E-ISSN: 2547 - 9431

BAGCILAR MEDICAL BULLETIN

Bağcılar Tıp Bülteni

Volume 7, Issue 1, March 2022

ORIGINAL RESEARCHES / ARAŞTIRMALAR

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

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

EDITORIAL BOARD / EDİTÖRLER KURULU

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor
Publication Coordinator
Burak Sever
Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül
Gülay Saday

Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş
Project Coordinators
Aysel Balta
Duygu Yıldırım
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ

Research&Development
Melisa Yiğitoğlu
Nihan Karamanlı
Digital Marketing Specialist
Ümit Topluoğlu

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: March 2022
E-ISSN: 2547-9431
International scientific journal published quarterly.

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

ADVISORY BOARD / DANIŞMA KURULU

ADVISORY BOARD / DANIŞMA KURULU

ABOUT US

Journal History

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

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

English Title: Bagcilar Medical Bulletin

Turkish title: Bağcılar Tıp Bülteni

Official abbreviation: Bagcilar Med Bull

E-ISSN: 2547-9431

Free-of-Charge Publication

No fee is charged from the authors during the submission, evaluation and publication process. Journal practices, ethical rules, technical information and necessary forms are specified on the journal's web page.

The manuscripts must be submitted via the EjManager online article system, represented on the journal website.

Abstracting and Indexing

- TÜBİTAK/ULAKBİM
- EBSCO
- Gale
- Türk Medline
- Turkey Citation Index
- Index Copernicus
- ProQuest
- J-Gate
- ScopeMed

Copyright

Digital Archiving and Preservation Policy

Digital preservation is a set of processes and activities that ensure the retrieval and distribution of information now available in digital formats to guarantee long-term, perpetual access. The preservation policy includes the following measures:

Website archiving

All of the electronic content (website, manuscript, etc.) is stored in three different sources. Content on a server is online and accessible to readers. A copy of the same content is preserved as a backup on other servers. Should a server fail, other resources can be brought online, and the website is expected to be available in 24-36 hours.

ABOUT US

Abstracting/Indexing services

Our journal's Abstracting/Indexing services store essential information about articles. In addition, some of our journals' Abstracting/Indexing services archive metadata about the article and electronic versions of the articles.In this way, copies of articles are presented to the scientific community through these systems as an alternative to journals.

Author Self-Archiving Policy

Abstract and citation information

Authors may reuse the Abstract and Citation information (e.g. Title, Author name, Publication dates) of their article anywhere at any time including social media such as Facebook, blogs and Twitter, providing that where possible a link is included back to the article on the Bagcilar Medical Bulletin website.

Accepted manuscript

The Accepted Manuscript (AM) is the final draft author manuscript, as accepted for publication by a journal, including modifications based on referees' suggestions, before it has undergone copyediting, typesetting and proof correction. This is sometimes referred to as the post-print version. Authors of Open Access articles are free to post and distribute their links anywhere immediately upon publication.

HAKKIMIZDA

Tarihçe

Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin (BTB), 2016'dan beri Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi'nin süreli bilimsel yayınıdır. Uluslararası, hakem değerlendirmeli, İngilizce ve açık erişim olarak yılda 4 sayı (Mart, Haziran, Eylül, Aralık) yayınlanan bilimsel bir dergi olup, tıbbın tüm alanlarındaki bilgi birikiminin uluslararası bilimsel platformda yayılabilmesini amaçlamaktadır. Bu amaçla tıbbın her alanında yapılmış orijinal klinik ve deneysel çalışmalar ve ilginç olgu sunumları ile konusunda uzman yazarların yaptığı literatür derlemeleri yayın için değerlendirmeye alınır.

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

Derginin Sahibi

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

Dergi Adı (İngilizce): Bagcilar Medical Bulletin

Dergi Adı (Türkçe): Bağcılar Tıp Bülteni

Resmi Kısaltma: Bagcilar Med Bull

E-ISSN: 2547-9431

Yayın Politikası

Gönderim, değerlendirme ve yayın sürecinde yazarlardan herhangi bir ücret talep edilmez. Dergi uygulamaları, etik kurallar, teknik bilgiler ve gerekli formlar derginin web sayfasında belirtilir.

Yazılar, dergi web sitesinde temsil edilen EjManager çevrimiçi makale sistemi aracılığıyla gönderilmelidir.

Indekslenme

- TÜBİTAK/ULAKBİM
- EBSCO
- Gale
- Türk Medline
- Türkiye Atıf Dizini
- Index Copernicus
- ProQuest
- J-Gate
- ScopeMed

Telif Hakkı

Yayın kararı alındıktan ve kabul edildikten sonra başvurulara "Telif Hakkı Devir Formu" eklenmelidir. Form, derginin makale gönderme ve değerlendirme sitesinden de indirilebilir. Telif Hakkı Devir Formu, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve bu ıslak imzalı belgenin taranmış bir versiyonu gönderilmelidir.

HAKKIMIZDA

Yazar(lar), makalelerinin yayına kabul edilmesi durumunda, makalelerinin telif haklarını Bağcılar Tıp Bülteni'ne devrederler. Telif hakkı, makalenin herhangi bir biçimde (baskı, elektronik ortam veya başka bir biçimde) çoğaltılması ve dağıtılması için münhasır ve sınırsız hakları kapsar; ayrıca tüm diller ve ülkeler için çeviri haklarını da kapsar.

Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative (BOAI) kuralları esas alınarak uygulanmaktadır.

Yayınlanan tüm içerikler çevrimiçi ve ücretsiz olarak behmedicalbulletin.org mevcuttur. Derginin içeriği, üçüncü şahısların, orijinal çalışmaya atıfta bulunmak ve ticari amaçlarla kullanmamak şartıyla, içeriği paylaşmasına ve uyarlamasına izin veren Creative Commons Attribution-NonCommercial (CC BY-NC-ND) 4.0 Uluslararası Lisansı ile lisanslanmıştır.

Dijital Arşivleme ve Koruma Politikası

Dijital koruma, uzun vadeli, sürekli erişimi garanti etmek için artık dijital formatlarda mevcut olan bilgilerin alınmasını ve dağıtılmasını sağlayan bir dizi süreç ve aktivitedir. Koruma politikası aşağıdaki eylemleri içerir:

Web Sitesi

Elektronik içeriğin tamamı (web sitesi, makale vb.) üç farklı kaynakta saklanmaktadır. Bir sunucudaki içerik çevrimiçidir ve okuyucular tarafından erişilebilir. Aynı içeriğin bir kopyası, diğer iki kaynakta yedek olarak korunur. Bir sunucu arızalanırsa, diğer kaynaklar çevrimiçi hale getirilebilir ve web sitesinin 24-36 saat içinde kullanıma sunulması beklenir.

İndeksleme Hizmetleri

Dergimizin indeksleme hizmetleri, makaleler hakkında temel bilgileri depolar. Ayrıca bazı indeksleme servisleri makale ile ilgili metadataları ve makalelerin elektronik versiyonlarını arşivlemektedir. Bu sayede dergilere alternatif olarak makalelerin kopyaları bu sistemler aracılığıyla bilim camiasına sunulmaktadır.

AIMS AND SCOPE

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

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

Owner of the Journal

In the name of T.C. Health Ministary, Health Sciences University, İstanbul Bağcılar Training and Research Hospital, Hospital Administrator Assoc. Prof. Ozan Beytemür (T.C. Health Ministary, Health Sciences University, İstanbul Bağcılar Training and Research Hospital, Clinic of Orthopedics and Traumatology, Istanbul, Turkey).

English Title: Bagcilar Medical Bulletin

Turkish title: Bağcılar Tıp Bülteni

Official abbreviation: Bagcilar Med Bull

E-ISSN: 2547-9431

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Author(s) and copyright owner(s) grant access to all users for the articles published in the Bagcilar Medical Bulletin as free of charge. Articles may be used provided that they are cited.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI). By “open access” to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Bagcilar Medical Bulletin does not demand any subscription fee, publication fee or similar payment for access to electronic resources.

Creative Commons

Open access is an approach that supports interdisciplinary development and encourages collaboration between different disciplines. Therefore, Bagcilar Medical Bulletin contributes to the scientific publishing literature by providing more access to its articles and a more transparent review process.

AIMS AND SCOPE

Advertisement Policy

This journal's advertising sales and editorial processes are separated to ensure editorial independence and reduce the effects of financial interests.

Advertisers are responsible for ensuring that their advertisements comply with applicable laws regarding deceptive and/or offensive content and ethical issues.

Material Disclaimer

Statements or opinions stated in articles published in the journal do not reflect the views of the editors, editorial board and/or publisher; The editors, editorial board and publisher do not accept any responsibility or liability for such materials. All opinions published in the journal belong to the authors.

Contact

Permissions & Advertisement

Publisher: Galenos

Adress: Molla Gürani Mah. Kaçamak Sok. 21/1 Fındıkzade, Fatih, Istanbul/Turkey

Telephone: +90 212 621 99 25

Fax: +90 212 621 99 27

Web page: galenos.com.tr

E-mail: info@galenos.com.tr

AMAÇ VE KAPSAM

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

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

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

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

Dergi Adı (İngilizce): Bagcilar Medical Bulletin

Dergi Adı (Türkçe): Bağcılar Tıp Bülteni

Resmi Kısaltma: Bagcilar Med Bull

E-ISSN: 2547-9431

Açık Erişim Politikası

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

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

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

Gönderim, değerlendirme ve yayın sürecinde yazarlardan herhangi bir ücret talep edilmez.

Creative Commons

Reklam Politikası

Potansiyel reklam verenler, Yazı İşleri ile iletişime geçmelidir. Reklam görselleri sadece Genel Yayın Yönetmeni'nin onayı ile yayınlanır.

AMAÇ VE KAPSAM

Materyal Sorumluluk Reddi

Dergide yayınlanan makalelerde yer alan ifadeler veya görüşler editörlerin, yayın kurulunun ve/veya yayıncının görüşlerini yansıtmaz. Editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Dergide yayınlanan tüm görüşler, makalelerin yazarlarına aittir.

Yayınevi Yazışma Adresi

Galenos Yayınevi

Adres: Molla Gürani Mah. Kaçamak Sk. No: 21, 34093 Fındıkzade-İstanbul/Türkiye

Tel.: +90 212 621 99 25

Faks: +90 212 621 99 27

E-posta: info@galenos.com.tr

INSTRUCTIONS TO AUTHORS

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 an 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 uses EjManager online manuscript submission, review and tracking system .

Editorial Policies and Review Process

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

Publication Policy

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

General Principles

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 authors. The 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.

For quoted texts, tabulated data and graphics from published papers, the author has to obtain permission from the author(s) or the owner of the publishing rights of the source article and indicate the allowance in the paper. Author(s) is responsible for obtaining such permissions.

Short presentations that took place in scientific meetings can be referred to if announced in the article. The editor hands over the formally acceptable papers to at least two national/international referees for evaluation and gives the green light for publication upon modification by the authors in accordance with the referees' claims. Changing the name of an author (omission, addition or order) in papers submitted to the journal requires thepermission of all declared authors. Refused papers and graphics are not returned to the author.

Author Rights

Authors transferring the copyright of their article to the journal retain their right to use the article in its published form in their other work, in part or whole, without any revision or modification and to expand it into a book form on condition that they give appropriate attribution to the publication in the journal explicitly as stated in Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License and in the journal's open-access policy. When the article is to be re-used by the author

INSTRUCTIONS TO AUTHORS

as a book chapter or in a collection or compilation or expanded into a book for commercial purposes, permission is required to be sought from the journal, which reserves its right to levy or waive a fee for such re-use, and appropriate attribution is required to be given to the original publication in the journal explicitly.

Author Responsibilities

It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors should ensure that the submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere in any language. Applicable copyright laws and conventions should be followed. Copyright material (e.g. tables, figures or extensive quotations) should be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources should be appropriately credited and referenced. The author(s) must have contributed to the submitted manuscript and must declare that they were involved in substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Those who do not meet all the above criteria should be named in the acknowledgements. Fundraising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The order of names in the author list of an article should be a co-decision, and it should be indicated in the Copyright Transfer Form. The individuals who do not meet the authorship criteria but contributed to the study should take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing general support, providing material or financial support are examples to be indicated in the acknowledgement section. Written informed consent should be taken from the persons whose participation are indicated in the acknowledgement section.

All authors must disclose all issues concerning financial relationships, conflict of interest, and competing interests that may potentially influence the results of the research or scientific judgment. All financial contributions, supports or sponsorship of projects must be clearly explained.

When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor-in-Chief to provide retractions or corrections of mistakes. The Author Contribution Form, indicating the authors' contribution to the manuscript and the ICJME Form for Potential Conflicts of Interest should be sent together with the manuscript. Please read ICMJE recommendations on roles and responsibilities of authors.

Responsibility for the Editors, Reviewers and Review Process

Editors evaluate manuscripts for their scientific content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. They provide a fair double-blind peer-review of the submitted articles for publication. They ensure that all the information related to submitted manuscripts is kept as confidential before publishing.

Editors are responsible for the contents and overall quality of the publication. They should publish errata pages or make corrections when needed. Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for the final decision for the publication of the manuscripts in Bagcilar Medical Bulletin.

Please review the COPE publication ethics guidelines by clicking here.

Reviewers evaluate manuscripts based on content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. They should have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments should be objective.

Reviewers should identify the relevant published work that has not been cited by the authors. They must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the Editor-in-Chief if they are aware of copyright infringement and plagiarism on the author's side.

INSTRUCTIONS TO AUTHORS

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the Editor-in-Chief and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The reviewers are not allowed to have copies of the manuscripts for personal use and they cannot share manuscripts with others. Unless the authors and editor permit, the reviews of referees cannot be published or disclosed. The anonymity of the referees is important. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point. Please review the COPE publication ethics guidelines by clicking here.

Standards and Principles

Bagcilar Medical Bulletin is committed to upholding the highest standards of publication ethics and observes the following guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Each manuscript is reviewed by one of the editors and at least two referees under double-blind peer review process. We reserve the right to use plagiarism detecting software to screen submitted papers at all times. We check for plagiary and fraudulent data, falsification (fabrication or manipulation of research data, tables, or images) and improper use of humans or animals in research. All manuscripts not in accordance with these standards will be removed from the publication. This also contains any possible malpractice discovered after the publication. In accordance with the code of conduct we will report any cases of suspected plagiarism or duplicate publishing.

We follow the COPE Ethics Flowcharts for dealing with cases of possible scientific misconduct and breach of publication ethics.

Human and Animal Rights, Informed Consent, Conflict of Interest

The Bagcilar Medical Bulletin adopts highest ethical and scientific standards and ensures that it is free of influences regarding commercial interests. It is authors' responsibility that the articles are in accordance with ethical codes of conduct. Bagcilar Medical Bulletin takes as principle to comply with the ethical standards of Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects as revised in 2013.

For this reason, regarding the subjects of clinical experiments, it should be indicated in the submitted manuscripts definitely that the above mentioned codes of conduct were applied. Besides approvals, from national or local ethical committees should be sent together with the papers as well. Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children and those under wardship or with confirmed insanity, authors are asked to include information about whether the legal custodian's assent was obtained. And a letter of affirmation signed by all authors, confirming the collection of informed consents has to be sent to the journal.

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

INSTRUCTIONS TO AUTHORS

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

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

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

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

Language

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

Manuscript Organization And Format

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

Title Page

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

Abstract and Keywords

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

Manuscript Types

Original Research

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

INSTRUCTIONS TO AUTHORS

Abstract

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

Keywords

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

Introduction

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

Material and Methods

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

The selection and description of the participants

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

Technical information

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

Statistics

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

Results

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

INSTRUCTIONS TO AUTHORS

be emphasized or summarized. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Discussion

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

Conclusions

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

Tables, Graphics and Illustrations

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

Brief Research

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

Case Report

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

Review

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

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

INSTRUCTIONS TO AUTHORS

Letter to the Editor

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

Tables

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

Illustrations (Figures)

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

Legends for Illustrations (Figures)

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

Units of Measurement

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

INSTRUCTIONS TO AUTHORS

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

Abbreviations and Symbols

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

Acknowledgement(s)

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

Case Reports and Word Limitation

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

Preparation of Manuscripts

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

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

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

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

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

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

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

References

Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can

INSTRUCTIONS TO AUTHORS

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

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

Reference Style and Format

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

Examples for References:

1. For articles in journals:

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

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

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

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

2. For the supplement:

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

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

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

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

3. For articles in press:

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

4. For the citations from books:

Books edited by one editor:

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

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

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

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

INSTRUCTIONS TO AUTHORS

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.

INSTRUCTIONS TO AUTHORS

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

-Title page

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

-All authors and their affiliations

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

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

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

-Body text

-Acknowledgement

-Reference

-All tables (including title, description, footnotes)

CONTACT

Publisher: Galenos

Address: Molla Gürani Mahallesi Kaçamak Sokak No: 21 34093 Fındıkzade - İstanbul/Turkey

Phone: +90 (212) 621 99 25

E-mail: info@galenos.com.tr

INSTRUCTIONS TO AUTHORS

Peer Review, Publication Ethics and Malpractice Statement

Peer- Review

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

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

Submitted manuscripts are subjected to double-blinded peer-review. The scientific board guiding the selection of the papers to be published in the journal consists of elected specialists of the journal and, if necessary, selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section associate editors, and at least two external expert reviewers.

Human and Animal Rights

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

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

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

Plagiarism and Ethical Misconduct

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

Plagiarism: To republish whole or part of a content in another author's publication without attribution.

Fabrication: To publish data and findings/results that do not exist.

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

Salamisation: Creating multiple publications by abnormally splitting the results of a study.

Data Manipulation/Falsification: Manipulating or deliberately distorting research data to give a false impression.

We disapprove of such unethical practices and of efforts to influence the review process with such practices as gifting authorship, inappropriate acknowledgements, and references in line with the COPE flowcharts.

Submitted manuscripts are subjected to automatic software evaluation for plagiarism and duplicate publication. Authors are obliged to acknowledge if they published study results in whole or in part in the form of abstracts.

INSTRUCTIONS TO AUTHORS

DUTIES OF PUBLISHER:

Handling of unethical publishing behaviour

The publisher will take all appropriate measures to modify the article in question, in close cooperation with the editors, in cases of alleged or proven scientific misconduct, fraudulent publication, or plagiarism. This includes the prompt publication of an erratum, disclosure, or retraction of the affected work in the most severe case. Together with the editors, the publisher will take reasonable steps to detect and prevent the publication of articles in which research misconduct occurs and will under no circumstances promote or knowingly allow such abuse to occur.

Editorial Autonomy

The Bagcilar Medical Bulletin is committed to ensuring the autonomy of editorial decisions without influence from commercial partners.

Intellectual Property and Copyright

The Bagcilar Medical Bulletin protects the property and copyright of the articles published in the journal and maintains each article's published version of the record. The journal provides the integrity and transparency of each published article.

Scientific Misconduct

The Bagcilar Medical Bulletin's publisher takes all appropriate measures regarding fraudulent publication or plagiarism.

DUTIES OF EDITORS:

Decision on Publication and Responsibility

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

Objectivity

Articles that are submitted to the journal are always evaluated without any prejudice.

Confidentiality

The editor must not disclose any information about a submitted article to anyone other than editorial staff, reviewers, and publisher.

Conflicts of Interest and Disclosure

The Bagcilar Medical Bulletin does not allow any conflicts of interest among authors, reviewers, and editors. Unpublished materials in a submitted article must not be used by anyone without the express written assent of the author.

Fundamental Errors in Published Works

Authors are obliged to notify the journal's editors or publisher immediately and to cooperate with them to correct or retract the article if significant errors or inaccuracies are detected in the published work. If the editors or publisher learn from a third party that a published work contains a material error or inaccuracy, the authors must promptly correct or retract the article or provide the journal editors with evidence of the accuracy of the article.

INSTRUCTIONS TO AUTHORS

DUTIES OF REVIEWERS:

Evaluation

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

Confidentiality

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

Disclosure and Conflict of Interest

The reviewers have no conflicts of interest among authors, funders, editors, etc.

Contribution to editor

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

Objectivity

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

Acknowledgement of Sources

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

DUTIES OF AUTHORS:

Reporting Standards

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

Originality

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

Multiple Publications

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

Acknowledgement of Sources

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

INSTRUCTIONS TO AUTHORS

Authorship of a Paper

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

Disclosure and Conflicts of Interest

All sources of financial support should be disclosed. All authors should disclose if a meaningful conflict of interest exists in the process of forming their study. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board of the Bagcilar Medical Bulletin. The ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors to disclose a potential conflict of interest. The journal's Editorial Board determines cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

Conditions that provide financial or personal benefit bring about a conflict of interest. The reliability of the scientific process and the published articles is directly related to the objective consideration of conflicts of interest during the planning, implementation, writing, evaluation, editing, and publication of scientific studies.

Financial relations are the most easily identified conflicts of interest, and it is inevitable that they will undermine the credibility of the journal, the authors, and the science. These conflicts can be caused by individual relations, academic competition, or intellectual approaches. The authors should refrain as much as possible from making agreements with sponsors in the opinion of gaining profit or any other advantage that restrict their ability to access all data of the study or analyze, interpret, prepare, and publish their articles. Editors should refrain from bringing together those who may have any relationship between them during the evaluation of the studies. The editors, who make the final decision about the articles, should not have any personal, professional, or financial ties with any of the issues they are going to decide. Authors should inform the editorial board concerning potential conflicts of interest to ensure that their articles will be evaluated within the framework of ethical principles through an independent assessment process.

If one of the editors is an author in any manuscript, the editor is excluded from the manuscript evaluation process. In order to prevent any conflict of interest, the article evaluation process is carried out as double-blinded. Because of the double-blinded evaluation process, except for the Editor-in-Chief, none of the editorial board members, international advisory board members, or reviewers is informed about the authors of the manuscript or institutions of the authors.

Our publication team works devotedly to ensure that the evaluation process is conducted impartially, considering all these situations.

Conflict of Interest

The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

Appeals and complaints

Appeal and complaint cases are handled within the scope of COPE guidelines by the Editorial Board of the journal. Appeals should be based on the scientific content of the manuscript. The final decision on the appeal and complaint is made by Editor in Chief. An Ombudsperson or the Ethical Editor is assigned to resolve cases that cannot be resolved internally. Authors should get in contact with the Editor in Chief regarding their appeals and complaints via e-mail at info@galenos.com.tr.

YAZARLARA BİLGİ

Hakem Değerlendirmesi, Yayın Etiği ve Kötüye Kullanım

Hakem Değerlendirmesi

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

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

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

İnsan ve Hayvan Araştırmaları

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

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

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

İntihal ve Etik Suistimal

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

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

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

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

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

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

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

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

YAZARLARA BİLGİ

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

A. YAYINCININ GÖREVLERİ:

Etik Olmayan Yayınlama Davranışının Ele Alınması

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

Editöryal Özerklik

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

Fikri Mülkiyet ve Telif Hakkı

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

Bilimsel Suistimal

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

B. EDİTÖRLERİN GÖREVLERİ:

Yayın Kararı ve Sorumluluğu

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

Nesnellik

Dergiye gönderilen makaleler her zaman önyargısız olarak değerlendirilir.

Gizlilik

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

Çıkar Çatışmaları ve İfşa

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

Yayımlanan Eserlerde Temel Hatalar

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

YAZARLARA BİLGİ

C. HAKEMLERİN GÖREVLERİ:

Değerlendirme

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

Gizlilik

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

Çıkar Çatışmaları ve İfşa

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

Editöre Katkı

Hakemler, editöre karar vermede ve makaleyi geliştirmede yardımcı olabilir.

Nesnellik

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

Kaynakların Onaylanması

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

D. YAZARLARIN GÖREVLERİ:

Raporlama Standartları

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

Özgünlük

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

Çoklu Yayınlar

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

Kaynakların Belirtilmesi

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

Makale Yazarlığı

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

YAZARLARA BİLGİ

Çıkar Çatışmaları ve İfşa

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

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

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

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

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

YAZARLARA BİLGİ

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

Editoryal Politikalar ve Hakem Süreci

Yayın Politikası

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

-Orijinal araştırmalar,

-Kısa araştırmalar,

-Olgu sunumları,

-Derlemeler,

-Editöre mektup

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

Genel İlkeler

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

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

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

Yazar Hakları

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

Yazarların Soru mluluğu

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

YAZARLARA BİLGİ

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

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

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

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

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

Editör ve Hakem Sorumlulukları ve Değerlendirme Süreci

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

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

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

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

YAZARLARA BİLGİ

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

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

Açık Erişim İlkesi

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

Yayın Etiği

İlke ve Standartlar

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

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

İnsan ve Hayvan Hakları, Bilgilendirilmiş Olur, Çıkar Çatışması

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

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

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

YAZARLARA BİLGİ

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

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

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

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

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

Dil

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

Yazıların Hazırlanması

Aksi belirtilmedikçe gönderilen yazılarla ilgili tüm yazışmalar ilk yazarla yapılacaktır. Gönderilen yazılar, yazının yayınlanmak üzere gönderildiğini ve Bağcılar Tıp Bülteni`nin hangi bölümü (Orijinal Araştırma, Kısa Araştırma, Olgu Sunumu, Derleme, Editöre Mektup) için başvurulduğunu belirten bir mektup, yazının elektronik formunu içeren Microsoft Word 2003 ve üzerindeki versiyonları ile yazılmış elektronik dosya ile tüm yazarların imzaladığı 'Telif Hakkı Devir Formu' , Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışması Beyan Formu eklenerek gönderilmelidir. Yazıların alınmasının ardından yazarlara makalenin alındığı, bir makale numarası ile bildirilecektir. Tüm yazışmalarda bu makale numarası kullanılacaktır. Makaleler sayfanın her bir kenarından 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 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

YAZARLARA BİLGİ

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

Makale Türleri

Orijinal Araştırma

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

Öz

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

Anahtar Kelimeler

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

Giriş

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

Yöntem ve Gereçler

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

Olguların Seçimi ve Tanımlanması

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

Teknik Bilgi

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

YAZARLARA BİLGİ

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

İstatistik

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

Bulgular

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

Tartışma

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

Sonuçlar

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

Tablo, Grafik ve Şekiller

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

Kısa Araştırma

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

YAZARLARA BİLGİ

Olgu Sunumu

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

Derleme

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

Editöre Mektup

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

Tablolar

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

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

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

Şekiller

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

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

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

YAZARLARA BİLGİ

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

Şekillerin Dipnotları

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

Ölçüm Birimleri

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

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

Teşekkür(ler)

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

Kelime Sayısı Sınırlandırması

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

Makale Hazırlığı

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

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

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

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

STROBE gözlemsel çalışma raporlarında yer alması gereken maddelerin kontrol listesi,

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

YAZARLARA BİLGİ

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

Kaynaklar

Kaynaklarla İlgili Genel Konular

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

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

Referans Stili ve Formatı

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

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

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

Kaynaklar için örnekler aşağıda belirtilmiştir:

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

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

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

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

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

YAZARLARA BİLGİ

4. Kitaptan alıntılar:

Tek yazarlı kitaptan alıntı için:

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

Kitaptan bir bölüm için, editör(ler) varsa:

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

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

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

Çeviri Kitaptan Alıntı için:

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

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

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

Makalenin Dergiye Gönderilmesi

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

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

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

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

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

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

YAZARLARA BİLGİ

SON KONTROL LİSTESİ

• Editöre sunum sayfası

- Makalenin kategorisi

- Başka bir dergiye gönderilmemiş olduğu bilgisi

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

- İstatistik kontrolünün yapıldığı (araştırma makaleleri için)

- İngilizce yönünden kontrolünün yapıldığı

- Telif Hakkı Devir Formu

- Yazar Katkı Formu

- ICMJE Potansiyel Çıkar Çatışması Beyan Formu

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

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

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

• Kapak sayfası

- Makalenin Türkçe ve İngilizce başlığı (tercihen birer satır)

- Yazarlar ve kurumları

- Tüm yazarların yazışma adresi, iş telefonu, faks numarası, GSM, e-posta adresleri

• Özler (400-500 kelime) (Türkçe ve İngilizce)

• Anahtar Kelimeler: 3-10 arası (Türkçe ve İngilizce)

• Tam metin makale

• Teşekkür

• Kaynaklar

• Tablolar-Resimler, Şekiller

Yayınevi Yazışma Adresi

Galenos Yayınevi

Adres: Molla Gürani Mah. Kaçamak Sk. No: 21, 34093 Fındıkzade-İstanbul/Türkiye

Tel.: +90 212 621 99 25

Faks: +90 212 621 99 27

E-posta: info@galenos.com.tr

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

CONTENTS / İÇİNDEKİLER

ORIGINAL RESEARCHES / ARAŞTIRMALAR

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

CONTENTS / İÇİNDEKİLER

CASE REPORTS / OLGU SUNUMLARI

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):1-5
DOI: 10.4274/BMB.galenos.2021.2021-09-097

Tp-e Interval, Tp-e/QT and Tp-e/QTc Ratios in Female Patients with Small Heart Syndrome

Küçük Kalp Sendromlu Kadın Hastalarda Tp-e Aralığı, Tp-e/QT ve Tp-e/QTc Oranları

Ersin İbişoğlu[1], Bedrettin Boyraz[2]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]Doruk Hospital, Clinic of Cardiology, Bursa, Turkey

Abstract

Objective: The relevance of Tp-e, QT dispersion and the ratios between these two as predictive variables of ventricular arrhythmias, particularly ventricular prematurity depolarization and sudden cardiac death, were assessed in this study of patients who were identified with small heart syndrome.

Method: The study included 94 female patients, as 47 small-heart and 47 normal-heart patients, by calculating their cardiothoracic ratios. We measured QT_{max}, QT_{min}, QRS, JT and Tp-e intervals, Tp-e/QT_{max}, Tp-e/QTc_{max}, Tp-e/JT and Tp-e/JTc rates and estimated QTc_{max}, QTc_{min}, cQTd and JTc intervals.

Results: cQTd, Tp-e, Tp-e/QTc_{max}, and Tp-e/JTc values were significantly higher in the small heart patient group. QTc_{min} and QTcmin values were significantly lower.

Conclusion: Tp-e and QT dispersion values are important markers in patients with small heart syndrome in terms of predicting ventricular repolarization and a possible ventricular arrhythmia.

Keywords: Electrocardiogram, small heart syndrome, ventricular repolarization

Öz

Amaç: Tp-e, QT dispersiyonu ve bu ikisi arasındaki oranlar ventriküler aritmilerin, özellikle ventriküler prematürite depolarizasyonunun ve ani kardiyak ölümün öngörücü değişkenleri olarak, bu çalışmada küçük kalp sendromu ile tanımlanan hastalarda değerlendirildi.

Yöntem: Kardiyotorasik oranları hesaplanarak 47'si küçük kalpli, 47'si normal kalpli 94 kadın hasta çalışmaya alındı. QT_{maks}, QT_{min}, QRS, JT ve Tp-e intervalleri, Tp-e/QT_{maks}, Tp-e/QTc_{maks}, Tp-e/JT ve Tp-e/JTc oranları ölçüldü ve QTc_{maks}, QTc_{min}, cQTd ve JTc intervalleri hesaplandı.

Bulgular: Küçük kalp hasta grubunda cQTd, Tp-e, Tp-e/QTc_{maks} ve Tp-e/JTc değerleri anlamlı olarak daha yüksekti ve QTc_{min} değerleri anlamlı olarak daha düşüktü.

Sonuç: Küçük kalp sendromlu hastalarda Tp-e ve QT dispersiyon değerleri ventriküler repolarizasyonu ve olası bir ventriküler aritmiyi öngörme açısından önemli belirteçlerdir.

Anahtar Kelimeler: Elektrokardiyografi, küçük kalp sendromu, ventriküler repolarizasyon

Introduction

Small heart syndrome, also known as neurocirculatory asthenia, is related to a small heart shadow on chest X-rays. Fatigue or exhaustion, tachycardia, pain in the abdomen, difficulty in breathing, anxiousness, shaking, sweating, and loss of consciousness are the most common conditions which are also the most detectable symptoms of cardiac arrhythmia patients (1,2).

As clinical manifestations of cardiac arrhythmias like palpitations and chest pain, fatigue may also occur in our clinical routine. While arrhythmias could be reported with 24-hour electrocardiography (ECG) reading during rhythm

Address for Correspondence: Ersin İbişoğlu, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Cardiology, İstanbul, Turkey
E-mail: e_ibisoglu@hotmail.com **ORCID:** orcid.org/0000-0002-1231-0933 **Received:** 14.09.2021 **Accepted:** 10.12.2021

Cite this article as: İbişoğlu E, Boyraz B. Tp-e Interval, Tp-e/QT and Tp-e/QTc Ratios in Female Patients with Small Heart Syndrome. Bagcilar Med Bull 2022;7(1):1-5

follow-up, these arrhythmias can also be difficult to identify. Therefore, ECG results may also be helpful (3,4).

The repolarization process offers useful knowledge as an indicator of arrhythmia in cardiac electrophysiology relating to the chance of having an arrhythmia. As it involves the depolarization step, the QT distance is important, so the JT distance belongs to the repolarization step. Recently, in terms of sensitivity of ventricular arrhythmias and the chance of sudden cardiac death, Tp-e values, one of the determinant criteria for ventricular arrhythmias, and their association with QT and JT distances are useful measurements (5,6).

The relevance of Tp-e, QT dispersion and the ratios between these two as predictive variables of ventricular arrhythmias, particularly ventricular prematurity depolarization and sudden cardiac death, were assessed in this study of patients who were identified with small heart syndrome.

Materials and Methods

The study complies with the Declaration of Helsinki. University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital approved the study protocol on 15/01/2021 with the number of 625 and informed consent was obtained from participants participating in the study in this article.

Study Design and Population

Ninety-four female patients, including 47 small-heart and 47 normal-heart patients, who registered between March 2018 and February 2020, were included in the study for evaluating their chest X-ray cardiothoracic ratios (CTR) (Figure 1), after obtaining the ethical committee approval. The patients were selected from those who presented to the cardiology outpatient clinic with the complaint of chest pain. None of patients have a history of coronary artery disease or another cardiac disease. Exercise test was applied to all patients and no pathology was found in the effort test. Patients and hospital registrations provided the required demographic and clinical features. Patients with metabolic or electrolyte abnormalities, systemic heart failure, acute or chronic infections, or those taking drugs that might affect the P wave, PR segment, QT and QTc intervals were not involved in the study. Complete blood count and biochemical assessments on all patients were previously carried out and the outcomes of each patient were reported.

Chest Roentgenograms

In the posteroanterior projection on the chest roentgenogram, the calculated CTR was described as small heart of ≤42% (7-9). Throughout the right-to-left projection of the lateral view on the chest X-ray, the existence or lack of narrow chest indications, involving the posterior-anterior chest and straight back, was evaluated. Once the anteroposterior diameter was measured laterally less than 40% of the transversal diameter at the level of the diaphragm of the thoracic cavity, a narrow chest was identified.

ECG Analysis

After resting for 10 minutes, twelve leading ECGs were collected with a magnitude of 10 mm/mV and a frequency of 25 mm/s with typical lead positions in the standard position with a commercially available instrument. The ECG duration is 10 s, so there were 4 to 6 beats per lead, based on the heart rate. ECG measurements were taken manually by using a magnifying glass (TorQ 150 mm Optical Caliper LCD) by two random cardiologists who had no patient data. By measuring the Pearson's correlation coefficient (r=0.93), interobserver agreement for PWPT was assessed. The QT interval of the surface ECG was calculated as the period between the starting of the QRS and the termination of the T wave. The Hodges formula was used to calculate the QTc intervals.

QT Indices

From the beginning of the QRS complex to the end of the T wave, which was described as its returning to the TP baseline, QT intervals were collected. The QT interval to the lowest point of the curve between the T and U waves

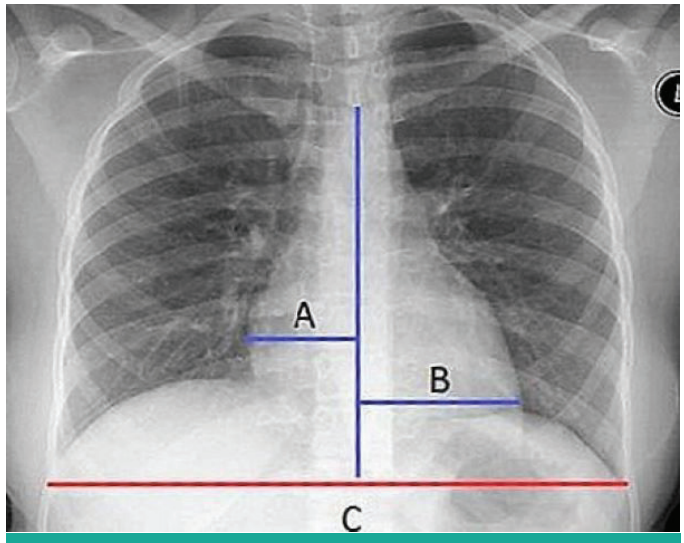


Figure 1. Measurement of cardiothoracic ratio

was calculated when U waves were present. To determine the heart rate and compensate for the QT interval (QTc), the R-R interval was calculated and used with the Hodge's equation (10,11). QT dispersion (QTd) was defined as the difference in separate leads between the longest and shortest QT intervals. From the T wave peak to the end of the T wave, the Tp-e interval was described. Tp-e interval calculations were conducted from precordial points. The Hodge's formula [QTc=QT+0.00175 × (HR-60)] was used to measure the rate of QTc and the corrected QT dispersion (cQTd). JT intervals were calculated from the endpoint of the QRS complex (J point) through the ending of the T wave (JTend interval). In order to calculate JTc, the Hodge's formula [JTc=JT+0.00175 × (HR-60)] was used. The ratios of Tp-e/QT, Tp-e/QTc, Tp-e/JT, and Tp-e/JTc were also measured. No patient had an observable lead of less than nine. For assessments, the intra- and interobserver variations were <5%.

Statistical Analysis

The analysis was carried out using the SPSS 23.0 Statistical Package Software for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were presented as mean ± standard deviation, and qualitative variables were expressed as numbers and percentages. Variations within independent variables were evaluated by the Student's t-test for normally distributed numerical variables and the Mann-Whitney U test for non-normal distributed variables and the chi-square analysis for qualitative variables. The Kolmogorov-Smirnov test was used to determine the normality of the data. The Levene's test was employed to assess the variance homogeneity. A p-value <0.05 was regarded as statistically significant.

Results

There was no significant difference between the patients in the study and the control group in terms of age, weight, height, platelet, hemoglobin, creatinine, urea, alanine aminotransferase, troponin, or aspartate aminotransferase. The body mass index in the small heart group was detected as low (Table 1). In the small heart patient group, significantly higher values were recorded for cQTd (24.246±9.046 ms vs. 35.495±14.358 ms, p<0.001), Tp-e (67.32±11.661 ms vs. 72.67±11.028 ms, p=0.04), Tp-e/QTc_{max} (0.166±0.028 vs. 0.181±0.027, p=0.012), Tp-e/JTc (0.214±0.038 vs. 0.232±0.034, p=0.022). Also, the values of the small heart group for QTc_{min} (379.34±20.064 ms vs. 364.71±23.149 ms, p=0.004) were significantly lower. No significant difference was found in the heart rate (87.81±15.532 bpm vs. 83.81±14.372 bpm, p=0.223), QRS (83.23±6.948 ms vs. 81.91±10.052 ms, p=0.206), QT_{max} (354.93±26.796 ms vs. 358.54±28.434 ms, p=0.528), QT_{min} (330.68±26.611 ms vs. 323.04±30.829 ms, p=0.202), JT (265.7±25.16 ms vs. 271.88±23.104 ms, p=0.218), QTc_{max} (403.59±18.208 ms vs. 400.20±18.336 ms, p=0.371), JTc (314.37±21.325 ms vs. 313.55±22.526 ms, p=0.856) Tp-e/QT_{max} (0.190±0.034 vs. 0.203±0.031, p=0.063), Tp-e/JT (0.255±0.047 vs. 0.267±0.036, p=0.295) between the small heart group and control group (Table 2). For the JT, QT, and Tp-e measurements, the intra-observer difference between cardiologists was 2.5%, 3.4%, and 4.3%, respectively. Both the small heart group and control group shared a similar systematic error between the cardiologists.

Discussion

In this research, it has been found that there is a significant association between elevated cQTd, Tp-e interval, Tp-e/QTc_{max}, and Tp-e/JTc ratios on surface ECG and small heart patients, in which they were considered to be correlated with ventricular arrhythmias and sudden death. We found that our literature review revealed no current study on the relationship between small heart syndrome and ventricular arrhythmia.

A variety of cardiac problems associated with low output syndrome are caused by small heart syndrome. In the assessment of those patients, diagnostic methods are particularly relevant, specifically chest radiography and ECG. The outcome of myocardial damage is low output

Table 1. Demographic and laboratory characteristics

	Control group (n=47)	Small heart group (n=47)	p
Cardio-thoracic ratio	46.413+3.007	38.530+2.642	<0.001*
Age; years	24.74+4.989	22.87+5.029	0.073
Height; cm	1.600+0.058	1.622+0.063	0.086
Weight; kg	59.51+13.592	54.15+8.041	0.061
Body mass index; kg/cm^2	23.122+4.448	20.597+3.031	0.002*
Systolic tension; mmHg	98.53+5.120	98.36+4.775	0.868
Diastolic tension; mmHg	65.57+3.781	67.43+4.596	0.052
Alanine aminotransferase; IU/mL	16.94+14.039	15.43+6.746	0.847
Aspartate aminotransferase; IU/mL	18.60+7.039	18.98+4.528	0.146
Creatinine; mg/dL	0.726+0.143	0.757+0.219	0.950
Urea, mg/dL	22.515+5.568	22.134+5.627	0.309
Platelet; 10^3/µL	261.04+74.246	255.30+59.553	0.563
Hemoglobin; mg/dL	13.670+1.233	13.832+1.064	0.498

and it can end up causing ventricular arrhythmias. In patients with low output, malignant arrhythmias have been confirmed to be present (12).

The repolarization process offers valuable knowledge as a marker of arrhythmia in cardiac electrophysiology within the context of the probability of developing arrhythmia. QT range is significant in this regard in the 12-lead ECG. The QT interval is predominantly defined by the repolarization duration that refers to the JT interval. Thus, as a more acceptable indicator of ventricular repolarization than the QT, the JT interval has been suggested (13). In addition, through the analysis of the JT instead of the QT interval, the probability of incident cardiovascular episodes was better estimated (14,15). In addition to the value of QT and JT intervals, useful parameters in terms of sensitivity to ventricular arrhythmias are Tp-e measurements, which are the predictors of ventricular arrhythmias, and their interaction with QT and JT distances (16-18). Cardiac screening should be carried out in younger patients with palpitations, chest pressure, and difficulty of breathing, by considering chest radiographs (19). Based on disorders like anxiety and panic attacks, the symptoms of these patients are normally dismissed by cardiologists. Furthermore, panic disorder patients demonstrated even greater ventricular repolarization parameters than healthy controls (20). Nevertheless, as our research indicates, these patients should bear in mind that, as they appear to have ventricular arrhythmias, supervision should be continued for more than 24 hours.

Table 2. Electrocardiographic findings

	Control group (n=47)	Small heart group (n=47)	p
Heart rate, bpm	87.81+15.532	83.81+14.372	0.223
QRS; ms	83.23+6.948	81.91+10.052	0.206
QT max; ms	354.93+26.796	358.54+28.434	0.528
QT min; ms	330.68+26.611	323.04+30.829	0.202
JT; ms	265.7+25.16	271.88+23.104	0.218
QTc max; ms	403.59+18.208	400.20+18.336	0.371
QTc min; ms	379.34+20.064	364.71+23.149	0.004*
JTc; ms	314.37+21.325	313.55+22.526	0.856
cQTd; ms	24.246+9.046	35.495+14.358	<0.001*
Tp-e; ms	67.32+11.661	72.67+11.028	0.04*
Tp-e/QT max	0.190+0.034	0.203+0.031	0.063
Tp-e/QTc max	0.166+0.028	0.181+0.027	0.012*
Tp-e/JT	0.255+0.047	0.267+0.036	0.295
Tp-e/JTc	0.214+0.038	0.232+0.034	0.022*

bpm: Beat per minute, ms: millisecond, QTc_{max}: Corrected QT_{max}, QTc_{min}: Corrected QT_{min}, JT interval (JT): Were measured from the end of the QRS complex (J point) to the end of the T wave (JTend interval), JTc: Corrected JT interval, cQTd: cQT dispersion (QTd) was determined as the difference between the maximum and minimum QTc interval, Tp-e: T peak and end interval

This idea is supported by the connection between this condition and chronic fatigue syndrome. Previous studies have identified the association between chronic fatigue syndrome and low output syndrome (21,22). A widespread and complex chronic pain disorder, impacting 1% to 5% of the population, Fibromyalgia (FM) is defined as a chronic systemic pain that lasts for more than 3 months without any apparent organic lesion (23-25). Furthermore, it is known that chronic fatigue syndrome is connected with fibromyalgia, which is one of the leading symptoms of abnormal chest pain. The susceptibility of this group of patients with anxiety and depression to ventricular arrhythmias is also established (26,27).

Study Limitations

A significant drawback is to make manual calculations rather than computer-based calculations for the quantities. For calculating QT values, automated measurement programs have been designed. Nevertheless, there have been still some challenges present with these systems (28). Based on several parameters, especially coronary artery disease and hormones, ventricular repolarization may differ (29). Since we did not get coronary angiography, we did not have adequate evidence to explain this concern. Analyses were conducted on the ECGs of the patients and echocardiography did not support these results.

Conclusion

As in the result of this retrospective study, it should be noted that when any arrhythmias are detected, patients having small hearth syndrome with improved prediction levels of ventricular arrhythmia should be monitored more closely through sequential ECG shots and reconfiguration. With this monitoring, the possibility of hemodynamic dysfunction that can lead to arrhythmia or cardiac arrest that can contribute to death can be reduced. To validate our findings, long term monitoring and extensive prospective investigations are necessary.

Ethics

Ethics Committee Approval: The study complies with the Declaration of Helsinki. University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital approved the study protocol at 15/01/2021 with number of 625.

Informed Consent: Informed consent was obtained from participants participating in the study in this article.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.İ., Design: E.İ., Data Collection or Processing: B.B., Analysis or Interpretation: B.B., Drafting Manuscript: E.İ., Critical Revision of Manuscript: B.B., Final Approval and Accountability: E.İ.

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. Master AM. Neurocirculatory asthenia due to small heart. Med Clin North Am 1944;28(3):577-588.
2. Miwa K, Fujita M. Is small heart syndrome a "heart" disease or low output syndrome? Int J Cardiol 2011;146(1):95-96.
3. Pelter MM, Suba S, Sandoval C, Zègre-Hemsey JK, Berger S, Larsen A, et al. Actionable Ventricular Tachycardia During In-hospital ECG Monitoring and its Impact on Alarm Fatigue. Crit Pathw Cardiol 2020;19(2):79-86.
4. Suba S, Sandoval CP, Zègre-Hemsey JK, Hu X, Pelter MM. Contribution of Electrocardiographic Accelerated Ventricular Rhythm Alarms to Alarm Fatigue. Am J Crit Care 2019;28(3):222-229.
5. Tse G, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. Europace 2017;19(5):712-721.
6. Inanir M, Sincer I, Erdal E, Gunes Y, Cosgun M, Mansiroglu AK. Evaluation of electrocardiographic ventricular repolarization parameters in extreme obesity. J Electrocardiol 2018;53:36-39.
7. Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. Clin Cardiol 2008;31(7):328-333.
8. Fukuda K, Straus SE, Hickle I, Sharpe Mc, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121(12):953-959.
9. Abe T. Small heart syndrome. Asian Med J 1990;33:295-302.
10. Hodges M, Salerno D, Erlien D. Bazett's QT correction reviewed. Evidence that a linear QT correction for heart is better. J Am Coll Cardiol 1983;1:694.
11. Hnatkova K, Johannesen L, Vicente J, Malik M. Heart rate dependency of JT interval sections. J Electrocardiol 2017;50(6):814-824.
12. Cantillon DJ, Saliba WI, Wazni OM, Kanj M, Starling RC, Tang WHW, et al. Low Cardiac Output Associated With Ventricular Tachyarrhythmias in Continuous-Flow LVAD Recipients With a Concomitant ICD (LoCo VT Study) J Heart Lung Transplant 2014;33(3):318-320.
13. Spodick DH. Reduction of QT-interval imprecision and variance by measuring th eJT interval. Am J Cardiol 1992;70(1):628-629.
14. Tsai SF, Houmsse M, Dakhil B, Augostini R, Hummel JD, Kalbşeisch SJ, et al. QTc compared to JTc for monitoring drug-induced repolarization changes in the setting of ventricular pacing. Heart Rhythm 2014;11(3):485-491.
15. Zulqarnain MA, Qureshi WT, O'Neal WT, Shah AJ, Soliman EZ. Risk of mortality associated with QT and JT interval sat different levels of QRS duration (from the third national health and nutrition examination survey). Am J Cardiol 2015;116(1):74-78.
16. Monitillo F, Leone M, Rizzo C, Passantino A, Iacoviello M. Ventricular repolarization measures for arrhythmic risk stratification. World J Cardiol 2016;8(1):57-73.
17. Miwa K, Fujita M. Small heart with low cardiac output for orthostatic intolerance in patients with chronic fatigue syndrome. Clin Cardiol 2011;34(12):782-786.
18. Miwa K, Fujita M. Cardiovascular dysfunction with low cardiac output due to a small heart in patients with chronic fatigue syndrome. Intern Med 2009;48(21):1849-1854.
19. Katz C, Martin RD, Landa B, Chadda KD. Relationship of psychologic factors to frequent symptomatic ventricular arrhythmia. Am J Med 1985;78(4):589-594.
20. Jones GT, Atzeni F, Beasley M, FluB E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015;67(2):568-575.
21. Choi DH and, Kim HS. Quantitative analysis of nailfold capillary morphology in patients with fibromyalgia. Korean J Intern Med 2015;30(4):531-537.
22. Son CN, Kim SH, Chang HW, Kim JM. A neurometabolite study of chronic daily headache in patients with systemic lupus erythematosus using magnetic resonance spectroscopy: comparison with fibromyalgia patients and healthy controls. Korean J Intern Med 2016;31(6):1171-1177.
23. Siepmann M, Kirch W. [Psychosomatic aspects of cardiac arrhythmias]. Med Klin (Munich) 2010;105(7):479-484.
24. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease. Circulation 2009;119(5):663-670.
25. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak to tend interval on the resting electrocardiogram is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011;4(4):441-447.
26. Miwa K, Fujita M. Cardiac Function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart". J Cardiol 2009;54(1):29-35.
27. Afsin A, Asoğlu R, Orum MH, Cicekci E. Evaluation of TP-E Interval and TP-E/QT Ratio in Panic Disorder. Medicina (Kaunas) 2020;56(5):215.
28. Grasser EK, Ernst B, Thurnheer M, Schultes B. QT interval shortening after bariatric surgery depends on the applied heart rate correction equation. Obes Surg 2017;27(4):973-982.
29. James AF, Choisy SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. Prog Biophys Mol Biol 2007;94(3):265-319.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):6-11
DOI: 10.4274/BMB.galenos.2021.2021-08-088

Comparison of Radiological Imaging and Reverse Transcriptase Polymerase Chain Reaction Test in Preoperative Screening for Detection of COVID-19

Preoperatif Değerlendirmede COVID-19 Tanısında Radyolojik Görüntülemenin ve Ters Transkriptaz Polimeraz Zincir Reaksiyonu Testinin Karşılaştırılması

Güler Özgül[1], Efsun Gonca Uğur Chousein[2]

[1]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Chest Diseases and Tuberculosis, İstanbul, Turkey
[2]University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases and Tuberculosis, İstanbul, Turkey

Abstract

Objective: It was aimed to compare the diagnostic rates of radiological diagnostic methods such as chest X-rays and chest computerized tomography (CCT) and swab (throat and nose) reverse-transcriptase polymerase chain reaction test (RT-PCR) in preoperative screening for the detection of Coronavirus disease-2019 (COVID-19) infection.

Method: One hundred-seven preoperative patients who were asymptomatic for COVID-19 were retrospectively evaluated. Their demographic data were evaluated along with RT-PCR test results, chest X-rays and CCTs defined according to the Radiological Society of North America expert consensus on COVID-19.

Results: Chest X-rays were performed in 55 (51.4%) cases, and CCT in 52 (48.6%) patients. None of the chest X-rays displayed findings of COVID-19 infection. In 2 (3.8%) CCTs, typical findings of COVID-19 infection were observed. Four (3.7%) cases were RT-PCR positive. The diagnostic rate of radiological methods (chest X-rays and CCT) for COVID-19 was 1.8%, while that of RT-PCR was 3.7%. CCT had a sensitivity of 50%, a specificity of 98%, and accuracy of 96% when compared to RT-PCR for the diagnosis of COVID-19 infection during the preoperative screening of asymptomatic patients.

Conclusion: Radiological diagnostic methods such as chest X-ray and CCT should not be mandatorily/routinely suggested because of their low sensitivity in the diagnosis of COVID-19 infection in preoperative

Öz

Amaç: Preoperatif değerlendirmede Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu tespiti için akciğer grafisi ve toraks bilgisayarlı tomografisi (TBT) gibi radyolojik tanısal yöntemlerin, burun ve boğazdan alınan sürüntüde çalışılan ters transkriptaz-polimeraz zincir reaksiyonu (RT-PZR) testinin tanı oranlarının karşılaştırılması amaçlandı.

Yöntem: Preoperatif değerlendirilen ve COVID-19 açısından asemptomatik olan 107 olgu; demografik verileri, sürüntü RT-PZR testi sonuçları, akciğer grafileri ve Kuzey Amerika Radyoloji Derneği uzman konsensus COVID-19'a göre tanımlanan TBT'leri ile retrospektif olarak değerlendirildi.

Bulgular: Elli beş (%51,4) olgunun akciğer grafisi, 52 (%48,6) olgunun TBT'si vardı. Akciğer grafisi çekilen tüm olguların COVID-19 enfeksiyonu açısından radyolojisi normaldi. TBT çekilen olguların 2'sinde (%3,8) COVID-19 enfeksiyonu açısından tipik görüntü izlendi. RT-PZR testi sonuçlarına bakıldığında 4 (%3,7) olgunun sonucunun pozitif olduğu görüldü. Akciğer grafisi ve TBT ile yani radyolojik olarak COVID-19 tanı oranımız %1,8, RT-PZR ile %3,7 olarak saptandı. TBT çekilen grupta RT-PZR testi referans olarak alındığında preoperatif asemptomatik olgularda COVID-19'u saptamada toraks TBT'nin sensitivitesi %50, spesifitesi %98 ve doğruluk oranı %96 olarak saptandı.

Sonuç: COVID-19 açısından asemptomatik olan preoperatif olgularda COVID-19 enfeksiyonunu saptamada RT-PZR'ye ek olarak akciğer grafisi

Address for Correspondence: Güler Özgül, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Chest Diseases and Tuberculosis, İstanbul, Turkey
E-mail: gulerozgul@hotmail.com **ORCID:** orcid.org/0000-0002-1048-1683 **Received:** 01.08.2021 **Accepted:** 19.12.2021

Cite this article as: Özgül G, Uğur Chousein EG. Comparison of Radiological Imaging and Reverse Transcriptase Polymerase Chain Reaction Test in Preoperative Screening for Detection of COVID-19. Bagcilar Med Bull 2022;7(1):6-11

screening for asymptomatic cases. More studies with larger patient populations will be more illuminating on this issue.

Keywords: Chest computerized tomography, COVID-19, preoperative screening, RT-PCR test

ve TBT gibi radyolojik tanısal yöntemlerin uygulanması düşük sensitivitesi nedeniyle rutin olarak önerilmemelidir, ancak daha fazla sayıda hasta ile daha çok çalışma yapılması bu konuda daha fazla aydınlatıcı olacaktır.

Anahtar kelimeler: COVID-19, preoperatif değerlendirme, RT-PZR testi, toraks bilgisayarlı tomografi

Introduction

The ongoing epidemic due to severe acute respiratory syndrome-coronavirus-2, which emerged due to a highly contagious RNA virus, was declared a global epidemic (pandemic) by the World Health Organization on March 11, 2020, and Turkey announced its first official case on the same day. Although the virus predominantly affects the upper and lower respiratory tract, it can also cause gastrointestinal, hepatic, renal, cardiac and neurological symptoms, and the disease it causes was named Coronavirus disease-2019 (COVID-19) (1,2).

The most common and specific/typical symptoms of COVID-19 include fever, dry cough, shortness of breath, myalgia, fatigue, headache, sore throat, and diarrhea. While 15.6% (95% confidence interval, 10.1-23.0) of confirmed COVID-19 patients may be asymptomatic, the severity of illness can range from simple upper respiratory tract infection to severe pneumonia and acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute cardiac injury, secondary infection, acute kidney injury, and death (3,4).

Preoperative screening for COVID-19 infection during the pandemic aims to protect both patients undergoing surgery and other patients treated in the same ward, as well as the surgical team. The presence of COVID-19 in the preoperative and perioperative period was found to be significantly related to postoperative morbidity and mortality (5). The pulmonary complication rate in COVID-19 patients who underwent surgery was 51.2%, and the mortality rate in these patients was 38% (6). Based on expert opinion in the early stages of the pandemic and publications in the later periods, reverse transcriptase-polymerase chain reaction (RT-PCR), chest X-ray and chest computed tomography (CCT) were used to detect COVID-19 in preoperative screening. It has been reported that chest X-rays are mostly diagnostic in advanced stages of the disease and have a sensitivity between 37% and 57%, even in confirmed COVID-19 patients who are symptomatic (7). Therefore, in most centers, the CCT has been a more common imaging modality for radiological diagnosis.

The aim of the study is to compare the diagnostic rates of these three diagnostic methods in the detection of COVID-19 in pre-operative screening and to determine the most convenient method that can be used in daily practice.

Materials and Methods

The study was approved by the Scientific Board of Yedikule (22.04.2020/114) and the Ministry of Health of the Republic of Turkey (2021-02-05T22_34_57), and it was also carried out in accordance with the Declaration of Helsinki. We retrospectively evaluated 113 patients who presented for preoperative evaluation between August 2020 and December 2020 to the Chest Diseases and Tuberculosis Clinics of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital. Six patients with a history of prior COVID-19 infection were excluded; the remaining 107 patients were included in the study. Patients were destined for either elective or emergency surgery. Patient data including age, gender, smoking history, concurrent diseases, respiratory examination findings, oxygen saturation, chest X-ray, CCT, swab RT-PCR for COVID-19 and the referring clinic were recorded. CCT findings were determined according to the expert consensus on COVID-19 of the Radiological Society of North America (RSNA) (8). According to this,

1- Typical appearance;

a. Peripheral, bilateral, ground glass opacity (GGO) with or without consolidation or visible intralobular lines (“crazy-paving”).

b. Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (“crazy-paving”).

c. Reverse halo sign or other findings of organizing pneumonia (seen later in the disease).

2- Indeterminate appearance;

Absence of typical features and presence of:

a. Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral.

b. Few very small GGO with a non-rounded and non-peripheral distribution.

3- Atypical appearance;

Absence of typical or indeterminate features and presence of:

a. Isolated lobar or segmental consolidation without GGO.

b. Discrete small nodules (centrilobular, "tree-in-bud").

c. Lung cavitation.

d. Smooth interlobular septal thickening with pleural effusion.

4-Negative for pneumonia;

No CT features to suggest pneumonia.

Swab RT-PCR test, chest X-ray, and CCT were compared for their contribution to COVID-19 diagnosis in the preoperative screening.

Results

A total of 107 patients were included in the study, 61 (57%) were male and their mean age was 56.8±14.5 years. Sixty (56.1%) cases had a smoking history (active or ex-smoker) with a mean 38.9±25.7 pack years. Sixty-six (61.7%) patients had comorbid diseases such as hypertension in 35 (32.7%), diabetes mellitus in 27 (25.2%), coronary artery disease in 16 (15%), malignancy in 10 (9.3%), chronic obstructive lung disease in 7 (6.5%), neurologic diseases (Alzheimer's disease, epilepsy, multiple sclerosis, migraine) in 9 (8.4%), hypothyroidism in 4 (3.7%), asthma in 3 (2.8%), and chronic renal failure in 1 (0.9%). All patients were asymptomatic for COVID-19. Abnormal respiratory physical examination findings were detected in 6 patients while oxygen saturation was <90% in 2 (Table 1).

Considering their distribution according to the referring clinics for preoperative evaluation, it was seen that 31 (29%) of them were referred from general surgery, 18 (16.8%) from cardiovascular surgery, 15 (14%) from urology, 11 (10.3%) from neurosurgery, 9 (8.4%) from otorhinolaryngology, 7 (6.5%) from gynecology, 6 (5.6%) from orthopedics, 5 (4.7%) from cardiology, 4 (3.7%) from plastic and reconstructive surgery, and 1 (0.9%) from ophthalmology (Table 1).

Fifty-five (51.4%) patients were preoperatively screened with chest X-rays, and 52 (48.6%) with CCT. None of the chest X-rays revealed the findings of COVID-19 infection. According to the RSNA, CCT findings were negative for pneumonia in 35 (67.3%), typical appearances for COVID-19 infection were detected in 2 (3.8%), undetermined appearances in 5 (9.6%), and atypical appearances in 10 (19.2%). All cases were evaluated with nasal-throat swab RT-PCR test, which was positive in 4 (3.7%) cases and negative in 103 (96.3%) cases (Figure 1). Two of the RT-PCR positive cases had normal chest X-rays and were subsequently evaluated with CCTs. One had typical appearance for COVID-19 and 1 had undetermined appearance. For the diagnosis of COVID-19 in asymptomatic preoperative patients, the diagnostic rate of radiological evaluation including chest X-ray and tomography was 1.8%, while the diagnostic rate of RT-PCR was 3.7%.

In the preoperative screening of cases for COVID-19 infection, the diagnostic contribution of the swab RT-PCR test was higher than radiological evaluation. This result was attributed to the fact that all cases were asymptomatic, CCT was not obtained from all patients. Because, in our study, all chest X-rays were normal for COVID-19, cases with the CCTve RT-PCR test were separately examined. When the RT-PCR test was taken as a reference, the sensitivity of the

Table 1. General characteristics of study population

		n	%
Age (mean ± SD)		56.8±14.5	
Gender	Female	46	43.0
	Male	61	57.0
Smoking history	No	47	43.9
	Yes	60	56.1
Pack/years (mean ± SD)		38.9±25.7	
Comorbid diseases	Yes	41	38.3
	No	66	61.7
Hypertension		35	32.7
Diabetes mellitus		27	25.2
Coronary artery disease		16	15.0
Malignancy		10	9.3
Neurological disease		9	8.4
COPD		7	6.5
Hypothyroidism		4	3.7
Distribution of cases according to departments			
General surgery		31	29
Cardiovascular surgery		18	16.8
Urology		15	14
Brain and neurosurgery		11	10.3
Ear nose throat		9	8.4
Gynecology and obstetrics		7	6.5
Orthopedics and traumatology		6	5.6
Cardiology		5	4.7
Plastic and reconstructive surgery		4	3.7
Ocular surgery		1	0.9

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease

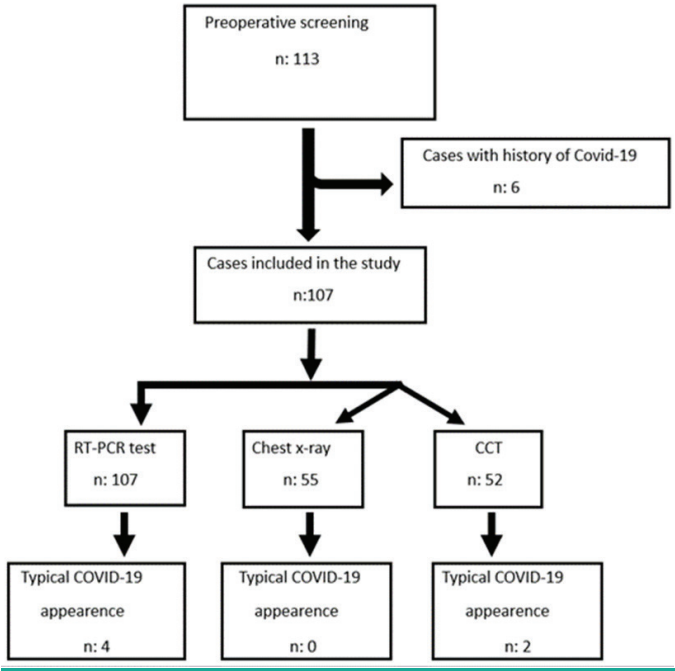


Figure 1. Flow-chart of the study population

COVID-19: Coronavirus disease-2019, CCT: Chest computerized tomography, RT-PCR: Reverse transcriptase-polymerase chain reaction

CCT was 50%, its specificity was 98%, and its accuracy was 96% in preoperative asymptomatic cases (Table 2).

Statistical Analysis

Statistical analysis was performed using the SPSS 27.0 program. All categorical variables are presented as percentages. Variables are given as mean with standard deviation, continuous variables are presented as median and range. The Kolmogorov-Smirnov test was used for the distribution of variables.

Discussion

The use of chest X-ray and/or CCT along with RT-PCR in the diagnostic evaluation of COVID-19 during pandemic has led to many debates. Many studies on this subject reported various conflicting results (9). It is possible that variable factors such as the differences in the possibility of accessing diagnostic tests at different times and incidence periods of COVID-19 and the fact that the studies including the present study were conducted in risky areas such as hospitals and residential areas, where the probability of encountering COVID-19 is high, might have led to these different results. Also, higher incidence of COVID-19 detection in the study population (3.8%) than general population can be explained by the same reasons (2).

Table 2. Comparison of diagnostic methods for asymptomatic preoperative cases for COVID-19

		n	%
RT-PCR	Yes	107	100
RT-PCR result	Positive	4	3.8
	Negative	103	96.2
Sensitivity/specificity/accuracy	-	-	-
Diagnostic rate	-	-	3.8
Chest X-ray	Yes	55	51.4
Typical COVID-19 appearance	Yes	0	0
	No	55	100
Sensitivity/specificity/accuracy	-	-	-
Diagnostic rate		0	0
Chest CT	Yes	52	48.6
Typical COVID-19 appearance	Yes	2	3.8
Negative image for COVID-19	No	35	67.3
Undetermined appearance	No	5	9.6
Atypical appearance	No	10	19.2
Sensitivity (RT-PCR taken as a reference)			50
Specificity (RT-PCR taken as a reference)			98
Accuracy (RT-PCR taken as a reference)			96
Diagnostic rate			1.8

SD: Standard deviation, RT-PCR: Reverse transcriptase-polymerase chain reaction, CT: Computerized tomography, COVID-19: Coronavirus disease-2019

Considering that preoperative screening during the COVID-19 pandemic should be different from routine screening programs especially in asymptomatic patients, the study was planned to evaluate the contributions of RT-PCR, chest X-ray and CCT to the diagnosis separately and to determine the most convenient one. It was found that the diagnostic rate of the RT-PCR test for detecting COVID-19 was higher than radiological evaluation with a percentage of 3.8 compared to 1.8.

It is known that chest X-rays can often detect COVID-19 lung involvement in the advanced stages of the disease. However, it can be preferably used as an initial radiologic imaging for case detection in endemic areas or during peak periods of the disease because of its low cost, wide availability and the ease of use of a portable form (10). Sensitivity and specificity of chest X-rays have been found at rates ranging from 25-67% to 90%, even in symptomatic COVID-19 patients (7,9). Some studies have suggested that chest X-rays should not be used for screening tests or patient follow-up, especially in asymptomatic or oligosymptomatic patients (1,10). In accordance with these suggestions, it was found that none of the chest X-rays of 55 asymptomatic cases showed findings consistent with COVID-19, and 2 (3.6%) cases had positive RT-PCR.

Different diagnostic sensitivity rates have been reported for CCT, which is used as another radiological diagnostic method in the detection of COVID-19. It was found that CCT's sensitivity is higher but specificity is lower in symptomatic COVID-19 patients. On the other hand, on asymptomatic COVID-19 patients, CCT appears to have lower sensitivity, but higher specificity. In a study by Ai et al. (11), RT-PCR positivity rate among symptomatic patients was found to be 59% while 88% of their CCTs had findings compatible with COVID-19. The sensitivity of CCT in detecting COVID-19 was 97%, and its specificity was 25%. The difference between the results of different studies may be attributed to the heterogeneity of the study populations. One study group may consist of contact cases in quarantine, while another group may consist of preoperative cases without any contact. Another reason may be the changing prevalence of the infection with time in that population (12).

Callaway et al. (13) found the sensitivity of CCT as 68.4% and its specificity as 87.9% in a study population of mostly negative RT-PCR confirmed 820 cases in whom emergent and elective surgeries were performed in a short time interval with some incomplete data such as whether there was a known delay to surgery and whether the patient subsequently tested positive.

In our study, it was observed that the sensitivity of CCT was 50%, which is low, and its specificity was 98%, which may be explained by the fact that all of our cases were asymptomatic (13).

Gümüs et al. (14), in their study of preoperative 218 asymptomatic cases, had typical CCT findings for COVID-19 pneumonia in 1 (0.5%) patient. They found typical CT findings in only one of the 3 (1.4%) cases who were RT-PCR test positive. Similarly, only 1 of the 4 (0.9%) RT-PCR positive cases in our study showed typical findings in the CCT. When compared to the RT-PCR test, they found that the sensitivity, specificity and accuracy of the CCT in the diagnosis of COVID-19 infection were 33.3%, 90.7%, and 90.0% respectively; these results are similar to ours (14). When the results of Chetan et al.'s (15) study were compared to those in the present study, similarity in normal chest X-rays (all normal), typical CCT appearance (3%), and a slightly higher RT-PCR positivity ratio (1.6%) was found.

Study Limitations

Limited number of study patient population, from a city with a high burden COVID-19 incidence during a short course of pandemic period including a peak time, should all be accepted as the limitations of the study.

Conclusion

Radiological diagnostic methods such as chest X-ray and CCT should not be mandatorily/routinely suggested because of their low sensitivity in the diagnosis of COVID-19 infection in preoperative asymptomatic cases.

Ethics

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (approval no: 2021/114).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.Ö., E.G.U.C., Design: G.Ö., Data Collection or Processing: G.Ö., E.G.U.C., Analysis or Interpretation: G.Ö., E.G.U.C., Literature Search: G.Ö., E.G.U.C., Writing: G.Ö., Manuscript Review and Revisation: G.Ö., E.G.U.C.

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

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

References

1. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The Role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Radiology 2020;296(1):172-180.
2. Recent coronavirus status in Turkey, Ministry of Health Turkey. Erişim adresi: https://covid19.saglik.gov.tr. Published November 01, 2021.
3. He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis. J Med Virol 2021;93(2):820-830.
4. Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine 2020;21:100331.
5. Kovoor JG, Tivey DR, Williamson P, Tan L, Kopunic HS, Babidge WJ, et al. Screening and testing for COVID-19 before surgery. ANZ J Surg 2020;90(10):1845-1856.
6. COVID Surg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative

SARS-CoV-2 infection: an international cohort study. Lancet 2020;396(10243):27-38.

7. Ippolito D, Pecorelli A, Maino C, Capodaglio C, Mariani I, Giandola T, et al. Diagnostic impact of bedside chest x-ray features of 2019 novel coronavirus in the routine admission at the emergency department: case series from lombardy region. Eur J Radiol 2020;129:109092.
8. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America expert consensus statement on reporting chest CT findings related to COVID-19 endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA—secondary publication. J Thorac Imaging 2020;35(4):219-227.
9. Choi H, Qi X, Yoon SH, Park SJ, Lee KH, Kim JY, et al. Extension of coronavirus disease 2019 on chest CT and implications for chest radiographic ınterpretation. Radiol Cardiothorac Imaging 2020;2(2):e200.
10. Chamorro EM, Tascón AD, Sanz LI, Vélez SO, Nacenta SB. Radiologic diagnosis of patients with COVID-19. Radiologia (Engl Ed) 2021;63(1):56-73.
11. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing for Coronavirus Disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020;296(2):E32-E40.
12. Vafea M, Atalla E, Kalligeros M, Mylona EK, Shehadeh F, Mylonakis E. Chest CT findings in asymptomatic cases with COVID-19: a systematic review and meta-analysis. Clin Radiol 2020;75(11):876.
13. Callaway M, Harden S, Ramsden W, Beavon M, Drinkwater K, Vanburen T, et al. A national UK audit for diagnostic accuracy of preoperative CT chest in emergency and elective surgery during COVID-19 pandemic. Clin Radiol 2020;75(9):705-708.
14. Gümüs T, Kabaoglu ZU, Coskun B, Kartal F, Artukoglu F, Atasoy KC. Preoperative computerized tomography screening for COVID-19 pneumonia in asymptomatic patients: experiences from two centers. Jpn J Radiol 2021;39(3):240-245.
15. Chetan MR, Tsakok MT, Shaw R, Xie C, Watson RA, Wing L, et al. Chest CT screening for COVID-19 in elective and emergency surgical patients: experience from a UK tertiary centre. Clin Radiol 2020;75(8):599-605.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):12-19
DOI: 10.4274/BMB.galenos.2021.2021-11-120

A Retrospective Analysis of the Most Common Bone Metastases of Various Malignant Tumors with Cross-sectional Imaging and 18-FDG-PET/CT Data

Kesitsel Görüntüleme ve 18-FDG-PET BT Verileri ile Çeşitli Malign Tümörlerin En Sık Görülen Kemik Metastazlarının Retrospektif Analizi

Mehmet Öncü[1], Deniz Özel[2]

[1]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırçay University Çiğli Training and Research Hospital, Clinic of Radiology, İzmir, Turkey

Abstract

Objective: To evaluate bone metastases quantitatively and qualitatively with cross-sectional imaging and fluor-18 fluorodeoxyglucose-positron emission tomography (18-FDG-PET) computed tomograph (CT) data.

Method: To obtain study data, the archive of the nuclear medicine of our institute was retrospectively searched for the period from January 2015 to December 2018. For magnetic resonance imaging (MRI) evaluation, the signal intensity ratio of involved tissue to normal adjacent tissue was chosen. For CT evaluation, metastases were labelled to be lytic or sclerotic with regard to the mean density values. Finally, the maximum and the mean standardized uptake values and metabolic tumor volume values were evaluated quantitatively.

Results: All bone metastases presented hypointensity on T1 sequences whereas 96.4% of them presented hypointensity on T2 and hyperintensity on short tau inversion recovery (STIR) sequences. STIR images were found to be valuable to detect metastases. 18-FDG-PET/CT metabolic tumor volume values showed statistically significant difference with regard to the metastatic tumor types. There was not a statistically significant difference between 18-FDG-PET/CT parameters of lytic and sclerotic metastases.

Conclusion: We recommend performing STIR images in routine protocol being performed for other reasons such as disc pathologies to detect incidental bone metastases. MRI signal intensity and SUV values cannot be used to predict the tumor histopathology. Sclerotic or lytic appearance does not correlate 18-FDG-PET/CT parameters for breast and SUV_{max} values for lung cancers. Metabolic tumor volume values differ with the primary tumor histopathology and are also defined to be a promising prognostic factor in the future.

Keywords: 18-FDG-PET/CT, bone metastases, CT, MRI

Öz

Amaç: Kesit görüntüleme ve flor-18 florodeoksiglikoz-pozitron emisyon tomografi (18-FDG-PET) bilgisayarlı tomografi (BT) verileri ile kemik metastazlarını kantitatif ve kalitatif olarak değerlendirmektir.

Yöntem: Çalışma verilerini elde etmek için, enstitümüzün nükleer tıp arşivi, Ocak 2015-Aralık 2018 arasındaki dönem için geriye dönük olarak araştırıldı. Manyetik rezonans görüntüleme (MRG) değerlendirmesi için ilgili dokunun normal bitişik dokuya sinyal yoğunluğu oranı seçildi. BT değerlendirmesi için, ortalama yoğunluk değerlerine göre metastazlar litik veya sklerotik olarak tanımlandı. Son olarak, 18-FDG-PET BT'de maksimum ve ortalama standart uptake değerleri ve metabolik tümör hacmi değerleri kantitatif olarak değerlendirildi.

Bulgular: Tüm kemik metastazları T1 sekanslarında hipointens iken, %96,4'ü T2'de hipo ve kısa tau inversiyon kurtarma (STIR) sekanslarında hiperintensite göstermiştir. STIR görüntüleri metastazı saptamada daha etkin bulundu. Çeşitli tümör tipleri arasında istatistiksel olarak anlamlı bir MRG sinyal yoğunluğu farkı yoktu. 18-FDG-PET/BT metabolik tümör hacmi değerleri metastatik tümör tiplerine göre istatistiksel olarak anlamlı fark gösterdi. Litik ve sklerotik metastazların 18-FDG-PET/BT parametreleri arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Rastlantısal kemik metastazlarını saptamak için disk patolojileri gibi diğer nedenlerle rutin protokolde STIR görüntülerinin yapılmasını öneriyoruz. MRG sinyal yoğunluğu ve SUV değerleri, tümör histopatolojisini tahmin etmek için kullanılamaz. Meme kanseri metastazları için sklerotik veya litik görünüm 18-FDG-PET/BT parametrelerini ve akciğer kanserleri için SUV_{maks} değerlerini etkilemez. Metabolik tümör hacim değerleri, bazı yeni makalelerde belirtildiği gibi prognostik faktör olarak tanımlanabilir.

Anahtar kelimeler: 18-FDG-PET/BT, BT, kemik metastazları, MRG

Address for Correspondence: Deniz Özel, University of Health Sciences Turkey, Bakırçay University Çiğli Training and Research Hospital, Clinic of Radiology, İzmir, Turkey
E-mail: denizozel34@hotmail.com **ORCID:** orcid.org/0000-0002-4950-001X **Received:** 25.11.2021 **Accepted:** 29.12.2021

Cite this article as: : Öncü M, Özel D. A Retrospective Analysis of the Most Common Bone Metastases of Various Malignant Tumors with Cross-sectional Imaging and 18-FDG-PET/CT Data. Bagcilar Med Bull 2022;7(1):12-19

Introduction

The skeletal system is one of the three most occupied regions by the metastases of malignant tumors following the lung and the liver. The presence of bone metastases may be the first evidence while the primary tumor is yet unknown. Defining additional metastases will change the treatment options for cancer patients. In nuclear imaging, fluor-18 fluorodeoxyglucose-positron emission tomography (18-FDG-PET) computed tomography (CT) is an accurate technique "for the detection of skeletal metastases and is superior to bone scan in several studies especially for osteoblastic metastases" (1,2). Considering the difficulties of obtaining pathological specimens, metastatic involvements are often evaluated with cross-sectional and nuclear medicine data. The aim of this study was to evaluate the bone metastatic involvement of various malignancies with cross- sectional and 18-FDG-PET/CT data.

Materials and Methods

The archive of the nuclear medicine clinic and the picture archiving and communication system (PACS) of our institute were retrospectively reviewed from January 2015 to December 2018. We chose the initial date when PACS got functional. This was a single-center study.

All magnetic resonance imaging (MRI) examinations were performed by means of a 1.5 Tesla superconducting magnet with high-speed gradients (Signa Excite, GE Medical Systems, Waukesha, Wisconsin, USA) with a dedicated coil.

Inclusion-exclusion criteria: Patients having malignant tumors with bone metastatic involvement were included in the study. All patients had at least one magnetic resonance (MR) and corresponding PET-CT images obtained after at least 1 month after chemotherapy and radiotherapy. The diagnoses were performed with biopsy results from the primary tumor or if possible, directly from the metastatic lesions.

For each MRI evaluation, two or three planar images were obtained, consisting of fat-suppressed short tau inversion recovery (STIR) images [TR/TE=2400-6280/50-70 ms, FOV=350-400×350-400 mm^2, matrix=192-320×192-240, slice thickness (ST)=4-6 mm, inversion time=170-220 ms], T1-weighted (TR/TE=240-718 ms/5-10 ms, FOV=280-400×280-400 mm^2, matrix=256×256, ST=4-6 mm), and T2-weighted images (TR/TE=1400-6640/80-120 ms, FOV=280-400×280-400 mm^2, matrix=256-330×256-252, ST=4-6 mm).

Nuclear medicine: The patients fasted for at least 6 hours and their blood glucose levels were measured immediately before the administration of FDG. All blood glucose levels were lower than 200 mg/dL. PET/CT images were acquired fifty to sixty minutes after the intravenous injection of 18F-FDG (5-6 MBq/kg body weight). All 18F-FDG PET/CT scans were obtained with a dedicated PET/CT scanner (Siemens Biograph 6, Chicago, IL, USA). After the initial low-dose CT (50 mAs, 140 kV, and 5-mm section thickness), PET images were acquired for 3 minutes per bed position in the 3-dimensional mode.

The FDG-PET/CT images were analyzed by an experienced nuclear medicine specialist using dedicated analysis software (Syngo.via, Siemens Healthcare, Knoxville, TN). The spherical volume of interest (VOI) was drawn to include metastatic bone lesion. Physiologic FDG uptakes of neighbor organs were not included in the VOI. Metabolic tumor volume (MTV) was defined as metastatic tumor volume with a standardized uptake value (SUV) threshold of 2.5. The SUV value was calculated as (the decay-corrected activity of tissue volume)/(injected activity/body mass). MTV, the maximum value of SUV (SUV_{max}) and the mean of SUV (SUV_{mean}) were automatically calculated.

Cross-sectional evaluating: Signal intensity ratios were evaluated by the same experienced radiologist with the PACS software in a largest possible region of interest. The target parameters were chosen to be T1, T2, STIR signal intensity of MRI. In MR imaging, the ratio of tumor-invaded bone marrow signal to the adjacent (nearest possible) non-occupied bone marrow signal was calculated for each parameter (For T1, T2 and STIR signals).

For the tumors with multiple foci, parameters were calculated for the largest lesion.

CT density values were used to define the metastatic involvement, as the groups of lytic and sclerotic with PET-CT images. If the mean density value of involved bone tissue was less than the mean density value of non-occupied bone tissue, this involvement was labelled as lytic and for the opposite situation they labelled as sclerotic. The metastases, showing both cystic and lytic components, were labelled with the dominant involvement.

Statistical Analysis

The power analysis was used to calculate the minimum patient data required for each comparison. Univariate variance analysis was used to compare signal intensity ratios for cross-sectional imaging and to compare 18-FDG-PET/CT parameters with regard to different malignancies with bone metastases. The Student's t-test was used to compare 18-FDG-PET/CT parameters for lytic and

sclerotic metastases for each malignancy. The chi-square test was employed for categorical comparisons namely in the evaluation of the distribution of lytic and sclerotic metastases. Microsoft Excel Program Version 1811 was used for storage and calculations. A p-value of less than 0.05 was considered to be significant.

Ethical approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our IRB (date: 11.9.2018, no: 978). Informed consent was obtained from all individual participants included in the study.

Results

The total number of patients having malignant tumors with bone metastases was 225. One hundred thirty-eight (61.3%) of the patients were female and 87 (38,7 %) were male. The mean age of the patients was 57.1 years, ranging from 13 to 86 years. The distribution of the malignant tumors is shown in Table 1.

Table 1. The demographic data and the distribution of malignancies with bone metastases

Source of bone metastases	The mean age	Female (%)	No of patients	%
Breast	55.85	99.3	139	61.78
Lung	59.6	10.3	39	17.33
Prostate	70.2	0	12	5.33
Colon	60.2	58.3	11	4.88
Urinary bladder	59.4	60	5	2.22
Nasopharynx	40.5	0	4	1.78
Renal	63	0	3	1.34
Thyroid	56	33.3	3	1.34
Miscellaneous	53.8	22	9	4
Overall	57.2	61.3	225	100

All bone metastases presented hypointense on T1 images with the signal ratios between 0 and 1. The mean ratio was higher and closer to 1 for T2 images but there was not a statistically significant difference between the various tumor types. Most of the tumors (217 tumors and 96.4%) presented hyperintensity on STIR images and the mean signal ratio was greater than 1. There was not a statistically significant difference in various tumor types. The lytic-sclerotic distribution was different for each tumor metastases (Table 2). Figure 1 shows multiple breast cancer metastasis.

18-FDG-PET/CT SUV_{max} and SUV_{avg} values showed no statistically significant difference with regard to the tumor types except for MTV (Table 3). There were no statistically significant differences between PET-CT values of lytic and sclerotic metastases (Table 4). Figure 2 shows a breast cancer metastasis to the iliac bone with an MTV value of 16.8. Figure 3 shows increased detectability of the lesions with STIR image compared to T2 in a nasopharynx cancer case with multiple vertebral metastases. Figure 4 summarizes the cross-sectional image characteristics and PET-CT parameters of various bone metastases.

Discussion

The most common malignant tumor with bone metastases was breast cancer in our study. More than 60% of all patients had breast cancer. This tumor is commonly seen and tends to spread to bone tissues. According to our demographic data, the group with the highest mean age was the prostate, the lowest was the nasopharyngeal cancer cases. Metastatic breast cancer was seen nearly always among females (except 1 case). Metastatic lung cancer was mostly seen among males.

After obtaining CT density values, all prostate metastases were defined to be sclerotic. There was a balance for the lung metastases. Breast and colon metastases showed sclerotic predominance. Our results were concordant with

Table 2. Signal intensity ratios for CT and MRI. Data presented as mean ± standard deviation and range in brackets [F=0.88 (T1), 2.36 (T2), 0.04 (STIR)] (chi-square: 11.57)

Source of bone metastases	T1 (Mean ± SD)	T2 (Mean ± SD)	STIR (Mean ± SD)	Lytic metastases predominance (%)
Breast (n=139)	0.43±0.14 (0.2-0.81)	0.57±0.18 (0.3-1)	2.5±2.14 (0.33-15)	38.1
Lung (n=39)	0.47±0.17 (0.2-0.9)	0.68±0.26 (0.23-1)	2.61±0.87 (1.2-4.8)	51.3
Prostate (n=12)	0.4±0.11 (0.3-0.6)	0.67±0.09 (0.6-0.7)	2.56±0.9 (1.4-4.6)	0
Colorectal (n=11)	0.47±0.15 (0.3-0.7)	0.68±0.12 (0.6-0.81)	2.3±1.24 (1.2-3.9)	27.2
p	0.42	0.09	0.99	<0.01

SD: Standard deviation, CT: Computed tomography, MRI: Magnetic resonance imaging, STIR: Short tau inversion recovery

Table 3. Comparison of nuclear medicine parameters regards to different malignancies with bone metastases. Data presented as mean ± standard deviation and range in brackets (other metastatic tumors were not included in the statistical evaluation because the number of cases was not sufficient)
[F=2.53 (SUV_{max}), 2.36 (SUV_{avg}), 3.85 (MTV)]

Source of bone metastases	SUV_{max} (Mean ± SD)	SUV_{avg} (Mean ± SD)	MTV (Mean ± SD)
Breast cancer (n=139)	10.18±5.17 (2.63-22.83)	5.01±1.3 (0.05-8.05)	16.2±20.1 (0.05-108)
Lung cancer (n=39)	14.85±11.04 (5.46-60.23)	6.15±2.1 (3.59-17.37)	45.7±37.3 (0.99-264.5)
Prostate cancer (n=12)	8.58±10.4 (5.62-13.56)	4.57±2.04 (3.96-5.37)	39.3±38.6 (3.37-117.5)
Colorectal cancer (n=11)	9.27±9.52 (3.99-13.15)	4.7±1.96 (3.18-5.94)	55.4±39.2 (4.61-141.77)
p	0.32	0.29	<0.01

SUV: Standardized uptake value, SD: Standard deviation, MTV: Metabolic tumor volume

Table 4. Comparing nuclear medicine parameters for lytic and sclerotic metastases for each malignancy. Data presented as mean ± standard deviation

	SUV_{max} (Mean ± SD)	SUV_{avg} (Mean ± SD)	MTV (Mean ± SD)	p
Lytic breast cancer metastases (n=53)	10.22±4.97	4.86±1.45	20±14.54	SUV_{max}: NA
Sclerotic breast cancer metastases (n=86)	10.99±5.04	5.17±1.37	13.1±13.94	SUV_{avg}: NA MTV: 0.10
Lytic lung cancer metastases (n=20)	19.1±8.37	7.16±4.34	20.02±55.43	SUV_{max}: 0.07
Sclerotic lung cancer metastases (n=19)	12.03±5	5.36±3.45	13.16±50.13	SUV_{avg}: NA MTV: NA
Lytic colorectal cancer metastases (n=3)	11±2.55	5.35±2.58	80.7±30.8	SUV_{max}: NA
Sclerotic colorectal cancer metastases (n=8)	9.28±1.91	4.63±2.88	50.4±35.3	SUV_{avg}: NA MTV: NA

NA: Not applicable due to power analysis, SD: Standard deviation, SUV: Standardized uptake value, MTV: Metabolic tumor volume

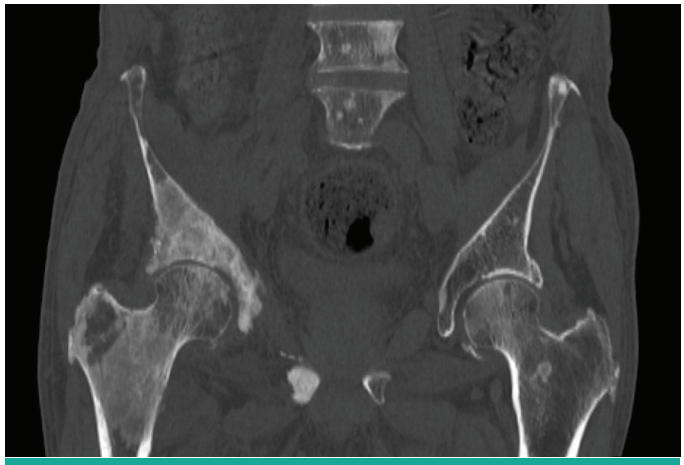


Figure 1. Shows multiple breast cancer metastasis

a review article (3). That was the only semi-quantitative parameter we evaluated in this study. The bone densities show large variability for each patient and it seems to be impossible to standardize them because can be affected by many parameters such as, age, gender, drug use etc. So, we grouped bone metastases as lytic and sclerotic. With this study, SUV and MTV values were also compared to evaluate if these values could be affected in terms of lytic and sclerotic metastases for different malignancies.

There was not a statistically significant difference between SUV values of lytic and sclerotic metastases. We must remind the readers about the limited data for many different cancer metastases at this point. The number of cases allowed to evaluate two kinds of tumor's metastatic lesions. They were breast and lung cancer metastases. Our results were concordant with an article and the authors declared that PET with 18F-fluoride showed no differences in "the uptake of 18F between lytic and sclerotic lesions for breast cancer metastases" and the substance used in this study was also different (4). Likewise, Koolen et al. (5) reported 4 cases of FDG-avid sclerotic bone metastases in breast cancer patients.

Choosing the quantitative parameters for MRI was important from the very beginning of the study. The signal intensity of the tissue alone would not be an optimal choice because the signal intensity of bone marrow can be affected by several issues such as red-yellow marrow distribution

Figure 2. Shows a breast cancer metastasis to the iliac bone with a MTV value of 16.8

MTV: Metabolic tumor volume, CT: Computed tomography, PET: Positron emission tomography

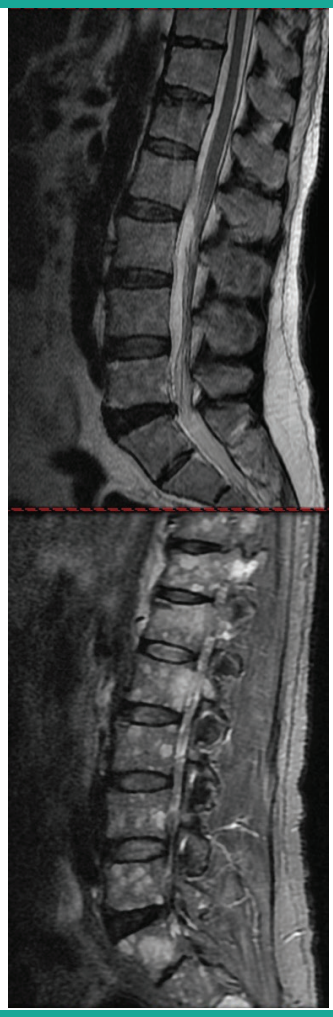


Figure 3. Shows increased detectability of the lesions with STIR image compared with T2 in a nasopharynx cancer case with multiple vertebral metastases

STIR: Short tau inversion recovery

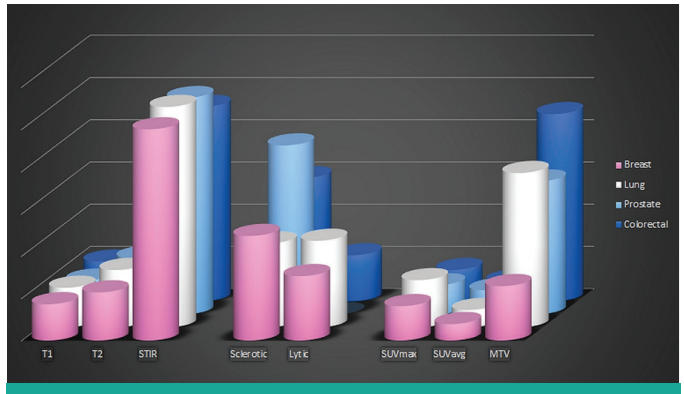


Figure 4. The chart summarizes the cross-sectional image characteristics and PET-CT parameters of various bone metastases

PET-CT: Positron emission tomography-computed tomography, SUV: Standardized uptake value, MTV: Metabolic tumor volume, STIR: Short tau inversion recovery

or hemopoietic diseases such as anemia. We experienced that even the patient's weight might affect alone the signal intensity. We decided to use the lesion intensity ratio to nearby non-occupied tissue intensity ratio to standardize the results.

In evaluating T1 signal intensity, all ratio values were between 0 and 1, which indicates that all bone metastases were hypointense on T1 images. It can be justified that T1 hyperintensity can exclude metastasis alone. On the other hand, we must note that we encountered only one patient with bone metastases from malignant melanoma and melanin was a known T1 hyperintense substance. However, this patient's metastases also showed T1 hypointensity.

According to our results, most of the bone metastases showed hyperintensity on STIR images and the mean STIR intensity was higher than 1 for bone metastases. On the other hand, the mean T2 signal intensity was higher than the mean T1 signal intensity and was closer to 1, which indicates that bone metastases were hypointense as they were on T1 images most of the time (93%) 4.6% of the bone metastases the ratio was 1 indicates bone metastases were completely invisible on T2 sections. As a well-known entity, one of the most important factors for a lesion to be detected is its contrast with the adjacent or normal identical tissues. According to our results, the presence of T2 images cannot make a real contribution to existing parameters in order to define metastatic involvement. Instead, STIR sequences are potentially more applicable to detect them. In spinal MRI imaging, T2 sequences are obtained in a routine manner (for instance, degenerative disc pathologies). Here, we recommend obtaining both T2 and STIR images together in routine examinations to detect incidental metastasis of the patients being examined for the other reasons. As mentioned in the introduction, the presence of bone metastases may be the first evidence while the primary tumor is yet unknown. After a literature search, it was revealed that most of the studies were concerning about detectability of bone metastases for different modalities especially distinguishing bone metastases from the other lesions. Bratu et al. (6) concluded that bone metastases had no specific signal intensity. Velloni et al. (7) defined hepatocellular carcinoma metastases to be hyperintense on fat saturated images. A quantitative retrospective study was performed to distinguish lytic metastases from hemangiomas. Their parameters were T1 signal, chemical shift imaging, and diffusion-weighted imaging (8).

It was also planned to evaluate 18-FDG-PET/CT values qualitatively. For this purpose, SUV_{max} and SUV_{avg} values were examined. We did not find a statistically significant difference for both SUV_{max} and SUV_{avg} values for different tumor types. On the other hand, the mean MTV values were statistically different among tumor types. MTV represents the tissues showing active 18F-FDG uptake and consists of both the dual characteristics of volumetric data and the metabolic activity of the lesion (9). According to our results, colon cancer metastases showed the highest mean MTV values whereas breast cancer metastases showed the lowest. There are several studies mentioning the relationship between the mean MTV values and the prognostic outcome. First of them was a novel volume based on predictive values study promising prognostic indicators such as disease-free-survival. The parameters used in this study were MTV and total lesion glycolysis (10). Chung et al. (9) concluded that "MTV has a potential value in predicting short-term outcome and disease-free survival in patients with pharyngeal cancers". According to Ulaner et al. (11), "higher MTV values were associated with shorter overall survival for several different involvements (excluding bones)". They also concluded that "measures of FDG avidity are prognostic biomarkers in newly diagnosed metastatic bone cancers. SUV_{max} and TLG were both predictors of survival in breast cancer patients with bone metastases". There were two additional articles that mentioned MTV values to be used for clinical follow-up (12,13). It is necessary to remember that there are so many indicators to determine the disease's expected outcome, but MTV values may offer additional data.

According to recent studies, combining MRI and PET-CT values was found to be the most functional choice in evaluating bone metastases. There are many articles concerning the comparison of diagnostic performance for various PET-CT techniques. 18-FDG-PET/CT was defined as a superior technique for detecting bone metastases in several articles (14-17). Moreover, according to Avery and Kuo (18), "MRI and FDG-PET/CT outperformed CT in most situations. The diagnostic accuracy of X-ray and bone scintigraphy were notably inferior to other modalities". They performed a comparison among the five most common malignancies with bone metastases; they were lung cancer, breast cancer, multiple myeloma, lymphoma and prostate cancer with descending order. Furthermore, MRI was found to be better than other techniques on the per-patient and per-lesion basis for the diagnosis of vertebral metastases in another meta-analysis including 33 chosen studies (19). The radiologists tend to correlate imaging findings with SUV values before their final decision also vice versa for nuclear medicine specialists. In our case, we had the opportunity to discuss all cases in the multidisciplinary council.

When the subject is quantitative evaluation, we found an article which revealed quantitative signal parameters and compared healthy and metastatic tissues in terms of ADC values (20). This article was close to our subject but with the difference that we evaluated conventional T1, T2 signals.

Study Limitations

Contrast-enhanced slices were not standardized; some were obtained with gradient echo sequences and some were with spin echo sequences. Besides, contrast enhancement could be affected with other reasons such as the body weight,

administration process, and timing etc. Finally, some of the metastases were defined without contrast-enhanced slices. To obtain objective results, we felt ourselves to be forced to exclude contrast-enhanced images and this was the first limitation.

We could not include all tumor types in our study for statistical comparison because the total number of cases did not meet the requirements in power analysis. These tumors are grouped under the miscellaneous name. Our data were limited for different kinds of malignancies and this should be counted as the second limitation.

Conclusion

Obtaining STIR images to define incidental bone metastases in the routine protocol is recommended. The presence of an additional bone involvement of any malignancy will substantially change the outcome and intervening the therapy can positively affect the treatment. All bone metastases were T1 hypointense and STIR images were more applicable compared to T2 images. MRI signal intensity and SUV values cannot be used to distinguish the primary tumor. Sclerotic or lytic appearance does not affect 18-FDG-PET/CT parameters for breast and SUV_{max} values for lung cancers. MTV values differ with the primary tumor and that was assigned as a promising prognostic factor in recent studies.

Acknowledgement

We would like to thank nuclear medicine clinic for sharing their data.

Ethics

Ethics Committee Approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by our IRB (date: 11.9.2018, no: 978).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ö., D.Ö., Desing: M.Ö., D.Ö., Data Collection or Processing: M.Ö., D.Ö., Analysis or Interpretation: M.Ö., D.Ö., Drafting Manuscript: M.Ö., D.Ö., Final Approval and Accountability: M.Ö., D.Ö.

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

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

References

1. Chang CY, Gill CM, Simeone FJ, Taneja AK, Huang AJ, Torriani M, et al. Comparison of the diagnostic accuracy of 99 m-Tc-MDP bone scintigraphy and 18 F-FDG PET/CT for the detection of skeletal metastases. Acta Radiol 2016;57(1):58-65.
2. Uchida K, Nakajima H, Miyazaki T, Tsuchida T, Hirai T, Sugita D, et al. (18)F-FDG PET/CT for Diagnosis of Osteosclerotic and Osteolytic Vertebral Metastatic Lesions: Comparison with Bone Scintigraphy. Asian Spine J 2013;7(2):96-103.
3. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, et al. Bone Metastases: An Overview. Oncol Rev 2017;11(1):321.
4. Petrén-Mallmin M, Andréasson I, Ljunggren O, Ahlström H, Bergh J, Antoni G, et al. Skeletal metastases from breast cancer: uptake of 18F-fluoride measured with positron emission tomography in correlation with CT. Skeletal Radiol 1998;27(2):72-76.
5. Koolen BB, Vegt E, Rutgers EJ, Wouter VV, Marcel P, Stokkel MP, et al. FDG-avid sclerotic bone metastases in breast cancer patients: a PET/CT case series. Ann Nucl Med 2012;26(1):86-91.
6. Bratu AM, Raica VP, Săcianu IA, Zaharia C, Popa VB, Lupu AR, et al. MRI differential diagnosis: bone metastases versus bone lesions due to malignant hemopathies. Rom J Morphol Embryol 2017;58(4):1217-1228.
7. Velloni F, Ramalho M, AlObaidy M, Matos AP, Altun E, Semelka RC. Bone Metastases of Hepatocellular Carcinoma: Appearance on MRI Using a Standard Abdominal Protocol. AJR Am J Roentgenol 2016;206(5):1003-1012.
8. Shi YJ, Li XT, Zhang XY, Liu YL, Tang L, Sun YS. Differential diagnosis of hemangiomas from spinal osteolytic metastases using 3.0 T MRI: comparison of T1-weighted imaging, chemical-shift imaging, diffusion-weighted and contrast-enhanced imaging. Oncotarget 2017;8(41):71095-71104.
9. Chung MK, Jeong HS, Park SG, Jang JY, Son YI, Choi JY, et al. Metabolic tumor volume of [18F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts short-term outcome to radiotherapy with or without chemotherapy in pharyngeal cancer. Clin Cancer Res 2009;15(18):5861-5868.
10. Satoh Y, Onishi H, Nambu A, Araki T. Volume-based parameters measured by using FDG PET/CT in patients with stage I NSCLC treated with stereotactic body radiation therapy: prognostic value. Radiology 2014;270(1):275-278.
11. Ulaner GA, Eaton A, Morris PG, Lilienstein J, Jhaveri K, Patil S, et al. Prognostic value of quantitative fluorodeoxyglucose measurements in newly diagnosed metastatic breast cancer. Cancer Med 2013;2(5):725-733.
12. Kim YI, Kang HG, Kim SK, Kim JH, Kim HS. Clinical outcome prediction of percutaneous cementoplasty for metastatic bone tumor using (18)F-FDG PET-CT. Ann Nucl Med 2013;27(10):916-923.
13. Cysouw M, Bouman-Wammes E, Hoekstra O, Eertwegh AVD, Piet M, Moorselaar JV et al. Prognostic Value of [18F]-Fluoromethylcholine Positron Emission Tomography/Computed Tomography Before

Stereotactic Body Radiation Therapy for Oligometastatic Prostate Cancer. Int J Radiat Oncol Biol Phys 2018;101(2):406-410.

14. Capitanio S, Bongioanni F, Piccardo A, Campus C, Gonella R, Tixi L et al. Comparisons between glucose analogue 2-deoxy-2-(18F) fluoro-D-glucose and 18F-sodium fluoride positron emission tomography/computed tomography in breast cancer patients with bone lesions. World J Radiol 2016;8(2):200-209.

15. Seo HJ, Kim GM, Kim JH, Kang WJ, Choi HJ. 18F-FDG PET/CT in hepatocellular carcinoma: detection of bone metastasis and prediction of prognosis. Nuc Med Commun 2015;36(3):226-233.

16. Ito S, Kato K, Ikeda M, Iwano S, Makino N, Tadokoro M, et al. Comparison of 18F-FDG PET and bone scintigraphy in detection of bone metastases of thyroid cancer. J Nucl Med 2007;48(6):889-895.

17. Lange MB, Nielsen ML, Andersen JD, Lilholt HJ, Vyberg M, Petersen LJ. Diagnostic accuracy of imaging methods for the diagnosis of skeletal malignancies: A retrospective analysis against a pathology-proven reference. Eur J Radiol 2016;85(1):61-67.

18. Avery R, Kuo PH. 18F Sodium Fluoride PET/CT Detects Osseous Metastases From Breast Cancer Missed on FDG PET/CT With Marrow Rebound. Clin Nucl Med 2013;38(9):746-748.

19. Liu T, Wang S, Liu H, Meng B, Zhou F, HE F, et al. Detection of vertebral metastases: a meta-analysis comparing MRI, CT, PET, BS and BS with SPECT. J Cancer Res Clin Oncol 2017;143(3):457-465.

20. Jacobs MA, Macura KJ, Zaheer A, Antonarakis ES, Stearns V, Wolff AC, et al. Multiparametric Whole-body MRI with Diffusion-weighted Imaging and ADC Mapping for the Identification of Visceral and Osseous Metastases from Solid Tumors. Acad Radiol 2018;25(11):1405-1414.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):20-26
DOI: 10.4274/BMB.galenos.2022.2021-10-105

Critically Ill Obstetric Patients in Intensive Care Unit: A Single-center Ten-year Retrospective Cohort Study

Yoğun Bakım Ünitesindeki Kritik Obstetrik Hastalar: Tek Merkezli On Yıllık Geriye Dönük Kohort Çalışması

Mehmet Salih Sevdi

University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Abstract

Objective: In critically ill obstetric patients (COPs), an exacerbation of both a pre-pregnancy disease and newly emerging additional diseases during and after pregnancy may occur. There are limited data on intensive care unit (ICU) follow-up of COPs in literature. The aim of this retrospective study was to evaluate the COPs that we have followed in ICU in the last 10 years, to investigate the frequency and the reasons of admission to the ICU, and the factors affecting outcomes and mortality.

Method: This study was planned retrospectively on COPs who were followed up in the ICU of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between 2011 and 2021.

Results: A total of 220 patients aged 18-50 years, who were diagnosed as COPs, were included in the study. The most frequent admission type to the ICU was after caesarian section (n=129, 58.6%) and the most frequent indication was obstetric hemorrhage (n=56, 25.4%). The average length of stay in the ICU was 2 days (3.5±4), the average length of hospitalization was 6 days (9.1±7.9), the rate of discharge from the ICU was 95.5%, and mortality rate was 4.5%. Gestational age was lower (p<0.05) and first 24 hours acute physiological and chronic health evaluation II and sequential organ failure assessment scores were found significantly higher in the mortal cases (p<0.001).

Conclusion: The most frequent admission type to ICU was due to cesarean section (n=129, 58.6%) and the most common indication for admission was obstetric hemorrhage (n=56, 25.4%). Mortality rate was determined as 4.5%. In COPs, we should be prepared for complications that may arise, and these patients should be followed up and treated appropriately.

Keywords: Critically ill obstetric patient, intensive care unit, maternal mortality

Öz

Amaç: Kritik obstetrik hastalarda (KOPs) hem gebelik öncesi var olan bir hastalığın hem de gebeliğin kendisi ve sonrasında yeni ortaya çıkan ek hastalıkların şiddetlenmesi söz konusudur. Literatürde KOPs'nin takibine yönelik sınırlı sayıda veri bulunmaktadır. Bu çalışmanın amacı yoğun bakım ünitemizde son 10 yılda takip ettiğimiz KOPS'nin retrospektif taranması ile yoğun bakım ünitesine (YBÜ) kabul sıklığı, nedenleri, sonuçları ve mortaliteye etki eden faktörleri araştırmaktır.

Yöntem: Çalışmamız Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi YBÜ'de 2011-2021 tarihleri arasında yatan KOPs üzerinde retrospektif olarak planlandı.

Bulgular: KOPs tanısı alan 18-50 yaş arası 220 hastanın bilgileri çalışmaya dahil edildi. YBÜ'ye hasta kabulü sebebi en sık sezaryen (n=129, %58,6), en sık kabul endikasyonu ise kanama idi (n=56, %25,4). YBÜ yatış süresi ortalama 2 (3,5±4) gün, hastanede yatış süresi ise 6 (9,1±7,9) gün olup, YBÜ'den taburculuk oranı %94,5, mortalite oranı %4,5 olarak tespit edildi. Mortalite görülen hastalarda gestasyonel yaş daha düşük (p<0,05), ilk 24 saat akut fizyoloji ve kronik sağlık değerlendirmesi II skoru, ardışık organ yetmezliği değerlendirme skoru anlamlı olarak daha yüksek bulundu (p<0,001).

Sonuç: YBÜ'ye hasta kabulü en sık sezaryen (n=129, %58,6) sebebiyle; en sık kabul endikasyonu ise obstetrik kanama idi (n=56, % 25,4). Mortalite oranı %4,5 olarak tespit edildi. KOPs ortaya çıkabilecek komplikasyonlara karşı hazırlıklı olunmalı ve bu hastaların takip ve tedavileri uygun şekilde yapılmalıdır.

Anahtar kelimeler: Kritik obstetrik hasta, maternal mortalite, yoğun bakım

Address for Correspondence: Mehmet Salih Sevdi, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
E-mail: salihsevdi@yahoo.com **ORCID:** orcid.org/0000-0001-7484-7501 **Received:** 05.10.2021 **Accepted:** 31.01.2022

Cite this article as: Sevdi MS. Critically Ill Obstetric Patients in Intensive Care Unit: A Single-center Ten-year Retrospective Cohort Study. Bagcilar Med Bull 2022;7(1):20-26

Introduction

Critically ill obstetric patients (COPs) usually consist of young and healthy individuals. In this patient population, an exacerbation of both a pre-pregnancy disease and newly emerging additional diseases during and after pregnancy may occur. In addition, as a result of the complications associated with the applied procedures, a series of events that may result in the death of the mother and the baby can be observed (1,2).

The third of the Millennium Development Goals determined by the United Nations has been determined as reducing the maternal mortality rate in the world (3). According to the 2018 report of the World Health Organization, while the maternal mortality rate was 239/100.000 births in developing countries, it was 12/100.000 births in developed countries (4). According to the data published by the Ministry of Health of the Republic of Turkey in 2019, the maternal mortality rate was 13.1/100.000 live births (5). When maternal mortality rates are examined, it is found that most of them are due to obstetric causes and can be prevented with a quality care. In order to protect maternal and infant health, it is important to detect obstetric problems at the earliest stage and to apply the appropriate intervention as quickly as possible (6).

In the literature, the rate for admission to intensive care unit (ICU) varies between 0.7% and 16%, depending on the level of development (7-10). COPs admitted to the ICU may exacerbate due to both a pre-pregnancy disease and a new comorbidity during and after pregnancy (11). Most of the COPs (75%) are admitted to the ICU, usually due to postpartum complications (12).

In our country, the number of studies on COPs followed in the ICU, explaining maternal mortality and morbidity, is limited and these studies reported low mortality rates (13). The aim of this study is to evaluate the COPs we have followed in our ICU in the last 10 years, to investigate the causes and consequences of admission to ICU and the factors affecting mortality and morbidity retrospectively. These data, which we presented in our study, are important in terms of increasing scientific awareness and for expectant mothers to get the necessary follow-up and treatment before they become COPs.

Materials and Methods

This retrospective study was planned in patients followed up for obstetric reasons in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital ICU between 2011 and 2021, after getting approval from University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, dated 19.04.2021 and numbered 169.

COPs aged 18 years and older, who were treated in the ICU for at least 24 hours, were retrospectively included in the study. Patients who were under the age of 18 years, who had a length of stay in the ICU for less than 24 hours, and who were admitted to the ICU for the second time after discharge were excluded from the study. Demographic characteristics of the patients, maternal age (years), gestational age (weeks), first 24 hours acute physiological and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, duration of mechanical ventilation (days), length of ICU stay (days), length of hospital stay (days) and ICU outcome were recorded. The number of discharged patients and patients who developed mortality in the ICU were recorded. The type of admission to the ICU, e.g. after caesarean section, being transferred from other hospitals or from Obstetrics Clinic of hospital, was reported. Specific interventional procedures in the ICU, invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV), high-flow nasal oxygenation (HFNO), oxygen requirement by mask, need for intubation or tracheotomy, need for plasmapheresis, need for renal replacement therapy, vasoactive agent use, nosocomial infections encountered 48 hours after ICU admission and up to day 10, and the localizations of infection were evaluated. Maternal age, gestational age, APACHE II and SOFA scores of surviving and mortal patients were compared and their effects on mortality were investigated. Univariate and multivariate logistic regression analyses were performed to evaluate mortality in patients.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was assessed with the Kolmogorov-Smirnov test, and the Mann-Whitney U test was used to analyze quantitative independent data. A univariate model was used to find the level of effect on mortality, and a multivariate model logistic analysis was used to find the independent factors that were effective. All statistical analyses were conducted by using SPSS 27.0 program (IBM, USA).

Results

All data of 220 COPs followed up in the ICU of hospital were evaluated in ten years. The distribution of patients

according to the years in our study was 2011 (n=15), 2012 (n=16), 2013 (n=14), 2014 (n=16), 2015 (n=15), 2016 (n=28), 2017 (n=28), 2018 (n=60), 2019 (n=6), 2020 (n=10), and 2021 (n=12).

Demographic and clinical characteristics of the patients were indicated in Table 1. The mean maternal age was 30 (30.7±8.1) years, the mean gestational age was 32 (31.5±3.1) weeks, the median APACHE II score was 16 (5-35), and the median SOFA scores was 2 (0-16). On the other hand, the mean duration of IMV was 1 (2.2±2.9) days, the mean duration of ICU stay was 2 (3.5±4) days; and the mean duration of hospitalization was 6 (9.1±7.9) days. The discharge rate from the ICU was found as 95.5% (n=210), and the mortality rate was 4.5% (Table 1).

Mortality was higher in patients with lower gestational age [30 (29.5±4.18)] compared to those with higher gestational age [32 (31.6±2.98)] ($p<0.05$), and mortality was also higher in patients with higher APACHE II scores [28 (25-35)] and SOFA scores [13 (9-16)] than in those with lower APACHE II [15 (5-35)] and SOFA scores [2 (0-2)] ($p<0.001$). Comparison of the surviving patients and patients with mortality in terms of maternal age, gestational age and APACHE II and SOFA scores are presented in Table 2.

Logistic regression analysis showed that gestational age, APACHE II and SOFA scores were significantly correlated with mortality ($p<0.05$) ($p<0.001$) (Table 3).

Table 1. Demographic and clinical variables

		Min-max	Median	Mean ± SD/n-%
Maternal age (year)		18-50	30	30.7±8.1
Gestation weeks		20-36	32	31.5±3.1
APACHE II score		5-35	16	-
SOFA score		0-16	2	-
Length of mechanical ventilation (days)		1-2	1	2.2±2.9
Length of ICU stay (days)		2-3	2	3.5±4.0
Length of hospital stay (days)		4-10	6	9.1±7.9
ICU outcome (n%)				210/95.5
The reasons for mortality (n%)	Mortality			10/4.5%
	Septic shock			4/1.8%
	CSD			3/1.35%
	DIC			2/0.9%
	Preeclampsia/ eclampsia			1/0.45%

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, ICU: Intensive care unit, MOF: Multiple organ failure, CSD: Cardiovascular system diseases, DIC: Disseminated intravascular coagulation, SD: Standard deviation

The most common type of admission was after caesarean section (n=129; 58.6%). Twenty eight patients (12.7%) were transferred from other hospitals and 63 (28.7%) were transferred from obstetrics clinic of our hospital. The ICU indications were obstetric hemorrhage in 56 patients (25.4%), preeclampsia/eclampsia in 42 patients (19.1%), atypical hemolytic uremic syndrome (HUS) in 31 patients (14.1%), hemolysis elevated liver enzymes low platelet syndrome in 21 patients (9.5%), septicemia in 20 patients (9.1%), shock due to ectopic pregnancy rupture in 16 patients (7.3%), cardiovascular system diseases in 14 patients (6.3%), pulmonary embolism in 7 patients (3.2%), neurological system diseases in 6 patients (2.7%), pneumonia in 5 patients (2.3%), disseminated intravascular coagulation (DIC) in 1 patient (0.45%), and diabetic ketoacidosis in 1 patient (0.45%). Pregnant and COPs with a diagnosis of Coronavirus disease-2019 (COVID-19) were not followed up in our ICU (Table 4).

A total of 131 (59.4%) patients were supported by mechanical ventilation. IMV was performed in 120 patients (54.5%). One hundred eighteen patients (53.6%) were intubated due to respiratory failure and hemodynamic instability. These causes were determined as atonic obstetric hemorrhage, septicemia, HUS, respiratory, neurological and cardiovascular system diseases. Two patients (0.9%)

Table 2. Comparison of patients with mortality and patients who were discharged in terms of their demographic and clinical parameters [data are mean ± SD/median (min-max)]

	Mortality	Discharged	p
Maternal age (year)	30 (31.00±5.83)	30 (30.71±8.16)	0.909[m]
Gestation week	29.55±4.18	31.63±2.98	**0.034**[m]
APACHE II score	28 (25-35)	15 (5-35)	**<0.001**[m]
SOFA score	13 (9-16)	2 (0-9)	**<0.001**[m]

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score. [m]Maternal age and gestational week: Mean ± SD, scores were median (min-max), SD: Standard deviation

Table 3. Regression analysis of the factors affecting mortality

	Univariate model			Multivariate model		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Maternal age	1.00	0.93-1.08	0.908[LR]	0.90	7.02-1.17	0.467[LR]
Gestational age	0.84	0.71-0.98	**0.034**[LR]	0.79	4.74-1.33	0.385[LR]
APACHE II	1.35	1.18-1.54	**<0.001**[LR]	0.78	5.53-1.11	0.181[LR]
SOFA	2.24	1.54-3.28	**<0.001**[LR]	3.47	1.40-8.60	**0.007**[LR]

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, CI: Confidence interval, OR: Odds ratio, [LR]: Lojistic regresyon (forward LR)

Table 4. Diagnosis at the admission and indication to the ICU over the 10-year period (n, %)

Admission type	**n**	**(%)**
After caesarian section	129	58.6
Transferred from other hospitals	28	12.7
From obstetrics clinic of our hospital	63	28.7
ICU indication	**n**	**(%)**
Obstetric hemorrhage	56	25.4
Preeclampsia/eclampsia	42	19.1
Atypical hemolytic uremic syndrome	31	14.1
HELLP syndrome	21	9.5
Sepsis	20	9.1
Ectopic pregnancy rupture	16	7.3
Cardiovascular system diseases	14	6.4
Pulmonary embolism	7	3.2
Neurologic system diseases	6	2.7
Pneumonia	5	2.3
DIC	1	0.45
Diabetic ketoacidosis	1	0.45
Other	0	0.0

HELLP: Hemolysis, elevated liver enzymes low platelet syndrome, DIC: Disseminated intravascular coagulation, ICU: Intensive care unit

Table 5. Specific interventions performed at the ICU (n, %)

	Number of patients	
	(n)	**(%)**
Mechanical ventilation	131	59.5%
Non-invasive mechanical ventilation	11	5.0%
Invasive mechanical ventilation	120	54.5%
High flow nasal oxygen	15	6.80%
Mask	74	33.7%
Intubated	118	53.6%
Tracheostomy	2	0.90%
Plasmapheresis	8	3.6%
Renal replacement therapy (continuous hemofiltration)	32	14.5%
Vasoactive agent use	61	27.7%
Blood transfusion	151	68.6%
Whole blood	68	31.0%
Fresh frozen plasma	110	50.0%
Platelet suspension	62	28.2%
Erythrocyte suspension	139	63.2%
Fibrinogen	40	18.1%

ICU: Intensive care unit

underwent tracheostomy due to prolonged mechanical ventilation. On the other hand, 11 (5.0%) received NIMV support. Fifteen (6.81%) patients required HFNO and 74 (33.6%) patients received oxygen support via face mask.

Plasmapheresis was applied to 8 (3.63%) patients due to atypical HUS. Continuous renal replacement therapy was applied to 32 (14.5%) patients who developed acute renal failure (ARF) and were hemodynamically unstable. Vasoactive agent was used in patients (n=61, 27.7%) to provide hemodynamic stabilization. Totally 151 blood and protects transfusion were performed. One hundred thirty nine units of erythrocyte suspension (ES), 110 units of fresh frozen plasma (FFP), 68 units of whole blood, 62 units of platelet suspension, and 40 flacon fibrinogen were transfused (Table 5).

Nosocomial infections were observed at a rate of 20% in COPs. Most commonly, the infection was localized in genitourinary system (52.3%) and that was followed by soft tissue (22.7%), deep tracheal aspirate (18.2%) and systemic circulatory tract (6.8%). The microbiological analyses revealed the most common infectious agents as *Escherichia coli* (27.3%), *Klebsiella pneumonia* (20.4%), and *Acinetobacter baumanii* (18.2%) (Table 6).

Table 6. Infection data of patients (n, %)

	(n)	**(%)**
Infection occurring after 48 hours	44	20.0
Localizations of infection		
Urine	23	52.3
Soft tissue	10	22.7
Deep tracheal aspiration	8	18.2
Blood	3	6.8
Microorganism		
Escherichia coli	12	27.3
Klebsiella pneumoniae	9	20.4
Acinetobacter baumannii	8	18.2
Candida albicans	7	15.9
Klebsiella oxytoca	2	4.5
Staphylococcus aureus	2	4.5
Proteus mirabilis	1	2.3
Pseudomonas aeruginosa	1	2.3
Staphylococcus agalactiae	1	2.3
Staphylococcus epidermis	1	2.3

Discussion

The mean maternal age of 220 COPs followed in our multidisciplinary ICU was found as 30 (30.7±8.1) years, and the mean gestational age was 32 (31.5±3.1) weeks. The mean gestational and maternal ages of the survival and mortality patients in our study were higher when compared

to the study of Demirkiran et al. (14). It was similar to the study of Dirik et al. (1). The rate of discharge or mortality was similar to that in the studies of Dirik et al. (1), Tezcan Keleş et al. (2) and Demirkiran et al. (14). The reasons for maternal mortality, which were more common in young mother population in our study, may be lack of follow-up, being inexperienced in pregnancy, and presence of a serious disease.

Complications occurring during emergency cesarean section are the most important reasons for hospitalization in the ICU in the perioperative and postoperative period. Consistent with other studies, most of our patients were admitted from the operating room. It has been reported in various studies that patients were transferred to further centers for further follow-up and surgical intervention (9,15). Similarly, 12.7% of the patients who were admitted to the ICU constitute the group of patients referred from other hospitals for further examination and treatment. Although the number of studies on critical COPs is limited, studies have found a correlation between transfer from another hospital and mortality (16-19). In our study, all 220 patients whose follow-up and treatment processes were completed were discharged to the obstetrics clinic of our hospital. No patient was transferred to another center.

Mechanical ventilation support is needed mostly due to pregnancy-related complications (20). Like our results, in the literature, the need for mechanical ventilation support has been reported between 19% and 60%, (8,19,21). In the studies conducted by Tripathi et al. (22) and Togal et al. (23), this rate was 64-85% and was higher than that in our study. The duration of mechanical ventilation of obstetric patients was reported as 3.8±3.5 days in the study conducted by Tezcan Keleş et al. (2) and 4.9 days in the study conducted by Dirik et al. (1). In our study, the mean duration of mechanical ventilation was 1 (2.2±2.9) days. The reason for this was that the weaning processes of the patients were preferred to be performed after their transfer to the ICU rather than in the operating room due to perioperative hemodynamic instability. The mean length of stay in ICU was 4.4 days in the study conducted by Platteau et al. (24), 8 days in the study conducted by Demirkiran et al. (14), 7 days in the study conducted by Togal et al. (23) and 6 days in the study conducted by Dirik et al. (1), while it was 2 (3.5±4) days in our study.

In COPs, prognosis can be predicted by using the APACHE II scoring system (25). Lapinsky et al. (26) defended the opposite of this view in their study (9). In our study, the median APACHE II and SOFA scores were found to be higher in non-survived patients, similar to the studies of Dirik et al. (1) ($p<0.001$). In addition, SOFA score was determined as the only independent factor among the risk factors affecting mortality, similar to the study of Dirik et al. (1) ($p<0.05$).

In COPs, the mortality rate changes between 5% and 27%; however, it has been stated that the causes of mortality include hypertensive diseases (eclampsia and severe preeclampsia), obstetric hemorrhages, sepsis, amniotic fluid embolism, and DIC (27,28). Moreover, inadequate antenatal care significantly increases the risk of pregnancy-related death (29). Hypertensive diseases and obstetric hemorrhages are the two most common obstetric causes requiring ICU (30-32). These three reasons for admission differ due to geography, race, socio-economic status, environmental factors, and different surgical techniques performed (33). Eclampsia is the major cause of maternal mortality in developing countries (34). Demirkiran et al. (14) reported in their study that 73.6% of COPs were admitted due to eclampsia and 11.2% of them due to hemorrhage. Tezcan Keleş et al. (2), on the other hand, reported that COPs were admitted most frequently because of hypertensive diseases (38.7%). Akköz Çevik (28) reported that the major reason for admission to the ICU was obstetric hemorrhages (57%). Ülger et al. (35) reported that the most common reason for admission to the ICU was postpartum hemorrhage (31%) and that was followed by preeclampsia/eclampsia (26%). In the study of Arıcı et al. (27), 46% of the patients had postpartum hemorrhage and 5% of the patients had preeclampsia/eclampsia while Singh et al. (36) reported that 43% of the patients admitted had postpartum bleeding and 31% of the patients had preeclampsia/eclampsia. Our results, similar to all these studies, showed that 25.4% of the patients admitted had obstetric hemorrhage and 19.1% of the patients admitted had preeclampsia/eclampsia.

COVID-19 patients were followed up in our ICU and hospital clinical services between March 15, 2019 and April 20, 2021. Since there was no indication to our ICU between these dates, no obstetric patient with a diagnosis of COVID-19 was hospitalized. A limited number of COPs were admitted to our ICU postoperatively and from the emergency department. For this reason, the number of COPs decreased at the time of our study.

Infection and sepsis are among the important causes of maternal mortality in COPs and this rate has increased within the last 10 years (37,38). The main cause of maternal sepsis is genitourinary infections due to curettage (39).

Group A Streptococcus, staphylococcus, Escherichia coli, anaerobic bacteria and *Candida* are the most common microorganisms causing infections (10). Shields et al. (39) reported an ICU admission rate of 38% with a diagnosis of sepsis. Hedriana et al. (40) reported an ICU admission rate of 24%, Wanderer et al. (31) reported an ICU admission rate of 7.1% and Pollock et al. (7) reported an ICU admission rate of 5.0% due to sepsis. Our ICU acceptance rate due to maternal sepsis was 9.1%. Genitourinary infection was the most common reason for nosocomial infection with a rate of 52.3%. The most common microorganism causing the infection was *Escherichia coli* with a rate of 27.3%, in our study.

Hemorrhage is a common complication in pregnancy and is still almost the most frequent cause of maternal mortality (9,14,41). The rate of hospitalization in the ICU due to pregnancy-related hemorrhage varies significantly. Limited number of studies in the literature reported precise values for blood loss (14). In our study, 56 patients (25.4%) were hospitalized in the ICU due to obstetric hemorrhage and 16 patients (7.6%) were hospitalized due to early uterine rupture. We transfused ES, FFP, platelet, fibrinogen and whole blood, when necessary, and all patients treated for hemorrhage were discharged, except 2 patients who died because of DIC. The mortality of the women due to bleeding during or after childbirth is largely due to their inability to access adequate obstetric care on time (42). Concomitant hemorrhage treatment and the strategy of using blood products are extremely important.

ARF, preeclampsia-eclampsia, postpartum hemorrhage, sepsis, and atypical HUS are frequently seen in obstetric patients due to secondary renal and systemic alterations (33,43). Although its incidence is low, it can be a major cause of morbidity and mortality. Özçelik et al. (13) and Jonard et al. (43) performed dialysis on 14.6% and 29% postpartum patients, respectively. Özçelik et al. (13) reported that plasmapheresis was performed in 21 patients (43.8%) in the postpartum period, and Zhao et al. (37) performed plasmapheresis in 17 patients (3.46%). Like Zhao's study, 3.6% patients received plasmapheresis treatment due to atypical HUS in our ICU.

Study Limitations

The major limitation of our study was its retrospective design. Some of the patient data could not be reached due to insufficient medical records. Another limitation is that it is a single-center study.

Conclusion

This study investigated the way and reasons for admission of COP patients to the ICU and the invasive procedures applied. Our retrospective data showed our mortality rate to be 4.5%. In CPOs, lower gestational age and higher APACHE II and SOFA scores were found to be associated with mortality. There are limited data on the follow-up of COPs in our country. We believe that more studies are needed at the national level in order to determine the factors affecting mortality and morbidity better in this specific patient group.

Ethics

Ethics Committee Approval: This retrospective study was planned in patients followed up for obstetric reasons in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital ICU between 2011 and 2021, after getting approval from University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, dated 19.04.2021 and numbered 169.

Informed Consent: Informed consent was obtained prior to intensive care admission.

Peer-review: Externally and internally peer-reviewed.

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

References

1. Dirik H, Bulut K, Sipahioğlu H, Sungur M, Gündoğan K. Evaluation of critically obstetric ill patients in intensive care unit follow-up: A retrospective 10-year. J Critical Care 2019;10(1):18-22.
2. Tezcan Keleş G, Topçu İ, Kefi A, Ekici Z, Sakarya M. Obstetric patients in intensive care unit. Firat Medical Journal 2006;11(1):62-65.
3. Shayan NA, Özcebe LH. Maternal mortality: A comparison of Afghanistan and its neighboring countries. Turk J Public Health 2017;15(3):222-232.
4. World Health Statistics 2018: Monitoring health for the SDGs, sustainable development goals. Available from: https://www.who.int/docs/default-source/gho-documents/world-health-statistic-reports/6-june-18108-world-health-statistics-2018.pdf
5. TC. Sağlık Bakanlığı Sağlık istatistikleri yıllığı 2019. Erişim linki: https://sbu.saglik.gov.tr/Ekutuphane/kitaplar/saglik-istatistikleri-yilligi-2019pdf.pdf https://www.saglikaktuel.com/d/file/40564,saglik-istatistikleri-yilligi-2019pdf.pdf
6. Ganesan C, Maynard SE. Acute kidney injury in pregnancy: the thrombotic microangiopathies. J Nephrol 2011;24:(5)54-63.
7. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med 2010;36(9):1465-1474.

8. Vasquez DN, Estenssoro E, Canales HS, Reina R, Saenz MG, Das Neves AV, et al. Clinical characteristics and outcomes of obstetric patients requiring ICU admission. Chest 2007;131(3):718-724.

9. Çeray Y, Yılmaz C, Cengiz M, Kaplan S, Ramazanoğlu A. Critically ill obstetric patients. Turk J Intensive Care 2017;15(1):124-129.

10. Vasquez DN, Plante L, Basualdo MN, Plotnikow GG. Obstetric disorders in the ICU. Semin Respir Crit Care Med 2017;38(2):218-234.

11. Baskett TF. Epidemiology of obstetric critical care. Best Practice Res Clin Obstet Gynaecol 2008;22(5):763-767.

12. Gilbert TT, Smulian JC, Martin AA, Ananth CV, Scorza W, Scardella AT; Critical Care Obstetric Team. Obstetric admissions to the intensive care unit: outcomes and severity of illness. Obstet Gynecol 2003;102(5 Pt 1):897-903.

13. Özçelik M, Turhan S, Bermede O, Yılmaz AA, Ünal N, Bayar MK. Outcomes of antepartum and postpartum obstetric admissions to the intensive care unit of a tertiary university hospital: An 8-year review. Turk J Anaesthesiol Reanim 2017;45(5):303-309.

14. Demirkiran O, Dikmen Y, Utku T, Urkmez S. Critically ill obstetric patients in the intensive care unit. Int J Obstet Anesth 2003;12(4):266-270.

15. Dasgupta S, Jha T, Bagchi P, Singh SS, Gorai R, Choudhury SD. Critically ill obstetric patients in a general critical care unit: A 5 years' retrospective study in a public teaching hospital of eastern India. Indian J Crit Care Med 2017;21(5):294-302.

16. Hanane T, Keegan MT, Seferian EG, Gajic O, Afessa B. The association between nighttime transfer from the intensive care unit and patient outcome. Crit Care Med 2008;36(8):2232-2237.

17. Flabouris A, Hart GK, George C. Outcomes of patients admitted to tertiary intensive care units after interhospital transfer: Comparison with patients admitted from emergency departments. Crit Care Resusc 2008;10(2):97-105.

18. Kilpatrick SJ, Matthay MA. Obstetric patients requiring critical care. A five-year review. Chest 1992;101(5):1407-1412.

19. Collop NA, Sahn SA. Critical illness in pregnancy. An analysis of 20 patients admitted to a medical intensive care unit. Chest 1993;103(5):1548-1552.

20. Jenkins TM, Troiano NH, Graves CR, Baird SM, Boehm FH. Mechanical ventilation in an obstetric population: Characteristics and delivery rates. Am J Obstet Gynecol 2003;188(2):549-552.

21. Selo-Ojeme DO, Omosaiye M, Battacharjee P, Rezan AK. Risk factors for obstretric admissions to the intensive care unit in a tertiary hospital: a case-control study. Arch Gyncol Obstet 2005;272(3):207-210.

22. Tripathi R, Rathore AM, Saran S. Intensive care for critically ill obstetric patients. Int J Gynecol Obstet 2000;68(3):257-258.

23. Togal T, Yucel N, Gedik E, Gulhas N, Toprak HI, Ersoy MO. Obstretric admissions to the intensive care unit in a tertiary referral hospital. J Crit Care 2010;25(4):628-633.

24. Platteau P, Engelhardt T, Moodley J, Muckart DJ. Obstetrican gynaecological patients in an intensive care unit: a 1 year review. Trop Doct 1997;27(4):202-206.

25. Karnad DR, Lapsia V, Krishnan A, Salvi VS. Prognostic factors in obstetric patients admitted to an Indian intensive care unit. Crit Care Med 2004;32(6):1294-1299.

26. Lapinsky SE, Kruczynski K, Seaward GR, Farine D, Grossman RF. Critical care management of the obstetric patient. Can J Anaesth 1997;44(3):325-329.

27. Arıcı S, Karaman S, Yılmaz Doğru H, Çakmak B, Tapar H, Karaman T, et al. Multidisipliner Yoğun Bakım Ünitesinde Obstetrik Olgular: Retrospektıf Analiz. Çağdaş Tıp Dergisi 2014;4(1):14-17.

28. Akköz Çevik S. Obstetric cases in the intensive care unit. Perinatal Journal 2011;19(3):118-122.

29. Berg CJ, Atrash HK, Koonin LM, Tucker M. Pregnancy-related mortality in the United States, 1987-1990. Obstet Gynecol 1996;88(2):161-167.

30. Guntupalli KK, Hall N, Karnad DR, Bandi V, Belfort M. Critical illness in pregnancy-Part I: An approach to a pregnant patient in the ICU and common obstetric disorders. Chest 2015;148(4):1093-1104.

31. Wanderer JP, Leffert LR, Mhyre JM, Kuklina EV, Callaghan WM, Bateman BT. Epidemiology of obstetric related intensive care unit admissions in Maryland: 1999-2008. Crit Care Med 2013;41(8):1844-1852.

32. De Greve M, Van Mieghem T, Van Den Berghe G, Hanssens M. Obstetric admissions to the intensive care unit in a tertiary hospital. Gynecol Obstet Invest 2016;81(4):315-320.

33. Einav S, Leone M. Epidemiology of obstetric critical illness. Int J Obstet Anesth 2019;40(1):128-139.

34. Walker JJ. Pre-eclampsia. Lancet 2000;356(9237):1260-1265.

35. Ülger F, Tosun M, Çelik H, Dilek A, Azar H, Malatyalıoğlu E, et al. Obstetric intensive care admissions: a four-year review in a tertiary care centre. Obstetrics 2010;6(19):29-33.

36. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia 2012;67(1):12-18.

37. Zhao Z, Han S, Yao G, Li S, Li W, Zhao Y, et al. Pregnancy-related ICU admissions from 2008 to 2016 in China: A first multicenter report. Crit Care Med 2018;46(10):1002-1009.

38. Oud L, Watkins P. Evolving trends in the epidemiology, resource utilization, and outcomes of pregnancy-associated severe sepsis: A population-based cohort study. J Clin Med Res 2015;7(6):400-416.

39. Shields LE, Wiesner S, Klein C, Pelletreau B, Hedriana HL. Use of maternal early warning trigger tool reduces maternal morbidity. Am J Obstet Gynecol 2016;214(4):527.e1-527.e6.

40. Hedriana HL, Wiesner S, Downs BG, Pelletreau B, Shields LE. Baseline assessment of a hospital-specific early warning trigger system for reducing maternal morbidity. Int J Gynaecol Obstet 2016;132(3):337-341.

41. Zeeman GG. Obstetric critical care: a blueprint for improved outcomes. Crit Care Med 2006;34(Suppl 9):208-214.

42. Karasu Y, Üstün Y. Obstetric problems requiring intensive care unit admission: Ankara Training and Research Hospital experience. Med J Ankara Tr Res Hosp 2018:51(1):50-53.

43. Jonard M, Bouthors ASD, Boyle E, Aucourt M, Gasan G, Jourdain M, et al. Postpartum acute renal failure: a multicenter study of risk factors in patients admitted to ICU. Ann Intensive Care 2014;4:36.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):27-31
DOI: 10.4274/BMB.galenos.2022.2021-09-095

Relationship Between HbA1c Level and Triglyceride/HDL Cholesterol Ratio and Triglyceride Glucose Index in Diabetes Patients

Diyabetik Hastalarda HbA1c Düzeyi ile Trigliserit/HDL Kolesterol Oranı ve Trigliserit Glikoz İndeksi Arasındaki İlişki

Mustafa Asım Gedikli, Betül Sarı Kalın, Ahmet Aktaş

Sivas Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Sivas, Turkey

Abstract

Objective: To compare HbA1c level with triglyceride/HDL cholesterol (TG/HDL-C) ratio and triglyceride glucose (TyG) Index and to show its relationship with HbA1c level.

Method: Our study was carried out retrospectively on patients who applied to the Department of General Internal Medicine, Sivas Cumhuriyet University Hospital, Turkey, between January 1, 2015 and January 1, 2020. The study is a retrospective review of 2,938 patients. HbA1c, triglyceride, and glucose values of the patients were recorded. TyG index and TG/HDL-C) ratio were found by calculating. Patients were grouped according to their HbA1c levels, TyG index and triglyceride/HDL cholesterol ratios.

Results: We found that the TG/HDL-C ratio and the TyG index were statistically significantly lower as the HbA1c level decreased. When we grouped the patients according to their gender, we found that male patients had higher HbA1c, higher TyG index and TG/HDL-C ratio than female patients.

Conclusion: We found a positive correlation between HbA1c levels and TG/HDL-C ratio and TyG index. Considering other studies in the literature, according to the results of our study, we predict an increased risk of coronary artery disease and cerebrovascular disease in patients with poor glycemic control.

Keywords: Diabetes mellitus, triglyceride glucose index, triglyceride/HDL cholesterol ratio

Öz

Amaç: Çalışmamızdaki amacımız diyabetik hastalarda HbA1c düzeyini trigliserit/HDL kolesterol (TG/HDL-C) oranı ve trigliserit glikoz (TyG) indeksi ile karşılaştırmak ve HbA1c düzeyi ile ilişkisini göstermektir.

Yöntem: Çalışmamız 1 Ocak 2015-1 Ocak 2020 tarihleri arasında Sivas Cumhuriyet Üniversitesi Hastanesi, Genel Dahiliye Anabilim Dalı'na başvuran hastalar üzerinde retrospektif olarak yapılmıştır. Çalışmaya 2.938 hasta dahil edilmiştir. Hastaların HbA1c, trigliserit ve glikoz değerleri kaydedildi. TyG indeksi ve TG/HDL-C Oranı hesaplandı. Hastalar HbA1c düzeylerine göre gruplara ayrılarak TyG indeksi ve TG/HDL-C oranları karşılaştırıldı.

Bulgular: Hastalardaki HbA1c düzeyi azaldıkça TG/HDL-C oranı ve TyG indeksinin istatistiksel olarak anlamlı derecede düşük olduğu izlendi. Hastaları cinsiyetlerine göre grupladığımızda erkek hastaların HbA1c, TG/HDL-K oranı ve TyG indeksinin kadın hastalara göre daha yüksek olduğu görüldü.

Sonuç: Çalışmamızda HbA1c düzeyleri ile TG/HDL-C oranı ve TyG indeksi arasında pozitif korelasyon bulduk. Literatürdeki diğer çalışmalar göz önünde bulundurularak, çalışmamızın sonuçlarına göre glisemik kontrolü kötü olan hastalarda koroner arter hastalığı ve serebrovasküler hastalık riskinde artış olduğunu öngörüyoruz.

Anahtar kelimeler: Diabetes mellitus, trigliserit glikoz indeksi, trigliserit/HDL kolesterol oranı

Address for Correspondence: Mustafa Asım Gedikli, Sivas Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Sivas, Turkey
E-mail: asimgedikli@gmail.com **ORCID:** orcid.org/0000-0002-3494-7935 **Received:** 05.09.2021 **Accepted:** 09.02.2022

Cite this article as: Gedikli MA, Sarı Kalın B, Aktaş A. Relationship Between HbA1c Level and Triglyceride/HDL Cholesterol Ratio and Triglyceride Glucose Index in Diabetes Patients. Bagcilar Med Bull 2022;7(1):27-31

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by high blood sugar levels. It has been found that there is a decrease in insulin secretion or a resistance mechanism against insulin in peripheral tissues in its pathophysiology (1). When the high blood sugar level, which causes diabetes to occur, does not remain at target levels, some chronic complications such as retinopathy, nephropathy, peripheral neuropathy, autonomic neuropathy, and coronary artery disease (CAD) occur (2).

Hemoglobin A1c (HbA1c) is a marker that shows glucose tolerance and glucose regulation in diabetes, which is formed by slow and non-enzymatic glycosylation of hemoglobin. In laboratory tests, it is presented as the value obtained by dividing HbA1c into total hemoglobin. Today, HbA1c is used in blood sugar regulation in diabetic patients and in predicting the risk of complications that may occur due to diabetes (3).

Diabetic dyslipidemia is the most critical risk factor for DM patients with cardiovascular diseases (CVD). Serum triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio, which is accepted as the atherogenic plasma index, poses the most critical risk for CVD and metabolic syndrome (4,5). A high TG/HDL-C ratio causes endothelial dysfunction. The TG/HDL-C ratio is high in patients with insulin resistance. Therefore, TG/HDL-C ratio can be considered as a determinant of glycemic control in obese patients with insulin resistance. When diabetic patients were compared according to their HbA1C levels, it was shown that patients with low HbA1C levels had approximately 3-4 times lower TG/HDL-C ratio. Based on these previous data, it can be said that high TG/HDL-C ratio may be closely associated with poor glycemic control and metabolic syndrome (6).

Triglyceride-glucose index (TyG index) calculated according to fasting blood glucose (FBG) and triglyceride (TG) measurements can also be used as an indicator of insulin resistance (7). The TyG index is calculated as ln [fasting TG (mg/dL) x FBG (mg/dL)/2]. It has been shown that the TyG index is a better marker in determining the diabetes risk than FPG and TG measurement in patients with blood glucose below 100 (8). When patients were compared according to their HbA1C levels, low HbA1C levels were found to have a lower TyG index. The lower the TyG index in individuals, the lower the risk of developing diabetes. This increase is 2 times higher for men and 4 times higher for women. All these data conclude that as both TG/HDL-C ratio and TyG index increase, HbA1c level increases in diabetic patients (9,10).

This study aimed to show whether there was a relationship between HbA1c levels and lipid profiles, TG/HDL-C ratio and TyG index in diabetic patients.

Materials and Methods

The Type of the Study

Our study was conducted as a single-center and retrospective.

The Population and the Sample of the Study

The results of a total of 2,938 patients who applied to the Internal Medicine Outpatient Clinic of Sivas Cumhuriyet University Medical Faculty Hospital between January 1, 2015 and January 1, 2020 were analyzed and recorded. The patients included in our study applied to the outpatient clinic for the first time.

The patients were divided into four groups according to their HbA1c levels. A healthy control group had HbA1c less than 6%. Those with HbA1c higher than 6-8%, 8-10%, and 10% were separated as the diabetic patient groups.

Diabetes was diagnosed according to the 75 gram oral glucose tolerance test (OGTT) results. The patients were administered 75 g OGTT after 8 hours of fasting. Diabetes was defined as those with a fasting plasma glucose result of ≥126 or a plasma glucose result of ≥200 at the 2nd hour after 75 g OGTT (11).

Patients younger than 18 years of age, with a history of malignancy, hemoglobinopathy, lipid-lowering therapy, pregnancy, and anemia were excluded from the study.

Laboratory Measurements

Blood samples were taken from the antecubital vein after 8 hours of fasting. FBG, HbA1c, creatinine, AST, ALT, triglyceride, HDL, LDL, and total cholesterol levels were measured during the biochemical analysis.

The TG/HDL-C ratio was calculated by dividing the serum concentration of TG by HDL-C. Triglyceride and HDL results were measured in mg/dL. When calculating the TG/HDL-C ratio, mg/dL was converted to mmol/L according to the formula ''1 mg/dL=0.0555 mmol/L''. TyG index was calculated based on the formula Ln [TG (mg/dL) x FG (mg/dL)/2] according to previous studies.

Statistical Analysis

Statistical comparisons were made using the statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and Kruskal-Wallis tests were

used to test the fit of the data to the normal distribution. For both tests, the analyses were continued non-parametrically, since the data did not fit the normal distribution. The quantitative variables were expressed as mean ± standard deviation and median (interquartile range: 5th percentile-75th percentile) while qualitative variables were given as frequencies and percentages. The significance level was accepted as 0.05.

Results

Among 2,938 patients included in our study, the number of men was 1.213 (41.3%), the number of women was 1725 (58.7%), and the mean age was 57.42±13.22 years. The mean HbA1c was 8.28±2.55 (%); triglyceride average was 1.99±1.25 (mmol/L); the mean HDL cholesterol was 1.13±0.31 (mmol/L); triglyceride/HDL cholesterol ratio was 2.02±1.77; the mean triglyceride glucose index was 9.64±9.07 (Table 1).

The average age of 561 patients, including 357 women (63.6%) and 204 men (36.4%) with HbA1c level below 6 (%), was 52.93±13.8 years; the mean triglyceride was 1.66 0.94 (mmol/L); the mean HDL cholesterol was 1.22±0.34 (mmol/L); triglyceride/HDL cholesterol ratio was 1.55±1.31; the mean triglyceride glucose index was 4.78±2.94. The average age of 1.006 patients, including 606 females (60.2%) and 400 males (39.8%) with HbA1c level between 6 (%) and 8 (%), was 58.61±12.27 years; the mean triglyceride value was 1.90±1.10 (mmol/L); the mean HDL cholesterol was 1.15±0.31 (mmol/L); triglyceride/HDL cholesterol ratio was 1.87±1.72; the mean triglyceride glucose index was 7.43±5.24. The mean age of 684 patients, including 372 women (54.4%) and 312 men (45.6%) with HbA1c levels between 8 (%) and 10 (%), was 59.13±13.12 years; the mean triglyceride was 2.10±1.31 (mmol/L); the mean HDL cholesterol was 1.09±0.30 (mmol/L); triglyceride/HDL cholesterol ratio was 2.15±1.67; the mean triglyceride glucose index was found to be 11.22±8.85. The average age of 687 patients, including 390 women (56.8%) and 297 men (43.2%) with HbA1c level above 10 (%), was 57.63±13.37 years; the mean triglyceride was 2.28±1.52 (mmol/L); the mean HDL cholesterol was 1.05±0.29 (mmol/L); triglyceride/HDL cholesterol ratio was 2.48±2.13; the mean triglyceride glucose index was 15.26±12.91 (Table 2).

Table 1. Demographic characteristics of the patients included in the study

	Mean
Gender	
Male	1,213 (41.3%)
Female	1,725 (58.7%)
Age (year)	57.42±13.22
Fasting blood glucose (mg/dL)	165.14±71.59
Creatinine (mg/dL)	0.92±0.57
AST (mg/dL)	21.37±11.65
ALT (mg/dL)	24.16±17.63
HbA1c (%)	8.28±2.55
Triglyceride (mmol/L)	1.99±1.25
HDL cholesterol (mmol/L)	1.13±0.31
Triglycerid/HDL-cholesterol ratio	2.02±1.77
Triglyceride glucose index	9.64±9.07

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein

According to the HbA1c level, the patients were grouped as those with triglyceride/HDL cholesterol ratio lower than 6 (%), between 6-8 (%), between 8-10 (%) and over 10 (%) (1.30; 1.50; 1.73, and 1.87, respectively) (p<0.001). Triglyceride glucose index was 4.07, 6.05, 8.84, and 12.03, respectively (p<0.001) (Table 3).

When we grouped the patients by gender, the mean age of 1,725 female patients was 57.48±13.46 years, the mean HbA1c was 8.15±2.51 (%), the triglyceride average was 1.95±1.15 (mmol/L), the HDL cholesterol average was 1.19±0.33 (mmol/L), triglyceride/HDL cholesterol ratio was 1.87±1.65 and the average triglyceride glucose index was 9.23±8.37. The mean age of 1,213 male patients in the study was 57.34±12.85 years, the mean HbA1c was 8.46±2.60 (%), the triglyceride average was 2.05±1.37 (mmol/L), the HDL cholesterol average was 1.03±0.27 (mmol/L), the triglyceride/HDL cholesterol ratio was 2.23±1.92. The mean triglyceride glucose index was 1.92 and 10.22±9.96 (Table 4).

Discussion

As the main result of our study, when the HbA1c levels increased in diabetic patients, that is, in patients with poor glycemic control, both triglyceride glucose index and triglyceride/HDL cholesterol ratio were found to be high. However, these relationships should be interpreted with caution because high triglycerides and a decrease in HDL cholesterol levels are seen as a characteristic features of insulin resistance and diabetes. Recent studies show that low HDL-C levels can exacerbate abnormal glucose metabolism (12). Triglyceride and HDL cholesterol levels may be affected by blood sugar regulation in patients with diabetes, as triglyceride levels and HDL C levels are thought to change due to insulin resistance (13).

Table 2. Characteristics of the patients according to HbA1c levels

HbA1c	<6	6-8	8-10	>10
Gender				
Male	204 (36.4%)	400 (39.8%)	312 (45.6%)	297 (43.2%)
Female	357 (63.6%)	606 (60.2%)	372 (54.4%)	390 (56.8%)
Age (year)	52.93±13.8	58.61±12.27	59.13±13.12	57.63±13.37
FBG (mg/dL)	102.47±23.98	139.39±44.40	185.79±58.70	233.44±76.61
Creatinine (mg/dL)	0.89±0.67	0.90±0.50	0.97±0.62	0.91±0.52
AST (mg/dL)	20.08±8.72	20.93±9.86	21.32±11.83	23.11±15.24
ALT (mg/dL)	22.47±15.23	23.91±15.43	24.63±18.43	25.44±21.22
Triglyceride (mmol/L)	1.66±0.94	1.90±1.10	2.10±1.31	2.28±1.52
HDL cholesterol (mmol/L)	1.22±0.34	1.15±0.31	1.09±0.30	1.05±0.29
Triglyceride/HDL-cholesterol ratio	1.55±1.31	1.87±1.72	2.15±1.67	2.48±2.13
Triglyceride glucose index	4.78±2.94	7.43±5.24	11.22±8.85	15.26±12.91

FBG: Fasting blood glucose, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein

Table 3. Comparison of triglyceride/HDL cholesterol and triglyceride glucose indices according to HbA1c levels

HbA1c	<6	6-8	8-10	>10	p
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	
Triglyceride/HDL-cholesterol ratio	1.30 0.80-1.92	1.50 0.99-2.28	1.73 1.12-2.60	1.87 1.18-2.95	p<0.001
Triglyceride glucose index	4.07 2.86-5.93	6.05 4.20-8.97	8.84 5.97-13.63	12.03 7.56-18.02	p<0.001

HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, IQR: Interquartile range

Table 4. Examination of patient characteristics according to gender

Gender	Male (n=1,213)	Female (n=1,725)
Age (year)	57.34±12.85	57.48±13.46
FBG (mg/dL)	171.08±74.81	160.95±68.94
Creatinine (mg/dL)	1.04±0.59	0.83±0.54
HbA1c (%)	8.46±2.60	8.15±2.51
Triglyceride (mmol/L)	2.05±1.37	1.95±1.15
HDL cholesterol (mmol/L)	1.03±0.27	1.19±0.33
Triglyceride/HDL-cholesterol ratio	2.23±1.92	1.87±1.65
Triglyceride glucose index	10.22±9.96	9.23±8.37

FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein

Studies have shown that the triglyceride/HDL-C ratio is associated with cardiovascular risk, mainly associated with insulin resistance. Finally, they have shown that triglyceride/HDL-C may be a marker of glycemic control, especially in patients with type 2 diabetes (14,15). In our study, the ratio of triglyceride/HDL cholesterol was found to be higher as the HbA1c level increased, and it was found to be affected by poor glycemic control. In addition, our study found that the triglyceride/HDL cholesterol ratio was higher in male patients than in female patients.

In a study conducted by da Silva et al. (16), it was shown to be associated with a higher prevalence of CAD in patients with a high TyG index, and in this study, they showed that the TyG index could be used as a marker for atherosclerosis. Recent studies show that the TyG index is widely used as a marker of insulin resistance. In the study conducted by Luo et al. (17), it has been shown that a high TyG index is associated with an increased risk of cardiac and cerebrovascular events in patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention. In the study conducted by Shi et al. (18), they showed an increase in the risk of ischemic stroke parallel to the increase in the TyG index. In another study conducted by Zhao et al. (8), they showed that a high TyG index was significantly associated with a higher risk of microvascular damage and arterial stiffness.

In the light of previous studies, it was seen that triglyceride/HDL cholesterol ratio and high TyG index were associated with increased poor glycemic control, increased risk of cerebrovascular disease, and increased risk of CAD (19,20). In our study, we found high triglyceride/HDL cholesterol and TyG index in patients with poor glycemic control and high HbA1c levels. And the increase in these rates seems to increase as the HbA1c level rises.

Study Limitations

Since our study was planned as a retrospective study, we only recorded the laboratory values of the patients in the system, but we could not question and evaluate the patients in terms of current cardiac risk or cerebrovascular disease risk.

Conclusion

Triglyceride/HDL cholesterol ratio and TyG index are associated with insulin resistance, and in our study, we retrospectively demonstrated a poor glycemic index, that is, the increase in HbA1c level, and the triglyceride/HDL cholesterol ratio and TyG index. Further prospective studies are needed to demonstrate that the TyG index and triglyceride/HDL cholesterol ratio are associated with increased risk of cardiac and cerebrovascular disease in diabetic patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Clinical Studies at Sivas Cumhuriyet University by the date of 08.07.2020 and the number of 2020-07/25. Our study was carried out in accordance with the principles of the Declaration of Helsinki.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A.G., Design: M.A.G., B.S.K., A.A., Data Collection or Processing: M.A.G., A.A., Analysis or Interpretation: B.S.K., A.A., Literature Search: M.A.G., B.S.K., A.A., Writing: M.A.G., A.A.

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

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

References

1. Valaiyapathi B, Gower B, Ashraf AP. Pathophysiology of type 2 diabetes in children and adolescents. Curr Diabetes Rev 2020;16(3):220-229.
2. Ryder RE. Real-world diabetes prevention: from theory to practice. Lancet Diabetes Endocrinol 2018;6(10):756-757.
3. Tucker LA. Limited Agreement between Classifications of Diabetes and Prediabetes Resulting from the OGTT, Hemoglobin A1c, and Fasting Glucose Tests in 7412 U.S. Adults. J Clin Med 2020;9(7):2207.
4. Ardahanli I, Celik M, Takir M. Relationship between Neutrophil/Lymphocyte Ratio and Cardiometabolic Values in Patients with Prediabetes. Glob J Endocrinol Metab 2018;2(4):1-4.
5. Aktaş A, Gedikli MA, Şahin A. Ailesel Akdeniz Ateşi hastalarının trigliserid/yüksek dansiteli lipoprotein oranına göre karşılaştırılması. ADYÜ Sağlık Bilimleri Derg 2021;7(1):20-25.
6. Babic N, Valjevac A, Zaciragic A, Avdagic N, Zukic S, Hasic S. The Triglyceride/HDL Ratio and Triglyceride Glucose Index as Predictors of Glycemic Control in Patients with Diabetes Mellitus Type 2. Med Arch 2019;73(3):163-168.
7. Navarro-González D, Sánchez-Íñigo L, Pastrana-Delgado J, Fernández-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. Prev Med 2016;86:99-105.
8. Zhao S, Yu S, Chi C, Fan X, Tang J, Ji H, et al. Association between macro-and microvascular damage and the triglyceride glucose index in community-dwelling elderly individuals: the Northern Shanghai Study. Cardiovasc Diabetol 2019;18(1):95.
9. Park GM, Cho YR, Won KB, Yang YJ, Park S, Ann SH, et al. Triglyceride glucose index is a useful marker for predicting subclinical coronary artery disease in the absence of traditional risk factors. Lipids Health Dis 2020;19(1):1-7.
10. Hameed EK. TyG index a promising biomarker for glycemic control in type 2 diabetes mellitus. Diabetes Metab Syndr 2019;13(1):560-563.
11. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(Suppl 1):S15-S33.
12. Zhang Y, Qin P, Lou Y, Zhao P, Li X, Qie R, et al. Association of TG/HDLC ratio trajectory and risk of type 2 diabetes: A retrospective cohort study in China. J Diabetes 2020. doi: 10.1111/1753-0407.13123.
13. Bjornstad P, Eckel RH. Pathogenesis of lipid disorders in insulin resistance: a brief review. Curr Diab Rep 2018;18(12):127.
14. Quispe R, Martin SS, Jones SR. Triglycerides to high-density lipoprotein–cholesterol ratio, glycemic control and cardiovascular risk in obese patients with type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2016;23(2):150-156.
15. Wen J, Huang Y, Lu Y, Yuan H. Associations of non-high-density lipoprotein cholesterol, triglycerides and the total cholesterol/HDL-c ratio with arterial stiffness independent of low-density lipoprotein cholesterol in a Chinese population. Hypertens Res 2019;42(8):1223-1230.
16. da Silva A, Caldas APS, Hermsdorff HHM, Bersch-Ferreira ÂC, Torreglosa CR, Weber B, et al. Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care. Cardiovasc Diabetol 2019;18(1):89.
17. Luo E, Wang D, Yan G, Qiao Y, Liu B, Hou J, et al. High triglyceride–glucose index is associated with poor prognosis in patients with acute ST-elevation myocardial infarction after percutaneous coronary intervention. Cardiovasc Diabetol 2019;18(1):150.
18. Shi W, Xing L, Jing L, Tian Y, Yan H, Sun Q, et al. Value of triglyceride-glucose index for the estimation of ischemic stroke risk: Insights from a general population. Nutr Metab Cardiovasc Dis 2020;30(2):245-253.
19. Zorlu M, Helvacı A, Kıskaç M, Yolbaş S, Ardıç C, Oran M, et al. Silent myocardial ischemia and related risk factors in patients with type 2 diabetes mellitus. Dicle Med J 2010;37(2):140-124.
20. Aktaş A, Gedikli MA, Kara C, Bakır MR. Can the Triglyceride/HDL Ratio in Chronic Kidney Disease be Predictive of Cardiac Risk? F.U. Med.J.Health.Sci. 2021;35(1):35-39.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):32-37
DOI: 10.4274/BMB.galenos.2022.2021-10-112

The Role of MPV-to-Lymphocyte Ratio and MPV-to-Platelet Ratio in Predicting Mortality in Patients with Acute Myocardial Infarction

Akut Miyokard Enfarktüslü Hastalarda Mortaliteyi Öngörmede MPV-Lenfosit Oranı ve MPV-Trombosit Oranının Rolü

Serkan Karahan[1], Fahrettin Katkat[2], Sinan Varol[1], Mehmet Rıfat Yıldırım[1], Orhan İnce[1], İrfan Şahin[1], Ertuğrul Okuyan[1]

[1]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

Abstract

Objective: In this study, we aimed to evaluate the relationship between the laboratory parameters of mean platelet volume/lymphocyte ratio (MPVLR) and mean platelet volume/platelet ratio (MPVPR) with prognosis and mortality in patients with hospitalized glomerular filtration rate (GFR) <60 and a diagnosis of acute myocardial infarction (AMI).

Method: This study was designed as a retrospective cohort study. Two hundred myocardial infarction (MI) patients over the age of 18 years and with GFR <60, who were hospitalized in our hospital between January 01, 2018 and January 01, 2021, were included in the study. The patients were divided into 2 groups, as the survivor and mortality groups. The two groups were compared in terms of demographic characteristics and clinical data (symptoms, comorbidities, laboratory findings, GFR, coronary angiography, drugs used and complications). MPVLR was found by dividing the mean platelet volume to lymphocyte count. MPVPR was found by dividing the mean platelet volume to platelet count.

Results: The mean age of the survivor group was 64.3±10.4. In the mortality group, the mean age was 70.02±9.3. MPVLR levels were statistically significantly higher in the mortality group (8.39±5.9) compared to the survivor group (6.58±5.4) (p=0.011). However, MPVPR levels were statistically significantly lower in the mortality group (0.041±0.01) compared to the survivor group (0.044±0.01) (p=0.048). According to the results of ROC analysis in patients with mortality, sensitivity was 50.0% and specificity was 68.6% for MPVLR (p=0.010); sensitivity was 41.0% and specificity was 47.9% for MPVPR. The risk factors found to be significantly associated with mortality in the regression analysis included

Öz

Amaç: Bu çalışmada, hastanede yatan glomerüler filtrasyon hızı (GFR) <60 olan akut miyokard enfarktüsü (AMI) tanısı alan hastalarda ortalama trombosit hacmi/lenfosit oranı (MPVLR) ve ortalama trombosit hacmi/trombosit oranı (MPVPR) laboratuvar parametrelerinin prognoz ve mortalite ile ilişkisini değerlendirmeyi amaçladık.

Yöntem: Bu çalışma retrospektif bir kohort çalışması olarak tasarlanmıştır. 01 Ocak 2018-01 Ocak 2021 tarihleri arasında hastanemizde yatan 18 yaş üstü ve GFR <60 olan 200 miyokard enfarktüsü (MI) hastası çalışmaya dahil edildi. Hastalar sağkalım ve mortalite olarak 2 gruba ayrıldı. İki grup demografik özellikler, klinik veriler (semptomlar, komorbiditeler, laboratuvar bulguları, GFR, koroner anjiyografi, kullanılan ilaçlar ve hastalardaki komplikasyonlar) açısından karşılaştırıldı. MPVLR, ortalama trombosit hacminin kan basıncına bölünmesiyle bulundu. MPVPR ortalama trombosit hacminin trombosit sayısına bölünmesi ile bulundu.

Bulgular: Hayatta kalanların yaş ortalaması 64,3±10,4 idi. Mortalite grubunda ortalama yaş 70,02±9,3 idi. MPVLR düzeyleri mortalite grubunda (8,39±5,9), sağ kalan gruba (6,58±5,4) göre istatistiksel olarak anlamlı derecede yüksekti (p=0,011). Ancak MPVPR düzeyleri mortalite grubunda (0,041±0,01), hayatta kalan gruba (0,044±0,01) (0,01-0,16) göre istatistiksel olarak anlamlı derecede düşüktü (p=0,048). Mortalite grubundaki hastalarda ROC analizi sonuçlarına göre, MPVLR için duyarlılık %50,0 ve özgüllük %68,6 (p=0,010); MPVPR için duyarlılık %41,0 ve özgüllük %47,9 idi. Regresyon analizinde mortalite ile anlamlı olarak ilişkili bulunan risk faktörleri arasında MPVPR (β: 0,045, olasılık oranı (%95 güven aralığı): 0,945 (0,899-1,001), p=0,032] yer aldı.

Address for Correspondence: Serkan Karahan, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
E-mail: drserkankarahan@gmail.com **ORCID:** orcid.org/0000-0002-1203-7615 **Received:** 28.10.2021 **Accepted:** 06.02.2022

Cite this article as: Karahan S, Katkat F, Varol S, Yıldırım MR, İnce O, Şahin İ, Okuyan E. The Role of MPV-to-Lymphocyte Ratio and MPV-to-Platelet Ratio in Predicting Mortality in Patients with Acute Myocardial Infarction. Bagcilar Med Bull 2022;7(1):32-37

MPVPR [β: 0.045, odds ratio (95% confidence interval): 0.945 (0.899-1.001), p=0.032].

Conclusion: As inexpensive and easily available new inflammatory markers, MPVLR and MPVPR were significantly higher in patients with GFR <60 and in those who died from AMI. In addition, MPVLR and MPVPR could predict mortality from MI.

Keywords: Acute myocardial infarction, mortality, MPV-to-lymphocyte ratio, MPV-to-platelet ratio

Sonuç: Ucuz ve kolay bulunabilen yeni enflamatuvar belirteçler olarak MPVLR ve MPVPR, GFR <60 olan ve AMI'dan ölen hastalarda anlamlı olarak daha yüksekti. Ek olarak, MPVLR ve MPVPR, MI'dan ölüm oranını tahmin edebildi.

Anahtar kelimeler: Akut miyokard enfarktüsü, mortalite, MPV-lenfosit oranı, MPV-trombosit oranı

Introduction

Heart failure (HF) is a major public health problem, affecting more than 23 million individuals worldwide, and its incidence increases with age. After the diagnosis of HF, the average life expectancy is 50% in 5 years and 10% in 10 years. Despite advanced modern treatment approaches, mortality rates are still high. Moreover, HF patients need long-term care, as it is a chronic disease that can be exacerbated by acute exacerbations (1). It is known that inflammation has an important role in the pathogenesis of atherosclerosis and thus cardiovascular diseases (CVDs) (2). The role of inflammation in HF has been demonstrated in many previous studies. HF syndrome is largely due to the imbalance between inflammatory and anti-inflammatory forces (3).

Mean platelet volume (MPV) blood test measures the average size of your platelets. The test can help diagnose bleeding disorders and diseases of the bone marrow. In recent years, MPV-to-lymphocyte ratio (MPVLR) and MPV-platelet ratio (MPVPR) have been shown to be important indicators of systemic inflammation (1,4-6). Recently, the MPV-to-lymphocyte ratio (MPVLR) has arisen as a prognostic marker in patients with CVDs (4). However, it was reported that elevated MPVPR values at admission are independently associated with the development of no-reflow phenomenon after primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) (4,7). However, there is no study investigating the association of MPVLR and MPVPR with the severity and complexity of acute myocardial infarction (AMI). In addition, MPV-platelet ratio (MPVPR) has also been shown to vary in various diseases and are associated with prognosis (8-11).

In this study, we aimed to evaluate the relationship between the laboratory parameters of MPVLR and MPVPR with prognosis and mortality in patients with hospitalized glomerular filtration rate (GFR) <60 mL/min and a diagnosis of AMI.

Materials and Methods

This study was designed as a retrospective cohort study. Before the study started, the study protocol was approved by Local Ethics Committee of İstanbul Medipol University (approval no: E-10840098-772.02-3976). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Two hundred myocardial infarction (MI) patients over the age of 18 years and with GFR <60 mL/min, who were hospitalized in our hospital between January 01, 2018 and January 01, 2021, were included in the study. The demographic characteristics of the patients and clinical data (symptoms, comorbidities, laboratory findings, GFR, coronary angiography, medications and complications that developed in the patients) were scanned.

The patients were divided into 2 groups, as the survivor and mortality groups. The two groups were compared in terms of demographic characteristics and clinical data. Fasting morning blood samples of the patients and control healthy subjects were collected through vein puncture. The MPVLR was found by dividing MPV to lymphocyte count. The MPVPR was found by dividing MPV to platelet count.

Statistical Analysis

The data obtained in this study were analyzed using SPSS v.25 (SPSS, Chicago, USA) statistical program. Descriptive statistics such as frequency distribution, mean and standard deviation were used to evaluate the data. The differences between the means of two independent groups were compared with the student's t-test, and the differences between more than two groups were compared with the analysis of variance with the parametric test. The Mann-Whitney U and Kruskal-Wallis tests, which are non-parametric alternatives of these tests, were used in cases where parametric test assumptions were not met. Categorical data were analyzed using the chi-square or Fisher's Exact test. Variables with a p-value ≤0.05 were entered in the regression model. Values of $p<0.05$ were considered statistically significant at 95% confidence interval (CI).

Results

Comparison of laboratory and socio-demographic findings between the mortality and survivor groups was shown in Table 1. The mean age of the survivor group was 64.3±10.4 years. In the mortality group, the mean age was 70.02±9.3 years. MPVLR levels were statistically significantly higher in the mortality group (8.39±5.9) compared to the survivor group (6.58±5.4) (p=0.011). However, MPVPR levels were statistically significantly lower in the mortality group (0.041±0.01) compared to the survivor group (0.044±0.01) (p=0.048).There was not any statistical significance between the groups in terms of gender, length of hospitalization, coronary artery disease, HF, STEMI, non-STEMI, hypertension, hyperlipidemia, diabetes mellitus, cigarette, nephropathy, acetyl salicylic acid, beta blocker, statins, angiotensin converting enzyme (ACE) inhibitors, GFR, hemoglobin (g/dL), creatinine (mg/dL), lymphocytes (10^9/L), and platelet (10^9/L) (Table 1).

ROC analysis results in patients with mortality are shown in Table 2. According to the results of ROC analysis in patients with mortality, sensitivity was 50.0% and specificity was 68.6% for MPVLR (p=0.010); and sensitivity was 41.0% and specificity was 47.9% for MPVPR (p=0.048) (Table 2, Figure 1).

Multiple logistic regression analysis of factors used for mortality was shown in Table 3. The risk factors found to be significantly associated with mortality in the regression analysis included MPVLR [β: 0.067, odds ratio (OR) 95% confidence interval (CI): 1.069 (1.016-1.125), p=0.010] and MPVPR [β: 0.045, OR (95% CI): 0.945 (0.899-1.001), p=0.032] (Table 3).

Discussion

In this study, the effects of retrospective clinical and laboratory data on mortality were evaluated in 200 MI

Table 1. The comparison of patients' socio-demographic, clinical and laboratory parameters

Parameters	Mortality (N=55, 27.5%) Mean ± SD (min-max), n (%)	Survive (N=145, 72.5%) Mean ± SD (min-max), n (%)	p
Age (year)	70.02±9.3 (43-103)	64.3±10.4 (30-97)	0.14
Gender			
Male	35 (63.6%)	89 (61.3%)	0.41
Female	20 (36.4)	56 (48.7%)	
Length of hospitalization	3.44±2.2 (1.0-12.0)	2.87±1.2 (1.0-13.0)	0.53
Coronary artery disease	18 (32.7%)	47 (32.4%)	0.92
Heart failure	7 (12.7%)	19 (13.1%)	0.90
STEMI	27 (49.0%)	85 (58.6%)	0.15
Non-STEMI	26 (47.2%)	63 (43.4%)	0.32
Hypertension	40 (72.7%)	118 (81.3%)	0.16
Hyperlipidemia	9 (16.3%)	26 (17.9%)	0.93*
Diabetes mellitus	21 (38.1%)	51 (35.1%)	0.71
Cigarette	9 (16.3%)	28 (19.3%)	0.62
Nephropathy	14 (25.4%)	45 (31.0%)	0.26*
Acetyl salicylic acid	55 (100.0%)	140 (96.5%)	0.88
Beta blocker	41 (74.5%)	110 (75.8%)	0.92*
Statins	48 (87.2%)	118 (81.3%)	0.17*
ACE inhibitors	19 (34.5%)	68 (46.8%)	0.09*
GFR	44.30±13.7 (4.0-55.0)	45.04±10.7 (4.0-55.0)	0.62
Hemoglobin (g/dL)	11.21±1.8 (5.7-15.8)	12.40±1.9 (1.2-17.1)	0.18
Creatinine (mg/dL)	1.64±1.4 (0.9-10.7)	1.51±1.4 (0.7-11.0)	0.29
MPV (10^9/L)	10.88±1.0 (8.1-13.9)	10.68±1.5 (7.1-19.1)	0.600
Lymphocytes (10^9/L)	1.91±3.9 (0.3-14.0)	2.49±2.6 (0.2-30.1)	0.146
Platelet (10^9/L)	261.13±69.5 (133.0-370.0)	247.10±71.8 (68.0-614.0)	0.181*
MPVLR	8.39±5.9 (0.8±28.4)	6.58±5.4 (0.3±52.7)	**0.011***
MPVPR	0.041±0.01 (0.01-0.09)	0.044±0.01 (0.01-0.16)	**0.048***

*Mann-Whitney U test used. STEMI: ST elevation myocardial infarction, ACE: Angiotensin converting enzyme, GFR: Glomerular filtration rate, MPVLR: Mean platelet volume/lymphocyte ratio, MPVPR: Mean platelet volume/platelet ratio, SD: Standard deviation, MPV: Mean platelet volume

Table 2. ROC analysis results in patients with mortality

	Cut-off	Sensitivity	Specificity	AUC (95% CI)	p
MPVLR	>6.88	50.0%	68.6%	0.607 (0.525-0.689)	**0.010**
MPVPR	<0.043	41.0%	47.9%	0.435 (0.353-0.516)	**0.048**

AUC: Area under the curve, MPVLR: Mean platelet volume/lymphocyte ratio, MPVPR: Mean platelet volume/platelet ratio, CI: Confidence interval

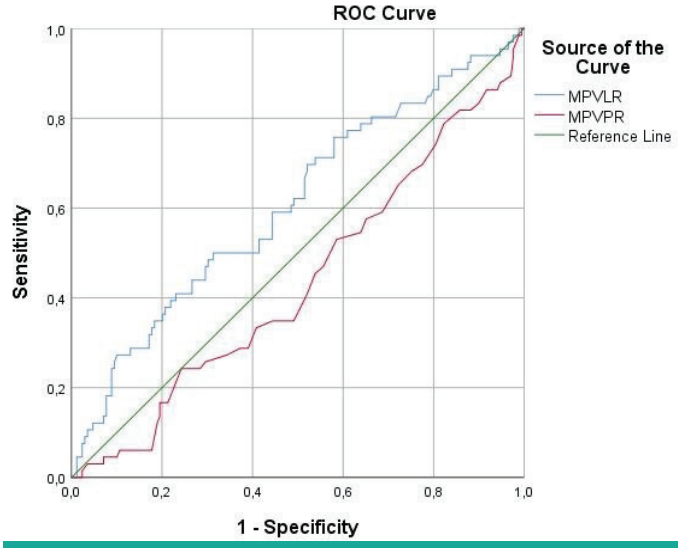


Figure 1. ROC analysis of MPVLR and MPVPR

MPVLR: Mean platelet volume/lymphocyte, MPVPR: Mean platelet volume/platelet ratio

Table 3. Multiple logistic regression analysis of factors used for mortality

	β	OR (95% CI)	p
MPVLR	0.067	1.069 (1.016-1.125)	**0.010**
MPVPR	0.045	0.945 (0.899-1.001)	**0.032**

MPVLR: Mean platelet volume/lymphocyte ratio; MPVPR: Mean platelet volume/platelet ratio, OR: Odds ratio, CI: Confidence interval

patients over 18 years of age and with GFR <60, who were hospitalized in coronary intensive care unit. There was a significant relationship between the laboratory markers obtained, especially MPVLR and MPVPR, and those who died from MI. MI is a disease with significant morbidity and mortality. While 145 (72.5%) patients survived in our study, 55 (27.5%) patients died in the hospital. MPVLR levels were statistically significantly higher in the mortality group compared to the survivor group. However, MPVPR levels were statistically significantly lower in the mortality group compared to the survivor group. The risk factors found to be significantly associated with mortality in the regression analysis included only MPVPR.

Increased inflammatory marker levels in the blood are associated with poor outcome in HF as in many chronic diseases. An increased inflammatory stimulus causes the secretion of many inflammatory cytokines. These inflammatory cytokines show detrimental effects on the myocardium, leading to decreased left ventricular function and thus HF (1,2,12-14). In one study, high neutrophil-lymphocyte ratio (NLR) values were associated with high mortality rates in individuals with acute decompensated HF, and the value of NLR in predicting death was superior to that of neutrophil count, total white blood cell count, and partially low lymphocyte count (15). Therefore, NLR has an important prognostic value in HF. On the other hand, previous studies have shown that high platelet and low lymphocyte counts are associated with poor cardiovascular outcomes (16-18). The value recently found and shown as one of the complete blood count parameters is the MPVLR. It was first reported by Hudzik et al. (5) in 2016 as a potential prognostic marker in patients with diabetes and MI. Życzkowski et al. (19) reported that prognostic relationship between high pre-operative MPVLR and higher long-term mortality of patients with clear cell renal cell carcinoma. In the study of Sut et al. (20) in 78 patients with breast cancer, they reported that MPVLR, NLR, and PLR levels were significantly higher in breast cancer patients compared to controls. In addition, a significant association was found between NLR and PLR but not MPVLR and low dietary polyphenol intake in breast cancer patients (20). In our study, MPVLR levels were statistically significantly higher in the mortality group compared to the survivor group. According to the results of ROC analysis in patients with mortality, sensitivity was 50.0% and specificity was 68.6% for MPVLR. However, in the regression analysis, risk factors were not found to be associated with mortality and MPVLR.

In the literature, studies examining the relationship of diseases with MPVPR are limited (7,8). Tezcan et al. (8) reported a prognostic relationship between MPVPR and Behçet's disease (BD), which determines the diagnosis and severity of BD. Bernardi et al. (7) reported a prognostic relationship between MPVPR and predictive markers of CVD. In a study conducted by Karakurt et al. (21) in complexity of coronary artery disease (CCAD) in patients with acute coronary syndrome (ACS), MPVPR and MPVLR were not independent predictors of CCAD in patients with ACS. In our study, MPVPR levels were statistically

significantly lower in the mortality group compared to the survivor group. According to the results of ROC analysis in patients with mortality, sensitivity was 41.0% and specificity was 47.9% for MPVPR. However, the risk factors found to be significantly associated with mortality in the regression analysis included MPVPR [β: 0.043, OR (95% CI): 0.435 (0.353-0.516), p=0.048].

Study Limitations

There were some limitations in our study. First, our study is a single-center and retrospective study. The small sample size of patients was the second limitation. Moreover, multi-center and prospective studies should be planned to support these pre-liminary results. However, the strengths of our study included that our sample was larger and our results were supported by logistic regression analysis.

Conclusion

As inexpensive and easily available new inflammatory markers, higher MPVLR and lower MPVPR were significantly in patients with GFR <60 and in those who died from MI. However, MPVLR levels may predict hemodynamically severe coronary obstruction better than MPVPR. The utility of this new marker warrants to be investigated in various cardiac situations. Large-scale, prospective, and multicenter studies will be necessary to clarify the relationship between MPVLR, MPVPR and MI.

Ethics

Ethics Committee Approval: The study protocol was approved by Local Ethics Committee of İstanbul Medipol University (approval no: E-10840098-772.02-3976).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.K., E.O., M.R.Y., Design: S.K., E.O., M.R.Y., Data Acquisition: S.K., F.K., S.V., O.İ., Data Collection or Processing: S.K., İ.Ş., Analysis or Interpretation: S.K., İ.Ş., Drafting Manuscript: S.K., E.O., M.R.Y., Critical Revision of Manuscript: S.K., F.K., S.V., O.İ., İ.Ş., Final Approval and Accountability: S.K., F.K., S.V., O.İ., İ.Ş., E.O., M.R.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. Carrabba M, Madeddu P. Current Strategies for the Manufacture of Small Size Tissue Engineering Vascular Grafts. Front Bioeng Biotechnol 2018;6:41.
2. Budzianowski J, Pieszko K, Burchardt P, Rzezniczak J, Hiczkiewicz J. The Role of Hematological Indices in Patients with Acute Coronary Syndrome. Dis Markers 2017;2017:3041565.
3. Karahan S, Okuyan E. Systemic Inflammatory Index and Platelet-to-Lymphocyte Ratio Predicted Mortality in patients with Acute Myocardial Infarction. Experimental Applied Medical Science 2021;2(2):146-153.
4. Kurtul A, Acikgoz SK. Usefulness of Mean Platelet Volume-to-Lymphocyte Ratio for Predicting Angiographic No-Reflow and Short-Term Prognosis After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction. Am J Cardiol 2017;120(4):534-541.
5. Hudzik B, Szkodzinski J, Lekston A, Gierlotka M, Polonski L, Gąsior M. Mean platelet volume-to-lymphocyte ratio: a novel marker of poor short- and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction. J Diabetes Complications 2016;30(6):1097-1102.
6. Inanir M. Evaluation of Platelet Indices in Diabetic Patients with Myocardial Bridges. Dicle Med J 2020;47(2):286-292.
7. Bernardi M, Fedullo AL, Di Giacinto B, Squeo MR, Aiello P, Dante D, et al. Cardiovascular Risk Factors and Haematological Indexes of Inflammation in Paralympic Athletes with Different Motor Impairments. Oxidative Medicine and Cellular Longevity 2019;2019:6798140.
8. Tezcan D, Körez MK, Gülcemal S, Hakbilen S, Akdağ T, Yılmaz S. Evaluation of diagnostic performance of haematological parameters in Behçet's disease. Int J Clin Pract 2021;75(10):e14638.
9. Bilgin S, Aktas G, Kahveci G, Atak BM, Kurtkulagi O, Duman TT. Does mean platelet volume/lymphocyte count ratio associate with frailty in type 2 diabetes mellitus? Bratisl Lek Listy 2021;122(2):116-119.
10. Wang H, Xing Y, Yao X, Li Y, Huang J, Tang J, et al. Retrospective Study of Clinical Features of COVID-19 in Inpatients and Their Association with Disease Severity. Med Sci Monit 2020;26:e927674.
11. Tekin YK, Tekin G. Mean Platelet Volume-to-Platelet Count Ratio, Mean Platelet Volume-to-Lymphocyte Ratio, and Red Blood Cell Distribution Width-Platelet Count Ratio as Markers of Inflammation in Patients with Ascending Thoracic Aortic Aneurysm. Braz J Cardiovasc Surg 2020;35(2):175-180.
12. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol 2015;105(6):606-613.
13. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest 2020;50(5):e13230.
14. Mirza AJ, Taha AY, Khdhir BR. Risk factors for acute coronary syndrome in patients below the age of 40 years. Egypt Heart J 2018;70(4):233-235.
15. Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011;107(3):433-438.

16. Yildiz A, Yuksel M, Oylumlu M, Polat N, Akyuz A, Acet H, et al. The Utility of the Platelet-Lymphocyte Ratio for Predicting No Reflow in Patients With ST-Segment Elevation Myocardial Infarction. Clin Appl Thromb Hemost 2015;21(3):223-228.

17. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013;8(7):e67688.

18. Oylumlu M, Yıldız A, Oylumlu M, Yüksel M, Polat N, Bilik MZ, et al. Platelet-to-lymphocyte ratio is a predictor of in-hospital mortality patients with acute coronary syndrome. Anatol J Cardiol 2015;15(4):277-283.

19. Życzkowski M, Kaletka Z, Rajwa P, Rempega G, Stelmach P, Bogacki R, et al. Mean platelet volume-to-lymphocyte ratio: a novel biomarker associated with overall survival in patients with nonmetastatic clear cell renal cell carcinoma treated with nephrectomy. Int Urol Nephrol 2020;52(5):885-891.

20. Sut A, Pytel M, Zadrozny M, Golanski J, Rozalski M. Polyphenol-rich diet is associated with decreased level of inflammatory biomarkers in breast cancer patients. Rocz Panstw Zakl Hig 2019;70(2):177-184.

21. Karakurt A, Yildiz C. Predictive values of inflammatory cell ratios for complexity of coronary artery disease in patients with acute coronary syndrome. Int J Cardiovasc Acad 2018;4(4):70.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):38-42
DOI: 10.4274/BMB.galenos.2022.2021-12-123

Retrospective Evaluation of Incidental Adnexal Masses Encountered During Cesarean Section

Sezaryen Sırasında Karşılaşılan Adneksiyel Kitlelerin Retrospektif Değerlendirilmesi

Semra Yüksel[1], Cemre Alan[2]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[2]Necmettin Erbakan University Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey

Abstract

Objective: Incidental adnexal masses can be present during cesarean section and management options differ according to the properties of the mass. The objective of this study was to outline and discuss the clinical features and management of adnexal masses that were encountered during a cesarean section.

Method: Records of 7,063 women who had cesarean section between November 2014 and December 2019 in a tertiary center were reviewed retrospectively. Sixty-four women who had an incidental adnexal mass and a pathology report were enrolled to this study.

Results: The incidence of adnexal masses that detected at cesarean section was found as 0.9%. The pathologic diagnoses of the masses were as follows: The non-neoplastic group: Paratubal or paraovarian cyst (25 women, 39%), simple serous cyst (7 women, 11%) and corpus luteum cyst (4 women, 8%); the neoplastic group: Mature cystic teratoma (11 women, 17%), mucinous cystadenoma (5 women, 8%) and adenofibroma (3 women, 5%). All the women in the non-neoplastic group had undergone cystectomy. Sixteen of women (72%) in the neoplastic group had undergone cystectomy and 6 of them (28%) had undergone salpingo-oopherectomy. There was no perioperative and postoperative the complication in any of the patients.

Conclusion: Surgical intervention in women who had incidental adnexal masses during cesarean section does not increase complication rate.

Keywords: Adnexal disease, cesarean section, incidental finding, pregnancy

Öz

Amaç: Sezaryen sırasında insidental olarak adneksiyal kitle tespit edilebilir ve yönetim şekli kitlenin özelliklerine göre değişiklik gösterir. Bu çalışmanın amacı, sezaryen sırasında karşılaşılan adneksiyal kitlelerin özelliklerini ve yönetimini analiz etmektir.

Yöntem: Üçüncü basamak merkezde Kasım 2014-Aralık 2019 tarihleri arasında sezaryen olan 7.063 hastanın kayıtları retrospektif olarak incelendi. Sezaryen sırasında insidental adneksiyel kitle saptanan ve patolojisi mevcut olan 64 hasta çalışmaya dahil edildi.

Bulgular: Sezaryen sırasında insidental adneksiyal kitle oranı %0,9 olarak bulundu. Non-neoplastik grubun patolojilerine baktığımızda en sık paratubal veya paraovarian kistler (25 hasta, %39), 2. en sık basit seröz kist (7 hasta, %11) ve 3. en sık korpus luteum kisti (4 hasta, %6) olduğu görüldü. Neoplastik olan grupta ise en sık matur kistik teratom (11 hasta, %17), sonrasında müsinöz kistadenom (5 hasta, %8) ve adenofibrom (3 hasta, %5) izlendi. Non-neoplastik grubun tamamına kistektomi yapıldı. Neoplastik grupta ise hastalardan 16'sına kistektomi (%72), 6'sına salpingo-ooferektomi (%28) yapıldı. Cerrahi yapılan hastalarda peri-operatif ve post-operatif komplikasyon izlenmedi.

Sonuç: Sezaryen sırasında karşılaşılan adneksiyal kitlelere cerrahi müdahale yapılması komplikasyon riskini artırmamaktadır.

Anahtar kelimeler: Adneksiyal hastalık, gebelik, insidental bulgu, sezaryen

Introduction

Adnexal masses, which are described as masses of the ovary, fallopian tube, or surrounding tissues, can be encountered in pregnancy or during cesarean section and its prevalence changes between 1/81 and 1/8.000 (1). Nowadays, increased number of adnexal masses during pregnancy can

Address for Correspondence: Cemre Alan, Necmettin Erbakan University Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey
E-mail: drcemrealan@gmail.com **ORCID:** orcid.org/0000-0002-6276-1345 **Received:** 10.01.2022 **Accepted:** 07.02.2022

Cite this article as: Yüksel S, Alan C. Retrospective Evaluation of Incidental Adnexal Masses Encountered During Cesarean Section. Bagcilar Med Bull 2022;7(1):38-42

be diagnosed with the widespread use of ultrasonography in routine prenatal care. Adnexal masses are categorized as simple or complex to evaluate the type of mass as benign or malignant. Ovarian cancer, as a second most common gynecological cancer encountered in pregnancy, was reported in 0.49% of the adnexal masses (2,3).

When an adnexal mass was detected during pregnancy, expectant management or elective surgery at second trimester can be preferred according to the properties of the mass (1,4). When elective surgery was preferred, the risk of preterm birth was reported more in laparotomy than in laparoscopy (11% vs 2%, respectively) (1). Furthermore, postoperative complication rate was reported as 16% after laparotomy (5).

Adnexal masses in pregnant women may not be diagnosed during pregnancy up to 50% to 70% of patients who come to routine prenatal care (6,7). Transabdominal ultrasonography is preferred more than transvaginal ultrasonography at earlier times of gestation and/or most of the adnexal masses that are smaller than 5 cm are asymptomatic. Hence, some of the adnexal masses can be diagnosed first time during cesarean section. Incidental adnexal masses may present management dilemmas for clinicians during cesarean section.

Our aim in this study is to evaluate the properties and surgical management of the adnexal masses encountered during cesarean section.

Materials and Methods

The patients who had a cesarean section (n=7,063) in our hospital between November 2014 and September 2019 were evaluated retrospectively. The women who had an incidental adnexal mass during cesarean section and had a definitive pathology report were enrolled. The ethical approval was obtained from a tertiary center (no: 135, 2020). The authors complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects and/or animals.

The clinical and pathological data and the results of the patients were recorded. Exclusion criteria were preoperative diagnosis of adnexal mass, intraligamentary myoma, and cases of ovarian cyst aspiration

Maternal age, gravida, parity, gestational age at the time of cesarean section, cesarean indication, perioperative complications, location, and size of the adnexal mass, surgical procedure (cystectomy or salpingo-oophorectomy), and definitive pathologies were evaluated. The size of the mass was taken as the average of the two longest diameters.

Statistical Analysis

Statistical analyses were performed with SPSS 22.0 for Windows (IBM SPSS Statistics, Chicago, IL, USA). Categorical data were given as numbers and percentages, and numerical data as mean ± standard deviation or median (minimum-maximum).

Results

A total of sixty-four women (0.9%) underwent a surgical procedure during cesarean section due to adnexal mass. The mean age of the patients was 30.2±6 years, the median parity was 1.5 (0-5), and the mean gestational age was 37.7±2.2 (Table 1). The most common indication for cesarean section was previous cesarean section (38 patients, 60%) (Table 2). Cesarean section was performed in 2 of the patients (3.1%) in the preterm period (<37 weeks) due to severe preeclampsia. Only one of the patients underwent cesarean section due to acute abdomen (ovarian torsion).

Sixty seven percent of the cases were in the non-neoplastic group and 33% of them were in the neoplastic group. Table 3 and Table 4 show the properties of the neoplastic and non-neoplastic groups. The most common pathologies found in non-neoplastic group were para-tubal or para-ovarian cysts (25 patients, 39%), simple serous cyst (7 patients, 11%), and corpus luteum cyst (4 patients, 6%),

Table 1. Demographic properties of the study group

	Mean ± SD	Minimum	Maximum
Age	30.2± 6.6	15	42
Parity	1.5±1.1	0	5
Gestational age	37.7±2.2	27	41
Hospital stay (days)	3.25±2.5	2	25

SD: Standard deviation

Table 2. Cesarean indications of the patients

	n (%)
CS* history	35 (55%)
Preeclampsia	4 (6%)
HELLP†	1 (1.6%)
Fetal distress	7 (10.9%)
Multiple pregnancy	1 (1.6%)
Cephalopelvic disproportion	5 (7.9%)
Prolonged labor	2 (3.1%)
Acute abdomen	1 (1.6%)
Placenta previa	1 (1.6%)
Malpresentation	7 (10.9%)
Total	64

*Cesarean section, †hemolysis, elevated liver enzymes, low platelet

Table 3. The localization and size of the non-neoplastic adnexal masses

Non-neoplastic	Right	Left	Bilateral	<5 cm	≥5 cm	Total
Serous cyst	1 (14%)	6 (86%)	0	4 (57%)	3 (43%)	7
Corpus luteum	2 (50%)	1 (25%)	1 (25%)	4 (100%)	0	5
Paraovarian or paratubal cyst	11 (44%)	12 (48%)	2 (8%)	22 (88%)	3 (12%)	25
Endometrioma	0	1 (100%)	0	1	0	1
Hemangioma	1 (100%)	0	0	1	0	1
Ovarian torsion	1 (100%)	0	0	1	0	1
Stromal fibrosis	2 (100%)	0	0	1	1	1

Table 4. The localization, size, and management of the neoplastic adnexal masses

Neoplastic	Right	Left	Bilateral	<5 cm	≥5 cm	Cystectomy	USO‡	Total
Mature cystic teratoma	4 (36%)	6 (55%)	1 (%9)	6 (55%)	5 (45%)	10 (91%)	1 (9%)	11
Serous cystadenoma	0	0	1	0	1 (100%)	1 (100%)	0	1
Mucinous cystadenoma	1 (20%)	4 (80%)	0	0	5 (100%)	2 (40%)	3 (60%)	5
Adenofibroma	1 (33%)	2 (67%)	0	1 (33%)	2 (67%)	3 (100%)	0	3
Dysgerminoma	0	1 (100%)	0	0	1 (100%)	0	1 (100%)	1
Borderline	0	1 (100%)	0	0	1 (100%)	0	1 (100%)	1

‡Unilateral salpingo-oophorectomy

respectively. Cystectomy was performed in all patients with non-neoplastic adnexal masses. Mature cystic teratoma was the most common pathology (11 patients, 17%) in the neoplastic group. Cystectomy was performed in 10 (91%) and unilateral salpingo-oophorectomy (USO) in 1 (9%) of the patients with mature cystic teratoma. Mucinous cystadenoma (5 patients, 8%) and adenofibroma (3 patients, 5%) were other common pathologies. Cystectomy was performed in 2 (40%) and USO in 3 (40%) women with mucinous cystadenoma. Cystectomy was performed in all women with adenofibroma.

One of the patients (27 years old) underwent USO due to giant mass at the left ovary (25 cm). Final pathology was dysgerminoma. Lymphadenectomy was not performed in our patient because there was no palpable pelvic lymph node. This patient was out of follow-up, and applied to our center with recurrence 1 year later. USO was performed in 1 patient (36 years old) with a borderline mucinous tumor.

Perioperative complications did not develop in our patients who underwent ovarian surgery during cesarean section. Erythrocyte suspension was transfused in 4 patients (6%). Subtotal hysterectomy was performed in 1 patient due to uterine atony.

Discussion

In this study, the rate of incidental adnexal mass during cesarean section was found as 0.9%. In previous studies, the incidence of adnexal masses encountered during cesarean section was reported as 0.3-1.64% (7-10). Adnexal masses can be diagnosed more frequently and easily during pregnancy, comparing the past with the use of ultrasonography in routine follow-up. Despite this, in a study in which almost all patients (99%) were followed up prenatally, it was seen that only 29.7% of adnexal masses could be diagnosed before cesarean section (6). Similarly, Baser et al. (7) reported that only 45% of adnexal masses observed at cesarean section were diagnosed during the prenatal follow-up.

The most common adnexal pathologies in non-neoplastic group were found as paratubal or paraovarian cysts, simple serous cysts, and corpus luteum cysts. Our findings were found to be consistent with previous studies (8). In contrast to Yu et al. (6), we did not observe theca lutein cysts or endometrioma as more frequent than other types. Simple serous cysts and the majority of corpus luteum cysts, especially uni-loculated ones, may undergo spontaneous resolution after the first trimester of pregnancy, as well as in the pre-pregnancy period. Although paratubal or

paraovarian cysts are benign, they can be observed relatively more frequently during cesarean section because of their higher persistence rates. Cystectomy or cyst aspiration can be performed during cesarean section for persistent simple serous or corpus luteum cysts (8).

The most common adnexal mass in the neoplastic group was found as mature cystic teratoma (6,9-11). Dermoid cyst, also known as mature cystic teratoma, can be diagnosed using transvaginal ultrasonography by experienced clinicians. However, some reasons like solid nature of the adnexal mass, change of mass location to the Douglas in pregnancy, and same echogenicity with fat tissue may lead to difficulty in its diagnosis at later weeks of gestation. In addition, we observed mucinous cystadenoma and adenofibroma most frequently in the neoplastic benign group. In cases of cystadenoma of 5 cm and larger, when frozen section cannot be performed, the clinician may prefer salpingo-oopherectomy instead of cystectomy due to malignancy concerns.

Li and Yang (12) reported the incidence of incidental malignant or borderline adnexal mass as 0.21% in cesarean section. In another study, malignancy was reported in 1% of simple adnexal masses and 9% of complex ones were diagnosed during pregnancy (1). As the most common ovarian malignancies in pregnancy, granulosa cell tumor and cystadenocarcinoma have been reported (7,13). We only observed borderline ovarian tumor in 1 of our patients (1.5%).

While ovarian dysgerminoma is seen less than 1% of all ovarian neoplasms, it constitutes 33% of malignant germ cell tumors (14). It benefits from surgery in the early stages and from chemotherapy in the later stages. Pathology of a patient who underwent salpingo-oopherectomy in our study was reported as stage IA dysgerminoma. In the study of Qin et al. (15), it was shown that per-operative lymphadenectomy did not make a difference in terms of survival in patients receiving adjuvant chemotherapy in stage 1 and 2 dysgerminomas.

When an adnexal mass is diagnosed during pregnancy, its management is controversial. Persistent adnexal masses may be malignant, as well as with increased risk of torsion, bleeding or rupture. Transvaginal ultrasonography and spectral, color Doppler ultrasonography are useful for differential diagnosis (16). For further evaluation, pelvic magnetic resonance imaging without contrast is a good option for characterization of complex adnexal masses to exclude malignancy (17,18). Elective surgery can be performed for persistent adnexal masses >5 cm or complex cysts which have a high malignancy risk during the second trimester (5,19). The duration of surgery and hospital stay were found to be shorter in patients who underwent laparoscopy compared to those who underwent laparotomy (20). Torsion in adnexal masses >5 cm without elective surgery can cause serious morbidity and requires urgent surgical intervention. There was 1 (1.6%) case of torsion in our patient group with a similar frequency to previous studies (6). We do not know the exact incidence as the patients who were operated due to torsion during follow-up were not included in our study.

Study Limitations

We have some limitations in this study. First of all, the retrospective nature of the study may prevent the evaluation of all cases. The patients had a pathology material included, so we could not know the exact number of all cysts encountered during cesarean section. We had a relatively small size of the study population.

Conclusion

Surgical intervention for incidental adnexal masses during cesarean section did not seem to increase the risk of complications. Depending on the characteristics of the detected mass, cystectomy or salpingo-oophorectomy can be performed for incidental adnexal masses during cesarean section. This approach may prevent further surgery after cesarean section in most of the patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Gaziosmanpasa Training and Research Hospital (no: 135, 2020).

Informed Consent: Informed consent of patient was not obtained because it was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.A., Design: C.A., Data Collection or Processing: C.A., S.Y., Analysis or Interpretation: S.Y., Writing: C.A., S.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. Webb KE, Sakhel K, Chauhan SP, Abuhamad AZ. Adnexal mass during pregnancy: a review. Am J Perinatol 2015;32(11):1010-1016.
2. Oheler MK, Wain GV, Brand A. Gynaecological malignancies in pregnancy: a review. Aust N Z J Obstet Gynaecol 2003;43:414-420.
3. Nazer A, Czuzoj-Shulman N, Oddy L, Abenhaim HA. Incidence of maternal and neonatal outcomes in pregnancies complicated by ovarian masses. Arch Gynecol Obstet 2015;292(5):1069-1074.
4. Whitecar P, Turner S, Higby K. Adnexal masses in pregnancy: A review of 130 cases undergoing surgical management. Am J Obstet Gynecol 1999;181(1):19-24.
5. Balthazar U, Steiner AZ, Boggess JF, Gehrig PA. Management of a persistent adnexal mass in pregnancy: what is the ideal surgical approach? J Minim Invasive Gynecol 2011;18(6):720-725.
6. Yu C, Wang J, Lu W, Xie X, Cheng X, Li X. Analysis of adnexal mass managed during cesarean section. Adv Clin Exp Med 2019;28(4):447-452.
7. Baser E, Erkilinc S, Esin S, Togrul C, Biberoglu E, Karaca MZ, et al. Adnexal masses encountered during cesarean delivery. Int J Gynaecol Obstet 2013;123(2):124-126.
8. Cengiz H, Kaya C, Ekin M, Yeşil A, Yaşar L. Management of incidental adnexal masses on caesarean section. Niger Med J 2012;53(3):132-134.
9. Ulker V, Gedikbasi A, Numanoglu C, Saygi S, Aslan H, Gulkilik A. Incidental adnexal masses at cesarean section and review of the literature. J Obstet Gynaecol Res 2010;36(3):502-505.
10. Güler A E, Güler Demirel Z Ç, Kinci Şehirli Ö. Sezaryen doğumda persistan adneksiyal kitlelerin yönetimi. Perinatoloji Dergisi 2019;27(2):56-61.
11. Dede M, Yenen MC, Yilmaz A, Goktolga U, Baser I. Treatment of incidental adnexal masses at cesarean section: a retrospective study. Int J Gynecol Cancer 2007;17(2):339-341.
12. Li X, Yang X. Ovarian Malignancies Incidentally Diagnosed During Cesarean Section: Analysis of 13 Cases. Am J Med Sci 2011;341(3):181-184.
13. Wróbel A, Rechberger E, Magnowska M, Banach P, Filipczak A, Nowak-Markwitz E, et al. Rak jajnika w ciazy--opisy trzech przypadków oraz aktualne algorytmy postepowania diagnostyczno-terapeutycznego [Ovarian cancer during pregnancy--presentation of three cases and current diagnostic and treatment algorithms]. Ginekol Pol 2015;86(11):872-878.
14. Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, Qualls CR. Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol 2006;107(5):1075-1085.
15. Qin B, Xu W, Li Y. The impact of lymphadenectomy on prognosis and survival of clinically apparent early-stage malignant ovarian germ cell tumors. Jpn J Clin Oncol 2020;50(3):282-287.
16. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Gynecology. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. Obstet Gynecol 2016;128(5):e210-e226.
17. Thomassin-Naggara I, Fedida B, Sadowski E, Chevrier MC, Chabbert-Buffet N, Ballester M, et al. Complex US adnexal masses during pregnancy: Is pelvic MR imaging accurate for characterization? Eur J Radiol 2017;93:200-208.
18. Yacobozzi M, Nguyen D, Rakita D. Adnexal masses in pregnancy. Semin Ultrasound CT MR 2012;33(1):55-64.
19. Senarath S, Ades A, Nanayakkara P. Ovarian cysts in pregnancy: a narrative review. J Obstet Gynaecol 2020:1-7.
20. Shigemi D, Aso S, Matsui H, Fushimi K, Yasunaga H. Safety of Laparoscopic Surgery for Benign Diseases during Pregnancy: A Nationwide Retrospective Cohort Study. J Minim Invasive Gynecol 2019;26(3):501-506.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):43-48
DOI: 10.4274/BMB.galenos.2022.2021-12-124

Comparison of Body Mass Index and Bioelectric Impedance Analysis Methods in the Evaluation of Body Composition and Obesity in Women

Kadınlarda Vücut Kompozisyonu ve Obezitenin Değerlendirilmesinde Beden Kütle İndeksi ve Biyoelektrik İmpedans Analiz Yöntemlerinin Karşılaştırılması

Fatih Sırıken[1], Ersen Ertekin[2], Cengiz Ünsal[3], Arif Aktuğ Ertekin[4], Hakan Öztürk[5], Anna Beatriz Rodriguez[6], Ayla Gülden Pekcan[7]

[1]Aydın Adnan Menderes University Research Hospital, Clinic of Nutrition and Dietetics, Aydın, Turkey
[2]Aydın Adnan Menderes University Faculty of Medicine, Department of Radiology, Aydın, Turkey
[3]Aydın Adnan Menderes University Faculty of Veterinary, Department of Physiology, Aydın, Turkey
[4]Üsküdar University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey
[5]Aydın Adnan Menderes University Faculty of Medicine, Department of Bioistatistic, Aydın, Turkey
[6]University of Extramadura Faculty of Science, Department of Physiology, Badajoz, Spain
[7]Hasan Kalyoncu University Faculty of Health Science, Department of Nutrition and Dietetics, Gaziantep, Turkey

Abstract

Objective: Body mass index (BMI) is often used to diagnose obesity, although it has the disadvantage of not being able to reveal body fat content. Our study aimed (1) to evaluate the obesity status using BMI and body fat percentage (BF_{BIA}%) determined by bioelectric impedance analysis (BIA) method among women aged 20-60 years who were admitted the outpatient nutrition clinic, and (2) to evaluate the relationship between BMI and BF_{BIA}%.

Method: This study enrolled 100 women aged 20-60 years. It was a descriptive study. The study data and the BF_{BIA}% values were obtained from outpatient BMI data recorded between October 2020 and November 2020. BMI was calculated using body weight (kg) and body height (m^2). The prevalence of obesity was determined using BMI and BF_{BIA}%. Statistical analyses were performed using the Pearson's correlation test and One-Way analysis of variance.

Results: Prevalence of obesity, based on BMI and BF_{BIA}%, was 53% and 46%, respectively and no significant difference was determined (p=0.322). Subjects determined to be obese based on the BMI had a mean BF_{BIA}% of 40±18%. The subjects determined to be obese, overweight and normal

Öz

Amaç: Obezite tanısında sıklıkla beden kütle indeksi (BKİ) kullanılmakla birlikte, vücut yağ düzeyini ortaya koymaması dezavantajlı noktasıdır. Bu çalışmanın amaçları diyet polikliniğine başvuran, (1) 20-60 yaş grubu kadın bireylerde, BKİ ve biyoelektrik impedans analiz yöntemi (BİA) ile doğrudan saptanan vücut yağ yüzdesini ($VY_{BİA}$%) kullanarak obezite durumunu ve (2) BKİ ve $VY_{BİA}$% arasındaki ilişkiyi değerlendirmektir.

Yöntem: Çalışma 20-60 yaş arası 100 kadın bireyle yürütülmüştür. Bu araştırma tanımlayıcı tiptedir. Araştırma verileri ve vücut yağ yüzdesi (% $BF_{BİA}$) değerleri, poliklinik BİA kayıtlarından Ekim-Kasım 2020 arasında elde edilmiştir. Vücut ağırlığı ve boy uzunluğu ölçümleri kullanılarak BKİ hesaplanmıştır. Bireylerde obezite görülme sıklığı BKİ ve vücut yağ yüzdesi ($VY_{BİA}$%) kullanılarak belirlenmiştir. İstatistik olarak Pearson korelasyon testi ve tek-yönlü varyans analizi kullanılmıştır.

Bulgular: BKİ'ye göre kadınların %53'ü, BİA ile elde edilen vücut yağ yüzdesine göre %46'sı obez bulunmuştur. BKİ ve vücut yağ yüzdesi kullanılarak saptanan obezite arasında anlamlı bir fark bulunmamıştır (p=0,322). BİA'ya göre obez bireylerin ortalama vücut yağ yüzdesi ($VY_{BİA}$%) %40±18 olarak saptanmıştır. BİA yöntemi kullanılarak BKİ'ye göre şişman, hafif şişman ve normal vücut ağırlığındaki kadınların vücut

Address for Correspondence: Fatih Sırıken, Aydın Adnan Menderes University Research Hospital, Clinic of Nutrition and Dietetics, Aydın, Turkey
E-mail: fatihsiriken@hotmail.com **ORCID:** orcid.org/0000-0001-5119-8772 **Received:** 10.12.2021 **Accepted:** 24.01.2022

Cite this article as: Sırıken F, Ertekin E, Ünsal C, Ertekin AA, Öztürk H, Rodriguez AB, Pekcan AG. Comparison of Body Mass Index and Bioelectric Impedance Analysis Methods in the Evaluation of Body Composition and Obesity in Women. Bagcilar Med Bull 2022;7(1):43-48

based on the BMI had a mean BF_{BIA}% of 40.4±5.3, 34.4±4.1, and 23.2±6.2, respectively (p<0.001).

Conclusion: The obesity rates determined by BMI and BF_{BIA}% were similar. Since both BMI and BF_{BIA}% have different disadvantages, their combined use may yield better results in obesity screening in outpatients.

Keywords: Bioelectric impedance analysis, body fat percentage, body mass index, obesity

yağ yüzdeleri ise sırasıyla %40,4±5,30, %34,4±4,1, ve %23,2±6,2 olarak belirlenmiştir (p<0,001).

Sonuç: BKİ ve $VY_{BİA}$% birbiriyle pozitif olarak ilişkilidir. Vücut yağ yüzdesinin eşlik ettiği BKİ, kadın bireylerde şişmanlığın daha iyi bir tanımlanmasını sağlayabilir.

Anahtar kelimeler: Beden kütle indeksi, biyoelektrik impedans analizi, obezite, vücut yağ yüzdesi

Introduction

The prevalence of obesity is increasing among children and adolescents as well as adults worldwide. Obesity is one of the important health problems in developed and developing countries, being responsible for an increased incidence of non-communicable diseases such as cardiovascular diseases, hypertension, type 2 diabetes, hyperlipidemia, stroke, some type of cancers and diseases such as sleep apnea, liver and gall bladder diseases, osteoarthritis and gynecological problems (1). According to the body mass index (BMI) classification recommended by World Health Organization, the Turkish Nutrition and Health Study 2010 reported that overall 35.6% (men: 39.1%; women: 29.7%) were overweight and 30,3% (men: 20.5%; women: 41.0%) were obese (2).

Defining body composition has an important role in the assessment of an individual's health status. The metabolic tissue in human body is composed of 1) lean body mass consisting of intracellular fluid, extracellular fluid, and bone tissue, and 2) fat mass. The main goal of the evaluation of an individual's obesity status is to determine the fat tissue (3).

The methods used to assess the body composition are categorized as the direct and indirect methods. The direct methods calculate the chemical composition of the body. They include isotope and chemical dilution method (body water, body potassium), body density and volume (underwater measurement, plethysmographic method, BODPOD), total body electric conductivity and bioelectric impedance analysis (BIA), imaging methods (USG), computerized topography, magnetic resonance, dual-energy X-ray absorptiometry (DEXA), and whole body neutron activation analysis. The indirect methods are skin fold thickness measurement, upper arm fat are, waist/hip ratio, waist circumference/height ratio, and BMI (4).

Although DEXA and magnetic resonance imaging are considered gold standard for determining body, their disadvantages such as the need for equipment and trained personnel, and high cost limit their use. Thus, BIA analysis is more practical and more widely used (5). BIA can be used for non-invasive tissue characterization because tissues produce a complex electrical impedance depending on their composition, structure, health status, and the applied signal frequency. This method is based on the electrical conductivity difference between lean tissue mass and fat mass. In this method, weak electrical current impedance is measured. Hand to hand, hand to foot, and foot to foot measurements with different BIA analysis tools could be done. A wide range of information is obtained, such as body fat content, lean body mass, body water content, and fat mass distribution in various body parts (6).

An adult human body is approximately composed of 16% protein, 15-20% fat, 0.5% carbohydrates, 4.5% minerals, and 60% water (7). Overweight and obesity are defined as abnormal or excessive fat accumulation in the body, which poses a risk to health. Based on an individual's BMI, overweight is defined as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2. Percentage of body fat (BF_{BIA}%) corresponds to 30 kg/m^2 (8).

The use of BIA may not be reliable in patients with a BMI outside the range of 16 to 34 kg/m^2, any abnormality of body shape, impaired hydration, impaired extracellular and intracellular fluid distribution, liver cirrhosis, renal failure, cardiac failure, and morbid obesity (9). Although BIA method is reliable, there is no international standardization of device manufacturing, which causes various devices to yield different results and prevents a direct comparison between studies and establishing generally accepted reference values (10). In BIA, body composition is determined by different formulae using resistance, reactance, age, gender, and different anthropometric parameters (11). Since BIA's accuracy mainly depends on the equation used, many researchers have developed special equations to be used in obese adult populations (12-14). However, definitive conclusions cannot be drawn regarding the predictive ability of these equations.

The objective of our study was to compare the obesity status that was determined by simple body fat percentage directly determined by BIA and the one that was determined by BMI in female outpatients admitted to the diet outpatient clinic. The number of studies conducted in Turkey on this subject is limited and very few of them are related to the patient population, so this study is important in terms of providing data on the patient population.

Materials and Methods

This descriptive and retrospective study was approved by Adnan Menderes University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (committee decision no: 9, dated: 17.09.2020). Informed consent forms were obtained from the patients before the procedure. The study group was composed of 100 female patients aged 20-60 years who visited Aydın Adnan Menderes University Research and Training Hospital outpatient nutrition clinic between October 2020 and November 2020. The patient records determined by BIA and body weight and height measurements were recorded. The study excluded males, in-patients, morbid obese patients, cancer patients, and patients with kidney disease. As the prevalence of obesity is higher in females than in the males, females are included in the study.

Tanita BC418 device (Tanita BC418 Tanita Corp, Tokyo, Japan) (eight-contact electrode system Model BC-418 analyzer) was used for BIA analysis method. Body weight (kg), body fat mass (BFM_{BIA}-kg), body fat percentage ($\%BF_{BIA}$), lean mass (LBM_{BIA}-kg), and total body water percentage (%TBW) were determined by BIA.

BMI was calculated using the formula [weight (kg)/height (m^2)] (14). Women with a BMI of 18.5-24.9 kg/m^2 were defined as normal, those with a BMI of 25.0-29.9 kg/m^2 as pre-obese, and those with a BMI of 30.0-39.9 kg/m^2 as obese (2). In the literature, among individuals diagnosed with obesity by BMI, BF_{BIA}% corresponding to 30 kg/m^2 is defined as >25% for men and >35% for women (8). In our study, women with a BF_{BIA}% ≥35 were considered obese. The reliability study of Tanita BC418 device for use by health professionals was performed (15). Its confirmation study was conducted with dual energy X-ray absorptionmetry (DEXA), which is considered a gold standard (16).

Statistical Analysis

Statistical analyses were performed with SPSS 18 software package (IBM SPSS Inc. Chicago, USA). Normality of data distribution was tested with the Kolmogorov-Smirnov test. Descriptive statistics were given as mean ± standard deviation and frequency (percentage) for quantitative and qualitative variables, respectively. Whether the qualitative variables were independent of each other was tested by chi-square analysis. Analysis of One-Way ANOVA was used to compare the BMI groups, and the correlation between BMI and BIA measurements was determined using Pearson's correlation analysis. p-values less than 0.05 were considered statistically significant.

Results

The female individuals had a mean age, height and body weight of 45.6±11 years, 1.58±0.6 (m), and 78.9±16 (kg), respectively (Table 1). According to the BIA method, the mean fat percentage (BF_{BIA}%) was determined as 36.2±7.0%, fat mass as 29.7±11 kg, total body water content as 36.1±5.0 kg, and lean body mass as 49.2±7.0 kg. Women determined to be obese according to BMI values had a mean body fat percentage of 40±18% (Table 1).

Obesity rate was 46% by BIA body fat percentage (BF_{BIA}%) and 53% by BMI. No significant difference was found between the obesity rates determined by BMI and BIA body fat percentage (p=0.322) (Graphic 1).

The prevalence of normal, overweight and obesity among females were determined using BMI values, as 12 (13%), 35 (34%), and 53 (53%), respectively (Table 2).

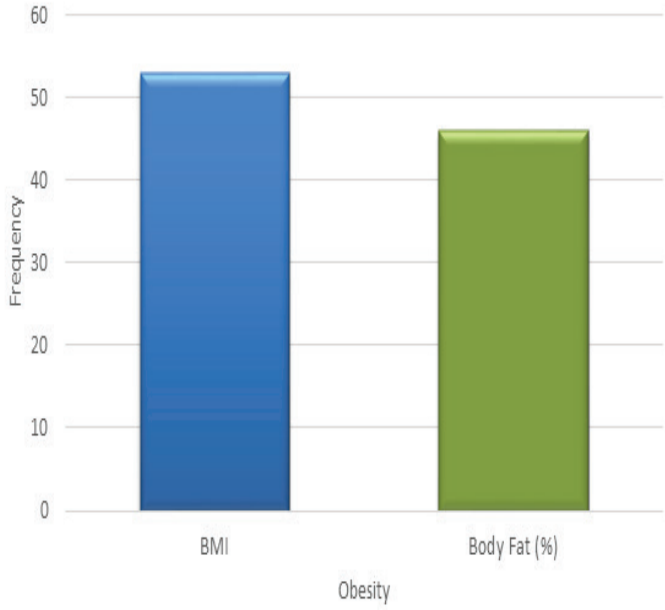
The body fat percentages ($\%BF_{BIA}$) of obese, overweight, and normal women determined by BIA were 40.4±5.3%, 34.4±4.1%, and 23.2±6.2%, respectively and BMI groups were statistically different from each other (p<0.001). Body fat percentage increased as the BMI values increased (Table 2).

Table 1. Anthropometric measurements of individuals (n=100)

Characteristics of the study sample	Mean ± SD
Age (y)	45.6±11
Height (m)	1.58±0.6
Body weight (kg)	78.9±16
BMI (kg/m^2)	31.49±6.0
BIA, body fat (BF, %)	36.2±7.0
BIA, body fat mass (FM, kg)	29.7±11
BIA, total body water (kg)	36.1±5.0
BIA, fat free mass (FFM, kg)	49.2±7.0

BMI: Body mass index, SD: Standard deviation, BIA: Bioelectric impedance analysis

There was a very strong positive linear correlation between BMI and BF% (BIA) (r=0.798) (p<0.001) (Graphic 2).



Graphic 1. Comparison of obesity rates determined by body mass index (BMI) and body fat percentage (BIA) (p=0.322)

Table 2. The distribution of obesity and body fat percentage (BIA) according to the BMI of individuals

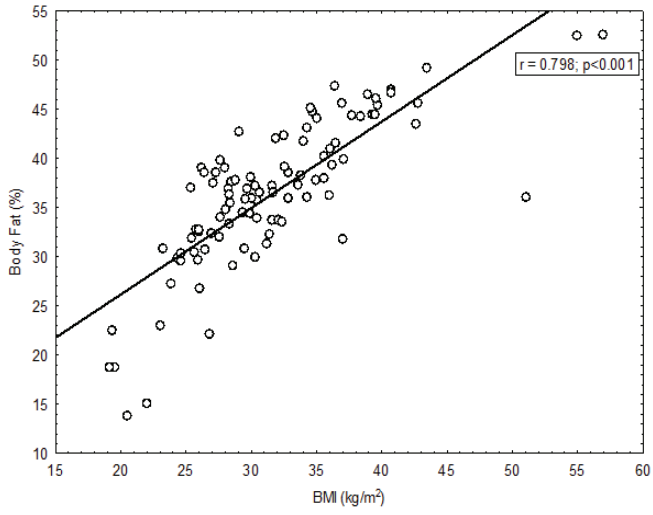
BMI (kg/m²)	n (%)	%BF_{BIA}	p	F
Normal (18.5-24.9)	12 (13%)	23.2±6.2	<0.001*	59.165*
Overweight (25.0-29.9)	35 (34%)	34.4±4.1	-	-
Obese (30.0-39.9)	53 (53%)	40.4±5.3	-	-

*Analysis of One-Way ANOVA, BMI: Body mass index, BIA: Bioelectric impedance analysis

Discussion

In a report dated 2004, ESPEN (European Society for Clinical Nutrition and Metabolism) stated that MF-BIA (Multi-frequency BIA) and segmental-BIA could be used in patients with a BMI of 16-34 kg/m² and without abnormal hydration, provided that the results were carefully interpreted (17). In this study, patients had a mean BMI of 31.49±6.0 kg/m².

This study compared the efficacy of BMI and BIA in the diagnosis of obesity. Women with a BF_{BIA}%>35 were considered obese. Our study determined that the obesity prevalence was 53% by BMI and 46% by body fat percentage (BF_{BIA}%). There was no significant difference between BMI and BF_{BIA}% in this regard (p=0.322).



Graphic 2. Determination of the relationship between body mass index (BMI) and body fat percentage (%BF_{BIA})

BMI strongly correlated with BF % estimated by bioelectrical impedance in our study (Graphic 2) (r=0.798) (p<0.001). Our results are corelated with the results of Ranasinghe et al. (18).

Women who were obese by BMI were found to have a BFBIA% of 40.4±5.3. A study carried out in Brazil revealed a BFBIA% of 41.0±3.0% among obese women with a mean age of 50 years (19).

In a study conducted among 136 obese women with a mean age of 48.1±7.7 years and a BMI of 30.4±2.9 kg/m², the mean BF_{BIA}% was found as 41.0% by using BIA (TanitaBC-418) device, which is also used in this study (20). The values of prevalences were found similar for the obese women. Chen et al. (21) reported a mean BF_{BIA}% of 29.85±7.93% in 299 healthy women with a mean age of 37.49 years and a mean BMI of 23.57±4.51 kg/m².

We determined a mean BF_{BIA}% of 23.2±6.2% in our study for normal BMI group. Willett et al. (13) evaluated the reports provided by various clinicians and reported that BF_{BIA}% was not superior to BMI as a marker of general lipoidosis in both sexes in a general population with a mean age of 21-70 years. We also reached to similar results. In a study, where Tanita Bc-418 and DEXA were used, Majeed et al. (22) compared healthy adults and reported that the strongest agreement between BIA and DEXA occurred for the estimation of total body fat percentage and the weakest in the estimation of extremity fat mass content. Uğraş and Özdenk (23) compared BMI and BIA measurements in 175 sedentary men and 105 sedentary women at the age of 18 to 25 years. They reported that BMI and BIA showed a

strong correlation for healthy body composition in both genders, being statistically significant for women (r=0.879, p<0.001). Saygın et al. (24) investigated the prevalence of obesity and body analysis values in female individuals admitted to the outpatient diet clinic. A total of 7267 women had a mean age of 37.18±13.64 years, a mean BMI of 31.33±7.35 kg/m^2, and a mean BF_{BIA}% of 36.77±7.49%. In this study it was found that 100 women with a mean age of 45.6±11 years had a mean BMI of 31.49±6.0 kg/m^2, and a mean BF_{BIA}% of 36.2±7.0%. Saygın et al. (24) used the same BIA device model as the one used in our study. We believe that the reason why we found a higher BF_{BIA}% in our study is that the females were admitted to the outpatient diet clinic for a disease event or for weight reduction diets. BIA methods is not recommended that Segal correction equation be used if a multifrequency BIA device is not used in morbid obese patients (25). We excluded morbid obese (BMI: >40 kg/m^2) patients for this reason. In our study, the BIA method determined that obese, overweight, and normal weight women had body fat percentages (BF_{BIA}%) of 40.4±5.3, 34.4±4.1, and 23.2±6.2, respectively (p<0.001). There was a significant difference in BF_{BIA}% between the groups (p<0.001). Kaner et al. (26) found body fat percentages of 41.2±4.2, 33.5±3.6, and 26.4±4.4 using BIA in obese, overweight, and normal weight women aged 20-49 years, respectively. These findings are in parallel with our study findings. Gallagher et al. (27), in a study conducted in 2000, measured body fat percentage using DEXA, the gold standard for this indication. They found body fat percentages as 21-33% in subjects with a BMI <18.5 kg/m^2 for the age groups of 20-39 and 40-50 years, respectively. Percentage of 33-34% was found in subjects with a BMI ≥25 kg/m^2 and 39-40% in subjects with a BMI≥30 kg/m^2. These results are very similar to our results.

It was reported that BIA provides a relatively accurate estimation of BF_{BIA}% in overweight and obese individuals after the end of the weight loss program, but BIA provides a less accurate estimate of body fat percentage in obese individuals during the weight change program (28).

BMI is a practical, easy and a good tool to estimate excess body weight. However, it is not as useful in determining obesity due to high fat mass or individuals with a very high muscle mass (e.g athletes) and those with a low muscle mass (e.g. in elderly, sarcopenia). BMI was never designed to make diagnosis (1,29). In this study, the mean age of individuals was 45.6±11 years and the elderly people were not included in the study and the mean FFM was 49.2±7.0 kg.

Conclusion

In conclusion, although BMI maintains its importance for obesity screening, especially in large population-based studies, but adding a body fat percentage (BF_{BIA}%) estimate using BIA may provide a good estimate ability to determine excess body fat, especially in outpatient diet clinics and hospitals in the evaluation of obesity.

Ethics

Ethics Committee Approval: This descriptive and retrospective study was approved by Adnan Menderes University Faculty of Medicine Non-invasive Clinical Research Ethics Committee (committee decision no: 9, dated: 17.09.2020).

Informed Consent: Informed consent forms were obtained from the patients before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.S., Design: F.S., C.Ü., A.A.E., E.E., A.B.R., H.Ö., A.G.P., Supervision: C.Ü., A.A.E., A.B.R., H.Ö., A.G.K., Fundings: F.S., E.E., A.A.E., A.G.P., C.Ü., A.B.R., H.Ö., Materials: F.S., Data Collection or Processing: F.S., Analysis or Interpretation: H.Ö., Literature Search: F.S., A.G.P., C.Ü., E.E., A.A.E., A.B.R., Writing: F.S., E.E., C.Ü., A.G.P., A.A.E., H.Ö., A.B.R., Critical Review: A.G.P., C.Ü., A.A.E., A.B.R., E.E., A.B.R.

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. Williams EP, Mesidor M, Winters K, Dubbert PM, Wyatth SB. Overweight and obesity: Prevelance, consequences, and causes of a growing public health problem. Cur Obes Rep 2015;4(3):363-370.
2. World Health Organization. Physical Status: The use and interpretation of anthropometry. Report of a WHO Expert Committee. In: World Health Organization Technical Report Series 1995;854:1-452. Available from: https://www.who.int/childgrowth/publications/physical_status/en/;2020 Accessed: 30.12.2020
3. Köksal E, Küçükerdönmez Ö. Şişmanlığı saptamada güncel yaklaşımlar. Baysal A, Baş M (editör). Yetişkinlerde ağırlık yönetimi. İstanbul: Express Baskı, 2008:35-70.
4. Pekcan G. Hastanın beslenme durumunun saptanması. Ankara: Klaasmat Matbaacılık, 2008:1-50.
5. Melikoğlu M, Öner C, Tüzün S, Temizkan Ş, Orbay E. Comparison of new and old body shape indices to estimate body fat in obese

and morbid obese turkish females. Turk J Endocrinol Metab 2020;24:1-8.

6. TC Sağlık Bakanlığı. Beslenme drumunun saptanması. 1st ed. Ankara: Klasmat Matbacılık, 2008.
7. Aksoy M. Beslenme, Diyet ve Gıda Sözlüğü. Ankara: Hatiboğlu Yayınları, 2007.
8. World Health Organization. European Health Report 2018: More than numbers - evidence for all. Available at: https://www.euro.who.int/en/publications/abstracts/european-health-report-2018.-more-than-numbers-evidence-for-all-2018;2020 Accessed: 13.12.2020
9. Ayyıldız F, Köksal E. Current approach in the evaluation of nutrition, hydration status and disease risk: bioelectrical impedance vector analysis. Journal of Health Sciences 2016;25(3):155-160.
10. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr 2012;31(6):854-861.
11. Gray DS, Bray GA, Gemayel N, Kaplan K. Effect of obesity on bioelectrical impedance. Am J Clin Nutr 1989;50(2):255-260.
12. Gómez-Ambrosi J, Silva C, Galofré JC, Escalada J, Santos S, Millán D, et al. Body mas index classification misses subjects within creased cardiometabolic risk factors related to elevated adiposity. Int J Obes (Lond) 2012;36(2):286-294.
13. Willett K, Jiang R, Lenart E, Spiegelman D, Willett W. Comprarsion of bioelectrical impedance and BMI in predicting obesity-related medical condition. Obesity (Silver Spring) 2006;14(3):480-490.
14. Kaya H, Özçelik O. Comparison of Effectiveness of Body Mass Index and Bioelectric Impedance Analysis Methods on Body Composition in Subjects with Different Ages and Sex. F.U. Med. J. Health. Sci 2009;23(1):1-5.
15. Kelly JS, Metcalfe J. Validity and reliability of body composition analysis using the tanita BC418-MA. Journal of Exercise Physiology Online 2012;15(6):74-83.
16. Sluyter JD, Schaaf D, Scragg RKR, Plank LD. Prediction of fatness by standing 8-electrode bioimpedance:A multi ethnic population. Obesity (Silver Spring) 2010;18(1):183-189.
17. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice, Clin Nutr 2004;23(6):1430-1453.
18. Ranasinghe C, Gamage P, Katulanda P, Andraweera N, Thilakarathne S, Tharanga P. Relationiship between body mass index (BMI) and body fat percentage, estimated by bioelectrical impedance, in a group of Sri Lankan adults: a cross sectional study. BMC Public Health 2013;13:797.
19. Ravaglia G, Forti P, Maioli F, Boschi F, Cicognani A, Gasbarrini G. Measurement of body fat in healthy elderly men: a Comparison of Methods. J Gerontol A Biol Sci Med Sci 1999;54(2):70-76.
20. Pimentel GD, Bernhard AB, Frezza MRP, Rinhaldi AEM, Burini RC. Bioelectric impedance over estimates the body fat in overweight and underestimates in Brazilian obese women: a comparation with Segal Equation. Nutr Hosp 2010;25(5):741-746.
21. Chen KT, Chen YY, Wang CW, Chuang CL, Chiang LM, Lai CL, et al. Comparison of standing posture bioelectrical impedance analysis with DXA for body composition in a large, healthy chinese population. PLoS One 2016;11(7):e0160105.
22. Majeed KG, Sulyman SAA, Fathi HB. Estimation of segmental and total body fat in healthy adults: comparison of bio-electric impedance analysis and dual energy X-ray absorptiometry. Turk J Endocrinol Metab 2019;23:240-247.
23. Uğraş S, Özdenk Ç. Comparative evaluation of bioelectrical impedance analysis and anthropometric measurements of body composition in sedentary young male and female subjects. Journal of Health Sciences 2020;29(1):14-18.
24. Saygın M, Öztürk Ö, Akbulut S, Kılınç F, Saygın RR. Obesity prevalence in patients of SDU School of Medicine Hospital diet policlinic. Med J SDU 2015;22(3):53-59.
25. Segal KR, Loan MV, Fitzgerald PI, Hodgdon JA, Itallie TBV. Lean body mass estimation by bioelectrical impedance analysis: a four-site cross-validation study. Am J Clin Nutr 1988;47(1):7-14.
26. Kaner G, Pekcan G, Pamuk G, Pamuk BÖ. Skinfold thickness versus bioimpedance analysis: body fat prediction in adults. Bes Diy Derg 2015;43(2):111-118.
27. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges:An approach for devoloping guidelines based on body mass index. Am J Clin Nutr 2000;72(3):694-701.
28. Li YC, Li CI, Lin WY, Liu CS, Hsu HS, Lee CC, et al. Percentage of body fat assessment using bioelectrical impedance analysis and aual-energy X-ray absorntiometry in weight loss program for obese or overweight Chinese adult. PloS One 2013;8(4):e58272.
29. Bogin B, Varela-Silva. The body mass index: The good, the bad, and the horrid. Bulletin der Schweizerischen Gesellschaft für Anthropologie 2012;18(2):5-11.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):49-55
DOI: 10.4274/BMB.galenos.2022.2021-12-127

The Effect of the Endotracheal Cuff and Alveolar Pressures on Laryngopharyngeal Outcomes in Laparoscopic and Open Gynecological Procedure

Laparoskopik ve Açık Jinekolojik İşlemde Endotrakeal Kaf ve Alveolar Basınçların Laringofaringeal Sonuçlara Etkisi

Güneş Özlem Yıldız[1], Gökhan Sertçakacılar[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesia and Reanimation, İstanbul, Turkey
[2]Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract

Objective: High intra-abdominal pressure during laparoscopic surgery (LS) may increase endotracheal tube cuff pressure in patients. This study aimed to evaluate the effect of endotracheal tube cuff pressure and alveolar pressures on laryngopharyngeal outcomes at different time points during laparoscopic and open surgeries.

Method: Seventy patients who underwent open or LS were included in our study. The cuff pressure, peak inspiratory pressure (PIP), and plateau pressure values were measured after endotracheal intubation, at 15th, 30th, and 60th minutes after intra-abdominal carbon dioxide (CO_2) insufflation and before extubation. In addition, all patients were evaluated for sore throat using the visual analogue scale (VAS) at 1st, 12th, and 24th hours postoperatively by an observer blinded to the study groups.

Results: The patients in the LS group had statistically significantly higher cuff, PIP, and P-plateau levels at 15th, 30th, and 60th minutes after intubation and before extubation compared to those in the open surgery (OS) group (p <0.05 for all comparisons). At postoperative 12th hour, dysphagia was observed in four (10%) patients, and cough was present in 11 (30%) patients in the LS group. The VAS score for sore throat periods was significantly higher in the LS group than in the OS group at follow-up hours (p<0.05 for all comparisons). Extended operation time and cuff pressure at different time points were significantly associated with a sore throat (p<0.05 for all correlations).

Conclusion: Endotracheal tube cuff pressures and airway pressures should be monitored, especially in LS, to protect the mucosal layer of the trachea.

Keywords: Anesthesia, endotracheal, laparoscopic surgery, pneumoperitoneum, sore throat

Öz

Amaç: Laparoskopik cerrahi (LS) sırasında yüksek karın içi basıncı hastalarda endotrakeal tüp kaf basıncını artırabilir. Bu çalışma, laparoskopik ve açık ameliyatlar sırasında farklı zaman noktalarında endotrakeal tüp kaf basıncı ve alveoler basınçların laringofaringeal sonuçlara etkisini değerlendirmeyi amaçladı.

Yöntem: Çalışmamıza açık veya LS uygulanan yetmiş hasta dahil edildi. Kaf basıncı, tepe inspiratuar basınç (PIP) ve plato basınç değerleri endotrakeal entübasyondan sonra, karın içi karbonioksit (CO_2) insüflasyonundan 15, 30, 60 dakika sonra ve ekstübasyondan önce ölçüldü. Ek olarak, tüm hastalar çalışma gruplarına kör bir gözlemci tarafından postoperatif 1., 12. ve 24. saatlerde görsel analog skala (VAS) kullanılarak boğaz ağrısı açısından değerlendirildi.

Bulgular: LS grubundaki hastalarda entübasyondan 15, 30 ve 60 dakika sonra ve ekstübasyondan önce açık cerrahi (OS) grubuna kıyasla istatistiksel olarak anlamlı derecede yüksek kaf basıncı, PIP ve P-plato seviyeleri vardı (p<0,05 için tüm karşılaştırmalar). Postoperatif 12. saatte LS grubunda dört (%10) hastada disfaji, 11 (%30) hastada öksürük vardı. Takip edilen zaman dilimlerinde boğaz ağrısı için VAS skoru, takip saatlerinde LS grubunda OS grubuna göre anlamlı olarak daha yüksekti (tüm karşılaştırmalar için p<0,05). Farklı zaman noktalarında uzamış operasyon süresi ve kaf basıncı, boğaz ağrısı ile anlamlı şekilde ilişkiliydi (tüm korelasyonlar için p<0,05).

Sonuç: Trakeanın mukozal tabakasını korumak için özellikle LS'de endotrakeal tüp kaf basınçları ve hava yolu basınçları izlenmelidir.

Anahtar kelimeler: Anestezi, boğaz ağrısı, endotrakeal, laparoskopik cerrahi, pnömoperitoneum

Address for Correspondence: Güneş Özlem Yıldız, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesia and Reanimation, İstanbul, Turkey
E-mail: drgunesim@hotmail.com **ORCID:** orcid.org/0000-0002-4557-9517 **Received:** 30.12.2021 **Accepted:** 24.01.2022

Cite this article as: Yıldız GÖ, Sertçakacılar G. The Effect of the Endotracheal Cuff and Alveolar Pressures on Laryngopharyngeal Outcomes in Laparoscopic and Open Gynecological Procedure. Bagcilar Med Bull 2022;7(1):49-55

Introduction

Endotracheal intubation can cause upper respiratory tract complications. Tracheal mucosal injury due to decreased mucosal perfusion is one of the significant complications (1,2). In addition, the mucosal damage is associated with an increased endotracheal tube cuff pressure and is accused as the primary cause of postoperative hoarseness, dysphagia, and sore throat (1,2).

With the advances in technology and surgical experience, laparoscopic procedures have become the preferred choice by patients and surgeons due to fewer hospital stays and better postoperative outcomes (3). From the anesthesiological perspective, increased intra-abdominal pressure due to pneumoperitoneum can increase airway pressures and lung compliance (3). The high abdominal pressure may also increase endotracheal tube cuff pressure in patients undergoing laparoscopy compared to open surgery (4-6). However, there is still a lack of evidence and controversial data regarding the relationship between different endotracheal tube cuff pressures, operative time, type of surgery, and postoperative laryngopharyngeal complications. This study aimed to evaluate the effect of endotracheal tube cuff pressure and alveolar airway pressures on postoperative airway complications at different time points in laparoscopic and open surgeries for gynecological indications.

Materials and Methods

This prospective study was conducted after obtaining ethical approval from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee of the institution where the study took place (approval number: 2020/92, date: 17.02.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Between 1 April 2020 and 1 November 2020, seventy patients who underwent gynecological surgery and agreed to participate with written informed consent were included in the study. In addition, the study included patients aged 18-70 years with the American Society of Anesthesiologists (ASA) grade I-II. They were planning to undergo elective surgery due to a variety of gynecological pathologies.

The exclusion criteria included patients with tracheostomy, tracheal stricture, history of laryngeal surgery or obstruction, chronic obstructive pulmonary disease (COPD), ASA ≥4, those in whom endotracheal intubation was achieved after >2 attempts, candidates for emergency surgery, and those with oropharyngeal infection within two weeks before the planned surgery.

Patients assigned for laparoscopic surgery were defined as the LS group, and patients who would undergo open surgery were defined as the OS group (Figure 1). Demographic data of the study population were recorded. The patients were provided with standard monitoring (ECG, pulse oximetry, non-invasive blood pressure). Patients received a 3-minute FiO_2: 80% preoxygenation. Anesthesia induction was achieved by intravenous (i.v.) administration of 0.05 mg/kg midazolam, 1-2 µg/kg fentanyl, propofol 2-3 mg/kg, and 0.6 mg/kg rocuronium. The muscle relaxant effect was planned to be controlled via train-of-four (TOF) neuromuscular blockade monitorization. After adequate muscle relaxation was achieved, all patients were intubated using high-volume, low-pressure cuffed endotracheal intubation tubes (ETT) (Bıçakçılar, İstanbul, Turkey). The endotracheal tube diameter was decided by evaluating the patient's age and body mass index (BMI). ETT cuff pressure was set as 25 cmH_2O so that there was no air leakage during inspiration. Anesthesia was maintained with sevoflurane (minimal alveolar concentration 0.8-1) and i.v. remifentanyl infusion (0,05-0,1 µg/kg/min). Rocuronium was administered when necessary according to the TOF evaluation. Depth of anesthesia was maintained in the range of 25-50 patient state index (SEDLine, Masimo, CA). All patients received 100 mg i.v. Tramadol and 1 g paracetamol before the end of surgery to achieve effective pain control. The patients were

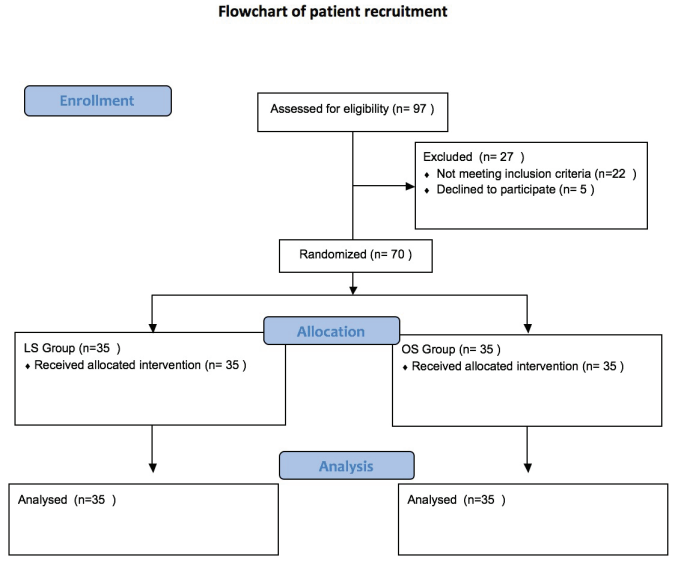


Figure 1. Consort flow chart of the study
OS: Open surgery, LS: Laparoscopic surgery

planned to be extubated after administering neostigmine 0.03 mg/kg and atropine 0.01 mg/kg. Patients who were connected to a mechanical ventilator during the operation were ventilated according to the protocol applied by our clinic. In volume control ventilation, tidal volume was adjusted to be 6-8 mL/kg (ideal body weight), I: E ratio of 1:2, positive end-expiratory pressure of 5 cmH_2O and respiratory rate, end-tidal carbon dioxide value of 35-45 mmHg.

The patients were placed in a supine position for the operation. The pneumoperitoneum and steep Trendelenburg position were used for the patients in the LS group. During the procedure, the intra-abdominal pressure was 11-13 mmHg. The ETT cuff pressure, peak inspiratory pressure (PIP), and plateau pressure values were measured at 5 minutes after intubation, at 15., 30., and 60. minutes after intra-abdominal CO_2 insufflation, and before extubation. Cuff pressure was not intervened unless a leak was detected during the measurements. The duration of anesthesia and surgery were recorded.

All patients were postoperatively evaluated for sore throat by an observer blinded to study groups using a 10-point Likert type visual analogue scale (VAS) (0: no pain, 10: the worst pain ever experienced) at 20 minutes in the recovery room and 1, 12, 24 hours in the patient room. In addition to sore throat, the presence of dysphagia, cough, and hoarseness was also questioned and recorded.

Statistical Analysis

Based on previous studies (3,5,6), a difference of at least seven mmHg in cuff pressure levels between the LS group and the OS group was considered significant. Therefore, it was determined that the study population should consist of at least 50 individuals, including at least 25 patients in each group, to achieve 95.5% power to reject the null hypothesis of equal means when the population means the difference is 2.5 with standard deviations of 4.0 for LS and 2.0 for OS, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. A total of 70 patients were included in the study as a precaution against patient loss due to the patient or other factors. Additionally, the study did not bring any additional cost to the hospital.

The patients' demographic characteristics and the study variables were analyzed in IBM SPSS® (Statistical Package for the Social Sciences) version 23. The variables were presented as mean, maximum, and minimum values, and percentages were used to define qualitative variables. The continuous variables with homogenous distribution were compared via the Student's t-test. The Pearson's chi-square test or Fisher's Exact test analyzed qualitative variables. Non-parametric continuous variables were analyzed as median and compared using the Mann-Whitney U test. A repeated Two-Way ANOVA test reached the repeated cuff, peak, and plateau airway pressures at different time points. The Pearson correlation coefficient (r) was used to analyze correlations between study variables. A p-value <0.05 was considered statistically significant.

Results

Demographic data are presented in Table 1. The mean age of the study population was 47.1±13.4 years (range 19-70). There was no statistical difference between the groups regarding demographic data, surgery, and total anesthesia time. However, the patients who underwent hysterectomy + bilateral salpingo-oophorectomy (BSO) and hysterectomy-only were more common in the OS group compared to the LS group (55.6% vs. 44.4% and 52.9% vs. 47.1%, respectively; p<0.001).

Table 1. The comparison of demographic characteristics of the study groups

	Total	LS group (n=35)	OS group (n=35)	p
Age (year) mean ± SD	47.1±13.4	45.4±15.1	48.9±11.4	0.431
Height (cm) mean ± SD	163.7±5.1	163.4±5.5	164±4.7	0.438
Weight (kg) mean ± SD	78.3±12	76.7±13.3	79.9±10.6	0.374
Body mass index	29.3±4.8	28.8±5.2	29.8±4.5	0.601
Duration of surgery (min.) mean ± SD	154.8±45	154.7±48.9	155±41.4	0.782
Duration of anesthesia (min.) mean ± SD	139.1±47.7	137.7±51.6	140.5±44.2	0.773
Type of surgery n (%)				
BSO	17 (24.3%)	10 (58.8%)	7 (41.2%)	
Cystectomy	9 (12.9%)	5 (55.6%)	4 (44.4%)	0.793
Hysterectomy	17 (24.3%)	8 (47.1%)	9 (52.9%)	
Hysterectomy + BSO	27 (38.6%)	12 (44.4%)	15 (55.6%)	

BSO: Bilateral salpingooophorectomy, SD: Standard deviation, OS: Open surgery, LS: Laparoscopic surgery

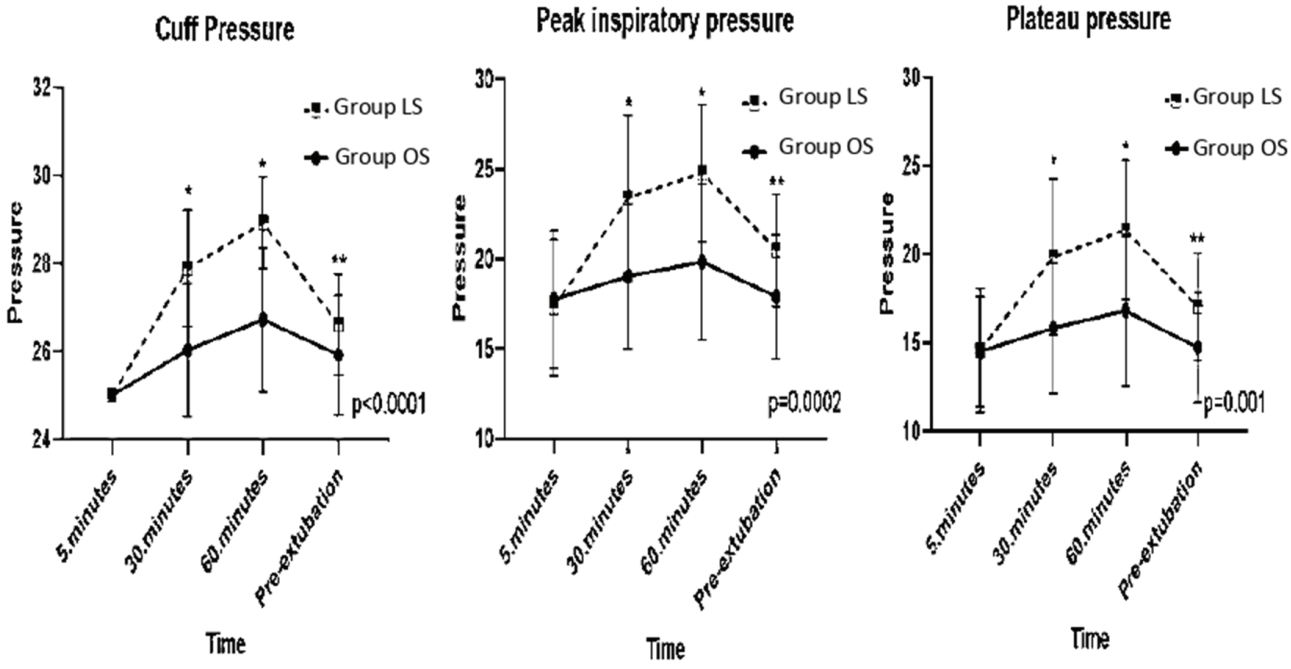


Figure 2. The comparison of ETT cuff, PIP and P plateau measurements in different time periods
PIP: Peak inspiratory pressure, ETT: Endotracheal intubation tubes

There was no difference between the study groups at 5 minutes after intubation about changes in cuff pressure, PIP, and plateau pressure values. However, the patients in the LS group had statistically significantly higher cuff, PIP, and P-plateau values compared to those in the OS group at all measurement time points after insufflation (p<0.05 for all comparisons) (Figure 2) (Table 2). In addition, the cuff pressure was significantly higher before extubation in the LS group compared to the OS group (26.6±1.2 vs. 25.9±1.4, p=0.022).

The association between cuff pressure levels at different time points and PIP and plateau pressure changes were evaluated, revealing no significant correlation between the OS and LS groups (Table 3). In the postoperative 12-hour follow-up, dysphagia was observed in four (10%) patients, and 11 (30%) patients had a cough in the LS group, which was significantly higher than that in the OS group (p<0.05). There was no significant difference between the two groups in terms of complications at the 1st and 24th hours postoperatively (Table 4). When postoperative sore throat VAS scores were evaluated, significantly higher rates were observed in the LS group at 1., 12., and 24. hours (p<0.05 for all comparisons).

The correlation analysis of cuff pressure, sore throat, BMI, and duration of surgery in different periods revealed that cuff pressure measurements at 15., 30., and 60. minutes after intra-abdominal insufflation were positively correlated with sore throat VAS scores at postoperative 1., 12., and 24. hours (p<0.05 for all correlations). Moreover, the duration of surgery also had a positive correlation with 1, 12, and 24-hour sore throat VAS scores (p<0.05 for all correlations) (Table 5).

Discussion

In our study, cuff pressure, PIP, and P-Plateau measurements were significantly higher in the LS group than in the OS group at 15., 30., and 60. minutes. Furthermore, a significant positive correlation was observed between postoperative sore throat VAS scores and cuff pressure levels at different time points.

Laparoscopic surgeries are associated with increased alveolar and endotracheal pressures (7). These increased pressures may be related to the increased intra-abdominal pressure due to pneumoperitoneum. Geng et al. (3) compared cuff pressure and airway pressure measurements in a study including 60 patients who underwent gynecological surgery. The authors evaluated 30 patients in the laparotomy group and 30 patients in the laparoscopic group and reported increases in airway pressure and

Table 2. Comparison of the study group regarding cuff pressure, PIP and plateau pressures in different time periods

	LS group (n=35)	OS group (n=35)	p
Cuff pressure			
5. min	25±0	25±0	1.000
15. min	30.3±1.7	26±1.5	**<0.001**
30. min	32±1.8	26.7±1.6	**<0.001**
60. min	29.4±1.4	25.9±1.1	**<0.001**
Before extubation	26.6±1.2	25.9±1.4	**0.022**
PIP			
5. min	17.3±3.8	18.1±4.1	0.439
15. min	23.4±4.6	19±3.9	**<0.001**
30. min	24.8±3.8	19.5±4	**<0.001**
60. min	21.6±3.8	17.7±3.5	**<0.001**
Before extubation	19.4±3.1	17.9±3.5	0.061
P plateau			
5. min	14.6±3.5	14.7±3.2	0.887
15. min	19.8±4.4	15.8±3.6	**<0.001**
30. min	21.4±3.9	16.6±4	**<0.001**
60. min	17.9±3.3	13.8±3.1	**<0.001**
Before extubation	16.3±3	14.7±3.1	0.061
Mean pressures*			
Mean cuff pressure	28.7±1.1	25.9±0.9	**<0.001**
Mean PIP	21.3±3.3	18.4±3.4	**<0.001**
Mean P plateau	18±3.1	15.1±3	**<0.001**

*The mean values comprised of 5. min, 15. min, 3.0 min and 6.0 min values, PIP: Peak inspiratory pressure, OS: Open surgery, LS: Laparoscopic surgery

Table 3. The correlation analysis of cuff pressure, PIP and plateau pressures in different time periods

	OS group		LS group	
	r	p	r	p
15. min cuff and PIP	0.073	0.680	0.179	0.304
15. min cuff and P plateau	0.172	0.330	0.138	0.428
30. min cuff and PIP	0.241	0.170	0.010	0.956
30. min cuff and P plateau	0.328	0.059	-0.002	0.993
60. min cuff and PIP	0.017	0.923	0.132	0.449
60. min cuff and P plateau	0.172	0.332	0.084	0.631
Before extubation cuff and PIP	0.003	0.988	0.085	0.626
Before extubation cuff and P plateau	0.139	0.434	0.092	0.599
Peroperative mean cuff and mean PIP	0.036	0.838	0.166	0.342
Peroperative mean cuff and mean P plateau	0.171	0.334	0.123	0.480

PIP: Peak inspiratory pressure, OS: Open surgery, LS: Laparoscopic surgery

Table 4. Comparison of postoperative laryngopharyngeal complications

	OS group (n=35)	LS group (n=35)	p
1. hour			
Cough, n (%)	4 (10.0%)	6 (20.0%)	0.498
Sore throat, n (%)	20 (60.0%)	25 (70.0%)	0.216
12. hour			
Cough, n (%)	3 (10.0%)	11 (30.0%)	**0.018**
Sore throat, n (%)	20 (60.0%)	25 (70.0%)	0.216
24. hour			
Cough, n (%)	4 (10.0%)	9 (30.0%)	0.127
Sore throat, n (%)	12 (30.0%)	19 (50.0%)	0.094
Sore throat VAS			
1. h, mean ± SD	2.37±2.17	3.6±2.5	**0.014**
12. h, mean ± SD	1.46±1.4	2.17±1.56	**0.032**
24. h, mean ± SD	0.51±0.78	1.09±1.04	**0.02**

SD: Standard deviation, VAS: Visual analogue scale

Table 5. The correlation analysis of cuff pressure, sore throat, BMI and duration of surgery in different time periods

	r	p
BMI		
15. min cuff	0.065	0.594
30. min cuff	0.079	0.517
60. min cuff	0.083	0.496
Before extubation cuff	0.107	0.380
1 h sore throat		
15. min cuff	0.421	**<0.001**
30. min cuff	0.356	**0.003**
60. min cuff	0.291	**0.015**
Before extubation cuff	0.259	**0.030**
12 h sore throat		
15. min cuff	0.415	**<0.001**
30. min cuff	0.36	**0.002**
60. min cuff	0.304	**0.010**
Before extubation cuff	0.233	0.053
24 h sore throat		
15. min cuff	0.437	**<0.001**
30. min cuff	0.395	**0.001**
60. min cuff	0.303	**0.011**
Before extubation cuff	0.243	**0.042**
Duration of surgery		
1 h sore throat	0.304	**0.011**
12 h sore throat	0.322	**0.007**
24 h sore throat	0.456	**<0.001**

BMI: Body mass index

cuff pressure in the laparotomy group. In addition, the patients in the laparoscopic group significantly suffered from sore throat, which was consistent with previous data (4,8). Rosero et al. (7) reported that ETT cuff pressures were associated with changes in mean airway and peak pressures in their study on obese patients. In addition, the authors concluded that the Trendelenburg position was significantly associated with increased endotracheal tube cuff pressures (7).

In contrast to other studies in the literature, we evaluated the airway pressures in different periods in addition to the cuff pressure (3-8). In line with the current knowledge, we also observed increased pressure levels in the LS group than in the OS group. The increase in the endotracheal cuff and airway pressures can be related to increased intra-abdominal pressure and trendelenburg position. In addition, the higher airway pressures result from reduced lung capacity due to diaphragm elevation and pneumoperitoneum. Overinflation of the tube cuff or intubation exceeding 180 minutes may increase the risk of tracheal ulceration (8). It was also reported that the steep Trendelenburg position might cause venous engorgement and reduced tracheal mucosal perfusion (7,8). Seet et al. (9) used a standard manometer to measure intra-cuff pressure to reduce pharyngolaryngeal complications in a study. They concluded that dysphagia and hoarseness rates were significantly decreased when the ETT cuff pressure was below 60 cmH_2O. In another study, Wong et al. (10) showed that postoperative laryngopharyngeal complications could be reduced when the cuff pressure was below 44 cm H_2O. On the other hand, Kang et al. (11) concluded that 25 cmH_2O intracuff pressure was sufficient for ventilation and was associated with fewer complications after laparoscopic surgery.

Regarding side effects, patients may have a sore throat, hoarseness, and cough after surgery. (12). The incidence of sore throat after endotracheal intubation ranges from 14.4% to 50% (13-15). Yildirim et al. (4) reported a higher rate of postoperative sore throat after laparoscopic surgery than after laparatomic surgery. We may speculate that sore throat could be related to gender, age, BMI, the diameter of the endotracheal tube, cuff pressure, and any movement or displacement of the tracheal tube during the operation.

In our study, significantly increased dysphagia and cough at 12 hours and higher sore throat VAS scores at different time points were observed in the LS group compared to the OS group. Besides, cuff pressures at 15., 30., and 60. minutes after insufflation were significantly correlated with sore throat VAS scores at 1., 12., and 24. hours. Moreover, the duration of surgery also showed a positive correlation with a sore throat at 1., 12., and 24. hours. The presence of sore throat may be associated with a longer duration of surgery, increased cuff pressure, and lung pressures, which may be a consequence of mucosal damage and irritation.

The strength of our study is its prospective design, which reduces the bias risk and the measurement of alveolar and tube pressures at different time points. The limitation of our study is the heterogeneity between the two groups in terms of patient position during surgeries. Although the increase in abdominal and airway pressure in the LS group was primarily due to CO_2 insufflation, the Trendelenburg position might have also contributed to increased airway pressure. However, we could not assess to what extent the position and the tube diameter contributed to the increase in airway pressures. Further studies could be designed considering our study limitations.

Conclusion

Endotracheal tube cuff pressures and alveolar pressures should be monitored, especially in laparoscopic surgeries, to protect the mucosal layer of the trachea. The clinical importance of continuous monitoring of cuff pressures is that it may prevent intubation-related complications such as sore throat in patients undergoing prolonged surgeries.

Ethics

Ethics Committee Approval: This prospective study was conducted after obtaining ethical approval from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee of the institution where the study took place (approval number: 2020/92, date: 17.02.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.Ö.Y., Design: G.Ö.Y., G.S., Data Collection or Processing: G.Ö.Y., G.S., Drafting Manuscript: G.Ö.Y., G.S., Critical Revision of Manuscript: G.Ö.Y., G.S., Final Approval and Accountability: G.Ö.Y., G.S.

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

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

References

1. Combes X, Schauvliege F, Peyrouset O, Motamed C, Kirov K, Dhonneur G, et al. Intracuff pressure and tracheal morbidity: influence of filling cuff with saline during nitrous oxide anesthesia. Anesthesiology 2001;95(5):1120-1124.
2. Svenson JE, Lindsay MB, O'Connor JE. Endotracheal intracuff pressures in the ED and prehospital setting: is there a problem? Am J Emerg Med 2007;25(1):53-56.
3. Geng G, Hu J, Huang S. The effect of endotracheal tube cuff pressure change during gynecological laparoscopic surgery on postoperative sore throat: a control study. J Clin Monit Comput 2015;29(1):141-144.
4. Yildirim ZB, Uzunkoy A, Cigdem A, Ganidagli S, Ozgonul A. Changes in cuff pressure of endotracheal tube during laparoscopic and open abdominal surgery. Surg Endosc 2012;26(2):398-401.
5. No autthors listed. Current world literature. Obstetric and gynaecological anaesthesia. Curr Opin Anaesthesiol 2006;19(3):346348.
6. Park SJ, Han SS, Ryu J, Do SH, Choi WJ, Kim YH, et al. Endotracheal cuff pressure change during gynecologic laparoscopic surgery: effect on the incidence of postoperative airway complications. Anesth Pain Med 2013;8:190-195.
7. Rosero EB, Ozayar E, Eslava-Schmalbach J, Minhajuddin A, Joshi GP. Effects of increasing airway pressures on the pressure of the endotracheal tube cuff during pelvic laparoscopic surgery. Anesth Analg 2018;127(1):120-125.
8. Liu J, Zhang X, Gong W, Li S, Wang F, Fu S, et al. Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicenter study. Anesth Analg 2010;111(5):1133-1137.
9. Seet E, Yousaf F, Gupta S, Subramanyam R, Wong DT, Chung F. Use of manometry for laryngeal mask airway reduces postoperative pharyngolaryngeal adverse events: a prospective, randomized trial. Anesthesiology 2010;112(3):652-657.
10. Wong JG, Heaney M, Chambers NA, Erb TO, von Ungern-Sternberg BS. Impact of laryngeal mask airway cuff pressures on the incidence of sore throat in children. Paediatr Anaesth 2009;19(5):464-469.
11. Kang JE, Oh CS, Choi JW, Son IS, Kim SH. Postoperative pharyngolaryngeal adverse events with laryngeal mask airway (LMA Supreme) in laparoscopic surgical procedures with cuff pressure limiting 25 cmH_2O: prospective, blind, and randomised study. ScientificWorldJournal 2014;2014:709801.
12. Christensen AM, Willemoes-Larsen H, Lundby L, Jakobsen KB. Postoperative throat complaints after tracheal intubation. Br J Anaesth 1994;73(6):786-787.
13. McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. Anaesthesia 1999;54(5):444-453.
14. Ganason N, Sivanaser V, Liu CY, Maaya M, Ooi JSM. Post-operative sore throat: comparing the monitored endotracheal tube cuff pressure and pilot balloon palpation methods. Malays J Med Sci 2019;26(5):132-138.
15. Sejkorová A, Bolcha M, Beneš J, Kalhous J, Sameš M, Vachata P. Intraoperative Measurement of Endotracheal Tube Cuff Pressure and Its Change During Surgery in Correlation With Recurrent Laryngeal Nerve Palsies, Hoarseness, and Dysphagia After Anterior Cervical Discectomy and Fusion: A Prospective Randomized Controlled Trial. Global Spine J 2021;21925682211046895.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):56-62
DOI: 10.4274/BMB.galenos.2022.2021-10-110

Quantitative Volumetric CT Analysis of COVID-19 Pneumonia and Correlation with Neutrophil-lymphocyte Ratio

COVID-19 Pnömonisinin Kantitatif Hacimsel BT Analizi ve Nötrofil-lenfosit Oranı ile Korelasyonu

Bora Kalaycıoğlu[1], Bahattin Özkul[2], Onural Öztürk[3]

[1]Memorial Sloan Kettering Cancer Center, Department of Radiology, New York, USA
[2]İstanbul Atlas University Faculty of Medicine, Department of Radiology, İstanbul, Turkey
[3]Bitlis Tatvan Public Hospital, Clinic of Radiology, Bitlis, Turkey

Abstract

Objective: Although scientific community has various knowledge about coronavirus pandemic, further studies are needed about its nature. The aim of our study is to explore the relationship between the imaging and laboratory findings of Coronavirus disease-2019 (COVID-19).

Method: Our study is a retrospective single-center study on patients with COVID-19. Patients with chest computed tomography and with positive reverse-transcription polymerase chain reaction test results were examined. Total lung volume and lesion volume were calculated semi-automatically by Osirix software. Interclass correlation coefficient was used for testing consistency between the observers. Patients were divided into three groups as mild, moderate, and severe considering the involved lung volume. The relationship between laboratory findings and radiological severity investigated with area under the curve in receiver operating characteristic plot.

Results: One hundred and six patients were included (female: 44, male: 62) in this study and the median age was 55 years. The most common radiologic features were peripheral, multifocal, ground glass opacities with sub-pleural and basal distribution. A positive and moderate correlation was found between the percentage of involvement and the neutrophil to lymphocyte ratio (N/L) (rho=0.635, p<0.001), which was the most correlated laboratory feature with radiological severity. The cut-off value was 1.1195 for N/L ratio (95.5% sensitivity, 85.7% specificity, 0.845 area under the curve, 0.742-0.948 95% confidence interval).

Conclusion: The percentage of involvement can be used as a predictor to decide the severity of the disease in patients, who are thought to have COVID-19 pneumonia.

Keywords: Computed tomography, COVID-19, neutrophil to lymphocyte ratio

Öz

Amaç: Bilim dünyasının koronovirüs pandemisi hakkında çeşitli bilgileri olmasına rağmen, virüsün doğası hakkında daha fazla çalışmaya ihtiyaç duyulmaktadır. Çalışmamızın amacı, Koronavirüs hastalığı-2019'un (COVID-19) görüntüleme ve laboratuvar bulguları arasındaki ilişkiyi araştırmaktır.

Yöntem: Çalışmamız, COVID-19 hastalarının dahil edildiği retrospektif tek merkezli bir çalışmadır. Göğüs bilgisayarlı tomografisi olan ve ters transkripsiyon polimeraz zincir reaksiyonu testi pozitif olan hastalar değerlendirildi. Toplam akciğer hacmi ve lezyon hacmi Osirix yazılımı ile yarı otomatik olarak hesaplandı. Gözlemciler arasındaki tutarlılığı test etmek için sınıf içi korelasyon katsayısı kullanıldı. Hastalar tutulan akciğer hacmine göre hafif, orta ve şiddetli olmak üzere üç gruba ayrıldı. Laboratuvar bulguları ile radyolojik tutulum şiddeti arasındaki ilişki, alıcı işletim karakteristik grafiğinde eğri altındaki alan ile incelendi.

Bulgular: Bu çalışmaya 116 hasta (kadın: 44, erkek: 62) dahil edildi ve ortanca yaş 55 idi. En yaygın radyolojik özellikler periferik, multifokal, subplevral ve bazal dağılımlı buzlu cam opasiteleriydi. Tutulum yüzdesi ve radyolojik şiddet ile en çok ilişkili laboratuvar özelliği olan nötrofil/lenfosit oranı arasında pozitif ve orta düzeyde korelasyon (rho=0,635, p<0,001) bulundu. N/L oranı için cut-off değeri 1,1195 idi (duyarlılık %95,5, özgüllük 85,7, eğri altındaki alan 0,845, %95 güven aralığı 0,742-0,948).

Sonuç: COVID-19 pnömonisi olduğu düşünülen hastalarda hastalığın ciddiyetine karar vermek için tutulum yüzdesi bir öncü gösterge olarak kullanılabilir.

Anahtar kelimeler: Bilgisayarlı tomografi, COVID-19, nötrofil/lenfosit oranı

Address for Correspondence: Bahattin Özkul, İstanbul Atlas University Faculty of Medicine, Department of Radiology, İstanbul, Turkey
E-mail: bahozkul@yahoo.com **ORCID:** orcid.org/0000-0003-3339-8329 **Received:** 21.10.2021 **Accepted:** 02.03.2022
Cite this article as: Kalaycıoğlu B, Özkul B, Öztürk O. Quantitative Volumetric CT Analysis of COVID-19 Pneumonia and Correlation with Neutrophil-lymphocyte Ratio. Bagcilar Med Bull 2022;7(1):56-62

Introduction

In December 2019, a novel type of Coronavirus emerged in Wuhan City, China. It quickly spread through China and to other countries with remarkable speed. The infection agent was named by the International Committee on Taxonomy of Viruses acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2) (1). The World Health Organization (WHO) officially named the clinical features as Coronavirus disease-2019 (COVID-19) on February 11, 2020 (2).

Earlier in the 21st century, Asia suffered from two other Coronavirus outbreaks. The former occurred between 2002 and 2003 in China with SARS-COV as the responsible agent. The latter occurred in Saudi Arabia between 2012 and 2013, with the Middle East respiratory distress syndrome-coronavirus (MERS-CoV) as the responsible agent (3). SARS-COV, SARS-CoV-2 and MERS-CoV belong to the same subtype of Coronavirus family namely Betacoronaviridae. Despite being a zoonotic agent, a high rate of human to human transmission made COVID-19 progress rapidly and on March 11, 2020, the WHO announced it as a pandemic.

SARS-COV-2 is a zoonotic, positive-strand RNA virus, causing different scales of clinical features mostly high fever, coughing and respiratory distress at any level (3,4). The disease course varies from asymptomatic to severe respiratory distress and death. Patients with underlying comorbidities such as diabetes, atherosclerotic vascular diseases, hypertension, immune deficiencies, and other chronic systemic disorders are more vulnerable to COVID-19 infection and often need to be managed in critical care units compared to patients who have no comorbidities (5).

The gold standard test for establishing diagnosis is reverse transcriptase-polymerase chain reaction (RT-PCR). However, a variety of false negative results of RT-PCR complicates the diagnosis and patient management and impacts community health due to the high social transmission rates (6,7). Computed tomography (CT) is an important tool to either support or establish a diagnosis from time to time, especially in patients with a suspended diagnosis. The most prominent alterations in the chest CT for COVID-19 are peripheral, patchy, usually bilateral ground glass opacities in the basal segments of the lungs, which often show progression into consolidation, a crazy paving pattern. Nodules, mediastinal and hilar lymph nodes, and pleural effusion are less likely to be seen (8,9).

The aim of our study is to quantitatively measure the lesion volume in both lungs, to examine the relationship between the blood cell counts, to analyze acute phase reactants for further understanding of blood test changes, to interpret radiological and biochemical features, and to seek predictors for the severity of the disease.

Materials and Methods

Study Design

Between March 10, 2020 and April 25, 2020, we performed a retrospective, single-center study of the SARS-CoV-2 laboratory-confirmed cases, which included 106 patients.

Ethical Committee Approval

This study was approved by the institutional review board and protocol review committee of University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (approval number: 2020-66). Due to pandemic, informed written consent was waived by the committee decision.

Patients

One hundred and six patients with COVID 19 were enrolled in this retrospective study from March 10th, 2020 to April 25th, 2020. Patient selection for this study was consecutive. The thorax CT images and laboratory results of all the patients were collected from the hospital database. Patients with cardiac and other systemic disorders effecting pulmonary parenchyma, those suffering from chronical interstitial lung diseases and those with advanced fibrosis and with extensive atelectasis were excluded.

Laboratory Findings

All blood test results were obtained from the hospital information system after image analysis. Neutrophil to lymphocyte (N/L) ratio was also noted. All blood samples were analyzed at the point of admission to the hospital and there were no delays longer than one day. A confirmed case was defined as positive by high throughput sequencing or real-time reverse-transcriptase polymerase-chain-reaction (rRT-PCR) assay of the nasal and pharyngeal swab specimens.

CT Acquisition

Scanning of all patients was performed in the supine position at the end inspiration on a 128 slice multi-detector row CT scanner (GE healthcare, Chicago, Illinois, United States) without using intravenous contrast media. All images were obtained with standard dose protocol, reconstructed at 1 mm slice thickness, with a 1 mm increment, with a matrix of 512 mm x 512 mm. The lung window setting was with a

window level of -500 Hounsfield units (HU) and a window width of 1.400 HU.

Interpretation of Images

All images derived from CT were evaluated independently by two radiologists with 10 and 8 years of experience in imaging (B.K. and B.O), who were blinded to the clinical and laboratory findings, with the food and drug administration approved Osirix 11.0 Dicom viewer. When there was a disagreement between the two radiologists, the final decision was reached by consensus.

For each of the 106 patients, the CT scan was evaluated for the following characteristics: (a) location: Unilateral or bilateral, (b) distribution: Subpleural, peribronchovascular or both (c) involvement pattern: GGO, consolidation and mixed. All GGO, consolidation and linear bands were assessed to calculate the total pathologic volume. GGO was defined as hazy increased lung attenuation with the preservation of the bronchial and vascular margins, and consolidation was defined as opacification with the obscuration of the margins of vessels and airway wall (10).

Image Quantitative Evaluation

Total lung volume of all the patients was analyzed using the threshold method and calculated with Osirix applications automatically (Figure 1). Pathologic densities were drawn using a manual region of interest method, then the total pathologic volumes of these densities were calculated by Osirix software semi-automatically (Figure 2). The percentage of pathologic volume was calculated by dividing the total pathologic volume by the total lung volume for each patient. The percentage of volume was divided into three groups and defined as follows: <25% was mild, ≥25-<50 was moderate, and ≥50 was a severe disease.

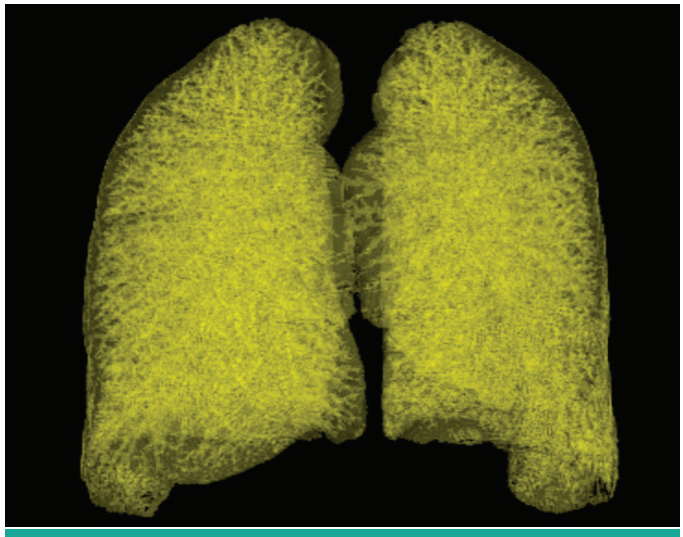


Figure 1. A 47-year-old female patient with COVID-19 pneumonia. FDA approved Osirix (version 11.0) software was used for calculating the total lung volume. The software algorithm calculated lung parenchyma without vessel and airways in 3D volume rendered reconstruction

FDA: Food and drug administration

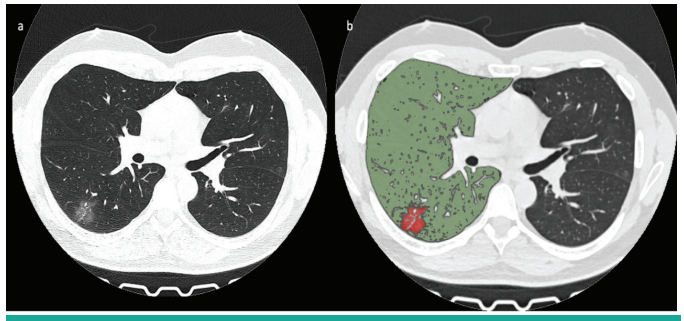


Figure 2. a) Ground glass density area accompanied with vascular enhancement at the lower lobe of the right lung observed on the non-contrast thorax CT of a 34-year-old male patient. b) Total lung volume of lung (green areas, each lung separately) calculated with automatically and pathologic volumes (red areas), calculated using semi-automatic methods

CT: Computed tomography

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS version 25 for macOS) software was used for statistical analysis. Consistency between the raters in the total involvement volume, which was calculated semi-automatically, was tested by intragroup correlation coefficient (ICC). An ICC value bigger than 0.75 was considered as having good repeatability. Whether the numerical data were normally distributed or not was evaluated by the Kolmogorov-Smirnov test. Due to the non-normal distribution of the measured indices, the correlation between the percentage of the pathologic volume and the N/L was performed using the Spearman's rank correlation. Difference between the N/L according to the percentage of pathologic volume was determined by the Kruskal-Wallis H test. The Games-Howell non-parametric method was used for post-hoc analysis and Bonferroni correction was done. The cut-off value, discriminating mild disease from a moderate-severe disease, was determined by receiver operating characteristic (ROC) analysis with the maximum Youden index. The area under the curve (AUC), sensitivity and specificity were calculated for N/L with the exact binominal confidence intervals (95% confidence level). $p<0.05$ was considered as statistically significant.

Results

Inter-observer Consistency

There was a good repeatability with ICC value 0.991 (95% confidence interval 0.987-0.994) between the two observers in evaluating total pathologic lung volume.

Demographic Characteristics

One hundred-six patients were included in the study. Sixty-two patients were male (mean age: 49.76-17.15 years, range: 18-92 years) and 44 patients were female (mean age: 55.16-15.30 years, range: 23-81 years). Considering the percentage of involved volume, the patients were classified as follows: 84 (79.2%) had a mild, 12 (11.3%) had a moderate and 10 (9.4%) had a severe disease. The distribution of age by sex and severity of disease was shown in boxplot graphics (Figure 3).

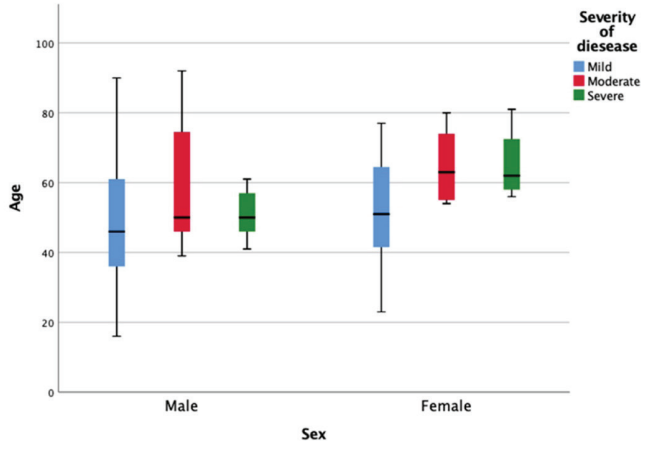


Figure 3. The distribution of ages according to the severity of the disease in males and females

Radiological and Clinical Findings

Eighty-nine (84%) patients had bilateral, 6 (5.6%) patients had right lung, and 11 (10.4%) patients had left lung involvement. Fourty-five (42.5%) cases had peripheral, 2 (1.9%) cases had peribronchovascular, and 59 (55.6%) had diffuse distribution. Seventy-four (69.8%) cases had ground-glass opacities, 2 (1.9%) cases had consolidation, and 30 (28.3) cases had mixed pattern (Table 1).

The total lung volume and the patients' ages showed a normal distribution and the mean total lung volume and SD was 3185.48-1188.08 cm^3. Table 2 presents the median and interquartile range values according to sex, total involvement lung volume, percentage of involvement, neutrophil count, lymphocyte count, N/L ratio, and C-reactive protein (CRP).

Table 1. Side, pattern and distribution of COVID-19

		Number	Percent
Side	Bilateral	89	84%
	Right	6	5.6%
	Left	11	10.4%
Pattern	GGO	74	69.8%
	Consolidation	2	1.9%
	Mixed	30	28.3%
Distribution	Peripheral	45	42.5%
	Peribronchovascular	2	1.9%
	Diffuse	59	55.6%

GGO: Ground glass opacity, COVID-19: Coronavirus disease-2019

Negative and weak correlation was determined between total lung volume and age (rho: -0.330, p<0.001). The percentage of involvement, which was a quantitative parameter, showed a weak dependence on CRP, neutrophil count and lymphocyte count with the Spearman correlation coefficients of 0.352 (p<0.001), 0.307 (p<0.001) and -0.435 (p<0.001), respectively (Table 3). However, a positive and moderate correlation was found between the percentage of involvement and the neutrophil-lymphocyte ratio (rho: 0.635, p<0.001).

The median and interquartile range values were found according to the severity of the disease as follows: Mild was 2.1257 (1.4922-3.5541), moderate was 4.5377 (3.6996-6.1429), and severe was 9.1559 (5.6190-12.5581). Significant differences were found between the groups (p<0.0001). After the Kruskal-Wallis test was performed, statistically significant differences were determined by the post-hoc analysis between a mild and moderate, between a moderate and severe, and between a mild and a severe disease (p=0.044, p=0.039 and p=0.002, respectively, Table 4).

ROC curve analysis (Figure 4) yielded an AUC, which is 0.845 for N/L with a standard error of 0.053 and 95% confidence interval of 0.742-0.948. The cut-off value was found to be 1.1195 for N/L ratio, with a 95.5% sensitivity and an 85.7% specificity.

Eighteen of the 106 (16.98%) patients were hospitalized with dyspnea. The mean hospitalization time was 10.5 (range: 5-19) days. Seventeen of 18 (94.44%) patients who needed hospitalization had both bilateral involvement and diffuse distribution. No patients died during this study.

Table 2. Median and interquartile range values according to sex for non-normally distributed data

	Male			Female		
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75
Total lung volume (cm^3)	3561.5	2728.0	4312.0	2451.5	1885.0	3310.0
Percentage	5.79	1.54	16.53	4.53	1.10	18.43
Neutrophil ($10^3/\mu L$)	3.76	2.79	5.57	3.61	2.48	4.73
Lymphocyte ($10^3/\mu L$)	1.60	1.17	2.01	1.44	0.91	1.87
N/L	2.31	1.53	4.51	2.59	1.70	4.61
CRP (mg/dL)	4.52	1.29	15.52	2.70	0.83	13.19

N: Number of patients, N/L: Neutrophil to lymphocyte ratio, CRP: C-reactive protein

Table 3. Correlation between the percentage of involvement and blood parameters

	rho	p
CRP	0.352	<0.001
Neutrophil	0.307	<0.001
Lymphocyte	-0.435	<0.001
N/L	0.635	<0.001

CRP: C-reactive protein, N/L: Neutrophil to lymphocyte ratio, Spearman's rank correlation was performed

Table 4. Differences between the N/L values according to the disease severity

		p
Mild (2.12)	Moderate (4.54)	0.044
Moderate	Severe (9.16)	0.039
Mild	Severe	0.002

Median value of the N/L was shown in the brackets, Kruskal-Wallis test was used for statistical analysis and post-hoc analysis was performed, N/L: Neutrophil to lymphocyte ratio

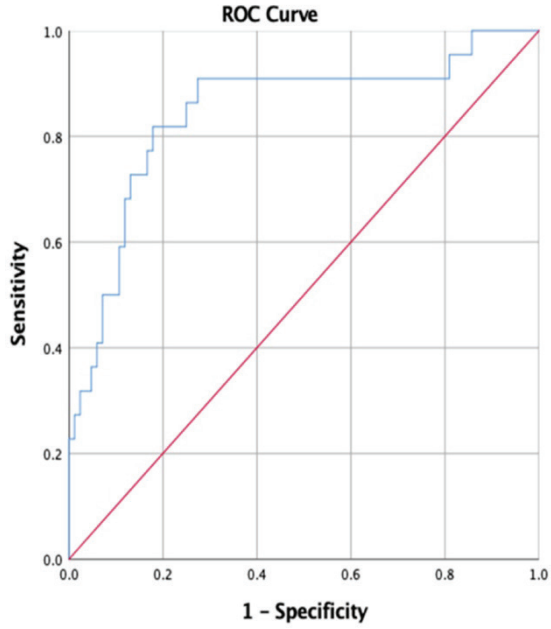


Figure 4. Graphic of receiver operating characteristics for N/L

N/L: Neutrophil to lymphocyte ratio

Discussion

COVID-19 is a serious condition especially in patients with comorbidities. Clinical condition, radiological features and biochemical changes might show inconsistency in some cases. For early detection and prediction of an aggravated clinical condition, radiologic features, biochemical findings and clinical findings should be assessed together. The severity of COVID-19 pneumonia increases with age, acute phase reactants, neutrophil, neutrophil/lymphocyte ratio, and with a decrease of lymphocyte count. Age is the most prominent predictor of the disease severity in COVID-19, as with other viral pneumonias.

The first stage of COVID-19 pneumonia is presented with alveolar edema which is depicted in CT imaging as patchy ground glass opacities. In the first stage of disease, alveoli are not completely filled with exudate. With disease progression, alveolar exudates expand through surrounding alveoli via foraminal paths. At this disease stage, CT reveals crazy paving pattern and patchy consolidations sometimes with "air bronchus sign". In severe cases, extension of these lesions is seen (11).

The most common radiologic features in our study group were peripheral, multifocal, ground glass opacities with subpleural and basal distribution. Consolidation was the second most radiologic feature usually accompanied with more lesion burden compared to patients with only ground glass opacity lesion type. Pleural effusion was extremely rare and no mediastinal lymph node was detected with pathologic appearance.

The findings in our study are consistent with the previous studies and reports (8,11-13). Lymphopenia and increased neutrophil and N/L ratio express the unusual manner of

COVID-19, that is unlikely in other viral infections. On the other hand, radiological features of COVID-19 pneumonia also have some different presentations. Most other viral and atypical bacterial pneumonias show peribronchial nodules, which is not a major manifestation of COVID-19 pneumonia. Underlying mechanisms of these blood changes and unusual radiological features are not well explained yet.

In several previous studies (2,8), radiologic severity degree is obtained by an involved lung lobe and focal lesion count. Contrarily, we classified patients into 3 groups as mild, moderate and severe with a quantitative volumetric approach. In previous studies, the volumetric percentage of lung involvement shows a more specific relationship with clinical changes. Colombi et al. (12) in their study displayed that patients with a lower volume of well aerated lung areas were at high risk of intensive care unit admission and death. Shen et al. (8) in their study depicted that a higher lesion volume was highly related to clinical severity. MuLBSTA score (multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age) can also be applied to the COVID-19 infection to determine clinical severity and a 90-day survival rate (8,14). With this point of view, we investigated the blood changes of patients with the variable radiological disease severity, to reveal effectivity of commonly used biochemical markers.

Patients managed in intensive care units show more laboratory abnormalities compared to those not requiring intensive care unit management (15,16). In the radiological aspect of severity, the N/L ratio showed the highest correlation with lesion burden. Other biochemical features showing a different level of correlation are lymphopenia, neutrophil increase, and CRP increase. Liu et al. (13) in their study found N/L ratio as the most predictive blood change to display a clinical severity and prognosis and showed more sensitivity and specificity compared to the MuLBSTA score N/L ratio, which is consistent with our findings. They also proposed a new patient management method using N/L ratio and age (13). In our study, we found that the percentage of the involvement was correlated with N/L. In this context, we think that the percentage of involvement can be used as a predictor of the disease severity.

Study Limitations

The major limitation of our study was its retrospective design. Another limitation was that the majority of our subjects' disease course had not finished. Although no patient died during our study, some of the subjects were still active COVID-19 bearers. Hence, certain results for the disease process and the overall results could not be obtained. Our suggestion for researchers planning to study this topic is to assess the clinical condition together with the radiological and biochemical findings. Additionally, blood gas analysis could be included in the biochemical analysis and the interobserver consistency could be tested with less experienced raters. Lastly, automatic segmentation methods could be utilized to work with a broad range of patients.

Conclusion

Biochemical blood changes are highly correlated with radiological features. Age is the most significant reason for clinical and radiological severity. The most correlated hematological change in our study is the N/L, along with an increase of neutrophil, CRP, and a decrease of lymphocyte. So, we have concluded that quantitative volumetric CT analysis is correlated with N/L in COVID-19 pneumonia and can be used as a predictor of the disease severity. Further studies will provide a better understanding of the disease mechanism and the disease course.

Ethics

Ethics Committee Approval: This study was approved by the institutional review board and protocol review committee of University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (approval number: 2020-66).

Informed Consent: Due to pandemic, informed written consent was waived by the committee decision.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.K., B.Ö., Design: B.K., B.Ö., Data Collection or Processing: B.K., B.Ö., O.Ö., Analysis or Interpretation: B.K., B.Ö., Drafting Manuscript: B.K., B.Ö., O.Ö., Critical Revision of Manuscript: B.K., Final Approval and Accountability: B.K., B.Ö., O.Ö.

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

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

References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020;92(4):401-402.

2. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y,et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol 2020;30(8):4407-4416.

3. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.

4. Oñate JM, Rodriguez-Morales AJ, Moreno GC, Ramírez HM, Sabogal IAR, Moreno CA. A new emerging zoonotic virus of concern: the 2019 novel Coronavirus (SARS CoV-2). Infectio 2020;24:187-192.

5. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55(5):2000524.

6. Wikramaratna PS, Paton RS, Ghafari M, Lourenço J. Estimating the false-negative test probability of SARS-CoV-2 by RT-PCR. Euro Surveill 2020;25(50)2000568.

7. Han X, Cao Y, Jiang N, Chen Y, Alwalid O, Zhang X, et al. Novel Coronavirus Disease 2019 (COVID-19) Pneumonia Progression Course in 17 Discharged Patients: Comparison of Clinical and Thin-Section Computed Tomography Features During Recovery. Clin Infect Dis 2020;71(15):723-731.

8. Shen C, Yu N, Cai S, Zhou J, Sheng J, Liu K, et al. Quantitative computed tomography analysis for stratifying the severity of Coronavirus Disease 2019. J Pharm Anal 2020;10(2):123-129.

9. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X. et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology 2020;295(1):202-207.

10. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246(3):697-722.

11. Zhao X, Liu B, Yu Y, Wang X, Du Y, Gu J, et al. The characteristics and clinical value of chest CT images of novel coronavirus pneumonia. Clin Radiol 2020;75(5):335-340.

12. Colombi D, Bodini FC, Petrini M, Maffi G, Morelli N, Milanese G, et al. Well-aerated Lung on Admitting Chest CT to Predict Adverse Outcome in COVID-19 Pneumonia. Radiology 2020;296(2):86-96.

13. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med 2020;18(1):206.

14. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. Front Microbiol 2019;10:2752.

15. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health 2020;13(5):667-673.

16. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):63-69
DOI: 10.4274/BMB.galenos.2022.2021-05-057

Recombinant FSH Versus Highly Purified Urinary FSH in Patients with Polycystic Ovary Syndrome Undergoing ICSI Cycles: A Prospective Randomized Study

ICSI Uygulanan Polikistik Over Sendromlu Hastalarda Rekombinant FSH ve Yüksek Saflaştırılmış Üriner FSH'nin Etkinliklerinin Karşılaştırılması

Öner Aynıoğlu[1], Yasin Ceylan[2], Bertan Akar[3], Sebiha Özdemir Özkan[4], Eray Çalışkan[5], Emek Doğer[6], Yiğit Çakıroğlu[7]

[1]Private Kocaeli Hospital, Clinic of Obstetrics and Gynecology, Kocaeli, Turkey
[2]University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[3]İstinye University Faculty of Medicine; Private Kocaeli Hospital, Clinic of Obstetrics and Gynecology, Kocaeli, Turkey
[4]Medicalpark Kocaeli Hospital, Clinic of Obstetrics and Gynecology, Kocaeli, Turkey
[5]Okan University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey
[6]Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology, Kocaeli, Turkey
[7]Acıbadem Maslak Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Objective: To compare efficacy and safety of recombinant follicule stimulating hormone (r-FSH) and highly purified urinary FSH (HP-uFSH) in polycystic ovary syndrome (PCOS) patients undergoing intracytoplasmic sperm injection (ICSI).

Method: This was a prospective randomized study conducted at Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology, in vitro fertizilization (IVF) Unit. A total of 91 PCOS patients undergoing ICSI were randomly assigned to receive either r-FSH (n=46) or HP-uFSH (n=45) with a gonadotropin releasing hormone (GnRH) antagonist protocol. The main outcome measures were the number of mature oocytes retrieved, embryo quality, pregnancy rates, implantation rates.

Results: The number of mature oocytes retrieved, fertilization rates, the number of cryopreserved embryos were significantly higher in r-FSH group (p=0.024, p=0.023, p=0.026 respectively) while the total dose of FSH used was significantly lower in the same group (p=0.023). Pregnancy rates, clinical pregnancy rates were higher in r-FSH group although not

Öz

Amaç: ICSI uygulanan PCOS hastalarında rekombinant FSH (r-FSH) ve yüksek oranda saflaştırılmış üriner FSH'nin (HP-uFSH) etkinliğini ve güvenliğini karşılaştırmaktır.

Yöntem: Kocaeli Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Tüp Bebek Ünitesi'nde yürütülen prospektif randomize bir çalışmadır. ICSI uygulanan toplam 91 PCOS hastası, bir GnRH antagonist protokolü ile r-FSH (n=46) ve HP-uFSH (n=45) almak üzere rastgele belirlendi. Ana sonuç ölçütleri; alınan olgun oosit sayısı, embriyo kalitesi, gebelik oranları, implantasyon oranlarıydı.

Bulgular: Alınan olgun oosit sayısı, döllenme oranları, dondurularak saklanan embriyo sayısı r-FSH grubunda anlamlı olarak daha yüksek (sırasıyla p=0,024, p=0,023, p=0,026), aynı grupta kullanılan toplam FSH dozu ise anlamlı olarak daha düşüktü (p=0,023). Gebelik oranları, klinik gebelik oranları r-FSH grubunda istatistiksel olarak anlamlı olmamakla birlikte daha yüksekti (sırasıyla %52,2'ye karşı %35,6, p=0,11, %37'ye karşı %28,9, p=0,41). Klinik gebelik başına genel tedavi maliyetleri, r-FSH

Address for Correspondence: Yasin Ceylan, University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
E-mail: md.yasinceylan@yahoo.com **ORCID:** orcid.org/0000-0001-5517-8461 **Received:** 15.06.2021 **Accepted:** 03.03.2022
Cite this article as: Aynıoğlu Ö, Ceylan Y, Akar B, Özdemir Özkan S, Çalışkan E, Doğer D, Çakıroğlu Y. Recombinant FSH Versus Highly Purified Urinary FSH in Patients with Polycystic Ovary Syndrome Undergoing ICSI Cycles: A Prospective Randomized Study. Bagcilar Med Bull 2022;7(1):63-69

statistically significant (52.2% versus 35.6%, p=0.11, 37% versus 28.9%, p=0.41 respectively). Overall therapy costs per clinical pregnancy were associated with a 9.94% increase in r-FSH group whereas costs per pregnancy were not different between groups.

Conclusion: r-FSH is superior than HP-uFSH in PCOS regarding fertilization rates, the number of mature oocytes retrieved and cryopreserved embryos, pregnancy rates although overall therapy costs per clinical pregnancy are higher.

Keywords: ART, HP-uFSH, PCOS, rec-FSH

grubunda %9,94'lük bir artışla ilişkilendirilirken, gebelik başına maliyetler gruplar arasında farklı değildi.

Sonuç: r-FSH, PCOS'de fertilizasyon oranları, alınan olgun oosit sayısı ve dondurularak saklanan embriyolar, gebelik oranları açısından HP-uFSH'den üstündür, ancak klinik gebelik başına genel tedavi maliyetleri daha yüksektir.

Anahtar kelimeler: ART, HP-uFSH, PCOS, rec-FSH

Introduction

Polycystic ovary syndrome is a challenging endocrine disorder clinically characterized by irregular menses, clinical/biochemical hyperandrogenemia, polycystic appearance of the ovaries on ultrasonography, and infertility (1). Pathophysiology still remains to be elucidated with a complex clinical background involving insulin resistance, hyperlipidemia, and a predisposition to certain malignancies.

Ovarian stimulation in infertile PCOS subjects is mostly complicated by under- or over- stimulation attributed to naturally narrow spectrum of follicular development in this group of patients (2).

Controlled ovarian stimulation (COH) as a primary part of IVF-ET is achieved by the implementation of exogenous gonadotropins in order to induce follicular recruitment and oocyte yield. FSH of different origins have been applied in clinical practice up to date. Urine derived gonadotropins having varying amounts of FSH together with urinary proteins have been available for years along with the drawbacks of requiring vast quantities of urine from multiple donors thus leading to discontinuity of the supply and batch-to-batch inconsistency (3). Recent advent of recombinant DNA technology using Chinese hamster ovary cells has provided recombinant FSH preparations with improved purity, higher specific activity, greater batch-to-batch consistency and independence of urine collection ensuring a constant FSH supply along with potentially higher medical costs (4,5). High purity is related to decreased immunogenicity thus conferring safety and tolerability (3,6).

Several comparative clinical trials and a meta-analysis have suggested better results with r-FSH in comparison with u-FSH during ART cycles in terms of pregnancy rates, oocyte quality and ovarian hyperstimulation syndrome (OHSS) whereas some others have reported contradicting conclusions in favor of u-FSH (7-15).

In the present study, we aimed to compare the efficacy and safety of rr-FSH (Follitropin α) and HP-uFSH (urofollitropin) in patients with PCOS, undergoing ICSI cycles.

Materials and Methods

A prospective randomized study was conducted at Kocaeli University, IVF Unit with a total of 91 PCOS patients undergoing ICSI. Written consents were obtained from all participants.

PCOS diagnosis was made according to the criteria of the Rotterdam ESHRE-ASRM-sponsored PCOS consensus workshop group (2004) when two out of three criteria were present: Oligomenorrhea (fewer than six menstrual periods in the preceding year) and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; presence of ≥12 follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 mL) (16). Clinical evidence of hyperandrogenism was a Ferriman-Gallwey score (FG) of ≥8 indicating hirsutism (excessive growth of hair on androgen dependent body sites) and/or acne (17). Biochemical hyperandrogenism was defined as total testosterone and free androgen index >95th percentile for the control group studied, which were 3.8 nmol/L and 7% respectively. Any other etiologic factor leading to hirsutism and/or metabolic impairment such as type II diabetes mellitus, hyperprolactinemia, hypogonadotropic hypogonadism, thyroid disorder, congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome, acromegaly and pharmacologic remedies were excluded by appropriate laboratory work-up. The subjects received no medications including oral contraceptives, antiandrogens or any other agent affective on carbohydrate metabolism for the last 3 months.

PCOS cases with primary infertility, age of 18-39 years, undergoing their first ART trial, without severe male factor, endometriosis and tubal factor, with a normal uterine cavity, in good medical and mental health condition, with a basal FSH level <10 IU/L, estradiol level <80 pg/mL and prolactin level <25 ng/mL were included in the study.

Exclusion criteria were the presence of uterine fibroids, endometriosis, endocrine, metabolic and any other medical disease, a body mass index (BMI) of >35 kg/m^2, ovaries inaccessible for oocyte retrieval, persistent ovarian cysts >15 mm, hydrosalpinx if it had not been surgically removed or ligated previously, any contraindication for pregnancy, any genital bleeding of unknown origin, neoplasia, impaired hepatic or renal function, any concomitant medication that might interfere study evaluation, alcohol or drug abuse, history of chemotherapy or radiotherapy, hypersensitivity to any preparation used during the study.

Power analysis of the study showed that when effect size was 0.3, a total of 88 patients were required to be randomized at alpha=0.05 and power of 80%. All the subjects were managed based on accepted principles of infertility practice. Standardized regimens for controlled ovarian hyperstimulation (COH), pituitary down regulation and ovulation triggering were instituted. Ninety-one PCOS subjects were randomized in order to receive GnRH antagonist protocol with r-FSH 225 IU/day (Gonal-f®,Serono,Switzerland) (n=46) and GnRH antagonist protocol with HP-uFSH 225 IU/day (Fostimon®, IBSA, Institut BiochemiqueSA, Lugano, Switzerland) (n=45). Randomization was done by means of a computer-generated randomization table and allocations were placed in consecutively numbered and sealed, opaque envelopes. Individualized step-down or step-up protocols were instituted and serial monitoring of ovarian response was assessed by ultrasonographic folliculometry and serum estradiol (E_2) assays. GnRH antagonist (Cetrotide® 0.25 mg, Serono, Switzerland) injections were started in a multidose flexible protocol as 14 mm follicle was determined by ultrasonography (USG). A single dose of 250 mcg human corionic gondotropin (hCG) (Ovitrelle®, Serono, Switzerland) was administered subcutaneously to trigger ovulation when 3 or more follicles were measured to be >17 mm and serum E_2 levels were increased approximately to 300-500 pg/mL per follicle larger than 17 mm. Transvaginal ultrasound guided oocyte retrieval under conscious sedation was performed 36 hours following hCG injection. Fertilization was assessed 17-18 hours after retrieval. One or two normally fertilized oocytes with the highest pronuclear score and the morphologic grade were considered for embryo transfer. Cleavage stage embryo transfers (in most cases 2 embryos) were carried out on day 3 or 5 under ultrasound guidance. Surplus embryos were cryopreserved. The luteal phase was daily supported by 8% progesterone gel (Crinone® 8% gel, Serono, Switzerland) initially for 14 days starting on oocyte retrieval day. A serum hCG pregnancy test was ordered in 12 days following embryo transfer.

Patient and cycle parameters were recorded, i.e. age, infertility etiology, infertility duration, BMI, baseline hormonal assessment of ovarian reserve (baseline FSH and E_2), IVF cycle stimulation protocol, duration of stimulation (days), total FSH amount (IU) for COH, number of follicles >15 mm on day of hCG, serum E_2 levels on day of hCG, serum estradiol levels following hCG injection, hCG day, day of embryo transfer, serum progesterone levels on hCG day, number of oocytes retrieved, number of mature oocytes, fertilization rates, quality of oocytes and embryos, number of transferred embryos, implantation rates and clinical pregnancy (CP) rates (CP-defined as intrauterine gestational sac visible on transvaginal ultrasound). Those variables were compared between two study groups. Cycle characteristics, embryology parameters and IVF outcome were defined. The primary outcome measures were the number of mature oocytes retrieved, embryo quality, pregnancy rates and implantation rates. Secondary outcome measures were duration of stimulation, total dose of gonadotrophins used, fertilization rates, embryo cleavage rates, cancellation rates and OHSS and multiple pregnancy rates and overall therapy costs.

Statistical Analysis

The collected data were processed using SPSS 11.0 (Statistical package for social sciences) software (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was analyzed by the Shapiro-Wilk normality tests. The continuous variables were expressed as mean ± standard deviation and compared by using the Student's t-test. Categorical data were expressed as numbers (percentages) and compared by X^2-test or Fisher's Exact test where appropriate. $p<0.05$ was considered to be statistically significant.

Results

Ninety-one PCOS subjects with an age range of 18-39 years were randomized in order to receive GnRH antagonist protocol with r-FSH 225 IU/day (n=46) and GnRH antagonist protocol with HP-uFSH 225 IU/day (n=45). Demographic data of the patients are shown in Table 1. Dysmenorrhea was significantly more common in the HP-uFSH group (p=0.043).

Hormonal data including (FSH, LH, estradiol, prolactin, TSH, free T_3 and free T_4) and fasting glucose, HbA1c levels did not differ significantly.

Table 1. Demographic data of the patients

Demographic data	r-FSH (n=46) (%, n)	HP- uFSH (n=45) (%, n)	p
Age (years)	28.2	29.8	NS
BMI (kg/m²)	24.5	24.4	NS
Duration of infertility (months)	76	89.9	NS
Hirsutism	67.4% (31)	53.3% (24)	NS
Galactorrhea	4.3% (2)	6.8% (3)	NS
Menses			
Regular	19.6% (9)	17.8% (8)	NS
Oligomenorrhea	47.8% (22)	37.8% (17)	NS
Hypomenorrhea	30.4% (14)	35.6% (16)	NS
Amenorrhea	2.2% (1)	4.4% (2)	NS
Acne	56.5% (26)	66.7% (30)	NS
Dysmenorrhea	28.3% (13)	48.9% (22)	0.043*
Dyspareunia	23.9% (11)	33.3% (15)	NS
Diabetes mellitus	6.5% (3)	0% (0)	NS
Thyroid disease	8.7% (4)	6.7% (3)	NS
Smoking	13% (6)	17.8% (8)	NS
Age of the partner	31.7	32.7	NS
Previous therapies			
CC	64% (9)	36% (5)	NS
CC+IUI	43% (9)	57% (12)	NS
Gonadotropin	50% (2)	50% (2)	NS
Gonadotropin + IUI	40% (13)	60% (20)	NS

BMI: Body mass index, CC: Clomiphene citrate, IUI: Intrauterine insemination, NS: Non-significant, *p<0.05 statistically significant

Table 2. Cycle characteristics of the patients

	r-FSH (n=46) (%, n)	HP u-FSH (n=45) (%, n)	p
Duration of stimulation (days)	9.8	9.9	NS
Total FSH dose used (IU)	2.494	2.872	NS
The first day of GnRH antagonist administration	8.2	8.2	NS
Duration of antagonist treatment (days)	4	4.1	NS
Coasting	6.5% (3)	0% (0)	NS
Folliculometry			
-Number of AF	21.8	20.1	NS
-Number of follicles 10-14 mm on hCG day	4.6	4.5	NS
	9.3	6.6	0.0001*
-Number of follicles 14-18 mm on hCG day	3.1	3.1	NS
-Number of follicles ≥18 mm on hCG day			
Estradiol level on day 6-7 (pg/mL)	1.212	1.159	NS
Estradiol level on hCG day (pg/mL)	2.590	2.416	NS
Basal endometrial thickness (mm)	5.06	4.1	NS
Endometrial thickness on hCG day (mm)	10.3	10.3	NS
Endometrial thickness on OPU day (mm)	10.7	10.7	NS
Endometrial thickness on transfer day (mm)	10.9	11.1	NS
hCG day	11.4	11.5	NS
OHSS	6.52% (3)	6.66% (3)	NS

OPU: Oocyte pick up, FSH: Follicle stimulating hormone, GnRH: Gonadotropin releasing hormone, AF: Antral follicle, OHSS: Ovarian hyperstimulation syndrome, NS: Non-significant, *p<0.05 statistically significant

Cycle characteristics and embryology data are demonstrated in Table 2 and Table 3, respectively. Number of follicles 14-18 mm on hCG day, number of oocytes retrieved, number of metaphase II oocytes, number of fertilized oocytes on day 1, number of cleaved embryos on day 2, and number of cryopreserved embryos were significantly higher in the r-FSH group (p<0.001, p=0.002, p=0.024, p=0.03, p=0.027, p=0.002, respectively).

OHSS complicated the cycles in 3 patients in each group. Only one case of the HP-uFSH group was moderate OHSS and was required to be hospitalized. Coasting was needed in 3 cases in the r-FSH group whereas no coasting was done in the HP-uFSH group. In 2 patients of the r-FSH group (due to no cleavage in 1 case and asynchronization in the other one) and in 6 patients of the HP-uFSH group (due to no fertilization in 3 cases, premature ovulation in 1 patient, asynchronization in 1 case and no cleavage in another one), embryo transfer was cancelled. ICSI outcomes of the groups are shown in Figure 1 and Table 4.

Fertilization rates (72% versus 63%), pregnancy rates [52.2% (24) versus 35.6% (16)], biochemical pregnancy rates [13.6% (6) versus 7.7% (3)], and CP rates [37% (17) versus 28.9% (13)] were found to be higher in the r-FSH group whereas multiple pregnancy rates [17.9% (7) versus 15.9% (7)] and implantation rates (21.3% versus 19.2%) were higher in the HP-uFSH group although none of the p-values demonstrated statistical significance.

Discussion

Recent advent of recombinant DNA technology has provided an alternative agent of ovarian stimulation to urine derived FSH preparations which are considered to be an important innovation in endocrine research area. In spite of several comparative studies which contribute to the growing body of evidence regarding this issue, which of the agents should be preferred for ovulation stimulation in IUI and ART cycles still remains to be clarified. Even the meta-analyses appear to suggest contradictory results.

Table 3. Embryology data of the patients

	r-FSH (n=44) (%, n)	HP u-FSH (n=39) (%, n)	p
Number of oocytes retrieved	19.1	12.5	0.002*
The rate of metaphase I oocytes	3.82	2.09	0.03*
The rate of metaphase II oocytes	13.9	9.7	0.024*
The rate of GV	2.3	1.6	NS
Number of good quality embryos (G1+G2)	2.7	3.0	NS
Number of G1 embryos (G1)	1.8	1.8	NS
Number of fertilized oocytes on day 1 (2 pn)	9.9	7.0	0.03*
Number of cleaved embryos on day 2	9.7	6.7	0.027*
The rate of embryo transfer	3.0 (n=44)	3.1 (n=39)	NS
Day of embryo transfer			
-Day 2 transfers	15.9% (7)	20.5% (8)	NS
-Day 3 transfers	63.6% (28)	71.8% (28)	NS
-Blastocyst transfer	20.5% (9)	7.7% (3)	NS
Cancelled transfer	25% (2)	75% (6)	NS
Easy transfer	86.4% (38)	97.4% (38)	NS
Cryopreserved embryos			
-Number of patients	22	9	0.003*
-Number of embryos	121	23	0.002*

GV: Germinal vesicle, G1: Grade 1, G2: Grade 2, NS: Non-significant, *p<0.05 statistically significant

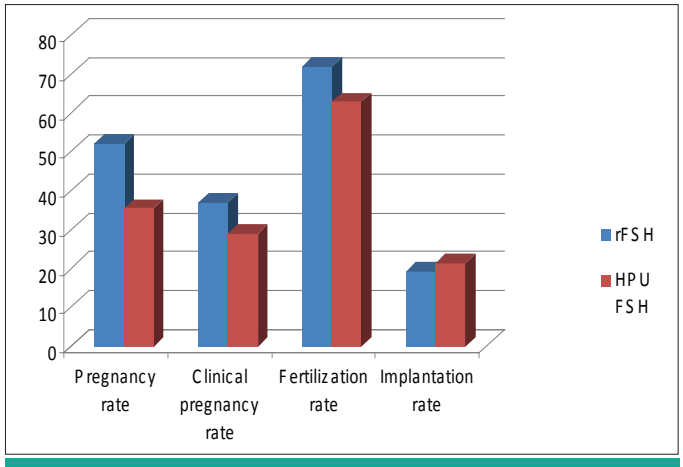


Figure 1. ICSI outcome of the patients

The meta-analysis of Daya and Gunby (7) pooling data of 12 randomized controlled studies compared treatment cycles of IVF/ICSI allocating 1.556 and 1.319 patients to r-FSH and u-FSH respectively in terms of cycle characteristics and IVF/ICSI outcome. Odds ratio for CP rate/cycle was 1.2 (95% confidence interval, 1.02-1.42, p<0.03) in favor of r-FSH thus concluding a significantly higher pregnancy rate with r-FSH in IVF/ICSI cycles (7). However, a Cochrane review of 4 randomized controlled trials comparing r-FSH and u-FSH in IUI cycles of PCOS patients demonstrated that there was no sufficient evidence to recommend one of those agents over the other (18).

Table 4. ICSI outcome of the patients

	r-FSH (n=44)	HP u-FSH (n=39)	p
Pregnancy rate	52.2% (24)	35.6% (16)	NS
Clinical pregnancy rate	37% (17)	28.9% (13)	NS
Biochemical pregnancy rate	13.6% (6)	7.7% (3)	NS
Multiple pregnancy rate	15.9% (7)	17.9% (7)	NS
Fertilization rate	72%	63%	NS
Implantation rate	19.2%	21.3%	NS

*p<0.05 statistically significant, NS: Non-significant

Several investigators comparing r-FSH and u-FSH in ART cycles in terms of efficacy and safety suggested higher efficiency in inducing multifollicular development with greater numbers of oocytes retrieved and embryos, higher embryo quality and decreased amount of total FSH used, shorter duration of stimulation in addition to higher rates of cryopreservation and pregnancy rates with the use of r-FSH (8-13). On the other hand, a group of other researchers have reported contradictory results. Mohamed et al. (14) compared those two preparations in older women undergoing ART cycles and found that oocyte retrieval and pregnancy rates did not differ significantly between groups and u-FSH appeared to be more cost-effective since the total amount of u-FSH used was lower than r-FSH in treatment cycles.

The results of clinical trials comparing r-FSH and u-FSH in IUI cycles also appeared to be controversial as they were in ART cycles. Some of them concluded that u-FSH was not less efficacious and safer than r-FSH in terms of ovulation rates, cycle cancellation rates, duration of stimulation, total dose of FSH used, OHSS and multiple pregnancy rates, pregnancy rates whereas the others reported better results with r-FSH in IUI cycles of patients with unexplained infertility and PCOS (1,19-22).

Another important issue to be considered with respect to the comparison of r-FSH and u-FSH is cost-effectiveness. Daya et al. (23) from UK, Silverberg et al. (24) from USA, and Romeu et al. (4) from Spain used Markov modelling to compare those two preparations in terms of therapy costs

and all concluded that r-FSH was found to be more cost-effective in their health care systems due to higher efficacy, decreased overall gonadotropin consumption, higher rates of cryopreservation, and need for fewer cycles to get one pregnancy. Only one group of researchers using the same Markov model found u-FSH to be more cost-effective (25). On the other hand, Revelli et al. (26) reported lower final economical costs per delivered baby with r-FSH since lower FSH dose used and slightly higher effectiveness of r-FSH in terms of delivered babies compensated for the higher costs per IU.

This great heterogeneity regarding the results of studies comparing r-FSH and u-FSH in either ART or IUI cycles may be attributed to different isoform profiles of FSH. Variable carbohydrate chains in size and structure, levels of sialylation and sulfation of FSH isoforms lead to significantly different ability of receptor binding and metabolic clearance thus causing variable *in vivo* biological activities (19). r-FSH contains higher proportions of less acidic forms whereas u-FSH presents a higher proportion of acidic forms. Less acidic isoforms are shown to bind to FSH receptors with a higher affinity. They are also associated with better proliferation of granulosa cells and estradiol production with faster circulatory clearance and a shorter half-life while acidic ones are more slowly cleared from the circulation (6).

Controversies regarding the efficacy and safety of different FSH preparations may be attributed to high purity and batch-to-batch consistency of r-FSH, varying patient selection criteria, pituitary suppression protocols, gonadotropin dose, administration route, and study design in addition to this varying isoform profile (14).

To the best of our knowledge, our study is one of the few prospective randomized studies to compare r-FSH and HP-uFSH in PCOS patients undergoing IVF/ICSI cycles (2). Aboulghar et al. (2) concluded that total dose of FSH used, duration of stimulation, number of retrieved oocytes, number of mature oocytes, number of transferred embryos, and ongoing pregnancy rates did not differ significantly. There were more fertilized oocytes, a higher fertilization rate, more top quality embryos, and more cryopreserved embryos in the HP-uFSH group. In our study, number of mature oocytes retrieved, fertilization rates, and number of cryopreserved embryos were found to be significantly higher in the r-FSH group while the total dose of FSH used was significantly lower in the same group. Pregnancy rates and CP rates were found to be higher in the r-FSH group although not statistically significant. Overall therapy costs per CP were associated with a 9.94% increase in the r-FSH group whereas costs per pregnancy were not different between groups. The duration of stimulation, the number of good quality embryos, implantation rates, OHSS, and multiple pregnancy rates did not differ significantly between two groups.

Conclusion

r-FSH was found to be more effective than HP-uFSH in PCOS patients undergoing ART cycles as it provides higher fertilization rates, higher numbers of collected mature oocytes and cryopreserved embryos, and lower FSH consumption. Pregnancy rates and CP rates were shown to be numerically higher with r-FSH. Although it is not statistically significant, it can be significant if the number of participants is increased. Higher overall therapy costs per CP with r-FSH should be considered as a major drawback. Further studies of cost-effectiveness using robust modelling procedures appropriate for each country's own health service systems and efficacy and safety trials involving a higher number of patients are required in order to get well-defined conclusions regarding this controversial subject.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of Kocaeli University (approval date: 30.01.2009).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., E.Ç., Concept: Ö.A., E.Ç., S.Ö.Ö.., E.D., Design: Y.C., B.A., E.Ç., S.Ö.Ö., Data Collection or Processing: S.Ö.Ö., Y.Ç., Analysis or Interpretation: E.D., Y.Ç., Literature Search: Y.C., B.A., E.D., Writing: Ö.A., Y.C., B.A., Y.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. Szilágyi A, Bártfai G, Mánfai A, Koloszár S, Pál A, Szabó I. Low-dose ovulation induction with urinary gonadotropins or recombinant follicle stimulating hormone in patients with polycystic ovary syndrome. Gynecol Endocrinol 2004;18(1):17-22.
2. Aboulghar M, Saber W, Amin Y, Aboulghar M, Mansour R, Serour G. Prospective, randomized study comparing highly purified urinary

follicle-stimulating hormone (FSH) and recombinant FSH for in vitro fertilization/intracytoplasmic sperm injection in patients with polycystic ovary syndrome. Fertil Steril 2010;94(6):2332-2334.

3. Lenton E, Soltan A, Hewitt J, Thomson A, Davies W, Ashraf N, et al. Induction of ovulation in women undergoing assisted reproductive techniques: recombinant human FSH (follitropin alpha) versus highly purified urinary FSH (urofollitropin HP). Hum Reprod 2000;15(5):1021-1027.

4. Romeu A, Balasch J, Ruiz Balda JA, Barri PN, Daya S, Auray JP, et al. Cost-effectiveness of recombinant versus urinary follicle-stimulating hormone in assisted reproduction techniques in the Spanish public health care system. J Assist Reprod Genet 2003;20(8):294-300.

5. Gerli S, Casini ML, Unfer V, Costabile L, Mignosa M, Di Renzo GC. Ovulation induction with urinary FSH or recombinant FSH in polycystic ovary syndrome patients: a prospective randomized analysis of cost-effectiveness. Reprod Biomed Online 2004;9(5):494-499.

6. Pacchiarotti A, Aragona C, Gaglione R, Selman H. Efficacy of a combined protocol of urinary and recombinant follicle-stimulating hormone used for ovarian stimulation of patients undergoing ICSI cycle. J Assist Reprod Genet 2007;24(9):400-405.

7. Daya S, Gunby J. Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction. Hum Reprod 1999;14(9):2207-2215.

8. Out HJ, Mannaerts BM, Driessen SG, Bennink HJ. A prospective, randomized, assessor-blind, multicentre study comparing recombinant and urinary follicle stimulating hormone (Puregon versus Metrodin) in in-vitro fertilization. Hum Reprod 1995;10(10):2534-2540.

9. Out HJ, Driessen SG, Mannaerts BM, Coelingh Bennink HJ. Recombinant follicle-stimulating hormone (follitropin beta, Puregon) yields higher pregnancy rates in in vitro fertilization than urinary gonadotropins. Fertil Steril 1997;68(1):138-142.

10. Bergh C, Howles CM, Borg K, Hamberger L, Josefsson B, Nilsson L, et al. Recombinant human follicle stimulating hormone (r-hFSH; Gonal-F) versus highly purified urinary FSH (Metrodin HP): results of a randomized comparative study in women undergoing assisted reproductive techniques. Hum Reprod 1997;12(10):2133-2139.

11. Frydman R, Howles CM, Truong F. A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-F) with highly purified urinary FSH (Metrodin) HP) in women undergoing assisted reproductive techniques including intracytoplasmic sperm injection. The French Multicentre Trialists. Hum Reprod 2000;15(3):520-525.

12. Khalaf Y, Taylor A, Pettigrew R. The relative clinical efficacy of recombinant follicle stimulating hormone to the highly purified urinary preparation. Assist Reprod Genet 2000;546-552.

13. Schats R, Sutter PD, Bassil S, Kremer JA, Tournaye H, Donnez J. Ovarian stimulation during assisted reproduction treatment: a comparison of recombinant and highly purified urinary human FSH. On behalf of The Feronia and Apis study group. Hum Reprod 2000;15(8):1691-1697.

14. Mohamed MA, Sbracia M, Pacchiarotti A, Micara G, Linari A, Tranquilli D, et al. Urinary follicle-stimulating hormone (FSH) is more effective than recombinant FSH in older women in a controlled randomized study. Fertil Steril 2006;85(5):1398-1403.

15. Selman HA, De Santo M, Sterzik K, Coccia E, El-Danasouri I. Effect of highly purified urinary follicle-stimulating hormone on oocyte and embryo quality. Fertil Steril 2002;78(5):1061-1067.

16. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-47.

17. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961;21:1440-1447.

18. Bayram N, van Wely M, van Der Veen F. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2001;(2):CD002121.

19. Balen A, Platteau P, Andersen AN, Devroey P, Helmgaard L, Arce JC, et al. Highly purified FSH is as efficacious as recombinant FSH for ovulation induction in women with WHO Group II anovulatory infertility: a randomized controlled non-inferiority trial. Hum Reprod 2007;22(7):1816-1823.

20. Gerli S, Casini ML, Unfer V, Costabile L, Bini V, Di Renzo GC. Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: a prospective, randomized analysis of cost effectiveness. Fertil Steril 2004;82(3):573-578.

21. Yarali H, Bukulmez O, Gurgan T. Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomiphene citrate-resistant, normogonadotropic, chronic anovulation: a prospective randomized study. Fertil Steril 1999;72(2):276-281.

22. Demirol A, Gurgan T. Comparison of different gonadotrophin preparations in intrauterine insemination cycles for the treatment of unexplained infertility: a prospective, randomized study. Hum Reprod 2007;22(1):97-100.

23. Daya S, Ledger W, Auray JP, Duru G, Silverberg K, Wikland M, et al. Cost-effectiveness modelling of recombinant FSH versus urinary FSH in assisted reproduction techniques in the UK. Hum Reprod 2001;16(12):2563-2569.

24. Silverberg K, Schertz J, Falk B, Beresniak A. Impact of urinary FSH price: a cost-effectiveness analysis of recombinant and urinary FSH in assisted reproduction techniques in the USA. Reprod Biomed Online 2002;5(3):265-269.

25. Hatoum HT, Keye WR Jr, Marrs RP, Walton SM, Marshall DC. A Markov model of the cost-effectiveness of human-derived follicle-stimulating hormone (FSH) versus recombinant FSH using comparative clinical trial data. Fertil Steril 2005;83(3):804-807.

26. Revelli A, Poso F, Gennarelli G, Moffa F, Grassi G, Massobrio M. Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis. Reprod Biol Endocrinol 2006;4:38.

ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(1):70-76
DOI: 10.4274/BMB.galenos.2022.2022-01-02

What is the Role of Mucocutaneous Manifestations in the Clinical Presentation of Monogenic Autoinflammatory Diseases? A Single-center Experience

Monogenik Otoenflamatuvar Hastalıkların Klinik Prezentasyonunda Mukokutanöz Bulguların Payı Nedir? Tek Merkez Deneyimi

Oya Köker[1], Nuray Aktay Ayaz[2]

[1]Marmara University, Pendik Training and Research Hospital, Clinic of Pediatric Rheumatology, İstanbul, Turkey
[2]İstanbul University Faculty of Medicine, Department of Pediatric Rheumatology, İstanbul, Turkey

Abstract

Objective: The aim of the study was to determine the distribution, frequency, and characteristics of mucocutaneous manifestations along with other clinical and laboratory data in the presentation of monogenic autoinflammatory diseases.

Method: The study was performed with the patients being followed up with a diagnosis of autoinflammatory diseases at the Pediatric Rheumatology Department in İstanbul University Faculty of Medicine. Medical records on clinical and laboratory characteristics covering the date range from January 1, 2018 to September 1, 2021 were retrospectively reviewed.

Results: The study cohort (n=97) demonstrated a distribution as familial Mediterranean fever (n=64, 66%), mevalonate kinase deficiency (n=16, 16.5%), cryopyrin-associated periodic syndromes (n=11, 11.3%), and TNF receptor-associated periodic syndrome (n=6, 6.2%). Among the entire cohort, 59.8% was female. The median age at diagnosis and at the study were 71 (3-195) and 147 (34-253) months, respectively. Mucocutaneous involvement (34%, n=33) appeared as erysipelas-like, urticaria-like, maculopapular or morbilliform in character. The location and extent of rash differed between the subgroups, limited to a localized area in patients with familial Mediterranean fever, but scattered in patients with cryopyrin-associated periodic syndromes.

Conclusion: The location and character of the mucocutaneous signs demonstrated a consistent distribution according to the subgroups. Skin

Öz

Amaç: Çalışmanın amacı monogenik otoenflamatuvar hastalıkların sunumunda mukokütanöz bulguların dağılımını, sıklığını ve özelliklerini diğer klinik ve laboratuvar verilerle birlikte belirlemekti.

Yöntem: Çalışma İstanbul Üniversitesi Tıp Fakültesi Çocuk Romatoloji Bilim Dalı'nda otoenflamatuvar hastalık tanısı ile takip edilen hastalarla gerçekleştirildi. 1 Ocak 2018-1 Eylül 2021 tarih aralığındaki klinik ve laboratuvar özelliklerin ayrıntılarına ilişkin medikal kayıtlar geriye dönük olarak incelendi.

Bulgular: Çalışma kohortu (n=97) ailesel Akdeniz ateşi (n=64, %66), mevalonat kinaz eksikliği (n=16, %16,5), kriyopirin ilişkili periyodik sendromlar (n=11, %11,3), TNF reseptörü ilişkili periyodik sendrom (n=6, %6,2) şeklinde dağılım göstermiştir. Çalışma grubunun %59,8'i kız hastalardı. Tanı anındaki ve çalışmadaki ortanca yaşlar sırasıyla 71 (3-195) ve 147 (34-253) aydı. Mukokütanöz tutulum (%34, n=33) erizipel benzeri, ürtiker benzeri, makülopapüler veya morbilliform karakterdeydi. Döküntülerin yeri ve yaygınlığı alt gruplar arasında farklılık gösterdi; ailesel Akdeniz ateşi olan hastalarda lokalize alanla sınırlıyken, kriyopirin ilişkili periyodik sendrom tanılı hastalarda dağınık yerleşimliydi.

Sonuç: Mukokütanöz bulguların yeri ve karakteri alt gruplara göre tutarlı bir dağılım göstermiştir. Deri bulguları hemen hemen tüm alt tiplere eşlik eder ve hastalığın alt bölümlerine ve patolojik mekanizmasına ilişkin bir ipucu sağlayabilir.

Address for Correspondence: Oya Köker, Marmara University, Pendik Training and Research Hospital, Clinic of Pediatric Rheumatology, İstanbul, Turkey
E-mail: oyakoker@hotmail.com **ORCID:** orcid.org/0000-0002-0101-9585 **Received:** 04.01.2022 **Accepted:** 02.03.2022

Cite this article as: Köker O, Aktay Ayaz N. What is the Role of Mucocutaneous Manifestations in the Clinical Presentation of Monogenic Autoinflammatory Diseases? A Single-center Experience. Bagcilar Med Bull 2022;7(1):70-76

manifestations accompany almost all subtypes and may provide a clue regarding the subdivision and pathological mechanism of the disease.

Keywords: Autoinflammatory diseases, mucocutaneous manifestations, pediatric rheumatology

Anahtar kelimeler: Mukokutanöz belirtiler, otoenflamatuvar hastalıklar, pediyatrik romatoloji

Introduction

Autoinflammatory diseases are a group of disorders associated with an overactivation of the cytokines and other components of the innate immune system and clinically characterized by uncontrolled systemic inflammation leading to recurrent episodes of fever along with the involvement of the joints, eyes, skin, and serosal surfaces (1). The term "autoinflammatory diseases" was first used in 1999 to describe a group of rare diseases driven by autoinflammatory mechanisms (2,3). Since then, with deepening awareness of the genetic polymorphisms and their association with proteins of the inflammasome complex and other regulatory proteins, the diseases have begun to be more identified, and the spectrum has continued to grow.

Monogenic, polygenic, and multifactorial disorders are among the range of autoinflammatory diseases. The classical monogenic group consists of familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and cryopyrin-associated periodic syndromes (CAPS) derived from various mutations in a single gene leading to unregulated innate immunity and overexpression of interleukin (IL)-1β (4). Clinical inflammation is recurrent or rarely persistent, usually manifested by fever and involvement of the serous membranes. Mucocutaneous lesions are the hallmark of the spectrum as they may have a role in the initial presentation or the activation stage of autoinflammatory diseases.

The cutaneous features may solely be the dominant sign in the clinical picture or one of the indispensable manifestations guiding the differential diagnosis. In contrast to the overlapping clinical features such as fever and joint involvement, the cutaneous signs in monogenic diseases may display a consistent morphological and topographic distribution among the subgroups and provide a clue regarding the subdivision and pathological mechanism of the disease. However, in these diseases, genotype and phenotype correlation is not always compatible, and may lead to individual differences and heterogeneous clinical presentations (5). The aim of this study is to determine the distribution, frequency, and characteristics of mucocutaneous features along with other clinical and laboratory data in the presentation and the course of monogenic autoinflammatory diseases.

Materials and Methods

Patient Selection

The study was performed with the patients being followed up with a diagnosis of autoinflammatory diseases at the Pediatric Rheumatology Department in İstanbul University Faculty of Medicine. In the definition of the patients, genotype, clinical manifestations, and expert opinion were regarded in the light of recommended classification criteria (6, 7). Special attention has been given to include patients who were diagnosed after excluding all existing causes, and who did not have any signs that would raise diagnostic suspicion during the follow-up and treatment process.

Autoinflammatory diseases other than monogenic periodic syndromes were not included in the study. Since the diagnoses may demonstrate a wide age distribution, patients between the ages of 0-18 years were included in the study. The patients with missing or insufficient data and without regular follow-up were excluded from the study. Each participant and his/her legal representative approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study. Approval was obtained from the Ethics Committee of İstanbul University Faculty of Medicine for the study (2021-622903).

Data Collection

Medical records covering the date range from January 1, 2018 to September 1, 2021 were retrospectively reviewed. The details of clinical and laboratory characteristics were recorded by using a standardized form for all subjects. Demographic (age, gender) and disease-related data (age at diagnosis, duration of symptoms before the diagnosis, disease duration from the diagnosis to the time of the study, disease pattern, detailed history of initial symptoms, medication history) were assessed. It was verified whether the physical signs within the criteria were accurately and consistently documented at the time of the diagnosis. Baseline laboratory data including leukocyte and platelet

count, C-reactive protein, erythrocyte sedimentation rate, serum amyloid a were investigated both from their own records and from the hospital database.

Genetic Analyses

Genetic tests were primarily ordered based on clinical pictures and laboratory data of the patients. In case of suspicion of FMF, genomic DNA from peripheral blood samples of the suspected patients was genotyped for the specific candidate gene MEFV using Sanger sequencing. For patients who were clinically incompatible with the MEFV mutation, who displayed episodes of atypical inflammation and who did not respond to colchicine therapy and who were suggestive of other monogenic types, a gene panel including NLRP3, MVK, TNFRSF1A, NLRP12, PSTPIP1, NOD2, ELANE, IL1RN, MEFV, LPIN2, TNFRSF11A, CARD14, PSMB8, IL10RA, IL10RB, NLRP7 or whole-exome sequencing method was utilized. Variants found in patients were analyzed by searching on the ClinVar or the Infevers.

Statistical Analysis

Statistical analyses were performed by using the IBM SPSS Statistics for Windows 21.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA) and Microsoft Excel (Redmond, WA). The visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) were performed to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis, and the data are presented as percentage (%), median with minimum and maximum values. In the comparison and assessment of the data, non-parametric tests, and Kruskal-Wallis test were performed. Statistical significance was defined as p-value <0.05.

Results

Nine patients were excluded from the study because of missing or insufficient data, while 97 patients with the diagnosis of monogenic autoinflammatory diseases were enrolled. The study cohort demonstrated a distribution as FMF (n=64, 66%), MKD (n=16, 16.5%), CAPS (n=11, 11.3%), TRAPS (n=6, 6.2%).

Among the entire cohort, 59.8% were female. The median age at diagnosis and at the study were 71 (3-195) and 147 (34-253) months, respectively. The median disease duration was 78 (13-207) months. According to gender distribution, the ratio of females n (%) among the groups were 41 (64.1) in FMF patients, 7 (63.6) in CAPS patients, 9 (56.3) in MKD patients and 1 (16.7) in TRAPS patients. The age at the study by months were 160 (51-253) in FMF, 156 (54-216) in CAPS, 96 (34-180) in MKD and 94 (50-160) in TRAPS. The current age revealed a significant difference among the subgroups (p=0.00), yet there was no difference in terms of gender distribution (p=0.84). The age at the diagnosis by months were 72 (13-195) in FMF, 96 (3-185) in CAPS, 41.5 (6-120) in MKD and 54 (36-132) in TRAPS. The disease duration by months was 75 (13-207) in FMF, 80 (47-170) in CAPS, 81 (31-174) in MKD and 66.5 (30-98) in TRAPS. There was no significant difference between the subgroups in terms of the age at diagnosis and the disease duration with p=0.16 and p=0.81, respectively. Early signs and symptoms with initial laboratory data of the entire cohort were demonstrated in Table 1. The table illustrates the general distribution of the different characters of the skin involvement. Distribution of clinical and demographic manifestations among the subgroups is presented in Table 2 with the details of mucocutaneous signs.

Discussion

Autoinflammatory diseases have a wide distribution within themselves, therewithal, skin lesions diversify according to subgroups. Although monogenic autoinflammatory diseases often have cutaneous manifestations as part of their presentation, clinical data and studies on dermatological involvement are limited. As presenting the clinical presentation of monogenic autoinflammatory diseases, we aimed to determine the presence, rate, and distribution of mucocutaneous features in the portrayal.

The study cohort, comprised of different monogenic autoinflammatory diseases, frequently exhibited fever as expected, and serositis in the initial presentation. The reason behind the superiority of serositis over other symptoms is that FMF constituting the majority of the cohort most often presents with episodes of peritonitis. On the other hand, pleural and pericardial involvement are rarer manifestations in monogenic autoinflammatory diseases (4). Fever and joint involvement mostly as arthralgia were the primary complaints in the presentation of the disease. Neurological symptoms rarely accompany monogenic autoinflammatory diseases excluding moderate and severe forms of CAPS (8). In our cohort, although rare, neurologic manifestations such as febrile convulsions and headache were observed among non-FMF autoinflammatory diseases. Mucocutaneous lesions were among the most striking presentations with a frequency of 34%. Skin involvement may be included in the initial picture as a key symptom, or conversely, can be incorporated into the clinical picture

Table 2. Demographic and clinical manifestations according to the subgroups of monogenic autoinflammatory diseases

AIDs (n=97)	FMF (n=64)	CAPS (n=11)	MKD (n=16)	TRAPS (n=6)	p
Gender (female)	41 (64.1)	7 (63.6)	9 (56.3)	1 (16.7)	p=0.84
Age at the study (m)	160 (51-253)	156 (54-216)	96 (34-180)	94 (50-160)	p=0.00
Age at the diagnosis (m)	72 (13-195)	96 (3-185)	41.5 (6-120)	54 (36-132)	p=0.16
Disease duration (m)	75 (13-207)	80 (47-170)	81 (31-174)	66.5 (30-98)	p=0.81
Fever	36 (56.3)	8 (72.7)	16 (100)	6 (100)	
Duration (days)	3 (1-10)	3 (1-7)	4 (2-10)	5.5 (2-8)	
Cutaneous involvement	5 (7.8)	9 (81.8)	3 (18.8)	2 (33.3)	p=0.00
Character	Erysipelas-like	Diffuse erythematous, edematous plaques	Intensive maculopapular, morbilliform	Macules	
Location and Distribution	The anterior-lower surface of the tibia, ankle	Face, trunk, symmetrically on the extremities	Trunk, upper and lower extremities	Trunk and upper extremities	
Duration (days)	4 (3-7)	3 (1-24)	3 (2-5)	6 (4-8)	
Scar	None	77%	None	50%	
Oral mucosa	3 (4.7)	3 (27.3)	5 (31.3)	3 (50)	p=0.001
Lymphadenopathy	-	1 (9.1)	3 (18.8)	-	
Organomegaly	-	-	2 (12.5)	-	
Peritonitis	56 (87.5)	1 (9.1)	-	-	
Bouts of diarrhea	-	1 (9.1)	9 (56.3)	-	
Arthralgia	31 (48.4)	9 (81.8)	9 (56.3)	4 (66.7)	
Arthritis	9 (14.1)	5 (45.5)	2 (12.5)	2 (33.3)	
Duration (days)	3 (1-15)	7 (2-17)	4 (2-7)	6 (4-10)	
Muscle involvement	9 (14.1)	-	3 (18.8)	3 (50)	
Neurological involvement	-	2 (18.2)	3 (18.8)	2 (33.3)	
Eye involvement	-	-	-	3 (50)	
Wbc ($x10^9$/L)	7.98 (3.61-29.6)	10.8 (6.2-24)	11.09 (5.9-18.2)	11 (10.2-14)	
Neutrophil (%)	55 (27-80)	52 (30-78)	55 (38-80)	53.5 (25-56)	
Platelet ($x10^9$/L)	302 (161-667)	303 (255-519)	298 (108-392)	354 (208-402)	
CRP (mg/L)	2,1 (0-151)	14 (1-299)	72 (1-222)	23 (5-61)	
ESR (mm/h)	13 (1-110)	17 (2-140)	31 (5-100)	37 (18-48)	
SAA (mg/L)	5.2 (0-1200)	23.5 (1-349)	8.5 (0-233)	1 (0-4)	

WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SAA: Serum amyloid a. Kruskal-Wallis test was used to compare demographic and clinical features and mucocutaneous manifestations

after months or even years (9). In another single-center study in which autoinflammatory diseases were evaluated comprehensively, skin lesions were more prominent with a frequency of 76% (10). The rate and distribution of clinical manifestations in the cohort were presumably influenced by the prevalence of subgroups.

Differential diagnosis of autoinflammatory diseases is not always feasible due to their non-specific and overlapping features. The presentation of the disease may manifest a heterogeneous picture, notably when individual differences are considered, and genetic tests with a long turnaround time may not be guiding at the early stage of diagnosis. Furthermore, the diagnostic performance of genetic tests is not fully comprehensive and pathogenic variants may display variable expression. Nonetheless, the medical history of persistent or recurrent episodes of inflammation is the hallmark for diagnosis.

Still, at least 40% of patients with a possible autoinflammatory disease do not comply with any of the known diseases and are considered as the ''undifferentiated'' group (1). Although the symptoms overlap significantly in the clinical presentation of different diseases, some clues in the clinical picture can determine the subtype of hereditary periodic fever syndrome. Although it does not occupy considerable

Table 1. Clinical presentation of the cohort of monogenic autoinflammatory diseases

Entire cohort	**n=97**
Clinical presentation	**n (%)**
Fever	66 (68)
Cutaneous involvement	19 (19.6)
Maculopapular	8 (8.2)
Urticarial	5 (5.1)
Morbilliform	1 (1)
Erysipela-like rash	5 (5.1)
Oral mucosal involvement	14 (14.4)
Lymphadenopathy	4 (4.1)
Hepatomegaly and/or splenomegaly	2 (1.9)
Serositis	57 (58.8)
Diarrhea	10 (10.3)
Joint involvement	53 (54.6)
Muscle involvement	15 (15.5)
Neurological involvement	7 (7.2)
Eye involvement	3 (3.1)
Baseline laboratory data	**Med (min-max)**
Wbc (x10^9/L)	8.820 (3.610-29.600)
Neutrophil (%)	55 (25-80)
Platelet count (x10^9/L)	303,000 (108,000-667,000)
CRP (mg/L)	5.1 (0-299)
ESR (mm/h)	16 (1-140)
SAA (mg/L)	5.1 (0-1200)

WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SAA: Serum amyloid a

space in the general presentation, distinct types of cutaneous and mucosal involvement were remarkable in the cohort. Correspondingly, the study groups differed from each other in terms of rash characteristics. The recurrent episodes of a specific type of rash may be a guide in determining the subgroup of systemic autoinflammatory diseases at diagnosis.

FMF is the most common monogenic autoinflammatory disease with short-term and self-limiting episodes. Erysipelas-like erythema accompanies approximately 20% of disease attacks in children, but their frequency may vary geographically (11-13). The lesion appears as tender and erythematous plaque, 10-15 centimeters in diameter located below the knee and on the dorsal aspect of the feet (12,14). In a patient presenting with inflammatory attacks of rash, the query of the location may be a guide in determining the subtype of the autoinflammatory disease as FMF rash is typically distributed on the lower extremities. As a result of a 10-year retrospective study, Gezgin Yildirim et al. (15) detected erysipelas-like erythema in 59 of 782 patients and emphasized that 11 (18.6%) of them were the initial symptoms. As in our cohort, this rate may be lower at the onset and the cutaneous involvement may be included in the course of the disease. However, since it is the pathognomonic cutaneous sign, its initial presence is substantial for the diagnosis. Of note, the presence of vascular rash or mucosal involvement in FMF requires further evaluation in terms of IgA vasculitis, polyarteritis nodosa and Behçet's disease (16,17). On the other hand, Ben-Chetrit and Yazici (18) have suggested that it could be considered as an atypical manifestation of the disease rather than comorbidity.

The inflammatory episodes of TRAPS have longer duration compared to FMF. Cutaneous lesions may present as large erythematous migratory patches or plaques. A study including 25 TRAPS patients aged 4 to 56 years demonstrated that precursor skin lesions emerged in the first 2 years of life and lasted for a mean of 13 days. In our patients with TRAPS, macules were distributed on the trunk and upper extremities with a median duration of 6 days. Scar was observed in our cohort, but the sample size was insufficient to determine the rate.

Mucocutaneous involvement occurs in 70% of the patients with MKD. Non-specific maculopapular or morbilliform eruptions located on the extremities and trunk are the most common but diverse skin lesions can be observed. Aphthous oral ulcers and sometimes genital ulcers are seen in 50% of patients (19). The skin involvement of our patients exhibited a typical distribution. Oral mucosa involvement was detected in 31.3%, but genital ulcer was not observed in the cohort. In an international study evaluating the clinical characteristics at disease onset and diagnosis of patients with MKD, the rate of rash was %13 (n=5) (20). More research is required to describe the distribution and diversity of skin manifestations in MKD.

CAPS represent three phenotypes of varying severity. The typical cutaneous sign, defined clinicopathologically as neutrophilic urticarial dermatosis, is the most significant shared feature of the three entities (21,22). Skin involvement is expected to predominate in the initial picture of the disease complex. Urticaria-like lesions, symmetrical and widespread distribution, and histopathological demonstration of neutrophils are crucial for the diagnosis (22). Patients with a diagnosis of CAPS in our cohort presented with diffuse urticaria-like erythematous plaques lasting up to 24 days, the majority of which healed with scarring. Particularly, resistant recurrent urticaria without

an antihistaminic response, accompanied by signs of inflammation, should be examined for CAPS (22).

Autoinflammatory diseases may display overlapping symptoms. The number of studies on clinical presentations is limited. Since there are various mutations for each subtype, the study was designed according to clinical classification and definition and gene analyses were not presented separately. Except for FMF, the prevalence of other subtypes is quite low. Although the current study is based on a small sample of participants and non-homogeneous distribution, it represents a comprehensive analysis of the initial symptoms, signs, and mucocutaneous lesions.

Conclusion

The clinical framework and classification of autoinflammatory diseases are growing day by day through the identification of new molecular mechanisms. Monogenic autoinflammatory diseases can be recognized by recurrent episodes of inflammation. Recognizing the system and organ involvement in these attacks aids in the diagnosis. Mucocutaneous signs were not frequently included in the presentation of the disease in our study cohort, but the location and character of the lesions demonstrated a consistent distribution according to the subgroups. Skin manifestations accompany almost all subtypes and may provide a clue regarding the subdivision and pathological mechanism of the disease. Hence, the awareness of the distinctive mucocutaneous manifestations and their correlation with subgroups provides a convenient definition, well-timed control of the underlying condition.

Acknowledgement

We are grateful to all the healthcare professionals who were involved in the diagnosis and treatment process of the patients in our study.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of İstanbul University Faculty of Medicine for the study (2021-622903).

Informed Consent: Each participant and his/her legal representative have approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.A.A., O.K., Design: N.A.A., O.K., Data Collection or Processing: O.K., Analysis or Interpretation: N.A.A., O.K., Writing: O.K.

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

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

References

1. Lachmann HJ. Periodic fever syndromes. Best Pract Res Clin Rheumatol 2017;31(4):596-609.
2. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997;17(1):25-31.
3. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999;97(1):133-144.
4. Marino A, Tirelli F, Giani T, Cimaz R. Periodic fever syndromes and the autoinflammatory diseases (AIDs). J Transl Autoimmun 2020;3:100031.
5. Martorana D, Bonatti F, Mozzoni P, Vaglio A, Percesepe A. Monogenic Autoinflammatory Diseases with Mendelian Inheritance: Genes, Mutations, and Genotype/Phenotype Correlations. Front Immunol 2017;8:344.
6. Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009;48(4):395-398.
7. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019;78(8):1025-1032.
8. Levy R, Gérard L, Kuemmerle-Deschner J, Lachmann HJ, Koné-Paut I, Cantarini L, et al. Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry. Ann Rheum Dis 2015;74(11):2043-2049.
9. Figueras-Nart I, Mascaró JM Jr, Solanich X, Hernández-Rodríguez J. Dermatologic and Dermatopathologic Features of Monogenic Autoinflammatory Diseases. Front Immunol 2019;10:2448.
10. Wang W, Yu Z, Gou L, Zhong L, Li J, Ma M, et al. Single-Center Overview of Pediatric Monogenic Autoinflammatory Diseases in the Past Decade: A Summary and Beyond. Front Immunol 2020;11:565099.
11. Onen F. Familial Mediterranean fever. Rheumatol Int 2006;26(6):489-496.
12. Shwin KW, Lee CR, Goldbach-Mansky R. Dermatologic Manifestations of Monogenic Autoinflammatory Diseases. Dermatol Clin 2017;35(1):21-38.
13. Kolivras A, Meiers I, Sass U, Thompson CT. Histologic Patterns and Clues to Autoinflammatory Diseases in Children: What a Cutaneous Biopsy Can Tell Us. Dermatopathology (Basel) 2021;8(2):202-220.

14. Barzilai A, Langevitz P, Goldberg I, Kopolovic J, Livneh A, Pras M, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. J Am Acad Dermatol 2000;42(5 Pt 1):791-795.

15. Gezgin Yildirim D, Seven MB, Gönen S, Söylemezoğlu O. Erysipelas-like erythema in children with familial Mediterranean fever. Clin Exp Rheumatol 2020;38(Suppl 127):101-104.

16. Rigante D, Cantarini L. Monogenic autoinflammatory syndromes at a dermatological level. Arch Dermatol Res 2011;303(6):375-380.

17. Moreira A, Torres B, Peruzzo J, Mota A, Eyerich K, Ring J. Skin symptoms as diagnostic clue for autoinflammatory diseases. An Bras Dermatol 2017;92(1):72-80.

18. Ben-Chetrit E, Yazici H. Non-thrombocytopenic purpura in familial Mediterranean fever-comorbidity with Henoch-Schönlein purpura or an additional rare manifestation of familial Mediterranean fever? Rheumatology (Oxford) 2016;55(7):1153-1158.

19. van der Hilst JCH, Bodar EJ, Barron KS, Frenkel J, Drenth JPH, van der Meer JWM, et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine (Baltimore) 2008;87(6):301-310.

20. Ozen S, Kuemmerle-Deschner JB, Cimaz R, Livneh A, Quartier P, Kone-Paut I, et al. International Retrospective Chart Review of Treatment Patterns in Severe Familial Mediterranean Fever, Tumor Necrosis Factor Receptor-Associated Periodic Syndrome, and Mevalonate Kinase Deficiency/Hyperimmunoglobulinemia D Syndrome. Arthritis Care Res (Hoboken) 2017;69(4):578-586.

21. Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. Medicine (Baltimore) 2009;88(1):23-31.

22. Marzano AV, Damiani G, Genovese G, Gattorno M. A dermatologic perspective on autoinflammatory diseases. Clin Exp Rheumatol. 2018;36(Suppl 110):32-38.

CASE REPORT

Bagcilar Med Bull 2022;7(1):77-79
DOI: 10.4274/BMB.galenos.2022.2021-09-100

Focal Seizure After Status Epilepticus in a Bupropion Intoxication: Case Report

Bupropion Zehirlenmesine Bağlı Status Epileptikus Sonrası Fokal Nöbet: Olgu Sunumu

Nihal Akçay, Hasan Serdar Kıhtır, Mey Talip Petmezci, Ülkem Koçoğlu Barlas, Esra Şevketoğlu

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey

Abstract

A 13-month-old boy presented with a tonic-clonic seizure after bupropion intake. Physical examination revealed tachycardia, tachypnea, dry oral mucosa, and dilated pupils. The patient with status epilepticus and cardiac involvement was treated with intravenous thiopental infusion and lipid emulsion therapy. We observed focal seizures in the form of licking and perioral clonic contractions showing bilateral temporal epileptic activity in electrocardiography. As known, there are many reported cases of status epilepticus associated with bupropion poisoning; however, none of them had late focal seizures and our case is the youngest patient in the literature.

Keywords: Bupropion poisoning, focal seizure, lipid emulsion therapy, long QTc, status epilepticus

Öz

On üç aylık erkek hasta bupropion alımı sonrası tonik-klonik nöbet ile başvurdu. Fizik muayenede taşikardik, takipneik, oral mukozası kuru ve dilate pupilleri vardı. Status epileptikus ve kardiyak tutulumu olan hasta, intravenöz tiyopental enfüzyonu ve lipid emülsiyon uygulanması ile tedavi edildi. Elektrokardiyografide bilateral temporal epileptik aktiviteyi içeren yalama, perioral klonik kasılma şeklinde fokal nöbetler gözlendi. Bildiğimiz kadarıyla, bupropion zehirlenmesi ile ilişkili status epileptikus gösteren çok sayıda olgu bildirilmiştir; ancak bunların hiçbirinde geç fokal nöbet yoktur ve olgumuz literatürdeki en genç olgudur.

Anahtar kelimeler: Bupropion zehirlenmesi, fokal nöbet, lipid emülsiyon tedavisi, status epileptikus, uzun QTc

Introduction

Bupropion is a selective inhibitor of the reuptake of dopamine, norepinephrine, and serotonin. It also has an anticholinergic effect. The mechanism of action in smoking cessation is not known exactly (1). Overdose of bupropion intake causes central nervous system symptoms such as hallucination, agitation, and seizures (2). We aim to draw attention to the treatment of side effects of bupropion intake by presenting a case with status epilepticus and long QTc, as a result of slow-releasing bupropion overdose.

Case Report

A 13-month-old previously healthy boy was admitted to our hospital one hour after the ingestion of 7 tablets of 150 mg (87.5 mg/kg), slow-releasing bupropion (Wellbutrin XL). He was conscious when he came to the emergency room, then gastric lavage and activated charcoal were applied to the patient. However, he developed generalized tonic-clonic seizures. Seizures were treated first with rectal diazepam, then with IV midazolam and phenobarbital.

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

Address for Correspondence: Nihal Akçay, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey
E-mail: drnihalakcay@gmail.com **ORCID ID:** orcid.org/0000-0002-8273-2226 **Received:** 27.09.2021 **Accepted:** 21.06.2022

Cite this article as: Akçay N, Kıhtır HS, Petmezci MT, Koçoğlu Barlas Ü, Şevketoğlu E. Focal Seizure After Status Epilepticus in a Bupropion Intoxication: Case Report. Bagcilar Med Bull 2022;7(1):77-79

Because the seizures could not be controlled, the patient was admitted to the pediatric intensive care unit with a provisional diagnosis of status epilepticus due to drug intoxication. Physical examination on admission revealed a Glasgow Coma scale of 8 on the fourth hour of drug ingestion. He had shallow breathing and his respiratory rate was 38/min and his heart rate was 165/min. His arterial blood pressure was 82/49 mmHg and his capillary refill time was 2 seconds. No other pathological finding was detected on systemic physical examination. Venous blood gas results were as follows; pH: 7.30, pCO_2: 43mmHg, HCO_3: 20.7, and lactate level: 2.1 mmol/L. The other laboratory parameters were in normal ranges. The patient was intubated because of shallow breathing and ongoing seizures. He was sedated with thiopental before the procedure and thiopental infusion was continued to provide sedation and benefit from its anticonvulsant effect. Fentanyl was used to provide analgesia. Since his QTc read 0.50 seconds on an electrocardiogram, propranolol was added to his treatment lipid emulsion therapy was initiated because of ongoing epileptical activity and cardiac involvement (20% of lipid solution was loaded as 1 g/kg in 1 hour, then continued as an infusion at a rate of 1 g/kg/day). According to the close follow-up of the patient's triglyceride levels, lipid infusion was titrated up to 3 g/kg/day after 48 hours. Propranolol treatment was ceased on the 72nd hour of hospitalization since the QTc interval was normalized and thiopental infusion was stopped and replaced with phenobarbital treatment. Lipid infusion was weaned. The patient was extubated on day 4 since his consciousness level and breathing efforts were adequate. Then, he began to have focal seizures in the form of licking and perioral clonic contractions. Lipid infusion was titrated up to 3 g/kg/day again and followed by EEG monitoring. Then, levetiracetam was added to his antiepileptic treatment. Focal seizures disappeared on day 5 and the patient became completely conscious on day 6. Lipid infusion was ceased due to the absence of seizures within the last 24 hours and his mental and motor functions being completely normal. The patient was discharged with levetiracetam and phenobarbital antiepileptic therapies and consulted with pediatric neurology for future follow-up. The written informed consent for the publication was obtained from the parents on behalf of the patient.

Discussion

We observed status epilepticus, long QTc, tachycardia, and lethargy in our patient during the first phase. We achieved a burst suppression on EEG via thiopental infusion which was ceased 72 hours later. Then, the patient was observed to have focal seizures accompanied by bilateral temporal epileptic activity on EEG. There is no specific therapy, the treatment is symptomatic. Activated charcoal can be useful to eliminate bupropion absorption when used at the appropriate time. There is no known specific antidote. Lipid emulsion therapy has been suggested for the treatment of life-threatening bupropion-induced cardiovascular collapse after other interventions have failed. However, it is not suggested to be used in non-life-threatening conditions (3). More recently, a case series of bupropion overdose, from the Illinois Poison Center, has argued that lipid emulsion therapy for bupropion overdose may not be as efficient as suggested previously (4). There is no specific dose interval on literature about lipid emulsion therapy in children; however, publications suggest that a dosage up to 3 g/kg/h is safe. Still, in the case of prolonged and refractory status epilepticus, it seems reasonable to try lipid emulsion therapy (3). We continued lipid emulsion therapy after the cessation of thiopental infusion since the patient continued to have focal seizures. We believe that lipid emulsion therapy could also eliminate late phase effects. It has been associated with transient lipemia, hypertriglyceridemia, and mild pancreatitis (5).

In conclusion, our case serves to demonstrate some rare consequences of bupropion overdose, such as long QTc and status epilepticus in a pediatric patient. In our case, early diagnosis and supportive therapy improved the clinical outcome of the patient but new case reports and further studies are necessary to establish whether lipid emulsion therapy is indicated for bupropion toxicity or not.

Ethics

Informed Consent: The written informed consent for the publication was obtained from the parents on behalf of the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A., H.S.K., M.T.P., Design: N.A., H.S.K., M.T.P., Data Collection or Processing: N.A., Ü.K.B., E.Ş., Analysis or Interpretation: N.A., M.T.P., Ü.K.B., Drafting Manuscript: N.A., H.S.K., Writing, N.A., Ü.K.B., Critical Review: N.A., E.Ş., Supervision: N.A., E.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. Morazin F, Lumbroso A, Harry P, Blaise M, Turcant A, Montravers P, et al. Cardiogenic shock and status epilepticus after massive bupropion overdose. Clin Toxicol (Phila) 2007;45(7):794-797.
2. Jepsen F, Matthews J, Andrews FJ. Sustained release bupropion overdose: an important cause of prolonged symptoms after an overdose. Emerg Med J 2003;20(6):560-561.
3. Gosselin S, Hoegberg LC, Hoffman RS, Graudins A, Stork CM, Thomas SH, et al. Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning. Clin Toxicol (Phila) 2016;54(10):899-923.
4. Chhabra N, DesLauriers C, Wahl M, Bryant SM. Management of severe bupropion poisoning with intravenous lipid emulsion. Clin Toxicol (Phila) 2018;56(1):51-54.
5. Bucklin MH, Gorodetsky RM, Wiegand TJ. Prolonged lipemia and pancreatitis due to extended infusion of lipid emulsion in bupropion overdose. Clin Toxicol (Phila) 2013;51(9):896-898.

CASE REPORT

Bagcilar Med Bull 2022;7(1):80-84
DOI: 10.4274/BMB.galenos.2022.2021-11-116

Tracheostomy on COVID-19 Pediatric Patients

COVID-19 Enfeksiyonu Olan Çocuk Hastalarda Trakeostomi

Nihal Akçay[1], Zahide Mine Yazıcı[2], Mehmet Emin Menentoğlu[1], Ayşe İrem Sofuoğlu[1], İbrahim Sayın[2], Esra Şevketoğlu[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey

Abstract

This article reports four cases of pediatric patients who underwent tracheostomy after Coronavirus disease-2019 (COVID-19) infection. The common feature of these patients was not only prolonged intubation but also the presence of significant comorbidities. Tracheostomy was well tolerated by all patients and resulted in improved outcomes. Although tracheostomy is an old surgical procedure, there is not enough experience on COVID-19 patients in terms of indications, technique, and actual timing. We presented a single-center experience and discussed the management of COVID-19 pediatric patients with preexisting comorbidities who were candidates for a surgical tracheostomy.

Keywords: COVID-19, pediatric, tracheostomy

Öz

Makalemizde Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonundan sonra trakeostomi uygulanan dört çocuk hasta bildirilmektedir. Bu hastaların ortak özelliği sadece uzun süreli entübasyon değil, aynı zamanda önemli komorbiditelerin olmasıdır. Trakeostomi tüm hastalar tarafından iyi tolere edildi ve sağkalımla sonuçlandı. Trakeostomi çok eski bir cerrahi prosedür olmasına rağmen endikasyon, teknik ve zamanlama açısından COVID-19'lu çocuk hastalarda yeterli deneyim bulunmamaktadır. Tek merkez deneyimimizi sunarak, cerrahi trakeostomi adayı olan, önceden mevcut komorbiditeleri olan COVID-19'lu çocuk hastalarda trakeostomi yönetimini tartıştık.

Anahtar kelimeler: COVID-19, pediatrik, trakeostomi

Introduction

Children infected with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which causes the Coronavirus disease-2019 (COVID-19), have usually fewer clinical manifestations and less hospitalization when compared with adults. According to the American Academy of Pediatrics, 14.1% of all cases were children indicating an overall 5.307 cases per 100,000 children in the general population. Children constitute 1.4-3.2% of total reported hospitalizations. In the pediatric age group, 0.1-1.9% of COVID-19 patients require hospitalization (1). The increased number of COVID-19 patients with acute respiratory distress syndrome (ARDS) for prolonged ventilation, compromised airway required intubation with a ventilator. The most common indication for pediatric tracheostomy includes prolonged ventilation and obstruction of the airway (2).

During the COVID-19 pandemic, the timing of tracheostomy is controversial. The benefit of a tracheostomy is not clear. Besides, tracheostomy is an aerosol-generating procedure that carries a transmission risk for healthcare workers (3). The decision of tracheostomy should be made with a multidisciplinary approach during the COVID-19 pandemic, especially in the pediatric age group. Indications and stages of the surgical procedure should be reconsidered, as the tracheostomy procedure is a droplet-spreading procedure,

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

Address for Correspondence: Nihal Akçay, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey
E-mail: drnihalakcay@gmail.com **ORCID ID:** orcid.org/0000-0002-8273-2226 **Received:** 21.11.2021 **Accepted:** 28.02.2022

Cite this article as: Akçay N, Yazıcı ZM, Menentoğlu, ME, Sofuoğlu Aİ, Sayın İ, Şevketoğlu E. Tracheostomy on COVID-19 Pediatric Patients. Bagcilar Med Bull 2022;7(1):80-84

causes a significant amount of aerosol formation, and provides a basis for the spread both during surgery and in the postoperative period.

Our pediatric intensive care unit (PICU) interned 35 COVID-19 infected patients. The polymerase chain reaction (PCR) tests of all patients were positive. All children had a family history of infection contact. Four of our patients (11%) who were treated in 35 pediatric intensive care units required tracheostomy. Considering the indications for tracheostomy in the PICU, the COVID-19 disease did not change the indications much, but only the COVID-19 infection of the patients with additional comorbidities increased the length of the stay in the intensive care unit. Although tracheostomy indications did not change with COVID-19 infections, the recovery of severe ARDS in children and the necessity of tracheostomy under general anesthesia extended our time. Moreover, additional morbidity (there was pontocerebellar dysplasia in Case 1 and bronchopulmonary dysplasia in Case 2) also extended timing. We discussed our single-center experiences of the management of patients with COVID-19 who underwent surgical tracheostomy in light of the literature.

Since all of our patients did not have emergency indications, we discussed with the intensive care doctors and waited for the PCR results to become negative, then patients underwent to the operation.

Case Reports

Case 1

A 10-year-old boy previously diagnosed with pontocerebellar hypoplasia presented with respiratory distress after 2 days of fever. He had been transferred to our PICU from another center due to his worsening dyspnea/hypoxia. He underwent tracheal intubation. His chest computed tomography (CT) showed both-side diffuse ground-glass opacity, peripheral zone consolidations (Figure 1A). On the 20th day of intubation, tracheostomy was planned in accordance with the consensus of PICU specialists and ear nose throat (ENT) specialists because the patient had been intubated for three weeks and it was not anticipated that he would be extubated in the near future. Open surgical tracheostomy was performed in operating room conditions. After the tracheostomy procedure, he was discharged with home-type mechanical ventilation (MV). The patient had severe ARDS. It was difficult for us to make a clear judgment about whether the neurological sequelae due to pontocerebellar hypoplasia, with which he was diagnosed within the neonatal period, worsened the clinical picture of the patient.

Case 2

A 6-month-old boy previously diagnosed with bronchopulmonary dysplasia presented with persistent fever, dyspnea, tachypnea, intercostal and subcostal retractions. He was admitted to the PICU for non-invasive MV due to acute hypoxemic respiratory failure while the chest X-ray showed bilateral interstitial consolidations of the lung parenchyma (Figure 1B). On day 22, he could not be tolerated weaning for a non-invasive MV, chest CT and bronchoscopy showed signs of tracheal stenosis. In the light of the bronchoscopy report and recommendations of the pediatric chest specialist, we planned to open a tracheostomy for the child and decided to wait for the surgical decision for stenosis until the age of 2 years. On day 28, a tracheostomy was performed.

Case 3

A 4-year-old previously healthy girl presented with pediatric acute respiratory distress associated with SARS-CoV-2. She had been transferred to our PICU from another center due to hypoxia and her oxygen saturation levels were not improving. Her chest CT showed both-side diffuse ground-glass opacity and consolidation (Figure 1C). On day 30, tracheostomy was performed to reduce the sedation and by this way to allow a neurological assessment and reduce the MV support. The reason for the delay in the tracheostomy procedure is that the general condition of the patient was expected to be suitable for transport to the operating room and to receive general anesthesia. After tracheostomy, she was still under high peep on invasive MV and had high oxygen requirement. The patient could be discharged on the 142nd day without being decannulated due to the development of multi-organ failure and the continued need for MV.

Case 4

A 6-year-old boy presented with symmetric ascending paralysis progressed over a 4-day course and 2 days of fever. He had bilateral lower and upper limb flaccid weakness of 1/5 with absent deep tendon reflexes. He had severe respiratory muscle weakness requiring invasive MV. On admission, SARS-CoV-2 turned as positive by real-time PCR on a nasopharyngeal swab. He was diagnosed with Guillain-Barre syndrome (GBS) associated with SARS-CoV-2 infection. He was admitted to the PICU for severe respiratory muscle weakness requiring invasive MV. He underwent tracheal intubation despite his chest X-ray being

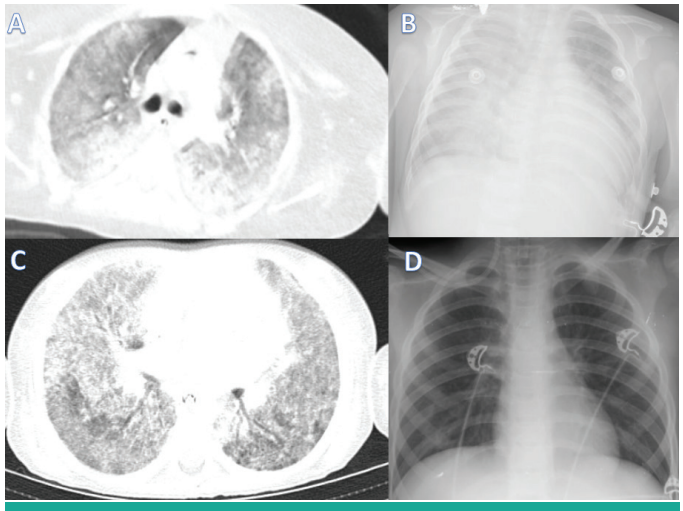


Figure 1. A) A 10-year-old boy's chest CT showed both-side diffuse ground-glass opacity, peripheral zone consolidation, B) A 6-month-old boy' tchest X-ray showed bilateral interstitial consolidation of the lung parenchyma, C) A 4-year-old girl's chest CT showed both-side diffuse ground-glass opacity and consolidation, D) A 6-year-old boy's chest X-ray was normal

CT: Computed tomography

normal (Figure 1D). We hypothesize that there is a causal relationship between GBS and SARS-CoV-2 infection, but there is no evidence of direct invasion of nerves or nerve roots by a virus. On day 30, a tracheostomy was performed due to ongoing respiratory muscle weakness with respiratory failure and bulbar involvement. The patient's need for MV continued due to bulbar involvement, and decannulation was not considered. This case was reported as a case report in another journal (4).

Technical Details About Tracheostomy

Here, we gave the details of tracheostomy procedure during the COVID-19 pandemic period. During the pandemic process, requirement of the tracheostomy started to develop, we prepared our patients according to the guideline review in the literature (5,6). Intensive care unit physicians and ENT physicians consulted on the appropriateness of tracheostomy in a COVID-19 infected patient. One day before the procedure, the anesthesia team and the ENT team hold a meeting to evaluate all the steps of the procedure. We preferred an open surgical procedure in a negative pressure operating room. The most experienced physicians and allied health personnel were involved to ensure that the procedure was accurate, fast, and safe. A few team members and personnel were employed, and the number of unnecessary team members was reduced. The use of appropriate personal protective equipment was required for all staff. Surgical team members wore Dräger X-plore® 8000 powered air-purifying respirator before the procedure. Cuffed and non-fenestrated tracheostomy cannula were used, and the robustness of the cuff was checked before starting the procedure. The syringe which the cuff would be inflated was attached to the cannula. The patients were fully curated during the procedure. For children who needed a tracheostomy, a vertical incision was made in the midline of the skin. After dissection, the thyroidal isthmus was retracted and tracheal rings were identified. A tracheal incision was performed between rings 3 and 5 in the vertical incision. The tracheal wall was sutured with 0 polypropylene suture material to the skin and a patent tracheostomy was performed. The appropriate diameter tracheostomy tube was inserted. The tube was secured with stay sutures. No tracheal ring was removed and no horizontal incision was used.

After the operation, all patients were reconnected to the ventilator and transferred back to the PICU by the transport team. Fourteen days after the tracheostomy, all participating medical staff members were healthy and asymptomatic and we also had no complications with the tracheostomy.

All patients' clinical situations and outcomes before and after tracheostomy are shown in Table 1. MV parameters and oxygen requirement of all of our patients decreased after tracheostomy which enabled us to make a better neurologic evaluation and helped to decrease in sedation dosage. Written informed consent for publication was obtained from the parents on behalf of the patients.

Discussion

We reported 4 cases of pediatric patients with or without comorbidities who developed respiratory failure due to COVID-19 infection and performed tracheostomy after long-term MV support.

The COVID-19 pandemic has presented health care systems with critical respiratory illness. During surgical tracheostomy, there is a high risk of spreading the aerosols to the surrounding health care providers. Therefore, two negative PCR tests in 24 h before performing a surgical tracheostomy on COVID-19 patients are required. A minimal number of staff in the operating room and adequate sedation should be provided to eliminate the risk of coughing during the procedure, even though the child is paralyzed (7). In all our patients, we had two negative PCR tests in 48 h.

Table 1. Clinical characteristics and outcomes in four patients with COVID-19

	Case 1	Case 2	Case 3	Case 4
Age/gender	10 years old/male	6 months old/male	4 years old/female	6 years old/male
Comorbidity	Pontocerebellar hypoplasia	Bronchopulmonary dysplasia	No	No
Concomitant illness	No	Yes	Yes	Yes
SARS-CoV-2 PCR	Positive	Positive	Positive	Positive
Symptoms	Fever, respiratory distress	Fever, dyspnea, tachypnea, intercostal and subcostal retraction	Fever, respiratory distress, shock	Fever, symmetric ascending paralysis
Presentations	PARDS	PARDS	PARDS	GBS
Vital signs				
SpO_2 (%)	79	85	91	92
Pulse rate (per min)	142	174	84	102
Blood pressure (mmHg)	82/53	86/51	89/56	95/64
Respiratory rate (per min)	25	55	25	35
Body temperature (°C)	39	38.9	37	39.6
PELOD-2 score (%)	10 (71)	4 (58.9)	10 (79.7)	15 (90.7)
PRISM-3 score (%)	22 (32)	12 (8.8)	34 (87.9)	20 (26.1)
PIM-2 %	45	6.8	99.8	4.3
Intubation duration	33 days	11 days	40 days	30 days
Mechanical ventilator settings before tracheostomy	SIMV PC+PS PIP: 20, PEEP: 7, VR: 20, FiO_2: 50	NIV IPAP: 12, EPAP: 6, VR: 20 FiO_2: 50	PC PIP: 35 PEEP: 15 VR: 30 FiO_2: 100	SIMV PC + PS PIP: 20, PEEP: 5, VR: 10, FiO_2: 40
Tracheostomy time	20th day	28th day	30th day	30th day
Tracheostomy technique	Surgical	Surgical	Surgical	Surgical
Tracheostomy cannula size	5.5 cuffed	4 cuffed	6 cuffed	5.5 cuffed
Complication	No	No	No	No
Mechanical ventilator settings after tracheostomy	SIMV PC + PS PIP: 15, PEEP: 5, VR: 20, FiO_2: 30	Only O_2 supplement	SIMV PC + PS PIP: 30, PEEP: 10, VR: 20, FiO_2: 80	SIMV PC + PS PIP: 15, PEEP: 5, VR: 10, FiO_2: 30
Discharge	55. day with home MV	38. day without MV	142. day with home MV	50. day with home MV

COVID-19: Coronavirus disease-2019, PARDS: Pediatric acute respiratory distress syndrome, GBS: Guillain-Barre syndrome, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, PCR: Polymerase chain reaction, PELOD-2: Pediatric logistic organ dysfunction-2 score, PRISM-3: Pediatric risk of mortality-3, PIM-2: Pediatric index of mortality, SIMV PC + PS: Synchronized intermittent mandatory ventilation with pressure controlled and supported breath, NIV: Non-invasive ventilation, PC: Pressure control, PIP: Peak inspiratory pressure, PEEP: Positive end-expiratory pressure, VR: Ventilation rate, FiO_2: Fractional concentration of oxygen in inspired air, IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure

Tang et al. reported a retrospective study about tracheostomy in COVID-19 patients. This study showed most tracheotomies were performed by ICU physicians and using percutaneous techniques at the ICU bedside. The most common complication was stoma bleeding. Percutaneous tracheostomy is more likely to cause aerosol formation compared to surgical approaches. Therefore, surgical tracheostomies should generally be preferred to percutaneous tracheostomies during the COVID-19 pandemic (8). Our patients' tracheostomies were performed by ENT specialists and using surgical techniques. The timing of tracheostomy is important and remains one of the issues discussed during the pandemic process. Tracheostomy should be avoided or delayed even beyond 2 weeks because of the exposed high viral load during the procedure and subsequent tracheostomy care (9). Early tracheostomy should be avoided in the COVID-19 patients because of the higher viral load. Early tracheostomy is not related to less ICU stay and improved mortality (10). In all of the study cases, tracheostomies were done after at least 14 days of orotracheal intubation. Our approximate tracheostomy time is longer than adult cases, with an average of 21 days. To be suitable both for the transportation of the general condition of the

patients to the operating room and for receiving general anesthesia.

When we decided to perform this study, we aimed to evaluate the clinical profile and consequence of surgical tracheostomy on pediatric COVID-19 patients at the ICU, and we could find less study on pediatric COVID-19 related tracheostomy in the literature.

Our case series have limitations, such as that decannulation in PICU could not be performed because ventilatory support was required, cough/swallow was not adequate, and suctioning was not minimal. Although the sample size is small, the result of this study is an important message for other doctors and patients at the PICU.

Conclusion

For children with COVID-19 who were intubated and mechanically ventilated for long-term, tracheostomy performed earlier in the course of hospital admission may be associated with improved survival.

Ethics

Informed Consent: Written informed consent for publication was obtained from the parents on behalf of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A., Z.M.Y., M.E.M., Desing: M.E.M., N.A., A.İ.S., Data Collection or Processing: İ.S., N.A., Z.M.Y., Drafting Manuscript: E.Ş., N.A., A.İ.S., Analysis or Interpretation: İ.S., N.A., Z.M.Y., Final Approval and Accountability: N.A., Z.M.Y., E.Ş., Critical Revision of Manuscript: Z.M.Y., İ.S., Supervision: E.Ş., İ.S.

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

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

References

1. American Academy of Pediatrics Children and COVID-19: State-Level Data Report [Internet]. [cited 2021 May) https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/
2. Swain SK, Sahu A. Performing tracheostomy on COVID-19 pediatric patients at intensive care unit: Our experiences. Indian J Health Sci Biomed Res 2021;14:131-136.
3. Schultz MJ, Teng MS, Brenner MJ. Timing of Tracheostomy for Patients With COVID-19 in the ICU-Setting Precedent in Unprecedented Times. JAMA Otolaryngol Head Neck Surg 2020;146(10):887-888.
4. Akçay N, Menentoğlu ME, Bektaş G, Şevketoğlu E. Axonal Guillain-Barre syndrome associated with SARS-CoV-2 infection in a child. J Med Virol 2021;93:5599-5602.
5. David AP, Russell MD, El-Sayed IH, Russell MS. Tracheostomy guidelines developed at a large academic medical center during the COVID-19 pandemic. Head Neck 2020;42(6):1291-1296.
6. Tang Y, Wu Y, Zhu F, Yang X, Huang C, Hou G, et al. Tracheostomy in 80 COVID-19 Patients: A Multicenter, Retrospective, Observational Study. Front Med (Lausanne) 2020;7:615845.
7. McGrath BA, Ashby N, Birchall M, Dean P, Doherty C, Ferguson K, et al. Multidisciplinary guidance for safe tracheostomy care during the COVID-19 pandemic: the NHS National Patient Safety Improvement Programme (NatPatSIP). Anaesthesia 2020;75(12):1659-1670.
8. Tay JK, Khoo ML, Loh WS. Surgical Considerations for Tracheostomy During the COVID-19 Pandemic: Lessons Learned From the Severe Acute Respiratory Syndrome Outbreak. JAMA Otolaryngol Head Neck Surg 2020;146(6)517-518.
9. Framework for Open Tracheostomy in COVID-19 Patients. Available from: https://www.entuk.org/sites/default/files/COVID%20tracheostomy%20guidance_compressed. pdf. [Last accessed on 2020 Apr 15].
10. Young D, Harrison DA, Cuthbertson BH, Rowan K; TracMan Collaborators. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: The TracMan randomized trial. JAMA 2013;309:2121-2129.