted covariates of patients based on the coexistance of incidental micropapillary carcinoma

	OR	95% CI	p
Age	1.010	0.988-1.033	0.340
Thyroid function	1.616	1.063-2.456	0.024*
Surgery	5.900	1.879-18.525	0.002*
Hypo echogenicity	0.942	0.524-1.694	0.844
Irregular margin	1.012	0.521-1.967	0.970
Increased vascularity	0.714	0.312-1.634	0.042*
Microcalcifications	1.355	0.583-3.144	0.479
Loss of halo	2.683	1.086-6.627	0.032*
Cervical lymph nodes	0.933	0.519-1.678	0.818
FNAC findings	0.631	0.090-0.885	0.0277
Pathology	1.866	0.997-3.494	0.051
Overall pathology	0.353	0.196-0.636	0.0005*
Nodule size	1.066	0.757-1.501	0.712

OR: Odds ratio, FNAC: Fine needle aspiration cytology, CI: Confidence interval, *p-value <0.05

There are various controversies about the nodule size, as a variable for predicting malignancy, and the management of treatment. Currently, Al-Hakami et al. (23) reported that the majority of malignancy risk was found in nodules less than 2 cm in contrast to nodules larger than 2 cm. The baseline cancer risk of 64.8% was observed in the thyroid nodules diameter of 1.0-1.9 cm. The general ratio of malignancy in nodules larger than 2 cm were 17.6%, 10.6%, and 7% (nodules 4.0 cm) (20). In the present study, we divided the nodule sizes into three groups as 0-1.0 cm, 1.1-2.0 cm, and the size larger than 2 cm. The patients with medium-sized nodules (1.1-2.0 cm) showed more malignancy in overall pathology while the patients with smaller and larger sizes showed more likely benign pathology.

In the present study, the incidence of IMC was higher among the patients with nodule size between 1.1 cm and 2.0 cm but no significance was shown between the groups regarding the coexistence of IMC. Al-Hakami et al. (23) demonstrated that the nodular size of 1.0-1.9 cm was

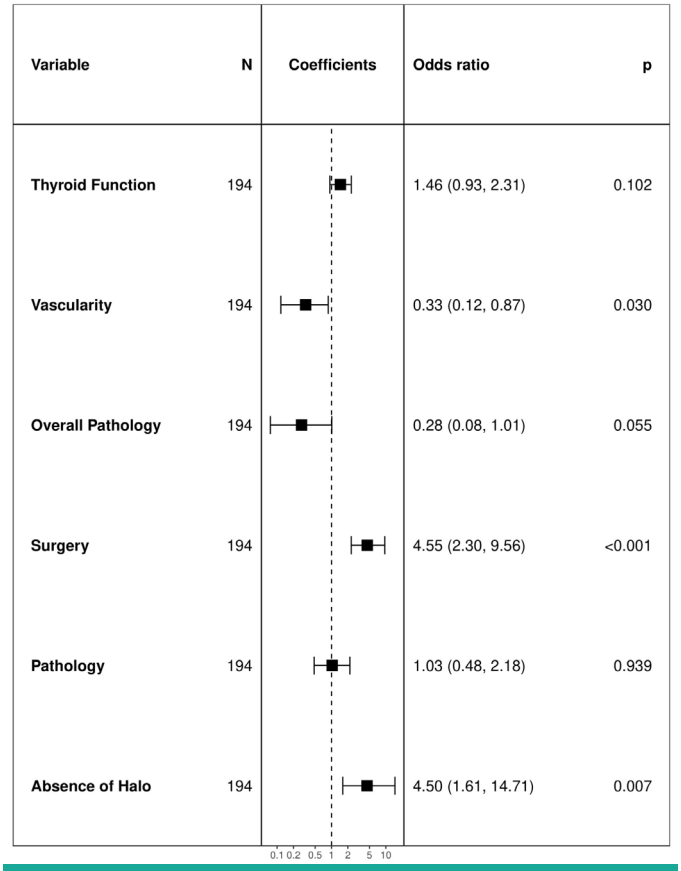

Figure 1. Adjusted covariates for the coexistance of incidental micropapillary carcinoma

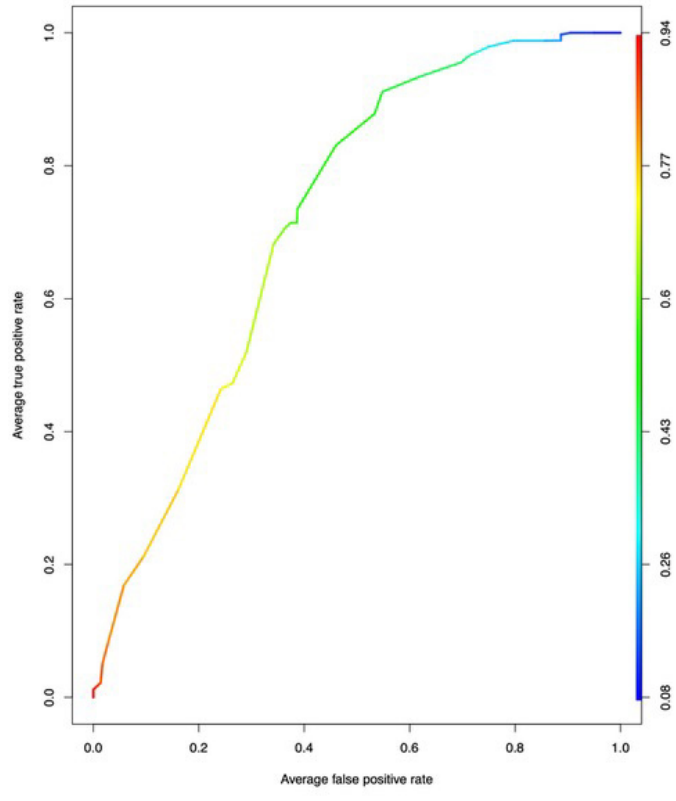

Figure 2. Prediction model of incidental micropapillary carcinoma

primarily contained in the papillary carcinoma, likewise Kamran et al. (24) observed that increasing nodule size had a contrary correlation with a papillary carcinoma, which is similar to our findings (49% vs. 46.2% vs. 35.2%, p=0.124). Contrary to our findings, El-Gammal et al. (25) have shown that larger nodule sizes over 2 cm have more papillary carcinomas. Therefore, we observed that the size of the nodule had a low potential to be a predictive factor for the coexistence of IMC in the thyroid gland (p=0.712).

Study Limitations

The limitations in our study were that small sample size was analyzed from the data of a single center and thyroid surgery group was from a restricted region, which may limit the generalization to other regions and groups. Secondly, our study was limited by its retrospective analysis including measurement, observation, and recall biases. Also, no stepwise or any other machine learning models were further used to measure the performance of our prediction model.

Conclusion

Despite these limitations, this study is a clinically valuable diagnostic tool showing that the nodule size might be a good predictor for the coexistence of IMC in the thyroid gland regarding the absence of halo and vascularity. Another strength of the study was the outcome that the patients diagnosed with IMC more likely had euthyroidism or hyperthyroidism and were observed mostly in total thyroidectomy specimens. However, there are still debates about the pathological assessment of IMC in the thyroid gland. Therefore, defining a cut-off nodule size for the potential coexistence of IMC in a thyroid gland requires studies with large sample size and further clinical trials.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital approved the study protocol (decree number: 2020.02.1.03.021, date of approval: 07/02/2020). All procedures performed in this study involving human participants were under the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Patient consent form was not required due to the nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A.H., Y.A., A.A., G.E., Design: N.A.H., Y.A., A.A., G.E., Data Collection or Processing: Y.Ü., T.V.A., M.T., S.M., A.A., Analysis or Interpretation: N.A.H., C.E., G.E., Y.Ü., A.A., Drafting Manuscript: N.A.H., Y.A., M.V., T.V.A., Critical Revision of Manuscript: Y.A., C.E., S.M., M.V., Final Approval and Accountability: N.A.H., S.M., G.E., M.T., Y.A., Technical or Material Support: Y.Ü., G.E., T.V.A., C.E., M.T., Supervision: N.A.H., Y.A., M.V.

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

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

References

1. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clin Endocrinol Metab 2008;22(6):901-911.
2. Fink A, Tomlinson G, Freeman JL, Rosen IB, Asa SL. Occult micro-papillary carcinoma associated with benign follicular thyroid disease and untreated thyroid neoplasms. Mod Pallid 1996;9(8):816-820.
3. Nanjappa N, Kumar A, Swain SK, Aroul TT, Smile SR, Kotasthane D. Incidental thyroid carcinoma. Indian J Otolaryngol Head Neck Surg 2013;65(1):37-39.
4. Zalzali M, Debreuve A, Richard C, Filieri C, Schvartz C. Micropapillary carcinoma: Description and rise in incidence in the French Marne-Ardennes thyroid cancer registry. Ann Endocrinol (Paris) 2019;80(4):229-233.
5. Kang KW, Kim SK, Kang HS, Lee ES, Sim JS, Lee IG, et al. Prevalence and risk of cancer of focal thyroid incidentaloma identified by 18F-fluorodeoxyglucose positron emission tomography for metastasis evaluation and cancer screening in healthy subjects. J Clin Endocrinol Metab 2003;88(9):4100-4104.
6. Lyu YJ, Shen F, Yan Y, Situ M, Wu W, Jiang G, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules <10 mm in the maximum diameter: does size matter? Cancer Manag Res 2019;11:1231-1236.
7. Gao X, Zhang X, Zhang Y, Hua W, Maimaiti Y, Gao Z. Is papillary thyroid microcarcinoma an indolent tumor?: a retrospective study on 280 cases treated with radioiodine. Medicine (Baltimore) 2016;95(40):e5067. doi: 10.1097/MD.0000000000005067.
8. Yaprak Bayrak B, Eruyar AT. Malignancy rates for Bethesda III and IV thyroid nodules: a retrospective study of the correlation between fine-needle aspiration cytology and histopathology. BMC Endocr Disord 2020;20(1):48.
9. Kim DW, Park AW, Lee EJ, Choo HJ, Kim SH, Lee SH, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules smaller than 5 mm in the maximum diameter: assessment of efficacy and pathological findings. Korean J Radiol 2009;10(5):435-440.
10. Rosario PW, Silva AL, Calsolari MR. Is fine needle aspiration really not necessary in patients with thyroid nodules ≤ 1 cm with highly suspicious features on ultrasonography and candidates for active surveillance? Diagn Cytopathol 2017;45(4):294-296.

11. Zhong LC, Lu F, Ma F, Xu HX, Li DD, Guo LH, et al. Ultrasound-guided fine-needle aspiration of thyroid nodules: does the size limit its efficiency? Int J Clin Exp Pathol 2015;8(3):3155-3159.

12. Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? Cancer 2017;123(3):372-381.

13. Wu Q, Li Y, Liu Y, Shen J, Wang Y, Yi X, et al. The value of conventional sonography and ultrasound elastography in decision-making for thyroid nodules in different categories of the Bethesda system for reporting thyroid cytopathology. Clin Hemorheol Microcirc 2020;74(3):255-266.

14. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid 2009;19(11):1159-1165.

15. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351(17):1764-1771.

16. Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C, et al. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid 2005;15(7):708-717.

17. De Matos PS, Ferreira AP, Ward LS. Prevalence of papillary microcarcinoma of the thyroid in Brazilian autopsy and surgical series. Endocr Pathol 2006;17(2):165-173.

18. Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB, et al. Ultrasonography-guided fine needle aspiration of thyroid incidentaloma: correlation with pathological findings. Clin Endocrinol (Oxf) 2004;60(1):21-28.

19. Kim DW, Lee EJ, Kim SH, Kim TH, Lee SH, Kim DH, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules: comparison in efficacy according to nodule size. Thyroid 2009;19(1):27-31.

20. Zafón C, Obiols G, Mesa J. Preoperative TSH level and risk of thyroid cancer in patients with nodular thyroid disease: nodule size contribution. Endocrinol Nutr 2015;62(1):24-28.

21. Kim EK, Park CS, Chung WY, Oh KK, Kim DL, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178(3):687-691.

22. Popoveniuc G, Jonklaas J. Thyroid nodules. Med Clin North Am 2012;96(2):329-349.

23. Al-Hakami HA, Alqahtani R, Alahmadi A, Almutairi D, Algarni M, Alandejani T. Thyroid nodule size and prediction of cancer: a study at tertiary care hospital in Saudi Arabia. Cureus 2020;12(3):e7478. doi: 10.7759/cureus.7478.

24. Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, et al. Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 2013;98(2):564-570.

25. El-Gammal Ahmed S, E-Balshy Mohammed A, Zahran Kareem M. Relationship between thyroid nodule size and incidence of thyroid cancer. Menoufia Med J 2019; 32(3):1142-1148.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):242-247
DOI: 10.4274/BMB.galenos.2021.03.033

The Effect of Endoprosthesis Selection on Functional Outcomes in the Elderly with Femoral Neck Fractures

Femoral Boyun Kırığı Olan Yaşlılarda Endoprotez Seçiminin Fonksiyonel Sonuçlar Üzerine Etkisi

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Abstract

Objective: Hemiarthroplasty is the most common treatment for femoral neck fractures in patients aged ≥60 years. In this study, we aimed to compare the functional outcomes of unipolar and bipolar endoprostheses used in hemiarthroplasty in the elderly with femoral neck fractures.

Method: A total of 63 patients aged ≥60 years, who underwent hemiarthroplasty for femoral neck fractures between 2004 and 2019, were included. A unipolar and bipolar endoprosthesis was applied to 36 and 27 patients, respectively. All patients were followed for minimum 12 months. The fractures were assessed using the Pauwels classification. Demographic and clinical characteristics of the patients were recorded. Postoperative hip function was evaluated using the Harris hip score (HHS).

Results: The mean age was 74.1±7.3 years in the unipolar endoprosthesis group and 72.9±8.3 years in the bipolar endoprosthesis group. There was no significant difference in the age, sex, and localization of the fracture between the groups. A significant difference in the fracture types according to the Pauwels classification was observed between the two endoprosthesis groups (p<0.01). Follow-up duration, dislocation, reoperation, and wound infection were similar between the groups. The mean limp, ability of putting on socks, mobility, and ability of using public transportation subscale scores of the HHS were significantly higher in the patients undergoing bipolar arthroplasty (p=0.014, p=0.020, p=0.026, and p=0.03, respectively). However, the total HHS was comparable between the groups (p=0.728).

Conclusion: Our study results show that bipolar arthroplasty yields more favorable results in patients with a better predictable mobilization based on the HSS subscale scores. Of note, unipolar arthroplasty is a more low-cost treatment method in the elderly patients with femoral neck fractures.

Keywords: Femoral neck fracture, Harris hip score, hemiarthroplasty

Öz

Amaç: Hemiartroplasti, ≥60 yaş hastalarda femur boyun kırıklarının tedavisinde en sık kullanılan tedavidir. Bu çalışmada, femur boyun kırıklı yaşlı hastalarda hemiartroplastide kullanılan unipolar ve bipolar endoprotezlerin fonksiyonel sonuçları karşılaştırıldı.

Yöntem: Bu çalışmaya 2004-2019 yılları arasında femur boyun kırığı nedeniyle hemiartroplasti yapılan ≥60 yaş üzeri toplam 63 hasta alındı. Hastaların 36'sına unipolar, 27'sine ise bipolar endoprotez takıldı. Tüm hastalar en az 12 ay süreyle takip edildi. Kırıklar Pauwels sınıflandırmasına göre değerlendirildi. Hastaların demografik ve klinik özellikleri kaydedildi. Ameliyat sonrası kalça fonksiyonları, Harris kalça skoru (HHS) ile değerlendirildi.

Bulgular: Unipolar endoprotez implante edilen grubun ortalama yaşı 74,1±7,3 yıl, bipolar endoprotez takılan grubun ortalama yaşı 72,9±8,3 yıl idi. Gruplar arasında yaş, cinsiyet ve kırık lokalizasyonu açısından anlamlı bir fark izlenmedi. Pauwels sınıflandırmasına göre kırık tipleri açısından iki endoprotez grubu arasında anlamlı bir fark vardı (p<0,01). Takip süresi, dislokasyon ve yara yeri enfeksiyonu gruplar arasında benzerdi. HHS'nin ortalama topallama, çorap giyme, hareket kabiliyeti ve toplu taşıma aracına binme alt başlıklarının ortalama skoru, bipolar artroplasti uygulanan hastalarda anlamlı düzeyde daha yüksekti (sırasıyla; p=0,014, p=0,020, p=0,026, ve p=0,03). Ancak toplam HHS skoru, gruplar arasında benzerdi (p=0,728).

Sonuç: Çalışma sonuçlarımız HSS alt başlık skorlarına göre mobilizasyonun daha iyi öngörülebildiği hastalarda bipolar artroplastinin daha iyi sonuçlar verdiğini göstermektedir. Bununla birlikte unipolar artroplasti, femur boyun kırığı olan yaşlı hastalarda daha düşük maliyetli bir tedavi yöntemidir.

Anahtar kelimeler: Femur boyun kırığı, Harris kalça skoru, hemiartroplasti

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Cite this article as: May H, Katı YA. The Effect of Endoprosthesis Selection on Functional Outcomes in the Elderly with Femoral Neck Fractures. Bagcilar Med Bull 2021;6(3):242-247

Introduction

Hip fractures are debilitating conditions which make patients dependent on a constant care due to reduced mobilization and are associated with high morbidity and mortality rates in the elderly (1). With the aging population and high incidence of osteoporosis, these fractures remain an important public health issue (1,2). According to the Swedish National Hip Fracture Registry, also called RIKSHÖFT, femoral neck fractures account for nearly half of all hip fractures and two-thirds of them are displaced fractures (3). In addition, the majority of displaced hip fractures require surgical treatment with a high cost burden on the healthcare system.

The main goals of surgical treatment are to relieve pain promptly, to enable early mobilization and rehabilitation, and to minimize procedure-related complications (4). Although the most optimal treatment of femoral neck fractures has been a long debate, there are two main methods used in the treatment: internal fixation and arthroplasty. In principle, internal fixation enables the reduction of the fracture and prevents displacement. However, this procedure is associated with several complications such as non-union and avascular necrosis in the elderly, leading to reduced function and increased morbidity (5). Arthroplasty is a surgical procedure in which the prosthetic replacement of the femoral head and neck is performed and is helpful to prevent complications related to internal fixation that makes arthroplasty a feasible alternative, particularly in the elderly (6). Nevertheless, there is no consensus on the optimal treatment of displaced intracapsular fractures in patients aged ≥60 years (7).

The selection of unipolar versus bipolar endoprostheses is still a matter of debate for the treatment of displaced femoral neck fractures in the elderly. Theoretically, bipolar prostheses have certain advantages, as they are specifically designed to enable motion at its inner bearing in addition to the prosthesis-acetabulum interface, thereby, decreasing the amount of acetabular erosion and reducing pain (2). However, some authors have advocated reduced inner bearing mobility over time and that these prostheses act similarly to the unipolar ones (8,9). In addition, unipolar prostheses are more cost-effective than the bipolar prostheses and are easy-to-apply during surgery (9).

In the literature, there are randomized-controlled studies showing that bipolar hemiarthroplasty is more advantageous than the unipolar hemiarthroplasty, while some others have found no significant difference, leading to inconsistent results (8,10). In the present study, we aimed to compare the functional outcomes of unipolar and bipolar endoprostheses used in hemiarthroplasty in the elderly with femoral neck fractures.

Materials and Methods

Study Design and Study Population

This double-centered, retrospective study was conducted at Dr. Muhittin Ülker First Aid Training and Research Hospital and Antalya Training and Research Hospital between January 2004 and December 2019.

A total of 63 patients aged ≥60 years, who underwent hemiarthroplasty for isolated and displaced femoral neck fractures and were followed for minimum 12 months, were included in the study. Patients who were surgically treated with the methods other than unipolar or bipolar endoprostheses were excluded from the study. Those having pathological fractures and multiple fractures, requiring additional surgical treatment, and having missing follow-up data were also excluded. Since functional evaluation was aimed in the study, patients who died during the follow-up were also excluded from the study. The patients were divided into two groups as those receiving a unipolar endoprosthesis (n=36) and those receiving a bipolar endoprosthesis (n=27). The fractures were assessed using the Pauwels classification. Demographic and clinical characteristics of the patients including age, sex, fracture type, complications and procedure-related complications (i.e., wound infection, dislocation or reoperation) were obtained from the hospital records. Postoperative functional outcomes were evaluated based on the phone calls to patients and/or their relatives. Postoperative hip function was evaluated using the Harris Hip Score (HHS) at the 12th month.

Surgical Procedure

The surgery was performed in the lateral decubitus position using a posterior incision by a single surgeon. All patients were administered prophylactic antibiotherapy and prophylactic treatment for venous thromboembolism. In the postoperative period, early mobilization and full weight bearing were allowed depending on each individual patient. Mobilization was maintained in all patients during the hospital stay and the patients were discharged with home-based exercises. Following surgery, the patients were scheduled for follow-up in the outpatient setting and the functional outcomes were evaluated using the HHS.

Statistical Analysis

Statistical analysis was performed using the SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). The normality assumption was checked using the Shapiro-Wilk test. Descriptive data were expressed in mean ± standard deviation or median (minimum-maximum) for continuous variables and in number and frequency for categorical variables. The mean differences in ages and follow-up duration between the unipolar and bipolar groups were compared using the Student's t-test, while the Mann-Whitney U test was performed for the comparison of the scores of HSS. Categorical data were analyzed using the Pearson's chi-square (χ^2) or Fisher-Freeman-Halton test, where applicable. A p-value of <0.05 was considered statistically significant.

Results

Of all patients, 26 were males and 37 were females with a mean age of 73.57±7.8 (range, 60-90) years. Of the unipolar prosthesis group, 15 were male and 21 were female with a mean age of 74.1±7.3 years. Of the bipolar prosthesis group, 11 were male and 16 were female with a mean age of 72.9±8.3 years, indicating no statistically significant difference between the groups (p=0.941). The mean follow-up was 31.4±10.0 months and 36.0±12.8 months in the unipolar and bipolar prosthesis groups, respectively, indicating no statistically significant difference between the groups (p=0.111) (Table 1).

According to the Pauwels classification, seven (19.4%) patients had type I, 17 (47.2%) patients had type II, and 12 (33.3%) patients had type III fractures in the unipolar prosthesis group. All cases were displaced femur neck fracture. These figures were one (3.7%), five (18.5%), and 21 (77.8%) patients, respectively, in the bipolar prosthesis group. The number of type I (n=7 vs. n=1, respectively, p<0.001) and type II fractures (n=17 vs. n=5, respectively, p<0.001) was significantly higher in the unipolar prosthesis group, while the number of type III fractures was significantly higher in the bipolar prosthesis group (n=21 vs. n=12, respectively, p<0.001) (Figure 1). Of the unipolar prosthesis group, 18 had right femoral neck fractures and 18 had left femoral neck fractures. Of the bipolar prosthesis group, 12 had right femoral neck fractures and 15 had left femoral neck fractures, which indicated no statistically significant difference (p=0.662) (Table 1).

According to the postoperative complications affecting the functional outcomes, four patients had postoperative dislocation in the unipolar prosthesis group, while reoperation was needed in only one of these patients. In the bipolar prosthesis group, three patients had postoperative dislocation and one of them required reoperation. There was no significant difference in the development of hip dislocation and need for reoperation between the groups (p=0.991). In addition, four patients experienced superficial infection, while one patient had deep infection in the unipolar prosthesis group. In the bipolar prosthesis group, two patients had superficial infection and one patient had deep infection, indicating no significant difference between the groups (p=0.892). Surgical debridement was performed in only one of the patients having infection (n=1, bipolar prosthesis group), while the remaining patients were treated with antibiotherapy.

Table 1. Demographic and clinical characteristics of patient groups

Variable	Unipolar (n=36)	Bipolar (n=27)	p
Age (year)	74.1±7.3	72.9±8.3	0.548†
Sex	-	-	0.941‡
Female	21 (58.3%)	16 (59.3%)	-
Male	15 (41.7%)	11 (40.7%)	-
Localization	-	-	0.662‡
Right	18 (50.0%)	12 (44.4%)	-
Left	18 (50.0%)	15 (55.6%)	-
Pauwels classification	-	-	**<0.001¶**
I	7 (19.4%)	1 (3.7%)	-
II	17 (47.2%)	5 (18.5%)	-
III	12 (33.3%)	21 (77.8%)	-
Follow-up (months)	31.4±10.0	36.0±12.8	0.111†
Dislocation/ reoperation	4 (11.1%)	3 (11.1%)	>0.991§
Wound infection	5 (13.9%)	3 (11.1%)	>0.892§

†Student's t-test, ‡Pearson chi-square test, ¶Fisher-Freeman-Halton test, §Fisher's Exact test. Data are given in mean ± standard deviation or number and frequency, unless otherwise stated

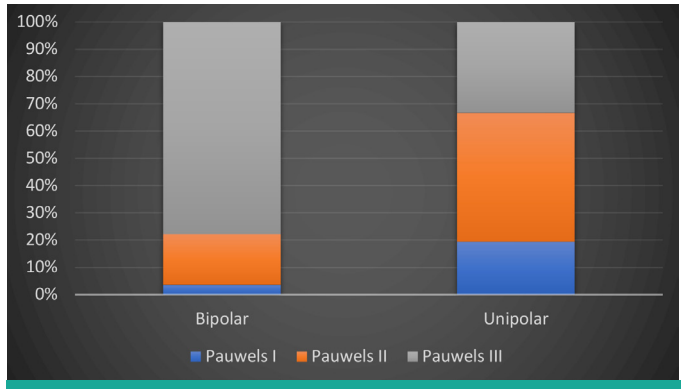

Figure 1. Type of fractures according to the Pauwels classification

Table 2. Total Harris hip scores and subscale scores of patient groups

	Unipolar (n=36)	Bipolar (n=27)	p†
Pain	41.72±4.66	41.11±4.41	0.455
Limp	8.58±1.73	9.67±1.73	**0.014***
Support	6.97±3.14	5.96±2.71	0.296
Distance	6.67±3.62	7.00±2.76	0.768
Climbing stairs	2.00±1.12	1.59±1.28	0.099
Putting on shoes and socks	2.61±1.25	3.33±0.96	**0.020***
Sitting	4.78±0.64	5.00±0.00	0.076
Using public transportation	0.69±0.47	0.93±0.27	**0.026***
Deformity	3.94±0.33	4.00±0.00	0.386
Mobility	4.14±0.80	4.67±0.68	**0.003***
Total	82.11±12.33	83.26±10.84	0.728

†Mann-Whitney U test. Data are given in mean ± standard deviation, unless otherwise stated.

*p<0.005

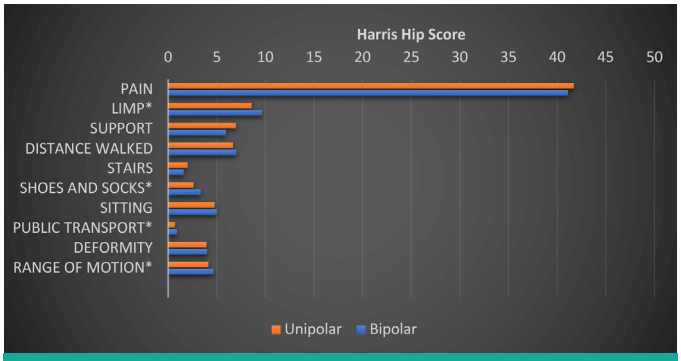

Figure 2. Functional outcomes according to the Harris hip scores

Functional outcomes were evaluated using the HHS following surgery. There was no significant difference in the mean and total subscale scores of the HHS including pain, amount and type of support used, limp, distance that could be walked, climbing stairs, and deformity between the unipolar and bipolar prosthesis groups (p>0.05). However, the mean limp, ability of putting on socks, mobility, and ability of using public transportation subscale scores of the HHS were significantly higher in the patients undergoing bipolar arthroplasty (p=0.014, p=0.020, p=0.026, and p=0.03, respectively) (Table 2) (Figure 2).

Discussion

Due to the aging population, femoral neck fractures have become an increasingly serious public health problem in the elderly and a growing burden on global healthcare systems in recent years (11). With the increasing rate of osteoporosis and non-union complications in this group of patients, novel surgical procedures which allow early mobilization have been widely adopted. In the literature, hemiarthroplasty is recommended as an effective treatment modality for femoral neck fractures, particularly in patients aged ≥60 years (11-15).

There is a variety of prosthetic types and designs used in hemiarthroplasty. Unipolar prostheses have a one-piece design where the hip movement occurs between the prosthesis and the acetabulum, while bipolar prostheses have an additional artificial joint between the two components of the prosthesis. In addition, the bipolar head offers a second articulation between an inner smaller head and the polyethylene liner of the larger outer head (11). Both treatment methods are clinically proven and certain merits and demerits. To illustrate, unipolar prostheses are cost-effective and associated with a lower rate of hip dislocation and improved stability (15). However, acetabular erosion with the use of a monoblock prosthetic design is a well-documented complication (13). Although bipolar prostheses result in less acetabular erosion thanks to their dual-articulation design, the implementation of these prostheses is more difficult than the unipolar ones (11,13,16).

In the present study, we observed no significant difference in the age, sex, location of the fractures, and functional outcomes between the unipolar and bipolar prosthesis groups. In advanced age, unipolar prostheses are more commonly preferred, owing to the relatively low dislocation incidence, easy-to-use design in a timely manner, and cost-efficacy (15,17). The cost is an important variable for these patients. Advanced age has been shown to be associated with poor functional outcomes (17). However, poor functional outcomes have not been fully proven to be linked to advanced age or prosthetic material used (13,16). Although studies investigating the effect of sex on hip fracture have demonstrated a relationship between the male sex and the increased mortality (9,18), no significant effect of sex on functional outcomes has been shown (13,16).

Procedure-related complications such as dislocation and need for reoperation impair the quality of life of patients and increase the mortality and health expenditures (19). In our study, all surgeries were performed using a single surgical technique with a posterior incision. This technique poses a higher risk for dislocation than the anterolateral approach (20). In this study, we observed no significant difference

in the rate of dislocation and reoperation between the unipolar and bipolar prosthesis groups. According to the RIKSHÖFT, which contains data on more than 300,000 hip fractures since the late 1980s, bipolar implants have a lower risk of reoperation than the unipolar implants, irrespective of dislocations or periprosthetic fractures (21). However, recent metaanalyses revealed that the rate of dislocation and reoperation was comparable between the unipolar and bipolar prostheses, consistent with our study findings (14,22). Additionally, in the current study, the rate of superficial and deep wound infections was similar between the two prosthesis groups, which is consistent with the literature (12).

Although the functional outcomes can be evaluated using specific tools such as the Western Ontatio and McMaster University, osteoarthritis index, short form-36, and health-related quality of life, the HHR is the most widely used outcome measure for the assessment of hip fractures, particularly of the hip function before and after hip arthroplasties (14). Similarly, we used the HHS for the evaluation of postoperative functional outcomes in our study. Theoretically, bipolar prostheses seem to be more advantageous than the unipolar implants thanks to their motion at the inner bearing and prosthesis-acetabulum interface, resulting in less acetabular erosion. In this context, some authors reported similar functional outcomes with these two prostheses, while some others suggested that bipolar hemiarthroplasty was associated with more favorable functional outcomes (13,17). In our study, the total HHS was comparable between the two prosthesis groups, consistent with the previous studies. However, the mean limp, ability of putting on socks, mobility, and ability of using public transportation subscale scores of the HHS were significantly higher in the patients undergoing bipolar arthroplasty. Similarly, in their study, De los Santos et al. (23) found no significant difference in the total HSS between the unipolar and bipolar prosthesis groups, although the ability of walking and support (i.e., using canes) subscale scores significantly improved in the patients undergoing surgery with bipolar prosthesis. The discrepancy between the studies was attributed to the age of the patients included in the studies (i.e., younger ones were included in some of the studies) and already better functional scores before the development of fractures (23,24). In our study, however, we found a significant difference in the HHS subscale scores which cannot be explained by the age of the patients, as the mean age was similar between the groups. Indeed, the three subscales of HHS (the ability of putting on socks, mobility, and ability of using public transportation) measure the joint range of motion. This finding, therefore, indicates that bipolar arthroplasty can offer a more favorable joint range of motion.

Total hip arthroplasty is another option that can be applied in femoral neck fractures. It can be a good alternative to hemiarthroplasty, especially in patients with a good general condition and high functional capacity (25). Considering data about the two methods, it is seen that total hip arthroplasty has a better effect and function in treatment. However, long operation time and postoperative recovery time are a disadvantage for THA treatment. On the contrary, patients undergoing hemiarthroplasty have shorter operation time and faster recovery. These two conditions constitute very important advantages for the elderly patients. Therefore, the choice of adopting treatment plan in clinical practices should be made by combining the conditions of the patients with the advantages of the treatment measures (26).

Study Limitations

Nonetheless, there are some limitations to this study. First, the study design is retrospective with a relatively small sample size, indicating a low level of evidence. Second, we were unable to compare pre- and postoperative functional scores of the patients and, thus, independent factors affecting the surgical success may have had an effect on the functional outcomes. However, demographic characteristics of the patients are highly homogeneous. Finally, although there are similar studies on this research topic in the literature, the ideal choice for partial arthroplasty is still controversial.

Conclusion

Unipolar and bipolar arthroplasty are widely used in the treatment of femoral neck fractures in patients aged ≥60 years. Based on our study results, we recommend bipolar prostheses for patients requiring early mobilization, while similar results can be achieved with unipolar prostheses which are more cost-effective alternatives.

Ethics

Ethics Committee Approval: This study was approved by the Antalya Training and Research Hospital, Ethics Committee with the approval no. 2020-228 and date: 23/07/2020.

Informed Consent: A written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.M., Y.A.K., Design: H.M., Y.A.K., Data Collection or Processing: H.M., Y.A.K., Analysis or Interpretation: H.M., Y.A.K., Writing: H.M., Y.A.K.

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

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

References

1. Giannoudis PV, Kontakis G, Christoforakis Z, Akula M, Tosounidis T, Koutras C. Management, complications and clinical results of femoral head fractures. Injury 2009;40(12):1245-1251.
2. Sterling RS. Gender and race/ethnicity differences in hip fracture incidence, morbidity, mortality, and function. Clin Orthop Relat Res 2011;469(7):1913-1918.
3. Thorngren KG, Hommel A, Norrman PO, Thorngren J, Wingstrand H. Epidemiology of femoral neck fractures. Injury 2002;33(3):1-7.
4. Lowe JA, Crist BD, Bhandari M, Ferguson TA. Optimal treatment of femoral neck fractures according to patient's physiologic age: an evidence-based review. Orthop Clin North Am 2010;41(2):157-166.
5. Lu-Yao GL, Keller RB, Littenberg B, Wennberg JE. Outcomes after displaced fractures of the femoral neck. A meta-analysis of one hundred and six published reports. J Bone Joint Surg Am 1994;76(1):15-25.
6. Van Vugt AB. The unsolved fracture. A prospective study of 224 consecutive cases with an intracapsular hip fracture. Thesis, University of Nijmegen, Nijmegen: 1991.
7. Nicoll EA. The unsolved fracture. J Bone Joint Surg Br 1963;45(2):239-241.
8. Inngul C, Hedbeck CJ, Blomfeldt R, Lapidus G, Ponzer S, Enocson A. Unipolar hemiarthroplasty versus bipolar hemiarthroplasty in patients with displaced femoral-neck fractures: A four-year follow-up of a randomised controlled trial. Int Orthop 2013;37(12):2457-2464.
9. Ong BC, Maurer SG, Aharonoff GB, Zuckerman JD, Koval KJ. Unipolar versus bipolar hemiarthroplasty: functional outcome after femoral neck fracture at a minimum of 36 months of follow-up. J Orthop Trauma 2002;16(5):317-322.
10. Calder SJ, Anderson GH, Jagger C, Harper WM, Gregg PJ. Unipolar or bipolar prosthesis for displaced intracapsular hip fracture in octogenarians: A randomised prospective study. J Bone Joint Surg Br 1996;78(3):391-394.
11. Zhou Z, Yan F, Sha W, Wang L, Zhang X. Unipolar versus bipolar hemiarthroplasty for displaced femoral neck fractures in elderly patients. Orthopedics 2015;38(11):697-702.
12. Somashekar, Krishna SV, Sridhara Murthy J. Treatment of femoral neck fractures: unipolar versus bipolar hemiarthroplasty. Malays Orthop J 2013;7(2):6-11.
13. Filippo M, Driessen A, Colarossi G, Quack V, Tingart M, Eschweiler J. Bipolar versus monopolar hemiarthroplasty for displaced femur neck fractures: A meta-analysis study. Eur J Orthop Surg Traumatol 2020;30(3):401-410.
14. Yang B, Lin X, Yin XM, Wen XZ. Bipolar versus unipolar hemiarthroplasty for displaced femoral neck fractures in the elder patient: A systematic review and meta-analysis of randomized trials. Eur J Orthop Surg Traumatol 2015;25(3):425-433.
15. Jia Z, Ding F, Wu Y, Li W, Li H, Wang D, et al. Unipolar versus bipolar hemiarthroplasty for displaced femoral neck fractures: a systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res 2015;10:8.
16. Emirhan N, Albayrak A, Çamurcu İ, Üçpunar H, Yapıcı F, Çöbden A. Comparison of mortality after cemented and cementless hemiarthroplasty for the treatment of femoral neck fracture in patients aged over 65 years old mortality after hemiarthroplasty. Bozok Tıp Dergisi 2020;10(2):177-183.
17. Bölük K, Bilgen M, Durak K. İleri yaş ayrılmış femur boyun kırıklarında unipolar ve bipolar protez uygulamaları. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2008;34(2):41-44.
18. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Survival experience of aged hip fracture patients. Am J Public Health 1989;79(3):274-278.
19. Blewitt N, Mortimore S. Outcome of dislocation after hemiarthroplasty for fractured neck of the femur. Injury 1992;23(5):320-322.
20. Woo RY, Morrey BF. Dislocations after total hip arthroplasty. J Bone Joint Surg Am 1982;64(9):1295-306.
21. Leonardsson O, Kärrholm J, Åkesson K, Garellick G, Rogmark C. Higher risk of reoperation for bipolar and uncemented hemiarthroplasty. Acta Orthop 2012;83(5):459-466.
22. Enocson A, Hedbeck CJ, Törnkvist H, Tidermark J, Lapidus LJ. Unipolar versus bipolar Exeter hip hemiarthroplasty: a prospective cohort study on 830 consecutive hips in patients with femoral neck fractures. Int Orthop 2012;36(4):711-717.
23. De los Santos R, Cordero-Ampuero J, Rodriguez- Salvanés F, González R. Comparison of radiological acetabular erosion between hemiarthroplasties: cemented Thompson unipolar vs. uncemented HAP Furlong bipolar. Eur Orthop Traumatol 2012;3(2):115-120.
24. Parker MJ, Gurusamy KS, Azegami S. Arthroplasties (with and without bone cement) for proximal femoral fractures in adults. Cochrane Database Syst Rev 2010;(6):CD001706. doi: 10.1002/14651858.CD001706.pub4
25. Wei X, Hao L. Study of curative effect of cemented hemiarthroplasty and total hip replacement in treatment of elderly patients with femoral neck fracture. Med Health Care 2014;22:46.
26. Ren C, Guo J, Gao Y. Comparison of total hip arthroplasty and hemiarthroplasty in elderly patients with femoral neck fracture. Biomed Res 2017;28(16):7127-7130.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):248-256
DOI: 10.4274/BMB.galenos.2021.12.086

Rates of Incidental Thyroid Nodule and Thyroid Cancer Detection in Routine Check-up Examinations: A Single-center Study

Rutin Check-up Muayenesi ile İnsidental Tiroid Nodulü ve Tiroid Kanseri Saptanma Oranı: Tek Merkezli Çalışma

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Abstract

Objective: Check-up examinations have gained importance in the last decade and become a common reason for people to refer to healthcare institutions to seek medical help. Thyroid nodules are frequently detected during check-up examinations. This study aimed to determine the frequency of thyroid nodules and the rate of thyroid cancer development in patients presenting for a check-up and to define the role of variables in thyroid cancer detection.

Method: The computer database of the patients, who applied for a check-up examination, was systematically screened, and the records of thyroid ultrasonography (US) were accessed. Patients with any known history of thyroid disease or thyroid cancer and those using medication for an existing thyroid disease were excluded. The demographic data, thyroid US reports, cytology and histopathology results, and free t3 (fT3), free t4 (fT4), and thyroid-stimulating hormone (TSH) levels were evaluated and recorded. Body mass index (BMI) was calculated. Data were analyzed using SPSS v. 25.

Results: Of the 30,449 check-up patients, 24,362 were evaluated. Incidental thyroid nodules were detected in 5.645 (23.17%) patients. The mean BMI of these patients was 56±2.01 kg/m^2, and their mean TSH, fT3 and fT4 values were 2.87±0.45 mIU/mL, 3.76±0.87 pg/mL and 1.23±0.24 pg/mL, respectively. The mean nodule size was 1.31±0.56 mm. While 2.936 (52.01%) of the nodules were solid, 1.377 (24.39%) were cystic and 1.332 (23.59%) were mixed. Of all the nodules, 1.916 (33.94%) were in the TIRADS 2 category, 3.273 (57.98%) in the TIRADS 3 category, 234 (4.31%) in the TIRADS 4a category, 114 (1.27%) in the TIRADS 4b category, 72 (1.27%) in the TIRADS 4c category, and 36 (0.63%) in the TIRADS 5 category. For 392 patients that underwent a biopsy, the

Öz

Amaç: Check-up muayeneleri son on yılda önem kazanmış ve tıbbi yardım isteme amaçlı sağlık kurumlarına başvuruların en yaygın nedenleri arasında yerini almıştır. Tiroid nodülleri, check-up muayenesi sırasında sıklıkla tespit edilmektedir. Çalışmamızın amacı, check-up muayenesine başvuran bireylerde tiroid nodülü sıklığını ve tiroid kanseri gelişme oranını belirlemek ve tiroid kanseri saptanmasında değişkenlerin rolünü tanımlamaktır.

Yöntem: Check-up muayenesi için başvuran hastaların bilgisayar database kayıtları sistematik biçimde taranarak, tiroid ultrasonografisi (USG) yapılan hasta kayıtlarına erişildi. Öncesinde bilinen herhangi bir tiroid hastalığı veya tiroid kanseri öyküsü olan ve mevcut bir tiroid hastalığı için ilaç kullanan hastalar çalışma dışı bırakıldı. Hasta grubunun demografik bilgileri, tiroid USG raporları, sitoloji ve histopatoloji sonuçları ile serbest T3 (sT3), serbest T4 (sT4) ve tiroid stimulan hormon (TSH) düzeyleri değerlendirilerek kaydedildi. Vücut kitle indeksleri (VKİ) hesaplandı. Veriler, SPSS 25 istatistik paket programı ile analiz edildi.

Bulgular: Otuz bin dört yüz kırk dokuz check-up hastasının 24.362'si değerlendirildi. Beş bin altı yüz kırk beş (%23,17) hastada insidental tiroid nodülü saptandı. Bu hastaların ortalama VKİ'si 56±2,01 kg/m^2, TSH değeri 2,87±0,45 mIU/mL, sT3 değeri 3,76±0,87 pg/mL ve sT4 değeri 1,23±0,24 pg/mL idi. Ortalama nodül boyutu 1,31±0,56 mm iken, nodüllerin 2,936'sı (%52,01) solid nodül, 1,377'si (%24,39) kistik nodül, 1,332'si (%23,59) mikst nodül olarak gözlendi. Nodüllerin 1,916'sı (%33,94) TIRADS 2, 3,273'ü (%57,98) TIRADS 3,234'ü (%4,31) TIRADS 4a, 114'ü (%1,27) TIRADS 4b, 72'si (%1,27) TIRADS 4c ve 36'sı (%0,63) TIRADS 5 kategorisindeydi. Biyopsi yapılan 392 hastanın 224'ünün (%57,14) sonucu benign, 100'ünün (%25,51) şüpheli malign ve 68'inin (%17,34) malign olarak raporlandı.

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Cite this article as: Arğun D, Basım P. Rates of Incidental Thyroid Nodule and Thyroid Cancer Detection in Routine Check-up Examinations: A Single-center Study. Bagcilar Med Bull 2021;6(3):248-256

Abstract

results were reported as benign for 224 (57.14%), suspected malignancy for 100 (25.51%), and malignant for 68 (17.34%). The rates of patients diagnosed with papillary, follicular and medullary thyroid cancers were 63.15%, 34.21% and 2.63%, respectively. When the multinominal logistic regression analysis was applied to all significant variables in the univariate analysis, the risk of thyroid cancer was increased 1.7-fold by increased BMI [odds ratio (OR): 1.71, 95% confidence interval (CI): 1.43-2.96], 1.8-fold by female gender [OR: 1.79, (CI): 1.21-2.67], 1.6-fold by solid structure nodule type [OR: 1.62, (CI): 1.27-3.54], 2.7-fold by increased nodule size [OR: 2.71, (CI): 1.11-3.31], and 4.7-fold by increased TIRADS [OR: 4.73, (CI): 1.76-7.31].

Conclusion: The main difficulty in evaluating and managing thyroid nodules is to avoid the inappropriate overuse of thyroid US, thyroid biopsy, and surgery while trying to identify clinically significant malignant nodules. Concerning the diagnosis of thyroid cancer through a check-up examination, the data obtained as a result of more detailed studies should be evaluated, and it should be kept in mind that the increase in the incidence of thyroid cancer in the last three decades may be due to not only overdiagnosis but also a real increase in incidence. However, considering that early diagnosis of thyroid cancer without lymph node involvement can reduce both surgical complications and prevent the risks of radioactive iodine treatment, it is concluded that thyroid cancer being detected at an early stage constitutes an important advantage for the healthy population undergoing a check-up.

Keywords: Check-up examination, thyroid cancer, thyroid nodule

Öz

Papiller tiroid kanseri tanısı konulan hastaların oranı %63,15, foliküler tiroid kanseri %34,21 ve medüller tiroid kanseri %2,63 olarak tespit edildi. Univariate analizlerde anlamlı bulunan tüm değişkenlere multinominal lojistik regresyon analizi uygulandığında artan VKİ'nin 1,7 kat [olasılık oranı (OO): 1,71, %95 güven aralığı (GA): 1,43-2,96], kadın cinsiyetin 1,8 kat [OO: 1,79, (GA): 1,21-2,67], solid nodül yapısının 1,6 kat [OO: 1,62, (GA): 1,27-3,54], artan nodül çapının 2,7 kat [OO: 2,71, (GA): 1,11-3,31], ve artan TIRADS skorunun 4,7 kat [OO: 4,73, (GA): 1,76-7,31] tiroid kanseri gelişimini artırıcı etkisi olduğu tespit edildi.

Sonuç: Tiroid nodüllerini değerlendirme ve yönetmedeki ana zorluk bir yandan tiroid US, tiroid biyopsisi ve cerrahinin uygunsuz aşırı kullanımından kaçınırken, diğer yandan klinik olarak önemli malign olanları tanımlamaya çalışmaktır. Check-up muayenesi ile tiroid kanseri tanısı koyma ile ilgili olarak, daha ayrıntılı çalışmaların sonucunda elde edilen veriler değerlendirilmeli ve son otuz yılda tiroid kanseri insidansının artmasının sadece aşırı tanıdan değil, gerçek bir insidans artışından kaynaklanabileceği akılda tutulmalıdır. Öte yandan lenf nodu tutulumsuz erken tanı tiroid kanseri ile hem cerrahi komplikasyonların azaltılabileceği hem de radyoaktif iyot tedavisinin risklerinden korunabileceği göz önünde bulundurulduğunda, evrece erken yakalanmış tiroid kanserlerinin, check-up amacıyla başvuran sağlıklı popülasyon için önemli bir avantaj olduğu kanısına varılmıştır.

Anahtar kelimeler: Check-up muayenesi, tiroid kanseri, tiroid nodülü

Introduction

Check-up examinations have gained importance in the last decade and are now among the most common reasons for adults to present to healthcare institutions (1). In the literature, a check-up examination, which is also referred to as a physical or preventive health examination, is defined as seeking health care motivated by the need for general health assessment, and the purpose of this examination is to define risk factors and early signs of disease, as well as preventing future diseases through early interventions (2). The main goal of this early evaluation program is to manage diseases that are usually diagnosed late since they show less symptoms in the progression process. Routine medical check-ups include blood tests, liver and kidney function tests, electrocardiogram, echocardiogram, abdominal ultrasound (US), and thyroid US. Although routine control has little value in identifying acute diseases, a growing body of evidence shows the effects of early diagnosis on certain diseases, such as diabetes, cardiovascular disorders, liver dysfunction, gynecological diseases, and malignancy (3). However, the views and information presented in the literature differ concerning whether a routine control can benefit patients' prognosis and have an impact on the final prognosis or have equal value for different diseases, and no specific consensus-based algorithm has yet been established. Therefore, it is important to estimate the value of check-up examinations in the early detection of specific diseases and improving clinical outcomes.

Thyroid nodules are a common clinical problem mostly detected incidentally in all populations. Epidemiological studies have shown that the prevalence of palpable thyroid nodules in iodine-sufficient regions of the world is approximately 5% in women and 1% in men (4). However, with the introduction of high-resolution US into clinical practice, the rate of thyroid nodule detection in randomly selected individuals has increased to 19-68% (5). The clinical significance of thyroid nodules is based on the need to exclude thyroid cancer seen in 7-15% of cases depending on age, gender, radiation exposure history, family history, and other factors (6). In the United States, it is estimated that around 53,000 new cases of thyroid cancer will be diagnosed in 2020, compared to 37,200 in 2009 (7). This annual incidence has almost tripled from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009, and this significant increase in the rate of cancer development from nodules places a greater responsibility on physicians in the process of excluding a cancer diagnosis (8). This change in detection rates has been mostly attributed to an increased

incidence of papillary thyroid cancer (PTC). Furthermore, while only 25% of new thyroid cancers diagnosed in 1988-1989 were 1 cm, this rate increased to 39% in new thyroid cancer diagnoses in 2008-2009 (8). This change over the years is considered to be due to the increased use of thyroid US or other imaging modalities, and early diagnosis and treatment (9). In a population-based study, it was reported that the incidence of thyroid cancer doubled from 2000 to 2012 compared to the previous decade, and this situation could also be associated with clinically occult cancers being detected incidentally on imaging or pathological analyses (10).

Thyroid nodules are frequently detected in patients being evaluated for other medical conditions with no thyroid-related symptoms or undergoing a routine check-up examination (5). Thyroid US provides the opportunity to evaluate the size and location of nodules, their benign or suspicious characters, nodule composition, and presence of cervical lymph nodes. The evaluation of a thyroid nodule on US is valuable in terms of providing information on the localization of the nodule in the gland, its size (three-dimensional), its echo structure (solid, cystic, complex), shape, imaging features (echogenicity, calcifications, margin pattern, presence of halo, blood flow, and extrathyroidal spread) and presence of lymphadenopathy (11). During a check-up examination, the US features of a nodule that may increase the risk of cancer should be evaluated. The main reason for evaluating nodules with US is to investigate features that may predict malignancy risk. It is known that the malignancy risk of a nodule increases in the presence of certain US features. In US, a nodule being hypoechogenic compared to normal thyroid parenchyma, irregular and indeterminate infiltrative borders, presence of microcalcification(s), absence of halo, height of the nodule being greater than its transverse dimension, and increased intranodular blood supply increase the risk of malignancy. In addition, the characteristic appearance of some types of cancer can also be guiding. For example, PTC is usually solid or predominantly solid and hypoechoic, and it often presents with infiltrative irregular borders and microcalcification. In contrast, follicular thyroid carcinoma (FTC) is generally isoechoic and rarely hyperechoic; it is thick and presents with an irregular halo but not microcalcification.

In the detection of nodules, it is vital to make a benign and malignant differentiation. A thyroid fine-needle aspiration biopsy (FNAB) is the most convenient, inexpensive and reliable method to reveal this situation and is the gold standard test in distinguishing benign and malignant thyroid nodules (12). The indication for a thyroid FNAB is basically determined by staging based on the size and US features of the nodule. When a thyroid biopsy is performed, the next management step (follow-up or surgery) of the nodule depends on the outcome of the biopsy, molecular markers and/or repeat thyroid FNAB, as well as the individual preferences of the patient (13).

An average of 5% of all thyroid nodules are cancerous and the clinical presentation finding of thyroid cancers is usually in the form of a palpable or incidentally detected thyroid nodule (4). An early and accurate diagnosis is vital for people with thyroid cancer, as in the case of other cancer types. Although thyroid cancer is known to have the best cure and long survival rates and generally well-differentiated histological features compared to other cancers, its early diagnosis is still crucial since it significantly reduces distant metastasis and mortality rates in individuals (14).

Due to the localization of the thyroid gland, it is easy to diagnose thyroid nodules and a possible thyroid cancer early with US and thyroid FNAB. For this reason, a routine check-up examination can be considered as the most effective way to detect thyroid cancer at an early stage. The aim of our study is to determine the frequency of thyroid nodules, the rate of thyroid cancer development, and their relationship with the variables in individuals without any known thyroid disease, who presented to our hospital for a check-up examination for general health evaluation.

Materials and Methods

The study was approved by the Ethics Committee of Medipol University (10840098-604.01.01-E.17833 number: 535) and conducted in accordance with the principles of the Declaration of Helsinki. The computer database records of the patients who presented to Medipol Mega University Hospital for a routine check-up examination between 2015 and 2020 were screened. The hospital's database was systematically screened, and after accessing the thyroid US records, the demographic data of the patients, thyroid US reports, cytology and histopathology results, free t3 (fT3), free t4 (fT4) and thyroid-stimulating hormone (TSH) levels were evaluated and recorded. Body mass index (BMI) was calculated by dividing the body weight by the square of the height (kg/m^2) and recorded.

The US evaluation was performed using three separate Logic P5 devices and a 10-12 mHz probe available in the hospital. The US characteristics were evaluated in three categories:

the presence of nodule (yes, no), nodule composition (solid, cystic, and mixed), and nodule diameter (mm). In addition, the nodules were scored according to the thyroid imaging reporting and data system (TIRADS) classification, which is a scoring system based on the evaluation of the composition of the nodule and its microcalcifications, echogenicity, shape, margin structure, and the presence of bright foci. Accordingly, the nodules were categorized as TIRADS 1 (normal thyroid gland), 2 (benign lesions), 3 (possible benign lesions), 4a (one suspicious feature), 4b (two suspicious features), 4c (three to four suspicious features) and 5 (all five suspicious traits). The presence of solid components, significant hypoechogenicity, microlobulation, microcalcification, and an increased vertical-horizontal height ratio were considered as suspicious features. In the presence of multiple nodules, the nodule with the highest TIRADS score was taken into consideration irrespective of size.

As a result of the evaluated data, the patients who were considered to be suitable for thyroid FNAB were determined. The cytology results were evaluated in three categories: benign, suspicious for malignancy, and malignant. The operation types of the surgical patients were recorded. All patients who were recommended a surgical operation but were not operated in our hospital were contacted by telephone to confirm that they had not undergone any thyroid operation or follow-up of nodules prior to the study date. Patients with a prior history of any known thyroid disease or thyroid cancer and those using any medication for an existing thyroid disease were excluded. The histopathology results were classified as benign, PTC, FTC, and medullary thyroid carcinoma (MTC).

Statistical Analysis

In the study, the data collected from the hospital database were analyzed using SPSS v. 25. All the data belonging to the study showed normal distribution according to the Kolmogorov-Smirnoff test. Thyroid cancer detection rates and related factors were investigated using the Student's t-test (continuous variables) and the chi-square test (categorical variables). A p-value of less than 0.05 was considered statistically significant. Variables found significant in the Student's t-test were analyzed with decision groups. Possible factors determined as a result of one-way analysis were further analyzed with a multinominal logistic regression analysis to identify the independent predictors of the disease. The variables with a confidence interval (CI) of 95% and an odds ratio (OR) of >1 were accepted to indicate an increased risk of detecting thyroid cancer in existing nodules.

Results

A total of 30,449 patients, including 12,207 (40.09%) male and 18,242 (59.91%) female, were determined to have applied to the hospital for check-up purposes. The mean age of all these patients was 39.3±2.2 years. Table 1 shows the general characteristics of the check-up patients. The mean BMI was 25.12±3.76 kg/m², and the mean TSH, fT3 and fT4 values were 2.15±0.62 mIU/mL, 3.88±0.69 pg/mL, and 1.38±0.33 pg/mL, respectively. A total of 6,087 patients with a previously known thyroid disease [followed up thyroid nodules, 1,216 (3.99%); hypothyroidism, 4,683 (15.38%); and hyperthyroidism, 188 (0.63%)] were excluded from the study.

Thyroid nodules were incidentally detected in 5,645 of the 24,362 patients who were evaluated. Based on this number, it was determined that 23.17% of all check-up patients had thyroid nodules. The characteristics of the patients with incidentally detected thyroid nodules are shown in Table 2. While 3,014 (53.39%) of these patients were female, 2,631(46.61%) were male. The patients with thyroid nodules had a mean BMI of 27.56±2.01 kg/m², a mean TSH value of 2.87±0.45 mIU/mL, a mean fT3 value of 3.76±0.87 pg/mL, and a mean fT4 value of 1.23±0.24 pg/mL. The mean nodule size was 1.31±0.56 mm, and 2,936 (52.01%) of the detected nodules were solid, 1,377 (24.39%) were cystic, and 1,332 (23.59%) were mixed. When the nodules were categorized according to the TIRADS classification in US imaging, 1,916 (33.94%) were evaluated as TIRADS 2, 3,273 (57.98%) as TIRADS 3, 234 (4.31%) as TIRADS 4a, 114 (1.27%) as TIRADS 4b, 72 (1.27%) as TIRADS 4c, and 36 (0.63%) as TIRADS 5.

Table 1. Characteristics of the check-up patients

Variable	
Age (mean ± SD)	39.3±2.2 years
Gender (n=30.449)/%	
Male	12,207 (40.09%)
Female	18,242 (59.91%)
Body mass index (kg/m²)	25.12±3.76
TSH value (mean ± SD) mIU/L	2.15±0.62
Free T3 value (mean ± SD) pg/mL	3.88±0.69
Free T4 value (mean ± SD) pg/mL	1.38±0.33
Known thyroid disease	
None	24,362 (80.00%)
Followed up thyroid nodule	1,216 (3.99%)
Hypothyroidism	4,683 (15.38%)
Hyperthyroidism	188 (0.63%)

TSH: Thyroid-stimulating hormone, SD: Standard deviation

Since 122 of 514 patients who were recommended a biopsy did not undergo this procedure in our hospital, the results of the remaining 392 patients were evaluated. Table 3 demonstrates the characteristics of the patients who underwent a biopsy. The biopsy results were reported as benign for 224 (57.14%) patients, suspected malignancy for 100 (25.51%), and malignant for 68 (17.34%). Thyroid surgery was performed in 142 of 168 patients, who were recommended to undergo an operation, in our hospital. The surgical procedures performed in these patients were lobectomy in 36 patients (25.35%), bilateral total thyroidectomy in 96 (67.60%), and bilateral total thyroidectomy + central neck dissection in 10 (7.04%). According to the final pathology report of 142 operated patients, there were malignant thyroid tumors in 114 patients (80.28%), of whom 40.35% were male and 59.65% were female. The rates of patients diagnosed with PTC, FTC and MTC were 63.15%, 34.21%, and 2.63%, respectively. Eight patients (7.01%) had lymph node metastasis. Radioactive iodine treatment was used in 36% of the patients after surgery. When the tumor diameters were evaluated according to cancer types, the mean tumor diameters in PTC, FTC and MTC were 0.9±0.12 mm, 1.7±0.41 mm, and 1.1±0.12 mm, respectively.

When the relationship between the demographic and other characteristics of the patients with nodules and the risk of thyroid cancer was evaluated, thyroid cancer risk had no relationship with the TSH, fT3 and fT4 values and age but was found to be related to BMI, gender, nodule structure and diameter, and TIRADS score (Table 4). A

Table 2. Characteristics of the patients with thyroid nodules incidentally detected during the check-up examination

Variable	
Thyroid nodule presence (n=24,362)/%	
Absent	18,717 (76.82%)
Present	5,645 (23.18%)
Gender in nodule presence (n=5.645)/%	
Male	2,631 (46.61%)
Female	3,014 (53.39%)
BMI in nodule presence (kg/m²)	27.56±2.01
Nodule structure (n, %)	
Solid	2,936 (52.01%)
Cystic	1,377 (24.39%)
Mixed	1,332 (23.59%)
Mean nodule size (cm)	1.31±0.56
TSH value (mean ± SD) mIU/L	2.87±0.45
Free T3 value (mean ± SD) pg/mL	3.76±0.87
Free T4 value (mean ± SD) pg/mL	1.23±0.24
TIRADS classification (n, %)	
TIRADS 2	1,916 (33.94%)
TIRADS 3	3,273 (57.98%)
TIRADS 4a	234 (4.31%)
TIRADS 4b	114 (2.01%)
TIRADS 4c	72 (1.27%)
TIRADS 5	36 (0.63%)

TSH: Thyroid-stimulating hormone, SD: Standard deviation, BMI: Body mass index, TIRADS: Thyroid imaging reporting and data system

Table 3. Characteristics of the patients that underwent a biopsy with incidentally detected thyroid nodules

Variable	
Patients with incidentally detected thyroid nodules (n=5,645)	
Biopsy not recommended	4,617 (81.79%)
Biopsy recommended	514 (9.10%)
Biopsy performed	392 (6.94%)
Biopsy not performed	122 (2.16%)
Biopsy result (n=392)	
Benign	224 (57.14%)
Suspected malignancy	100 (25.51%)
Malignant	68 (17.34%)
Operation type (n=142)	
Right total lobectomy	24 (16.90%)
Left total lobectomy	12 (8.45%)
Bilateral total thyroidectomy	96 (67.60%)
Bilateral total thyroidectomy + central neck dissection	10 (7.04%)
Histological type of tumor (n=114)	
Papillary thyroid cancer	72 (63.15%)
Follicular thyroid cancer	39 (34.21%)
Medullary thyroid cancer	3 (2.63%)
Gender in tumor presence (n=114)	
Male	46 (40.35%)
Female	68 (59.65%)
Tumor diameter according to histological type (mean ± SD)	
Papillary thyroid cancer	0.9 ±0.12 cm
Follicular thyroid cancer	1.7±0.41 cm
Medullary thyroid cancer	1.1±0.12 cm
Lymph node metastasis	
Present	8 (7.01%)
Absent	106 (92.98%)
RAI treatment	
Present	36 (31.57%)
Absent	78 (68.42%)

RAI: Radioactive iodine, SD: Standard deviation

multinominal logistic regression analysis was applied to all variables found significant in the univariate analysis (backward stepwise method). According to the results, the risk of thyroid cancer was increased 1.7-fold by increased BMI (OR: 1.71, 95% CI: 1.43-2.96), 1.8-fold by female gender (OR: 1.79, CI: 1.21-2.67), 1.6-fold by solid structure nodule type (OR: 1.62, CI: 1.27-8.54), 2.7-fold by increased nodule size (OR: 2.71, CI: 1.11-3.31), and 4.7-fold by increased TIRADS (OR: 4.73, CI: 1.76-7.31) (Table 5).

Table 4. Comparison of variables between the patients with benign thyroid nodules and those with thyroid cancer

Variable	Benign group	Cancer group	p
Age (years)	34.52 (±2.44)	36.57 (±2.84)	**0.396**
Gender (n, %)	-	-	**0.037***
Male	2,605 (46.93)	46 (40.35)	-
Female	2,946 (53.07)	68 (59.65)	-
BMI (kg/m^2)	26.4 (±1.5)	29.6 (±2.3)	**0.034***
Nodule structure (n, %)	-	-	**0.021***
Solid	2,840 (51.35)	96 (84.21)	-
Cystic	1,377 (24.89)	0 (0)	-
Mixed	1,314 (23.76)	18 (15.79)	-
Mean nodule size (mm)	0.98 (±0.11)	1.56 (±0.84)	**0.031***
Mean TSH value	2.52 (±0.24)	2.91 (±0.36)	0.342
Mean T3 value	3.81 (±0.45)	3.65 (±0.29)	0.714
Mean T4 value	1.52 (±0.24)	1.19 (±0.049)	0.374
TIRADS classification	-	-	**0.017***
TIRADS 1-2	1.916 (34.64)	0 (0)	-
TIRADS 3	3.269 (59.10)	4 (3.51)	-
TIRADS 4	344 (6.22)	76 (66.67)	-
TIRADS 5	2 (0.003)	34 (29.82)	-

TSH: Thyroid-stimulating hormone, SD: Standard deviation, BMI: Body mass index, TIRADS: Thyroid imaging reporting and data system, *Statistically significant at 0.05

Table 5. Multivariate logistic regression analysis of the presence of thyroid cancer (dependent: thyroid cancer; independent: investigated variables)

	Exp (B)	p	OR	OR (95% CI)
Gender	2,918	**0.004***	1.79	(1.21-2.67)
BMI	2,312	**0.004***	1.71	(1.43-2.96)
Nodule structure (solid)	1,189	**0.035***	1.62	(1.27-3.54)
Nodule size	2,117	**0.012***	2.71	(1.11-3.31)
TIRADS staging	2,745	**0.002***	4.73	(1.76-7.31)

*Statistically significant at 0.05. Backward method, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, TIRADS: Thyroid imaging reporting and data system

Discussion

Check-up examinations, which have become increasingly important in the last decade, are among one of the most common reasons for adults to seek medical help (1). Diagnostic centers and hospitals offer various health check-up ''packages'' to meet this need (15). The purpose of a routine health check should be to identify risk factors and early signs of disease, as well as to prevent the development of future diseases with early intervention or to prevent the manifestation of diseases by changing risk factors (16). Furthermore, routine health checks are often comprehensive in their approach and involve the evaluation of multiple organ systems simultaneously to detect health problems. However, this non-specific method can sometimes cause more harm than good due to overdiagnosis, overtreatment, distress or injury caused by invasive follow-up tests, anxiety caused by false positive test results, false assurance due to false negative test results, and possible continuation of negative health behaviors.

Check-up ''packages'' include blood tests, electrocardiogram, echocardiogram, abdominal US and thyroid US scans. Among these, thyroid US is the gold standard in the diagnosis of thyroid nodules. Non-palpable nodules detected during US or other imaging methods are called ''incidental nodules'' or ''incidentalomas''. In fact, thyroid nodules are frequently encountered in clinical practice. It is known that the prevalence of thyroid nodules in the general population is 4-7% based on detection by palpation alone (4). On the other hand, with the development of modern diagnostic technology and the introduction of high-resolution US into clinical practice, there has been a significant increase in the detection of thyroid incidence in recent years. It should also be noted that the rate of thyroid nodule detection gradually has also increased with the wide use of US in check-up screening in healthy individuals. In this study, we determined the prevalence of thyroid US incidentaloma as 23.18% while the prevalence of thyroid cancer was 0.47%. The clinical importance of detecting thyroid nodules by US is based on the need to exclude thyroid cancer, which is seen in 7-15% of cases depending on various factors (6). Of all the thyroid nodules detected in our study, 1.98% were malignant, which is consistent with the rates reported in the literature (5).

The main point to be discussed based on this study is that in research conducted in countries, such as the United States and South Korea, where cancer statistics are recorded without exception, there has been a significant increase in the incidence of thyroid cancer within the last

three decades according to epidemiological information; however, thyroid cancer-related mortality has not increased during this period and remained at a constant rate of 0.5 per 100,000 (8,17). Although we were not able to obtain the data on the long-term results and mortality of our patients since they presented to our hospital for a check-up examination and some were already being followed up in different health institutions, we consider that the general knowledge that the early diagnosis of cancer can be life-saving may not always be valid for thyroid cancer, and routine check-up controls may lead to the overdiagnosis of this cancer. On the other hand, in patients diagnosed early, surgical treatment is performed when the tumor is small and there is no capsule infiltration or lymph node metastasis; thus, there is less surgical morbidity, such as recurrent nerve injury and reduced need for radioactive iodine treatment.

In our report, although the demographic data were consistent with female dominance reported in previous studies, the female-male ratio was 1.14 in the presence of thyroid nodules and 1.47 in thyroid cancer, which are lower compared to the literature data (18-20). As a result of the multivariate logistic regression analysis performed by ignoring the difference between the rates of nodule detection between genders, we have demonstrated that the rate of thyroid cancer development in patients with nodules in the female gender is significantly higher compared to the male gender.

There was no significant difference in age between the patients with and without malignant nodules. Although many studies reported a higher incidence of malignancy in the elderly individuals (19), there are also researchers showing that malignant nodules are more common among patients aged ≤45 years (21,22). When we evaluated our data in terms of cancer types, PTC was the most common at a frequency of 63.15%, followed by FTC at 34.21% and MTC at 2.63%. The results in our study are consistent with the literature in terms of PTC being the most common among the differentiated thyroid cancers, and its predominance was also observed in all previous studies (4,23,24). In our study, total thyroidectomy was performed in 67.60% of the cases, lobectomy in 25.35%, and total thyroidectomy with central neck dissection in 7.04% (1.6%).

The main radiological evaluation of thyroid nodules is always performed by US, and it is known that some sonographic findings are observed more frequently in malignant nodules. The sonographic size of the nodule is used as a basis for performing thyroid FNAB and determining the scope of the surgery to some extent. Whether the size of the thyroid nodule affects the risk of malignancy or the accuracy of thyroid FNAB remains controversial, but this parameter is often used in decision-making regarding surgical and medical treatment. Therefore, it is important to determine whether there is a relationship between nodule size and malignancy risk. In our study, a statistically significant difference was found between the size of the malignant and non-malignant nodules, and it was observed that the incidence of malignancy detection increased as the nodule diameter increased. However, there are conflicting findings in the literature concerning the relationship between nodule diameter and malignancy (25-28). Some authors suggested that nodule size was a reliable determinant of malignancy and reported a non-linear relationship between cancer risk and increased thyroid nodule size (25). Supporting this, another study showed that the risk of malignancy was higher in nodules of 2 cm or larger (26). In contrast, other studies suggested that the size of thyroid nodules was inversely related to the risk of malignancy, with lower rates of malignancy seen in larger nodules (27,28).

It is also commonly accepted knowledge that solitary thyroid nodules have higher malignant potential than cystic nodules. Although a completely cystic nodule is rare (<2% of all nodules), it is probably not malignant. In addition, the spongy appearance, which is defined as more than half of the nodule volume filled with multiple microcystic contents, indicates a benign thyroid nodule at a rate of 99.7% (4). In our study, when the variables of the patients with benign thyroid nodules and thyroid cancer were compared, a high significant statistical association was found between the solid structure of the nodule and thyroid cancer. However, the multivariate analysis revealed that the presence of solid nodules was not the only criterion for malignancy, and only when combined with ultrasonographic TIRADS staging, it showed a significant association for thyroid cancer.

In thyroid nodules, in addition to the size and/or solitary nature, the likelihood of cancer is higher if it presents with certain sonographic features, including higher hypoechogenicity compared to normal thyroid parenchyma, increased intranodular vascularity, irregular infiltrative borders, presence of microcalcification, absence of a halo, and the height of the nodule being greater than its transverse dimension (4). Except for suspected non-sensitive cervical lymphadenopathy that is specific for malignancy, no sonographic finding alone or in combination is sufficient to detect all malignant nodules. However, some features and their combination are of

high predictive value for malignancy. Therefore, score-based classifications are used, in which each sonographic suspicious finding is considered as a separate risk factor for malignancy and the risk of malignancy increases as the number of these findings increases in a nodule (23). In our study, it was shown that the risk of malignancy significantly increased in patients with TIRADS 4c and 5 nodules compared to the other TIRADS groups among the cases that were recommended a biopsy.

In our study, the mean TSH value of the patients with thyroid nodules was found to be 2.87±0.45. It remains unclear whether TSH plays a role in the development or progression of this disease, or both. The results of many studies have supported the association between high TSH levels and the risk of thyroid cancer in nodular thyroid disease (29). However, in our study, when the variables of the patients with benign thyroid nodules and those with thyroid cancer were compared, no statistically significant relationship was found between the TSH value and thyroid cancer.

It is well known that increased BMI constitutes a risk factor for different types of cancer (30). In addition, there are different studies showing a positive relationship between thyroid cancer and BMI (31-33). In our study, the mean BMI of the patients detected to have thyroid nodules during the check-up examination was calculated to be 27.56±2.01. There was also a statistically significant relationship between BMI and thyroid cancer, and the thyroid cancer risk was observed to increase with the increase in BMI. These results were similar to the data in the literature.

Study Limitations

Our study has certain limitations and strengths. The most important limitation is the retrospective design and that not all patients recommended a biopsy underwent this procedure. However, it is useful to note that almost all patients with a high thyroid cancer risk according to TIRADS staging (TIRADS 4b, 4c, 5) were biopsied. The patient group in which a biopsy could not be performed was the TIRADS 4a group, and the risk of malignancy in this group of patients is around 3% according to our review of the literature. In addition, the most important aspect of this study is that it included the highest number of check-up patients that were incidentally detected to have thyroid nodules. All patients were ultrasonographically examined by expert radiologists, and TIRADS staging was used as standard in all cases.

Conclusion

The main difficulty in evaluating and managing thyroid nodules is to avoid the inappropriate overuse of thyroid US, thyroid FNAB and surgery while trying to identify clinically significant malignant nodules. In doing so, although clinical studies have provided strong evidence on screening methods to clarify international guidelines, hard data on the benefits and harm of various screening tests are still lacking, and the role of check-up examinations and thyroid cancer screening in the general population remains controversial. Regarding the diagnosis of thyroid cancer through a check-up examination, the data obtained as a result of more detailed studies should be evaluated and the increased incidence of thyroid cancer in the last three years may not only be as a result of overdiagnosis but also due to a real increase in incidence caused potentially modifiable factors, such as radiation exposure, iodine intake, and lifestyle. However, considering that early diagnosis of thyroid cancer without lymph node involvement can reduce both surgical complications and prevent the risks of radioactive iodine treatment, it is concluded that thyroid cancer being detected at an early stage constitutes an important advantage for the healthy population undergoing a check-up.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Medipol University (10840098-604.01.01-E.17833 number: 535).

Informed Consent: Due to the retrospective nature of the study, we did not seek informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.A., Design: D.A., P.B., Data Collection or Processing: D.A., P.B., Analysis or Interpretation: P.B., Literature Search: D.A., Writing: D.A.

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

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

References

1. Mehrotra A, Zaslavsky AM, Ayanian JZ. Preventive health examinations and preventive gynecological examinations in the United States. Arch Intern Med 2007;167(17):1876-1883.
2. Sox HC. The health checkup: Was it ever effective? Could it be effective? JAMA 2013;309(23):2496-2497.

3. Song CY, Shen Y, Lu YQ. Role of routine check-up in the prognosis of patients with pancreatic cancer: A puzzling phenomenon. Hepatobiliary Pancreat Dis Int 2021;20(1):67-73.

4. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1-133.

5. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 2009;39(8):699-706.

6. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004;351(17):1764-1771.

7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7-30.

8. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140(4):317-322.

9. Leenhardt L, Bernier MO, Boin-Pineau MH, Conte DB, Maréchaud R, Niccoli-Sire P, et al. Advances in diagnostic practices affect thyroid cancer incidence in France. Eur J Endocrinol 2004;150(2):133-139.

10. Brito JP, Al Nofal A, Montori V, Hay ID, Morris JC. The impact of subclinical disease and mechanism of detection on the rise in thyroid cancer incidence: a population-based study in Olmsted County, Minnesota during 1935 through 2012. Thyroid 2015;25(9):999-1007.

11. Singh Ospina N, Iñiguez-Ariza NM, Castro MR. Thyroid nodules: diagnostic evaluation based on thyroid cancer risk assessment. BMJ 2020;368:l6670.

12. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167-1214.

13. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, et al. AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules--2016 Update. Endocr Pract 2016;22(5):622-639.

14. Jameson JL, De Groot JL. Endocrinology adult and pediatric. In: Thyroid Neoplasia, Pacini F, Marchisotta S, De Groot JL (editors). 6th ed., Philadelphia: Saunders Elsevier, 2010:1668-1701.

15. Krogsbøll LT, Jørgensen KJ, Grønhøj Larsen C, Gøtzsche PC. General health checks in adults for reducing morbidity and mortality from disease: cochrane systematic review and meta-analysis. BMJ 2012;345:e7191. doi: 10.1136/bmj.e7191.

16. Gøtzsche PC, Jørgensen KJ, Krogsbøll LT. General health checks don't work. BMJ 2014;348:g3680. doi: 10.1136/bmj.g3680.

17. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"-screening and overdiagnosis. N Engl J Med 2014;371(19):1765-1767.

18. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Curr Opin Endocrinol Diabetes Obes 2017;24(5):332-336.

19. Figge JJ. Epidemiology of thyroid cancer. In Thyroid Cancer: A Comprehensive Guide to Clinical Management. 2nd ed., New York: Springer, 2006:9-13.

20. Preston-Martin S, Franceschi S, Ron E, Negri E. Thyroid cancer pooled analysis from 14 case–control studies: What have we learned? Cancer Causes Control 2003;14(8):787-789.

21. Rago T, Fiore E, Scutari M, Santini F, Di Coscio G, Romani R, et al. Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease. Eur J Endocrinol 2010;162(4):763-770.

22. Bessey LJ, Lai NB, Coorough NE, Chen H, Sippel RS. The incidence of thyroid cancer by fine needle aspiration varies by age and gender. J Surg Res 2013;184(2):761-765.

23. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, et al. Thyroid imaging reporting and data system for US features of nodules: A step in establishing better stratification of cancer risk. Radiology 2011;260(3):892-899.

24. Chow SM, Law SC, Au SK, Leung TW, Chan PT, Mendenhall WM, et al. Differentiated thyroid carcinoma: comparison between papillary and follicular carcinoma in a single institute. Head Neck 2002;24(7):670-677.

25. Kamran SC, Marqusee E, Kim MI, Frates MC, Ritner J, Peters H, et al. Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 2013;98(2):564-570.

26. Raparia K, Min SK, Mody DR, Anton R, Amrikachi M. Clinical outcomes for "suspicious" category in thyroid fine-needle aspiration biopsy: patient's sex and nodule size are possible predictors of malignancy. Arch Pathol Lab Med 2009;133(5):787-790.

27. Cavallo A, Johnson DN, White MG, Siddiqui S, Antic T, Mathew M, et al. Thyroid nodule size at ultrasound as a predictor of malignancy and final pathologic size. Thyroid 2017;27(5):641-650.

28. Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006;91(9):3411-3417.

29. Zafón C, Obiols G, Mesa J. Preoperative TSH level and risk of thyroid cancer in patients with nodular thyroid disease: Nodule size contribution. Endocrinol Nutr 2015;62(1):24-28.

30. Pischon T, Nimptsch K. Obesity and risk of cancer: an introductory overview. Recent Results Cancer Res 2016;208:1-15.

31. Han JM, Kim TY, Jeon MJ, Yim JH, Kim WG, Song DE, et al. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. Eur J Endocrinol 2013;168(6)879-886.

32. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005;23(21):4742-4754.

33. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, et al. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. Int J Cancer 2012;131(6):E1004-E10014. doi: 10.1002/ijc.27601

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):257-263
DOI: 10.4274/BMB.galenos.2021.02.020

The Effectiveness of CT Enterography in the Radiological Evaluation of Crohn's Disease

Crohn Hastalığının Radyolojik Değerlendirmesinde BT Enterografisinin Etkinliği

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Abstract

Objective: The aim of this study is to evaluate the effectiveness of computed tomography enterography (CTE) in demonstrating luminal and extraluminal pathologies in patients diagnosed with Crohn's disease (CD).

Method: In 20 symptomatic patients histopathologically diagnosed with CD, CTE findings obtained after optimal bowel distension with oral contrast material were evaluated retrospectively. The involved segment was evaluated in terms of the presence of intestinal wall thickening (focal or diffuse), pathological contrast enhancement in the intestinal wall, increased vascularity in the intestinal mesentery, mesenteric lymphadenopathy, intraperitoneal fluid, enteric fistula, and intraabdominal abscess. In addition, evaluation was made in terms of extraintestinal findings that might be related to the disease.

Results: A total of 20 patients (11 females, 9 males; age range: 24 to 61 years, mean age: 39.7±11.4 years) were included in the study. The most frequently affected intestinal segment was the terminal ileum (n=10, 50%). Pathological intestinal wall enhancement was detected in 14 patients (70%), mesenteric lymphadenopathy in 16 patients (80%), and comb sign in 15 patients (75%). Intraabdominal abscess was detected in 4 cases (20%) and enteric fistula in 4 cases (20%). Related to the disease, kidney stones in one patient and previous cholecystectomy findings in two patients were observed.

Conclusion: CTE is a very effective method that can simultaneously monitor the intestinal and extraintestinal findings of the symptomatic patients with CD and guide the treatment choice.

Keywords: Abscess, complication, Crohn's disease, CT enterography, enteroclysis, fistula, wall thickening

Öz

Amaç: Bu çalışmanın amacı, bilgisayarlı tomografi enterografisinin (BTE) Crohn hastalığı (CH) tanısı almış hastalarda lümen içi ve lümen dışı patolojileri göstermedeki etkinliğini değerlendirmektir.

Yöntem: Histopatolojik olarak CH tanısı konulan semptomatik 20 hastada oral kontrast madde ile optimal barsak distansiyonu sonrası elde edilen BTE bulguları geriye dönük olarak değerlendirildi. Tutulan segment intestinal duvar kalınlaşması (fokal veya diffüz), bağırsak duvarında patolojik kontrastlanma, intestinal mezenterde artmış vaskülerite, mezenterik lenfadenopati, intraperitoneal sıvı, enterik fistül, intraabdominal apse varlığı açısından değerlendirildi. Ayrıca hastalığa bağlı olabilecek ekstraintestinal bulgular açısından değerlendirme yapıldı.

Bulgular: Çalışmaya toplam 20 hasta (11 kadın, 9 erkek; yaş aralığı: 24-61 yıl, ortalama yaş: 39,7±11,4 yıl) dahil edildi. En sık etkilenen bağırsak segmenti terminal ileumdu (n=10, %50). On dört hastada (%70) patolojik bağırsak duvarında kontrastlanma, 16 hastada (%80) mezenterik lenfadenopati ve 15 hastada (%75) tarak işareti saptandı. Dört olguda (%20) karın içi apse ve 4 olguda (%20) enterik fistül tespit edildi. Hastalıkla ilgili olarak, bir hastada böbrek taşı ve iki hastada geçirilmiş kolesistektomi bulguları izlendi.

Sonuç: BTE, CH olan semptomatik hastaların intestinal ve ekstraintestinal bulgularını eş zamanlı olarak izleyebilen ve tedavi seçimine yön verebilen çok etkili bir yöntemdir.

Anahtar kelimeler: Apse, BT enterografisi, Crohn hastalığı, duvar kalınlaşması, enterokliz, fistül, komplikasyon

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Cite this article as: Herdem N, Tekcan Şanlı DE. The Effectiveness of CT Enterography in the Radiological Evaluation of Crohn's Disease. Bagcilar Med Bull 2021;6(3):257-263

Introduction

Crohn's disease (CD) is a transmural disease that can affect all parts of the gastrointestinal tract from the mouth to the anus, which typically involves the terminal ileum (1). The disease, which progresses with relapses and remissions, shows a bimodal distribution, and most frequently affects young adults. Inflammation, which is limited to the mucosa in the early period, deepens as the disease progresses and affects other layers of the intestine and may even exceed the serosa, leading to complications such as perforation, abscess, and fistula (2-4). It may involve multiple segments where the loops remain normal (skip lesion). While obstruction secondary to spasm due to mucosal inflammation and irritation can be seen in the intestinal passage in the acute or active period (string sign), in the chronic period, obstructions due to strictures that occur as a result of healing with fibrosis can be seen. In addition, in the active phase of the disease, prominence of mesenteric vascular structures (comb sign), mesenteric lymphadenopathy and intraabdominal fluid can be seen (2).

Despite technological advances in imaging methods, difficulties are still encountered in the diagnosis of CD. Since it is difficult to reach the small intestine with endoscopic methods, the effectiveness of endoscopy is limited in the histopathological diagnosis of the disease that mainly affects the small intestine. Although new techniques such as capsule endoscopy and double balloon endoscopy have been developed, their use has not become widespread because they require expensive equipment, do not show extraluminal pathologies and do not allow therapeutic procedures (5-7). Therefore, radiological methods still maintain their importance not only in the diagnosis of CD but also in showing the signs of activation and complications. Until the 2000s, enteroclysis has been the gold standard method in CD imaging because it allows the evaluation of mucosal pathologies and bowel functions (8-10). Enteroclysis has begun to leave its place to cross- sectional imaging methods because it is an invasive method, unable to show extraluminal pathologies. Another disadvantage of enteroclysis is excessive radiation exposure. With the isotropic resolution properties of multi-detector computed tomography (CT) devices developed in recent years, images with a thickness of less than 1 mm and multiplanar reformat images obtained during a single breath hold allow much more detailed evaluation of small bowel pathologies and extraluminal findings, and play an important role in revealing complications (11-14). Similarly, with the high soft tissue resolution and the development of rapid new sequences, magnetic resonance imaging (MRI) has taken its place among the radiological methods in the diagnosis of CT enterography (CTE) and revealing complications (15-18).

In this study, we aimed to evaluate luminal and extraluminal pathologies detected by CTE in symptomatic cases with histopathologically diagnosed CD and to compare our findings with the literature.

Materials and Methods

Study Population

Between August 2014 and February 2016, imaging findings of 65 patients who underwent CTE due to the diagnosis or activation suspicion of CD were evaluated retrospectively. Fourty-five patients were excluded because they had no histopathological diagnosis of CD. In addition, patients over 65 years of age, patients with benign prostatic hyperplasia, myasthenia gravis, congestive heart failure, glaucoma, and patients with contrast allergy were not included in the study. Ethics committee approval of Erciyes University numbered 2016/291 was obtained for the study.

Imaging Method

Liquid diet was applied to all patients for 1 day before the examination and all patients fasted for 8 hours before the procedure. In order to provide bowel distension, the patients were given an oral contrast solution obtained from 1 liter of drinking water and 1 liter of 20% mannitol within 45 minutes before the examination. In the 45th minute, the patients were taken to the CT unit and manually 20 mg intravenous (I.V.) hyosine-n-butyl bromide (Buscopan) and 120 mL I.V. non-ionic iodine concentration 350 mg/100 mL contrast material were given via automatic injector at 4 mL/sec. and in the 30th second, single- phase acquisition was made with a 320-detector CT device (Toshiba Aquilion ONE 320 detector CT scanner). After obtaining images with 5 mm sections and 1.25 mm thin sections in the axial plan, reformatted images were created in the coronal and sagittal planes.

Image Analysis

Measuring the intestinal wall thickness above 3 mm in the distended bowel segments was considered pathological. Intestinal segments with higher density than normal bowel segments were evaluated in favor of pathological wall enhancement. Mesenteric lymph nodes with a short axis greater than 5 mm were considered pathological. Linear

tracts observed between two epithelial surfaces in the intestinal loops were evaluated as fistula, and peripheral contrast-enhancing fluid collections as abscesses. In addition, evaluation was made in terms of extraintestinal findings that might be related to the disease (cholelithiasis, nephrolithiasis).

Statistical Analysis

SPSS 21 (SPSS Inc. IBM company, Chicago) program was used for statistical analysis. Descriptive data were presented as mean, standard deviation, minimum and maximum values, frequency and ratio. As the overall number of cases was relatively small, no inferential statistical analysis was undertaken.

Results

Of the patients participating in the study, 9 (45%) were male and 11 were female (55%). The average age of the patients was 39.7±11.4 (24-61) years. The most commonly involved segment was terminal ileum (n=10, 50%). Pathological wall thickening was detected in 15 patients (75%) and wall enhancement in 14 patients. Pathological wall thickening was detected in all patients with wall enhancement. No intestinal segment involvement was observed in five patients. All involved segments in order of frequency were demonstrated in Table 1.

Abscess was detected in four cases (20%). One patient with an abscess had undergone surgery previously because of colon perforation and a colostomy was present on CTE. Bowel involvement was not present in one case with multiple intraabdominal abscesses. In another case, pathological wall thickening and wall enhancement were observed in the ascendant colon, and the abscess appeared as microabscesses around the colon. The fistula was observed in 4 cases (20%). There were ileoileal and ileojejunal fistulas in one case and ileocolic in the other cases. Fistula and abscess were present together in two cases.

Mesenteric lymphadenopathy (LAP) was detected in 16 cases (80%) and comb sign in 15 cases (75%). Comb sign and mesenteric LAP were present in all cases with pathological wall thickening. The case with mesenteric LAP without intestinal involvement was a 32-year-old female patient diagnosed with CD three years ago. Ileus was detected in 1 case and ileocecal invagination in 1 case. Pathologic findings of CD on CTE was demonstrated in Table 2.

Among the extraintestinal findings that may be associated with the disease, kidney stones in 1 case and findings from previous cholecystectomy in 2 cases were observed. In addition, findings not related to CD, nodule in the liver in three cases, infarct in the spleen in one case, and mass in the uterus in one case were detected incidentally. Sample cases were shown in Figures 1-5.

Table 1. Involved bowel segments in order of frequency

Involved segment	Number (n) percent (%)
Terminal ileum	10 (50%)
Distal ileum	7 (35%)
Cecum	6 (30%)
Sigmoid colon	4 (20%)
Ascending colon	4 (20%)
Transverse colon	3 (15%)
Rectum	3 (15%)
Jejunum	2 (10%)
Descending colon	2 (10%)
Appendix	1 (5%)

Discussion

Enteroclysis, which is the gold standard diagnostic method in the evaluation of CD and other small bowel pathologies, has begun to be abandoned today because of its invasive nature, and diagnostic quality depends on the practitioner and the device (19). It is not available in every center and the examination period is long (8-10). In addition to the diagnosis of the disease with cross-sectional imaging methods, the simultaneous detection of activation and complication findings is one of the important reasons leading to this situation. In studies comparing enteroclysis and CTE, no significant difference was found between the two methods in terms of their ability to show mucosal and mural pathologies (19). In addition, CTE has been shown to be superior in detecting transmural spread patterns such as fistula and abscess, which are important for treatment planning and patient management, intra-abdominal fluid, mesenteric LAP, increased vascularity and extraintestinal involvement (20-23). Also, evaluation of upper gastrointestinal

Table 2. Pathologic findings of Crohn's disease on CTE

Finding	Number (n) percent (%)
Intestinal wall thickening	15 (75%)
Mural enhancement	14 (70%)
Abscess	4 (20%)
Fistula	4 (20%)
Mesenteric LAP	16 (80%)

CTE: Computed tomography enterography, LAP: Leukocyte Lymphadenopathy, comb sign 15 (75%)

and colon involvement, detection of skip lesions and detection of conglomeration-separation findings in the intestinal folds were found to be higher in CTE (20-23).

One of the most important aspects in the detection of small bowel pathologies, especially mucosal lesions, pathological wall thickening, presence of fistula and the degree of obstruction is to provide optimal intestinal distension (24,25). It may cause false positives in the evaluation of wall thickening and deficiencies in stenotic segment-stricture evaluations in insufficiently distended bowel loops. Also, artifacts caused by intestinal peristaltic activity limit the evaluation of mucosal and mural lesions in particular. With the development of multidetector CT devices, serial images can be obtained in a very short time and by the development of rapid MRI sequences, the wrong evaluations due to these artifacts have been relatively prevented. In addition, I.V. hyosine-n-butyl bromide

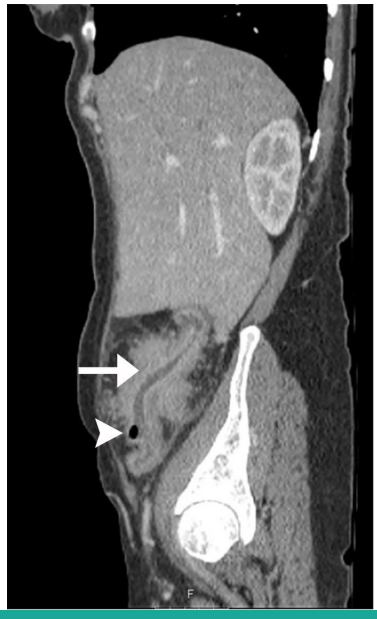

Figure 1a. In a 42-year-old female case, sagittal CTE image shows thickening, enhancement of the mucosa (white arrow) and gas density (arrowhead) adjacent to the anterior colon wall

CTE: Computed tomography enterography

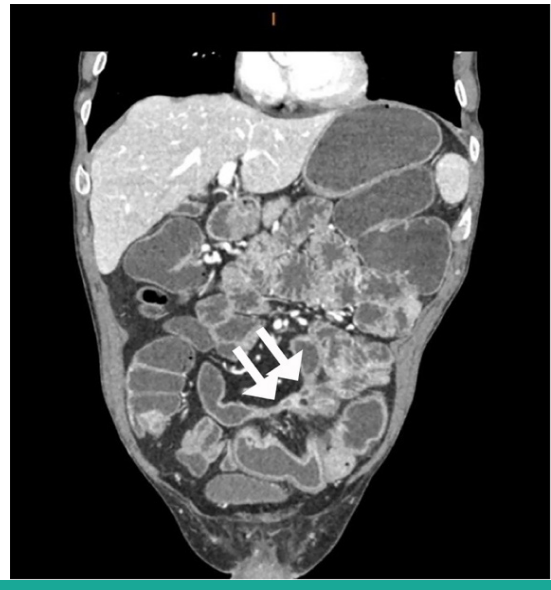

Figure 2a. In a 46-year-old male case, coronal CTE image shows fistula tracts (white arrow) extending from the distal ileum to the sigmoid colon

CTE: Computed tomography enterography

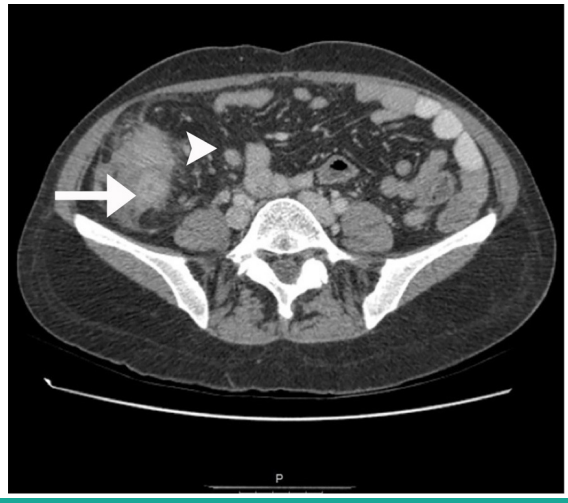

Figure 1b. In the axial view, the lymph node (arrowhead) is seen in the mesenteric fatty plans, adjacent to the thickening and enhancement of the wall (white arrow), with a peripheral enhancing microabscess (arrowhead)

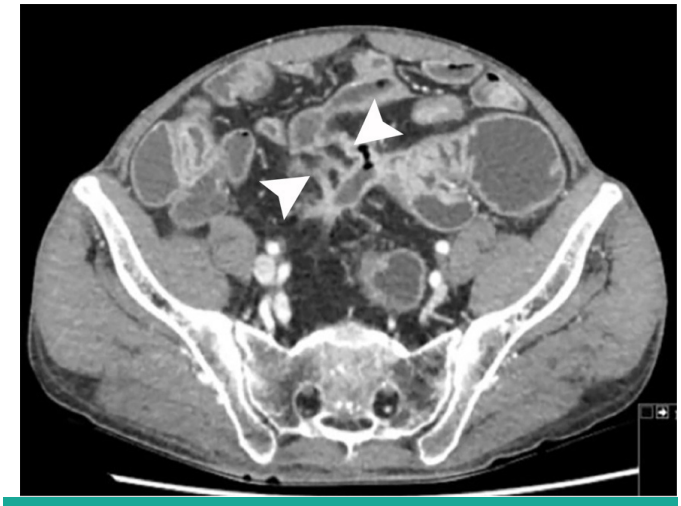

Figure 2b. In the axial section, fistula tracts (arrowheads) extending between the ileal loops and sigmoid colon, and also the neighboring mesenteric fatty tissues are contaminated

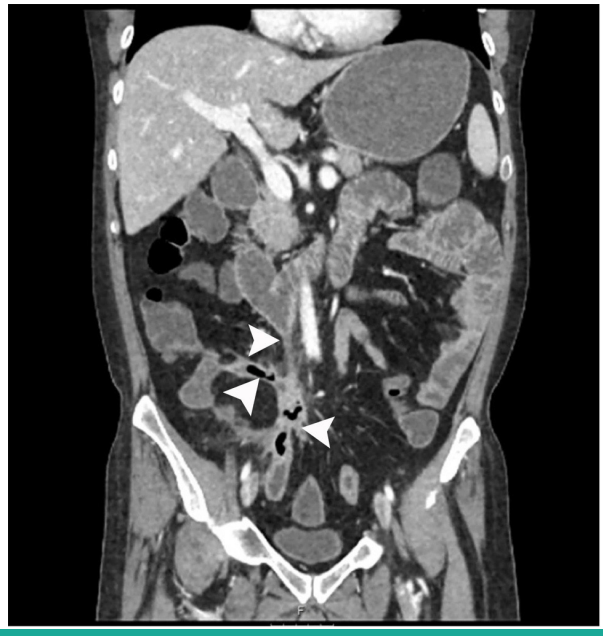

Figure 3. In a 43-year-old male patient, multiple fistula tracts (arrowheads) are observed between the ileal and jejunal segments in the coronal CTE image

CTE: Computed tomography enterography

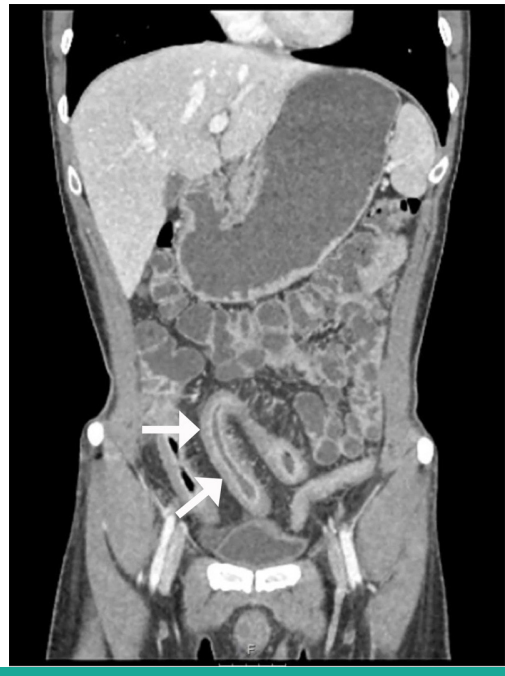

Figure 4b. In the coronal view, wall thickening and mucosal enhancement in the ileum (white arrows) and adjacent vascular engorgement-comb sign are seen

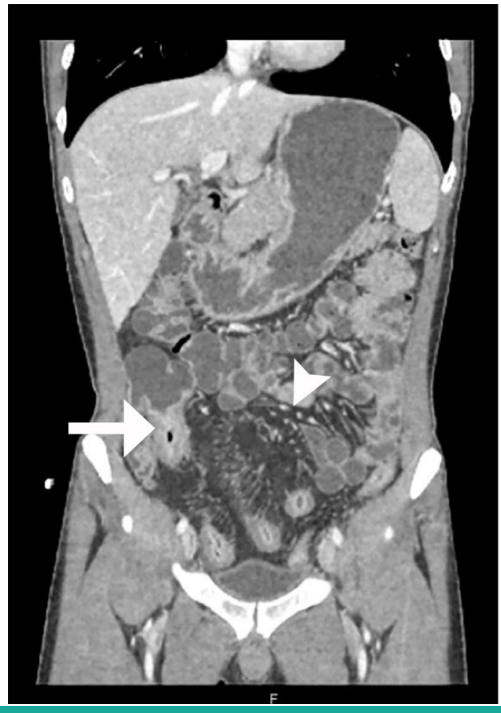

Figure 4a. In a 31-year-old male patient with a history of operation due to Crohn's disease, coronal CTE image shows thickening of the ileum wall adjacent to the anastomosis line and mucosal enhancement (white arrow). Note the increase in mesenteric vascularity (comb sign) (arrowheads)

CTE: Computed tomography enterography

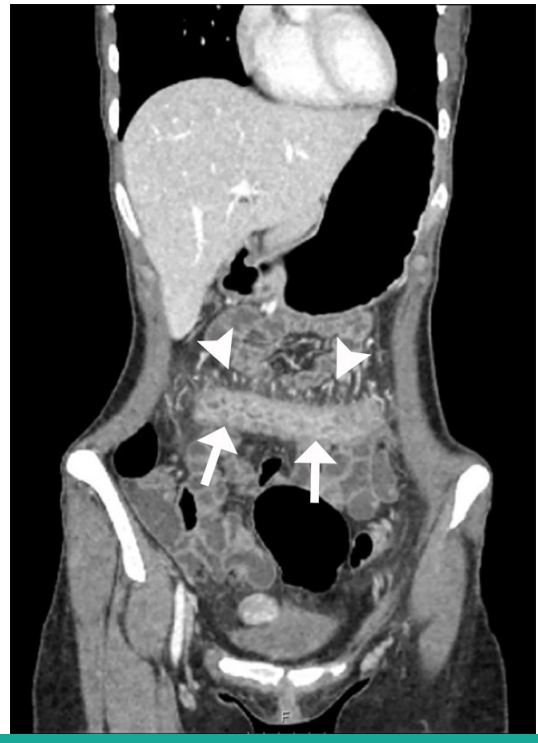

Figure 5. A 23-year-old female case, the coronal CTE image shows diffuse wall thickening of the transverse colon, cobblestone pattern (white arrows), and adjacent mucosal enhancement with venous engorgement (arrowheads) and lymph node

CTE: Computed tomography enterography

(buscopan), which is administered just before extraction in order to reduce bowel movements, helps to overcome this limitation (24,25).

In the diagnosis of CD and the detection of complications, CTE is a very useful and practical imaging method compared to other radiological methods because it is a non-invasive method that is easy to access and apply. The most important disadvantage of CTE is radiation exposure (26). Due to the fact that the majority of the patients are young and the nature of the disease is relapse-remission, this situation becomes more frightening in repeated applications (9,27). However, with new and fast devices and calibration settings that keep up with developing technological changes, the radiation effect has been reduced to insignificant levels.

In this study, in accordance with the literature, the most commonly involved segment was terminal ileum. In addition to diffuse colonic involvement, isolated appendix involvement was found in one case. Isolated appendix involvement in CD is very rare in the literature (28,29).

Lo Re et al. (30) reported upper gastrointestinal system involvement as 3.2% in their study. In our study, esophagus-stomach involvement of the upper gastrointestinal system was not detected. In our study, the rate of fistula detection was found to be 20%, and all of them were entero-enteric fistulas. Similar rates were obtained in studies aiming to measure the prevalence of penetrating disease and extraintestinal pathology. The rate of fistula and sinus tract was reported as 32% by Goldberg et al. (31), and 17% by Bruining et al. (21). Also, abscess detection rate (20%) in our study was consistent with the literature (32).

Study Limitations

The major limitation of our single center retrospective study was the small number of patients. In addition, we could not compare the luminal and extraluminal CTE findings of the disease with other radiological methods such as enteroclysis and MRI. In this respect, studies that compare with other modalities with higher number of patients can be tried in the future.

Conclusion

CTE plays a key role in patient management and treatment planning in CD, as it provides the opportunity to show diagnosis-activation-complication findings in a single session. Although radiation exposure seems to be a disadvantage especially for the young patient group, this handicap has been prevented with new multidetector CT devices.

Ethics

Ethics Committee Approval: Ethics committee approval of Erciyes University Faculty of Medicine numbered 2016/291 was obtained for the study.

Informed Consent: Written informed consent was not necessary because no patient data have been included in the manuscript.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.H., D.E.T.Ş., Design: N.H., D.E.T.Ş., Data Collection or Processing: N.H., D.E.T.Ş., Analysis or Interpretation: N.H., D.E.T.Ş., Writing: N.H., D.E.T.Ş.

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

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

References

1. Lopes S, Andrade P, Afonso J, Cunha R, Rodrigues-Pinto E, Ramos I, et al. Monitoring Crohn's disease activity: endoscopy, fecal markers and computed tomography enterography. Therap Adv Gastroenterol 2018;11:1756284818769075.
2. Carbo AI, Reddy T, Gates T, Vesa T, Thomas J, Gonzalez E. The most characteristic lesions and radiologic signs of Crohn disease of the small bowel: air enteroclysis, MDCT, endoscopy, and pathology. Abdom Imaging 2014;39(1):215-234.
3. Scharitzer M, Koizar B, Vogelsang H, Bergmann M, Primas C, Weber M, et al. Crohn's disease: prevalence, MR features, and clinical significance of enteric and colonic sinus tracts. Eur Radiol 2020;30(10):5358-5366.
4. Lightner AL, Ashburn JH, Brar MS, Carvello M, Chandrasinghe P, van Overstraeten AB, et al. Fistulizing Crohn's disease. Curr Probl Surg 2020;57(11):100808.
5. Yang DH, Keum B, Jeen YT. Capsule Endoscopy for Crohn's Disease: Current Status of Diagnosis and Management. Gastroenterol Res Pract 2016;2016:8236367.
6. Huang Z, Liu X, Yang F, Wang G, Ge N, Wang S, Guo J, Sun S. Diagnostic efficacy of double-balloon enteroscopy in patients with suspected isolated small bowel Crohn's disease. BMC Gastroenterol 2020;20(1):42.
7. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2015;47(4):352-376.
8. Akman C, Korman U, Oğüt G, Kuruğoğlu S, Urger E, Ulus S, et al. A combination of small bowel imaging methods: conventional enteroclysis with complementary magnetic resonance enteroclysis. Clin Radiol 2005;60(7):778-786.
9. Masselli G, Vecchioli A, Gualdi GF. Crohn disease of the small bowel: MR enteroclysis versus conventional enteroclysis. Abdom Imaging 2006;31(4):400-409.

10. Korman U, Kurugoglu S, Ogut G. Conventional enteroclysis with complementary MR enteroclysis: a combination of small bowel imaging. Abdom Imaging 2005;30(5):564-575.

11. Bodily KD, Fletcher JG, Solem CA, Johnson CD, Fidler JL, Barlow JM, et al. Crohn Disease: mural attenuation and thickness at contrast-enhanced CT Enterography--correlation with endoscopic and histologic findings of inflammation. Radiology 2006;238(2):505-516.

12. Hara AK, Leighton JA, Sharma VK, Heigh RI, Fleischer DE. Imaging of small bowel disease: comparison of capsule endoscopy, standard endoscopy, barium examination, and CT. Radiographics 2005;25(3):697-711; discussion 711-718.

13. Macari M, Megibow AJ, Balthazar EJ. A pattern approach to the abnormal small bowel: observations at MDCT and CT enterography. AJR Am J Roentgenol. 2007;188(5):1344-1355.

14. Maglinte DD, Sandrasegaran K, Tann M. Advances in alimentary tract imaging. World J Gastroenterol 2006;12(20):3139-3145.

15. Fidler J. MR imaging of the small bowel. Radiol Clin North Am 2007;45(2):317-331.

16. Prassopoulos P, Papanikolaou N, Grammatikakis J, Rousomoustakaki M, Maris T, Gourtsoyiannis N. MR enteroclysis imaging of Crohn disease. Radiographics 2001;21 Spec No: S161-172. doi: 10.1148/radiographics.21.suppl_1.g01oc02s161.

17. Masselli G, Gualdi G. MR imaging of the small bowel. Radiology 2012;264(2):333-348.

18. Fujii T, Naganuma M, Kitazume Y, Saito E, Nagahori M, Ohtsuka K, et al. Advancing magnetic resonance imaging in Crohn's disease. Digestion 2014;89(1):24-30.

19. Sanli DET, Sanli AN, Kandemirli SG, Esmerer E, Kayadibi Y, Demiryas S, Korman MU. The mutually complementary role of magnetic resonance enterography and conventional enteroclysis in patients with complicated and/or advanced stage of Crohn's disease. Bratisl Lek Listy 2021;122(4):270-276.

20. Solem CA, Loftus EV Jr, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointest Endosc 2008;68(2):255-266.

21. Bruining DH, Siddiki HA, Fletcher JG, Tremaine WJ, Sandborn WJ, Loftus EV Jr. Prevalence of penetrating disease and extraintestinal manifestations of Crohn's disease detected with CT enterography. Inflamm Bowel Dis 2008;14(12):1701-1706.

22. Higgins PD, Caoili E, Zimmermann M, Bhuket TP, Sonda LP, Manoogian B, et al. Computed tomographic enterography adds information to clinical management in small bowel Crohn's disease. Inflamm Bowel Dis 2007;13(3):262-268.

23. Paulsen SR, Huprich JE, Hara AK. CT enterography: noninvasive evaluation of Crohn's disease and obscure gastrointestinal bleed. Radiol Clin North Am 2007;45(2):303-315.

24. Grand DJ, Beland MD, Machan JT, Mayo-Smith WW. Detection of Crohn's disease: Comparison of CT and MR enterography without anti-peristaltic agents performed on the same day. Eur J Radiol 2012;81(8):1735-1741.

25. Grand DJ, Kampalath V, Harris A, Patel A, Resnick MB, Machan J, et al. MR enterography correlates highly with colonoscopy and histology for both distal ileal and colonic Crohn's disease in 310 patients. Eur J Radiol 2012;81(5):e763-769.

26. Ryan ER, Heaslip IS. Magnetic resonance enteroclysis compared with conventional enteroclysis and computed tomography enteroclysis: a critically appraised topic. Abdom Imaging 2008;33(1):34-37.

27. Estay C, Simian D, Lubascher J, Figueroa C, O'Brien A, Quera R. Ionizing radiation exposure in patients with inflammatory bowel disease: are we overexposing our patients? J Dig Dis 2015;16(2):83-89.

28. Crellin AJ, Musbahi O, Onwu N, Singh S. Appendiceal Crohn's disease: a rare differential of right iliac fossa pain. BMJ Case Rep 2020;13(2):e232549. doi: 10.1136/bcr-2019-232549.

29. Rábeková Z, Vacková Z, Šerclová Z, Malušková J, Bennett R, Martínek J. Crohns disease of the appendix - a case report. Rozhl Chir 2018;97(12):563-567. (English)

30. Lo Re G, Cappello M, Tudisca C, Galia M, Randazzo C, Craxì A, et al. CT enterography as a powerful tool for the evaluation of inflammatory activity in Crohn's disease: relationship of CT findings with CDAI and acute-phase reactants. Radiol Med 2014;119(9):658-666.

31. Goldberg HI, Gore RM, Margulis AR, Moss AA, Baker EL. Computed tomography in the evaluation of Crohn disease. AJR Am J Roentgenol 1983;140(2):277-282.

32. Yamaguchi A, Matsui T, Sakurai T, Ueki T, Nakabayashi S, Yao T, et al. The clinical characteristics and outcome of intra-abdominal abscess in Crohn's disease. J Gastroenterol 2004;39(5):441-448.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):264-270
DOI: 10.4274/BMB.galenos.2021.04.043

The Effectiveness of CT Metal Artifact Reduction Technique and Its Contribution to Radiological Evaluation in Lumbar Stabilization

Lomber Stabilizasyonda BT Metal Artefakt Azaltma Tekniğinin Etkinliği ve Radyolojik Değerlendirmeye Katkısı

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Abstract

Objective: Metal artifact reduction (MAR) systems, which have been patented by the firms and specific to them, have been developed to reduce the losses in the images, which are caused by artifacts, and to increase the diagnostic value of computed tomography (CT). The objective of this study is to determine the effectiveness of the MAR technique, which minimizes the image loss caused by metal artifacts in CTs taken for the lumbar spinal region where metallic implants are located, and its contributions to radiological evaluation.

Method: Patients with spinal stabilization, whose CT imaging records of both standard and smartMAR (SMAR) reconstruction were performed between June 2020 and March 2021 and could be accessed, were evaluated. Critical anatomical structures were defined as: spinal canal (SC), neural foramen (NF), and prevertebral-paravertebral area (P-PA). The image quality of critical anatomical structures were evaluated using a 5-point image quality scale for soft tissue (400/35 HU) and bone window settings (2.500/480 HU) on standard and SMAR reconstructed CT images. In addition, the size of the flame artifact was measured and recorded in millimeters in standard and SMAR images.

Results: Of the 24 patients with lumbar spinal stabilization who met the inclusion criteria, 8 were male, and 16 were female (66%). The age range was determined to be between 26 and 82 years (mean=60). The stabilization of all patients was in the form of posterior transpedicular screw and rod fixation. The radiation dose distribution ranged between 3.23 and 14.1 millisieverts (mSv) (mean=8.95 mSv). The worst visualization score was obtained on SC imaging, which was evaluated in the soft tissue window. In bone window evaluations of these structures, the visualization

Öz

Amaç: Radyolojik görüntülerde artefakta bağlı oluşan kayıpları azaltmak ve çekilen bilgisayarlı tomografinin (BT) tanısal değerini artırmak üzere firmalara özel patentli metal artefaktı azaltma (MAR) sistemleri geliştirilmiştir. Bu çalışmanın amacı, metalik implantların bulunduğu lomber spinal bölgeye yönelik çekilen BT'lerde, metal artefaktından kaynaklanan görüntü kayıplarını minimalize etmeye yarayan MAR tekniğinin etkinliğini ve radyolojik değerlendirmeye katkılarını belirlemektir.

Yöntem: Haziran 2020-Mart 2021 tarihleri arasındaki dönemde, spinal stabilizasyonu olan hem standart hem de smartMAR (SMAR) rekonstrüksiyon uygulanmış BT kayıtlarına ulaşılan hastalar değerlendirildi. Kritik anatomik yapılar olarak tanımlanan spinal kanal (SK), nöral foramenler (NF) ve prevertebral-paravertebral alan (P-PA), standart ve SMAR rekonstrüksiyonlu BT görüntülerinde, yumuşak doku (400/35 HU) ve kemik pencere (2,500/480 HU) için 5 puanlı görüntü kalite ölçeği kullanılarak değerlendirildi. Ayrıca, alev artefaktının boyu standart ve SMAR'li görüntülerde milimetre olarak ölçülerek kaydedildi.

Bulgular: Çalışmaya dahil edilme kriterlerini karşılayan lomber spinal stabilizasyonlu 24 hastanın, 8'i erkek ve 16'sı kadındı (%66). Yaş aralığı 26-82 yaş arasında (ortalama=60) bulundu. Hastaların hepsinin stabilizasyonu posterior transpediküler vida ve rod fiksasyon şeklindeydi. Radyasyon doz dağılımı 3,23 ile 14,1 milliSievert (mSv) (ortalama=8,95 mSv) arasındaydı. En kötü vizualizasyon skoru yumuşak doku penceresinde değerlendirilen SK görüntülemesinde elde edildi. Bu yapıların kemik pencere değerlendirmelerinde, SK için vizualizasyon skorları (medyan) standart ve SMAR'li görüntülemelerde sırasıyla 3 ve 4 (Z=-3,926, p<0,001), NF için 4 ve 5 (Z=-3,666, p<0,001), P-PA için 4

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Cite this article as: Baş NS, Baş S. The Effectiveness of CT Metal Artifact Reduction Technique and Its Contribution to Radiological Evaluation in Lumbar Stabilization. Bagcilar Med Bull 2021;6(3):264-270

Abstract

scores (median) in standard and SMAR imaging's were found to be 3 and 4 (Z=-3.926, p<0.001) for SC, 4 and 5 for NF (Z=-3.666, p<0.001), and 4 and 5 (Z=-4.203, p<0.0001) for P-PA, respectively. These differences were also significant. Bone cortex visualization score (median), measured on bone window images, were determined to be 4 (minimum:2, maximum:5) and 5 (minimum:4, maximum:5) (Z=-4.028, p<0,0001) in standard and SMAR imagings, respectively. As an objective criterion, the flame artifact length, which was evaluated only in bone window images, was 26 mm on average (standard deviation ±9.78) (minimum:8, maximum:54 mm) in standard imaging, whereas it decreased to 3.66 mm (standard deviation ±2.54) (minimum:0, maximum:7 mm) in reconstructions via SMAR.

Conclusion: The MAR technique significantly reduces the artifacts occurring with standard techniques in adjacent tissues applied for medical treatment purposes and allows a clearer evaluation of this region by the radiologist. The use of this technique enhances the quality of CT images and the diagnostic value of radiological examination. However, there is a need for the development of MAR software for optimal imaging.

Keywords: Computed tomography, flame artifact, lumbar stabilization, metal artifact

Öz

ve 5 (Z=-4,203, p<0,0001) olarak bulundu. Bu farklar da istatistiki olarak anlamlıydı. Kemik pencere görüntülerinde ölçüm yapılan kemik korteks vizualizasyon skoru (medyan), standart ve SMAR'li çekimlerde sırasıyla 4 (minimum:2, maksimum:5) ve 5 (minimum:4, maksimum:5) (Z=-4,028, p<0,0001) olarak bulundu. Objektif kriter olarak değerlendirilen alev artefakt boyu standart çekimlerde ortalama 26 mm (standart sapma ±9,78) (minimum:8, maksimum:54 mm) iken SMAR'li rekonstrüksiyonlarda 3,66 mm'ye (standart sapma ±2,54) (minimum:0, maksimum:7 mm) düştü.

Sonuç: MAR tekniği, komşu dokularda oluşan artefaktları belirgin olarak azaltmakta ve radyolog tarafından bu bölgenin daha net değerlendirilebilmesine imkan vermektedir. Bu tekniğin kullanımı, BT görüntülerinin kalitesini ve radyolojik incelemenin tanısal değerini artırır. Ancak optimal görüntüleme için MAR yazılımlarının geliştirilmesine ihtiyaç vardır.

Anahtar kelimeler: Alev artefakt, bilgisayarlı tomografi, lomber stabilizasyon, metal artefakt

Introduction

The use of spinal metallic instrumentation for medical applications such as instability and/or reducing pain is considerably common in neurosurgery practice. The number and variety of these stabilization surgeries have increased gradually over the years (1). Computed tomography (CT) and magnetic resonance imaging (MRI) are used for both the diagnosis and postoperative follow-up evaluation of the patients. Hence, metallic artifacts are often encountered in spinal imaging (2). The lumbar region is the spinal area where metallic stabilization material is used mostly. Artifacts related to spinal stabilization materials in standard CT and MRI scans reduce diagnostic confidence by hiding the anatomy and/or pathology in adjacent tissues (2-4). Because of this, metal artifact reduction (MAR) systems, which have been patented by the firms and are specific to them, have been developed for modalities both to reduce the losses in the images, which are caused by artifacts, and to increase the diagnostic value of CT and MRI (2). The objective of this study is to determine the effectiveness of the MAR technique, which minimizes the image loss caused by metal artifacts in CTs taken for the lumbar spinal region where metallic implants are located, and its contributions to radiological evaluation.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul Yeni Yüzyıl University (date: 05.04.2021/no. 2021/04-653). Informed consent forms were obtained from the patients before the CT procedure.

Patients with spinal stabilization, whose CT imaging records of both standard and SMAR reconstruction were performed between June 2020 and March 2021 and could be accessed, were evaluated. Patients who had only CT imaging with standard technique and did not have MAR reconstruction, as well as the patients who underwent CT scans for regions other than the lumbar region, were excluded from the evaluation. Twenty-four lumbar stabilization patients who met these criteria were included in the study.

CT Acquisition and Image Reconstruction

The CT examinations were performed with a single source, 512 slice multidetector CT scanner (Revolution CT, GE Healthcare, Milwaukee, WI). The scanning mode had the following parameters: Tube voltage 120 kVp assist mode, tube current SmartmA mode (100-500 mA), detector coverage 40 mm, helical pitch 0.0992, rotation time 0.80 s, slice thickness 1.25 mm, slice interval 1.25 mm, and scan FOV 50 cm.

CT images were reconstructed by using a conventional (standard) weighted filtered back-projection (wFBP) and prototype SMAR algorithm (spine parameters). SMAR was performed by using a vendor-specified ''spine'' setting, which entails predetermined SMAR reconstruction parameters appropriate for spinal anatomy and hardware.

Each study was evaluated by viewing wFBP and SMAR images side-by-side, first with soft tissue settings [window width, 400 hounsfield units (HU); window level, 35 HU] and subsequently with bone window settings (window width, 2500 HU; window level 480 HU). Images were only evaluated in the axial plane without multiplanar reformations. After reconstructions, images were loaded onto the Advantage Windows Workstation 4.7 (GE Healthcare, Milwaukee, Wisconsin/USA) for viewing.

Subjective Evaluation Criteria and Image Analysis

As the study was limited to the instrumentations in the lumbar region, critical anatomical structures were defined as: spinal canal (SC), neural foramen (NF), and prevertebral-paravertebral area (P-PA). Two radiologists concurrently evaluated the image quality of critical anatomical structures using a 5-point image quality scale for soft tissue (400/35 HU) and bone window settings (2.500/480 HU) on standard and SMAR reconstructed CT images of the same patient, which was placed side by side (Figure 1, 2). The scale was rated as follows: 1) Severe artifact with invisibility of surrounding structures. 2) Obvious artifacts with significant distortion and insufficient identification of surrounding structures. 3) Moderate artifacts that allow identification of surrounding structures. 4) Mild artifacts with blurring of surrounding structures. 5) No artifacts. A total of 12 separate scorings was made by assessing the soft tissue and bone window separately for the standard and SMAR images of critical anatomical structures.

Moreover, the bone cortex visualization score was evaluated in standard and SMAR imagings, only in bone window images, and scored based on the same scale. The joint scoring decisions of the radiologists were recorded as the visualization score. This procedure was applied to all patients.

Scoring values of 3 and above were diagnostically significant.

Objective Evaluation Criteria

For an objective evaluation, the ‘‘flame’’ artifact, which reflects the length of intense beam hardening and is seen as a dark zone at the tip of the metal, was measured parallel to the pedicle screw in the vertebra. For this measurement, the linear dark band emerging from the screw tip was measured and recorded in millimeters on both standard and SMAR images (Figure 3).

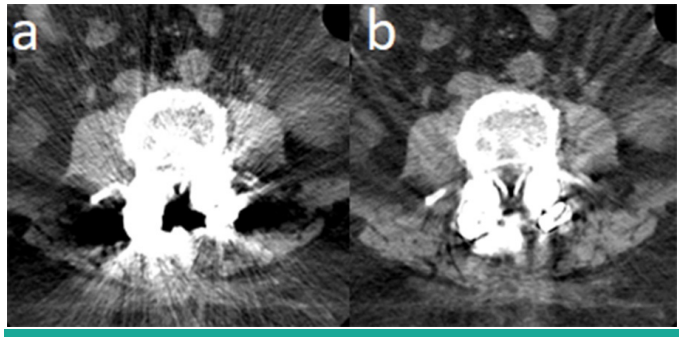

Figure 1. The spinal canal is obscured by artifacts on standard (a) image with soft-tissue window settings. SMAR (b) image with soft-tissue window settings at the same level improved visualization of the spinal canal

SMAR: Smart metal artifact reduction

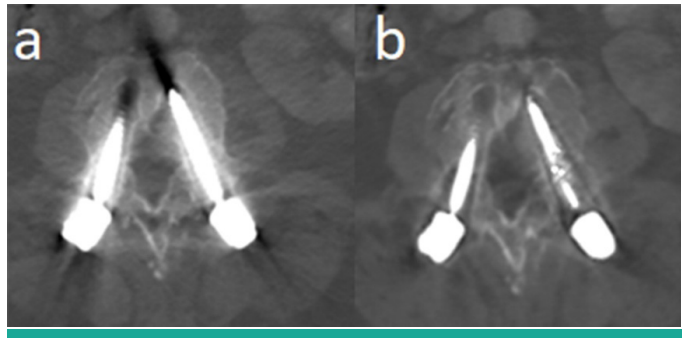

Figure 2. A 72-year-old woman status post L3- to-L5 pedicle screw. Standard (a) and SMAR (b) images at the L5 level using bone window settings demonstrate lucency about both L5 screws, consistent with hardware loosening

SMAR: Smart metal artifact reduction

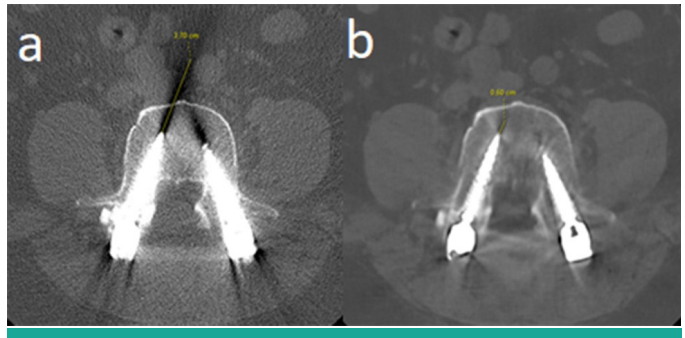

Figure 3. Extent of the flame artifact was measured in millimeters from the tip of the metal object to the end of the linear dark band at the same level on both standard (a) and SMAR images (b). Improvement in artifact severity is demonstrated on the SMAR image

SMAR: Smart metal artifact reduction

Statistical Analysis

The Wilcoxon signed-rank test was performed by comparing the categorical scores provided by the radiologists for critical anatomical structures (lumbar SC, NF, pre-paravertebral

Table 1. Standard and SMAR, subjective and objective analysis results

Radiologist evaluation	Standard (min-max)			SMAR (min-max)			p
	SC	NF	P-PA	SC	NF	P-PA	
Subjective (median)							
-Soft-tissue window visualization score	1 (1-2)	3 (1-4)	2 (1-4)	3 (2-3)	4 (3-5)	4 (3-5)	p<0.0001
-Bone window visualization score	3 (1-5)	4 (2-5)	4 (1-5)	4 (3-5)	5 (3-5)	5 (4-5)	p<0.0001
-Bone cortex visualization score	4 (2-5)			5 (4-5)			p<0.0001
Objective (mean) -Length of flame artifact (mm)	26 (8-54)			3.66 (0-7)			p<0.0001

SC: Spinal canal, NF: Neural foramen, P-PA: Prevertebral-paravertebral area, SMAR: Smart metal artifact reduction

area) using standard and SMAR in soft tissue and bone window images, depending on the image quality and the ability to evaluate. The paired t-test was used to compare flame artifacts on standard and SMAR images, as the data were normally distributed (SPSS 13.0, SPSS Inc., Chicago, IL). For all comparisons, statistical significance was defined as $p<0.05$.

Results

Of the 24 patients with lumbar spinal stabilization, who met the inclusion criteria, 8 were male and 16 were female (66%). The age range was determined to be between 26 and 82 years (mean=60). The stabilization of all patients was in the form of posterior transpedicular screw and rod fixation. The number of stabilization segments was determined to be at least 2 and at most 9 (from dorsal to sacral) (median=3). The radiation dose distribution ranged between 3.23 and 14.1 millisievert (mSv) (mean=8.95 mSv).

Evaluation of Critical Anatomical Structures

Scores of critical structures from subjective criteria evaluated in the lumbar region (soft tissue and bone window, median, minimum-maximum), bone cortex visualization scores (only in bone window), and flame artifact length (only in bone window and mean value) as objective criteria scores and statistical data about these values are presented in Table 1.

In the evaluation of critical anatomical structures in the soft tissue window, the visualization scores (median) in standard and SMAR imagings were determined to be 1 and 3 ($Z=-4.16$, $p<0.0001$) for SC, 3 and 4 ($Z=-4.420$, $p<0.0001$) for NF, and 2 and 4 ($Z=-4.367$, $p<0.0001$) for P-PA, respectively, and the differences between them were statistically significant. The worst visualization score was obtained on SC imaging, which was evaluated in the soft tissue window. In bone window evaluations of these structures, the visualization scores (median) in standard and SMAR imagings were found to be 3 and 4 ($Z=-3.926$, $p<0.001$) for SC, 4 and 5 for NF ($Z=-3.666$, $p<0.001$), and 4 and 5 ($Z=-4.203$, $p<0.0001$) for P-PA, respectively. These differences were also significant.

Bone cortex visualization scores (median) measured on bone window images were determined to be 4 (minimum:2, maximum:5) and 5 (minimum:4, maximum:5) ($Z=-4.028$, $p<0.0001$) in standard and SMAR imagings, respectively.

Objective Artifact Evaluation Measurements

As an objective criterion, the flame artifact length, which was evaluated only in bone window images, was 26 mm on average (standard deviation ±9.78) (minimum:8, maximum: 54 mm) in standard imaging, whereas it decreased to 3.66 mm (standard deviation ±2.54) (minimum:0, maximum:7 mm) in reconstructions via SMAR.

Discussion

Metallic artifacts in spinal and cranial CTs can be caused by stabilization instruments, foreign bodies, metallic materials used in cranioplasty, aneurysm clips, endovascular embolization coils, dental prostheses, and fillings (5). The prevalence of spinal stabilization surgeries has increased over the years, and accordingly, artifacts caused by the used instruments are encountered more commonly (1,2). The first study on MAR was conducted by Kalender et al. (6). Although there have been significant improvements in CT image quality over the last decade, the metal artifact problem has not been eliminated. Artifacts caused by metal implants generate different degrees of severity depending on the shape, size, and variety of the metals used.

Depending on its location, it impairs the image quality of adjacent critical anatomical structures. It restrains the ability to make clear decisions for evaluating physicians and reduces the diagnostic value of CT (7). It limits the evaluation of conditions such as adjacent SC, NF, P-PA anatomy and pathologies, fracture and loosening of the instrumentation material in lumbar metallic materials (3). Thus, CT manufacturers have developed special patented MAR systems to reduce the losses caused by artifact in images and increase the diagnostic value of the captured CTs. The most used commercial patented MAR methods in CT imaging in the presence of clinical real metal implants are as follows: SEMAR (single-energy MAR, Canon Medical Systems, Otawara, Japan), O-MAR (orthopedic MAR, Philips Healthcare, Best, Netherlands), SMAR and MARS (Smart MAR and MAR Sequence, respectively, GE Healthcare, Milwaukee, WI/USA), and MARIS and iMAR (MAR in Image Space and iterative MAR, respectively, Siemens Healthineers, Erlangen, Germany) (7,8).

It is the SMAR (Smart MAR, GE Healthcare, Milwaukee, WI/USA) software, which was used in our study. Smart MAR algorithm firstly identifies the metal in an image, the metal is then removed, and a "metal mask" is generated. An image without metal is then reconstructed, and finally, the metal identified in the first stage is placed over the new images as a "metal mask" (9).

Metal artifact formation occurs thanks to the contribution of beam hardening, scatter, noise, photon starvation, and edge effects. Beam hardening results in dark streaks between high attenuating objects. The scattering shifts the direction of the photons. Noise and photon starvation can be seen in metals with high density and metals with high atomic numbers. This results in completely white dark lines in the final reconstructed image involving the metal (7,10).

In the literature, the number of publications on the effects of various MAR technologies on implant-related CT artifacts on patients is limited. Most studies evaluating MAR algorithms have evaluated orthopedic hardware (such as prostheses) in phantoms, and generally, these studies do not have spinal fixations (3). Besides, most of the studies published on MAR in the literature are the studies conducted with dual-energy CT (5,11).

It has been revealed in the pilot study of Kotsenas et al. (3) that the IMAR reconstruction technique is crucial in visualizing critical anatomical structures such as SC and adjacent paravertebral soft tissues. In addition to that, this technique has been reported to reduce the linear ''flame'' artifact size and enhance the visualization of the vertebral body cortex. Radiologists in this study suggested routine reconstruction of IMAR images in 90% of cases (3). Wang et al. (5) utilized MAR algorithms, which have been generated using dual-energy virtual monochromatic kilo electron volt (keV) images in 18 patients with metal spinal fusion and stabilization material. They conducted the image quality assessment with a subjective 5-point image quality scale, as in our study (5). In this study, screw widths were tried to be measured, and measurements could be achieved with small errors over 100 keV.

The radiation dose distribution administered to the patients in our study ranged between 3.23 and 14.1 mSv (mean=8.95 mSv). In the study of Kotsenas et al. (3), like our study, the radiation dose distribution was reported to be between 5.9 and 40.7 milli Grays (mean=19.6 mGy) (1 mGy=1mSv, updated dose unit mSv). In another study by Aissa et al. (12), the radiation dose was reported as 1.7-34.9 mGy (mean=15.9). These doses are considerably high compared to our study. The reason for this may be the significant reduction in radiation doses administered to patients in all CT examinations thanks to the significant developments in CT technology compared to 2012-2013 when the Kotsenas's study was conducted and 2015-2016 when the Aissa's study was conducted, and/or the use of different brands of CT scanners.

In our study, the worst score from the obtained images was attained as 1 in the SC evaluation in the standard imaging that was performed in the soft tissue window. This score increased to 3 when the SMAR reconstruction was conducted. The best scores were obtained in NF and P-PA evaluation on images with SMAR reconstruction in the bone window, with 5. Although the increase in bone cortex visualization score was more limited, all the score changes between standard and SMAR reconstruction were determined to be significant ($p<0.0001$). Flame artifacts of different lengths were observed in all patients in standard imaging, whereas no flame artifact was observed in 6 (25%) patients in reconstructions with SMAR. Regarding the flame artifact, a remarkable decrease was determined in the size of the artifact between standard and SMAR images (from 26 mm to -3.66 mm), and the difference ($p<0.0001$) was statistically significant as well. It can be suggested that the SMAR technique is successful, particularly in flame artifacts. Our results were found to be compatible with the literature (3,13). Among the critical anatomical structures, the SC score is lower than the NF and P-PA scores in all evaluated imaging parameters. Hence, it can be stated

that metal artifact makes SC evaluation most difficult. This finding has been confirmed by Kotsenas et al. (3) as well.

In our study, in which the scores of 3 and above were considered as diagnostically significant, it is noticed that it is impossible to perform an adequate and safe radiological diagnostic evaluation in SC and P-PA images, which were 1 and 2 points, respectively, in soft tissue standard imaging. On the other hand, with the application of SMAR reconstruction to the same images, these scores increased to 3 for SC and 4 for P-PA; thus, it has gained an improvement that will allow diagnostic evaluation.

Metallic artifact is related to density, and less CT artifact is generated from less dense materials. The artifact density created by the materials is as follows: plastic<titanium<vitallium<stainless steel<cobalt-chromium (2). It has been revealed that the type of metal used in spinal stabilization and the application site may have an impact on MAR performance. Hence, to achieve the best results, it might be important to have the specific metal types and the MAR algorithms to be applied to these metals instructed by the vendors (13).

MAR algorithms are used to reduce cranial deep brain stimulation artifacts as well as improving spinal and other orthopedic prosthesis/implant artifacts (14). It is also helpful in reducing aneurysm clip-coil artifacts and enhancing image quality in axial CT and CT angiography (15,16). In this way, the number of invasive procedures could be reduced. Nonetheless, DSA angiography remains the gold standard for now (15).

Contrary to these, it has been suggested that none of the MAR technologies are useful for heterogeneous, metal-dense dental filling artifacts, even creating new artifacts (17).

Conclusion

The MAR technique significantly reduces the artifacts occurring with standard techniques in adjacent tissues in the presence of metal implants applied for medical treatment purposes and allows a clearer evaluation of this region by the radiologist. The use of this technique in the presence of metal in the scanned area enhances the quality of CT images and the diagnostic value of radiological examination. However, there is a need for the development of MAR software for optimal imaging, albeit they provide significant improvement in metallic artifacts compared to standard images.

Acknowledgments

The authors thank Assistant Prof. Dr. Utku Alkara and Associate Prof. Dr. Burak Eren for their help on this study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul Yeni Yüzyıl University (date: 05.04.2021/no: 2021/04-653).

Informed Consent: Written informed consent was obtained from the patients/ legal guardians for publication of this case report and any accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Martin BI, Mirza SK, Spina N, Spiker WR, Lawrence B, Brodke DS. Trends in lumbar fusion procedure rates and associated hospital costs for degenerative spinal diseases in the United States, 2004 to 2015. Spine (Phila Pa 1976) 2019;44(5):369-376.
2. Malhotra A, Kalra VB, Wu X, Grant R, Bronen RA, Abbed KM. Imaging of lumbar spinal surgery complications. Insights Imaging 2015;6(6):579-590.
3. Kotsenas AL, Michalak GJ, DeLone DR, Diehn FE, Grant K, Halaweish AF, et al. CT metal artifact reduction in the spine: can an ıterative reconstruction technique ımprove visualization? AJNR Am J Neuroradiol 2015;36(11):2184-2190.
4. Stradiotti P, Curti A, Castellazzi G, Zerbi A. Metal-related artifacts in instrumented spine. Techniques for reducing artifacts in CT and MRI: state of the art. Eur Spine J 2009;18(Suppl 1):102-108.
5. Wang Y, Qian B, Li B, Qin G, Zhou Z, Qiu Y, et al. Metal artifacts reduction using monochromatic images from spectral CT: evaluation of pedicle screws in patients with scoliosis. Eur J Radiol 2013;82(8):e360-e366. doi: 10.1016/j.ejrad.2013.02.024.
6. Kalender WA, Hebel R, Ebersberger J. Reduction of CT artifacts caused by metallic implants. Radiology 1987;164(2):576-577.
7. Wellenberg RHH, Hakvoort ET, Slump CH, Boomsma MF, Maas M, Streekstra GJ. Metal artifact reduction techniques in musculoskeletal CT-imaging. Eur J Radiol 2018;107:60-69.

8. Khodarahmi I, Isaac A, Fishman EK, Dalili D, Fritz J. Metal about the hip and artifact reduction techniques: from basic concepts to advanced imaging. Semin Musculoskelet Radiol 2019;23(3):e68-e81. doi: 10.1055/s-0039-1687898.

9. Smart Metal Artifact Reduction (SmartMAR), For Legacy software systems Quick Reference Guide Version 1.0, gehealthcare.com

10. Katsura M, Sato J, Akahane M, Kunimatsu A, Abe O. Current and novel techniques for metal artifact reduction at ct: practical guide for radiologists. Radiographics 2018;38(2):450-461.

11. Lee KYG, Cheng HMJ, Chu CY, Tam CWA, Kan WK. Metal artifact reduction by monoenergetic extrapolation of dual-energy CT in patients with metallic implants. J Orthop Surg (Hong Kong) 2019;27(2):2309499019851176. doi: 10.1177/2309499019851176.

12. Aissa J, Thomas C, Sawicki LM, Caspers J, Kröpil P, Antoch G, et al. Iterative metal artefact reduction in CT: can dedicated algorithms improve image quality after spinal instrumentation? Clin Radiol 2017;72(5):428.e7-428.e12. doi: 10.1016/j.crad.2016.12.006.

13. Guggenberger R, Winklhofer S, Osterhoff G, Wanner GA, Fortunati M, Andreisek G, et al. Metallic artefact reduction with monoenergetic dual-energy CT: systematic ex vivo evaluation of posterior spinal fusion implants from various vendors and different spine levels. Eur Radiol 2012 ;22(11):2357-2364.

14. Nagayama Y, Tanoue S, Oda S, Sakabe D, Emoto T, Kidoh M, et al. Metal artifact reduction in head ct performed for patients with deep brain stimulation devices: effectiveness of a single-energy metal artifact reduction algorithm. AJNR Am J Neuroradiol 2020;41(2):231-237.

15. Kuroda H, Toyota S, Kumagai T, Iwata T, Kobayashi M, Mori K, et al. Feasibility of smart metal artifact reduction algorithm on computed tomography angiography for clipping of recurrent aneurysms after coil embolization. World Neurosurg 2019;127:e1249-e1254.

16. Zopfs D, Lennartz S, Pennig L, Glauner A, Abdullayev N, Bremm J, et al. Virtual monoenergetic images and post-processing algorithms effectively reduce CT artifacts from intracranial aneurysm treatment. Sci Rep 2020;10(1):6629.

17. Huang JY, Kerns JR, Nute JL, Liu X, Balter PA, Stingo FC, et al. An evaluation of three commercially available metal artifact reduction methods for CT imaging. Phys Med Biol 2015;60(3):1047-1067.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):271-275
DOI: 10.4274/BMB.galenos.2021.03.036

The Impact of COVID-19 Pandemic on Female Sexual Behavior

COVID-19 Salgınının Kadın Cinsel Davranışına Etkisi

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Abstract

Objective: The Coronavirus disease-2019 (COVID-19) related isolation has resulted in economic damage, loneliness, fear of death, and depression all around the world. Self-isolation and social distance lead to unintended psychological effects and negatively affect sexual life. This study aimed to investigate women's sexual behavior during the COVID-19 pandemic in our country.

Method: This prospective, observational study was conducted in a tertiary referral hospital between June 27 and July 27, 2020. A questionnaire consisting of 13 questions regarding the sexual life during the COVID-19 pandemic was applied to 169 women aged 18-45 years. Demographic characteristics were recorded. The questions evaluating sexual behavior about the relationship with partner, sexual desire, frequency of intercourse, sexual satisfaction, and fertility desire were asked.

Results: The mean age of the participants was 32.9±7.74 years (18-45). Regarding the per capita monthly income, 84 (60%) patients had a decrease, 53 (37.9%) of them remained stable, and only 3 (2.1%) of them had an increase during the pandemic. Sexual desire was decreased by 32.9% of the participants and remained the same in 58.6% of the participants. A higher rate of 40.5% was observed in the decreased group than in the stable income group with 22.7% (p=0.03). A statistically significant difference was found between the decrease in sexual desire rates. However, when the change in income level of the groups and their sexual satisfaction rates were compared, it was found that sexual satisfaction increased in those with a lower income level, and the difference was statistically significant (p=0.04).

Conclusion: Acute stress caused by the COVID-19 pandemic negatively affected sexuality. The decreased income level reduces sexual desire, but we observed an increase in sexual satisfaction rates in this group.

Keywords: Coronavirus, COVID-19, pandemic, sexual behavior, sexual function

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) ile ilişkili izolasyon tüm dünyada ekonomik hasar, yalnızlık, ölüm korkusu ve depresyon ile sonuçlandı. Kendini izole etme ve sosyal mesafe, istenmeyen psikolojik etkilere neden olur ve cinsel yaşamı da olumsuz etkiler. Bu çalışma, ülkemizde COVID-19 salgını sırasında kadınların cinsel davranışlarını incelemeyi amaçlamaktadır.

Yöntem: Bu prospektif, gözlemsel çalışma, 27 Haziran-27 Temmuz 2020 tarihleri arasında üçüncü basamak bir hastanede gerçekleştirildi. COVID-19 salgını sırasında cinsel yaşam ile ilgili 13 sorudan oluşan bir anket, 18-45 yaş arasındaki 169 kadına uygulandı. Demografik özellikler kaydedildi. Partnerle ilişki, cinsel istek, ilişki sıklığı, cinsel doyum, doğurganlık isteği gibi cinsel davranışları değerlendiren sorular soruldu.

Bulgular: Katılımcıların ortalama yaşı 32,9±7,74 (18-45) idi. Pandemi sırasında, aylık gelirin 84 (%60) hastada azaldığı, 53 (%37,9) hastada aynı kaldığı, sadece 3 (%2,1) hastada arttığı görüldü. Katılımcıların %32,9'unda cinsel istek azalırken, %58,6'sında aynı kaldı. Geliri azalan grupta cinsel istekte azalma (%40,5), geliri değişmeyen gruba (%22,7) göre daha yüksek idi. Cinsel istek oranlarındaki azalma arasında istatistiksel olarak anlamlı bir fark bulundu (p=0,03). Ancak grupların gelir düzeyi değişikliği ile cinsel doyum oranları karşılaştırıldığında ise gelir düzeyi azalanlarda cinsel doyumun arttığı, farkın ise istatistiksel olarak anlamlı olduğu bulundu (p=0,04).

Sonuç: COVID-19 salgınının neden olduğu akut stres, cinselliği olumsuz etkilemiştir. Azalan gelir düzeyi cinsel isteği azaltır, ancak bizim çalışmamızda bu grupta cinsel doyum oranlarında artış gözlemlenmiştir.

Anahtar kelimeler: Cinsel davranış, cinsel işlev, COVID-19, koronavirüs, salgın

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Cite this article as: Kovalak EE, Karabay Akgül Ö, Karacan T, Aybek ÖY, Güraslan H. The Impact of COVID-19 Pandemic on Female Sexual Behavior. Bagcilar Med Bull 2021;6(3):271-275

Introduction

COVID-19 is a contagious disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), a new type of coronavirus. World Health Organization (WHO) first declared the presence of the virus on December 31, 2019, following spreading viral pneumonia cases in Wuhan, China. WHO declared the COVID-19 outbreak as a pandemic on March 11, 2020 (1).

SARS-CoV-2 is RNA virus that primarily affects the respiratory system and is transmitted by large respiratory droplets or direct contact. It can be fatal by causing pneumonia, bronchitis, and SARS (2,3). At the time of writing this study, 80,805,661 people were infected, and 1,766,726 people died because of the disease worldwide. Moreover, borders were closed, travel restrictions and lockdowns were imposed.

The first coronavirus case was reported on March 10, 2020 in our country (4). The health authorities also implemented strict restrictions such as self-isolation, the use of masks, and home quarantine to prevent the spread of the disease.

The disease-related isolation resulted in loneliness, fear of death, and depression. These restrictions also caused the separation of families and partners, and unemployment with loss of income, as observed in previous outbreaks (5,6). Rajkumar (7) reported increased anxiety, depression (experienced by 16-28% of the population), and self-reported stress (shared by 8% of the population) as the most common mental reactions during the COVID-19 pandemic.

Sexuality is a significant part of a couple's life, which may affect mental health (8). Due to the pandemic, self-isolation and social distance have negatively affected sexual life (9). However, there is still a lack of knowledge regarding the effect of pandemic and decreased income on female sexual life.

This study aimed to evaluate women's sexual behavior during the COVID-19 pandemic in our country.

Materials and Methods

This prospective, observational study was conducted in a tertiary referral hospital between June 27 and July 27, 2020. The approval for the study was obtained from the Ministry of Health (2020.05.25T22.02.17). Besides, ethical approval was obtained from the local ethics committee of our hospital (University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Clinical Research Ethics Committee, approval number: 2020.07.2.08.109). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. All participants were included after obtaining informed consent.

A questionnaire consisting of 13 questions regarding the sexual life during the COVID-19 pandemic was applied to 169 women aged 18-45 years, who were admitted to the gynecology outpatient clinic due to routine controls. The questionnaires from the recent studies of Jacob et al. (10) from the UK and Li et al. (11) from China on the same topic were taken as examples. Women with regular and active sexual life were included. The questions about patients' basic characteristics, such as age, education, marital status, monthly income, systemic disease, drug addiction, alcohol consumption, and smoking, were asked. The questions evaluating sexual behavior such as the relationship with partner, sexual desire, frequency of intercourse, sexual satisfaction, and fertility desire were then recorded. The exclusion criteria were as follows; not having a regular partner, COVID-19 positivity, history of cancer, endometriosis, pelvic pain, incontinence, menopause, vaginal atrophy, severe systemic disease (diabetes, hypertension, and coronary artery disease), mental disorders, and pregnancy or lactation. Twenty-nine patients who were not compatible with the inclusion criteria were excluded. One hundred forty women were included in the study. Women were divided into two groups as those above and below the monthly hunger limit. At the time of the study, the monthly hunger limit per person in our country was 2.500 Turkish Liras (TL). The participants in the increased income group were excluded since there were only three women in this group, which was insufficient for statistical comparisons.

The sample size was calculated via the G power program, version 3.1. The effect size to determine the sexual activity of the study group was determined as 0.26. The analysis with a 1-ß of 0,8 and alpha error of 0.05 revealed that 117 patients were required.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) 20 program (IBM Corp, Armonk, NY, USA). In addition to the descriptive statistical methods (mean, standard deviation), the Pearson's chi-square test and Fisher's Exact test were used to compare categorical variables. A p-value of <0.05 was considered statistically significant.

Results

The mean age of the participants was 32.9±7.74 years (18-45). The mean age of their spouse was 36.73±8.54 years. 93.6% of the participants were married, and 52.1% were primary school graduates. 49.3% of the participants had a monthly income below 2.500 TL. Regarding the monthly income, 84 (60%) patients had a decrease, 53 (37.9%) of them remained stable, and only 3 (2.1%) of them had an increase during the pandemic. The rate of living with their parents was 18.6%. Demographic features and the economic status of all participants were shown in Table 1.

16.4% of participants had a worsened relationship with their partner during the COVID-19 pandemic. Sexual desire of the participants was decreased by 32.9% and remained the same in 58.6% of the participants. The frequency of sexual intercourse was the same in 55.7% of women, decreased in 33.6% of women, and increased in 10.7% of women. During the COVID-19 pandemic, sexual satisfaction decreased in 27.9% of participants. 25.7% of respondents reported a reduced fertility desire (Table 2).

The study groups were divided into the stable and decreased income groups after excluding three patients with an increased income due to a low number of participants. No statistically significant difference was found between the groups regarding the relationship with a partner, frequency of sexual intercourse, and fertility desire (p>0.05). However, a statistically significant difference was found between the decrease in sexual desire rates. A higher rate of 40.5% was observed in the decreased group than in the stable income group with 22.7% (p=0.03).

A statistically significant difference was found in terms of sexual satisfaction rates between the income level groups. The rate of increase in sexual satisfaction in those with a decreased income was found to be higher than in those with a stable income (10.7% vs. 0, respectively, p=0.04) (Table 3).

Table 1. Demographic characteristics of women (n=140)

Characteristics	Mean ± SD	
Age (years)	32.90±7.74	
Partner age (years)	36.73±8.54	
	n	**%**
Marital status		
Single/divorced/widowed	9	6.4
Married	131	93.6
Education level		
Illiterate	2	1.4
Primary school graduate	73	52.1
High school graduate	36	25.7
Postgraduate	29	20.7
Per capita monthly income		
<2.500 TL/month	69	49.3
>2.500 TL/month	71	50.7
Monthly income		
Increased	**3**	**2.1**
Reduced	84	60
Remained the same	53	37.9
Living with parents		
Yes	26	18.6
No	114	81.4
Smoking		
Yes	35	25
No		75
Drug and alcohol consumption		
Yes	2	1.43
No	138	98.57

TL: Turkish Lira, SD: Standard deviation

Discussion

In this study, relationship with partner, sexual desire, frequency of intercourse, sexual satisfaction, and fertility desire remained stable in most participants during the COVID-19 pandemic. However, considering the monthly income and evaluation of sexual life, sexual desire was less in the decreased income group. On the contrary, there was an increase in sexual satisfaction in the decreased income group. This may be associated with increased time spent together, less work stress, and less social or family obligations.

The social restrictions, decreased monthly income, fear of unemployment, loneliness, and fear of death increased stress, anxiety, and depression during the pandemic. Hamilton and Meston (12) have reported that prolonged exposure to the aforementioned stress reduces sexual desire.

Several publications have been reported on the effect of the COVID-19 pandemic on sexual functions. Karsiyakali et al. (13) designed a study comprising 1.356 men and women living in large and small cities. They concluded a decreased rate of sexual desire and intercourse frequency but an increased rate of masturbation during the COVID-19 pandemic. The decreased rates were more prominent in couples living in large cities than those living in small cities. These results are supposed to be associated with the population density and the high number of COVID-19 cases in large cities (13). Ibarra et al. (14) also emphasized

Table 2. Distributions related to sexual behaviors

	n	%
Relationship with partner		
Good	26	18.6
Poor	23	16.4
General	91	65
Sexual desire		
Increased	12	8.6
Reduced	46	32.9
Remained the same	82	58.6
Frequency of sexual intercourse		
Increased	15	10.7
Reduced	47	33.6
Remained the same	78	55.7
Sexual satisfaction		
Increased	10	7.1
Reduced	39	27.9
Remained the same	91	65
Fertility desire		
Increased	26	18.6
Reduced	36	25.7
Remained the same	78	55.7

Table 3. Comparison of the sexual behavior of the participants whose income level did not change with those whose income level decreased during the COVID-19 pandemic

	Decreased income (n=84)		Stable income (n=53)		Test statistics	p
	n	%	n	%		
Relationship with partner						
Average	52	61.9	37	69.8	χ^2=2.809	0.246
Good	19	22.6	6	11.3		
Poor	13	15.5	10	18.9		
Sexual desire						
Increased	9	10.7	3	5.7		
Reduced	34	40.5	12	22.7	χ^2=6.978	**0.031**
Remained the same	41	48.8	38	71.7		
Frequency of sexual intercourse						
Increased	11	13.1	3	5.7	χ^2=5.191	0.075
Reduced	32	38.1	14	26.4		
Remained the same	41	48.8	36	67.9		
Sexual satisfaction						
Increased	9	10.7	0	0	χ^2=6.283	**0.043**
Reduced	24	28.6	15	28.3		
Remained the same	51	60.7	38	71.7		
Fertility desire						
Increased	13	15.5	11	20.8	χ^2 =0.954	0.621
Reduced	24	28.6	12	22.6		
Remained the same	47	56	30	56.6		

COVID-19: Coronavirus disease-2019

that COVID-19 negatively affected sexual behaviors. A study conducted with 868 sexually active people in the United Kingdom reported worsening sexual desire, especially in older and single people (10). In another study conducted in China, 37% of the participants showed a decrease in the frequency of sexual intercourse during the pandemic. In this study, age, relationship status with the partner, and sexual desire were found to be closely related to the frequency of intercourse (11).

In a study evaluating sexual functions before and after quarantine during the COVID-19 pandemic, in which 764 women from Poland participated, a statistically significant decrease was observed in the female sexual function index (FSFI) scores. The reduction was higher in unemployed women (15). A study from Italy also found that total FSFI scores of women of reproductive age decreased during the COVID-19 pandemic. Besides, being unable to work at home, having postgraduates, and having multiparity are reported as independent risk factors for a low FSFI score (3).

On the contrary, Hall et al. (16) reported that women's sexual activity increased significantly during intense stress. In another study, Yuksel and Ozgor (17) reported that menstrual irregularities and desire for sexual intercourse increased during the pandemic and total FSFI scores were higher. Micelli et al. (18) found that the frequency of sexual intercourse did not decrease in the vast majority of Italians (66.4%) before and during the pandemic (18). Our results were also compatible with this study. However, more than a third of them decided to postpone having children. These results could be associated with economic instability and fear of the impact of COVID-19 infection on pregnancy outcomes.

Although the relationship between unemployment and sexual activity has not been clarified, unemployment is associated with an increased risk of depression (19). The unemployment and low income caused by the pandemic also support our results.

Controversial results have been reported regarding the effect of the COVID-19 pandemic on sexual functions (15-

19). Although our results are consistent with the decrease in sexual desire in the decreased income group, we may postulate that increased sexual satisfaction could be related to spending more time with the couples at home. The different study results could be explained by the different reactions of the countries to stress management.

Study Limitations

The present study has some limitations. The number of participants in the study group was relatively small. The strength of or study could be attributed to face-to-face interview approach that could lead to more reliable answers. Although the FSFI questionnaire seems to be an objective method to evaluate female sexual dysfunction, the entire parameters of FSFI were not compatible with our study design.

Conclusion

Sexuality is a complex phenomenon affected by a variety of factors. Acute stress caused by the COVID-19 pandemic has negatively affected the quality of life and sexuality. In our study, the decreased income level was associated with decreased sexual desire in women. The truth is that there are still many unknowns regarding both COVID-19 and sexuality. Therefore, larger prospective studies are needed.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the local ethics committee of our hospital (University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Clinical Research Ethics Committee, approval number: 2020.07.2.08.109).

Informed Consent: All participants were included after obtaining informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.E.K., Design: E.E.K., Data Collection or Processing: Ö.Y.A., Ö.K.A., Analysis or Interpretation: T.K., H.G., Drafting Manuscript: E.E.K., Ö.K.A., Ö.Y.A., Critical Revision of Manuscript: T.K., H.G., Final Approval and Accountability: E.E.K., Ö.K.A., Ö.Y.A., T.K., H.G.

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

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

References

1. World Health Organization (2020). Coronavirus disease (COVID-19) Last Accessed Date: 12.10.2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjwmeiIBhA6EiwA-uaeFfsV25bOK5FtIQvshTu_MUxK7znOarF9JP9D9Aiuq7XNPkPhtSRhZRoC50wQAvD_BwE.
2. Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units- the experience in Sichuan Province, China. Intensive Care Med 2020;46(2):357-360.
3. Schiavi MC, Spina V, Zullo MA, Colagiovanni V, Luffarelli P, Rago R, et al. Love in the time of COVID-19: sexual function and quality of life analysis during the social distancing measures in a group of Italian reproductive-age woman. J Sex Med 2020;17(8):1407-1413.
4. Ministry of Health of the Republic of Turkey. Available from: https://covid19.saglik.gov.tr/TR-66471/i.html.
5. Duan L, Zhu G. Psychological interventions for people affected by the COVID-19 epidemic. Lancet Psychiatry 2020;7(4):300-302.
6. Bao Y, Sun Y, Meng S, Shi J, Lu L. 2019-nCoV epidemic: address mental health care to empower society. Lancet 2020;395(10224):e37-e38. doi: 10.1016/S0140-6736(20)30309-3.
7. Rajkumar RP. COVID-19 and mental health: A review of the existing literature. Asian J Psychiatr 2020;52:102066.
8. Ventriglio A, Bhugra, D. Sexuality in the 21st century: Sexual fludity. East Asian Arch Psychiatry 2019;29(1):30-34.
9. Baldwin DS. Depression and sexual dysfunction. Br Med Bull 2001;57(1):81-99.
10. Jacob L, Smith L, Butler L, Barnett Y, Grabovac I, McDermott D, et al. Challenges in the practice of sexual medicine in the time of COVID-19 in the United Kingdom. J Sex Med 2020;17(7):1229-1236.
11. Li W, Li G, Xin C, Wang Y, Yang S. Challenges in the practice of sexual medicine in the time of COVID-19 in China. J Sex Med 2020;17(7):1225-1228.
12. Hamilton LD, Meston CM. Chronic stress and sexual function in women. J Sex Med 2013;10(10):2443-2454.
13. Karsiyakali N, Sahin Y, Ates HA, Okucu E, Karabay E. Evaluation of the sexual functioning of ındividuals living in Turkey during the COVID-19 pandemic: an internet-based nationwide survey study. Sex Med 2020 Oct 26;9(1):100279.
14. Ibarra FP, Mehrad M, Di Mauro M, Godoy MFP, Cruz EG, Nilforoushzadeh MA, et al. Impact of the COVID-19 pandemic on the sexual behavior of the population. The vision of the east and the west. Int Braz J Urol 2020;46(Suppl 1):104-112.
15. Fuchs A, Matonóg A, Pilarska J, Sieradzka P, Szul M, Czuba B, et al. The impact of COVID-19 on female sexual health. Int J Environ Res Public Health 2020;17(19):7152.
16. Hall KS, Kusunoki Y, Gatny H, Barber J. Stress symptoms and frequency of sexual intercourse among young women. J Sex Med 2014;11(8):1982-1990.
17. Yuksel B, Ozgor F. Effect of the COVID-19 pandemic on female sexual behavior. Int J Gynaecol Obstet 2020;150(1):98-102.
18. Micelli E, Cito G, Cocci A, Polloni G, Russo GI, Minervini A, et al. Desire for parenthood at the time of COVID-19 pandemic: an insight into the Italian situation. J Psychosom Obstet Gynaecol 2020;41(3):183-190.
19. Zuelke AE, Luck T, Schroeter ML, Witte AV, Hinz A, Engel C, et al. The association between unemployment and depression-results from the population-based LIFE-adult-study. J Affect Disord 2018;235:399-406.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):276-279
DOI: 10.4274/BMB.galenos.2021.02.028

Differentiation of Benign and Malignant Kidney Masses via Inflammation Parameters

Benign ve Malign Böbrek Kitlelerinin Enflamasyon Markerlarıyla Ayrımı

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Abstract

Objective: Despite the recent advances in imaging methods, the rate of 10-20% is still insufficient in predicting the pathology of renal masses. Therefore, we aimed to examine whether hematological inflammatory markers were useful in predicting pathology outcome.

Method: One hundred sixteen patients who were operated for kidney mass between January 2010 and October 2020 were included in the study. Retrospectively, preoperative platelets, neutrophils, lymphocytes and their rates were compared with pathology results.

Results: The mean age of 116 patients included in the study was 55.36±13.93 years. While pathology results of 26 (22.4%) patients were benign, results of 90 (77.6%) patients were malignant. The neutrophil and neutrophil lymphocyte ratio were significantly lower in the benign group. According to the Fuhrman grade of renal cell carcinoma, platelet and platelet lymphocyte ratio were higher in aggressive groups, whereas lymphocyte count was lower.

Conclusion: Hematological inflammatory markers are useful in predicting the pathology outcome of kidney masses before surgery.

Keywords: Blood platelets, kidney neoplasms, lymphocytes, neutrophils

Öz

Amaç: Görüntüleme yöntemlerindeki son gelişmelere rağmen, böbrek kitlelerinin patolojisini tahmin etmede hala %10-20 oranı yetersizdir. Bu nedenle, hematolojik enflamatuvar belirteçlerin patoloji sonucunu tahmin etmede yararlı olup olmadığını incelemeyi amaçladık.

Yöntem: Ocak 2010 ile Ekim 2020 tarihleri arasında böbrek kitlesi nedeniyle opere edilen 116 hasta çalışmaya dahil edildi. Retrospektif olarak preoperatif trombosit, nötrofiller, lenfosit sayıları ve oranları patoloji sonuçları ile karşılaştırıldı.

Bulgular: Çalışmaya alınan 116 hastanın yaş ortalaması 55,36±13,93 yıl idi. Yirmi altı (%22,4) hastanın patoloji sonuçları benign iken 90'ı (%77,6) malign idi. Nötrofil sayısı ve nötrofil lenfosit oranı benign grupta anlamlı olarak daha düşüktü. Renal hücreli karsinomlu hastalarda yüksek Fuhrman derecelerinde trombosit sayısı ve trombosit lenfosit oranı daha yüksek iken lenfosit sayısı ise daha düşüktü.

Sonuç: Hematolojik enflamatuvar belirteçler, ameliyattan öncesi böbrek kitlelerinin patoloji sonucunu tahmin etmede yararlıdır.

Anahtar kelimeler: Böbrek neoplazmaları, kan trombositleri, lenfosit, nötrofil

Introduction

Among urogenital tumors, renal tumors are seen in third place in order of incidence and in first place in order of mortality (1). Patients present to the clinic with the complaints of flank pain, palpable mass, and hematuria. However, this triad is present in 5-10% of cases and is associated with advanced disease (2).

Today, renal masses are incidentally detected earlier, thanks to the increasing use and the quality of imaging methods (3). Accordingly, surgical treatments give more positive results (4). Despite these improvements in radiological imaging, it is still insufficient to predict pathology of kidney tumors. In 10-20% of patients, especially in benign masses such as angiomyolipoma which has poor adipose tissue and oncocytoma, the distinction between benign and malignant cannot be made (5). For this reason, additional data are needed to predict the outcome of pathology before surgery.

Many studies have shown that systemic inflammation is effective in the formation and progression of

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Cite this article as: Demir M, Eryılmaz R, Aslan R, Ertaş K, Taken K. Differentiation of Benign and Malignant Kidney Masses via Inflammation Parameters. Bagcilar Med Bull 2021;6(3):276-279

cancer. Systemic inflammation increases in the number of platelets and neutrophils, and decreases in the number of lymphocytes. It has been shown in some studies that these hematological values can be used to predict prognosis in kidney tumors (6). However, we did not find any study in the literature regarding the use of these parameters to predict malignancy.

In this study, it was evaluated whether platelet, neutrophil, lymphocyte and their ratios could be used to predict pathology results in kidney masses.

Materials and Methods

After getting approval from the Local Ethics Committee (Van Yüzüncü Yıl University, KAEK, decision number: 2020/09-21, date: 04.12.2020) and obtaining consent form from patients, in accordance with the latest Helsinki Declaration, the files of patients who underwent radical and partial nephrectomy in our clinic between January 2010 and October 2020 were retrospectively reviewed. Age, gender, tumor side, diameter, operation, pathology results of the patients, platelet, neutrophil, lymphocyte values and ratios, platelet/lymphocyte (PLR), platelet/neutrophil (PNR), and neutrophil/lymphocyte rate (NLR) were evaluated together with pathology results. Fuhrman system was used for tumor grades. Patients with chronic diseases that could alter inflammatory parameters, such as diabetes mellitus, chronic kidney disease, chronic liver disease, sarcoidosis, amyloidosis, and inflammatory bowel diseases, were excluded from the study. And those using drugs such as steroid and anti-inflammatories, which could alter inflammatory parameters, were excluded from the study.

Statistical Analysis

Age, tumor size, neutrophil, lymphocyte, platelet, PLR, NLR, and PNR were expressed as mean and standard deviation, and gender, direction, and pathology results were expressed as numbers and percentages. One-Way analysis of variance was used to compare the groups in terms of inflammatory parameters. Statistical significance level was taken as 5% in calculations and SPSS (ver.21) statistical package program was used for analyses.

Results

The mean age of 116 patients included in the study at the time of diagnosis was 55.36±13.93 years. Seventy (60.3%) of the patients were male and 46 (39.7%) were female. Tumor size was 6.62±4.20 cm on average. Radical nephrectomy was applied to 77 of the patients (66.4%), and partial nephrectomy to 39 (33.6%) of the patients. While 90 (77.6%) of the pathology results were malignant, 26 (22.4%) of them were benign. Of the malignant pathologies, 86 were renal cell carcinoma (RCC), and 4 were transitional cell carcinomas. According to the Fuhrman grading of RCCs, 26 were grade 1, 38 were grade 2, 17 were grade 3, and 5 were grade 4. Of the benign pathologies, 12 were oncocytomas, 6 were angiomyolipoma, 4 were xanthogranulomatous pyelonephritis, and 4 were multicystic lesions. The preoperative platelet was 268,700±82,560, neutrophil was 5,430±2,220, lymphocyte was 2,140±750, PNR ratio was 55.21±21.55, PLR ratio was 140.99±70.88, NLR ratio was 2.82±1.53. The comparison of inflammatory parameters with pathology results are shown in Table 1, 2.

Discussion

Inflammation plays a key role in cancer (7). Cytokines and growth factors produced together with systemic inflammation trigger carcinogenesis and cause tumor development and proliferation. The inflammatory role of chronic inflammation in hepatocellular carcinoma caused by viral infection, in bladder cancer by chronic stones and infection, and in colon cancer by inflammatory bowel disease has been demonstrated (8-10).

After learning the role of inflammation in cancer, it has become important to show systemic inflammation in a correct, easy and cheap way. Complete blood count (CBC) shows systemic inflammation very easily, quickly, accurately and at a low cost for the patient and physician with many parameters it includes (11,12). The most important inflammatory markers of CBC are neutrophils, lymphocytes and thrombocytes. While neutrophilia is associated with chronic inflammation in cancer, studies have shown that lymphopenia and thrombocytosis are

Table 1. Comparison of pathology results with hematological parameters

	Benign	Malignant	p
Platelet (×1000/uL)	254.23±68.85	272.88±86.00	0.3
Neutrophil (×1000/uL)	4.38±1.13	5.73±2.37	0.006[a]
Lymphocyte (×1000/uL)	2.23±0.63	2.12±0.78	0.5
PNR	61.61±21.01	53.36±21.46	0.085
PLR	124.64±59.82	145.72±73.39	0.182
NLR	2.17±1.05	3.00±1.60	0.014[b]

One-Way analysis of variance, PNR: Platelet neutrophil ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, [a]Neutrophil count and [b]NLR significantly lower in benign group

Table 2. Comparison of Fuhrman grades with hematological parameters

	Grade 1	Grade 2	Grade 3	Grade 4	p
Platelet (×1000/uL)	244.42±58.18	252.45±61.79	318.41±103.75	355.60±131.78	0.001[a]
Neutrophil (×1000/uL)	5.58±1.91	5.56±2.30	5.61±2.74	6.66±4.41	0.816
Lymphocyte (×1000/uL)	2.47±0.95	2.01±0.66	1.99±0.72	1.66±0.36	0.041[b]
PNR	48.51±18.92	51.68±19.48	65.09±28.50	60.48±17.13	0.072
PLR	108.74±37.32	143.14±73.35	178.22±91.74	215.66±64.83	0.002[c]
NLR	2.59±1.58	3.00±1.46	3.13±1.93	3.90±1.87	0.358

PNR: Platelet neutrophil ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, One-Way analysis of variance, [a]Platelet: Significantly higher platelet count in Fuhrman 3 and 4 groups compared to group 1 and 2, [b]Lymphocyte count is significantly higher in Fuhrman 1 than Fuhrman 2, 3, 4, and significantly lower in Fuhrman 4 than Fuhrman 1, 2, 3, [c]PLR increases significantly in each group as the Fuhrman grade increases

associated with poor prognosis in many types of cancer (11). Also, studies show that CBC inflammation parameters can help in diagnosis. One study indicated that NLR and PLR could be used in some cases to differentiate benign prostatic hyperplasia from prostate cancer (13).

Platelet, one of the systemic inflammation parameters in CBC, is effective in tumor development. Thrombocytes produce these effects through vascular endothelial growth factor, platelet-derived growth factor (PDGF), fibroblast growth factor and transforming growth factor-beta (14). Both absolute neutrophil count and NLR are used as the markers of inflammation. Although neutrophils are the main defenders of the immune system, their increasing numbers both trigger the activation of tumor cells and cause suppression of anti-tumoral mechanisms (15). Neutrophils act through cytokines and growth factors (16). Lymphocytes, another element of the systemic response, inhibit tumor cell proliferation and migration, and kill tumor cells with a cytotoxic effect (17). Lymphocytes can suppress tumor cells through CD3, CD4, CD8, and p46 and improve survival in patients with cancer (2). Many studies have shown that neutrophil and neutrophil-lymphocyte ratios can be used to predict cancer prognosis (18). However, we could not see enough studies in the literature regarding the use of neutrophils to predict preoperative malignancy. In one of these studies, Tangal et al. (19) stated that neutrophil-lymphocyte ratios were not useful in predicting malignancy and the Fuhrman's degree in kidney masses. However, in our study, both the neutrophil value and the neutrophil-lymphocyte ratio were found to be significantly higher in the malignant group. It is observed that Tangal et al. (19) did not exclude patients with additional systemic diseases from the study. However, systemic diseases and malignancies change neutrophil and lymphocyte counts (11).

The other hematological parameter of systemic inflammation is lymphocytes. In none of the studies we encountered in the literature, the number of lymphocytes was evaluated alone, and in all studies, it was studied in the form of NLR or PLR. Increased NLR has been reported to be associated with poor prognosis in breast, colorectal, esophagus and prostate cancer (20-23). On the other hand, Karaoğullarından et al. (14) showed in their study that PLR increased in direct proportion to the diameter of the tumor (14). In addition, lymphocytopenia has been associated with poor prognosis in many studies (24). In our study, lymphocyte level was higher in benign tumors. However, it was not statistically significant. It is possible to obtain statistically significant results in studies with higher case series.

The Fuhrman histopathological rating system is the most commonly used method in RCCs today. The importance of Fuhrman core rating in predicting survival was demonstrated in the study of Gudbjartson et al. (25) on 629 patients. Although Viers et al. (26) showed an important relationship between NLR and Fuhrman's degree, no significant results were obtained in the study of Arda et al. (27). In our study, no relationship was found between neutrophil count, NLR and Fuhrman grade. However, in RCC patients, it was observed that platelets increased significantly as the degree of prostitution increased. We observed that the lymphocyte count decreased significantly inversely with the Fuhrman grade and the PLR significantly according to the Fuhrman grade.

The retrospective design and relatively small number of patients are the limitations of our study.

Conclusion

Systemic inflammation parameters such as neutrophil, lymphocyte and platelet levels can be used to predict postoperative pathology outcomes before surgery.

Ethics

Ethics Committee Approval: After getting approval from the Local Ethics Committee (Van Yüzüncü Yıl University, KAEK, decision number: 2020/09-21, date: 04.12.2020).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Li W, Cheng Y, Cheng Y, Ren H, Han N. Clinical efficacy of radical nephrectomy versus nephron-sparing surgery on localized renal cell carcinoma. Eur J Med Res 2014;19(1):1-6.
2. Lee CT, Katz J, Fearn PA, Russo P. Mode of presentation of renal cell carcinoma provides prognostic information. Urol Oncol 2002;7(4):135-140.
3. Şahin H, Akarken İ. Böbrek Tümörlerinde Etiyoloji, Klinik Tanı ve Evrelemesi. Turk Klin Urol 2019;12(4):1-9.
4. King SC, Pollack LA, Li J, King JB, Master VA. Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. J Urol 2014;191(6):1665-1670.
5. Morra MN, Das S. Renal oncocytoma: a review of histogenesis, histopathology, diagnosis and treatment. J Urol 1993;150(2 Pt 1):295-302.
6. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140(6):883-899.
7. Yildirim M, Kılınç Y, Ceyhan A. Behçet hastalığı patogenezindeki yenilikler. Suleyman Demirel Univ Tıp Fak Derg 2009;16(3):29-34.
8. Waldner MJ, Neurath MF. Colitis-Associated Cancer: the role of t cells in tumor development. Semin Immunol 2009;31(2):249-256.
9. Karin M. Nuclear factor-kappaB in cancer development and progression. Nature 2006;441(7092):431-436.
10. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, et al. A human colonic commensal promotes colon tumorigenesis via activation of t helper type 17 t cell responses. Nat Med 2009;15(9):1016-1022.
11. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. Sci Rep 2019;9(1):1-10.
12. Duran İ, Avcı V, Nazik S, Altun E. Çocukluk çağı apandisit tanısında nötrofil lenfosit oranı ve trombosit lenfosit oranı. Turk Klin Biyokim Derg 2017;15(1):1-7.
13. Kaynar M, Yildirim ME, Gul M, Kilic O, Ceylan K, Goktas S. Benign prostatic hyperplasia and prostate cancer differentiation via platelet to lymphocyte ratio. Cancer Biomark 2015;15(3):317-323.
14. Karaoğullarından Ü, Akkız H, Kuran S, Uskudar O, Taskaynatan H, Delik A. The relationship between thrombocyte lymphocyte ratio with tumor morphology and alpha fetoprotein in patients with hepatocellular carcinoma. Turk J Fam Med and Primary Care 2020;14(2):230-235.
15. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer 2013;109(2):401-407.
16. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 2003;6(4):283-287.
17. Mantovani A, Allavena P, Sica A, Ballkwill F. Cancer related inflammation. Nature 2008;454(7203):436-444.
18. Teramukai S, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, et al. Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. Eur J Cancer 2009;45(11):1950-1958.
19. Tangal S, Kutsal Ö, Yiğman M, Haliloğlu, A. Relation of neutrophil lymphocyte ratio with tumor characteristics in localized kidney tumors. New J Urol 2018;13(1):12-15.
20. Keizman D, Gottfried M, Ish-Shalom M, Maimon N, Peer A, Neumann A, et al. Pretreatment neutrophil-to-lymphocyte ratio in metastatic castration-resistant prostate cancer patients treated with ketoconazole: association with outcome and predictive nomogram. Oncologist 2012;17(12):1508-1514.
21. Mallappa S, Sinha A, Gupta S, Chadwick S. Preoperative neutrophil to lymphocyte ratio> 5 is a prognostic factor for recurrent colorectal cancer. Colorectal Dis 2013;15(3):323-328.
22. Sharaiha R, Halazun K, Mirza F, Port J, Lee P, Neugut A, et al. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol 2011;18(12):3362-3369.
23. Forget P, Machiels J, Coulie P, Berliere M, Poncelet A, Tombal B, et al. Neutrophil: lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Ann Surg Oncol 2013;20(3):650-660.
24. Fogar P, Sperti C, Basso D, Sanzari M, Greco E, Davoli C, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas 2006;32(1):22-28.
25. Gudhjartsson T, Hardarson S, Petursdottir V, Thoroddsen A, Magnusion J, Einarsson GV. Histological subtyping and nuclear gradingoi renal cell carcinoma and their implications for survival: a retrospective nation-wide study of 629 patients. Eur Urol 2005;48(4):593-600.
26. Viers B, Thompson R, Boorjian S, Lohse C, Leibovich B, Tollefson M. Preoperative neutrophil-lymphocyte ratio predicts death among patients with localized clear cell renal carcinoma undergoing nephrectomy. Urol Oncol 2014;32(8):1277-1284.
27. Arda E, Yuksel I, Cakiroglu B, Akdeniz E, Cilesiz N. Valuation of neutrophil/lymphocyte ratio in renal cell carcinoma grading and progression. Cureus 2018;10(1):1-9.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):280-286
DOI: 10.4274/BMB.galenos.2021.04.047

Risk Factors Effecting Conversion from Laparoscopic Cholecystectomy to Open Surgery

Kolesistektomi Esnasında Laparoskopik Cerrahiden Açık Cerrahiye Geçişi Etkileyen Risk Faktörleri

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Abstract

Objective: Laparoscopic cholecystectomy has obvious advantages over open surgery, such as shorter hospital stay, lower morbidity, better cosmetic results and faster return to daily activities. However, in some cases, conversion to open technique may be inevitable for patient safety or for the management of complications having occurred. Although various risk factors have been identified in many studies, variables such as technical facilities, surgical technique and experience affect risk factors. Our study aims to identify these risk factors.

Method: In this study, 2,483 cholecystectomy cases performed in the general surgery clinic of our hospital between December 2013 and 2016 were retrospectively analyzed. 110 cholecystectomy cases initiated with open surgery and performed during another operation were excluded from the study, and 88 patients who were started laparoscopic surgery and converted to open surgery were selected for the study. Information on the demographic and clinical characteristics of the patients was obtained from hospital records. The data of an equal number of consecutively selected patients from the patients who were completed laparoscopically were obtained and compared, and whether these factors had a significant effect on conversion to open surgery was evaluated.

Results: The rate of conversion from laparoscopic cholecystectomy to open surgery was 3.7%. The most common reason for conversion to open surgery was adhesion due to inflammation (n=65, 73.9%). While male gender, advanced age, diabetes, median incision above the umbilicus, multiple millimetric calculus and increased wall thickness in ultrasonography had a significant effect on the conversion to open surgery (p<0.001), there was no significant correlation with body mass index, pancreatitis, cholangitis, endoscopic retrograde cholangiopancreatography or abdominal surgery, anesthesia evaluation

Öz

Amaç: Laparoskopik kolesistektominin, ameliyat sonrası daha kısa hastanede kalış süresi, daha düşük morbidite, daha iyi kozmetik sonuçlar ve günlük aktivitelere daha hızlı dönebilme sağlaması gibi avantajları ile açık cerrahiye göre üstünlüğü aşikardır. Ancak bazı durumlarda açık tekniğe geçmek hasta güvenliği veya meydana gelmiş olan komplikasyonu yönetmek için kaçınılmaz olabilmektedir. Birçok çalışmada çeşitli risk faktörleri tanımlanmış olsa da teknik imkanlar, cerrahi teknik ve tecrübe gibi değişkenler risk faktörlerini etkilemektedir. Çalışmamız bu risk faktörlerinin tespit edilmesini amaçlamaktadır.

Yöntem: Çalışmada Aralık 2013-2016 tarihleri arasında hastanemiz genel cerrahi kliniğinde gerçekleştirilmiş 2,483 kolesistektomi olgusu retrospektif olarak incelenmiştir. Açık cerrahiyle başlanan ve başka bir operasyon sırasında uygulanan 110 kolesistektomi olgusu çalışma dışı bırakılarak, laparoskopik başlayıp açık cerrahiye geçilen 88 hasta araştırma için seçilmiştir. Hastaların demografik ve klinik özelliklerine ait bilgiler hastane kayıtlarından elde edilmiştir. Laparoskopik tamamlanan hastalardan ardışık seçilen eşit sayıda hastanın verileri elde edilerek karşılaştırılmış, bu faktörlerin açığa geçişe anlamlı etkisi olup olmadığı değerlendirilmiştir.

Bulgular: Laparoskopik kolesistektomiden açığa geçiş oranı %3,7, en sık açığa geçiş nedeni ise enflamasyona bağlı adezyon (n=65, %73,9) olarak bulunmuştur. Açığa geçiş üzerine erkek cinsiyet, ileri yaş, diyabet, göbek üstü medyan kesi, ultrasonografide multipl milimetrik kalkül ve duvar kalınlık artışı olmasının anlamlı etkisi olduğu tespit edilirken (p<0,001), vücut kitle indeksi, pankreatit, kolanjit, endoskopik retrograd kolanjiopankreatikografi ya da batın operasyonu geçirmiş olma öyküsü, anestezi değerlendirme skoru ve laboratuvar değerleri ile anlamlı ilişki tespit edilmemiştir (p>0,05). Yatış ve operasyon süreleri açığa geçilen grupta anlamlı olarak daha uzun bulunmuştur (p<0,001).

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Cite this article as: Acehan T, Köse E. Risk Factors Effecting Conversion from Laparoscopic Cholecystectomy to Open Surgery. Bagcilar Med Bull 2021;6(3):280-286

Abstract

score and laboratory values (p>0.05). The durations of hospitalization and operation were found to be significantly longer in the open group (p<0.001).

Conclusion: Male gender, advanced age, presence of diabetes, presence of supra-umbilical median incision, multiple millimetric calculus and increased wall thickness in ultrasonography are associated with increased rates of conversion from laparoscopic cholecystectomy to open surgery. If the coexistence of parameters that we find significant is detected in the preoperative period, it may be possible to take precautions such as involving the experienced surgical team in the operation, planning the operating room, and providing more detailed information to the patient.

Keywords: Laparoscopic cholecystectomy, open cholecystectomy, risk factor

Öz

Sonuç: Erkek cinsiyet, ileri yaş, diyabet varlığı, göbek üstü medyan kesi varlığı, ultrasonografide multipl milimetrik kalkül ve duvar kalınlık artışı olması artmış açığa geçiş oranları ile birliktedir. Anlamlı bulduğumuz parametrelerin birlikteliğinin preoperatif dönemde tespit edilmesi halinde zor kolesistektomi olabileceği ve açığa geçiş riskinin artabileceği düşünülerek eğitim olgusu olarak seçilmeyerek tecrübeli cerrahi ekibin ameliyata dahil edilmesi, ameliyathanenin planlanması, hastaya daha ayrıntılı bilgi verilmesi gibi önlemleri almamız mümkün olabilmektedir.

Anahtar kelimeler: Açık kolesistektomi, laparoskopik kolesistektomi, risk faktörü

Introduction

Laparoscopic cholecystectomy, which was successfully completed for the first time by Mouret in 1987, became popular in a short time with the experience of surgeons, although it had high morbidity in the first years and became the gold standard in gallbladder pathologies (1). Today, laparoscopic cholecystectomy is one of the most widely used laparoscopic operations worldwide, and according to many literatures, more than 85% is completed laparoscopically (1,2).

The shorter hospital stay, lower morbidity, better cosmetic results and faster return to daily activities are some of the reasons why laparoscopic cholecystectomy is advantageous compared to open surgery (3,4). Although it is a safe surgical procedure, laparoscopic cholecystectomy can cause serious complications such as bile duct injuries. Therefore, deciding when to prefer open surgery to laparoscopic surgery and predicting which cases may be problematic are important factors in preventing these injuries.

Although there are publications that give the rate of conversion to open surgery as high as 35%, the generally accepted rate is between 2% and 15% (1). Among the factors reported in the literature in relation to the high rate of conversion from laparoscopic to open surgery, advanced age, male gender, acute cholecystitis, obesity, unclear anatomy, bleeding, adhesions, bile duct injuries, and high leukocyte count can be listed (1,5,6). The patients at risk for the conversion to open surgery can be determined by evaluating the demographic, biochemical and radiological findings of the patients before surgical treatment. Identifying these risk factors and knowing the risk in advance will provide a great advantage in the management of gallbladder pathologies through appropriate surgical timing. With the successful estimation of the possibility of conversion to the open surgery, the optimal timing for surgery will be determined, thus it will be possible to avoid disadvantages such as long hospital stay, more common wound complications, or decrease in patient comfort, and to reduce the cost, and it will be possible to provide cost-effective treatment and prevent prolonged surgery time. In our study, it was aimed to determine these risk factors affecting the conversion to open surgery.

Materials and Methods

In our study, 2,483 cholecystectomy cases performed in the General Surgery Clinic of University of Health Sciences Turkey, Okmeydanı Training and Research Hospital between December 2013 and 2016 were retrospectively analyzed with the approval of the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee dated 08.11.2016 and numbered 538. Among these patients, 110 open cholecystectomy cases that were started with open surgery and applied during another operation were excluded from the study, and 88 patients who were started laparoscopically and converted to open surgery were included in the study.

Patients' age, gender, weight and height information, information about previous operations, additional diseases, symptoms and history of previous cholecystitis, parameters known to be related to cholecystopathy from routine preoperative laboratory examinations, ultrasonography (USG) findings and characteristics, if performed, preoperative endoscopic retograde cholangio-pancreaticography (ERCP) history and findings, surgical findings, information about the duration and type of the surgery, the American Society of Anaesthesiologists'

classification of Physical Health (ASA) scores (7) of the patients and the duration of hospitalization were obtained from the records of our hospital. The data of an equal number of patients, who were selected consecutively among the patients completed laparoscopically, were obtained and compared statistically, and it was evaluated whether there was a significant effect on conversion to open surgery.

Statistical Analysis

Mean, standard deviation, frequency and percentage values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. It was understood that the age variable showed a normal distribution, and all of the other continuous variables did not comply with the normal distribution. The relationship between the conversion to open surgery and age was evaluated by the independent sample t-test. The relationship between laboratory values, body mass index (BMI), duration of operation and hospitalization and conversion to open surgery was evaluated with the Mann-Whitney U test. The chi-square test was used in the analysis of qualitative independent data, and the Fischer's Exact test was used when chi-square test conditions were not met. SPSS 22.0 program was used in the analyses; $p<0.05$ was accepted as the limit of significance.

Results

In our study, 2,483 cholecystectomy cases performed between December 2013 and 2016 were analyzed retrospectively, 110 of these patients underwent cholecystectomy during another operation or with direct open surgery, and these patients were excluded from the study. The remaining 2,373 cases were planned and started as laparoscopic cholecystectomy operation, but during the operation, 88 (3.7%) of them were converted to open surgery for various reasons. When the reasons for converting to the open surgery during laparoscopic surgery were examined, the most common reason was adhesion due to inflammation with 73.9% (n=65), followed by adhesion due to the prior operation, inability to see the gallbladder hilus, peroperative bleeding and bile duct injury (Table 1).

Of the 176 patients included in the study (88 open, 88 laparoscopic completed), 53.4% (n=94) were male and 46.6% (n=82) were female. Male gender ratios were determined as 67% (n=59) and 39.8% (n=35) for the open surgery and laparoscopic completed surgery groups, respectively. Male gender was found to be significantly higher in the open surgery group (chi-square test, $p<0.001$) (Table 2).

Table 1. Reasons for conversion from laparoscopic cholecystectomy to open surgery

		Number	%
Conversion reasons	Adhesion due to inflammation	65	73.9%
	Adhesion due to previous operation	15	17.0%
	The gall bladder hilus cannot be seen	5	5.7%
	Bleeding	2	2.3%
	Bile duct injury	1	1.1%

The rate of patients with diabetes mellitus (DM), which is known to be significant in terms of the course of gallbladder diseases, was found to be 39.8% (n=35) and 17% (n=15), for the open surgery and laparoscopically completed surgery groups, respectively, and the presence of diabetes was found to be significantly higher in the open surgery group (chi-square test, $p=0.001$). The rates of patients with a history of pancreatitis were 2.3% (n=2) and 4.5% (n=4) for the open surgery and laparoscopically completed surgery groups, respectively. The rates of patients with a history of cholangitis were determined as 9.1% (n=8) and 2.3% (n=2), respectively, and there was no statistically significant difference between the groups ($p>0.05$). The rates of patients with a history of ERCP were determined as 13.6% (n=12) and 8% (n=7), respectively, and there was no statistically significant difference between the groups ($p>0.05$) (Table 2).

The rates of patients with multiple millimetric stones in the gallbladder and single stones larger than 1 cm on USG were 88.6% (n=78) and 11.4% (n=10) for the open surgery group. These rates were 63.6% (n=56) and 36.4 (n=32) for the laparoscopic group. The presence of multiple millimetric stones was found to be significantly higher in the open surgery group (chi-square test, $p<0.001$) (Table 2).

The rates of gallbladder wall thickness greater than 3 mm in USG were found to be 43.2% (n=38) and 8% (n=7), for the open surgery and laparoscopic groups, respectively. The presence of a gallbladder wall thickness higher than 3 mm was found to be significantly higher in the open surgery group (chi-square test, $p<0.001$). The majority of the patients in both groups were found to be ASA 1 and 2, and there was no statistically significant difference between the groups in terms of ASA score ($p>0.05$) (Table 2).

BMI values were found to be 29.8 kg/m² (±5.8) in the open surgery group and 28.6 kg/m² (±5.1) in the laparoscopic

Table 2. Gender and medical characteristics of patients

		Conversion group		Laparoscopic group		Total		p
		n	%	n	%	n	%	
Gender	Male	59	67	35	39.8	94	53.4	p<0.001
	Female	29	33	53	60.2	82	46.6	
Diabetes mellitus	Yes	35	39.8	15	17	50	28.4	p=0.001
	No	53	60.2	73	83	126	71.6	
Pancreatitis history	Yes	2	2.3	4	4.5	6	3.4	p>0.05
	No	86	97.7	84	95.5	170	96.6	
Cholangitis history	Yes	8	9.1	2	2.3	10	5.7	p>0.05
	No	80	90.9	86	97.7	166	94.3	
ERCP history	Yes	12	13.6	7	8	19	10.8	p>0.05
	No	76	85.2	81	92	157	89.2	
Prior abdominal operation	Yes	28	31.8	30	34.1	58	32.9	p>0.05
	No	60	68.2	58	65.9	118	67.1	
Stone number/size	>1 cm, single	10	11.4	32	36.4	42	23.9	p<0.001
	Multiple millimetric	78	88.6	56	63.6	134	76.1	
Gallbladder wall thickness	>3 mm	38	43.2	7	8	45	26.1	p<0.001
	<3 mm	50	56.8	81	92	131	73.9	
ASA score	ASA 1	34	38.6	41	46.6	75	42.6	
	ASA 2	39	44.3	41	46.6	80	45.5	p>0.05
	ASA 3	13	14.8	6	6.8	19	10.8	
	ASA 4	2	2.3	0	0	2	1.1	
	Total	88	100	88	100	176	100	-

ERCP: Endoscopic retograde cholangiopancreaticography, ASA: American Society of Anaesthesiologists

Table 3. Age, BMI, operating and hospitalization time information of the patients

	Conversion group	Laparoscopic group	p
The average age (± SD)	57.9 (±12.9)	50.2 (±14.9)	p<0.001
The average BMI (kg/m²) (± SD)	29.8 (±5.8)	28.6 (±5.1)	p>0.05
Operating time (min) (± SD)	116.1 (±21.5)	56.9 (±21.3)	p<0.001
Hospitalization time (day) (± SD)	5.4 (±3.1)	1.1 (±0.3)	p<0.001

BMI: Body mass index, SD: Standard deviation

group. There was no statistically significant difference between the groups (p>0.05). When the operation times were measured and analyzed as the time from the first incision to skin closure, the average operation time was found to be 116.1 (±21.5) minutes in the open surgery group and 56.9 (±21.3) minutes in the laparoscopic group, and it was significantly longer in the open surgery group (Mann-Whitney U test, p<0.001). The mean hospitalization period was 5.4 (±3.1) days in the open surgery group and 1.1 (±0.3) days in the laparoscopic group, and it was significantly longer in the open surgery group (Mann-Whitney U test, p<0.001) (Table 3).

There was no significant difference between the groups in the laboratory values of the patients in the preoperative period (p>0.05).

Discussion

It is very difficult to predict which patient will be converted to open surgery during laparoscopic cholecystectomy. Although many risk analysis scales have been created in the literature to predict this situation, there is no assessment system in routine use yet (1,2). Sutcliffe et al. (2) created a risk assessment system called conversion from laparoscopic to open cholecystectomy risk score. Various scores were given

according to age, gender, cholecystectomy indication, ASA score, gallbladder wall thickness, and common bile duct diameter, and patients with a total of 6 or less were considered as low-risk patients for conversion to open surgery, while those who scored above 6 were considered high-risk patients (2). According to this score, it has been argued that low-risk patients may be training cases in hospitals where resident training is given, but high-risk patients should be operated by more experienced surgeons.

In the literature, the rate of conversion laparoscopic to open surgery is reported between 1.3 and 24%, and inflammation in the Callot's triangle and related fibrosis have been reported as the most common reasons for conversion to open surgery (1,8,9). Sutcliffe et al. (2) examined the records of 8,820 patients in the United Kingdom database and 11 different studies and reported the rate of conversion to open surgery as 3.4%. Failure to provide safe vision and intraoperative complications such as intestinal perforation, hemorrhage, or bile duct injury have been reported as the most common conditions leading to conversion to open surgery (2). Beksac et al. (1) investigated 1,444 patients and found that the rate of conversion to open surgery was 7.7%, and the most common reason for conversion to open surgery was the inability to reveal anatomical formations (72.3%) due to inflammation and fibrosis. In our study, the rate of conversion during laparoscopic cholecystectomy was found to be 3.7%, which is consistent with the literature.

In our study, when the reasons for conversion to open surgery were examined, the most common cause was adhesions due to inflammation with a rate of 73.9%, followed by adhesions due to previous surgery, invisible gall bladder hilus, bleeding and bile duct injury, respectively. When the laparoscopically completed and conversion groups were compared in terms of gender, the number of male patients in the open surgery group was found to be significantly higher. Similarly, many authors reported male gender as a risk factor (10,11). In the study of Sözen et al. (12), this situation was interpreted that men were admitted to hospital less when symptoms began, similarly, men decided to undergo surgery later, and their admission to the hospital was delayed due to the fact that the daily activities of men were more intense in our country (12). According to Ekici et al. (13), women may be more sensitive to the inflammatory changes of cholecystitis. In addition, anatomical differences and changes in dietary habits may cause these changes between genders.

Older age is a risk factor for conversion to open surgery in laparoscopic cholecystectomy (14). In our study, the mean age was 57.9 in the exposed group, while it was 50.2 in the laparoscopic group, and the average age of the patients in the open surgery group was found to be significantly higher. The importance of age as a risk factor may also be due to the increase in the number of cholecystitis attacks with age, concomitant diseases that increase with age, or a more severe course of cholecystitis in elderly patients. Although there are many studies reporting that the rates of complications and conversion to open surgery in obese patients are comparable to non-obese patients, obesity has been reported as a risk factor in many studies (15,16). Beksac et al. (1) has found no significant relationship between obesity and conversion rates, and similarly, obesity was not found as a factor that significantly increased the risk in our study. In our study, when the groups were evaluated in terms of DM disease, which is known to be significant in terms of the course of gallbladder diseases, the rate of patients with DM was found to be significantly higher in the group that converted to open surgery. Studies show that the incidence of gangrenous cholecystitis increases in patients with diabetes and this situation increases the risk of conversion to open surgery. In addition, due to the rapid progression of cholecystitis in diabetic patients, early cholecystectomy is recommended instead of delayed cholecystectomy following conservative treatment (17).

Choledocholithiasis is the most common biliary disease observed in patients who underwent cholecystectomy due to cholelithiasis, and its frequency varies between 10% and 20% (18). After small stones fall from the cystic duct into the main bile duct, it can be complicated by conditions such as gallstone disease, pancreatitis or cholangitis. This may increase the possibility of adhesion formation due to inflammation in the operation area (18). However, in our study, no significant relationship was found between the history of pancreatitis and cholangitis and conversion to open surgery. In our study, it was determined that patients with multiple millimetric stones in the bladder have a significantly increased risk of conversion to open surgery compared to patients with stones larger than 1 cm and single stones. This situation can be explained by the fact that small stones cause cholecystitis by obstructing the cystic duct.

In the literature, there are studies reporting that having an abdominal operation poses a risk for conversion to open surgery (19,20). In our study, history of having an abdominal operation did not significantly affect the conversion to open surgery.

In the literature, there are studies reporting cholecystitis findings such as increased bladder wall thickness and presence of pericholecystic fluid in USG as risk factors (1,20). Chand et al. (3) investigated the effectiveness of preoperative USG in 50 patients. Various parameters in predicting the conversion to open surgery was investigated and it was reported that only the increased gallbladder wall thickness, increased common bile duct diameter, contraction of the gallbladder and the presence of impacted stones had a significant effect on the prediction of conversion to open surgery (3). In our study, gall bladder wall thickness higher than 3 mm, which is a sign of acute or previous cholecystitis, emerged as a parameter that significantly increased the risk in conversion to open surgery.

Bourgouin et al. (4) investigated the relationship between blood neutrophil and platelet count, prothrombin time, fibrinogen, C-reactive protein, gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) values and conversion rates. While the relationship between neutrophil count, fibrinogen level and ALP value was found to be statistically significant, no relationship was found between the other parameters and the conversion to open surgery (4). Beksac et al. (1) found that ALP value above 80 IU/L was a risk factor in their study, but no significant relationship was found between leukocyte, ALT, AST, GGT, total bilirubin values and the conversion rates. In the study, it was evaluated that the patients' episodes of cholecystitis might be responsible for the elevation of ALP (1). In our study, although the laboratory values of ALT, AST, ALP, GGT, amylase, total bilirubin, direct bilirubin, leukocyte and platelet counts and neutrophil and lymphocyte percentages were examined, no significant relationship was found between these values and conversion rates.

With the advancement of technology, laparoscopy devices have also improved and provided a better view. Similarly, although the development of surgical instruments has contributed to the advancement of surgical technique and skills, conversion to open surgery during laparoscopic cholecystectomy may still have to be carried out even in the best centers. It is very difficult to predict which patient will be exposed.

Conclusion

According to our study, the factors affecting the conversion to open surgery are the observation of male gender, advanced age, presence of diabetes, presence of supra-umbilical incision, multiple millimetric calculus and cholecystitis findings such as increased wall thickness in USG. If the concomitance of these parameters is determined in the preoperative period, it may be possible to take precautions such as involving the experienced surgical team in the operation, planning the operating room, and providing more detailed information to the patient, considering that it may be difficult cholecystectomy and the risk of conversion to open surgery may increase. In clinics such as our hospital, a scoring method can be developed to predict patients at high risk of exposure, and more experienced surgeons and more advanced technological devices can be used for these patients. In addition, the first approach to be preferred should be laparoscopic cholecystectomy, even in the presence of factors that increase the risk of opening, and high-risk patients should at least be given the chance to benefit from the advantages of laparoscopy. Since the design of our study is retrospective, patient consent could not be obtained.

Ethics

Ethics Committee Approval: In our study, 2,483 cholecystectomy cases performed in the General Surgery Clinic of University of Health Sciences Turkey, Okmeydanı Training and Research Hospital between December 2013 and 2016 were retrospectively analyzed with the approval of the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee dated 08.11.2016 and numbered 538.

Informed Consent: Since the design of our study is retrospective, patient consent could not be obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.A., E.K., Design: T.A., E.K., Data Collectionor Processing: T.A., E.K., Analysis or Interpretation: T.A., E.K., Writing: T.A., E.K.

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

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

References

1. Beksac K, Turhan N, Karaagaoglu E, Abbasoglu O. Risk factors for conversion of laparoscopic cholecystectomy to open surgery: a new predictive statistical model. J Laparoendosc Adv Surg Tech A 2016;26(9):693-696.

2. Sutcliffe RP, Hollyman M, Hodson J, Bonney G, Vohra RS, Griffiths EA; CholeS study group, West Midlands Research Collaborative. Preoperative risk factors for conversion from laparoscopic to open

cholecystectomy: A validated risk score derived from a prospective U.K. database of 8820 patients HPB (Oxford) 2016;18(11):922-928.

3. Chand P, Singh R, Singh B, Singla RL, Yadav M. Preoperative ultrasonography as a predictor of difficult laparoscopic cholecystectomy that requires conversion to open procedure. Niger J Surg 2015;21(2):102-105.
4. Bourgouin S, Mancini J, Monchal T, Calvary R, Bordes J, Balandraud P. How to predıct dıfficult laparoscopıc cholecystectomy? Proposal for a sımple preoperatıve scorıng system. Am J Surg 2016;212(5):873-881.
5. Gupta N, Ranjan G, Arora MP, Goswami B, Chaudhary P, Kapur A, et al. Validation of a scoring system to predict difficult laparoscopic cholecystectomy. Int J Surg 2013;11(9):1002-1006.
6. Atmaram DC, Lakshman K. Predictive factors for conversion of laparoscopic cholecystectomy. Indian J Surg 2011;73(6):423-426.
7. ASA Physical Status Classification System, American Society of Anesthesiologists, Approved by the ASA House of Delegates on October 15, 2014, and last amended on December 13, 2020. Available from: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system
8. Radunovic M, Lazovic R, Popovic N, Magdelinic M, Bulajic M, Radunovic L, et al. Complications of laparoscopic cholecystectomy: our experience from a retrospective analysis. Open Access Maced J Med Sci 2016;4(4):641-646.
9. Le VH, Smith DE, Johnson BL. Conversion of laparoscopic to open cholecystectomy in the current era of laparoscopic surgery. Am Surg 2012;78(12):1392-1395.
10. Kaafarani HM, Smith TS, Neumayer L, Berger DH, Depalma RG, Itani KM. Trends, outcomes, and predictors of open and conversion to open cholecystectomy in Veterans Health Administration hospitals. Am J Surg 2010;200(1):32-40.
11. Genc V, Sulaimanov M, Cipe G, Basceken SI, Erverdi N, Gurel M, et al. What necessitates the conversion to open cholecystectomy? A retrospective analysis of 5164 consecutive laparoscopic operations. Clinics (Sao Paulo) 2011;66(3):417-420.
12. Sözen S, Emir S, Bali I. Laparoskopik kolesistektomiden açık ameliyata geçme nedenleri. Int J Basic Clin Med 2014;2(1):8-13.
13. Ekici U, Tatlı F, Kanlıöz M. Preoperative and postoperative risk factors in laparoscopic cholecystectomy converted to open surgery. Adv Clin Exp Med 2019;28(7):857-860.
14. Warchałowski Ł, Łuszczki E, Bartosiewicz A, Dereń K, Warchałowska M, Oleksy Ł, et al. The analysis of risk factors in the conversion from laparoscopic to open cholecystectomy. Int J Environ Res Public Health 2020;17(20):7571.
15. Tang B, Cuschieri A. Conversions During Laparoscopic Cholecystectomy: Risk Factors And Effects On Patient Outcome. J Gastroıntest Surg 2006;10(7):1081-1091.
16. Malla B, Shakya Y, Rajbhandari N. Laparoscopic cholecystectomy: conversion rate and associated factors for Conversion. Kathmandu Univ Med J 2019;17(67):241-244.
17. Terho PM, Leppäniemi AK, Mentula PJ. Laparoscopic cholecystectomy for acute calculous cholecystitis: a retrospective study assessing risk factors for conversion and complications. World J Emerg Surg 2016;11:54.
18. Kwon YH, Cho CM, Jung MK, Kim SG, Yoon YK. Risk factors of open converted cholecystectomy for cholelithiasis after endoscopic removal of choledocholithiasis. Dig Dis Sci 2015;60(2):550-556.
19. Aksoy F, Demiral G, Ekinci Ö. Can the timing of laparoscopic cholecystectomy after biliary pancreatitis change the conversion rate to open surgery? Asian J Surg 2018;41(4):307-312.
20. Haji A, Khan A, Haq A, Ribeiro B. Elective laparoscopic cholecystectomy for surgical trainees: predictive factors of operative time. Surgeon 2009;7(4):207-210.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):287-294
DOI: 10.4274/BMB.galenos.2021.04.041

Evaluation of Two Consecutive High Sensitivity Cardiac Troponin T Measurements in Healthy Newborns and Newborns with Respiratory Failure

Sağlıklı Yenidoğanlarda ve Solunum Yetmezliği Olan Yenidoğanlarda Ardışık İki Yüksek Duyarlılıklı Kardiyak Troponin T Ölçümünün Değerlendirilmesi

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Abstract

Objective: Data on the umbilical cord and postnatal physiological limits of the high sensitivity cardiac troponin T (hs cTnT) in newborns are scarce. This study aims to determine the normal values and upper limits of hs cTnT in healthy newborns. In addition, its clinical significance and usability in neonatal respiratory failure were analyzed.

Method: In this non-invasive and retrospective, cross-sectional study, 113 healthy newborns and 93 newborns with non-cardiac respiratory failure, born between July 2018 and January 2020, were evaluated. Hs cTnT was measured in the umbilical cord and 24-96 h after birth in infants.

Results: In the healthy group, the median umbilical cord hs cTnT was 38 (17-156) ng/L and 99th percentile hs cTnT was 122 ng/L, and in the respiratory failure group, the median umbilical cord hs cTnT was 72 (27-326) ng/L. Postnatal day 2-4 median hs cTnT was 75 (10-194) ng/L and 99th percentile value was 194 ng/L in the healthy group, and the median hs cTnT was 145 (41-409) ng/L in the respiratory failure group. The calculated area under the ROC curve for umbilical cord hs cTnT was 0.848 [cut-off: 64, 95% confidence interval (CI): 0.79-0.90, sensitivity: 62.4%, specificity: 93.7%], suggesting that umbilical cord hs cTnT is a sensitive marker for the prediction of neonatal respiratory failure. The calculated area under the ROC curve for control hs cTnT was 0.851 (cut-off: 121.5, 95% CI: 0.79-0.90, sensitivity: 71%, specificity: 86.8%), suggesting that control hs cTnT is a sensitive marker for the prediction of neonatal respiratory failure.

Öz

Amaç: Yenidoğanlarda yüksek duyarlılıklı kardiyak Troponin T'nin (hs cTnT) göbek kordonu ve doğum sonrası fizyolojik sınırlarına ilişkin veriler azdır. Bu çalışma sağlıklı yenidoğanlarda hs cTnT'nin normal değerlerini ve üst sınırlarını belirlemeyi amaçlamaktadır. Ayrıca, yenidoğan solunum yetmezliğinde klinik önemi ve kullanılabilirliği analiz edilmiştir.

Yöntem: Bu invazif olmayan ve retrospektif, kesitsel çalışmada, Temmuz 2018 ile Ocak 2020 tarihleri arasında doğan 113 sağlıklı yenidoğan ve kalp dışı kaynaklı solunum yetmezliği olan 93 yenidoğan değerlendirildi. Hs cTnT, bebeklerde göbek kordonunda ve doğumdan 24-96 saat sonra ölçüldü.

Bulgular: Sağlıklı grupta umbilikal kord hs cTnT medyan 38 (17-156) ng/L; 99. persantil hs cTnT 122 ng/L, solunum yetmezliği grubunda umbilikal kord hs cTnT medyan 72 (27-326) ng/L bulundu. Sağlıklı grupta postnatal 2-4 gün hs cTnT medyan 75 (10-194) ng/L; 99. persantil 194 ng/L, solunum yetmezliği grubunda hs cTnT medyan 145 (41-409) idi. Göbek kordonu için hs cTnT ROC eğrisi eğrinin altındaki alan değeri 0,848 [cut-off 64: %95 güven aralığı (GA): 0,79-0,90, duyarlılık: %62,4, özgüllük: %93,7], göbek kordonu hs cTnT'nin yenidoğan solunum yetmezliğinin tahmini için duyarlı bir belirteç olduğunu düşündürmektedir. Kontrol hs cTnT ROC eğrisi eğrinin altındaki alan değeri 0,851 (cut-off: 121,5, %95 GA: 0,79-0,90, duyarlılık: %71, özgüllük: %86,8), kontrol hs cTnT'nin neonatal solunum yetmezliğinin tahmini için duyarlı bir belirteç olduğunu göstermektedir.

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Cite this article as: Tüfekci S, Kızılca Ö, Çelikkol A, Topçu B. Evaluation of Two Consecutive High Sensitivity Cardiac Troponin T Measurements in Healthy Newborns and Newborns with Respiratory Failure. Bagcilar Med Bull 2021;6(3):287-294

Abstract

Conclusion: The results show that the reference range of umbilical cord and postnatal hs cTnT in healthy newborns is higher than that in adults. Both hs cTnT values were higher in the neonatal respiratory failure group than those in the healthy group.

Keywords: Healthy newborn, high sensitive cardiac troponin T, neonatal respiratory failure, umbilical cord

Öz

Sonuç: Sağlıklı yenidoğanlarda umbilikal kord ve postnatal hs cTnT referans aralığının, erişkin değerlerine göre yüksek olduğu saptanmıştır. Her iki hs cTnT değeri, yenidoğan solunum yetmezliği grubunda sağlıklı gruba göre çok artmıştır.

Anahtar kelimeler: Göbek kordonu, sağlıklı yenidoğan, yenidoğan solunum yetmezliği, yüksek duyarlı kardiyak troponin T

Introduction

Cardiac troponins are protein components of the troponin-tropomyosin complex in the myocardium (1,2). Troponin complex consists of three different subunits that regulate the contractile process in muscle interfering calcium ions. The three subunits are troponin T, which binds to tropomyosin, troponin I, which binds to actin and inhibits the reaction between actin and myosin, and troponin C, which binds to calcium ions. Troponin I and troponin T are located in the skeletal and in the heart muscle but are coded to different genes and have a different arrangement of amino acids, which enables the production of antibodies specific to cardiac troponin form and determination in serum. Troponins appear in blood 2-4 h after insult, peak at about 12 h, and then remain elevated for 7-10 days (3,4). In newborn, elevated plasma concentrations of hs cTnT decrease to adult level within six months.

Cardiac troponin T and cardiac troponin I (cTnI) are released as a result of myocardial cell injury and are highly sensitive biomarkers of myocardial damage. Because cTnI is cleared more rapidly from the circulation than cTnT, its utility as a monitor of ongoing cardiac injury is limited. In healthy terms, cTnT is higher than that in adults (5,6). Troponin T subunit, which has molecular mass, is 35 kDa and therefore too large to be dispersed freely throughout the placenta. It is thought that there is no transplacental transmission. In the newborns, cTnT is most commonly used to determine cardiac stress associated with patent ductus arteriosus and neonatal asphyxia (7-9). However, reference ranges have not been exactly defined for newborns, which makes the interpretation of elevated cTnT values very difficult. If high cTnT values are incorrectly interpreted as abnormal, this may lead to unnecessary interventions. Because 99th percentile cTnT in healthy adults provides better sensitivity in individuals suspected of having acute coronary syndrome, the use of hs cTnT test has recently been recommended when analyzing cTnT. According to the guidelines, hs cTnT values >14 ng/L are considered pathological in adults (10). This study primarily aimed to determine the distribution of the umbilical cord and postnatal day 2-4 hs cTnT in healthy newborns. The secondary aim was to investigate the diagnostic value and clinical significance of hs cTnT measurements in newborns with respiratory failure.

Materials and Methods

Patients and Study Design

A total of 206 late preterm (at gestational week $34^{0/7}$-$36^{6/7}$) and term (at gestational week $37^{0/7}$-$41^{6/7}$) infants born between July 2018 and January 2020 were included in the study. Of the patients, 113 were healthy infants (group 1, control group) and 93 were infants with postnatal newborn respiratory distress syndrome (group 2, patient group). Blood gas and hs cTnT levels were analyzed in the blood taken from the umbilical cord artery and/or vein within the first 10 min after birth. Gestational weeks, birth weight, 1- and 5-minute Apgar scores, maternal age, gender, mode of delivery, and the need for mechanical ventilation in group 2 patients were investigated. Patients in group 1 with suspected heart disease during physical examination and all infants in group 2 were examined by a pediatric cardiologist at postnatal day 2-4, in terms of heart failure, congenital structural heart diseases, persistent pulmonary hypertension, patent ductus arteriosus, and myocarditis via physical examination, electrocardiography, and echocardiographic examination. Infants with cardiac problems were excluded from the study.

Other exclusion criteria were as follows: infants born before gestational week 34 and after gestational week 42, patients with stage 2-3 hypoxic ischemic encephalopathy, acute renal failure, neonatal sepsis, congenital anomalies, preeclampsia in the maternal history, maternal hypertension (>140/90 mmHg), and infants of mothers who required tocolysis and magnesium treatment.

Patients diagnosed with transient tachypnea of the newborn, neonatal respiratory distress syndrome, and neonatal pneumonia were included in the subgroups of neonatal respiratory failure. Differential diagnoses were made by a neonatologist according to the diagnostic guidelines based on the results of chest radiography, thoracic ultrasound, blood gas, blood culture, laboratory parameters, and clinical evaluation (11).

Sample Collection

In the first 10 min after birth, 0.5 mL of blood was taken from the umbilical cord artery and/or vein in a lithium heparin tube, and blood gas was analyzed within the first 15 min. Control hs cTnT was taken from venous blood after 2-4 days postnatally. Hs cTnT was analyzed within the first hour in the accredited laboratory of our hospital. Analysis of cTnT was performed using the electrochemiluminescence method (Cobas e602, Roche Diagnostics) as a high-sensitivity cTnT test and its unit was measured in ng/L (detection limit 5-10.000 ng/L).

Perinatal Factors

Naegele's formula was used in pregnant women whose gestational age was determined according to the pregnancy ultrasound performed at the beginning of the second trimester or in pregnant women who did not undergo ultrasound in the same period. The results of pH, base excess, and lactate in umbilical cord artery and/or vein blood were recorded in the first 10 min after delivery.

Ethical Approval

This study was a retrospective analysis of prospectively collected data. It is a cross-sectional study approved by the Tekirdağ Namık Kemal University Ethics Committee and it was conducted according to the principles of the Helsinki Declaration (protocol number:2020.14.01.14).

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 17.0 software. The normality of distribution of the variables was examined using histogram graphs and the Kolmogorov-Smirnov test. Median (interquartile range), minimum, and maximum values were used for descriptive analyses. Categorical variables were compared using the Pearson's chi-square test. The Mann-Whitney U test was used to evaluate non-parametric variables between two groups, and the Kruskal-Wallis test was employed when the evaluation was performed between more than two groups. The Spearman's rank correlation test was used in the analysis of the measurement data with each other. The changes in the hs cTnT values were examined within the group using the Wilcoxon test, while they were analyzed by repeated measures analysis between the groups. Note that $p<0.05$ was considered statistically significant.

Results

A total of 206 newborns, 113 in the healthy group and 93 in the neonatal respiratory failure group, were included in the study. A total of 69 (33.5%) babies were born late-preterm, including 21 (18.6%) infants in the healthy group and 48 (51.6%) infants in the patient group. There was no significant difference between the groups in terms of maternal age, 1- and 5- min Apgar scores, birth weight, and umbilical cord pH ($p>0.05$). Base excess and lactate were lower in the healthy group compared to those in the patient group ($p=0.02$, $p<0.01$) (Table 1).

Healthy Group

Of the 113 patients, 59.56% were female, 18.58% were born late-preterm, and 88.5% were born via the surgical method (mostly repetitive cesarean delivery). The median umbilical cord hs cTnT was 38 (17-156) ng/L and the median hs cTnT was 75 (10-194) ng/L at postnatal 24-96 h. In healthy infants, the 99th percentile umbilical cord hs cTnT was 122 ng/L, and the control 99th percentile hs cTnT was 194 ng/L after 24-96 h. There was no statistically significant difference found in the results based on the mode of delivery; however, the increase in follow-up hs TnT after cesarean section was significant ($p<0.01$). Umbilical cord and follow-up hs cTnT values for preterm infants were higher than in term babies; however, no statistically significant difference was present ($p=0.22$, $p=0.14$) (Table 2).

Neonatal Respiratory Failure Group

Of the 93 patients, 48 (51.61%) were male. Of the infants, 51.61% were born late-preterm and 83.87% by cesarean section. Late-preterm birth rate was higher in the patient group than in the healthy group. In newborns with respiratory distress, both of median hs cTnT results were higher than those of the control group ($p<0.01$) (Figure 1). Furthermore, we observed that the change between the umbilical cord hs cTnT and follow-up hs cTnT in patients with respiratory failure increased more than that in the control group ($p<0.01$). Umbilical cord hs cTnT was higher in late preterms/term with respiratory failure than that in healthy late-preterm/term infants ($p<0.01$). In addition, postnatal follow-up hs cTnT was higher in late-preterms/term with respiratory failure than that in healthy preterms/

Table 1. Demographic data in healthy newborns and patients

Feature	Healthy group (n=113)		Patient group (n=93)		Total (n=206)	
	n	%	n	%	n	%
Female	56	49.5	45	48.4	101	49
Male	57	50.5	48	51.6	105	51
Vaginal delivery	13	11.5	15	16.1	28	13.6
Cesarean	100	88.5	78	83.9	178	86.4
Late preterm	21	18.6	48	51.6	69	33.5
Term	92	81.4	45	48.3	137	66.5
	Median	Minimum-maximum	Median	Minimum-maximum	p	
Maternal age	28	15-41	30	18-45	0.35	
Gestational age (weeks)	38	34-39	37	34-42	0.13	
Birth weight (gram)	3,110	1,760-3,800	2,910	1,800-4,100	0.07	
Apgar 1. minute	8	3-9	8	4-9	0.80	
Apgar 5. minute	9	7-10	9	7-10	0.07	
Umbilical cord pH	7.35	7.18-7.45	7.35	7.05-7.56	0.50	
Base excess (mmol/L)	-3	-10-3.6	-3.6	-15-4.7	**0.02**	
Lactate (mmol/L)	1.91	1.1-7.4	2.63	1.07-10.18	**<0.01**	

Table 2. Hs cTnT by mode of delivery and gestational week in healthy newborns

Features		Median	P 25	P 75	p
Vaginal delivery	Umbilical cord	41.50	37.50	48.50	0.13
	Control	66.00	58.00	117.00	
Caesarean section	Umbilical cord	38.00	29.50	50.00	**<0.01**
	Control	75.50	58.50	96.50	
Late preterm	Umbilical cord	39.00	37.00	47.00	**0.01**
	Control	80.00	66.00	117.00	
Term	Umbilical cord	37.50	29.00	50.00	**<0.01**
	Control	73.00	57.00	94.00	
Total	Umbilical cord	38.00	30.00	50.00	**<0.01**
	Control	75.00	58.00	97.00	

Hs cTnT: High sensitive cardiac troponin T

term (p<0.01). Both measurements of hs cTnT were higher in term babies than in late-preterm babies in the patient group; however, the difference was not statistically significant (p=0.54, p=0.32). Calculated area under the ROC curve for umbilical cord hs cTnT was 0.848 [cut-off 64; 95% confidence interval (CI); 0.79-0.90: sensitivity 62.4%, specificity 93.7%], suggesting that umbilical cord hs cTnT is a sensitive marker for the prediction of neonatal respiratory failure. Calculated area under the ROC curve for control hs cTnT was 0.851 (cut-off 121.5; 95% CI: 0.79-0.90; sensitivity 71%, specificity 86.8%), suggesting that control hs cTnT is a sensitive marker for the prediction of neonatal respiratory failure (Table 3, Figure 2).

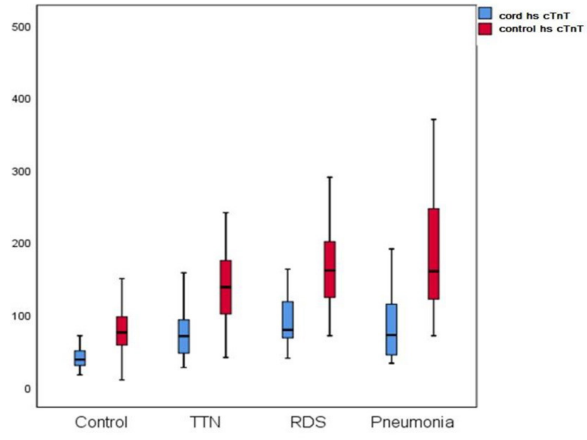

Figure 1. Hs cTnT in neonatal respiratory failure subgroups and control groups

Hs cTnT: High sensitivity cardiac troponin T, TTN: Transient tachypnea of the newborn, RDS: Respiratory distress syndrome

Transient Tachypnea of the Newborn

The median gestational week of the patients was 38 (34-41), and their median birth weight was 2,397 (1,800-3,400) gram. The median umbilical cord hs cTnT and the median follow-up hs cTnT results were higher in the patient group than those in the healthy control group (p<0.01).

Table 3. Hs cTnT ROC analysis in the patient group

Hs cTnT		AUC	p	95% CI	Cutt-off	Sensitivity (%)	Specificity (%)	PPD (%)	NPD (%)
TTN	UC	0.830	**<0.01**	0.75-0.90	54	68	86.6	69.4	85.8
	Control	0.824	**<0.01**	0.75-0.89	96.5	82	74.7	64.0	88.3
RDS	UC	0.919	**<0.01**	0.85-0.98	63.5	80.9	93.7	70.8	96.3
	Control	0.894	**<0.01**	0.82-0.96	109	85.7	79.1	48.6	96
NP	UC	0.824	**<0.01**	0.72-0.93	66	60	95.5	70.6	93.0
	Control	0.902	**<0.01**	0.83-0.97	92	95	71.4	42.2	98.5
All Patient	UC	0.848	**<0.01**	0.79-0.90	64	62.4	93.7	89.2	75.0
	Control	0.851	**<0.01**	0.79-0.90	121.5	71	86.8	84.6	74.5

Hs cTnT: High sensitive cardiac troponin T, TTN: Transient tachypnea of the newborn, RDS: Respiratory distress syndrome, NP: Neonatal pneumonia, UC: Umbilical cord, AUC: Area under curve, CI: Confidence interval, PPD: Positive predictive value, NPD: Negative predictive value

Table 4. Umbilical cord and follow-up hs cTnT in the healthy and patient groups

	N	Umbilical cord hs cTn T			Control hs cTnT			p
		Median	Minimum	Maximum	Median	Minimum	Maximum	
Total	206	47.00	17.00	326.00	106.50	10.00	409.00	**<0.01**
Healthy	113	38.00	17.00	156.00	75.00	10.00	194.00	**<0.01**
Patient	93	72.00	27.00	326.00	145.00	41.00	409.00	**<0.01**
TTN	50	70.50	27.00	176.00	138.00	41.00	409.00	**<0.01**
RDS	23	79.00	40.00	326.00	161.00	71.00	390.00	**<0.01**
Pneumonia	20	72.00	33.00	244.00	160.00	71.00	370.00	**<0.01**

TTN: Transient tachypnea of the newborn, RDS: Respiratory distress syndrome, Hs cTnT: High sensitive cardiac troponin T

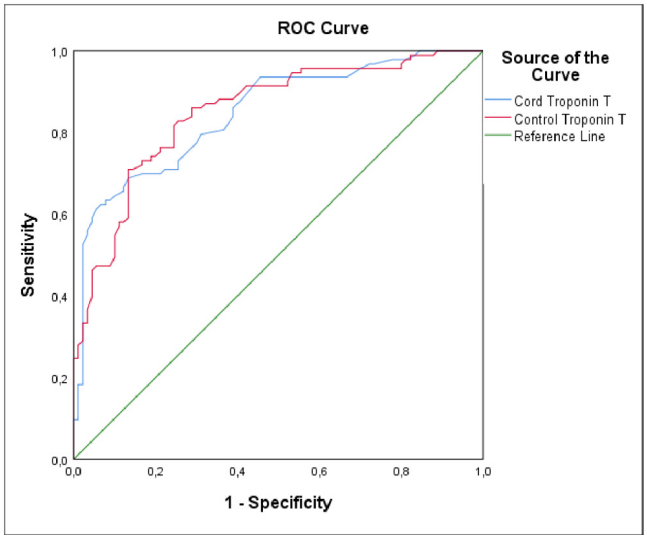

Figure 2. Predictive value of hs cTnT ROC analysis for neonatal respiratory failure group: sensitivity and specificity

Hs cTnT: High sensitivity cardiac troponin T

Respiratory Distress Syndrome

The median gestational week of the patients was 35 (34-37), and their median birth weight was 2.397 (1.800-3.400) gram. All were late-preterm infants. In patients, the median umbilical cord hs cTnT and the median follow-up hs cTnT were higher than those in the healthy group (p<0.01).

Neonatal Pneumonia

The median gestational week of the patients was 38 (35-41), and their median birth weight was 3,410 (2,390-4,100) gram. The median umbilical cord hs cTnT and postnatal median follow-up hs cTnT were higher than those of the healthy group (p<0.001) (Table 4). Hs cTnT ROC analysis in the patient subgroup is shown in Table 3.

A positive Pearson correlation was noted between the need for a mechanical ventilator and the umbilical cord and postnatal follow-up hs cTnT in patients hospitalized for respiratory failure. Because both hs cTnT values increased in the patients, the need for mechanical ventilation also increased (r=0.387, p<0.01, r=0.388, p<0.01).

Discussion

To the best of our knowledge, this study is the first one involving the measurements of hs cTnT at two separate time points in late-preterm/term newborns who are healthy and have respiratory failure.

Healthy Group

Compared to the healthy adult population, hs cTnT was higher in both healthy newborns and in newborns with respiratory distress. This study presents the reference range of hs cTnT in the umbilical cord and postnatal day 2-4 in healthy newborns. The 99th percentile umbilical cord hs cTnT was 65 ng/L, and postnatal the 99th percentile follow-up hs cTnT was 150 ng/L, which was higher than the results for the adult population (12). Hs cTnT significantly increases following delivery, and this is known to be normal for the neonatal period. Awada et al. (13) found that the 99th percentile value of cTnT measured using the classical method was 244 ng/L after birth in healthy infants. In Karlen's study on 158 healthy term newborns, the median umbilical cord hs cTnT was 34 ng/L (interquartile range: 26-44) and the 99th percentile value was 88 ng/L (14). In their study, the follow-up hs cTnT after 2-5 days was 92 (median; interquartile range: 54-158) ng/L and the 99th percentile value was 664 ng/L. However, Karlen's study did not include late-preterm babies. Moreover, their results were close to the mean umbilical cord and follow-up hs cTnT values of the healthy group in the present study. In a study by Jehlicka on umbilical cord or venous blood involving 241 healthy term newborns, the median hs cTnT was 38.2 ng/L and the 97.5th percentile value was 83 ng/L (CI: 74.1-106.9) (6). Most of the cTnT results obtained by conventional methods in healthy newborns were consistent with the present study. However, some previous studies in literature have yielded different results (5,7,15,16).

Causes of Elevated Umbilical Cord and Follow-up hs cTnT

It is possible to speculate that the functional hypoxemia of the fetus coupled with the added cardiovascular stress at the time of delivery leads to scanty myocyte loss within the heart and that in some babies, it causes high levels of cardiac troponin T, without clinical cardiorespiratory compromise (17). In an isolated heart rat model, chemically induced cardiac myocyte membrane damage caused the release of cardiac troponin T without myocardial necrosis. Therefore, it is possible to speculate that membrane disruption, without cell death, could lead to a small and transient rise of cardiac troponin T (18).

Differences in cTnT according to the mode of delivery in term newborns have been investigated in only a few studies, and the results are varied. In most of the studies, no significant difference has been found in cTnT values according to the mode of delivery (14,15,19,20). In patients in the healthy group, the significant increase in control hs cTnT after cesarean delivery may be misleading due to the low number of normal births (gynecology unit is a reference center for repeated cesarean deliveries and high risk pregnant women in a region with a population of 1.5 million people).

In the present study, 18.58% of healthy newborns were late-preterm and both measurements of the mean hs cTnT values were slightly higher than those in term babies. Previous studies have shown that cTnT was higher at baseline in premature infants than in healthy term infants. In a study involving 22 preterm patients born at 22-25 weeks, the mean cTnT was found to be 170 (0-310) ng/L (17). Our study did not include early-preterm infants.

In the present study, no significant correlation was found among maternal age, birth weight, 1- and 5- min apgar scores, umbilical cord blood gas pH values, and both hs cTnT levels in the patient and control groups. Base excess and lactate levels were lower in healthy newborns then in patients with respiratory distress ($p=0.026$, $p<0.001$). These results were similar to those obtained in literature (5,7,21).

Herein, no difference was found in umbilical cord hs cTnT levels in terms of gender. However, both hs cTnT levels were higher in male patients in the neonatal respiratory distress group. Although the results from three different studies including healthy newborns were in favor of male newborns (6,14,15), no gender-related difference was found in many other studies (5,9,13,20).

Neonatal Respiratory Failure Group

Respiratory distress syndrome; in a study of 46 patients, 26 preterm infants with RDS born at the gestational week ≤32 were compared with 20 infants without RDS. C TnT was high in the group with RDS on postnatal day 2 (16). In 113 healthy term infants and 49 preterm infants with respiratory distress, umbilical cord cTnT was found to be higher in infants with RDS compared to that in healthy term infants (5). A study involving 116 healthy infants and 48 infants with respiratory distress showed that the postnatal cTnT levels were higher in infants with RDS than those in healthy infants (13). Although conventional measurement methods were used in previous publications, the elevated cTnT level in infants with RDS was consistent with our results. The median hs cTnT values for both measurements were found to be twice as higher in our patients with RDS than in the healthy group ($p<0.01$).

An hs cTnT study including two separate measurements was performed for the first time in patients with TTN. In 50 patients, the umbilical cord and postnatal day 2-4 hs cTnT

were higher than those in the control group. In a study conducted with the conventional method, cTnT was found to be higher in 11 patients with TTN than that in the control group in the first 48 h after birth, similar to the results of the present study. An hs cTnT study was performed for the first time in patients with NP. In 20 patients, the umbilical cord and postnatal day 2-4 hs cTnT levels were higher than those in the control group. In a study conducted with the conventional method in 27 patients with NP, cTnT in the first 48 h after birth was found to be higher than in the control group (22).

Causes of Elevated hs cTnT

These increased concentrations could be related to the fact that primary respiratory diseases may lead to myocardial injury either through the decrease in cardiac output associated with mechanical ventilation or through cellular dysfunction leading to poor handling of oxygen, which leads to elevated cardiac biomarkers. Hs cTnT elevations may be associated with minimal myocardial histological changes that cannot be detected on echocardiography and electrocardiography (7,23). The exact cause or causes are still not fully known.

In the adult acute RDS study, cTnT elevation levels were found to be associated with adverse outcomes, such as death, multiple organ failure, and the need for a mechanical ventilator (24). Studies on this subject in the neonatal period are limited; however, a relationship was found between hs cTnT levels and the need for a mechanical ventilator in the present study. As hs cTnT values increase in patients, the need for mechanical ventilation increases. Adverse outcomes, such as multiple organ failure and death, were not observed in our patients. In the study of Awada et al. (13), a positive correlation was found between the duration of mechanical ventilation and cTnT levels in the neonatal period. Further studies are needed to determine the relationship between hs cTnT and multiple organ failure, death, and the need for mechanical ventilation in preterm and term newborns.

Strengths and Limitations of the Study

The present study includes late-preterm/term newborns who are healthy and have neonatal respiratory distress, and the number of patients and study planning are quite favorable. Furthermore, the study includes test results and clinical evaluations. Hs cTnT was measured twice in the umbilical cord and on postnatal day 2-4, and the results showed a significant increase in the postnatal period. Hs cTnT was investigated in three diseases that most commonly caused respiratory failure in newborns.

Limitations of this study are as follows: This is a single-center study; early preterm babies were excluded; the need for inotrope with mean blood pressure measurements, and long-term hs cTnT measurements beyond two weeks were not included.

Conclusion

We believe that the hs cTnT test will give more sensitive results in the cardiovascular adaptation process in newborns, in healthy babies and/or babies with respiratory failure. This study shows that umbilical cord and postnatal hs cTnT levels are significantly higher in RDS, TTN, and NP than in healthy newborns. These results suggest that even if there is no structural heart disease, the heart is affected in neonatal respiratory distress. The wide range in hs cTnT levels observed in healthy late-preterm/term infants in this study underlines the need for caution when using hs cTnT levels to evaluate cardiac insult in newborn infants.

Ethics

Ethics Committee Approval: It is a cross-sectional study approved by the Tekirdağ Namık Kemal University Ethics Committee and it was conducted according to the principles of the Helsinki Declaration (protocol number: 2020.14.01.14).

Informed Consent: Family signature is not required in retrospective studies.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.T., Design: S.T., Ö.K., A.Ç., Data Collection or Processing: S.T., A.Ç., Analysis or Interpretation: S.T., B.T., Literature Review: S.T., Ö.K., B.T., Writing: S.T., Ö.K., Manuscript Review and Revisation: S.T., A.Ç., B.T.

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

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

References

1. Bettencourt P. NT-proBNP and BNP: biomarkers for heart failure management. Eur J Heart Fail 2004;6(3):359-363.
2. Bhayana V, Henderson AR. Biochemical markers of myocardial damage. Clin Biochem 1995;28(1):1-29.
3. Simovic A, Stojkovic A. Correlation level of cardiac troponin-i with total duration of oxygen / ventilator therapy in the term newborns with respiratory distress. J Cardiovasc Dis Diagn 2014;2:5.

4. Braunwald E, Fauci AS, Kasper DL. Harrison's Principles of Internal Medicine, 15th ed. New York: McGraw-Hill; 2001.

5. Clark SJ, Newland P, Yoxall CW, Subhedar NV. Cardiac troponin T in cord blood. Arch Dis Child Fetal Neonatal Ed 2001;84(1):F34-F37.

6. Jehlicka P, Huml M, Rajdl D, Mockova A, Matas M, Dort J, et al. How to interpret elevated plasmatic level of high-sensitive troponin T in newborns and infants? Physiol Res 2018;67(2):191-195.

7. Clark SJ, Newland P, Yoxall CW, Subhedar NV. Concentrations of cardiac troponin T in neonates with and without respiratory distress. Arch Dis Child Fetal Neonatal Ed 2004;89(4):F348-F52.

8. Joseph S, Kumar S, Ahamed MZ, Lakshmi S. Cardiac troponin T as a marker of myocardial dysfunction in term neonates with perinatal asphyxia. Indian J Pediatr 2018;85(10):877-884.

9. El-Khuffash AF, Molloy EJ. Influence of a patent ductus arteriosus on cardiac troponin T levels in preterm infants. J Pediatr 2008;153(3):350-353.

10. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138(20):e618-e651.

11. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European Consensus Guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology 2019;115(4):432-450.

12. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56(2):254-261.

13. Awada H, Al-Tannir M, Ziade MF, Alameh J, El Rajab M. Cardiac troponin T: a useful early marker for cardiac and respiratory dysfunction in neonates. Neonatology 2017;92(2):105-110.

14. Karlén J, Karlsson M, Eliasson H, Bonamy AE, Halvorsen CP. Cardiac troponin t in healthy full-term ınfants. Pediatr Cardiol 2019;40(8):1645-1654.

15. Baum H, Hinze A, Bartels P, Neumeier D. Reference values for cardiac troponins T and I in healthy neonates. Clin Biochem 2004;37(12):1079-1082.

16. Trevisanuto D, Zaninotto M, Altinier S, Plebani M, Zanardo V. High serum cardiac troponin T concentrations in preterm infants with respiratory distress syndrome. Acta Paediatr 2000;89(9):1134-1146.

17. Fortunato G, Ciarrusso GP, Martinelli P, Sglavo G, Vassallo M, Tomeo L, et al. Cardiac troponin T and amino-terminal pro-natriuretic peptide concentrations in fetuses in the second trimester and in healthy neonates. Clin Chem Lab Med 2006;44(7):834-836.

18. Remppis A, Scheffold T, Greten J. Intracellular compartmentation of troponin T: release kinetics after global ischaemia and calcium paradox in the isolated perfused rat heart. J Moll Cell Cardiol 1995;27(2):793-803.

19. Shiva R, Maryam R, Hajie B. Cardiac troponin T levels of umbilical cord in neonates with abnormal fetal heart rate. Iran J Pediatr 2013;23(1):85-88.

20. Lipshultz SE, Simbre VC, Hart S, Rifai N, Lipsitz SR, Reubens L, et al. Frequency of elevations in markers of cardiomyocyte damage in otherwise healthy newborns. Am J Cardiol 2008;102(6):761-766.

21. El-Khuffash AF, Molly AJ. Serum troponin in neonatal intensive care. Neonatology 2008;94(1):1-7.

22. Fahmeya SS, Fathya H, Gabalb KA, Khairya H. Cardiac troponin T in neonates with respiratory distress. Gaz Egypt Paediatr Assoc 2018;66(4):100-102.

23. Anderson PA, Greig A, Mark T, Malouf NN, Oakeley AE, Ungerleider RM, et al. Molecular basis of human cardiac troponin T isoforms expressed in the developing, adult, and failing heart. Circ Res 1995;76(4):681-686.

24. Rivara MB, Bajwa EK, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Prognostic significance of elevated cardiac troponin-T levels in acute respiratory distress syndrome patients. PLoS One 2012;7(7):e40515.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):295-301
DOI: 10.4274/BMB.galenos.2021.05.064

Evaluation of Clinical Features of Patients Diagnosed with MIS-C

MIS-C Tanısıyla Takip Edilen Hastalarımızın Klinik Özelliklerinin Değerlendirilmesi

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Abstract

Objective: Evaluation of clinical features and results in multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease-2019.

Method: Patients diagnosed with MIS-C between September 1, 2020 and February 25, 2021, followed at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Pediatrics were included. Their clinical findings and laboratory results were evaluated retrospectively.

Results: The average age of 16 patients diagnosed with MIS-C was found to be 6.5 years; of them, 62.5% were male and 37.5% were female. Our patients had no chronic disease. Fever (100%) and stomachache (81.25%) were the most common symptoms. All patients had high levels of C-reactive protein, procalcitonin, D-dimer and pro-brain natriuretic peptide at the time of diagnosis. The average ejection fraction was found as 63.1% in echocardiography. Intravenous immunoglobulin, corticosteroids and acetylsalicylic acid were administered to all patients whereas enoxaparin and vasopressors were administered to 11 (68.75%) and 3 (18.5%) patients, respectively. Left ventricular ejection fraction was found to be within the normal range at all patients at the time of discharge. The average in patient follow-up was found to be 10 days.

Conclusion: It is important to have a long-term follow-up of MIS-C patients, who show similar symptoms to Kawasaki disease and yet have their own particular symptoms and cardiac involvement, in order not to miss the opportunity of early diagnosis as well as cardiac complications.

Keywords: COVID-19, MIS-C, pediatrics

Öz

Amaç: Çalışmada kliniğimizde izlediğimiz çocuk hastalarda koronavirüs hastalığı-2019 ile ilişkili multisistem enflamatuvar sendromunun (MIS-C) klinik özellikleri ve sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmaya 01/09/2020-25/02/2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Pediyatri Kliniği'nde takip edilen MIS-C'li çocuklar dahil edildi. Hastaların klinik özellikleri ve laboratuvar bulguları retrospektif olarak değerlendirildi.

Bulgular: MIS-C'li 16 çocuğun ortalama yaşı 6,5 yaş olup; %62,5'i erkek, %37,5'i kızdı. Hastalarımızın kronik hastalıkları yoktu. Ateş (%100) ve karın ağrısı (%81,25) en sık görülen semptomlardı. Tüm hastalarda C-reaktif protein, prokalsitonin, D-dimer ve pro-B-tipi natriüretik peptid seviyeleri tanı anında yüksekti. Ekokardiyografide ortalama ejeksiyon fraksiyonun %63,1 olduğu görüldü. Tedavi için intravenöz immünoglobulin, kortikosteroid, aspirin tüm hastalara verilirken, enoksaparin 11 (%68,75) ve vazopressörler 3 (%18,5) hastaya verildi. Hastalarımızın taburculuk öncesi yapılan kontrol ekokardiyografilerinde sol ventrikül ejeksiyon fraksiyonunun normal olduğu görüldü. Hastalarımız ortalama 10 gün yatırılarak izlendi.

Sonuç: Kawasaki hastalığı ile benzerlikler gösteren ancak kendine özgü özellikleri olan ve kardiyak tutulumla seyreden MIS-C'nin, klinik bulgularının atlanmaması, erken tanı konulup tedavi edilmesi önemlidir.

Anahtar kelimeler: COVID-19, MIS-C, pediyatri

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Cite this article as: Özel A, Erol M, Onan SH, Bostan Gayret Ö, Koçoğlu Barlas Ü, Mandel Işıklı S, Tosun V. Evaluation of Clinical Features of Patients Diagnosed with MIS-C. Bagcilar Med Bull 2021;6(3):295-301

Introduction

By the end of January 2020, World Health Organization identified coronavirus disease-2019 (COVID-19) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection as pandemic (1). COVID-19 is known to be affecting the respiratory system predominantly, with wide range of clinical features including mild upper respiratory system symptoms to severe acute respiratory distress syndrome (2,3).

By the end of April 2020, a new clinical feature was reported by the United Kingdom, as an hyperinflammation syndrome, similar to Kawasaki disease (KD) with multiple organ involvement. This clinical identification was used in describing children who were recently or currently diagnosed with COVID-19 infection with no known chronic disease (4). These reported cases directed pediatricians to investigate the possible linkage between multisystem inflammatory syndrome in children (MIS-C) and KD (4).

Following the first case reports from UK, similar cases were reported from several European countries and USA (4-8). On May 14th 2020, United States Centers for Disease Control and Prevention (CDC) reported a clinical description for MIS-C (9).

According to this report, MIS-C is described as patients under 21 years of age, with proof of COVID-19 infection or contact with someone who had COVID-19 4 weeks prior to first symptoms, together with persistent fever, and severe illness requiring hospitalization with increased inflammatory markers in laboratory findings and at least 2 system involvement with no other possible diagnosis but post-viral immune mediated multisystem clinical manifestation (9).

The data with regard to clinical and epidemiologic features of patients with MIS-C are still limited. In the reported cases, most common symptoms are nausea and vomiting, stomach pain and diarrhea, which are all related to gastrointestinal system involvement (4-6). Mucocutaneus involvement similar to KD headache, irritability and encephalopathy due to nervous system involvement and hypotension, and decreased ventricular function due to cardiac involvement are amongst other symptoms. In contrary to KD, coronary artery involvement is known to be rarer (4-6).

MIS-C is a clinical status in children due to COVID-19 infection, with no certain protocol in follow-up or treatment. Studies with regard to clinical and laboratory findings should continue in order to distinguish this particular disease. In this retrospective case series, we share our clinical experience of following and treating 16 patients diagnosed with MIS-C.

Materials and Methods

Design of the Study

Retrospective evaluation of 16 patients between the ages of 1 month-18 years, followed at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Pediatrics between Sep 1, 2020, and Feb 25, 2021 was performed.

Case description was done according to CDC criteria (https://www.cdc.gov/mis/hcp/index.html). At least two organ system involvement and one or more increased inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen, procalcitonin, ferritin, interleukin-6] were among the inclusion criteria. For viral proof, polymerase chain reaction (PCR) testing and IgG and IgM antibody tests against COVID-19 were done. Those who did not meet the criteria or those who were suspected to be ill without any proof were excluded from the study.

Currently, there is not any classification of the severity of the disease. The classification is done by vasoactive-inotropic score (VIS), requirement of respiratory support and laboratory findings (10). Because not every patient has the same organ system involvement, the clinical classification is done according to the system that is mostly affected.

In mild cases, the oxygen requirement is minimal, there is no need for inotropic agents and organ failure degree is minimal. In moderate cases, VIS is 10 or lower, obvious oxygen requirement and/or mild or isolated organ damage is present. In severe cases, VIS is greater than 10, invasive/non-invasive mechanical ventilation support and/or moderate or severe organ damage including ventricular dysfunction is present.

Data Collection and Analysis

Patients were divided into three groups depending on the clinical manifestation as mild, moderate and severe. The clinical, laboratory and radiologic data of the patients were gathered from official medical reports with a standardized data collection form. Medical consent forms were signed by the parents.

Statistical Analysis

Descriptive analyses were performed in order to provide information regarding the general characteristics of the

study groups. Data related to the continuous variables were given in the form of mean ± standard deviation and categorical variables were given as n (%).

Ethical approval was taken from the Ethical Board of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital on 22/03/2021 with the registry number E-48670771-514.10.

Clinical Findings

The average age of 16 patients who were included in the study (10 male, 6 female) was found to be 6.5±1.66 years at the time of diagnosis. Our patients had no chronic illnesses. Twelve patients (75%) were Turkish citizens and 4 (25%) were Syrian. Height and weight percentile values were within the normal range.

Our patients were divided into three categories depending on the clinical status of their disease. Ten patients (62.5%) were included in the mild clinic class and followed at the pediatric isolation unit. Four patients (25%) were placed in the moderate category, and of them, 2 (50%) were followed at the pediatric isolation unit and the other 2 (50%) were followed at the pediatric intensive care unit. Two patients were included at the severe illness category (12.5%) and followed at the pediatric intensive care unit. Eleven of our patients (68.75%) had a history of COVID-19 PCR positive family member within the same household. One patient had positive COVID-19 PCR test at the time of diagnosis. All 16 patients had positive COVID-19 IgG test. All patients had fever (100%) at the time of arrival to the hospital and average fever time was found to be 4.6 days (3-7 days). The most common symptom was stomach pain (81.25%) (13/16) due to gastrointestinal system involvement. Other gastrointestinal system related symptoms were vomiting (43.75%) (7/16) and diarrhea (75%) (12/16). Of those who had stomach pain, 7 were consulted to pediatric surgery in regard to acute abdomen; however, no surgical involvement was required. Seven patients (43.75%) had acute non-purulent bilateral conjunctivitis, 4 patients had unilateral cervical lymphadenopathy (25%), and 8 patients (50%) had rash. Eight patients (50%) had strawberry tongue and peeling around their lips due to oral mucosa involvement. Four patients (25%) had headache as a result of neurologic involvement. Demographic characteristics and clinical symptoms are shown in Table 1.

At the time of diagnosis, 9 patients (56.25%) had pericardial effusion, 7 patients (43.45%) had mitral insufficiency, 2 patients (12.5%) had tricuspid insufficiency and 3 patients (18.75%) had left coronary artery involvement. The average ejection fraction (EF) of patients was found to be 63.1 (47-79), the average fractional shortening was 34.4 (27-46). During to control echocardiography on the third day of our inpatient follow-up, 4 patients (25%) still had pericardial effusion, 8 patients (50%) had mitral insufficiency, 2 patients (12.5%) had tricuspid insufficiency and 3 patients (18.75%) had left coronary artery involvement. Three patients had normal echocardiography results on day 3. The average EF was 71.4 (55-78), fractional shortening was 39.8 (29-46). In the echocardiography done on the day of discharge, 10 patients (62.5%) had normal results. One patient (3.25%) had left coronary artery enlargement and 5 patients (31.25%) had continuing mitral valve insufficiency. In the echocardiography done prior to discharge, the average EF and fractional shortening were reported as 74.1 (66-80) and 42.7 (36-50), respectively (Table 2).

Table 1. Demographic characteristics, clinical symptoms and COVID-19 test results

Patient characteristics	All patients (n=16)
Age (range)	6.5 (2.5-14.66)
Sex, n (%)	Male 10 (62.5), female 6 (37.5)
Citizenship, n (%)	
Turkish	12 (75)
Syrian	4 (25)
Chronic illness	0 (0)
Fever time, days (range)	4 (3-7)
Initial symptoms, n (%)	
Fever	16 (100)
Gastrointestinal findings	
Stomach pain	13 (81.25)
Vomiting	7 (43.75)
Diarrhea	12 (75)
Pediatric surgery consultation	7 (43.75)
Rash	8 (50)
Conjunctivitis	7 (43.75)
Hyperemia in the oral mucosa (strawberry tongue)	8 (50)
Peeling of lips	2 (12.5)
Myalgia	12 (75)
Headache	4 (25)
Cervical lymphadenopathy	4 (25)
Shortness of breath	3 (18.75)
COVID-19 contact, n (%)	11 (68.75)
COVID-19 test, n (%)	
COVID-19 antibody positive (IgG)	16 (100)
COVID-19 RT-PCR positive	1 (6.25)

COVID-19: Coronavirus disease-2019, RT-PCR: Reverse transcription-polymerase chain reaction

Table 2. Cardiovascular system examination of patients diagnosed with MIS-C

Patient characteristics	Prior to treatment (n=16)	3rd day of treatment (n=16)	At discharge from the hospital (n=16)
Echocardiography			
Normal, n (%)	0 (0)	3 (18.75)	10 (62.5)
Ejection fraction, average (range)	63.1 (47-79)	71.4 (55-78)	74.1 (66-80)
Shortness fraction, average (range)	34.4 (27-46)	39.8 (29-46)	42.6 (36-50)
Pericardial effusion, n (%)	9 (56.25)	4 (25)	0 (0)
Mitral valve insufficiency, n (%)	7 (43.75)	8 (50)	5 (31.25)
Tricuspid valve insufficiency, n (%)	2 (12.5)	2 (12.5)	0 (0)
Left coronary artery enlargement, n (%)	3 (18.75)	3 (18.75)	1 (6.25)

MIS-C: Multisystem inflammatory syndrome in children

The detailed laboratory findings of 16 patients included in the study are given in Table 3. At the time of admission, the average white blood cell count was found as 10.651 (4.03-22.7)×10^3/uL and at discharge, the average was 20.66 (9.86-48,4)×10^3/uL. Neutrophil count at the time of admission and discharge were 8.646 (3.09-20.95)×10^3/uL and 2.513 (2.99-30)×10^3/uL, respectively. The average lymphocyte counts were 1.534 (0.62-4.15)×10^3/uL upon admission and 6.481 (1.64-21.75)×10^3/uL at the time of discharge. The average thrombocyte count at admission and at discharge were 151.871 (20.95-308)×10^3/uL and 551,625 (241-859)×10^3/uL, respectively.

The level of blood sodium at admission was 128 (122-138) mmol/L, 136.5 (134-142) mmol/L on the third day and 136.1 (131-140) mmol/L at discharge. Albumin levels at admission and discharge were 3.3 (2.5-4.15) g/dL and 3.92 (3.2-4.97) g/dL, respectively. CRP level at admission was 158.6 (40-358) mg/L and 3.59 (0.26-4.4) mg/L at discharge. The average procalcitonin levels at admission and at discharge were 7.27 (0.29-12.92) ng/mL and 0.09 (0.02-0.24) ng/mL, respectively. The average ferritin level was 404 (228-2.000) ng/mL at admission and 201.19 (48-483) ng/mL at discharge. The average erythrocyte sedimentation rate was 36.8 (5-63) upon admission and 16.4 (3-46) at discharge. Amongst the cardiac enzymes, troponin-t levels at the time of admission and discharge were 131 (3.7-27,600) ng/L and 4 (2-6.89) ng/L, respectively, while pro-brain natriuretic peptide (BNP) levels were 7.153 (307-27,600) pg/mL during admission and 166 (52-458) pg/mL by the time of discharge. We had no patients with positive blood culture results.

At the time of admission, 11 patients (68.75%) had no pathological findings in their chest imaging. 4 patients (25%) had evidence of bilateral infiltration in the lower zones, coherent with pneumonia and 1 patient (6.25%) had ground-glass opacification. In the abdominal ultrasound imaging, 2 patients (12.5%) had no pathological finding whereas 14 patients (87.5%) had free fluid in the lower right quadrant (Table 4).

As the first line of treatment, all patients were administered a single dose of 2 gr/kg intravenous immunoglobulin (IVIg). There was no need for a second dosage. Glucocorticoid (2 mg/kg) was administered to 13 patients (81.25%) on the first day of treatment. Three patients (18.75%) were started on the glucocorticoid treatment with 10 mg/kg, and continued with 2 mg/kg. Acetylsalicylic acid 3-6 mg/kg (antiaggregant dose) was administered to all patients. D-dimer levels of 2 and higher was accepted as the indication of anticoagulation treatment (11). Eleven patients were started on enoxaparin treatment and continued until discharge. Three patients required inotropic medication and milrinone was added to their treatment. The average inpatient follow-up was 10 days (7-17) (Table 5).

Discussion

In the time of no standardized treatment protocol and fewer reported case series of patients diagnosed with MIS-C, our clinic followed 16 patients with a wide range of clinical presentation from stable to severe illness with decreased ventricular function.

Even though MIS-C was thought as a SARS-CoV-2 related KD, the data that surfaced since the initial diagnosis showed that MIS-C was a completely different clinical diagnosis. In contrary to KD being seen under the age of 5 years, in our study, MIS-C, in coherence with other case series, was found to be seen at the average age of 6.5 years (4,6).

All 16 patients who were accepted to our study had IgG antibody positivity against SARS-CoV-2 (COVID-19). The average time of contact with a person infected with

Table 3. Laboratory findings of patients with MIS-C

	Prior to treatment (n=16)	3rd day of treatment (n=16)	At discharge from the hospital (n=16)
Laboratory finding results, average (range)			
White blood cell (×10³/uL)	10.651 (4.03-22.7)	15.92 (9.86-48.4)	20.66 (9.86-48.4)
Neutrophil count	8.646 (3.09-20.95)	9.986 (3.21-30)	12.513 (2.99-30)
Lymphocyte count	1.534 (0.62-4.15)	4.318 (16.4-21.75)	6.481 (1.64-21.75)
Hemoglobin (g/dL)	10.99 (7-12.6)	10.83 (9.6-12.7)	11.94 (9.6-15)
Thrombocyte count (×10³/uL)	151.871 (20.95-308)	320.313 (128-719)	551.625 (241-859)
Serum sodium (mmol/L)	128 (122-138)	136.5 (134-142)	136.1 (131-140)
Serum creatinine (mg/dL)	0.58 (0.17-2.85)	0.31 (0.2-0.45)	0.33 (0.17-0.5)
Aspartate transaminase (U/L)	43.8 (15-164)	33.5 (22-57)	34.88 (18-57)
Alanine transaminase (U/L)	41.4 (8-187)	29 (8-57)	37 (16-165)
Albumin (g/dL)	3.3 (2.5-4.15)	3.11 (2.57-3.9)	3.92 (3.2-4.97)
Prothrombin time	16.3 (13.7-19.5)	13.43 (12-14.8)	12.82 (12-13.8)
Active partial thromboplastin time	31.6 (26-41)	27.93 (22-30.8)	25.45 (21.2-29)
International normalized ratio)	1.23 (1-1.47)	1 (0.88-1.1)	0.96 (0.89-1.03)
Fibrinogen (mg/dL)	597 (303-771)	371,5 (13.8-636)	287.6 (189-358)
C-reactive protein (mg/L)	15.6 (40-358)	43.34 (2.68-111)	3.59 (0.26-4.4)
Procalcitonin (ng/mL)	7.27 (0.39-12.92)	0.88 (0.11-2.85)	0.09 (0.02-0.24)
Ferritin (ng/mL)	404 (228-2.000)	330.69 (125-997)	201.19 (48-483)
D-dimer (ng/mL)	2.62 (0.8-4.49)	2.13 (0.9-4.6)	0.83 (0.31-1.78)
Troponin-T (ng/L)	131 (3.7-27,600)	61 (3-697)	4 (2-6.89)
Pro-BNP (pg/mL)	7153 (307-27,600)	5011 (131-35,000)	166 (52-458)
Erythrocyte sedimentation rate	36.8 (5-63)	23.69 (4-63)	16.4 (3-46)
Amylase (U/L)	45.8 (13-145)	-	-
Lipase (U/L)	36.1 (8-194)	-	-
Triglyceride (mg/dL)	268.25 (106-586)	-	-
Positive blood culture	0 (0)	-	-

MIS-C: Multisystem inflammatory syndrome in children, BNP: Brain natriuretic peptide

Table 4. Radiologic findings of patients with MIS-C

Patient characteristic	All patients (n=16)
Chest imaging, n (%)	
Normal	11 (68.75)
Ground-glass opacification	1 (6.25)
Bilateral lower zone infiltration	4 (25)
Abdominal ultrasound, n (%)	
Normal	2 (12.5)
Free fluid in the lower right quadrant	14 (87.5)

MIS-C: Multisystem inflammatory syndrome in children

COVID-19 was found to be 4.9 weeks prior to illness. Only 1 patient had positive RT-PCR positivity. This finding and the IgG antibody positivity showed that the disease started slowly, depending on the immune reaction of the patient (5).

Fever, being the common symptom in all 16 patients, was found to be parallel with other case series. Gastrointestinal system involvement was very common and seen in 15 patients and similar to the literature (12).

The mechanism of myocardial involvement is unclear: however, since MIS-C presents following the antibody formation against COVID-19 and the clinic improves with admission of immunomodulators, the myocardial damage is thought to be secondary to inflammatory mediators (13,14). In our case series, the increased myocardial enzyme level and myocardial dysfunction upon admission and those parameters being improved on the third day of IVIg and steroid treatment and completely back to normal by the time of discharge are coherent with the literature.

Table 5. Follow-up times and treatment of patients with MIS-C

Patient characteristic	All patients (n=16)
Clinical status, n (%)	
Mild	10 (62.5)
Moderate	4 (25)
Severe	2 (12.5)
Treatment, n (%)	
Glucocorticoid (methylprednisolone)	16 (100)
IVIg (2 gr/kg)	16 (100)
Acetylsalicylic acid (antiaggregant dose)	16 (100)
Enoxaparin	11 (68.75)
Inotrope treatment	3 (18.5)
Follow-up clinic, n (%)	
Pediatric intensive care unit	4 (25)
Pediatric unit	12 (75)
Inpatient follow-up days, median (range)	10 (7-17)

IVIg: IV immunoglobulin, MIS-C: Multisystem inflammatory syndrome in children

In contrary to other European studies, our morbidity was lower (4,6) and 18.5% required inotrope agents. Our patients did not require invasive mechanical ventilation support or mechanical circulation support. In our case series, the average left ventricle EF was 63.1%, which is higher than the 35 patient case series of Belhadjer et al. (6) (LV EF <30%). Inotropic agent usage (80%), mechanical ventilation support (62%), mechanical circulation support (28%), IVIg (71%) and corticosteroid treatment (34%) were higher in the other cohort studies, compared to our study. In our case series, the left ventricle function's improvement and healing rate was 100% (16/16) whereas Belhadjer et al. (6) reported their rate as 71%. Improvement of ventricular function was found to be in correlation with the normal levels of troponin-I and pro-BNP levels prior to discharge. It is thought that the high morbidity rate of other studies is due to the fact that they faced this syndrome before it was better understood.

In the study by Radia et al. (15), 68% of MIS-C cases required pediatric intensive care unit admission, whereas in our series, 25% of our patient were followed in the pediatric intensive care unit.

In the laboratory findings, CRP, procalcitonin and ferritin were found to be severely increased. Other commonly seen abnormal levels were hyponatremia, hypoalbuminemia, abnormal kidney function tests, high troponin and pro-BNP. In the complete blood count, lymphopenia, neutrophilia and thrombocytopenia were the most common abnormalities (4-6). Increased levels of CRP, procalcitonin, troponin and pro-BNP were found to be severely high upon admission, lower on the third day of treatment and back to normal upon discharge. The sodium and albumin levels were found to be low at the beginning of the treatment and were seen to be within the normal range by the time of discharge. Laboratory findings were helpful in the diagnosis of our patients.

In pediatric population, MIS-C has similarities to hyper-inflammatory syndromes such as KD, hemophagocytic lymphohistiocytosis, macrophage activation syndrome and toxic shock syndrome (16). This similarity is expected since all these syndromes, with different etiologies, are results of uncontrolled activation of inflammatory pathways. There are multiple non-specific inflammatory markers reported for MIS-C, none of which is sensitive or specific to this syndrome.

Treatment modalities, used in other hyper-inflammatory syndromes, are used in order to control the hyper-inflammatory seen in MIS-C. There is no proof reported for the immunomodulatory treatment strategies in the treatment of MIS-C. The long-term effects of cardiac involvement are unclear; however, it may be of the same importance as similar hyper-inflammatory diseases such as KD (17).

Conclusion

In our study, important clinical, biochemical and radiologic findings of the MIS-C cases that we followed in our clinic were identified and our clinical and pediatric cardiology approaches were evaluated. More of multi centered studies including more patients are required in order to identify the clinical characteristics, risk factor, immunomodulatory treatments and supportive treatment options including the anticoagulant agents.

Being similar to KD, since it also has cardiac involvement, early diagnosis and treatment of MIS-C are of outmost importance in order to observe the possible long-term complications of cardiac involvement.

Ethics

Ethics Committee Approval: Ethical approval was taken from the Ethical Board of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu Training and Research Hospital on 22/03/2021 with the registry number E-48670771-514.10.

Informed Consent: Medical consent forms were signed by the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., M.E., Ö.B.G., Ü.K.B., S.H.O., Design: A.Ö., M.E., Ö.B.G., Ü.K.B., S.H.O., Data Collection or Processing: A.Ö., S.M.I., V.T., Analysis or Interpretation: A.Ö., M.E., S.H.O., Ö.B.G., Ü.K.B., Writing Draft: A.Ö., M.E., S.H.O., V.T., S.M.I., Final Approval and Responsibility: A.Ö., M.E., S.H.O., Ö.B.G., Ü.K.B., S.M.I., V.T.

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

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

References

1. She J, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. J Med Virol 2020;92(7):747-754.
2. Cruz AT, Zeichner SL. COVID-19 in Children: Initial Characterization of the Pediatric Disease. Pediatrics 2020;145(6):e20200834. doi: 10.1542/peds.2020-0834.
3. Ravikumar N, Nallasamy K, Bansal A, Angurana SK, Basavaraja GV, Sundaram M, et al; Intensive Care Chapter of Indian Academy of Pediatrics. Novel Coronavirus 2019 (2019-nCoV) infection: part ı - preparedness and management in the pediatric intensive care unit in resource-limited settings. Indian Pediatr 2020;57(4):324-334.
4. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607-1608.
5. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771-1778.
6. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acuteheartfailure in multisysteminflammatorysyndrome in children (MIS-C) in thecontext of global SARS-CoV-2 pandemic. Circulation 2020;142(5):429-436.
7. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem ınflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc 2020;9(3):393-398.
8. Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, Alonso-Cadenas JA, Gochi-Valdovinos A, González Brabin A, et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. Pediatr Infect Dis J 2020;39(8):e195-e198. doi: 10.1097/INF.0000000000002777.
9. CDC HealthAlert Network. MultisystemInflammatorySyndrome in Children (MIS-C) AssociatedwithCoronavirusDisease 2019 (COVID-19). Last Accessed Date: 16.10.2020. Available from: https://emergency.cdc.gov/han/2020/han00432.asp
10. McIntosh AM, Tong S, Deakyne SJ, Davidson JA, Scott HF. Validation of the vasoactive-inotropic score in pediatricsepsis. Pediatr Crit Care Med 2017;18(8):750-757.
11. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18(6):1324-1329.
12. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094. doi: 10.1136/bmj.m2094.
13. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol 2020;309:70-77.
14. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020;224:24-29.
15. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-57.
16. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347-358.
17. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020;4(9):669-677.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):302-305
DOI: 10.4274/BMB.galenos.2021.01.016

Port Catheterization: Our Clinical Experience with 156 Diseases

Port Kateterizasyonu: 156 Hastalık Klinik Deneyimimiz

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Abstract

Objective: Port catheterization, which can be practically applied by various clinical and surgical branches in our country, is an extremely comfortable procedure in patient groups requiring long-term parenteral treatment, especially malignancy patients.

Method: In this study, 156 patients who underwent port catheterization by an anesthesiologist after the approval of the local ethics committee were evaluated retrospectively.

Results: The procedure was performed in 98.1% of the patients due to malignancy (originated esophagus: 37.3%, stomach: 24.8%). The most common application part was the right internal jugular vein (65.4%). Sixty-two patients required two or more punctures. Port was removed due to port pocket infection in 1.9% of the patients.

Conclusion: In this study, we presented our port catheterization experience and aimed to contribute to the national literature.

Keywords: Anesthesia, complication, malignancy, port

Öz

Amaç: Ülkemizde pratikte çeşitli klinik ve cerrahi branşlar tarafından uygulanabilen port kateterizasyonu, malignite hastaları başta olmak üzere uzun süreli parenteral tedavi gerektiren hasta gruplarında son derece konforlu bir işlemdir.

Yöntem: Bu çalışmada yerel etik kurul onayı alındıktan sonra anestezi uzmanı tarafından port kateterizasyon uygulanmış olan 156 hasta retrospektif olarak değerlendirildi.

Bulgular: Hastaların %98,1'ine malignite (özofagus Ca: %37,3, mide: %24,8) nedeni ile işlem uygulandı. En sık uygulama yeri sağ internal juguler vendi (%65,4). Altmış iki hastada 2 veya daha fazla ponksiyon gerekti. Hastaların %1,9'unda port cebi enfeksiyonu nedeni ile port çıkarıldı.

Sonuç: Biz bu çalışmada port kateterizasyon deneyimimizi sunduk ve ulusal literatüre katkı sunmayı amaçladık.

Anahtar kelimeler: Anestezi, komplikasyon, malignite, port

Introduction

Port catheter applications are permanent vascular access applications that allow the administration of long-term, intermittent treatments for intravenous chemotherapy, long-term daily antiviral and antibiotic treatments, and parenteral nutrition (1-3). The ports have a reservoir placed in a pocket that opens into the subcutaneous tissue and a catheter that enters the santal vein through a tunnel opened under the skin and connected to this reservoir, and can be placed in the chest, arms, thighs and, abdomen depending on the vein that was catheterized (2). Early and late complications may occur during the insertion or use of port catheters, which provide great convenience for cancer patients (4,5).

Port procedures in various hospitals in our country are common interests of anesthesiologists, general surgeons,

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Cite this article as: Gönüllü E, Yeşiltaş S, Koca D, Aycan A, Doğan E. Port Catheterization: Our Clinical Experience with 156 Diseases. Bagcilar Med Bull 2021;6(3):302-305

thoracic surgeons, pediatric surgeons, radiologists, and cardiovascular surgeons; however, there is no final consensus on this issue (1). In this study, we aimed to present our clinical experience regarding our port catheter applications in a hospital in eastern Turkey and to contribute to the literature.

Materials and Methods

In this study, patients who were planned for long-term chemotherapy and parenteral nutrition between April 2012 and August 2013 in the Medical Oncology Clinic of Van Regional Training and Research Hospital and who were placed a total implantable port by an anesthesiologist were evaluated retrospectively after the approval of the local ethics committee, dated 19.06.2015 and numbered 2015/4.

All patients were informed about both the intervention to be performed and the complications before the procedure. The mass, infection, and previously received radiotherapy conditions in the intervention area were recorded. While the operation was planned under local anesthesia in all patients who were conscious and could tolerate the procedure, intravenous sedation was applied to patients with anxiety and cooperation disorder. Intravenous ceftriaxone was routinely administered to all patients one hour before the procedure. The patients' heart rhythm, peripheral oxygen saturation (SpO_2), and non-invasive blood pressure were monitored in the operating room. Those with oxygen saturation below 94% were given 2-3 Lt/min O_2. For venous port catheter implantation, local antisepsis was provided to patients, 1% lidocaine (Jetokain Simplex® amp, Adeka, İstanbul, Turkey) infiltration was applied to the puncture site and port pocket area of all patients. Puncture was performed by using the Seldinger technique after turning the patient's head slightly to the opposite direction when internal jugular vein (IJV) was used.

In this technique, the neck veins were expected to fill in the patient lying on their back. Patients whose veins collapsed during inspiration were taken to the 15-20° Trendelenburg position. Afterwards, the sternal and clavicular head of the sternocleidomastoid muscle and the clavicula bone were determined. The current triangle is located above the center of the IJV. Catheterization was performed at the apex of the existing triangle with a large 8-inch catheter. While the finger was held to feel the artery slightly, the puncture was performed at a 30-40 degree angle and directed towards the nipple on the same side. Upon the detection of the vein, the injector was removed and a one cm incision was performed, in which the guidewire would be in the middle, and the vein dilator and sheath were advanced over the guidewire with circular movements. The vascular dilator and guidewire were removed, the mouth of the sheath was closed, and the catheter was advanced through the sheath according to the length of the catheter. Then, the sheath was split in two and peeled off by pulling it up and out. A 2-3 cm incision was performed ensuring that port pocket was on the second rib, and a subcutaneous pocket was created in accordance with the reservoir dimensions by blunt dissection from the incision caudal. After washing the port reservoir with 100 u/mL heparinized liquid, it was locked by connecting with the catheter. The process took about 30 minutes from skin cleansing to suturing.

In patients who underwent femoral vein and subclavian catheterization, preparation and procedures after reaching the venous path were the same as for IJV catheterization. The subclavian vein (SV) extends behind the clavicle over the first rib, towards the anterior scalene muscle insertion. For puncture, the midpoint of the clavicle and the sternal notch were determined first, and the needle was inserted into the skin 1 cm below the midpoint of the clavicle. The needle was then held in the horizontal plane and advanced towards the back of the clavicle with the tip towards the sternal notch.

For femoral vein catheterization, the femoral artery, 1-2 cm below the inguinal ligament, was palpated and the needle was inserted 1 cm medial to where the femoral artery was palpated. Puncture was achieved by advancing the needle upwards and inwards at an angle of 20-30 degrees with the skin.

A port with a Braun® brand (Germany) titanium reservoir body with a single lumen, ''Huber'' needle was used in all patients. The ports consisted of a reservoir body with a single lumen attached to the catheter, while the intravascular catheter part was made of silicone and polyurethane like other central venous catheters. After the intervention, posterior anterior chest radiography was taken to check the port catheter location and to detect possible hemopneumothorax, and the patients were called for control examination one week after the procedure.

The hospital records of the patients were inspected for their demographic data, primary diagnosis, port placement indication, anesthesia method applied during the procedure, location of the procedure, problems related to the intervention, technique used, complications developed during and after the intervention related to the port, and the reasons for removal of the port.

Patients who had abnormal bleeding diathesis and thrombocyte count less than 50,000/mm^3 and who did not consent were excluded from the study.

Statistical Analysis

SPSS 15.0 for Windows program will be used for statistical analysis. Descriptive statistics will be given as frequency tables and cross tables for categorical variables, and as mean, median, standard deviation, minimum and maximum for numerical variables.

Results

Of the 156 patients included in the study, 95 (60.9%) were male and 61 (39.1%) were female. The patients were in the age range of 38-87 (median 67) years. Port catheterization was applied to 153 of the patients (98.1%) since long-term chemotherapy was planned due to malignancy, and to 3 of the patients (1.9%) due to long-term parenteral nutrition. Of the malignancy patients, 57 (37.3%) were esophagus, whereas the 38 (24.8%) were stomach, 22 (14.4%) colon, 13 (8.5%) head and neck, 9 (5.9%) pancreas, 8 (5.2%) breast, other 6 (3.9%) were solid and hematological malignancies.

Port catheterization was not successful in a single attempt in 62 patients, requiring 2 or more attempts. The procedure was performed through the right IJV in 102 (65.4%) patients, the left IJV in 20 (12.8%) patients, the right SV in 31 (19.9%) patients, and the femoral vein in 3 (1.9%) patients. Ultrasonography-guided IJV procedure was performed in one of the patients due to failure despite multiple attempts. Catheterization was performed through the right femoral vein in 3 patients whose all trials were unsuccessful, and the chamber was placed in the right lower-middle quadrant of the abdomen. One of these patients was an obese patient with a short, thick neck. One of the patients who had a port inserted by femoral vein catheterization was a patient in whom the guidewire could not be advanced despite blood coming from the vascular puncture after multiple trials. In the subsequent Doppler ultrasonography of this patient, thrombosis was observed in the superior vena cava including both the right and left SVs.

During the patient follow-up, 3 ports and port pockets were removed due to infection. The first of these was removed one month after the port was inserted and *Staphylococcus aureus* grew in the culture taken. The second port was removed 3 months after insertion, and *Coagulase negative staphylococcus* grew in the culture. The third port was removed 6 months after insertion and *Candida albicans* grew in the culture. Sepsis due to port catheter infection was not developed. One of the cases was treated conservatively, while two cases were treated with tube thoracostomy. Complications such as arteriovenous fistula, dislocation of the catheter, migration of the port reservoir, and extravascular fluid leakage from the catheter, which can be seen after port catheterization, were not observed in our patients. Complications occurring during and after the intervention are shown in Table 1.

Discussion

Cancer patients require multiple painful intravenous interventions for cytotoxic agents, antibiotics, blood products and nutritional supplements. Port applications have been widely used in oncology since the 1980s to eliminate this concern and provide patient comfort (6,7). In the literature, Schwarz et al. (8) presented a series of 680 cancer patients with port catheter implantation and noted that the port catheter procedure was well tolerated and found comfortable by cancer patients. In the same study, they observed that the port catheter was functional in 90% of those who survived 1 year and in 70% of those who survived 4 years (8). Barrios et al. (9) reported that it was safe and advantageous for oncology patients in their series of 218 patients.

In a study conducted in our country, Eldeş et al. (10) presented their port catheter experiences and reported 39.2% of their patients were women. In this study, port applications were applied by radiology specialists in the interventional radiology unit (10). In our study, the practitioner was an anesthesiologist and 39.1% of the patients were women. In our study, the indication for patients with ports inserted was malignancy at a rate of 98.9%, similar to the study of Eldeş et al. (10) Indian researchers reported that they most frequently used port catheters for solid organ malignancies with 38% breast cancer in their study.

Unlike our study, Eldeş et al. (10) used ultrasonography or fluoroscopy for venous catheterization and did not report

Table 1. Complications during and after port catheterization

	n	%
Arterial puncture	7	4.5
Pneumothorax	3	1.9
Cardiac dysrhythmia	4	2.6
Port pocket infection	3	1.9
Wound infection	2	1.3
Catheter thrombosis-venous thrombosis	2	1.3
Subcutaneous hematoma	2	1.3
Total	23	14.8

arterial puncture and pneumothorax. In our study, venous catheterization of 62 patients was unsuccessful in the first attempt. Madabhavi et al. (6) reported catheter thrombosis at a rate of 1% (n=1), early catheter infection at 4%, and late catheter infection at 4% in their study. Also, 2% of catheter displacement was found in their study. Madabhavi et al. (6) administered antibiotics prophylactically to their patients before port application. Barrios reported 1.7% pneumothorax and 2.6% venous thrombosis in his study. In the same study, port pocket infection at a rate of 2.2% was detected and it was reported that such catheters were removed. It was stated that sepsis developed in one of the Barrios's catheter-infected patients (9). In our study, the rates of pneumothorax (1.9%) and port pocket infection (1.9%) were similar to the Barrios' study, and the rate of venous thrombosis (1.3%) was lower. Our study showed no sepsis development in our patients with catheter infection. Similar to the study of Madabhavi et al. (6) we administered prophylactic antibiotics to all patients before the procedure. Our findings regarding the complication rates show that the use of imaging methods will decrease the complication rates such as arterial puncture and pneumothorax and increase the comfort of the procedure.

Conclusion

We presented a limited series of patients in which port catheter application, ensuring comfort in the treatment of patients by providing long-term venous vascular access, was applied by an anesthesiologist in our center. We believe that increasing the experience of using ultrasonography in clinics other than radiology during some clinical situations and procedures will decrease the number of interventions and complications.

Ethics

Ethics Committee Approval: In this study, patients who were planned for long-term chemotherapy and parenteral nutrition between April 2012 and August 2013 in the Medical Oncology Clinic of Van Regional Training and Research Hospital and who were placed a total implantable port by an anesthesiologist were evaluated retrospectively after the approval of the local ethics committee, dated 19.06.2015 and numbered 2015/4.

Informed Consent: All patients were informed about both the intervention to be performed and the complications before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.G., A.A., Design: E.G., A.A., Data Collection or Processing: E.G., D.K, E.D., A.A., Analysis or Interpretation: E.G., S.Y., E.D., Drafting Manuscript: E.G., S.Y., Critical Revision of Manuscript: E.D., D.K., A.A., Final Approval and Accountability: E.G., S.Y., D.K., A.A., E.D.

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

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

References

1. Özer AB, Bayar MK. İmplante edilebilir venöz port kateter uygulamalarımızın incelenmesi. Fırat Tıp Dergisi 2011;16(1):6-10.
2. Kutlu R. Geçici /kalıcı venöz kateterler ve port yerleştirme. Trd Sem 2015;3(2):298-315.
3. Biffi R, De Braud F, Orsi F, Pozzi S, Arnaldi P, Goldhirsch A, et al. A randomized, prospective trial of central venous ports connected to standard open-ended or Groshong catheters in adult oncology patients. Cancer 2001;92:1204-1212.
4. Ballarini C, Intra M, Pisani Ceretti A, Cordovana A, Pagani M, Farina G, et al. Complications of subcutaneous infusion port in the general oncology population. Oncology 1999;56(2):97-102.
5. Collier PE, Blocker SH, Graff DM, Doyle P. Cardiac tamponade from central venous catheters. Am J Surg 1998;176(2):212-214.
6. Madabhavi I, Patel A, Sarkar M, Anand A, Panchal H, Parikh S. A study of use of "PORT" catheter in patients with cancer: a single-center experience. Clin Med Insights Oncol 2017;11:1179554917691031. doi: 10.1177/1179554917691031.
7. Gyves J, Ensminger W, Niederhuber J, Liepman M, Cozzi E, Doan K, et al. Totally implanted system for intravenous chemotherapy in patients with cancer. Am J Med 1982;73(6):841-845.
8. Schwarz RE, Groeger J, Coit DG. Subcutaneously implanted central venous access devices in cancer patients: a prospective analysis. Cancer 1997;79(8):1635-1640.
9. Barrios CH, Zuke JE, Blaes B. Evaluation of an implantable venous access system in a general oncology population. Oncology 1992;49(6):474-478.
10. Eldeş T, Akmangit İ, Dede D, Yıldırım N, Sayın B, Polattaş P. Erişkin hastalarda 498 deri alti port kateter uygulamalari ve komplikasyonlarinin retrospektif değerlendirilmesi. Pam Tıp Derg 2019;12(2):209-214.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):306-313
DOI: 10.4274/BMB.galenos.2021.04.050

The Effect of COVID-19 Pandemic on Depression, Anxiety and Stress Levels of Pregnant Women

Hamile Kadınlarda COVID-19 Pandemisinin Depresyon, Anksiyete ve Stres Düzeyleri Üzerine Etkisi

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) pandemic has negatively affected the psychology of the society. In this study, it was aimed to determine the stress, anxiety and depression levels in pregnant women during the COVID-19 pandemic and to investigate the delivery method attitudes using various scales.

Method: The study included 151 pregnant women admitted to the obstetrics and gynecology clinic of our tertiary hospital for follow-up. A 31-question questionnaire containing demographic information and questions about COVID-19, impact of event scale (IES-R), depression anxiety stress scale-21 (DASS-21) and revised pregnancy-related anxiety questionnaire-revised (PRAQ-R) scales were applied.

Results: According to the classifications made in DASS-21 subgroups, 16.5% of the pregnant women had severe or extreme depression, 35.1% had severe or extreme anxiety, 11.2% had severe or extreme stress level. The mean IES-R and PRAQ-R scores were found to be significantly higher in those under 35 years of age than those aged 35 years and over (p=0.02 and p=0.01, respectively). PRAQ-R (p<0.001), DASS-21 total (p=0.019), DASS-21 anxiety (p=0.012) and DASS-21 stress (p=0.014) scores were significantly higher in those who had their first pregnancy compared to experienced pregnant women.

Conclusion: In the present study, it was determined that the pandemic had a negative effect on the depression, anxiety and stress levels of pregnant women, and this effect was higher especially in younger pregnant women and in those experiencing their first pregnancy.

Keywords: Anxiety, COVID-19, depression, pandemic, pregnancy

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) salgını toplumun psikolojisini olumsuz etkilemiştir. Bu çalışmada, gebelerde COVID-19 salgını sırasında yaşanan stres, anksiyete ve depresyon düzeylerinin belirlenmesi ve çeşitli ölçeklerle doğum yöntemi tutumlarının incelenmesi amaçlanmıştır.

Yöntem: Çalışmaya üçüncü basamak hastanemizin kadın hastalıkları ve doğum kliniğine takip için başvuran 151 gebe dahil edildi. Gebelerin hepsine demografik bilgilerini içeren ve COVID-19, olay etkisi ölçeği (IES-R), depresyon anksiyetesi stres ölçeği-21 (DASS-21) ve gözden geçirilmiş gebelikle ilgili anksiyete anketi (PRAQ-R) ile ilgili soruları içeren 31 soruluk bir anket uygulandı.

Bulgular: DASS-21 alt gruplarında yapılan sınıflandırmalara göre, gebelerin %16,5'i şiddetli veya aşırı depresyon, %35,1'i şiddetli veya aşırı anksiyete, %11,2'si şiddetli veya aşırı stres düzeyine sahipti. Otuz beş yaşın altındakilerde ortalama IES-R ve PRAQ-R puanları 35 yaş ve üzerindekilere göre anlamlı derecede yüksek bulundu (sırasıyla p=0,02 ve p=0,01). İlk defa hamile olanlarda PRAQ-R (p<0,001), DASS-21 toplam (p=0,019), DASS-21 anksiyete (p=0,012) ve DASS-21 stres (p=0,014) puanları daha önce gebelik geçiren kadınlara göre yüksekti.

Sonuç: Bu çalışmada, salgının gebelerin depresyon, anksiyete ve stres düzeylerini olumsuz etkilediği, bu etkinin özellikle genç gebelerde ve ilk gebeliğini yaşayanlarda daha da yüksek olduğu tespit edilmiştir.

Anahtar kelimeler: Anksiyete, COVID-19, depresyon, hamilelik, pandemi

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Cite this article as: Çiler Eren E, Gümüş Şanlı S. The Effect of COVID-19 Pandemic on Depression, Anxiety and Stress Levels of Pregnant Women. Bagcilar Med Bull 2021;6(3):306-313

Introduction

Pregnancy is a condition in which psychological sensitivity increases due to many hormonal and physiological factors. The threshold value for psychological disorders may decrease and abnormal psychological conditions can be seen more frequently in pregnancy (1,2). Psychological disorders that can be seen during pregnancy can mostly be well tolerated. However, in some cases, the excessive increase of the level of these disorders can lead to adverse situations and complications for the pregnant woman, pregnancy and the baby. Therefore, the psychological status of pregnant women should be closely followed up (1-3).

Various scales have been created to determine the psychological conditions, the presence of stress, anxiety and depression, and their levels in pregnant women (4). Some of these scales measure the psychological effects of environmental events on pregnant women, while others only determine the levels of anxiety about pregnancy and baby. The mental state of a pregnant determined by these scales can provide the necessary precautions to be taken more appropriately and early and an appropriate rehabilitation program to be implemented (4,5).

Coronavirus disease-2019 (COVID-19), known as the new coronavirus disease, has caused a major pandemic in 2020 and 2021. The COVID-19 pandemic has negatively affected the psychology of the pregnant women (6). In this study, it was aimed to determine the stress, anxiety and depression levels of pregnant women during the COVID-19 pandemic using various scales.

Materials and Methods

Approval was obtained from the University of Medipol Ethics Committee for non-interventional clinical trials within our institution (date: 02.01.2020; number: 001212). It was made with the permission of the Ministry of Health (2020-05-19T13_03_28). Written informed consent was obtained from all participants.

Patients

The study included 151 pregnant women who were admitted to the gynecology and obstetrics clinic of our tertiary care hospital for follow-up purposes and who had no health problems. Pregnant women who developed pregnancy-related complications, who had a previous history of psychiatric disease, and who had a history of a chronic disease were excluded from the study. All of these 151 patients were followed by the same author until the end of pregnancy.

Some scales have been developed to determine the levels of anxiety and depression in pregnant women. While these scales may have some advantages over each other, they may also have some shortcomings (7). Therefore, four separate scales were used in the present study and the effects of COVID-19 on pregnant women were tried to be determined from different aspects. A survey of 31 questions including demographic information and questions about COVID-19, impact of event scale (IES-R), depression anxiety stress scale-21 (DASS-21) and revised pregnancy-related anxiety questionnaire-revised (PRAQ-R) scales were applied to all participants. The scales were evaluated and analyzed by an experienced psychiatrist.

IES-R

IES-R is a scale that defines trauma-related psychological effects. It consists of 22 questions in total and is scored as never (0), a little (1), more or less (2), quite (3), and extreme (4). In this study, the main event was identified as the COVID-19 pandemic and questions were asked. Higher score means higher level of exposure (5,8).

Scores are classified as follows:

24-32: Those with these high scores, who do not have full post-traumatic stress disorder (PTSD), will have partial PTSD or at least some of the symptoms (9).

33-38: This represents the best cutoff for a probable diagnosis of PTSD (10).

39 and above: This is high enough to suppress your immune system's functioning (even 10 years after an impact event) (11).

DASS-21

DASS-21 is a questionnaire consisting of 21 questions about depression, anxiety and stress. The questions are scored as never (0), sometimes or occasionally (1), quite often (2) and always (3). Accordingly, each category was classified as normal, mild, moderate, severe and extreme (7,12). "Severe" was evaluated as 11 points and above in the depression subscale, as 8 points and above in the anxiety subscale, and as 13 points and above in the stress subscale.

PRAQ-R

PRAQ-R is a questionnaire consisting of 10 questions determining the anxiety levels of pregnant women related to pregnancy, birth and baby. The questions are scored as ''strongly disagree'' (1), ''disagree'' (2), ''slightly agree'' (3), ''agree'' (4) and ''strongly agree'' (5). The score can be between 10 and 50 points. Higher score means higher level of exposure (13,14).

Statistical Analysis

All statistical analyses in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as numbers and percentages. In terms of categorical variables, comparisons between groups were made with the Pearson's chi-square test and Fisher's Exact test. Whether continuous variables were suitable for normal distribution was confirmed by the Kolmogorov-Smirnov test. The differences between the groups in terms of continuous variables were analyzed using the Student's t-test, and the comparison of mean values between multiple groups by variance analysis. The relationship between continuous variables was tested using the Spearman's correlation analysis. The results were evaluated within the 95% confidence interval, and $p<0.05$ values were considered significant. Bonferroni correction was made where appropriate.

Results

The median age of the pregnant women included in the study was 30 years (22-44 years, minimum-maximum). A total of 129 women were under the age of 35 years, and 22 of them were 35 years old or older. The median week of gestation in women was 28 weeks (10-39 weeks, minimum-maximum) (Table 1).

In women, the mean total IES-R score was 24.9±12.2, the mean total PRAQ-R score was 27.4±7.4, the mean total DASS-21 score was 9.7±7.7. Among the DASS-21 subgroups, the mean depression score was 2.8±2.8, the anxiety score was 2.8±2.6, and the stress score was 4.1±3.2 (Table 1).

Table 1. The mean values of age, gestational week and total score percentages

	Mean	SD	Minimum	Maximum
Age (years)	30 (Median)	-	22	44
Pregnancy week (week)	28 (Median)	-	10	39
IES-R	24.9	12.2	0	53
PRAQ-R	27.4	7.4	11	49
DASS-21	9.7	7.7	0	38
DASS-21 depression score	2.8	2.8	0	15
DASS-21 anxiety score	2.8	2.6	0	11
DASS-21 stress score	4.1	3.2	0	13

IES-R: Impact of events scale, PRAQ-R: Pregnancy-related anxiety questionnaire, DASS-21: Depression anxiety stress scale-21, SD: Standard deviation

A total of 72.8% of the women had a university or higher education, 57% were working in a paid job. According to the classifications made in DASS-21 subgroups, 16.5% of the pregnant women had severe or extreme depression, 35.1% had severe or extreme anxiety, 11.2% had severe or extreme stress level. The rate of pregnant women who changed hospitals or physicians due to COVID-19 was 21.2% (Table 2).

The mean IES-R and PRAQ-R scores were found to be significantly higher in those under 35 years of age than those aged 35 years and over ($p=0.02$ and $p=0.01$, respectively). There was no difference in scale scores between the group with a family diagnosed with COVID-19 and the group with no relatives with COVID-19. DASS-21 ($p=0.019$), PRAQ-R ($p<0.001$), DASS-21 anxiety ($p=0.012$) and DASS-21 stress ($p=0.014$) scores were significantly higher in those who were experiencing their first pregnancy (Table 3).

There was no significant difference between education and job groups in terms of scale scores. PRAQ-R score was significantly higher in those living on minimum wage compared to other groups ($p=0.011$). The IES-R and DASS-21 scores were significantly lower in those who said they had sufficient or fair knowledge about COVID-19 than those who said they had little or moderate knowledge ($p=0.022$ and $p=0.001$, respectively) (Table 4).

Scale scores were found to be significantly correlated with each other in correlation analysis. Week of gestation was significantly correlated only with the IES-R score ($p=0.016$; $r=0.185$) (Table 5).

It was seen that the highest scores in the IES-R scale belonged to the perceptions about the pandemic, the DASS-21 scale to the unreasonable fears, and the PRAQ-R scale to the questions about pain, birth and baby's health. According to all scales, the anxiety about a possible harm to the baby and not getting medical help were found to be significant during the pandemic period (Table 6).

Discussion

In this study, it was determined that the pandemic had a negative effect on the depression, anxiety and stress levels of pregnant women, and this effect was higher especially in younger pregnant women and in those experiencing their first pregnancy. Therefore, women who are thinking of pregnancy during the pandemic process should be given information about the effects of the COVID-19 virus on pregnancy and support should be provided to reduce anxiety.

Table 2. Distributions of some variables and DASS-21 subgroups

	n	%
Education status		
Primary school	9	6.0
High school	32	21.2
University	100	66.2
Postgraduate	8	5.3
Doctorate	2	1.3
Working condition		
Self employed	8	5.3
Paid employee	78	51.7
Not working	65	43.0
COVID-19 in the family	10	6.6
Changing physician/hospital due to COVID-19	32	21.2
Anxiety of getting COVID-19		
Extreme	4	2.6
Very	10	6.6
Moderate	73	48.3
Little	47	31.1
None	17	11.3
Anxiety about harm to the baby		
Extreme	18	11.9
Very	43	28.5
Moderate	55	36.4
Little	25	16.6
None	10	6.6
DASS-21 subgroups	**n**	**%**
DASS-21 depression		
Extreme	12	7.9
Severe	13	8.6
Moderate	28	18.5
Mild	29	19.2
Normal	69	45.7
DASS-21 anxiety		
Extreme	32	21.2
Severe	21	13.9
Moderate	28	18.5
Mild	21	13.9
Normal	49	32.5
DASS-21 stress		
Extreme	7	4.6
Severe	10	6.6
Moderate	27	17.9
Mild	14	9.3
Normal	93	61.6

DASS-21: Depression anxiety stress scale-21, COVID-19: Coronavirus disease-2019

Table 3. Comparisons between mean score percentages according to some variables

	Age		**p**
	<35 years	**≥35 years**	
IES-R	25.9±11.5	19.4±14.2	**0.020**
PRAQ-R	28.1±7	23.7±9.1	**0.010**
DASS-21	9.9±7.7	7.5±7.4	0.166
DASS-21 depression score (%)	6±5	4.9±5.1	0.346
DASS-21 anxiety score (%)	6.8±5.5	5.1±5.2	0.164
DASS-21 stress score (%)	7±5.3	4.9±4.8	0.088
	COVID-19 in the family		**p**
	Present	**Absent**	
IES-R	23.4±12.2	25.1±12.2	0.675
PRAQ-R	29.6±5.3	27.3±7.6	0.356
DASS-21	12.4±6.8	9.3±7.7	0.224
DASS-21 depression score (%)	7.2±4.4	5.7±5	0.376
DASS-21 anxiety score (%)	8.9±4.4	6.4±5.5	0.164
DASS-21 stress score (%)	8.7±5.2	6.5±5.2	0.208
	Parity		**p**
	0-1	**2-4**	
IES-R	26.7±12.5	23.6±11.8	0.124
PRAQ-R	30.1±7	25.5±7.2	**<0.001**
DASS-21	11.2±8.4	8.3±6.8	**0.019**
DASS-21 depression score (%)	6.7±5.4	5.2±4.6	0.064
DASS-21 anxiety score (%)	7.8±6	5.6±4.8	**0.012**
DASS-21 stress score (%)	7.9±5.7	5.8±4.7	**0.014**

Independent samples t-test was used. IES-R: Impact of events scale, PRAQ-R: Pregnancy-related anxiety questionnaire, DASS-21: Depression anxiety stress scale-21, COVID-19: Coronavirus disease-2019

The COVID-19 pandemic has been a major public issue in terms of mental health (15). In a large-scale study, it was found that during the COVID-19 pandemic, pregnant women showed a significantly higher rate of depression and anxiety symptoms, dissociative symptoms, and PTSD symptoms compared to pregnant women before COVID-19 (16). Studies have reported that the level of depression and anxiety in pregnant women increased significantly during the COVID-19 pandemic (17-19). In this study, the mean IES-R, DASS-21 and PRAQ-R scores in women show that the COVID-19 pandemic causes an increase in anxiety, depression and stress levels in pregnant women. However, the fact that the PRAQ-R scale score is much higher than the other survey scores means that the pregnant women are in a state of stress associated with their pregnancy rather than anxiety against COVID-19. All these findings show

Table 4. Comparisons between mean score percentages by variables (mean ± SD)

		IES-R	PRAQ-R	DASS-21
Education level	**p**	0.735	0.706	0.308
Primary/high school		25.5±10.9	27.1±8	8.5±6.1
University or higher		24.8±12.6	27.6±7.3	9.9±8.2
Income level (5 groups)	**p**	0.942	**0.011***	0.724
Working status	**p**	0.615	0.16	0.12
Self employed		22.3±8.3	26.1±7.8	5.7±4.4
Paid employee		24.4±12.2	28.7±8	10.6±8.6
Not working		25.9±12.6	26.3±6.7	8.9±6.6
Knowledge level	**p**	**0.022**	0.099	**0.001**
Little/moderate		28.6±12.3	29.2±7.1	12.2±7.4
Sufficient/quite		23.6±11.8	26.9±7.5	8.5±7.5

One-Way ANOVA method was used. *Higher in the minimum wage group compared to other groups. IES-R: Impact of events scale, PRAQ-R: Pregnancy-related anxiety questionnaire, DASS-21: Depression anxiety stress scale-21, SD: Standard deviation

Table 5. Correlation analysis between gestational week and scale total scores

		Gestational week	IES-R	DASS-21
IES-R	**r**	0.185	-	-
	p	**0.016**	-	-
DASS-21	**r**	0.132	0.696	-
	p	0.085	**<0.001**	-
PRAQ-R	**r**	0.008	0.348	0.454
	p	0.920	**<0.001**	**<0.001**

IES-R: Impact of events scale, PRAQ-R: Pregnancy-related anxiety questionnaire, DASS-21: Depression anxiety stress scale-21

that the COVID-19 pandemic generally causes negative psychological effects in pregnant women.

It has been found that younger age in pregnant women is associated with a higher rate of maternal psychological stress disorder caused by COVID-19 (16). Wu et al. (20) found that pregnant women under 35 years of age had a higher risk of depression and anxiety during the pandemic period. Dagklis et al. (21) found that pregnant women aged 35 years and over had a 1.1-fold higher risk of anxiety caused by COVID-19 compared to those under the age of 35 years. In the present study, the mean IES-R score, PRAQ-R score and DASS-21 stress score were found to be significantly higher in women under the age of 35 years. These findings show that younger pregnant women are significantly more affected by the psychology of the COVID-19 pandemic, and that these pregnant women have a higher risk for increase in anxiety, depression and stress levels.

It has been found that low education level in pregnant women is associated with a higher rate of maternal psychological stress disorder caused by COVID-19 (18). Durankuş and Aksu (19) found that pregnant women with more education years had a lower level of depression. However, we did not find any difference between education groups. Similarly, Dong et al. (22) reported that there was no relationship between educational status and anxiety.

It has been stated that low income in pregnant women is associated with a higher rate of maternal psychological stress disorder caused by COVID-19 (16). Wu et al. (20) found that pregnant women with middle income had a higher risk of depression and anxiety during the pandemic. In the present study, the PRAQ-R score was significantly higher in the lowest income group living on the minimum wage compared to the other groups. This has shown us that the COVID-19 pandemic has a more negative psychological effect, especially in pregnant women with low income.

We found that COVID-19 had a more negative effect on the generally high stress levels of pregnant women experiencing the first pregnancy, and that these pregnant women were particularly concerned about their pregnancies and their children to be born. However, it has been reported that COVID-19 causes more negative psychological effects in pregnant women with more children (19). Dagklis et al. (21) reported that those with higher number of pregnancies had a 1.2-fold higher risk of anxiety caused by COVID-19 compared to women with first pregnancy. Conversely, Wu et al. (20) found that women experiencing the first pregnancy had a higher risk of depression and anxiety during the pandemic. According to these findings, it can be thought that the main concern in pregnant women with a high number of children is the pregnancy itself and not the child to be born, but their present children.

It has been stated that there is no significant relationship between the level of knowledge about COVID-19 and depression level caused by COVID-19 in pregnant women (19). In the present study, those who said they had sufficient or fair knowledge about COVID-19 were found to be significantly lower than those who said they had little or moderate knowledge in all three scales. The fact that the anxiety and depression scores due to COVID-19 are significantly lower in pregnant women who think that they have more knowledge may suggest that the information will have a positive effect on the psychological mood. Additionally, the rate of pregnant women infected by COVID-19 in their family was 6.6%. Although all scores were high in all of these cases, no statistical difference was

Table 6. The mean scores according to the groups of concern about harm to the baby and the groups of anxiety not to get medical help

	Groups of anxiety about harm to the baby					
	None	**A little**	**Moderate**	**Very much**	**Extreme**	**p**
IES-R total score	6.8±6.5	21.6±8.7	23.7±11.1	27.7±11	36.8±10.4	**<0.001**
PRAQ-R total score	17.4±7.8	25.6±5.3	25.8±5.3	30.6±6.7	33.2±8.6	**<0.001**
DASS-21 total score	1.3±2.1	7.5±6.7	8.3±6	11.6±8	17.3±8.2	**<0.001**
DASS-21 depression	0.3±0.7	2.5±3.3	2.5±2.2	3.3±3.2	4.6±2.6	**0.001**
DASS-21 anxiety	0.2±0.4	1.7±2	2.4±2.2	3.4±2.3	5.8±3.2	**<0.001**
DASS-21 stress	0.8±1.8	3.3±2.6	3.4±2.6	4.9±3.3	6.9±3.6	**<0.001**
	Groups of anxiety about not getting medical help					
	None	**A little**	**Moderate**	**Very much**	**Extreme**	**p**
IES-R total score	21±11.1	27.1±9.2	33.7±10.9	30±0	42.2±12.6	**<0.001**
PRAQ-R total score	25.6±7.2	30±6.5	29.4±6.5	40±0	36±6.7	**<0.001**
DASS-21 total score	7.5±5.9	13.6±8.8	12.7±9.3	4±0	17.2±9.1	**<0.001**
DASS-21 depression	2.1±2	4.3±3.6	3.8±3.5	0±0	4.8±3	**<0.001**
DASS-21 anxiety	2.1±2.1	4±3	3.9±3.1	3±0	5±3	**<0.001**
DASS-21 stress	3.3±2.7	5.3±3.7	5±3.5	1±0	7.4±3.9	**0.001**

IES-R: Impact of events scale, PRAQ-R: Pregnancy-related anxiety questionnaire, DASS-21: Depression anxiety stress scale-21

observed. However, it was observed that this did not affect the overall depression, stress and anxiety scores.

Dong et al. (22), in their study with 156 pregnant women, found no significant correlation between week of pregnancy and level of depression caused by COVID-19. In another study, it was found that anxiety level increased in the later trimesters (21). In the present study, in the correlation analysis performed, gestational week was found to be significantly correlated only with the IES-R score. These findings may show that pregnant women whose births were approaching may have been affected more negatively by the COVID-19 pandemic compared to the scale of the effects of the events.

Wu et al. (20) found that pregnant women working full-time have a higher risk of depression and anxiety during the pandemic. In the present study, there was no significant difference between the job groups in terms of scale scores. It may be more appropriate to evaluate the relationship of the job situation with the psychology of the COVID-19 pandemic together with the economic and social rights and socioeconomic status of pregnant women in each country.

In this study, it was observed that 35.1% of pregnant women had severe or very severe anxiety about harm to the baby due to COVID-19. Yang et al. (6) reported this rate as 7.8%. Ravaldi et al. (23) reported the rate of patients with anxiety symptoms as 21.7%. Corbett et al. (18) found that during the COVID-19 pandemic process, pregnant women experienced the most anxiety about their elderly relatives, children and unborn babies, respectively. Additionally, they found that pregnant women had least but still significant anxiety about their own health. Fakari and Simbar (24) also reported that pregnant women were most anxious about their relatives and unborn babies during the COVID-19 pandemic, and they determined that these pregnant women were hesitant to go to the hospital for controls. Studies show that, similar to our study, the proportion of pregnant women concerned about the health of their unborn babies is high (17,23).

It was seen that the highest scores in the IES-R scale belonged to the rate of thinking about the pandemic. This finding shows that pregnant women are aware of that the COVID-19 pandemic disturbs them, they unintentionally think about this pandemic and try to avoid this thought. It was observed that the highest scores in the DASS-21 scale belong to unreasonable fears. This finding may indicate that COVID-19 causes a negligible but significant deterioration in mental health of pregnant women. In the PRAQ-R scale, it was observed that the highest scores were related to pain, birth and the health of the baby. These items do not appear to be directly related to the COVID-19 pandemic. Scale scores were found to be significantly correlated with each other in correlation analysis. This finding shows that the scales are in accordance with each other.

Study Limitations

There were some limitations in the present study. Since the present study was planned on a cross-sectional and scale basis, the changes in the psychological states of pregnant women after pregnancy were not observed and evaluation could not be made on this issue.

Conclusion

The COVID-19 pandemic is deeply affecting the mental health of pregnant women, and pregnancy-specific anxiety changes seem to be caused by factors independent of pregnancy. This study is one of the few studies examining the psychological effects of the COVID-19 pandemic in pregnant women with scale data. It was determined that the pandemic had a negative effect on the depression, anxiety and stress levels of pregnant women, and this effect was higher especially in younger pregnant women and in those experiencing their first pregnancy.

Ethics

Ethics Committee Approval: Approval was obtained from the University of Medipol Ethics Committee for non-interventional clinical trials within our institution (date: 02.01.2020; number: 001212).

Informed Consent: It was made with the permission of the Ministry of Health (2020-05-19T13_03_28). Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Ç.E., S.G.Ş., Design: E.Ç.E., S.G.Ş., Data Collection or Processing: E.Ç.E., Analysis or Interpretation: S.G.Ş., Drafting Manuscript: E.Ç.E., S.G.Ş., Final Approval and Accountability: E.Ç.E., Supervision: E.Ç.E., S.G.Ş.

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

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

References

1. Becker M, Weinberger T, Chandy A, Schmukler S. Depression during pregnancy and postpartum. Curr Psychiatry Rep 2016;18(3):32.
2. Vigod SN, Wilson CA, Howard LM. Depression in pregnancy. BMJ 2016;352:i1547. doi: 10.1136/bmj.i1547.
3. Bayrampour H, Ali E, McNeil DA, Benzies K, MacQueen G, Tough S. Pregnancy-related anxiety: a concept analysis. Int J Nurs Stud 2016;55:115-130.
4. Mudra S, Göbel A, Barthel D, Hecher K, Schulte-Markwort M, Goletzke J, et al. Psychometric properties of the German version of the pregnancy-related anxiety questionnaire-revised 2 (PRAQ-R2) in the third trimester of pregnancy. BMC Pregnancy Childbirth 2019;19(1):242.
5. Brunet A, St-Hilaire A, Jehel L, King S. Validation of a French version of the impact of event scale-revised. Can J Psychiatry 2003;48(1):56-61.
6. Yang X, Song B, Wu A, Mo PKH, Di J, Wang Q, et al. Social, Cognitive, and eHealth Mechanisms of COVID-19-Related Lockdown and Mandatory Quarantine That Potentially Affect the Mental Health of Pregnant Women in China: Cross-Sectional Survey Study. J Med Internet Res 2021;23(1):e24495. doi: 10.2196/24495.
7. Barber CC, Steadman J. Distress levels in pregnant and matched non-pregnant women. Aust N Z J Obstet Gynaecol 2018;58(1):128-131.
8. Kotta S, Molangur U, Bipeta R, Ganesh R. A cross-sectional study of the psychosocial problems following abortion. Indian J Psychiatry 2018;60(2):217-223.
9. Asukai N, Kato H, Kawamura N, Kim Y, Yamamoto K, Kishimoto J, et al. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. J Nerv Ment Dis 2002;190(3):175-182.
10. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. Behav Res Ther 2003;41(12):1489-1496.
11. Kawamura N, Kim Y, Asukai N. Suppression of cellular immunity in men with a past history of posttraumatic stress disorder. Am J Psychiatry 2001;158(3):484-486.
12. Oei TP, Sawang S, Goh YW, Mukhtar F. Using the Depression Anxiety Stress Scale 21 (DASS-21) across cultures. Int J Psychol 2013;48(6):1018-1029.
13. Aksoy Derya Y, Timur Tashan S, Duman M, Durgun Ozan Y. Turkish adaptation of the pregnancy-related anxiety questionnaire-revised 2: Validity and reliability study in multiparous and primiparous pregnancy. Midwifery 2018;62:61-68.
14. Vázquez MB, Pereira B, Míguez MC. Psychometric properties of the spanish version of the Pregnancy Related Anxiety Questionnaire (PRAQ). Span J Psychol 2018;21:E64. doi: 10.1017/sjp.2018.67.
15. Kajdy A, Feduniw S, Ajdacka U, Modzelewski J, Baranowska B, Sys D, et al. Risk factors for anxiety and depression among pregnant women during the COVID-19 pandemic: A web-based cross-sectional survey. Medicine (Baltimore) 2020;99:e21279. doi: 10.1097/MD.0000000000021279.
16. Berthelot N, Lemieux R, Garon-Bissonnette J, Drouin-Maziade C, Martel É, Maziade M. Uptrend in distress and psychiatric symptomatology in pregnant women during the coronavirus disease 2019 pandemic. Acta Obstet Gynecol Scand 2020;99(7):848-855.
17. Moyer CA, Compton SD, Kaselitz E, Muzik M. Pregnancy-related anxiety during COVID-19: a nationwide survey of 2740 pregnant women. Arch Womens Ment Health 2020;23(6):757-765.
18. Corbett GA, Milne SJ, Hehir MP, Lindow SW, O'connell MP. Health anxiety and behavioural changes of pregnant women during the COVID-19 pandemic. Eur J Obstet Gynecol Reprod Biol 2020;249:96-97.
19. Durankuş F, Aksu E. Effects of the COVID-19 pandemic on anxiety and depressive symptoms in pregnant women: a preliminary study. J Matern Fetal Neonatal Med 2020:1-7. doi: 10.1080/14767058.2020.1763946. Epub ahead of print.

20. Wu Y, Zhang C, Liu H, Duan C, Li C, Fan J, et al. Perinatal depressive and anxiety symptoms of pregnant women along with COVID-19 outbreak in China. Am J Obstet Gynecol 2020;223(2):240.e1-240.e9. doi: 10.1016/j.ajog.2020.05.009.

21. Dagklis T, Tsakiridis I, Mamopoulos A, Athanasiadis A, Papazisis G. Anxiety During Pregnancy in the Era of the COVID-19 Pandemic. Lancet, 2020. (in press). (Available from: http://dx.doi.org/10.2139/ssrn.3588542).

22. Dong H, Hu R, Lu C, Huang D, Cui D, Huang G, et al. Investigation on the mental health status of pregnant women in China during the Pandemic of COVID-19. Arch Gynecol Obstet 2021;303(2):463-469.

23. Ravaldi C, Ricca V, Wilson A, Homer C, Vannacci A.Previous psychopathology predicted severe COVID-19 concern, anxiety, and PTSD symptoms in pregnant women during “lockdown” in Italy. Arch Womens Ment Health 2020;23(6):783-786.

24. Fakari FR, Simbar M. Coronavirus Pandemic and Worries during Pregnancy; a Letter to Editor. Arch Acad Emerg Med 2020;16;8(1):e21. https://pubmed.ncbi.nlm.nih.gov/32185371/

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):314-319
DOI: 10.4274/BMB.galenos.2021.05.056

NLR, MPV and RDW as Biomarkers in Operated and Non-operated Patients with Colorectal Adenocarcinoma

Opere ve Non-opere Kolorektal Adenokarsinoma Hastalarında Biyobelirteç Olarak NLR, MPV ve RDW

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Abstract

Objective: There is a need for inexpensive, reliable and readily available biomarkers in the early diagnosis and prediction of mortality, morbidity and treatment response in colorectal cancer (CRC). In our study, it was aimed to compare mean platelet volume (MPV), red cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) measurements in operated and non-operated patients with the diagnosis of CRC.

Method: In our study, we retrospectively reviewed 52 patients (including 26 operated patients and 26 non-operated patients) diagnosed as CRC with colonoscopic biopsy at endoscopy unit of gastroenterology department between 2016 and 2019. We extracted and compared demographic, colonoscopy, clinical, laboratory and surgical data in both groups.

Results: In our study, the mean age (60.04 years and 64.19 years, respectively) and gender distribution (female: male, 12/16 and 10/14, respectively) were comparable in operated and non-operated patients with CRC. MPV, RDW and NLR measurements were found to be significantly lower in patients who underwent surgery (operated) when compared to non-operated patients ($p<0.001$, $p=0.026$ and $p<0.001$, respectively).

Conclusion: There is strong evidence suggesting that inflammation plays a role in the pathogenesis of many disorders including malignancy. In our study, it was found that inflammatory markers, namely MPV, RDW and NLR values, were lower after surgery which removed tumor; thus, inflammation. These biomarkers can be suggestive for early diagnosis in CRC as well as response to surgical treatment.

Keywords: NLR (neutrophil-lymphocyte ratio), MPV (mean platelet volume), RDW (red cell distribution width), operation, colorectal adenocarcinoma

Öz

Amaç: Kolorektal kanserin (KRK) erken tanısında, mortalite, morbidite ve tedavi yanıtının tahmin edilmesinde kolayca ulaşılabilir, ucuz ve güvenilir biyobelirteçlere ihtiyaç vardır. Çalışmamızda KRK tanısı ile opere olan ve opere olmayan hastaların ortalama trombosit hacmi (MPV), eritrosit dağılım genişliği (RDW) ve nötrofil-lenfosit oranı (NLR) ölçümlerini karşılaştırmak amaçlanmıştır.

Yöntem: Çalışmamızda 2016-2019 yılları arasında hastanemiz gastroenteroloji kliniği, endoskopi ünitemizde kolonoskopik biyopsi ile KRK tanısı alan ve 26'sı opere, 26'sı non-opere toplam 52 hasta incelenmiştir. Her iki hasta grubuna ait demografik, kolonoskopik, klinik, laboratuvar ve operasyonel bilgiler restrosepektif olarak irdelenmiş ve karşılaştırılmıştır.

Bulgular: Çalışmamızda opere ve non-opere KRK hastaların yaş ortalamaları (60,04 ve 64,19 yaş) ve cinsiyet (kadın/erkek: 12/16 ve 10/14) özellikleri birbirine benzerdi. Opere olarak cerrahi tedavi uygulanan hastaların, cerrahi tedavi olmayan non-opere hastalara göre MPV, RDW ve NLR ölçümleri istatistiksel olarak anlamlı ölçüde düşük saptandı ($p<0,001$, $p=0,026$, $p<0,001$).

Sonuç: Kronik enflamasyonun, malignite dahil birçok hastalığın patogenezinde rol oynadığına dair güçlü kanıtlar mevcuttur. Çalışmamızda araştırdığımız enflamatuvar göstergeler olan MPV, RDW ve NLR düzeylerinin, tümörün ve dolayısıyla enflamasyonun ortadan kalkmasına neden olan operasyon sonrası düşük düzeylerde olduğu saptanmıştır. Bu biyobelirteçler KRK erken tanısı için fikir verebileceği gibi, cerrahi tedavi yanıtı hakkında da bilgi verebilir.

Anahtar kelimeler: NLR (nötrofil-lenfosit oranı), MPV (ortalama trombosit hacmi), RDW (eritrosit dağılım genişliği), operasyon, kolorektal adeno karsinom

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Cite this article as: Bulur A, Çakır AS. NLR, MPV and RDW as Biomarkers in Operated and Non-operated Patients with Colorectal Adenocarcinoma. Bagcilar Med Bull 2021;6(3):314-319

Introduction

Colorectal cancer (CRC) is the third most common cancer whereas fourth most common cause of cancer-related mortality worldwide (1). As similar to many other cancers, the likelihood of successful treatment is increased if diagnosed early (2). Although colonoscopy remains to be the most effective modality in detecting CRC, inconvenient experience, risk of complication and higher costs limit its use in screening settings (3,4). In CRC, fecal occult blood test and fecal immunochemical test are most commonly used biomarkers in CRC screening. However, the sensitivity of these tests is variable as they are affected from diet and unable to distinguish between upper and lower gastrointestinal bleeding (5,6). Despite apparent improvements in the diagnosis and treatment of CRC in recent years, the diagnosis is still made at advanced stages in majority of patients, resulting in poor prognosis. Thus, there is a need for biomarkers that improve survival and inform early diagnosis, treatment response and prognosis. There are clinical studies investigating non-invasive, readily available and inexpensive tumor biomarkers with high accuracy. These are mostly molecules that show elevated levels with inflammation and immune reactions. Chronic inflammation has been linked with many immune reactions, a number of disease and poor outcomes. In recent studies, growing evidence shows that inflammation and immune response play pivotal role in the development and progression of several cancers including CRC (7-9). It has been reported that inflammation can lead to CRC development through increased production of leukocyte-derived cytokines and reactive oxygen species resulting in DNA damage and subsequent dysplasia. In addition, inflammation may lead tumoral cell proliferation and promote angiogenesis (10). Systemic inflammation markers such as C-reactive protein, neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV) and red cell distribution width (RDW) were investigated in several studies and it was reported that the levels of these molecules were elevated in some cancers including CRC and that they were associated with poor differentiation, poor prognosis and mortality (11-17). These biomarkers can be analyzed in almost all healthcare facilities, which can be measured from peripheral blood samples using complete blood count (CBC) test. Neutrophils represent a large subclass of leukocytes. In carcinogenesis process, there was an increase in NLR due to increased neutrophil count and decreased lymphocyte count in peripheral blood (18). MPV, a marker for platelet size and activity, is accepted as an inflammatory marker in cardiovascular, cerebrovascular, rheumatoid and gastroenterological disorders. In addition, there are studies supporting that MPV can be a marker for early diagnosis in gastric, pancreatic, hepatocellular cancer and CRC (13,18,19). RDW is a parameter that represents size heterogeneity of red blood cells, which is used to discriminate several anemia types. In recent studies, it has been reported that RDW is a biochemical marker associated with many chronic inflammatory and cardiovascular disease and that it may be used as a prognostic marker in several cancers such as lung cancer, esophagus cancer, gastric cancer, hepatocellular carcinoma and breast cancer (20-22). Thus, it is reasonable to anticipate that treatment or surgical removal of tumor would cause decrease in these biomarkers. In a few studies, it was reported that NLR, platelet: lymphocyte ratio (PLR) and MPV values were regressed following surgical tumor resection in CRC when compared to preoperative values (13,19). The aim of this study was to elucidate effectiveness and capability of MPV, NLR and RDW as non-invasive diagnostic biomarkers in CRC and to investigate reduction anticipated in the markers following surgical treatment.

Materials and Methods

In this study, we retrospectively reviewed demographic, colonoscopic, clinical, laboratory data and histopathological features in 52 patients (aged >18 years) who were diagnosed as colorectal adenocarcinoma by colonoscopic biopsy performed for any reason in our endoscopy unit of gastroenterology department between 2016 and 2019. Of these patients, 26 were diagnosed as CRC in our endoscopy unit but not received any treatment (non-operated patients) while 26 patients were diagnosed as CRC in our endoscopy unit and followed in our outpatient clinic after surgery performed in different hospitals (operated patients). In our study, primary objective was to compare MPV, NLR and RDW values extracted from CBC studied in our laboratory between operated and non-operated ones. Blood samples (2 mL) were drawn from cubital vein following 8-hour fasting. Blood samples coagulated using EDTA were analyzed by hematology analyzer within 2-4 hours. The MPV and RDW results were directly extracted from CBC report while NLR was calculated by dividing absolute neutrophil count with absolute lymphocyte count. The normal values were 6-10 fL for MPV and 12-16% for RDW. The colonoscopy (Fujinon, ED550 colonoscopy device, Japan) was performed following 24-hour colon preparation and 8-hour fasting under sedation-analgesia supervised by an anesthesiologist. Multiple biopsies were taken from lesions seen during colonoscopy. The biopsy specimens

were placed in 10% formalin and sent to histopathology laboratory. There were comorbid diabetes mellitus, hypertension and chronic ischemic heart diseases. The patients with a history of secondary malignancy, patients with metastatic CRC, patients with fatal outcome at any time, those received blood product transfusion within prior 6 months and patients who underwent chemotherapy and radiotherapy were excluded. The study was approved by Institutional Ethics Committee.

Statistical Analysis

Continuous variables were presented as descriptive statistics (mean, standard deviation, minimum, median, maximum). Categorical variables were presented in frequency and percentage. The Mann-Whitney U test was used to compare two independent, continuous variables with skewed distribution. The Spearman's rho correlation test was used to assess the relationship between two continuous variables with skewed distribution. Statistical significance level was set as 0.05. All statistical analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

The study included 52 patients. The mean age was 62.12±12.5 years. There were 30 men and 22 women. Of 52 patients, 26 (50%) were non-operated CRC patients while 26 (50%) were operated CRC patients. The mean age was 60.04 years (35-71) in the operated group whereas 64.19 years (44-88) in the non-operated group. There were 12 women and 16 men in the operated group whereas 10 women and 14 men in the non-operated group. Sigmoid colon (n=19, 36.5%) and rectum (n=12, 23.1%) were found as the most common CRC localization cited in colonoscopy reports (Table 1). Table 2 summarizes the mean hemoglobin, MPC, RDW and NLR values of all patients included. Table 3 and Figure 1 summarize the comparison of mean MPV, RDW and NLR measurements between the operated and non-operated groups. The mean MPV, RDW and NLR measurements were found to be significantly lower in operated patients when compared to non-operated patients ($p<0.001$, $p=0.026$ and $p<0.001$, respectively). A significant correlation was detected in hemoglobin measurements of groups ($p=0.010$) and hemoglobin value was found to be higher in the operated group (Table 3, Figure 1).

Table 1. Demographics and tumor locations

		Mean ± SD	Med (min-max)
Age (year)		62.12+12.5	64 (35-88)
		N	**%**
Operation	**Operated**	26	50.0
	Non-operated	26	50.0
Gender	**Male**	30	57.7
	Female	22	42.3
Location	**Rectum**	12	23.1
	Sigmoid colon	19	36.5
	Descending colon	6	11.5
	Transverse colon	7	13.5
	Ascending colon	5	9.6
	Cecum	3	5.8

SD: Standard deviation

Table 2. The average of Hb, MPV, RDW, NLR

	Mean ± SD	Med (min-max)
Hb (gr/dL)	12.1+1.6	12.3 (8.9-14.8)
MPV (fL)	9.09+1.64	9.2 (5.7-12.3)
RDW (%)	15.4+3.83	14.5 (8.7-27.2)
NLR	2.42+0.94	2.39 (0.68-4.57)

SD: Standard deviation, Hb: Hemoglobin, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio

Discussion

The role of chronic inflammation has been extensively investigated in the carcinogenesis. In a study by Itzkowitz and Yio (9), it was reported that chronic inflammation led to CRC development without classical adenoma-carcinoma sequence in patients with inflammatory bowel disease (IBD). In addition, in a study supporting this assumption, Burr et al. (23) showed that non-steroidal anti-inflammatory drugs decreased CRC risk by decreasing systemic inflammation in IBD patients. Systemic inflammation is very important in early cancer development (24). Neutrophils provoke proliferation of tumor cells, angiogenesis and metastasis by activating production of growth factors such as vascular endothelial growth factor and PK2/Bv8 and cytokines such as IL-1, IL-6 and tumor necrosis factor (25,26).

NLR has been proposed as a good marker for systemic, low-grade inflammation which is associated with poorer prognosis in many diseases (27,28). In a meta-analysis on prognostic effect of NLR in several solid tumors, elevated NLR was linked to mortality in many cancer types at difference stages. In a milestone study by Walsh et al. (29), NLR>5 was found to be associated with decreased overall and cancer-specific survival. In another study, it was

Table 3. The comparison of operated and non-operated Hb, MPV, RDW, NLR

	Operated	Nonoperated	
	Mean ± SD Med (min-max)	Mean ± SD Med (min-max)	p*
Hb (gr/dL)	12.66±1.23 12.65 (10.5-14.8)	11.49±1.68 11.1 (8.9-14.5)	0.010
MPV (fL)	8.2±1.46 8.1 (5.7-11)	9.98±1.3 10.15 (7.4-12.3)	<0.001
RDW (%)	14.48±3.68 13.8 (10-27.2)	16.32±3.83 15.45 (8.7-23)	0.026
NLR	1.91±0.7 1.88 (0.68-3.49)	2.93±0.88 2.9 (1.27-4.57)	<0.001

*Mann-Whitney U test, SD: Standard deviation, Hb: Hemoglobin, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio

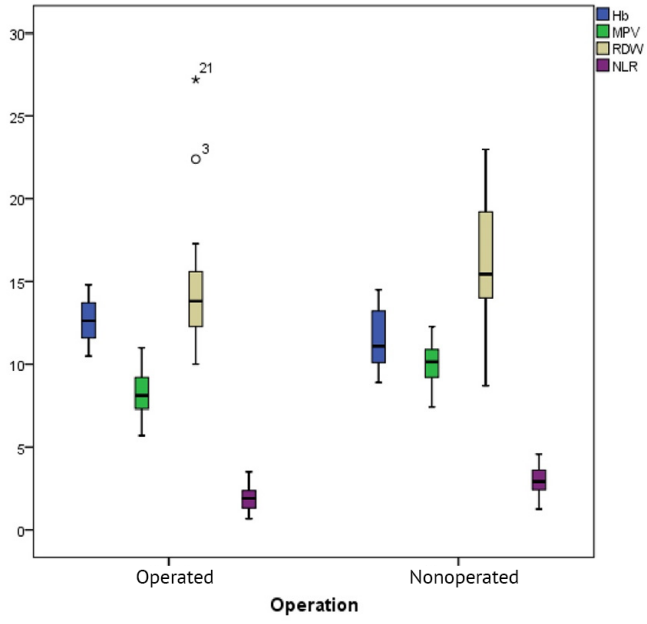

Figure 1. The measurements of Hb, MPV, RDW, NLR according to operation

Hb: Hemoglobin, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio

found that lower postoperative NLR was correlated with longer cancer-specific and disease-free survival in patients who underwent elective CRC resection (30). Again, it was reported that disease-free survival was decreased while cancer-mortality was increased in CRC patients with high preoperative NLR (>3) (31). In a study on patients with early stage CRC, who were candidates for curative surgery, it was found that 5-year disease-free survival and cancer-specific survival were significantly poorer in patients with high NLR values (32). In some studies, it was reported that there was an increase in perioperative complications including postoperative wound site infection, anastomosis dehiscence, morbidity and mortality in CRC patients with high NLR values (30,33,34). In our study, the mean NLR value was 1.91±0.7 in the operated group and 2.93±0.88 in the non-operated group; the mean NLR value was significantly lower in the operated group (p<0.001, Table 3, Figure 1).

In a study on 153 patients with resectable CRC, it was reported that patients with lower preoperative MPV values had more advanced disease, that MPV was increased by adjuvant chemotherapy while it was significantly decreased after surgery, and that preoperative MPV value<1 was associated with poorer survival (35). In CRC, it was reported that higher MPV level was associated with the presence of cancer, shorter overall survival and negative effect on progression-free survival (14,36-38). In our study, the mean MPV value was 8.2±1.46 fL in operated patients and 9.98±1.3 fL in non-operated patients. The mean MPV value was found to be significantly lower in operated patients (p<0.001, Table 3, Figure 1).

In many studies, RDW has been investigated as a potential prognostic marker for CRC. However, given the inconsistent results regarding malignancy, the role of RDW remains to be unclear in cancer. In a study, high RDW values were found to be associated with lower 10-year survival when compared to CRC patients with lower RDW values; however, no significant difference was observed in 5-year survival (39). In our study, the mean RDW was 14.48±3.68 in the operated group and 16.32±3.83 in the non-operated group. The mean RDW was significantly lower in the operated group (p<0.026, Table 3, Figure 1). In a study from Turkey, Kilincalp et al. (19) showed that NLR, PLR and MPV levels were significantly lower in patients with CRC when compared to controls and that there were significant reductions in NLR, PLR and MPV after surgical tumor resection. As similar to our study, authors suggested that this triple biomarker set could have clinical value in early diagnosis, screening and postoperative follow-up in CRC (19). In the literature, there are studies evaluating several biomarkers in CRC patients; however, to best of our knowledge, there is no study investigating these three biomarkers set together. In addition, in our study, the mean hemoglobin level was found to be significantly lower in operated patients when compared to non-operated patients (12.66±1.23 g/dL and 11.49±1.68 g/dL, Table 1). This may be linked with the treatment of tumor, which is a cause of anemia, but it may also be explained by iron

therapy and erythrocyte suspensions given before and after surgery.

Study Limitations

This study has some limitations including its retrospective design, relatively small sample size and surgery. Moreover, the fact that surgical treatment and postoperative care were performed in other facilities is another limitation. In the future, multi-center, prospective studies with larger sample size, which will involve preoperative and postoperative follow-up periods, could be designed.

Conclusion

In the literature, there are many biomarkers linked with inflammation and several malignancies, including NLR, MPV and RDW. In our study, NLR, MPV and RDW values were found to be significantly lower in patients who underwent surgical treatment when compared to non-operated patients. In conclusion, we believe that this triple biomarker set can provide important data for early diagnosis, screening and response to surgical treatment in CRC patients.

Ethics

Ethics Committee Approval: The study was approved by Zeynep Kamil Maternity and Children's Training and Research Hospital, Institutional Ethics Committee.

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Bhattacharjee D, Quirke P. What is the Role of the Neutrophil: Lymphocyte Ratio in Colorectal Cancer? Turk J Colorectal Dis 2021;31(1):1-12.
2. Levin TR, Jamieson L, Burley DA, Reyes J, Oehrli M, Caldwell C. Organized Colorectal Cancer Screening in Integrated Health Care Systems. Epidemiol Rev 2011;33(1):101-110.
3. Peng HX, Yang L, He BS, Pan YQ, Ying HQ, Sun HL, et al. Combination of preoperative NLR, PLR and CEA could increase the diagnostic efficacy for I-III stage CRC. J Clin Lab Anal 2017;31(5):e22075. doi: 10.1002/jcla.22075
4. Ribeiro MS, Wallace MB. Endoscopic treatment of early cancer of the colon. Gastroenterol Hepatol (N Y) 2015;11(7):445-452.
5. Song LL, Li YM. Current noninvasive tests for colorectal cancer screening: An overview of colorectal cancer screening tests. World J Gastrointest Oncol 2016;8(11):793-800.
6. Sanford KW, McPherson RA. Fecal occult blood testing. Clin Lab Med 2009;29:523-541.
7. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30(7):1073-1081.
8. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013;13(11):759-771.
9. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287(1):G7-17. doi: 10.1152/ajpgi.00079.2004
10. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454(7203):436-444.
11. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013;30(1):432.
12. Liu H, Wu Y, Wang Z, Yao Y, Chen F, Zhang H, et al. Pretreatment platelet-to-lymphocyte ratio (PLR) as a predictor of response to first-line platinum-based chemotherapy and prognosis for patients with non-small cell lung cancer. J Thorac Dis 2013;5(6):783-789.
13. Li JY, Li Y, Jiang Z, Wang RT, Wang XS. Elevated mean platelet volume is associated with presence of colon cancer. Asian Pac J Cancer Prev 2014;15(23):10501-10504.
14. Li N, Yu Z, Zhang X, Liu T, Sun YX, Wang RT, et al. Elevated mean platelet volume predicts poor prognosis in colorectal cancer. Sci Rep 2017;7(1):10261.
15. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133(4):628-632.
16. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009;169(6):588-594.
17. Cengiz M, Şahin A, Özdil K, Sökmen HM. Role of RDW and MPV in Diagnosis of Colorectal Polyps and Carcinoma: A Case-Control Study. Acta Oncologica Turcica · 2015. doi: 10.5505/aot.2015.96268
18. Lalosevic MS, Markovic AP, Stankovic S, Stojkovic M, Dimitrijevic I, Vujavic IR, et al. Combined diagnostic efficacy of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) as biomarkers of systemic ınflammation in the diagnosis of colorectal cancer. Dis Markers 2019;2019:6036979. doi: 10.1155/2019/6036979.
19. Kilincalp S, Çoban Ş, Akinci H, Hamamcı M, Karaahmet F, Coşkun Y, et al. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as potential biomarkers for early detection and monitoring of colorectal adenocarcinoma. Eur J Cancer Prev 2015;24(4):328-333.
20. Hu Z, Sun Y, Wang Q, Han Z, Huang Y, Liu X, et al. Red blood cell distribution width is a potential prognostic index for liver disease. Clin Chem Lab Med 2013;51(7):1403-1408.

21. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive ındicator for cardiovascular and cerebrovascular diseases. Dis Markers 2017;2017:7089493. doi: 10.1155/2017/7089493.

22. Hu L, Li M, Ding Y, Pu L, Liu J, Xie J, Cabanero M, et al. Prognostic value of RDW in cancers: a systematic review and meta-analysis. Oncotarget 2017;8(9):16027-16035.

23. Burr NE, Hull MA, Subramanian V. Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease? World J Gastroenterol 2016;22(13):3679-3686.

24. Mariani F, Sena P, Roncucci L. Inflammatory pathways in the early steps of colorectal cancer development. World J Gastroenterol 2014;20(29):9716-9731.

25. Tecchio C, Cassatella MA. Neutrophil-derived cytokines involved in physiological and pathological angiogenesis. Chem Immunol Allergy 2014;99:123-137.

26. Wang Z, Jin H, Xu R, Mei Q, Fan D. Triptolide downregulates Rac1 and the JAK/STAT3 pathway and inhibits colitis-related colon cancer progression. Exp Mol Med 2009;41(10):717-727.

27. Wan H, Wang Y, Fang S, Chen Y, Zhang W, Xia F, et al. Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes: a cross-sectional study. J Diabetes Res 2020;2020:6219545. doi: 10.1155/2020/6219545.

28. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS et al. Effect of preoperative neutrophil–lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. Int J Colorectal Dis 2011;26(8):1059-1065.

29. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 2005;91(3):181-184.

30. Kubo T, Ono S, Ueno H, Shinto E, Yamamoto J, Hase K. Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma. International J Colorectal Dis 2014;29(9):1091-1099.

31. Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis 2012;27(10):1347-1357.

32. Shin JS, Suh KW, Oh SY. Preoperative neutrophil to lymphocyte ratio predicts survival in patients with T1-2N0 colorectal cancer. J Surg Oncol 2015;112(6):654-657.

33. Haram A, Boland MR, Kelly ME, Bolger JC, Waldron RM, Kerin MJ. The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review. J Surg Oncol 2017;115(4):470-479.

34. Josse JM, Cleghorn MC, Ramji KM, Jiang H, Elnahas A, Jackson TD et al. The neutrophil-to-lymphocyte ratio predicts major perioperative complications in patients undergoing colorectal surgery. Colorectal Dis 2016;18:O236-O242. doi: 10.1111/codi.13373.

35. Qian W, Ge XX, Wu J, Gong FR, Wu MY, Xu MD, et al. Prognostic evaluation of resectable colorectal cancer using platelet-associated indicators. Oncol Lett 2019;18(1):571-580.

36. Pyo JS, Sohn JH, Kang G. Diagnostic and prognostic roles of the mean platelet volume in malignant tumors: a systematic review and meta-analysis. Platelets 2016;27(8):722-728.

37. Tuncel T, Ozgun A, Emirzeoglu L, Celik S, Bilgi O, Karagoz B. Mean platelet volume as a prognostic marker in metastatic colorectal cancer patients treated with bevacizumab-combined chemotherapy. Asian Pac J Cancer Prev 2014;15(15):6421-6423.

38. Wodarczyk M, Kasprzyk J, Sobolewska-Wodarczyk A, Wodarczyk J, Tchorzewski M, Dziki A, et al. Mean platelet volume as a possible biomarker of tumor progression in rectal cancer. Cancer Biomark 2016;17(4):411-417.

39. Pedrazzani C, Tripepi M, Turri G, Fernandes E, Scotton G, Conci S,et al. Prognostic value of red cell distribution width (RDW) in colorectal cancer. Results from a single-center cohort on 591 patients. Sci Rep 2020;10(1):1072.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):320-325
DOI: 10.4274/BMB.galenos.2021.05.066

Which Markers Play a Role in Diabetic Polyneuropathy and Neuropathic Pain?

Diyabetik Polinöropati ve Nöropatik Ağrıda Hangi Belirteçler Rol Oynuyor?

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Abstract

Objective: In diabetes mellitus (DM) patients, in the development of neuropathy and pain, uric acid (UA), C-reactive protein (CRP), γ-glutamyltransferase (GGT), erythrocyte sedimentation rate (ESR), and fibrinogen increased levels may affect the being of neuropathy by increasing oxidative stress through mechanisms related to inflammation and vascular impairment. In the study, we intended to compare serum UA, GGT, CRP, ESR, and fibrinogen levels in type 2 DM patients, with and without polyneuropathy.

Method: Ninety-six type 2 DM patients and 24 participants were included in the study. Physical examinations, neuropathic pain scales, laboratory tests (UA, GGT, CRP, ESR, and fibrinogen levels), and electroneuromyography were evaluated.

Results: Ninety-six type 2 DM patients and 24 healthy persons were included in the study as the study and control groups. Diabetic polyneuropathy (DPN) patients with neuropathic pain showed that CRP and low-density lipoprotein cholesterol levels were statistically significantly higher. No statistically significant difference was found between the groups in terms of UA, GGT, CRP, and fibrinogen levels.

Conclusion: Increased CRP levels in DPN patients with neuropathic pain may reflect the inflammatory mechanisms involved in the pathogenesis of pain associated with DPN.

Keywords: CRP, diabetes mellitus, diabetic neuropathic pain, diabetic peripheral neuropathy, uric acid

Öz

Amaç: Diabetes mellitus (DM) hastalarında nöropati ve ağrı gelişiminde ürik asit (UA), C-reaktif protein (CRP), γ-glutamiltransferaz (GGT), eritrosit sedimantasyon hızı (ESR) ve fibrinojen seviyelerinin artışı, enflamasyon ve vasküler hasara bağlı mekanizmalar yoluyla oksidatif stresi artırarak nöropati gelişiminde rol oynayabilir. Bu çalışmada polinöropati olan ve olmayan tip 2 DM'li hastalarda serum UA, GGT, CRP, ESR ve fibrinojen düzeylerini karşılaştırmayı amaçladık.

Yöntem: Çalışmaya toplam 96 tip 2 DM hastası ve 24 kişi (kontrol grubu) dahil edildi. Fizik muayeneler, nöropatik ağrı ölçekleri, laboratuvar testleri (UA, GGT, CRP, ESR ve fibrinojen seviyeleri) ve elektronöromiyografi değerlendirildi.

Bulgular: Doksan altı tip 2 DM hastası ve 24 sağlıklı kişi çalışma ve kontrol grubu olarak çalışmaya alındı. Nöropatik ağrısı olan diyabetik polinöropati (DPN) hastalarında CRP ve düşük yoğunluklu lipoprotein-kolesterol düzeylerinin istatistiksel olarak anlamlı derecede yüksek olduğu görüldü. Gruplar arasında UA, GGT, CRP ve fibrinojen düzeyleri açısından istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Nöropatik ağrılı DPN hastalarında artmış CRP seviyeleri, DPN ile ilişkili ağrı patogenezinde yer alan enflamatuvar mekanizmaları yansıtabilir.

Anahtar kelimeler: CRP, diabetes mellitus, diyabetik nöropatik ağrı, diyabetik periferik nöropati, ürik asit

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Cite this article as: Panpallı Ateş M, Ferik S, Güven H, Çomoğlu SS. Which Markers Play a Role in Diabetic Polyneuropathy and Neuropathic Pain? Bagcilar Med Bull 2021;6(3):320-325

Introduction

Diabetic polyneuropathy (DPN) is one of the furthest widespread long-term complications of type 2 diabetes mellitus (DM) that leads to significant disability and mortality among patients (1).

High serum uric acid (UA), γ-glutamyltransferase (GGT), C-reactive protein (CRP), fibrinogen levels, which are considered to be predictive of atherosclerosis, have also been associated with DPN (2-5).

UA is an effective extracellular radical scavenger and is responsible for the clearance of 60% of free radicals in human serum, as well as stimulating granulocyte adhesion to the endothelium and the release of peroxide and superoxide free radicals. It has been suggested that normal levels of UA have an antioxidant effect while high levels of UA have a prooxidant effect that increases oxidative stress. In the subsequent steps of the atherosclerosis (when serum UA levels rised to 6 mg/dL in women and 6.5-7.0 mg/dL in men), this antioxidant paradoxically becomes prooxidant (6).

GGT activity may act in the formation and progression of atherosclerotic lesions (4). Increased serum GGT activity is a marker that shows increased CRP in patients with coronary artery atherosclerosis and is associated with the severity and complications of this disease (5,7).

CRP is an acute-phase reactant synthesized by hepatocytes, which is used for diagnosis in individuals with infection or inflammation. CRP, an inflammatory marker, has been associated with the presence and progression of carotid atherosclerotic disease. Even, it has been found in atherosclerotic plaques and has been held responsible for plaque vulnerability. Besides, it has been reported that the formation of restenosis is triggered by increasing CRP (5,7-10).

Erythrocyte sedimentation rate (ESR) and CRP are a further inflammatory response marker associated with inflammation and tissue damage (8).

Fibrinogen, a coagulation factor, is also an acute phase reactant. Besides, inflammatory markers such as fibrinogen are related to a poor prognosis of the acute coronary syndrome (11).

In patients with DM, high UA, GGT, CRP, fibrinogen levels can lead to the development of neuropathy by increasing oxidative stress and causing vascular damage. Identifying and modifying indicators that can guess the risk of developing DPN may contribute to the diagnosis and treatment of DPN. Our purpose is to compare the serum UA, GGT, CRP, and fibrinogen levels in the polyneuropathy groups.

Materials and Methods

Ninety-six type 2 DM patients and 24 healthy participants aged between 18 and 70 years were recorded in the study. Patient histories, physical examinations, and laboratory tests were evaluated, and consequently, patients with additional potential etiologies in polyneuropathies other than DM, including toxic (e.g., alcohol or chemotherapy), genetic or inflammatory etiologies; patients with systemic diseases which may cause PNP (patients with connective tissue disease, chronic liver disease, malignancies, systemic diseases involving thyroid diseases, patients with low serum vitamin B12 levels or receiving vitamin B12 replacement); patients with a history of infection in the last two weeks; and individuals who took drugs that affected plasma UA levels were excluded from the study. Healthy volunteers at similar ages to the patient group, who did not have DM and had normal HbA1C levels and no PNP findings in an ENMG were enrolled in the control group.

The participants were examined with respect to the polyneuropathy protocol by electroneuromyography (ENMG) (Neuropack MEB-9200K, Nihon Kohden Co., Tokyo, Japan). In the right extremities, sensory and motor conductions of the median, ulnar, peroneal, posterior tibial nerves, and bilateral sural nerves were examined using disc electrodes. Diabetic sensorimotor polyneuropathy was diagnosed considering the patients' symptoms and ENMG results. For those subjects, considering the diagnostic criteria, the advised Toronto Expert Panel on diabetic neuropathy was used (12). For each patient, neuropathic symptoms' duration, Douleur Neuropathique en 4 questions scores, neuropathy symptoms score, neuropathy disability score (NDS), Leeds assessment of neuropathic symptoms and signs (LANSS) scale were assessed.

Patient demographic characteristics (gender, age, body mass index (BMI), age of DM onset, duration of disease, and treatments (oral antidiabetic drugs, insulin) were recorded. Also, patients were questioned regarding the history of HT, atherosclerotic heart disease and stroke, peripheral artery disease, smoking, and alcohol use.

The laboratory tests were taken and were investigated for serum UA, GGT, CRP, fibrinogen levels, hemogram, fasting blood glucose, serum HbA1c levels, C peptide,

serum creatinine, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), liver function tests (LFTs), ESR, ferritin levels, and thyroid function tests. Immunoelectrophoresis and urine tests were performed.

Statistical Analysis

Statistical analysis was applied using a Statistical Package for Social Sciences (SPSS®) 22.0 for Windows and Mac os x. The Shapiro-Wilk test was used to test the hypothesis of normality. During the assessment of study data, frequency distributions were provided for categorical variables, and descriptive statistics (mean ± standard deviation) were provided for constant variables. Descriptive statistics were used for continuous variables. The Independent Samples t-test was used to determine whether there was a difference between two independent groups for normally distributed variables. The chi-square test was used to examine the relationship in two independent categorical variables. Categorical variables were summarized as N (%), while normally distributed variables were summarized as mean (standard deviation) and continuous variables were summarized as median (minimum-maximum). p-values of less than 0.05 were accepted significant.

Results

Ninety-six type 2 DM patients (53 female, 43 male) and 24 healthy subjects as the control group (14 female, 10 male; 52.21±5.16) were included in the study. Depending on the Toronto Expert Panel on diabetic neuropathy, 60.6% of patients (n=62) were diagnosed with diabetic sensorimotor polyneuropathy (DSPN), 24 patients were diagnosed with confirmed clinical DSPN and 38 patients were diagnosed with probable DSPN (12). The demographic, clinical, and laboratory characteristics of the patient and control groups are shown in Table 1.

A comparison of the control group and patients with and without DPN revealed no statistical significance in terms of UA, GGT, CRP, and fibrinogen levels. HbA1C and ESR were significantly higher in the patient groups with or without DPN compared to the control group (p=0.000, p=0.001, respectively) (Table 1).

Table 1. The demographic and disease characteristics of the subjects

	Control (n=24)	DM without DPN (n=34)	DM with DPN (n=62)	p
Age	52.21±5.16	54.4±7.60	55.8±7.33	0.960
BMI (kg/m²)	28.8±6.7	31.1±5.3	30.9±5.1	0.456
Duration of DM (months)	-	111.1±85.48	127.5±89.81	0.386
HbA1C (%)	5.6±0.32	7.5±1.25	7.8±1.65	**0.000**
AST (U/L)	21.7±5.88	24.9±11.49	23.4±7.59	0.382
ALT (U/L)	22±12.55	29.9±19.37	26.5±11.07	0.112
GGT (U/L)	23.9±11.06	30.5±16.73	28.4±21.72	0.410
Total cholesterol (mg/dL)	197±40.48	193.1±33.46	198.4±44.33	0.935
HDL-C (mg/dL)	47.2±8.86	46.5±11.31	46.7±9.36	0.961
LDL-C (mg/dL)	128±34.4	117.4±26.79	121.4±36.86	0.505
TG (mg/dL)	170±80.05	172.1±93.69	187.5±98.50	0.637
TSH (pmol/L)	1.9±0.92	2.01±1.45	1.7±0.92	0.522
fT3 (pmol/L)	3.2±0.33	3.05±0.34	3±0.39	0.076
fT4 (pmol/L)	1.1±0.13	1.2±0.13	1.2±0.15	0.497
UA (mg/dL)	4.5±1.10	4.9±1.26	5.2±1.39	0.097
C-peptide	3.2±0.39	2.8±1.15	3.2±2.30	0.533
Vitamin B12	226.9±80.01	326.9±96.0	316.8±83.71	**0.000**
CRP	6±5.12	8.2±11.16	6.7±9.05	0.628
ESR	15.3±10.29	24.1±12.07	28.2±16.66	**0.001**
Fibrinogen	337.7±78.48	342.3±78.32	353.2±76.79	0.651

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, CRP: C-reactive protein, DM: Diabetes mellitus, DPN: Diabetic peripheral neuropathy, ESR: Erythrocyte sedimentation rate, fT3: Free triiodothyronine, fT4: Free thyroxine, GGT: γ-Glutamyl transferase, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglyceride, TSH: Thyroid-stimulating hormone, UA: Uric acid

A comparison of DPN patients with neuropathic pain (LANSS ≥12) and without neuropathic pain (LANSS <12) showed that CRP and LDL-C levels were statistically significantly higher in the group with neuropathic pain (p=0.008 and p=0.030, respectively) (Table 2).

Discussion

In our research, LDL-C and CRP levels were higher in painful DPN patients than in those without pain. UA, GGT, CRP, ESR, and fibrinogen levels were not different in DM patients with and without DPN and these indicators were not considered to be associated with the development of DPN.

The most common clinical form of DPN is chronic distal symmetric polyneuropathy, and patients with diabetes may develop asymmetric, focal, or multifocal neuropathies.

Table 2. Laboratory examinations of diabetic polyneuropathy patients with or without pain

	LANSS <12 (n=86)	LANSS ≥12 (n=10)	p
Age	55.2±7.32	56.4±8.55	0.690
BMI	30.7±4.96	31.6±6.32	0.705
Duration of DM (months)	122.6±85.94	114±110.88	0.815
HbA1C (%)	7.7±1.50	7.8±1.73	0.826
AST (U/L)	24.0±9.50	23.3±5.18	0.704
ALT (U/L)	27.8±15.13	26.5±8.50	0.666
GGT (U/L)	29.7±20.81	23.9±10.37	0.156
Total cholesterol (mg/dL)	197±39.93	174.1±42.89	0.135
HDL-C (mg/dL)	47.2±9.95	41.7±9.85	0.122
LDL-C (mg/dL)	121.9±34.2	103.5±21.38	**0.030**
TG (mg/dL)	183.5±100.02	169.6±61.97	0.543
TSH (pmol/L)	1.8±1.14	2.1±1.10	0.386
fT3 (pmol/L)	3.01±0.38	3.08±0.28	0.494
fT4 (pmol/L)	1.22±0.14	1.1±0.13	0.409
UA (mg/dL)	5.1±1.31	5.4±1.71	0.515
C-Peptide	3.1±2.07	2.5±0.84	0.112
Vitamin B12	320.4±85.61	320±110.95	0.990
CRP	7.5±10.30	4.1±1.95	**0.008**
ESR	26.9±15.18	25.2±16.62	0.751
Fibrinogen	348.5±78.05	355.8±71.81	0.771

LANSS: Leeds assessment of neuropathic symptoms and signs scale, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, fT3: Free triiodothyronine, fT4: Free thyroxine, GGT: γ-glutamyl transferase, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglyceride, TSH: Thyroid-stimulating hormone, UA: Uric acid

This clinical diversity in DPN is possibly related to different underlying pathophysiological mechanisms.

Although the pathogenesis has not been fully elucidated, the development of DPN has been attributed to vascular dysfunction caused by metabolic changes associated with chronic hyperglycemia. Chronic hyperglycemia leads to changes including shunting into the polyol pathway, reduced nerve and Schwann cell myo-inositol levels, oxidative and nitrative stress, lack of neurotrophic factors, and their uptake in microvessels and neurons (2). The complex interaction of these factors results in endothelial dysfunction, reduced nerve perfusion, and endoneurial hypoxia (1-3).

DPN is a microvascular complication of DM, and the pathogenesis of DPN development includes ischemia and vascular processes along with metabolic events associated with hyperglycemia. Like DM, DPN has been reported to be associated with cerebral microvascular damage (13). Here, the higher CRP levels in painful DPN patients suggest that inflammatory mechanisms also play a role in this process.

Early detection of DPN is crucial to identify and control risk factors and to prevent and slow down the DPN process.

UA, GGT, CRP, ESR, and fibrinogen are possible markers of the atherosclerotic process. Based on the assumption that these markers may be related to the vascular processes involved in the pathogenesis of DPN and may be considered as indicators of DPN, the relationship between UA, GGT, CRP, ESR, and fibrinogen, and DPN has been investigated in various studies (2,6,14-23). However, the results of these studies are conflicting.

At normal levels, UA is known to clear toxic reactants and provide protection opposed to oxidative stress. However, UA is seen to play a prooxidant part when increased by a third or more than normal levels (6). Endothelial dysfunction, platelet adhesion, and aggregation have been associated with hyperuricemia (14). The role of UA in DM patients has been investigated in various studies (14-17). UA levels are high in DM patients and it has been suggested that the cause of this elevation may be increased production or reduced excretion of UA. However, the pathophysiological mechanism has not been fully revealed. On the other hand, studies indicate that UA is reduced in DM, for which the reason has been indicated as increased UA clearance in DM, and again, the mechanism has not yet been clarified (15).

The number of studies investigating the relationship between DPN development and UA levels is limited. It

has been reported that UA levels are higher in patients with type 2 DM with neuropathy than patients without neuropathy. Hyperuricemia has been reported to be related to hyperglycemia, dyslipidemia, and metabolic syndrome, all of which are related to the development of DPN. UA can cause endothelial dysfunction, which may lead to the DPN. Type 2 DM patients with peripheral neuropathy have markedly increased serum UA levels and hyperuricemia is associated with a rising risk of peripheral neuropathy (15-17). In our study, there was not statistically difference of the two groups despite higher UA levels.

The correlation between UA levels and DPN was previously related to metabolic syndrome (7). In this study, the reason for no significant relationship between UA and DPN may be the fact that patients with metabolic syndrome due to BMI or other factors (the absence of certain microalbuminuria) were indirectly excluded, and that DM patients with characteristics similar to the controls were included in the study. Although the UA's role in the development of vascular adversities of diabetes has been known, its role in the development of DPN remains unclear.

CRP, a sensitive biomarker of subclinical systemic inflammation, is related to the development and progression of DPN (18). CRP levels have been shown to be related to the development of DPN (15,18).

There are enough studies in the literature investigating the role of dyslipidemia in the development of neuropathy and other microvascular complications in DM patients. Besides, different studies have shown that lipid-lowering treatment reduces the development of these complications. It has been experimentally proven that increased TG and LDL-C levels damage neurons through oxidative stress (19). Increased TG and LDL-C levels and decreased HDL-C levels constitute a risk for the development of DPN in diabetic patients. One study revealed that increased TG levels correlated with the development of DPN (20,21). In our study, although TG levels were found to be higher in DPN patients, no statistically significant difference was found.

There is also evidence of direct proinflammatory effects of CRP by triggering the synthesis of local adhesion molecules, reducing endothelial nitric oxide activity, altering LDL cholesterol uptake by macrophages, and inducing intravascular thrombosis (22).

In a previous study, it was shown that high CRP levels might be evidence of subclinical inflammation in peripheral DPN (20). In one study, it was found that increased biochemical markers included fibrinogen and CRP, reflecting inflammation and endothelial dysfunction in peripheral DPN (23).

In another study, higher levels of CRP were reported in painful DPN patients than those without pain, it was suggested that inflammation and endothelial dysfunction might play a role in the occurrence of painful neuropathy (23).

Inflammatory mediators, particularly cytokines, have been suggested a decisive role in the pathogenesis of neuropathic pain. In our study, a significant difference was not found in patients with and without DPN in terms of CRP levels, whereas patients with painful DPN had higher levels of CRP than the patients with painless DPN. In the literature, in neuropathic pain with sciatica patients, it has been reported that neuropathic pain is associated with high CRP levels (18).

Inflammation has been recommended to be a considerable risk factor in the formation of DPN as well as type 2 DM (1-3). However, there are limited data on the relationship between DPN, and vascular diseases and inflammation (13).

The higher level of CRP in painful DPN may be due to the inflammatory response created by this microvascular ischemic injury.

Conclusion

Although levels of UA, CRP, GGT, fibrinogen, and ESR were reported to be elevated in DPN patients, these biochemical parameters were not detected as markers for DPN in our study.

In this study, a significant relationship was found between DPN patients with neuropathic pain and increased CRP levels.

Increased CRP levels in DPN patients with neuropathic pain may reflect the inflammatory mechanisms involved in the pathogenesis of pain associated with DPN. The elevation of serum CRP levels in DPN patients with neuropathic pain is a remarkable finding. This condition indicates that CRP in DPN patients is closely associated with neuropathic pain.

Increased CRP, regardless of any other factor, in DPN patients with neuropathic pain indicates that this variable may be helpful to appropriately select patients for neuropathic treatment medicines.

Even, in DM patients who are considered normal by examination or ENMG, CRP levels can be used to help clinically "indeterminate" neuropathic pain patients.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Board of the Institutional Review Committee of the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (2014-15/9).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.P.A., S.F., H.G., Design: M.P.A., S.F., H.G., Data Collection or Processing: M.P.A., S.F., Analysis or Interpretation: M.P.A., H.G., S.S.Ç., Literature Search: M.P.A., S.S.Ç., Writing: M.P.A., S.S.Ç.

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

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

References

1. Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28(Suppl 1):8-14.
2. Stevens MJ, Feldman EL, Greene DA. The aetiology of diabetic neuropathy: the combined roles of metabolic and vascular defects. Diabet Med 1995;12(7):566-579.
3. Malik RA, Tesfaye S, Newrick PG, Walker D, Rajbhandari SM, Siddique I, et al. Sural nerve pathology in diabetic patients with minimal but progressive neuropathy. Diabetologia 2005;48(3):578-585.
4. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol 1995;142(7):699-708.
5. Backes JM, Howard PA, Moriarty PM. Role of C-reactive protein in cardiovascular disease. Ann Pharmacother 2004;38(1):110-118.
6. Demir M, Bulunmaz M, Müderrisoğlu C, Kose S, Erdem S, Polat H. Role of uric acid in determining cardiovascular risk. İstanbul Med J 2014;15:203-208.
7. Habib SS, A Al Masri A. Relationship of high sensitivity C-reactive protein with presence and severity of coronary artery disease. Pak J Med Sci 2013;29(6):1425-1429.
8. Ates U, Bahadir K, Ergun E, Gollu G, Durmaz M, Gunay F, et al. Determination of Pentraxin 3 levels in diagnosis of Appendicitis in children. Pediatr Int 2020;62(5):624-628.
9. Cengiz AB, Gümüşlü BC, Kayabaşı S, Tansuker HD, Öğreden Ş, Oktay MF. C-reactive protein to albumin ratio as a prognostic predictor in larynx cancer. Bagcilar Med Bull 2020;5(4):179-184.
10. Özyüncü N, Güleç HS, Özcan ÖU, Göksülük H, Gerede Uludağ DM, Erol Ç. Comparison of the Effects of Bare Metal Stents and Drug Eluting Stents on C-Reactive Protein Levels. J Ankara Univ Fac Med 2020;73(3):208-215.
11. Cook NS, Ubben D. Fibrinogen as a major risk factor in cardiovascular disease. Trends Pharmacol Sci 1990;11(11):444-451.
12. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011;27(7):620-628.
13. Ferik S, Güven H, Ateş MP, Conkbayır I, Çomoğlu S, Güven B. Diabetic polyneuropathy, deep white matter lesions, and carotid atherosclerosis: is there any association? Neurol Sci 2018;39(1):103-110.
14. Yu S, Chen Y, Hou X, Xu D, Che K, Li C, et al. Serum uric acid levels and diabetic peripheral neuropathy in type 2 diabetes: a systematic review and meta-analysis. Mol Neurobiol 2016;53(2):1045-1051.
15. Pafili K, Katsiki N, Mikhailidis DP, Papanas N. Serum uric acid as a predictor of vascular complications in diabetes: an additional case for neuropathy. Acta Diabetol 2014;51(5):893-894.
16. Kiani J, Habibi Z, Tajziehchi A, Moghimbeigi A, Dehghan A, Azizkhani H. Association between serum uric acid level and diabetic peripheral neuropathy (A case-control study) Caspian J Intern Med 2014;5(1):17-21.
17. Papanas N, Katsiki N, Papatheodorou K, Demetriou M, Papazoglou D, Gioka T, et al. Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. Angiology 2011;6(4):291-295.
18. Uher T, Bob P. Neuropathic pain, depressive symptoms, and C-reactive protein in sciatica patients. Int J Neurosci 2013;123(3):204-208.
19. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: A prospective study of the JUPITER trial. Lancet 2009;373(9670):1175-1182.
20. Ge S, Xie J, Zheng L, Yang L, Zhu H, Cheng X, et al. Associations of serum anti-ganglioside antibodies and inflammatory markers in diabetic peripheral neuropathy. Diabetes Res Clin Pract 2016;115:68-75.
21. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes 2009;58(7):1634-1640.
22. Ridker PM, Libby P. Risk factors for atherothrombotic disease. In: Bonow RO, Mann DL, Zipes DP, Libby P (editors). Braunwald's Heart Disease. Saunders Philadelphia: Elsevier, 2014;39:1003-1026.
23. Doupis J, Lyons TE, Wu S, Gnardellis C, Dinh T, Veves A. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. J Clin Endocrinol Metab 2009;94(6):2157-2163.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):326-333
DOI: 10.4274/BMB.galenos.2021.07.083

Evaluation of Axis I and Axis II Disorders Accompanied by Panic Disorder

Panik Bozukluğa Eşlik Eden Eksen I ve Eksen II Bozuklukların Değerlendirilmesi

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Abstract

Objective: Panic disorder (PD) is a disorder that progresses with relapses and reduces the quality of life. The frequent comorbidity of PD with other psychiatric diseases affects the course and treatment of the disease. In our study, it was aimed to evaluate the axis I and axis II disorders accompanying PD.

Method: The study was conducted in a university hospital psychiatry clinic with patients diagnosed with PD according to the diagnostic criteria of the diagnostic and statistical manual of mental disorders, revised 3rd edition (DSM-III-R) between February 1996 and June 1997. After psychiatric evaluation of 60 patients, socio-demographic and clinical information form, structured clinical interview for DSM-III-R (SCID-I), structured clinical interview for DSM-III-R personality disorders (SCID-II), Hamilton anxiety rating scale and Hamilton depression rating scale were applied. The chi-square (χ^2) and Mann-Whitney U tests were used to evaluate the data. Study groups were formed as pure PD (group 1), PD with comorbid axis I disorder (group 2), and PD with comorbid axis II disorder (group 3).

Results: In the study, 56.6% axis I and 43.3% axis II comorbidities were observed. Major depression, hypochondriasis, generalized anxiety disorder, social phobia, and obsessive-compulsive disorder were the most common Axis I comorbidities, respectively. Avoidant, dependent, obsessive-compulsive and histrionic personality disorders were the most common Axis II comorbidities, respectively.

Conclusion: A high rate of axis I and axis II disorders accompanying PD adversely affects treatment and prognosis. Considering this situation in the treatment and follow-up of patients with PD and adding psychotherapies that also consider personality disorders to pharmacotherapy may increase the success rate in treatment.

Keywords: Panic disorder, personality disorders, psychiatric diagnosis

Öz

Amaç: Panik bozukluğu (PB), tekrarlamalarla ilerleyen ve yaşam kalitesini düşüren bir bozukluktur. PB'nin diğer psikiyatrik hastalıklarla sık birlikteliği hastalığın seyrini ve tedavisini etkilemektedir. Çalışmamızda PB'ye eşlik eden eksen I ve eksen II bozuklukların değerlendirilmesi amaçlanmıştır.

Yöntem: Araştırma, bir üniversite hastanesi psikiyatri kliniğinde, diagnostic and statistical manual of mental disorders, revize 3. baskı (DSM-III-R) tanı kriterlerine göre PD tanısı almış hastalarla Şubat 1996 ile Haziran 1997 tarihleri arasında yürütülmüştür. Altmış hastanın psikiyatrik değerlendirmesinden sonra sosyo-demografik ve klinik bilgi formu, DSM-III-R için yapılandırılmış klinik görüşme (SCID-I), DSM-III-R kişilik bozuklukları için yapılandırılmış klinik görüşme (SCID-II), Hamilton anksiyete derecelendirme ölçeği ve Hamilton depresyon derecelendirme ölçeği uygulandı. Verilerin değerlendirilmesinde ki-kare (χ^2) ve Mann-Whitney U testleri kullanıldı. Çalışma grupları sadece PB (grup 1), eksen I bozukluğu olan PB (grup 2) ve eksen II bozukluğu olan PB (grup 3) olarak oluşturuldu.

Bulgular: Çalışmada %56,6 eksen I ve %43,3 eksen II komorbiditesi izlendi. Majör depresyon, hipokondriyazis, yaygın anksiyete bozukluğu, sosyal fobi ve obsesif-kompülsif bozukluk sırasıyla en sık görülen eksen I eştanılarıydı. Kaçınmacı, bağımlı, obsesif-kompülsif ve histrionik kişilik bozuklukları sırasıyla en sık görülen eksen II eştanılarıydı.

Sonuç: PB'ye eşlik eden eksen I ve eksen II bozukluklarının yüksek oranda olması tedavi ve prognozu olumsuz etkiler. PB hastalarının tedavi ve takibinde bu durumun göz önünde bulundurulması ve farmakoterapiye kişilik bozukluklarını da dikkate alan psikoterapilerin eklenmesi tedavideki başarı oranını artırabilir.

Anahtar kelimeler: Kişilik bozuklukları, panik bozukluk, psikiyatrik tanı

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Cite this article as: Namlı MN. Evaluation of Axis I and Axis II Disorders Accompanied by Panic Disorder. Bagcilar Med Bull 2021;6(3):326-333

Introduction

Panic disorder (PD) is an anxiety disorder characterized by recurrent, unpredicted panic attacks (1). Epidemiological studies have reported that the lifetime prevalence of the disorder is 3.4-4.1% (2,3), and the annual prevalence is 1-2% (4). The disorder is more common among women when compared to men (5). The age of onset exhibits a bimodal distribution, where the first peak is observed in the late adolescence and a second peak is observed in the mid-thirties (6).

A panic attack is a unique period where the individual feels intense and sudden anxiety, fear or horror, often accompanied by the ideation of heart attack, suffocation, losing one's mind, or imminent end of life. During these attacks, symptoms such as shortness of breath, palpitation, chest pain, feeling of discomfort in the chest, shortness of breath, sweating, trembling, dizziness, depersonalization, and derealization could be observed (1). The main characteristic of PD is persistent anxiety about having another panic attack for at least one month after the panic attack (anticipatory anxiety), concerns about the possible consequences of the panic attacks, or a significant behavioral change associated with the attacks (avoidance behavior) (1). Although PD has been identified for several years, the associated terminology and diagnostic criteria have significantly changed especially in the last century (2,7). PD was first classified as anxiety neurosis in the diagnostic and statistical manual of mental disorders, second edition (DSM-II) (8) and the International Classification of Disease-9 (9). In DSM-III, PD was discussed as a new disorder in the category of anxiety disorders based on clinical attributes such as with or without agoraphobia (10). PD was categorized in the DSM-IV as two disorders: PD without agoraphobia and PD with agoraphobia (11). In most studies, depression, hypochondriasis and obsessive-compulsive symptoms were found to be the most common comorbidities in patients with PD (12). Agoraphobia was no longer categorized within the PDs in the DSM-5 and considered a separate diagnosis (1). Clinical classifications have attributed a central role to PD and it was considered a distinct disorder. This was due to the observations of comorbidity of other psychiatric diseases. The interest in PD has increased since it was prevalent among individuals of a particular age group who are actively employed, and relapses in prognosis, reduced quality of life and frequent referrals to non-psychiatry outpatient clinics were observed. In recent years, studies on PD have shifted from diagnosis and etiology where the incidence of PD with comorbid anxiety disorders, mood disorders and personality disorders were investigated (12,13). Axis I and axis II comorbid disorders may affect the diagnosis of the PD, the severity of the symptoms, prognosis, and response to treatment (14).

The present study aimed to investigate the comorbid axis I and axis II disorders in PD patients diagnosed based on the diagnostic and statistical manual of mental disorders, revised 3rd edition, (DSM-III-R) diagnostic criteria.

Materials and Methods

The present study was conducted at the faculty of medicine hospital between February 1996 and June 1997 after the approval of the hospital directory was obtained. Informed consent form was read to the patients and all participants signed the form. The study was conducted based on the DSM-III-R criteria, the latest DSM diagnostic classification system at the time of the study (15). The study was conducted with successive outpatients or inpatients who were diagnosed with PD at the emergency department based on in-hospital consultations and psychiatric evaluation by the psychiatry clinic, met the study criteria and volunteered to participate in the study.

Patient Groups

The study group included 60 patients with PD and sub-groups with the following diagnoses:

- Pure PD (1st group)
- PD with comorbid axis I disorder (2nd group)
- PD with comorbid axis II disorder (3rd group)

Inclusion criteria:

- PB diagnosis based on DSM-III-R (15)
- Over the age of 18 years

Exclusion criteria:

- Presence of a physical pathology that may affect the distribution of psychiatric symptoms.
- Educational and language problem that may prevent a psychiatric interview for diagnosis.
- Drug or substances use during the previous two weeks that may affect the distribution of symptoms.

Two PD patients were not included in the study, since they were under the age of 18 years, an exclusion criterion in the study.

Socio-demographic and clinical information form, DSM-III-R structured clinical interview form (SCID-I), personality evaluation form (SCID-II) (16), Hamilton depression rating scale (HDRS) (17), and Hamilton anxiety rating scale (HARS) (18) were applied to the patients after psychiatric evaluation.

Socio-demographic and Clinical Information Form

The form was developed based on the study aim, clinical knowledge, and literature review. The form aimed to collect patient information such as age, gender, marital status, education level, income level, social security, occupation, place of residence, location in the region, age of onset of panic attacks, disease duration, and frequency of the attacks.

DSM-III-R SCID-I

SCID-I is a structured interview form developed for DSM-III and introduced by Spitzer in 1983 (19). In 1987, it was revised and published for DSM-III-R. SCID-I was translated into Turkish language by Sorias et al. (20), and the reliability of the form was confirmed in Turkish language (21). At the beginning of the interview, the clinician was allowed to determine the patient complaints and anamnesis, similar to a conventional interview. Furthermore, SCID-I is an interview model that allows the interviewer to employ all obtained data, and to confront the case with other data if necessary.

DSM-III-R Personality Evaluation Form (SCID-II)

SCID-II was developed by Spitzer for DSM-III and revised for the DSM-III-R in 1987 and has been used for the diagnosis of second axis personality disorders (16). SCID-II is a structured form for individuals, and patients are evaluated based on their responses to the questions in the form and clinical assessments during the interview (16). SCID-II includes items that probe adolescence symptoms for 12 personality disorders, including 3 cluster A personality disorders (paranoid, schizoid, schizotypal personality disorders), 4 cluster B personality disorders (histrionic, borderline, narcissistic, and antisocial personality disorders) and 5 cluster C personality disorders (avoidant, dependent, passive-aggressive, obsessive-compulsive and self-defeating personality disorders). The form was adopted to Turkish language by Sorias et al. (20), and reliability of the form was studied by Coşkunol et al. (22).

HDRS

The HDRS is the most frequently employed depression scale that aims to measure the severity of depression or to determine the symptoms and completed by the interviewer. It was developed by Hamilton and the scale includes 17 items. The scale sub-dimensions include depressive disposition, loss in work and activities, retardation, agitation, gastrointestinal symptoms, general somatic symptoms, hypochondriasis, insight, weight loss, insomnia and anxiety. A total score between 0 and 13 indicates no depressive syndrome. A score between 14 and 27 indicates mild, 28 and 41 indicates moderate, and 42 and 53 indicates severe depressive syndrome (17). The validity and reliability of the scale was determined by Akdemir et al. (23).

HARS

The HARS was developed by Hamilton in 1959 and employed to measure the severity of anxiety (18). It measures depressive symptoms as well as psychological and somatic anxiety. The presence and severity of the 14 scale items are based on the views of the interviewees at the time of the interviews. The scale is scored based on 14 symptoms including anxious mood, stress, fear, insomnia, concentration and memory difficulties, depressive mood, physical, emotional and cardiovascular symptoms, respiratory symptoms, gastrointestinal, genitourinary and autonomic symptoms, behavior during the interview, and each symptom is scored between 0 and 4 points. A total score between 0 and 5 points indicate no anxiety, 6 and 14 points indicate minor anxiety (mild-moderate), 15 points or higher indicate major anxiety (severe). The validity and reliability of the scale was determined by Yazici et al. (24).

Statistical Analysis

Statistical analysis was conducted with SPSS for Windows version 6.0. In data analysis, listing and percentages were presented, and the chi-square (χ^2) and Mann-Whitney U tests were employed in statistical analyses.

Results

The age of the patients in the study group was between 18 and 47 years. The mean age was 31.25±7.19 years. Of the patients, 42 (70%) were female and 18 (30%) were male. The socio-demographic patient data are presented in Table 1.

Participant Socio-demographics

The first study group included 21 patients (35%) with pure PD, the second group included 34 patients (56.6%) with PD and a comorbid axis I disorder, and the third group included 26 patients with PD and a comorbid axis II disorder (43.3%).

The mean patient age was 36.607±5.42 years in the first, 27.91±6.00 years in the second, and 26.92±6.77 years in the third group. The mean age of the second and third groups was statistically significantly lower than that of the first group (p<0.0001).

The male to female ratio was 2/19 in the first group, 14/20 in the second group, and 6/20, in the third group. Female patients were dominant in all study groups. The male to female ratio was statistically significantly lower for patients with pure PD (group 1) when compared to the other groups (p<0.05).

There were significant differences between the marital status, educational level, occupation, place of residence, location in the region, income level, and social security in the group with a comorbid axis I disorder (group 2), and between illiteracy, housemaker, residency in a village, domestic migration, social security (p<0.05) (Table 1). In the group with comorbid axis II disorder (group 3), there were statistically significant differences based on attendance to a university, a school, and domestic migration (p<0.05) (Table 1).

Comorbid Axis I Disorders

Thirty-four (56.6%) out of the 60 patients in the study group had comorbid axis I disorder along with PD. The patients had at least one and at most 4 comorbid disorders. Axis I comorbidity included a single disorder in six cases (17.6%). There was a statistically significant comorbidity of major depression (p<0.05). Moreover, social phobia was second most comorbid pathology. The comorbid axis I disorders to PD are presented in Table 2.

Agoraphobia was comorbid in 38.3% of the study group. Eighth percent of the patients with agoraphobia were female. The presence of agoraphobia was statistically significant in axis I and II comorbidities (p<0.05). The rate of agoraphobia comorbidity in the groups is presented in Table 3.

Table 1. Participant socio-demographics

		Group 1		Group 2		Group 3		Total		χ^2	p
		N	%	N	%	N	%	N	%	-	-
Marital status	Married	11	52.5	24	70	16	61.5	40	66.6	-	-
	Unmarried	6	28.5	8	23.5	8	30.7	14	23.3	-	-
	Widower	2	9.5	1	2.9	1	3.8	3	5	-	-
	Divorced	2	9.5	1	2.9	1	3.8	3	5	-	-
Education	Illiterate	9	42.8	4*	11.7	3	11.5	14	23.3	*13.09	*0.04
	Primary school	10	47.6	12	35.2	6	23	24	40	-	-
	Middle-high school	2	9.5	10	29.4	9	34.6	14	23.3	-	-
	College	0	0	8	23.5	8*	30.7	8	13.5	*16.10	*0.01
Occupation	Housemaker	17	80.9	8*	23.5	10	38.4	30	50	*27.71	*<0.0001
	Worker-civil servant	0	0	15	44.1	7	26.9	15	25	-	-
	Self-employed	2	9.5	2	5.8	0	0	4	6.6	-	-
	Student	0	0	9	26.4	9*	34.6	9	15	*21.52	*0.0002
	Unemployed	2	9.5	0	0	0	0	2	3.3	-	-
Place of residence	Village	3	14.2	0*	0	1	3.8	4	6.6	*12.28	*0.002
	Town	9	42.8	5	14.7	7	26.9	18	30	-	-
	City	9	42.8	29	85.2	18	69.2	38	63.3	-	-
Nativity	Native	19	90.5	27	79.4	20	76.9	51	85	-	-
	Domestic migrant	0	0	7*	20.5	6**	23	7	11.6	*7.75, **7.57	**0.02
	International migrant	2	9.5	0	0	0	0	2	3.3	-	-
Income level	High	3	14.2	2	5.8	1	3.8	5	8.3	-	-
	Medium	12	57.1	24	70.5	20	76.9	40	66.6	-	-
	Low	6	28.5	8	23.5	5	19.2	15	25	-	-
Social security	No	7	33.3	10	29.4	9	34.6	18	30	-	-
	Yes	14	66.6	24*	70.5	17	65.3	42	70	*0.093	*0.04

*p<0.001, **p<0.01

Comorbid Axis II Disorders

Twenty-six (43.3%) out of 60 patients in the study group had comorbid axis II disorders. Axis II disorder comorbidity included at least one and at most 4 personality disorders. One personality disorder comorbidity was determined in 4 cases (15.3%). The most prevalent comorbidities were avoidant, dependent, obsessive-compulsive and histrionic personality disorders, respectively. Comorbid axis II disorders are presented in Table 4.

Hamilton Anxiety and Depression Scores

The mean HARS score was 7.67±3.60, and the mean HDRS score was 19.68±8.02 in the study group. Based on the anxiety and depression scores, there was a statistically significant difference between the 2nd and 3rd groups (groups with comorbid axis I and II disorders) and the 1st group ($p<0.05$). The anxiety and depression scores were lower in the first group. The distribution of anxiety and depression scores by subgroups is presented in the Table 5.

Discussion

Previous studies reported that PD is prevalent in individuals between 18 and 45 years of age and the mean age is between 30 and 33 years (5). The patient age varied between 18 and 47 years and the mean age was 31.25±7.19 years in the present study, consistent with the literature. The mean age was significantly lower in the groups with comorbid axis I and II disorders in the present study, suggesting that young age increased the comorbidity risk. In previous studies, it was reported that patients with PD were predominantly female (75-80%) (5) and PD was 2.5-3.5 times more common in females when compared to males (25). In the present study, consistent with previous reports, 70% of the PD patients were female and the female to male ratio was 2.3. Female patients were dominant in all subgroups. Barlow reported that the higher prevalence of PD in women was associated with cultural factors (26). This is explained by the fact that it is more culturally acceptable for women to report their fears and exhibit avoidance behavior in several situations, while males, who are expected to be strong and brave, could not easily exhibit avoidance behavior, which is an expression of fear. Furthermore, in addition to the biological differences of females, they are more vulnerable to stress due to the historical and psychosocial gender roles assigned to women in Turkish society. This may explain the prevalence of anxiety disorders such as PD among females. The higher number of females with PD when compared to the males could also be associated with the fact that women seek more help and treatment. Consistent with the previous reports, the patients were married, housewives, and with middle income (27). The high number of patients who were urban residents, natives and with social security in the present study could be explained by the fact that the study was conducted in a university hospital in an urban center.

Table 2. Comorbid axis I disorders in the overall study group

	Pre-PD		Post-PD		Total		χ^2	p
	N	%	N	%	N	%		
Major depression	6	25	18	75	24	40		
Hypochondriasis	4	22.2	14	77.8	18	30		
Generalized anxiety disorder	10*	83.3	2	16.7	12	20	*21.24	0.0003
Social phobia	8	80	2	20	10	16.6		
Obsessive compulsive disorder	6	66.7	3	33.3	9	15		

*p<0.001, PD: Panic disorder

Table 3. The agoraphobia rate in the groups

Agoraphobia	Group 1		Group 2		Group 3		χ^2	p
	N	%	N	%	N	%		
No	15	71.4	14	41.1	8	30.7		
Yes	6	28.5	20*	58.8	18**	69.2	4.76, 7.69	0.02, 0.005

Table 4. The rate of personality disorders in the overall study group

Personality disorder	N	%
Paranoid	5	8.3
Schizoid	1	1.6
Schizotypal	2	3.3
Histrionic	9	15
Borderline	1	1.6
Narcissistic	3	5
Antisocial	1	1.6
Dissocial	15	25
Dependent	12	20
Passive-aggressive	1	1.6
Obsessive	11	18.3

Table 5. The mean group anxiety and depression scores

Mean score	1. group	2. group	3. group
Hamilton anxiety	5.7	9*	9.1**
Hamilton depression	11.4	26.1 ***	23.3***

*p<0.001, **p<0.01, ***p<0.0001

In the study, the mean disease duration was 31.15±13.16 months, consistent with the literature (28). It was observed that the duration of disease in groups with comorbid disorders was statistically significantly longer when compared to the group with pure PD, consistent with the findings of Noyes et al. (28). The frequency of events such as trying to adapt to a new region, school, circle of friends, exposure to a turbulent life that includes changes, separation and migration, life decisions, graduation, and further responsibilities among university students increases the PD risk (26).

Agoraphobia is the most common comorbid disorder in PD patients (29). In the literature, it was reported that 1/3-1/2 of the patients with PD also suffered from agoraphobia and the prevalence of the latter was higher among women (30). The National Comorbidity Study reported that agoraphobia comorbidity in PD was around 50% (30). In the present study, agoraphobia comorbidity in PD was 38.3% and 80% of these patients were female. It is known that a typical interpersonal problem associated with agoraphobia is shyness, and most patients with PD have a history of premorbid shyness and introversion (31). In the present study, a statistically significant correlation was determined between the presence of agoraphobia and a comorbid axis II disorder, consistent with the above-mentioned data.

The comorbidity rate in PD patients is high (14). Fifty-seven percent of these patients have a first axis disorder (32). In the literature, it has been reported that 63% of patients with PD experience at least one major depressive episode and 57% have a history of major depressive episodes (33,34). Various studies reported that the rate of comorbid depression in PD was between 31 and 65% (14,35). In the ECA study, it was determined that depression was 10 times more common in patients with PD when compared to those without PD (13). In the present study, the rate of a comorbid major depressive disorder was 40%, consistent with the literature. Previous studies associated the comorbid depressive disorder in PD with narcissistic conflicts, low self-esteem, cognitive distortions, and disability and intimidation due to the chronic and recurrent nature of the disease (29).

Hypochondriasis is the second most common comorbidity in PD, following depressive disorder, excluding agoraphobia. Cognitive reviews suggested similarities between the development mechanisms in these two disorders (36,37). It has been reported that patients with PD and hypochondria consider natural physiological stimuli as a serious physical illness, exhibit hypersensitivity to somatic symptoms, and tend to exaggerate these sensations (36). In different studies, the rate of hypochondriasis comorbidity in PD was reported as 25-50% (38,39). Consistent with the literature, the rate of hypochondriasis comorbidity in PD was 30% in our study. Starcevic, in a study where PD with and without comorbid hypochondriasis were compared, reported that patients with comorbid hypochondriasis exhibited higher levels of agoraphobia, and more severe depressive and obsessive-compulsive symptoms (40).

The rate of comorbid generalized anxiety disorder in PD was reported between 20 and 40% (41,42). In the present study, the comorbid generalized anxiety disorder in PD (20%) was consistent with these reports.

The rate of comorbid social phobia in PD was reported between 15 and 20% (42,43). The comorbid social phobia in PD increases the risk of the development of major depression (42). Clayton (44) reported that the rate of comorbid social phobia and major depression in PD was 94%. Consistent with the literature, the rate of comorbid social phobia was 16.6% in our study, and the correlation between major depression and social phobia was statistically significant. The rate of comorbid obsessive-compulsive disorder in PD was reported as 10-21% (42,45). In the present study, the rate of comorbid obsessive-compulsive disorder was 15%.

In previous studies, the rate of comorbid personality disorder (comorbid axis II disorder) in patients with PD was reported as 27-58% (46-49). It could be suggested that the differences between the rates reported in previous studies were due to research method differences. In the present study, personality disorder was identified in 43.3% of patients with PD, consistent with the literature.

It was reported that the most prevalent comorbid personality disorders in PD patients were avoidant, dependent, histrionic, obsessive-compulsive and borderline personality disorders (46). In the present study, it was determined that avoidant, dependent, obsessive-compulsive and histrionic personality disorders were the most common comorbid personality disorders in PD patients, consistent with the literature.

In the literature, it has been reported that comorbid axis I disorders in PD lead to more severe and several personality disorders, and axis I comorbidities are more common in patients with PD and comorbid personality disorders when compared to patients without comorbid personality disorders (49). Personality disorders may lead to the development of axis I pathologies as well as affect

the severity and prognosis of existing axis I pathology (50). Consistent with the literature, comorbid axis I and II disorders were diagnosed in 21 patients with PD in our study. This group included 61.7% of the patients with comorbid axis I disorders and 80.7% of the patients with comorbid axis II disorders.

It was reported that the comorbid disorders in PD increased anxiety and depression scores (49). In the present study, the anxiety and depression scores of the patients with comorbid disorders were statistically significantly higher, consistent with the literature.

Study Limitations

The present study has certain limitations. The study was conducted in a university hospital, where most patients were urban residents. This socio-demographic limitation may have affected the study findings. The larger the number of participants, the stronger the study findings.

Conclusion

In the study group, 56.6% of the patients had comorbid axis I disorder with PD. The most common axis I disorder was major depression. 43.3% of the study group had comorbid axis II disorders. The most prevalent comorbid disorders were avoidant, dependent, obsessive-compulsive and histrionic personality disorders, respectively. Mild anxiety and depression were observed in the study group. Anxiety and depression were significantly higher in the patients with comorbid axis I and II disorders when compared to those with pure PD. The high rate of comorbid axis I and axis II disorders in PD adversely affects treatment and prognosis. Considering this fact in the treatment and follow-up of patients with PD, and the inclusion of psychotherapies that also consider personality disorders in pharmacotherapy may improve the success of treatment. Future studies with a larger sample and participants with more homogeneous socio-demographic characteristics may contribute further to the literature.

Ethics

Ethics Committee Approval: Ethics committee approval could not be obtained since the formation of local and national ethics committees has not yet taken place at the time of this thesis-based study, but at that time, the study was carried out in Fırat University hospital and in accordance with the Declaration of Helsinki of the World Medical Association.

Informed Consent: Consent of patients received.

Peer-review: Externally peer-reviewed.

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

References

1. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and Statistical Manual Of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Association, 2013.
2. Gökalp PG. Anksiyete Bozuklukları. Ankara: Çizgi Tıp Yayınevi 2000:137-156.
3. Onur E, Alkın T, Monkul E, Fidaner H. Yaşam boyu panik-agorafobik spektrum ölçeği öz bildirim formunun (PASÖ-ÖB) Türkçe versiyonu geçerlilik ve güvenilirlik çalışması. New Symposium 2006;44(2):81-91.
4. American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association, 1994.
5. Ming T. Tsuang, Mauricio Tohen, P. Jones Epidemiology of anxiety disorders. Textbook in psychiatric epidemiology, 2011. (Ed. 3):311-328.
6. Kaplan HI, Sadock BJ. Comprehensive textbook of psychiatry/VI: Pennsylvania: Wiliams & Wilkins, 1995.
7. Onur E, Alkin T, Monkul S. Panik-agorafobi spektrumu kavrami [Panic-Agoraphobic Spectrum]. Türk Psikiyatri Dergisi 2004;15(3):215-223.
8. American Psychiatric Association. Committee on Nomenclature and Statistics. Diagnostic and Statistical Manual Of Mental Disorders. 2nd ed. Washington: American Psychiatric Association, 1968.
9. Organization WH. International classifcation of diseases (ICD 9). Geneva: Author, 1975.
10. American Psychiatric Association. Task Force on Nomenclature and Statistics., American Psychiatric Association. Committee on Nomenclature and Statistics. Diagnostic and statistical manual of mental disorders. 3d ed. Washington, DC: American Psychiatric Association, 1980.
11. American Psychiatric Association. Diagnostic criteria from DSM-IV. Washington, DC.: The Association, 1994.
12. Apfeldorf WJ, Spielman LA, Cloitre M, Heckelman L, Shear MK. Morbidity of comorbid psychiatric diagnoses in the clinical presentation of panic disorder. Depress Anxiety 2000;12(2):78-84.
13. Robins LN, Regier DA. Psychiatric disorders in America. The epidemiologic catchment area study 1991:155-180.
14. Konkan R, Yalçınkaya S, Erkıran M, Erkmen H. Panik bozukluğu ve komorbid tanılar. Düşünen Adam 2003;16(4):219-222.
15. American Psychiatric Association., American Psychiatric Association. Work Group to Revise DSM-III. Diagnostic and statistical manual of mental disorders: DSM-III-R. 3rd ed. Washington, DC: American Psychiatric Association, 1987.
16. Spitzer RL, First MB, Gibbon M, Williams JB. Structured clinical interview for DSM-III-R: American Psychiatric Press, 1990.
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23(1):56-62.

18. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32(1):50-55.

19. Spitzer R, Williams J, Gibbon M. DSM-III-R Yapılandırılmış Klinik Görüşme Formu. Türkçe Versiyonu Yatan (SCID-P) Hasta Formu. S Sorias, R Saygılı, H Elbi (çeviri editörü) İzmir: Ege Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı, 1988.

20. Sorias S, Saygılı R, Elbi H, Vahip S, Mete L, Nifime Z. DSM-III-R yapılandırılmış klinik görüşmesi türkçe versiyonu. Bornova: Ege Üniversitesi Basımevi, 1990.

21. Çorapçıoğlu A, Aydemir Ö, Yıldız M, Danacı A, Köroğlu E. DSM-IV Eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçeye uyarlanması ve güvenilirlik çalışması. İlaç ve Tedavi Dergisi 1999;12(4);233-236.

22. Coşkunol H, Bağdiken İ, Sorias S, Saygılı R. SCID-II (Türkçe versiyonu) görüşmesinin kişilik bozukluklarındaki güvenirliği. Türk Psikoloji Derg 1994;9(32):26-29.

23. Akdemir A, Örsel S, Dağ İ, Türkçapar H, İşcan N, Özbay H. Hamilton Depresyon Derecelendirme Ölçeği (HDDÖ)'nin geçerliği, güvenirliği ve klinikte kullanımı. Psikiyatri Psikoloji Psikofarmakoloji Dergisi 1996;4(4):251-259.

24. Yazici M, Demir B, Tanriverdi N, Karaagaoglu E, Yolac P. Hamilton anksiyete degerlendirme olcegi; degerlendiriciler arasi guvenirlik ve gecerlik calismasi. Turk Psikiyatri Derg 1998;9(2):114-117.

25. Crowe RR, Noyes R, Pauls DL, Slymen D. A family study of panic disorder. Arch Gen Psychiatry 1983;40(10):1065-1069.

26. Barlow DH. Anxiety and its disorders: the nature and treatment of anxiety and panic: New York: Guilford Press, 2004.

27. de Lijster JM, Dierckx B, Utens EM, Verhulst FC, Zieldorff C, Dieleman GC, et al. The age of onset of anxiety disorders: a meta-analysis. Can J Psychiatry 2017;62(4):237-246.

28. Noyes R, Reich J, Christiansen J, Suelzer M, Pfohl B, Coryell WA. Outcome of panic disorder. Relationship to diagnostic subtypes and comorbidity. Arch Gen Psychiatry 1990;47(9):809-818.

29. Amerikan Psikiyatri Birliği. Mental bozuklukların tanısal ve sayımsal elkitabı. 4th ed. Ankara: Hekimler Yayın Birliği, 1994.

30. Kessler RC, Wittchen HU, Abelson JM, McGonagle K, Schwarz N, Kendler KS, et al. Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US national comorbidity survey (NCS). Int J Methods Psychiatr Res 1998;7(1):33-55.

31. Kleiner L, Marshall W. The role of interpersonal problems in the development of agoraphobia with panic attacks. J Anxiety Disord 1987;1(4):313-323.

32. Biederman J, Petty C, Faraone SV, Hirshfeld-Becker D, Pollack MH, Henin A, et al. Moderating effects of major depression on patterns of comorbidity in patients with panic disorder. Psychiatry Res 2004;126(2):143-149.

33. Maddock RJ, Blacker KH. Response to treatment in panic disorder with associated depression. Psychopathology 1991;24(1):1-6.

34. Stein DJ, Scott KM, de Jonge P, Kessler RC. Epidemiology of anxiety disorders: from surveys to nosology and back. Dialogues Clin Neurosci 2017;19(2):127-136.

35. Yaluğ İ, Kocabaşoğlu N, Aydoğan G, Günel B. Obsesif kompulsif bozukluk ve panik bozuklukta depresyon ve kişilik bozukluğu komorbiditesi. Düşünen Adam 2003;16(4):28-34.

36. Olatunji BO, Deacon BJ, Abramowitz JS, Valentiner DP. Body vigilance in nonclinical and anxiety disorder samples: structure, correlates, and prediction of health concerns. Behav Ther 2007;38(4):392-401.

37. Hibbert GA. Ideational components of anxiety: their origin and content. Br J Psychiatry 1984;144(6):618-624.

38. Starcevic V. Boundaries and overlap between hypochondriasis and other disorders: Differential diagnosis and patterns of co-occurrence. Curr Psychiatry Rev 2014;10(1):24-33.

39. Bach M, Nutzinger DO, Hartl L. Comorbidity of anxiety disorders and hypochondrias is considering different diagnostic systems. Compr Psychiatry1996;37(1):62-67.

40. Starcevic V, Dellner R, Uhlenhuth E, Pathak D. Panic disorder and hypochondrical fears and believes. J Affect Disord 1992;24(2):73-85.

41. Breier A, Charney DS, Heninger GR. Agoraphobia with panic attacks. Development, diagnostic stability, and course of illness. Arch Gen Psychiatry 1986;43(11):1029-1036.

42. Tükel MR. Panik bozukluğu ve eşlik eden psikopatolojiler. Nöropsikiyatri Arsivi 1992;29:93-101.

43. Stein MB, Shea CA, Uhde TW. Social phobic symptoms in patients with panic disorder: practical and theoretical implications. Am J Psychiatry1989;146(2):235-238.

44. Clayton PJ. The comorbidity factor: establishing the primary diagnosis in patients with mixed symptoms of anxiety and depression. J Clin Psychiatry 1990;51(Suppl):35-39.

45. Hoffart A, Thornes K, Hedley LM, Strand J. DSM-III-R Axis I and II disorders in agoraphobic patients with and without panic disorder. Acta Psychiatr Scand 1994;89(3):186-191.

46. Mavissakalian M, Hamann MS. DSM-III personality disorder in agoraphobia. Compr Psychiatry 1986;27(5):471-479.

47. Friedman CJ, Shear MK, Frances A. DSM-III personality disorders in panic patients. J Pers Disord 1987;1(2):132-135.

48. Brooks RB, Baltazar PL, McDowell DE, Munjack DJ, Bruns JR. Personality disorders co-occurring with panic disorder with agoraphobia. J Pers Disord 1991;5(4):328-336.

49. Pollack MH, Otto MW, Rosenbaum JF, Sachs GS. Personality disorders in patients with panic disorder: association with childhood anxiety disorders, early trauma, comorbidity, and chronicity. Compr Psychiatry 1992;33(2):78-83.

50. Greenberg D, Witztum E. The influence of cultural factors on obsessive compulsive disorder: religious symptoms in a religious society. Isr J Psychiatry Relat Sci 1994;31(3):211-230.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):334-338
DOI: 10.4274/BMB.galenos.2021.07.085

Using mSIS, DNI, CRP, LDH and Albumin Levels for Predicting Burn-related Mortality

Yanık İlişkili Mortalitenin Öngörülmesinde mSIS, DNI, CRP, LDH ve Albümin Seviyelerinin Kullanılması

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Abstract

Objective: After major burn injury, patients suffer from massive systemic inflammatory response. Approximately 54% of burn-related deaths in modern burn units occur due to septic shock and multiple organ dysfunction syndrome instead of osmotic shock and hypovolemia, in 72 hours after admission. Early diagnosis and effective treatment of the sepsis would be a benefit for burn patients, especially those with severe burns. In this study, we aimed to use modified systemic inflammatory score (mSIS), C-reactive protein (CRP), delta neutrophil index (DNI), lactate dehydrogenase (LDH) and albumin (ALB) together to predict mortality of patients suffering from more than 30% of total body surface area (TBSA) burns.

Method: Between January 2020 and December 2020, the records of patients admitted to our center were analyzed retrospectively. Demographic and burn-related characteristics of patients and mortality were tabulated. DNI, CRP, serum ALB and LDH levels at the time of admission and discharge were also recorded. mSIS was calculated for all patients based on serum ALB levels and lymphocyte-to-monocyte ratio. The DNI, CRP, LDH and ALB levels both during admission and discharge were analyzed with ROC analysis.

Results: Totally 55 severe burn patients were admitted to burn intensive care unit in one year period. The mean age of the patients was 40.8 (18-89) years and the mean burned TBSA was 40.73%. There were 13 deaths with 23.6% mortality rate. The average length of stay for all patients was 35.3 days where all mortalities occurred after 72 hours of admission. Both admission and discharge CRP levels were significantly high for non-survivals (p=0.001 and p=0.000, respectively). When LDH, ALB and DNI values were compered between the groups, while LDH and DNI discharge levels were significantly high and ALB levels were significantly low for non-survivals, there were no difference at the admission levels. The ROC curve analysis was performed for the eligibility of the inflammatory biomarkers to predict the mortality. Continued high levels

Öz

Amaç: Majör yanık yaralanmalarından sonra hastalarda masif sistemik enflamatuvar yanıt görülmektedir. Modern yanık ünitelerinde yanığa bağlı ölümlerin yaklaşık %54'ü, ozmotik şok ve hipovolemi yerine başvurudan 72 saat sonra septik şok ve çoklu organ disfonksiyonu sendromu nedeniyle meydana gelmektedir. Sepsisin erken teşhisi ve etkin tedavisi, yanık hastalarında, özellikle ciddi yanıklarda fayda sağlayacaktır. Bu çalışmada toplam yanık vücut yüzey alanı (TVYA) %30'dan fazla olan hastalarda mortaliteyi tahmin etmek için sistemik enflamatuvar skor (mSIS), C-reaktif protein (CRP), delta nötrofil indeksi (DNI), laktat dehidrogenaz (LDH) ve albümini (ALB) birlikte kullanmayı amaçladık.

Yöntem: Ocak 2020 ile Aralık 2020 tarihleri arasında merkezimize başvuran hastaların hasta kayıtları geriye dönük olarak incelendi. Hastaların demografik ve yanık ile ilgili özellikleri mortalite varlığı durumuna göre analiz edilmiştir. Hasta kabulü ve taburculuk sırasındaki DNI, CRP, serum ALB ve LDH seviyeleri de kaydedildi. mSIS, tüm hastalar için serum ALB seviyelerine ve lenfosit-monosit oranına göre hesaplanmıştır. Hem yatış hem de taburculuk sırasında DNI, CRP, LDH ve ALB seviyeleri ROC analizi ile analiz edildi.

Bulgular: Bir yıllık süre içerisinde yanık yoğun bakım ünitesine toplam 55 ağır yanıklı hasta başvurdu. Hastaların ortalama yaşı 40,8 (18-89) yıl ve ortalama yanık TVYA'sı %40,73 idi. Hastaların 13'ü hayatını kaybetti (%23,6). Tüm hastalar için ortalama yatış süresi 35,3 gün olup, tüm ölümler başvurudan 72 saat sonra meydana gelmiştir. Hem yatış hem de taburculuk CRP düzeyleri ölen hastalar için anlamlı derecede yüksekti (sırasıyla p=0,001 ve p=0,000). Gruplar arasında LDH, ALB ve DNI değerleri karşılaştırıldığında, hayatını kaybeden hastalarda LDH ve DNI taburculuk düzeyleri anlamlı olarak yüksek, ALB anlamlı derecede düşüktü, ancak kabul düzeyleri arasında fark yoktu. Mortaliteyi tahmin etmek için enflamatuvar belirteçlerin uygunluğu için ROC eğrisi analizi yapıldı. Devam eden yüksek LDH, CRP ve DNI seviyeleri ve azalan ALB seviyelerinin (sırasıyla; 0,86, 0,92, 0,84) ölüm

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Cite this article as: Akın M, Akgün AE. Using mSIS, DNI, CRP, LDH and Albumin Levels for Predicting Burn-related Mortality. Bagcilar Med Bull 2021;6(3):334-338

Abstract

of LDH, CRP, and DNI and decreasing ALB levels predicts mortality better than abbreviated burn severity index and rBAUX according to the value of area under ROC curve (0.86, 0.92, 0.84, respectively).

Conclusion: Predicting the life expectancy of patient at the time of admission to the burn intensive care unit is the greatest help in deciding the treatment scheme. Burn severity scores are mostly used for mortality prediction, and widely used ones are based on TBSA and age. Sometimes, calculating the TBSA could be difficult especially for the patients referred from primary care. In regard to our study, accurate mortality prediction can be made with CBC, serum ALB and CRP levels and without TBSA. Moreover, during the intensive care unit stay, increasing levels of DNI, LDH and CRP levels and decreasing ALB levels should be alerting for mortality.

Keywords: Albumin, burn, CRP, DNI, LDH, mortality, mSIS

Öz

oranını kısaltılmış yanık şiddet indeksi ve rBAUX'ten daha iyi tahmin ettiği görülmüştür.

Sonuç: Hastanın yanık yoğun bakım ünitesine kabul edildiği andaki yaşam beklentisinin tahmin edilmesi, tedavi şemasının belirlenmesinde en büyük yardımcıdır. Mortalite tahmini için çoğunlukla yanık şiddeti skorları kullanılır ve bunlardan yaygın olarak kullanılanları TVYA ve yaşa dayanmaktadır. Bazen özellikle birinci basamaktan sevk edilen hastalar için toplam vücut yüzey alanının (TBSA) hesaplanması zor olabilir. Bu çalışma ile TBSA'dan bağımsız olarak, sadece tam kan sayımı, serum ALB ve CRP seviyeleri ile mortalite tahmininin mümkün olabileceği gösterilmiştir. Ayrıca, yoğun bakımda kalış sırasında artan DNI, LDH ve CRP seviyeleri ve azalan ALB seviyeleri mortalite için alarm verici olmalıdır.

Anahtar kelimeler: Albümin, CRP, DNI, LDH, mortalite, mSIS, yanık

Introduction

Burn injuries often result in extensive damage to the skin, which is the largest organ system, with resulting loss of the primary barrier to infection (1). After major burn injury, in addition to the lack of this barrier, patients also suffer from massive systemic inflammatory response, anemia, leukopenia, thrombocytopenia, and coagulopathy (2). Thus, although the severity and prognosis of burn injuries depend principally on the depth and size of the burn site, approximately 54% of burn-related deaths in modern burn units occur due to septic shock and multiple organ dysfunction syndrome instead of osmotic shock and hypovolemia, in 72 hours after admission (1,3). In patients with more than 20% burned total body surface area (TBSA), the incidence of sepsis is noted to be between 3% and 30% (1). Therefore, the early diagnosis and effective treatment of sepsis would be benefit for burn patients, especially for those with severe burns.

Previously lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, delta neutrophil index (DNI), C-reactive protein (CRP), and preoperative serum albumin (ALB) levels have been reported as prognostic factors in various tumors, sepsis, and trauma (4-6). And recently modified systemic inflammatory score (mSIS) based on preoperative serum ALB levels found to be prognostic factor in some cancers (5). Some inexpensive and routinely performed tests have been reported as early predictors of systemic inflammatory response for severe burn patients separately (2,4,7,8). But to our best knowledge, no study has used those markers and mSIS as mortality predictors for severe burn victims together.

In this study, we aimed to use mSIS, CRP, DNI, LDH and ALB together to predict mortality of those patients who suffer from more than of 30% TBSA burns.

Materials and Methods

Between January 2020 and December 2020, the records of patients admitted to our center were analyzed retrospectively after getting ethical approval from hospital ethical board (09/06/2021- E1-21-1838). Age, gender, burned TBSA, burn agent, burn depth, abbreviated burn severity index (ABSI), revised BAUX score (rBAUX) and mortality were tabulated. Lymphocyte, monocyte, neutrophil counts; DNI, CRP, serum ALB and LDH levels at the times of admission and discharge were also recorded. mSIS was calculated for all patients based on serum ALB levels and LMR. DNI, CRP, LDH and ALB level both during admission and discharge were analyzed with ROC analysis.

Statistical Analysis

Data were given as mean ± standard deviation for demographic and clinical data. The results were accepted with a 95% confidence interval and $p<0.05$ significance. Comparisons were made using t-tests and categorical data were analyzed using the Mann-Whitney U test. ROC curve analysis was used to compere the sensitivity and specificity of biomarkers with rBAUX and ABSI.

Results

Total 55 severe burn patients were admitted to our burn intensive care unit in one year period. The mean age of the patients was 40.8 (18-89) years. The mean burned TBSA was 40.73%. Five of the patients had inhalation injury and

13 of the patients died (23.6%) (Table 1). The average length of stay for all patients was 35.3 days where all mortalities occurred after 72 hours of admission.

Table 2 summarizes the patients burn related characteristics including burn etiology, burn wound depth, rBAUX and ABSI scores.

ABSI and rBAUX scores were significantly high for the non-survival group (p=0.002 and p=0.008, respectively). Although mSIS's at the time of admission and discharge were not significantly different between the survivals and non-survivals, both admission and discharge CRP levels were significantly higher for non-survivals (p=0.001 and p=0.000, respectively). When LDH, ALB and DNI values were compered between the groups, LDH and DNI discharge levels were significantly higher and ALB levels were significantly lower for non-survivals although the admission levels were not significantly different between the groups (Table 3).

The ROC curve analysis was performed for the eligibility of the biomarkers to predict the mortality. Continued high levels of LDH, CRP, and DNI and decreasing ALB levels predicts mortality better than ABSI and rBAUX according to the value of area under ROC curve (0.86, 0.92, 0.84, respectively) (Figure 1, Table 4).

Discussion

Although dramatic improvements have been made in the treatment of severe burns, the management of severely burned patients is still challenging. Predicting the life expectancy of the patient at the time of admission to the burn intensive care unit is the greatest help in deciding the treatment scheme. Recently, ABSI and rBAUX are the scoring systems commonly used as mortality predicting scores (9,10). Those burn severity scores are all based on the burned TBSA. Even though there are simple rules for calculating TBSA, it is mostly subjective as is human-related that real TBSA may be over/underestimated during the very first evaluation. Thermal injury may induce a marked systemic inflammatory response at early stage; however, SIRS scoring was not recommended by the American Burn Association (ABA) in burns, but there are still some controversial discussions on using the well-known inflammatory markers as a mortality predictor.

Dvorak et al. have concluded in their review that sepsis is the most potential mortality reason for severely burned patient (1). Recognizing sepsis by inflammatory markers at the very early stage may prevent patients suffering from septic complications. With this view, Wu et al. (11)

Table 1. Patient characteristics

Characteristics	Survival n=42	Non-survival n=13	Total n=55
Age (years)	38 years	50 years	40.8 (18-89)
Sex n (M/F)	30/12	7/6	37/18
Burned TBSA (%)	38.93%	46.54%	40.73%
Inhalation injury, n (%)	3 (7.1%)	2 (15.3%)	5 (9.1%)
LOS (days)	39.7	21.2	35.3
ICU-LOS (days)	22.6	17.9	20.4

TBSA: Total body surface area, ICU: Intensive care unit, LOS: Length of stay

Table 2. Patients' burn-related characteristics

	Score	Frequencies	Percentage (%)
rBAUX			
	40-50	2	3.6
	50-60	8	14.5
	60-70	6	10.9
	70-80	10	18.1
	80-90	10	18.1
	90-100	9	16.3
	100-110	4	7.27
	>110	6	10.9
ABSI			
	4-5	8	14.5
	6-7	16	29
	8-9	23	41.8
	10-11	7	12.7
	>12	2	3.6
Depth			
	2nd degree-superficial	1	1.8
	2nd degree -deep	17	30.9
	3rd degree	37	67.3
Etiology			
	Scald	11	20.0
	Concentrated liquid	3	5.5
	Fire	25	45.5
	Flushing	2	3.6
	Electric	8	14.5
	Chemical	3	5.5
	Contact	1	1.8
	Others	2	3.6
	Total	55	100.0

ABSI: Abbreviated burn severity index, rBAUX: Revised BAUX score

Table 3. Comparison of biomarkers' significance with ABSI and rBAUX

	Mortality	N	Mean	Std. deviation	Significance*
ABSI	-	41	3.44	0.923	**p=0.002**
	+	13	4.31	1.032	
rBAUX	-	42	78.14	20.240	**p=0.008**
	+	13	99.15	19.300	
mSIS admission	-	42	1.21	0.842	p=0.156
	+	13	1.62	0.506	
mSIS discharge	-	39	1.26	0.751	p=0.474
	+	13	1.46	0.519	
CRP admission	-	42	60.03	60.233	**p=0.001**
	+	13	161.38	99.006	
CRP discharge	-	42	37.27	49.853	**p=0.000**
	+	13	249.23	116.143	
LDH admission	-	42	458.17	368.563	p=0.797
	+	13	414.54	200.009	
LDH discharge	-	42	203.21	119.495	**p=0.000**
	+	13	504.62	259.382	
ALB admission	-	42	32.79	7.390	p=0.26
	+	13	27.15	6.619	
ALB discharge	-	42	32.88	10.590	**p=0.00**
	+	13	23.77	5.019	
DNI admission	-	40	4.492	12.3914	p=0.232
	+	13	6.685	7.5102	
DNI discharge	-	42	1.210	3.5043	**p=0.000**
	+	13	26.492	19.6571	

*Mann-Whitney U test, CRP: C-reactive protein, ABSI: Abbreviated burn severity index, LDH: Lactate dehydrogenase, DNI: Delta neutrophil index, ALB: Albumin, mSIS: Systemic inflammatory score

analyzed the prediction ability of SIRS score for severely burned patient, but they concluded SIRS score as having limited use for prognostic determinations. A 2018 study by Yan et al. (12) compared the ability of sepsis-3 SOFA score, ABA sepsis criteria, and Mann-Salinas novel predictors to diagnose sepsis based on positive blood or tissue cultures. Their study revealed that although the sepsis-3 criteria was the most predictive of the three, none of the criteria had the accuracy enough to be a diagnostic standard in burn patients (12).

Rafiezadeh Shahi et al. (4) reported that serum ALB levels slightly increased the accuracy of mortality predictions. Hu et al. (7) observed in their study that admission NLR above 14 was positively correlated with decreased survival, indicating a potential prognostic value of systemic inflammatory markers. In another clinical study, Osuka et al. (2) found early thrombocytopenia and lymphopenia to be independent risk factors for 60-day mortality in severely burned patients.

CRP is another biomarker of inflammation. In healthy individuals, the levels of CRP in plasma are almost undetectable, while more than 500 mg/L can be observed in patients with burn trauma. Its levels may further increase in burn patients with infection or sepsis, thus previous studies have suggested CRP as a good predictor of sepsis in burn patients (3). Kim and Ha (8) concluded that DNI might be used as an early marker of patients with burn sepsis. Our study showed that high and steady CRP levels are a mortality predictor.

From our literature review, we found that most of the inflammatory biomarkers and systemic inflammation

Table 4. Area under the curve

Test result variable (s)	Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval		
				Lower bound	Upper bound	Cut-off value
ABSI	0.738	0.080	0.011	0.581	0.895	4.5
ALB admission	0.323	0.085	0.060	0.157	0.490	17.5 (g/L)
ALB discharge	0.060	0.031	0.000	0.000	0.122	15.5 (g/L)
CRP admission	0.787	0.079	0.002	0.632	0.942	185.5 (mg/L)
CRP discharge	0.928	0.043	0.000	0.844	1.000	176 mg/L
DNI admission	0.605	0.104	0.264	0.402	0.808	13.4 (%)
DNI discharge	0.845	0.088	0.000	0.673	1.000	9.3 (%)
LDH admission	0.526	0.095	0.782	0.339	0.713	479.5 (U/L)
LDH discharge	0.864	0.058	0.000	0.750	0.977	524.5 (U/L)
mSIS admission	0.649	0.079	0.114	0.493	0.804	1.5
mSIS discharge	0.565	0.086	0.486	0.397	0.734	0.5
rBAUX	0.768	0.071	0.004	0.630	0.907	98

ABSI: Abbreviated burn severity index, LDH: Lactate dehydrogenase, DNI: Delta neutrophil index, ALB: Albumin, mSIS: Systemic inflammatory score, CRP: C-reactive protein, [a]: Under the non-parametric assumption, [b]: Null hypothesis: True area=0.5

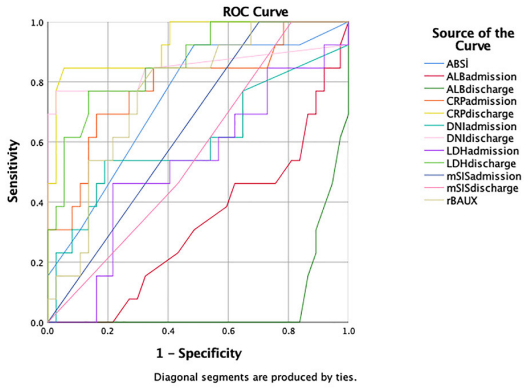

Figure 1. ROC curve analysis of inflammatory markers, ABSI and rBAUX score

ABSI: Abbreviated burn severity index, LDH: Lactate dehydrogenase, DNI: Delta neutrophil index, ALB: Albumin, mSIS: Systemic inflammatory score, CRP: C-reactive protein

scores were used for mortality prediction for burn patients. However, none of those studies had discussed mSIS, DNI, CRP, LDH, and ALB levels together comparing with ABSI and rBAUX.

In our study, we found that using those biomarkers during the admission, mortality prediction could be done as accurate as using ABSI or r BAUX. But, more importantly, the high levels of those biomarkers during discharge are more significant for predicting mortality and continuing high levels of DNI, CRP, LDH levels and continuing low levels of ALB should be alerting for severe burn patients.

Conclusion

Most widely used burn severity scores are based on TBSA and age. Sometimes, calculating the TBSA could be difficult especially for the patients referred from primary care. According to our study, calculations without TBSA, just with CBC, serum ALB and CRP levels, can make almost accurate mortality prediction possible. Moreover, during the intensive care unit stay, increasing levels of DNI, LDH and CRP and decreasing ALB levels should be alerting for mortality.

Acknowledgments

We would like to thank Prof. Dr. Ahmet Çınar Yastı for his contributions and help, especially in statistical analysis, during the writing of our article.

Ethics

Ethics Committee Approval: Between January 2020 and December 2020, the records of patients admitted to our center were analyzed retrospectively after getting ethical approval from Ankara City Hospital ethical board (09/06/2021- E1-21-1838).

Informed Consent: Retrospective study no need for consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Dvorak JE, Ladhani HA, Claridge JA. Review of sepsis in burn patients in 2020. Surg Infect (Larchmt) 2021;22(1):37-43.
2. Osuka A, Ishihara T, Shimizu K, Shintani A, Ogura H, Ueyama M. Natural kinetics of blood cells following major burn: impact of early decreases in white blood cells and platelets as prognostic markers of mortality. Burns 2019;45(8):1901-1907.
3. Zhang P, Zou B, Liou YC, Huang C. The pathogenesis and diagnosis of sepsis post burn injury. Burns Trauma 2021;9:tkaa047. doi: 10.1093/burnst/tkaa047.
4. Rafiezadeh Shahi H, Vahedian M, Movahedi M, Bahaadinbeigy K, Hashemian M, Mirafzal A. Measuring serum albumin levels at 0 and 24h: Effect on the accuracy of clinical evaluations in the prediction of burn-related mortality. Burns 2018;44(3):709-717.
5. Xu M, Wu Q, Cai L, Sun X, Xie X, Sun P. Systemic Inflammatory Score predicts Overall Survival in patients with Cervical Cancer. J Cancer 2021;12(12):3671-3677.
6. Hwang YJ, Chung SP, Park YS, Chung HS, Lee HS, Park JW, et al. Newly designed delta neutrophil index-to-serum albumin ratio prognosis of early mortality in severe sepsis. Am J Emerg Med 2015;33(11):1577-1582.
7. Hu L, Wang B, Hong Y, Xu L, Jiang Y, Wang C, et al. Admission Neutrophil-Lymphocyte Ratio (NLR) Predicts Survival in Patients with Extensive Burns. Burns 2021;47(3):594-600.
8. Kim CM, Ha CM. Delta neutrophil index as an early marker of sepsis in burn patients. J Korean Burn Soc 2019;22(2):38-44.
9. Osler T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the baux score. J Trauma 2010;68(3):690-697.
10. Tobiasen J, Hiebert JM, Edlich RF. The abbreviated burn severity index. Ann Emerg Med 1982;11(5):260-262.
11. Wu G, Zhuang M, Jiang Y, Fan J, Sun Y, Zhou Z, et al. Can systemic inflammatory response syndrome score at admission predict clinical outcome in patients with severe burns? Burns 2019;45(4):860-868.
12. Yan J, Hill WF, Rehou S, Pinto R, Shahrokhi S, Jeschke MG. Sepsis criteria versus clinical diagnosis of sepsis in burn patients: A validation of current sepsis scores. Surgery 2018;164(6):1241-1245.

ORIGINAL RESEARCH

Bagcilar Med Bull 2021;6(3):339-345
DOI: 10.4274/BMB.galenos.2021.07.084

Results of Favipiravir Combined Treatment in Intensive Care Patients with COVID-19

COVID-19 Tanılı Yoğun Bakım Hastalarında Favipiravir Kombine Tedavisinin Sonuçları

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) is a disease that has already taken place in human history. Although there is still no effective treatment protocol, different treatment options are being tried. In this study, it was aimed to determine the basic characteristics and changes in laboratory findings of patients who were hospitalized with the diagnosis of COVID-19 in the intensive care unit and underwent treatment protocol containing favipiravir.

Method: It was carried out with the data of 179 inpatients in an intensive care unit between 01.06.2020 and 30.06.2020. The inclusion criteria of the study were to have a diagnosis of COVID-19 confirmed by polymerase chain reaction test, to be hospitalized in the intensive care unit, to be receiving therapy combined with favipravir and to have access to its data through the automation system. According to literature, the socio-demographic characteristics, some basic characteristics and some laboratory findings of the patients were evaluated. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp.; Armonk, NY, USA).

Results: The average age of the study group was 60.9±16.4 years and 65.9% (n=118) of them were male. According to the clinical classification, more than half (50.8%, n=91) were included in the "high" clinical classification. The most common chronic disease was "hypertension (HT)" (42.5%, n=76) and the most common symptom was "fever" (57.5%, n=103). While 82.7% (n=148) had widespread computed tomography findings, C-reactive protein (CPR) positivity rate was 65.4% (n=117). Statistically significant difference was detected among three measurements of blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, CRP between during admisson, the 1st and the 3rd days.

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) insanlık tarihinde çoktan yerini almış bir hastalıktır. Halen etkili bir tedavi protokolü bulunmamakla birlikte farklı tedavi seçenekleri denenmektedir. Bu çalışmada yoğun bakım ünitesine COVID-19 tanısıyla yatırılan ve favipiravir içeren tedavi protokolü uygulanan hastaların temel özelliklerinin ve laboratuvar bulgularındaki değişikliklerin belirlenmesi amaçlanmıştır.

Yöntem: Çalışma 01.06.2020-30.06.2020 tarihleri arasında yoğun bakım ünitesinde yatan 179 hastanın verileriyle gerçekleştirilmiştir. Çalışmaya dahil edilme kriterleri; polimeraz zincir reaksiyon testi ile doğrulanmış COVID-19 tanısına sahip olmak, yoğun bakım ünitesinde yatırılmak, favipiravir ile kombine tedavi almak ve otomasyon sistemi üzerinden verilerine erişilebilmektir. Literatüre göre hastaların sosyo-demografik özellikleri, bazı temel özellikleri ve bazı laboratuvar bulguları değerlendirilmiştir. İstatistiksel analiz SPSS (Statistical Package for Social Sciences) versiyon 24.0 (IBM Corp.; Armonk,NY,ABD) kullanılarak yapılmıştır.

Bulgular: Çalışma grubunun yaş ortalaması 60,9±16,4 yıl olup, %65,9'u (n=18) erkektir. Klinik sınıflandırmaya göre yarıdan fazlası (%50,8, n=76) "yüksek" klinik sınıflandırmaya dahil edilmiştir. En sık görülen kronik hastalık "hipertansiyon" (%42,5, n=76) ve en sık görülen semptom "ateş"tir (%57,5, n=103). %82,7'sinde (n=148) yaygın bilgisayarlı tomografi bulguları bulunurken, C-reaktif protein (CPR) pozitiflik oranı %65,4'tür (n=117). Başvuru sırasında, birinci ve üçüncü günler arasında üç kan üre nitrojen, aspartat aminotransferaz, alanin aminotransferaz, CRP ölçümleri arasında istatistiksel olarak anlamlı bir fark tespit edilmiştir.

Sonuç: Favipiravir uygun bir güvenlik profili göstermektedir. Ancak yan etkileri, teratojenitesi, hiperürisemi ve düzeltilmiş QT aralığı uzaması

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Cite this article as: Yılmaz H, Güner AE, Altuntaş M. Results of Favipiravir Combined Treatment in Intensive Care Patients with COVID-19. Bagcilar Med Bull 2021;6(3):339-345

Abstract

Conclusion: Favipiravir demonstrates a proper safety profile. However, its side effects including teratogenicity, hyperuricemia and QTc (corrected QT interval) prolongation have not yet been adequately studied. It may be safe and tolerable in short-term use, but more evidence is needed to assess the longer-term effects of treatment.

Keywords: COVID-19, favipiravir, laboratory findings, side effect, treatment

Öz

henüz yeterince araştırılmamıştır. Kısa süreli kullanımda güvenli ve tolere edilebilir olabilir; ancak tedavinin uzun dönem etkilerini değerlendirmek için daha fazla kanıt gerekmektedir.

Anahtar kelimeler: COVID-19, favipiravir, laboratuvar bulguları, tedavi, yan etkiler

Introduction

In the twenty first century, three new life-threatening diseases caused by coronavirus emerged. These are Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) and the new lung disease Coronavirus disease-2019 (COVID-19) (1). All of them belong to the Coronaviridae family; kind of viruses that possess a positive-sense single-stranded RNA genome. Similar to other RNA viruses, this family is characterized by significant genetic variability and high recombination rate that enable them distributed easily among humans and animals worldwide (2). COVID-19 appeared in Wuhan, China in December 2019. It is a disease caused by the 2019 novel Coronavirus (2019-nCoV) that manifests itself with viral pneumonia in most patients (3). Due to its high infectivity and fatality rate, also the absence of specific medicine for 2019-nCoV, outbreak of the disease has brought heavy burden to the world.

Symptoms in COVID-19 may range from mild illness to acute respiratory distress syndrome. The common characteristics of people with severe disease are showing lymphocytopenia, being old and smoking (4). In addition, in a meta-analysis consisting of 15 studies, it was stated that severe disease was associated with an underlying hypertension (HT), diabetes, and a respiratory or cardiac pathology (5).

So far, there is no treatment protocol and vaccination for COVID-19 with proven safety and efficacy. Today, the main treatments are shaped according to our experiences with similar viruses such as SARS-Cov and MERS-Cov (3). In addition to symptomatic treatments, different treatment methods such as remdesivir, chloroquine and hydroxychloroquine, kaletra, favipiravir, tocilizumab, and stem cell therapy are used (6,7). As the virus causes endothelial dysfunction, procoagulant conditions and renin-angiotensin-aldosterone system imbalance, use of low molecular weight heparin, low dose aspirin, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker in the early period is also recommended (8). Despite all these, there is currently no effective treatment available for coronavirus infections. Hard works have been made to develop vaccines and therapeutic drugs. Preclinical evidence has proven the potential of several countermeasures, yet large scale trials are still needed (2).

Favipiravir, one of the mentioned treatment methods, is a kind of RNA-dependent RNA polymerase inhibitor, blocking RNA virus replication. It is a potential antiviral agent used against SARS-CoV-2 (9). Favipiravir is active against a variety of influenza viruses including A (H1N1) pdm09, A (H5N1) and A (H7N9) avian influenza viruses and has a synergistic effect with oseltamivir (10). It is an approved treatment for influenza. Besides, less studies have been published for favipiravir to treat SARS-CoV-2 compared to remdesivir. Indeed, favipiravir was approved by the National Medical Products Administration of China as the first anti-COVID-19 drug in March 2020, as the clinical trial had demonstrated efficacy with minimal side effects (2). It accelerates clinical recovery by reducing respiratory problems (3). The effective dose of favipiravir used is 1.600 mg twice daily (first day), 600 mg twice daily (days 2-5) and it is not used more than 14 days. However, favipiravir is contraindicated in pregnant women because of teratogenicity and embryotoxicity in animals (10,11). Since the effectiveness and tolerability of hydroxychloroquine in treatment contain some question marks, recently, researchers have started to work mostly on remdesivir and favipiravir (8). In contrast to remdesivir, the studies on favipiravir *in vitro* and *in vivo* are limited. However, there are still three active clinical trials regarding favipiravir that have begun enrolling patients in China (12).

The COVID-19 pandemic stands as a serious health threat to humanity. The data obtained show that the treatment approaches applied especially for patients, who are being treated during the intensive care period, can make serious differences on prognosis. In this study, it was aimed to determine the basic characteristics and changes in laboratory findings of patients who were hospitalized with

the diagnosis of COVID-19 in the intensive care unit of a training and research hospital and underwent treatment protocol containing favipiravir.

Materials and Methods

The study was planned in a retrospective, cross-sectional way. It was carried out with the data of inpatients at the University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital Adult Intensive Care Unit between 01.06.2020 and 30.06.2020. The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital, Turkey with the decision number 2020/0243. In addition, TR Ministry of Health Scientific Research Platform on COVID-19 has also obtained a work permit with the date 05.09.2020 and number T175416.

The inclusion criteria of the study are to have a diagnosis of COVID-19 confirmed by polymerase chain reaction (PCR) test, to be hospitalized in the intensive care unit, to be receiving favipiravir combined therapy and to have access to its data through the automation system. The study included data from 179 patients who met these criteria.

According to literature, the socio-demographic characteristics, some basic characteristics and some laboratory findings of the patients were obtained from the hospital computer records. Clinical status of the patients were classified as mild, moderate and high.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA). Means and standard deviations are given for the variables obtained by measurement, number and percentage distributions for the data obtained by counting. The Friedman test in non-parametric conditions and ANOVA (repeated measure) test for repeated measurements in parametric conditions were used in comparison of admission, 1st day and 3rd day values of laboratory examination results. Statistical significance level was accepted as $p<0.05$ considering the 95% confidence interval and 5% margin of error.

The Shapiro-Wilk test was used to adapt to normal distribution in the evaluation of parametric conditions. It was observed that BUN and procalcitonin 3rd day values did not comply with the normal distribution ($p<0.05$). Therefore, the Friedman test, which is a non-parametric test, was used in the analysis of these values. The ANOVA (repeated measure) test was used for repeated measurements, as the others conformed to the normal distribution. While evaluating the test results, Wilks' lambda p-value was taken into consideration when $p<0.05$ according to Mauchly Sphericity test.

Results

One hundred seventy nine patients were included in the study. The average age of the study group was 60.9±16.4 years and 65.9% (n=118) of them were male. According to the clinical classification, more than half (50.8%, n=91) were included in the ''high'' clinical classification. The most common chronic disease was ''HT'' (42.5%, n=76) and the most common symptom was ''fever'' (57.5%, n=103). While 82.7% (n=148) had widespread computed tomography findings, PCR positivity rate was 65.4% (n=117). The main characteristics of the patients are summarized in the table below (Table 1).

Table 1. Basic characteristics of the patients

	Group with favipiravir in the treatment regimen (n=179)
Gender n (%)	
Female	61 (34.1)
Male	118 (65.9)
Age n (%)	
<65	107 (59.8)
≥65	72 (40.2)
Clinical classification n (%)	
Mild	1 (0.6)
Moderate	87 (48.6)
High	91 (50.8)
Hypertension n (%)	76 (42.5)
Diabetes mellitus n (%)	52 (29.1)
Chronic obst. pul. disease n (%)	15 (8.4)
Asthma n (%)	9 (5.0)
Hearth disease n (%)	42 (23.5)
Cancer n (%)	5 (2.8)
Symptoms n (%)	
Fever	103 (57.5)
Dyspnea	76 (42.5)
Runny nose	4 (2.2)
Pneumonia n (%)	175 (97.8)
Tomography findings n (%)	
Local	22 (12.3)
Common	148 (82.7)
No evidence	9 (5.1)
PCR positivity n (%)	117 (65.4)

PCR: Polymerase chain reaction

Laboratory measurements were carried out on adimission to the intensive care hospitalization, on the 1st day and on the 3rd day.

The values of all patients who were admitted to the intensive care unit (ICU) and treated with favipiravir/favipiravir + tosilizumab given in Table 2. They were compared on the day of admission to the intensive care unit and 1st and 3rd days days of hospitalization and statistically significant difference was found for BUN (p=0.000), AST (p=0.029), ALT (p=0.001), CRP (p=0.001), ferritin (p=0.024) and D-dimer (p=0.000) (Table 2).

AST, ALT and D-dimer values increased in a statistically significant way in patients receiving favipiravir/favipiravir + tosilizumab treatment. It was seen that CRP and ferritin values increased on the 1st day and decreased on the 3rd day (Table 2).

The values of the patients treated with only favipiravir were given in Table 3. The BUN, ALT, CRP and D-dimer values of patients who were admitted to ICU and treated with favipiravir were compared on the day of admisson, day 1 and day 3 and a statistically significant difference was found for BUN (p=0.000), ALT (p=0.000), CRP (p=0.000) and D-dimer (p=0.000)]. ALT and D-dimer values increased significantly while CRP value increased on day 1 and decreased on day 3 (Table 3).

The values of the patients treated with favipiravir/tocilizumab combination were given in Table 4. Creatinine, ALT, CRP, ferritin and D-dimer values were compared on the admission, and days 0 and 3 of hospitalization in patients who were admitted to ICU and treated with combination of favipiravir and tocilizumab, and a statistically significant difference was found for creatinine (p=0.000), ALT (p=0.03), CRP (p=0.004), ferritin (p=0.03) and D-dimer (p=0.01). ALT and ferritin values increased significantly while CRP and D-dimer increased on day 1 and decreased on day 3 (Table 4).

Discussion

In Japan, favipiravir was approved as a stockpile against influenza pandemics and was distributed as an option against for SARS-CoV-2 under government control. Still, the efficacies of antiviral therapies have not been clarified clearly in the course of these patients. However, in the literature, there is a case report that emphasizes recovery two days after favipiravir treatment. This case suggests that favipiravir may be contributed to the amelioration of the lung lesion in COVID-19 (13).

In a large scale study, among the 1.023 deaths, the majority were among patients of ≥60 years of age. The ≥80 age group was characterized by the highest fatality rate (20.3%) among all age groups (14). Relatively fewer cases were reported among young children (0-9 years-old). While more males were affected by the disease, the male-to-female ratio varied between different populations. As the pathogen has been extraordinarily contagious, no deaths have occurred in mild or even severe cases; but the fatality rate reached 49% among patients that were classified as critical cases (14). These findings are compatible with the present study.

Table 2. Comparison of laboratory findings on hospitalization, 1st and 3rd days of treatment (favipiravir/favipiravir+tosiluzimab) in intensive care patients

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	8.03±4.28	8.1±4.22	8.31±4.51	0.270	0.300	0.082	0.159
Lymphocyte	1.29±0.93	1.19±0.84	1.22±0.78	0.590	0.203	0.858	0.433
BUN	42.96±28.77	42.07±33.24	42.71±36.87	0.000	0.006	0.095	0.682
Creatinine	1.33±1.13	1.35±1.33	1.33±1.05	0.110	0.007	0.515	0.522
AST	47.51±151.69	57.97±255.23	63.19±167.83	0.029	0.015	0.020	0.199
ALT	38.51±47.49	43.4±63.79	69.41±17197	0.001	0.081	0.000	0.000
CRP	81.02±74.86	114.9±78.21	89.81±79.5	0.001	0.000	0.269	0.000
Procalcitonin	1.18±3.09	2.12±9.12	2.77±11.36	0.099	0.030	0.388	0.059
Ferritin	1049.46±3642.29	1227.22±3574.8	1177.04±3108.04	0.024	0.000	0.001	0.449
D-dimer	1279.79±2589.74	2057.72±4252.65	2201.09±3693.58	0.000	0.008	0.000	0.019
Fi-O_2	45.7±28.62	53.85±25.91	54.8±26.83	0.680	0.206	0.213	0.445
Pa-O_2	70.44±27.65	68.23±30.24	82.72±24:9	0.480	0.109	0.866	0.088

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

A prospective, multicenter, open-label, randomized superiority trial examined the efficacy of favipiravir versus arbidol for treating COVID-19 (15). There was no difference in the 7-day clinical recovery rate for favipiravir versus arbidol in the overall population. However, this difference existed for a subgroup of non-critical patients without HT or diabetes (15). Three registered clinical trials are planned regarding the use of favipiravir against COVID-19 (16-18). The presented study was performed in an intensive care unit and parallel to the mentioned studies; 42.5% of the patients (n=76) had HT and 29.1% (n=52) had diabetes mellitus.

In the present study, the most common symptom was ''fever'' (57.5%, n=103) and second symptom was dyspnea (42.5%, n=76). In a similar study, the major symptom at the onset of illness was again fever (88.7%) (5). The other symptoms were cough (67.8%), fatigue (38.1%), dyspnea (18.7%), and myalgia (14.9%). Additionally, these symptoms could be followed by sputum production, dizziness, headache, vomiting, abdominal pain, diarrhea, sore throat, nasal congestion and rhinorrhea (5). Differently, in a small study, two patients reported diarrhea, one had liver injury and one had poor diet (19). The recent study from China reported favipiravir had fewer side effects such as diarrhea and transaminitis in non-transplant COVID-19 (20).

There are some studies about the heart related disorders during medical treatment combined with favipiravir. A

Table 3. Comparison of the laboratory findings of favipiravir treatment in hospitalized patients on admission, day 1 and day 3, in intensive care unit

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	7.8±4.22	7.89±4.01	8.12±4.1	0.27	0.48	0.11	0.13
Lymphocyte	1.31±0.95	1.2±0.87	1.25±0.79	0.39	0.10	0.68	0.23
BUN	44.14±30.32	42.92±34.69	43.2±37.42	0.00	0.00	0.06	0.48
Creatinine	1.35±1.21	1.37±1.41	1.36±1.06	0.37	0.04	0.84	0.45
AST	49.67±163.89	61.12±275.89	63.29±181.04	0.23	0.04	0.19	0.60
ALT	38.32±50.78	42.51±67.27	68.03±185.33	0.00	0.33	0.00	0.00
CRP	80.83±73.25	111.68±74.85	85.88±75.68	0.00	0.00	0.69	0.00
Procalcitonin	0.81±1.79	2.28±9.97	3.29±12.65	0.20	0.06	0.27	0.02
Ferritin	1088.98±3916.67	1236.21±3849.44	1169.39±3345.06	0.10	0.00	0.02	0.66
D-dimer	1374.14±2774.97	1822.96±3204.11	2035.12±3405.97	0.00	0.06	0.00	0.02
Fi-O_2	45.73±29.09	53.28±26.55	55.31±28.13	0.79	0.40	0.33	0.68
Pa-O_2	70.67±28.61	71.89±31.1	86.64±26.32	0.74	0.18	0.87	0.40

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 4. Comparison of laboratory findings on admission and days 1 and 3 of hospitalization in intensive care patients who received favipiravir and tosilizumab treatment together

Laboratory findings	Day 0	Day 1	Day 3	p	Days 0/1	Days 0/3	Days 1/3
Leukocyte	9.64±4.46	10.71±5.89	10.41±5.98	0.59	0.360	0.465	0.897
Lymphocyte	1.17±0.73	1.29±0.69	1.12±0.7	0.61	0.505	0.623	0317
BUN	37.71±15.68	38.06±16.78	38.29±19.62	0.98	0.783	0.906	0.653
Creatinine	1.21±0.33	1.06±0.24	1±0	0.00	0.018	0.012	0.317
AST	40.06±17.94	49.29±25.32	70.06±54.12	0.00	0.099	0.002	0.058
ALT	43.06±19.13	60.47±41.65	76.88±40.66	0.03	0.019	0.003	0.193
CRP	96.07±89.2	161.24±94.3	144.12±95.35	0.01	0.004	0.028	0.523
Procalcitonin	2.67±7.01	1±2	0.64±1.34	0.43	0.225	0.893	0.317
Ferritin	1121.31±1220.96	1499.67±1120.54	1551.25±1524.33	0.03	0.310	0.038	0.331
D-dimer	840.21±724.47	4877.38±9598.96	4230.18±5685.62	0.01	0.017	0.003	0.679
Fi-O_2	40.5±27.58	71.25±8.54	62.5±9.57	0.36	0.317	0.542	0.180
Pa-O_2	67±0	51.75±21.79	69±13.78	0.37	0.572	0.624	0.068

*Hosp. means hospitalization, CRP: C-reactive proetin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

study that reports prolonged QT interval due to favipiravir has been encountered (19). In another study, two patients who were followed up in the ICU with favipiravir combined treatment developed ventricular tachycardia; both had increased T peak to T end (Tp-e) interval and Tp-e/corrected QT interval (QTc) ratio despite normal QTc intervals before the treatment (21). In the present study 23.5% (n=42) of the patients had heart disease during the hospitalization but no heart related problem was detected during follow-up.

In the presented study, no significant adverse reactions were noted related to favipiravir or favipiravir/ticilizumab combined treatment group. In another study, favipiravir had significantly fewer adverse effects than the lopinavir/ritonavir group (22). Similarly, a trial conducted on patients with COVID-19 indicated better results in patients treated with favipiravir than the group treated with lopinavir/ritonavir. Additionally, less side effects were noted in the treatment group (20).

Studies have reported that lymphocytopenia occurs in severe types of COVID-19 (23). Again, lymphocytopenia and hyponatremia were detected in a patient who recovered after treatment for COVID-19 pneumonia (24). In a Japanese clinical trial with 501 patients, the main adverse reactions were detected as rising uric acid (n=24, 4.79%), diarrhea (n=24, 4.79%), neutropenia (n=9, 1.80%), increased AST (n=9, 1.80%) and increased ALT (n=8, 1.60%) (25). In a trial of favipiravir with patients with COVID-19, the most common adverse events were liver enzyme abnormalities, psychiatric, gastrointestinal symptoms and serum uric acid elevations (26). The overall adverse reactions were mild symptoms, but pregnant women should not be treated with favipiravir (25). In the presented study, serum uric acid levels were not evaluated but liver enzyme abnormalities were detected in parallel to the literature.

In a prospective, single-arm and multicenter study conducted in Italy with 63 patients with severe COVID-19, a decrease in CRP, ferritin and D-dimer levels was observed after tocilizumab treatment (27). In our study, when the laboratory values of the 3rd day were examined, it was observed that the D-dimer level increased in patients who received only favipiravir treatment, while the level of D-dimer decreased in those who received favipiravir+tocilizumab treatment. In a study conducted with 23 patients who had severe COVID-19 and were hospitalized in ICU in Turkey, it was shown that CRP and ferritin values decreased while D-dimer values increased after tocilizumab treatment (27).

Conclusion

Favipiravir demonstrates a proper safety profile. However, its side effects including teratogenicity, hyperuricemia and QTc prolongation have not yet been adequately studied. It may be safe and tolerable in short-term use, but more evidence is needed to assess the longer-term effects of treatment.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Göztepe Training and Research Hospital, Turkey with the decision number 2020/0243.

Informed Consent: The study was designed retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Y., Desing: H.Y., Data Collection or Processing: H.Y., Analysis or Interpretation: H.Y., M.A., Drafting Manuscript: H.Y., A.E.G., Critical Revision of Manuscript: H.Y., A.E.G., Final Approval and Accountability: H.Y., A.E.G., M.A., Technical of Material Support: H.Y., A.E.G., M.A., Supervision: H.Y., A.E.G., M.A.

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

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

References

1. Tsitoura E, Bibaki E, Bolaki M, Vasarmidi E, Trachalaki A, Symvoulakis EK, et al. Treatment strategies to fight the new coronavirus SARS-CoV: A challenge for a Rubik's Cube solver. Exp Ther Med 2020;20(1):147-150.
2. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT, et al. A review of SARS-CoV-2 and the ongoing clinical trials. Int J Mol Sci 2020;21(7):2657.
3. Yousefi B, Valizadeh S, Ghaffari H, Vahedi A, Karbalaei M, Eslami M. A global treatments for coronaviruses including COVID-19. J Cell Physiol 2020;235(12):9133-9142.
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-1720.
5. Matsushita K, Ding N, Kou M, Hu X, Chen M, Gao Y, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: a systematic review and meta-analysis. Glob Heart 2020;15(1):64.
6. INSERM: Launch of a European clinical trial against COVID-19 (press release). Available from http:// https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7281719/Accessed March 22, 2020.

7. World Health Organization: Launch of SOLIDARITY trial (press release). Accessed March 18, 2020.

8. Remport A, Gerlei Z, Creprekal O, Wagner L, Foldes K, Marton A, et al. Guidance on the special care of liver or kidney transplant recipients diagnosed with Covid-19. Orv Hetil 2020;161(32):1310-1321.

9. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19) Drug Discov Ther 2020;14(1):58-60.

10. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Research 2018;153:85–94.

11. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 2020;209:107512.

12. Duan Y. Advance of promising targets and agents against COVID-19 in China. Drup Discov Today 2020;25(5):810-812.

13. Takahashi N, Abe R, Hattori N, Taniguchi T, Igari H, Nakada T. Clinical course of a critically ill patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). J Artif Organs 2020;23(4):397-400.

14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395(10223):507-513.

15. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020.03.17.20037432 doi: 10.1101/2020.03.17.20037432

16. ClinicalTrials.gov. Various combination of protease inhibitors oseltamivir favipiravir hydroxychloroquine for treatment of COVID-19: a randomized control trial (THDMS-COVID-19). Available from: https://clinicaltrials.gov/ct2/show/NCT04303299. Accessed March 23, 2020.

17. ClinicalTrials.gov. Favipiravir combined with tocilizumab in the treatment of corona virus disease. Available from: https://clinicaltrials.gov/ct2/show/NCT04310228.Accessed March 23, 2020.

18. Newswire PR: Sihuan pharmaceutical announces clinical research of favipiravir, co-developed with the Academy of Military Medical Sciences of the People's Liberation Army, has commenced. Sihuan Pharmaceutical Holdings Group Ltd, 2020. Available from: https://en.prnasia.com/releases/apac/sihuan-pharmaceutical-announces-clinical-research-of-favipiravir-co-developed-with-the-academy-of-military-medical-sciences-of-the-people-s-liberation-army-has-commenced-273880.shtml. Accessed March 26, 2020.

19. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing) 2020;6(10):1192-1198.

20. Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E; INMI Ebola Team. QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. PLoS Negl Trop Dis 2017;11(12):e0006034. doi: 10.1371/journal.pntd.0006034.

21. Yenerçağ M, Arslan U, Doğduş M, Günal Ö, Öztürk ÇE, Aksan G, et al. Evaluation of electrocardiographic ventricular repolarization variables in patients with newly diagnosed COVID-19. J Electrocardiol 2020;62:5-9.

22. News. Last Accesed Date: 22.02.2020. Available from: http://www.szdsyy.com/News/0a6c1e58-e3d0-4cd1-867a-d5524bc59cd6.html. (Chinese).

23. Antonio R, Silvia M. Immunosuppression drug-related and clinical manifestation of coronavirus disease 2019: A therapeutical hypothesis. Am J Transplant 2020;20(7):1947-1948.

24. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? Am J Transplant 2020;20(7):1875-1878.

25. A Pharmacokinetics study of favipiravir in patients with severe influenza. Available from: https://clinicaltrials.gov/ct2/show/NCT03394209. Accessed March 26, 2020.

26. Sciascia S, Apra F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19. Clin Exp Rheumatol 2020;38(3):529-532.

27. Çiyilitepe F, Saraçoğlu A, Bilir Y, Akova Deniz E, Bombacı E, Saraçoğlu KT. The role of IL-6 receptor inhibitor treatment in critical patient monitoring with COVID-19. Signa Vitae 2021;17(3):174-180.

CASE REPORT

Bagcilar Med Bull 2021;6(3):346-349
DOI: 10.4274/BMB.galenos.2021.02.021

Remission of a Pregnant Woman with Persistent Hyperemesis Gravidarum with Corticosteroid Treatment

Dirençli Hiperemezis Gravidarumun Kortikosteroid ile Remisyonu

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Abstract

Nausea and vomiting affect more than 50% of pregnancies. It presents a broad spectrum of symptoms ranging from mild symptoms to severe weight loss and that may affect daily activities. Hyperemesis gravidarum is a severe pathologic form of nausea and vomiting of pregnancy characterized by a greater than 5% loss of weight and unexplained ketonuria. Hyperemesis gravidarum affects approximately 0.5% of pregnancies. The pathogenesis of hyperemesis gravidarum is not exactly known but multifactorial. Previous pregnancy history, low body mass index, maternal inheritance, maternal mood disorders are thought to be associated with. Other causes of nausea and vomiting, such as gastrointestinal tract, genitourinary system, central nervous system, toxic metabolism, must be ruled out. The risk factors include family history, obstetric history, molar pregnancy, multiple pregnancy, nulliparity, female fetus, hyperthyroidism, diabetes, asthma, depression, peptic ulcer or other gastrointestinal disorders. Severe symptoms affect daily activities, cause anxiety, and sometimes may even lead to the termination of pregnancy and cancellation of future pregnancy plans. The symptoms that started in the first trimester of pregnancy decrease and recover to starting of the second trimester. In our case, we will discuss the successful treatment of severe form of hyperemesis gravidarum with parenteral and oral corticosteroids atypically in the second trimester.

Keywords: Corticosteroids, hyperemesis gravidarum, *Helicobacter pylori*

Öz

Bulantı ve kusma, gebeliklerin %50'sinden fazlasını etkiler. Gebelik bulantı ve kusmaları hafif semptomlardan şiddetli kilo kaybına kadar değişen ve günlük aktiviteleri etkileyebilecek geniş bir semptom yelpazesi sunar.

Hiperemezis gravidarum, gebelikte bulantı ve kusmanın şiddetli patolojik bir formudur ve %5'ten fazla kilo kaybı ve açıklanamayan ketonüri ile karakterizedir. Hiperemezis gravidarum, gebeliklerin yaklaşık %0,5'ini etkiler. Hiperemezis gravidarumun patogenezi tam olarak bilinmemekle birlikte multifaktöriyeldir. Önceki gebelik öyküsü, düşük vücut kitle indeksi, annenin genetik öyküsü, anneden gelen duygudurum bozuklukları ile ilişkili olduğu düşünülmektedir. Gastrointestinal sistem, genitoüriner sistem, merkezi sinir sistemi gibi diğer bulantı ve kusma nedenleri ekarte edilmelidir. Risk faktörleri arasında aile öyküsü, obstetrik öykü, molar gebelik, çoğul gebelik, nulliparite, dişi fetüs, hipertiroidizm, diyabet, astım, depresyon, peptik ülser veya diğer gastrointestinal bozukluklar yer alır. Şiddetli semptomlar günlük aktiviteleri etkiler, kaygıya neden olur ve hatta bazen gebeliğin sonlandırılmasına ve gelecekteki gebelik planlarının iptal edilmesine neden olabilir. Gebeliğin ilk trimesterında başlayan semptomlar azalır ve ikinci trimesterın başlangıcına kadar düzelir. Olgumuzda atipik olarak ikinci trimesterde görülen şiddetli hiperemezis gravidarumun parenteral ve oral kortikosteroidlerle başarılı tedavisini tartışacağız.

Anahtar kelimeler: Hiperemezis gravidarum, *Helikobakter pilori*, kortikosteroid

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Cite this article as: Özcan Aydın T, Aybek ÖY, Su SN, Alptekin Karapolat T, Yesiralioğlu Ş. Remission of a Pregnant Woman with Persistent Hyperemesis Gravidarum with Corticosteroid Treatment. Bagcilar Med Bull 2021;6(3):346-349

Introduction

Nausea and vomiting affect more than 50% of pregnancies. It presents a broad spectrum of symptoms ranging from mild symptoms to severe weight loss, which may affect daily activities. Hyperemesis gravidarum is a severe pathologic form of nausea and vomiting of pregnancy, characterized by a greater than 5% loss of weight and unexplained ketonuria (1). Hyperemesis gravidarum affects approximately 0.5% of pregnancies (2). The pathogenesis of hyperemesis gravidarum is not exactly known but multifactorial. Previous pregnancy history, low body mass index, maternal inheritance, and maternal mood disorders are thought to be associated with it (3). Other causes of nausea and vomiting, such as gastrointestinal tract, genitourinary system, central nervous system, and toxic metabolism, must be ruled out (4). The risk factors include family history, obstetric history, molar pregnancy, multiple pregnancy, nulliparity, female fetus, hyperthyroidism, diabetes, asthma, depression, peptic ulcer or other gastrointestinal disorders (5). Severe symptoms affect daily activities, cause anxiety, and sometimes may even lead to the termination of pregnancy and cancellation of future pregnancy plans (6,7). The symptoms starting in the first trimester of pregnancy decrease and recover until the start of the second trimester. In our case, we will discuss the successful treatment of severe form of hyperemesis gravidarum with parenteral and oral corticosteroids atypical in the second trimester.

Case Report

A 21-year-old primigravid who had 18 weeks and 2 days pregnancy from her last period was admitted to the obstetrics and gynecology outpatient clinic with nausea and vomiting. In the detailed history, it was learned that the patient had no other known disease except gastritis, and had undergone endoscopy before pregnancy and had received antibiotherapy for *Helicobacter pylori* infection. She stated that the nausea and vomiting symptoms had started at the 6th week of pregnancy, showed continuity during the day, and awakened her from the night sleep. She had not benefited from the initial treatment and she had received medical treatment with hospitalization twice. Biopsies taken from the stomach antrum in the evaluation of endoscopy performed in the first trimester of pregnancy were reported as chronic antral gastritis but not *Helicobacter pylori* infection. The patient had been 45 kg at the beginning of pregnancy but she was 39 kg at our first examination. In the examination of the patient, the mucous membranes were dehydrated and pale, blood pressure was 100/70 mmHg, heart rate was 80/min, and body temperature was 36.4 °C. There was no abdominal sensitivity or contraction of uterus. She did not describe vaginal bleeding or premature rupture of membranes. In the ultrasonography evaluation, single, live fetus with measurements compatible with gestational week was observed. The placenta was grade 1 degree, natural, and located in the anterior of the uterus. The laboratory examinations of the patient were as follows: Hemoglobin: 11 g/dL, hematocrit: 30.8%, white blood cells: 8.98 m/uL, aspartate transaminase: 22 u/L, alanine transaminase: 13 u/L thyroid-stimulating hormone: 0.66 miu/L, free t3: 3.41 nmol/L, free t4: 0.94 nmol/L, and ketones 2+ in urinalysis. She stated that she had metoclopramide (metpamid® 10 mg once a day peroral), ginger extract (emetium® 200 mg twice a day peroral), trimetobenzamide hydrochloride (emedur® twice a day peroral) treatments and the last step treatment as ondansetron (zofran® 8 mg 3 times a day peroral) but she did not benefit any of them and hospitalized to our obstetrics and gynecology clinic. The oral intake of the patient was restricted and parenteral treatment was started. 3.000 cc balanced fluid per day, (1.000 cc lactated ringer, 1.000 cc 0.9% isotonic sodium chloride, 1.000 cc 10% dextrose) which included dekspanthenol (beheptal® 3 times a day), ascorbic acid (acmel® 3 times a day), metoclopramide (metpamid® 3 times a day), ranitidine (ragasit® 3 times a day) was applied as an initial treatment. When the patient did not benefit from these treatments, ondansetron (zofran® 8 mg intravenous once a day) and sodium alginate (gaviscon® 3 times a day peroral) were added to the current treatment. On the seventh day of ondansetron treatment, the patient's complaints continued and weight gain was not observed so we started glucocorticoid treatment. 16 mg methylprednisolone (prednol® 3 times a day intravenously) was given intravenously on the first two days of treatment and continued peroral. Oral treatment was started with 32 mg methylprednisolone and reduced to half-dose every two days and adjusted to 4 mg at the end of the first week. A dramatic regression of nausea and vomiting symptoms, weight gain and improvement in laboratory parameters were observed since corticosteroid treatment was initiated, so the patient was discharged with 4 mg oral steroid treatment in the second week of the hospitalization. The patient was 47 kg at discharge and she tolerated oral intake. 4 mg of oral steroid treatment was continued for one week and steroid treatment was terminated due to the obvious clinical and laboratory improvement.

Finally, she came with labor contractions and had 6 cm cervical dilation and 70% effacement in her vaginal examination, and was admitted for vaginal delivery in 37 weeks and 4 days of pregnancy. A female 2.980 gr baby, who had 9 APGAR scores at the first minute of birth and 10

APGAR scores at the fifth minute of birth, was born. The baby was examined at the age of one and her development was normal.

Discussion

Nausea and vomiting in pregnancy or severe form, which is hyperemesis gravidarum, is a clinical description without definitive diagnostic criteria. Epidemiology is unknown but multifactorial. Patients who are younger and have first pregnancy are more affected than older and multiparous patients, but there are no exact data (8). Risk factors include a history of hyperemesis in previous pregnancy, gastrointestinal diseases, history of migraine, molar pregnancy, and female fetus. Genetic factors also play a major role. The patients whose mother and sister are affected have excess risk (9). Considering the risk factors, our patient's history of *Helicobacter pylori* infection and gastritis warns us to see the severe form of nausea and vomiting of pregnancy.

The symptoms of hyperemesis gravidarum start at gestational weeks of 5-6, peak at 9th week, and decrease at weeks of 16-20. 15-20% of the patients can remain symptomatic until third trimester and rarely 5% until the birth (10-12). The symptoms of our patient started typically at week 6, and intensified and persisted until the 18th week of gestation. The pathogenesis of the disease is not known exactly but hormonal changes and gastrointestinal diseases are responsible. Many women with *Helicobacter pylori* infection do not develop severe nausea, but there are studies which take place in literature, showing that this infection is associated with hyperemesis. In the meta-analysis of 26 epidemiological studies published in 2014, it was found that Helicobacter pylori infection was significantly associated with nausea and vomiting and hyperemesis gravidarum compared to the asymptomatic control group (13). Our patient's medical history revealed endoscopic biopsy due to dyspeptic symptoms and *Helicobacter pylori* infection was detected. Although eradication has been achieved with antibiotherapy, recurrent complaints of the patient support the role of gastrointestinal system diseases in the underlying pathogenesis of resistant hyperemesis gravidarum. Nausea of pregnancy and hyperemesis gravidarum treatment is shaped according to the clinical status of the patient. Initial treatment approach includes diet and lifestyle change in patients with no symptoms of hypovolemia, ketonuria, electrolyte imbalance only with symptoms of nausea; and patients should avoid situations that trigger nausea. In patients with mild symptoms, ginger and/or pyridoxine can be used, and if symptoms persist, an antihistaminic group may be added to the treatment. Metoclopramide, promethazine, and prochlorperazine are other treatment options. Ondansetron can be given either orally or parenterally to resistant cases. Many patients benefit from treatment at this stage. Although a drug is used for a week and clinical symptoms do not improve, another drug group should be added (14). A randomized controlled trial of ondansetron showed a significant reduction in symptoms of nausea and vomiting compared to the combination of doxylamine and pyridoxine (15). In another randomized study, ondansetron has been shown to be effective in vomiting compared to metoclopramide but not to reduce the symptoms of nausea (16). In the studies performed, there was no evidence that ondansetron increased congenital malformations in early pregnancy, but in a few studies, ondansetron was associated with cardiovascular malformation and cleft palate (17). According to the stepwise treatment approach, we performed primarily lifestyle change and oral treatment to our patient. Ondansetron was given as the last step of oral treatment; however, with the increase in the severity of the symptoms including weight loss, laboratory parameters deterioration and difficult total oral intake, she was hospitalized for parenteral treatment. At this stage of treatment, oral intake of the patient who does not benefit from oral pharmacotherapy should be restricted, electrolyte imbalance and ketonuria should be followed. In addition to intravenous hydration and pharmacotherapy, thiamine (vitamin B1) should be given to prevent Wernicke's encephalopathy. We restricted oral intake of the patient and used intravenous hydration, vitamin B complex, intravenous metoclopramide and ondansetron treatments during the hospitalization. In spite of all these treatments, there was no regression in the symptoms and no improvement in laboratory findings and the patient was started on corticosteroids.

Although the mechanism of action is not understood, it is known that corticosteroid is used as an effective antiemetic agent in oncology patients. Several previous studies have reported successful responses in pregnant women, too. However, the studies on this subject are not strong. In a placebo-controlled randomized study of 126 women, there are no side effects on pregnant women and neonates using oral and parenteral corticosteroid therapy in hyperemesis gravidarum. In severe hyperemesis and placebo group study of 110 women, the hospitalization rate of women who used glucocorticoid was similar to the placebo group (17). According to a systematic review of 3 randomized clinical trials by McParlin et al. (18), patients who used glucocorticoid with placebo, glucocorticoid with promethazine or glucocorticoid with metoclopramide were compared and patients were reported to benefit from glucocorticoid. Symptoms were regressed with glucocorticoid in resistant hyperemesis gravidarum (18). It

has been shown to be associated with a slight increase in the risk of cleft palate before the 10th gestational week on glucocorticoid use. Therefore, the use of glucocorticoids in the first trimester should be avoided (19,20). After intravenous administration of glucocorticoids, oral form should be given and the treatment should be decreased and stopped.

Conclusion

Nausea of pregnancy and hyperemesis gravidarum are one of the most important diseases that can affect the pregnant women, limit their daily activities, and cause emotional and psychologic problems. In untreated cases, it may lead to general condition disorder due to deterioration in laboratory parameters such as electrolyte imbalance, even maternal and fetal death. There are various oral and parenteral pharmacological agents that are used in the treatment of hyperemesis gravidarum. Rarely, patients do not benefit from standard treatment. Short-term corticosteroid therapy can be used in resistant cases of hyperemesis gravidarum. Antenatal use of corticosteroids has been reported as safe after palate formation in pregnancies older than 10 weeks. Patients with severe hyperemesis gravidarum have a dramatic improvement in clinical and laboratory parameters with oral corticosteroid treatment following parenteral treatment.

Ethic

Informed Consent: Only consent of patient has taken because of case report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: T.Ö.A., Ö.Y.A., S.N.S., T.A.K., Ş.Y., Design: T.Ö.A., Ö.Y.A., S.N.S., T.A.K., Ş.Y., Critical Review of the Article: T.Ö.A., Ö.Y.A., S.N.S., T.A.K., Ş.Y., Writing: T.Ö.A., Ö.Y.A., S.N.S., T.A.K., Ş.Y.

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

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

References

1. Cappell MS. Obstetrics: normal and problem pregnancies, Chapter 48. Philadelphia: Elseiver; 2017:1012-1029.
2. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. Gastroenterol Clin North Am 2003;32(1):201-234, vi.
3. McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. Int J Womens Health 2014;6:719-725.
4. Campbell K, Rowe H, Azzam H, Lane CA. The Management of Nausea and Vomiting of Pregnancy. JGOC 2016;9(1):98-112.
5. Gabra A. Risk Factors of Hyperemesis Gravidarum: Review Article. Health Sci J 2018;12(6):603.
6. Tan A, Lowe S, Henry A. Nausea and vomiting of pregnancy: Effects on quality of life and day-to-day function. Aust N Z J Obstet Gynaecol 2018;58(3):278-290.
7. Heitmann K, Nordeng H, Havnen GC, Solheimsnes A, Holst L. The burden of nausea and vomiting during pregnancy: severe impacts on quality of life, daily life functioning and willingness to become pregnant again - results from a cross-sectional study. BMC Pregnancy Childbirth 2017;17(1):75.
8. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol 1985;66(5):612-616.
9. Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, et al. Familial aggregation of hyperemesis gravidarum. Am J Obstet Gynecol 2011;204(3):230.e1-e7. doi: 10.1016/j.ajog.2010.09.018.
10. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43(371):245-248. Erratum in: Br J Gen Pract 1993;43(373):325.
11. Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am 2008;35(3):401-417.
12. Fell DB, Dodds L, Joseph KS, Allen VM, Butler B. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. Obstet Gynecol 2006;107(2 Pt 1):277-284.
13. Niemeijer MN, Grooten IJ, Vos N, Bais JM, van der Post JA, Mol BW, et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol 2014;211(2):150.e1-e15. doi: 10.1016/j.ajog.2014.02.012
14. Smith AJ, Fox KA, Clark SM, Treatment and outcome of nausea and vomiting of pregnancy, Up to Date, aug, 2021, https//https://www.uptodate.com/contents/nausea-and-vomiting-of-pregnancy-treatment-and-outcome.
15. Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstet Gynecol 2014;124(4):735-742.
16. Kashifard M, Basirat Z, Kashifard M, Golsorkhtabar-Amiri M, Moghaddamnia A. Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study. Clin Exp Obstet Gynecol 2013;40(1):127-130.
17. Yost NP, McIntire DD, Wians FH Jr, Ramin SM, Balko JA, Leveno KJ. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. Obstet Gynecol 2003;102(6):1250-1254.
18. McParlin C, O'Donnell A, Robson SC, Beyer F, Moloney E, Bryant A, et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review. JAMA 2016;316(13):1392-1401.
19. Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, et al. Update on new developments in the study of human teratogens. Teratology 2002;65(4):153-161.
20. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999;86(3):242-244.

CASE REPORT

Bagcilar Med Bull 2021;6(3):350-354
DOI: 10.4274/BMB.galenos.2021.05.067

A COVID-19-Related Kawasaki Disease: Our First Multi-system Inflammatory Syndrome in Children Case

COVID-19 İlişkili Kawasaki Hastalığı: İlk Çocukluk Çağı Multisistem Enflamatuvar Sendrom Tanılı Olgumuz

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Abstract

A new type of coronavirus disease-2019 (COVID-19) epidemic, which started in the last months of 2019, has spread rapidly all over the world and caused many deaths, especially in adults. Recently, a syndromic condition caused by the hyperinflammatory response that is thought to be due to this new pandemic coronavirus factor has been identified, especially in the childhood age group. It has been stated that this response is particularly similar to Kawasaki disease and can manifest itself with multiorgan involvement. This new clinical condition was defined as pediatric inflammatory multi-system syndrome temporally associated with severe acute respiratory syndrome-coronavirus 2 or multi-system inflammatory syndrome in children associated with COVID-19.

In this case presentation, a nine-year-old male patient was admitted to our emergency department with complaints similar to ones in Kawasaki disease. The patient was followed up in our pediatric intensive care unit due to hypotension and myocarditis, as well as likely macrophage activation syndrome and simultaneous COVID-19 positivity. For Kawasaki disease, intravenous immunoglobulin, acetylsalicylic acid, low molecular weight heparin and methylprednisolone; for myocarditis, enalapril and furosemide; and for COVID-19, favipiravir was administered to the patient. We would like to present our case to exemplify clinicians dealing with pediatric patients and to assist in easier recognition, prevention, diagnosis and treatment of COVID-19 in all children worldwide.

Keywords: Children, COVID-19, multi-system inflammatory syndrome

Öz

2019 yılının son aylarında başlayan yeni tip koronavirüs hastalığı-2019 (COVID-19) salgını tüm dünyada hızla yayıldı ve erişkinler başta olmak üzere çok sayıda ölüme yol açtı. Son zamanlarda ise özellikle çocuk yaş grubunda bu yeni pandemik koronavirüs etkenine bağlı olduğu düşünülen hiperenflamatuvar yanıtın neden olduğu sendromik bir durum tanımlandı. Bu yanıtın özellikle Kawasaki hastalığına benzediği ve multiorgan tutulumuyla kendini gösterebileceği belirtildi. Bu yeni klinik durum, geçici olarak ağır akut solunum sıkıntısı sendromu-koronavirüs 2 ile ilişkili pediyatrik enflamatuvar multi-sistem sendrom veya COVID-19 ile ilişkili çocukluk çağı multi-sistem enflamatuvar sendrom olarak tanımlandı. Bu sunumda acil servisimize Kawasaki hastalığına benzer şikayetlerle başvuran dokuz yaşında erkek bir hasta anlatıldı. Hasta hipotansiyon, myokardit, olası makrofaj aktivasyon sendromu ve eş zamanlı COVID-19 pozitifliği nedeniyle çocuk yoğun bakım ünitemizde takip edildi. Kawasaki hastalığı için intravenöz immünoglobülin, asetilsalisilik asit, düşük molekül ağırlıklı heparin ve metilprednisolon, myokardit için enalapril ve furosemid, COVID-19 için favipiravir kullanıldı. Olgumuzu çocuk hastalarla uğraşan klinisyenlere örnek teşkil edebilmek ve dünya çapındaki tüm çocuklarda COVID-19'un daha kolay tanınması, önlenmesi, teşhisi ve tedavisi için yardımcı olabilmek adına sunmak istedik.

Anahtar kelimeler: Çocuk, COVID-19, multi-sistem enflamatuvar sendrom

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Cite this article as: Koçoğlu Barlas Ü, Onan SH, Erol M. A COVID-19-Related Kawasaki Disease: Our First Multi-system Inflammatory Syndrome in Children Case. Bagcilar Med Bull 2021;6(3):350-354

Introduction

Cases of Kawasaki disease (KD) or cases with Kawasaki-like clinical manifestations, which have recently been accompanied by the new type of coronavirus [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), coronavirus disease-2019 (COVID-19)], are gradually emerging (1). In this case presentation, we wanted to present incomplete KD (IKD) due to the progression of hypotension, myocarditis and macrophage activation syndrome (MAS), and simultaneous COVID-19 positivity was detected, which was treated successfully.

Case Report

A nine-year-old male patient was admitted to the pediatric emergency department with a five-day history of fever, vomiting, diarrhea, headache and abdominal pain. In his first examination, he was conscious and orientated and he had bilateral conjunctival injection, changes in lips and oral mucosa, and strawberry tongue. Scrotal edema was detected in the urogenital system examination. The first examinations of the patient conducted in the emergency room are shown in Table 1, in the second column (1st day). Echocardiography performed on the admission was normal. The examinations of the patient, who was hospitalized and followed up in our service, are shown in Table 1, in the third column (2nd day). Ceftriaxone was started due to the possibility of urinary tract infection and a pediatric surgery opinion was requested for acute appendicitis. On the second day of hospitalization, fever and diarrhea complaints continued at the same intensity and COVID-19 reverse transcription polymerase chain reaction (RT-PCR) was negative. Antibiotic therapy was replaced by vancomycin and meropenem due to no improvement in the clinical findings of the patient. Moreover, physical examination, as well as accompanying laboratory findings including elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin levels, neutrophil predominance in blood tests, IKD, was considered, and acetylsalicylic acid (ASA) treatment at a dose of 80 mg/kg/day with intravenous immunoglobulin (IVIG) at a dose of 2 g/kg was started. On the third day of his hospitalization, fever and diarrhea complaints continued, and were accompanied by hypotension (81/33 mmHg), hyperferritinemia, hypertriglyceridemia and thrombocytopenia (Table 1, fourth column, 3rd day), and the patient was hospitalized in pediatric intensive care unit (PICU) with the consideration of possibility of MAS.

The examinations performed on the first day of PICU monitoring are shown in Table 1, in the fifth column (4th day). Noradrenaline infusion was started at a dose of 0.05 µg/kg/min with human albumin at a dose of 1 g/kg. The second IVIG treatment was given 36 hours after the first IVIG treatment as the fever continued. The second echocardiography performed on the eighth day of the onset of complaints revealed mild dilatation in the left ventricle and decreased systolic functions, mitral valve insufficiency, hyperechogenicity and dilatation in the left coronary artery wall, and minimal pericardial effusion (Image 1, 2). Due to the current physical examination findings, echocardiographic findings, laboratory findings [(N-terminal pro-B-type natriuretic peptide (NT-proBNP) 6.950 ng/L (normal: 0-133 ng/L), troponin I 24.5 pg/mL (normal: 0-19.8 pg/mL)] and hypotension of the patient, evaluated as KD shock syndrome (KDSS) and myocarditis, ASA treatment was continued and furosemide, enalapril and low-molecular weight heparin were added to the treatment. The patient was positive for COVID-19 IgM and IgG, for

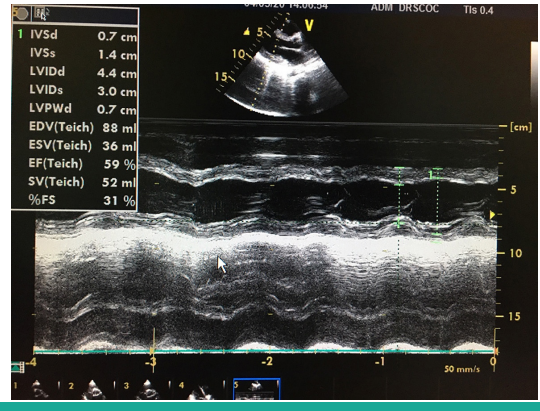

Image 1. Decreased systolic functions in echocardiography of the patient

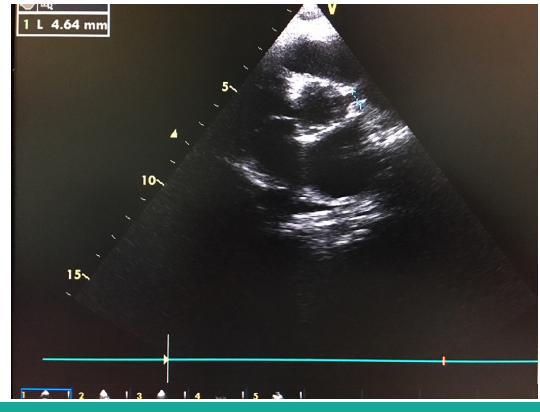

Image 2. Minimal pericardial effusion in echocardiography of the patient

which the test kit used in our hospital is based on the lateral flow immunochromatographic test for COVID-19 IgM and IgG antibodies. On the fourth day of intensive care follow-up [laboratory values are shown in Table 1, in the sixth column (7th day)], methylprednisolone at a dose of 2 mg/kg/day and favipiravir (FPV) were added to the treatment schedule because, 36 hours after the second IVIG treatment, there was no reduction in fever and there was an active left ventricular dysfunction. The patient did not need inotropes three days after hospitalization in PICU, there was no fever after the second IVIG treatment, the complaint of diarrhea was reduced and ceased. In the third echocardiography, regression in left ventricular dilation with cardiac functions within normal limits, and minimal mitral valve failure were observed as well as regression in the previous dilation of left coronary artery wall. He was discharged on the 13th day of hospitalization. Laboratory parameters examined before discharge are shown in Table 1, in the last column (13rd day).

Table 1. The patient's laboratory findings

	1st day	2nd day	3rd day	4th day	7th day	13th day
WBC	13.25	8.45	7.91	9.28	9.38	8.30
Neu	12.05	7.20	5.88	6.72	4.45	3.70
Lym	0.60	0.50	1.03	1.04	2.27	3.57
Hgb	12.60	11.30	9.80	9.40	9.00	9.70
Htc	36.10	33.50	28.00	27.30	26.60	30.60
Plt	180	161	146	172	275	475
ESR	-	33	-	52	49	-
CRP	154.79	114.61	-	91.9	20.87	3.18
PCT	-	31.53	29.80	20.90	1.49	0.09
Ferritin	-	-	1500	1396.9	397.7	380.8
Triglyceride	-	-	300	-	286	-
Fibrinogen	-	-	624	398	335	-
Na	123	125	127	131	134	134
Albumin	3.21	2.96	2	2.36	-	2.72
IL-6	-	-	-	-	24	2
D-dimer	-	0.11	-	3.37	-	2.28
NT-proBNP	-	6.410	-	-	6.950	60

WBC: White blood cell (normal: 4.31-11.00x10^3/uL), Neu: Neutrophil count (normal: 1.63-7.55x103/uL), Lym: Lymphocyte count (normal: 0.97-3.96x10^3/uL), Hgb: Hemoglobin (normal: 10.7-13.4 g/dL), Htc: Hematocrit (normal: 32.2%-39.8), Plt: Platelet count (normal: 206-369x10^3/uL), ESR: Erythrocyte sedimentation rate (normal: 0.00-15.00 mm), CRP: C-reactive protein (normal: 0-5 mg/L), PCT: Procalcitonin (normal: 0.02-0.5 ng/mL), Ferritin (normal: 23.9-336.2 ng/mL), Triglyceride (normal: 0-150 mg/dL), Fibrinogen (normal: 200-400 mg/dL), Na: Sodium (normal: 136-146 mmol/L), Albumin (normal: 3.5-5.2 g/dL), IL-6: Interleukin 6 (normal: <7 pg/mL), D-dimer (normal: 0.00-0.50 ug FEU/mL), NT-proBNP: N-terminal pro-B-type natriuretic peptide (normal: 0-133 ng/L)

Discussion

While prolonged fever accompanying four of the five classical findings makes the diagnosis of typical KD, the American Heart Association guidelines published in 2017 defined the patients having less than four findings with the laboratory findings such as ESR, CRP elevation, hypoalbuminemia, leukocytosis, and echocardiography findings such as left ventricular dysfunction as having IKD (2). In the acute phase, which is the first of the three phases of the disease, patients may present the clinical manifestation with valvulitis, myocarditis, pericarditis and KDSS (3). KDSS is characterized by hypotension, a decrease in basal systolic blood pressure by at least 20%, or signs of peripheral hypoperfusion (4). While the hypotension of patient was suggesting KDSS, it was thought that it did not fully meet MAS criteria due to the absence of organomegaly and the absence of hypofibrinogenemia (5), and the gradual decrease of ferritin in clinical follow-up led to avoiding this diagnosis.

Verdoni et al. (6) identified a new clinical type, which they called Kawasaki-like disease while comparing KD cases seen before and after a pandemic in their study. This type is characterized by prominent lymphopenia, thrombocytopenia and increased ferritin level, clinically leading to myocarditis, and a more severe disease progression with IVIG resistance, requirement of steroid use, biochemical markers of MAS and clinical characteristics similar to KDSS. Since the same condition is also observed in COVID-19 patients, especially due to the fact that our patient had long-term and severe complaints of diarrhea and fever, as well as lymphopenia, thrombocytopenia, D-dimer, ferritin and IL-6 elevation in the laboratory tests, a fever that was resistant to IVIG treatment and requirement for starting steroid treatment, and clinical manifestations of MAS and KDSS and the presence of myocarditis, we also considered diagnosis of COVID-19. The negative results of two RT-PCR tests for COVID-19 did not lead us to avoid the diagnosis because Riphagen et al. (7) mentioned the presence of a hyperinflammatory associated with COVID-19 condition in the patients that had been undergoing intensive care with similar complaints, the respiratory system findings were not at the forefront, and RT-PCR tests were negative. This condition has been associated with severe cytokine storm syndrome and even ventricular dysfunction caused by it in adult COVID-19 patients (8). Such cardiac findings may also result in myocarditis as a result of viremia in some viral diseases (9). We also considered a hyperinflammatory process that was

associated with COVID-19 in our patient and included FPV in his treatment due to existing myocarditis. In the study performed by Cai et al. (10), comparing FPV with lopinavir/ritonavir combination, the median time of viral clearance was significantly lower, the improvement rate in computed tomography scans was higher and the side effect rate was lower in the FPV group. No side effects were observed in our patient during short-term use.

In recent months, there has been an increase in admissions of children with clinical findings similar to KD, KDSS and toxic shock syndrome. This new clinical condition was defined as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIM-TS) or multi-system inflammatory syndrome in children (MIS-C) associated with COVID-19 (11). The diagnostic criteria of disease were determined by the World Health Organization (WHO) (12), the Royal College of Pediatrics and Child Health (13), and the centers for disease control and prevention (14). According to the definition of the WHO, fever of three days or more and elevated inflammatory markers between 0 and 19 years of age were accompanied by two of the following criteria: rash or bilateral non-purulent conjunctivitis or oral, hands, or feet mucocutaneous inflammation signs; hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (echocardiogram findings or elevated troponin or NT-proBNP); evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, D-dimers) and acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). The Royal College of Pediatrics and Child Health defined fever and elevated inflammatory markers as single or multiple organ dysfunction in children without specifying any age range. Centers for disease control and prevention included patients under 21 years of age with severe disease requiring hospitalization and multi-organ involvement for fever and elevated inflammatory markers. The common feature in all three definitions was that this condition could not be explained by another clinical condition nd positive PCR or antigen tests or contact with a COVID-19 positive person. We accepted our patient as MIS-C because he complied with the criteria listed.

Conclusion

In this case report, we wanted to present one of these different clinical manifestations caused by the new type of coronavirus and to share this relationship with the clinicians dealing with the same age group of children. In the future, multicenter research on the relationship between the new type of coronavirus and KD will enable us to better understand the relationship of this virus with KD, and perhaps to control the KD that increases periodically and sometimes be fatal. We think that MIS-C, which develops after COVID-19 infection, will be more easily recognized with the understanding of its pathophysiological mechanisms. With easier recognition of the disease, it will be easier to initiate proven treatment mechanisms.

Ethic

Informed Consent: Consent was obtained from the family to use information about the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Follow-up of the Case: Ü.K.B., M.E., S.H.O., Literature Search: S.H.O., M.E., Writing: Ü.K.B., M.E., S.H.O., Manuscript Review and Revisation: Ü.K.B., M.E.

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

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

References

1. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr 2020;10(6):537-540.
2. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):927-999.
3. Weiss PF. Pediatric vasculitis. Pediatr Clin North Am 2012;59(2):407-423.
4. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123(5):783-789.
5. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, et al. 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a european league against rheumatism/american college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative. Ann Rheum Dis 2016;68(3):566-576.
6. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395(10239):1771-1778.
7. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during covid-19 pandemic. Lancet 2020;395(10237):1607-1608.
8. Jacobs JP, Stammers AH, St Louis J, Hayanga JWA, Firstenberg MS, Mongero LB, et al. Extracorporeal membrane oxygenation in

the treatment of severe pulmonary and cardiac compromise in COVID-19: Experience with 32 patients. ASAIO J 2020;66(7):722-730.

9. Loomba RS, Villarreal E, Flores S. Covid-19 and Kawasaki syndrome: should we really be surprised? Cardiol Young 2020;30(7):1059-1060.

10. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing) 2020;6(10):11921198.

11. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20(11):e276-e288.

12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Last Accessed Date: 16.07.2020. Available from: https://www.int/publications/i/item/multisystem-inflammatory-syndrome-in children-and-adolescents-with-covid-19.

13. The Royal Collage of Paediatrics and Child Health. Guidance-paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). 2020. Last Accessed Date: 16.07.2020. Available from: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-sydrome-temporally-associated-covid-19-pims.

14. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome. 2020. Last Accessed Date: 16.07.2020. Available from: https://www.cdc.gov/mis-c/hcp/.