Chronicles of Precision Medical Researchers

ISSN: 2757-6124

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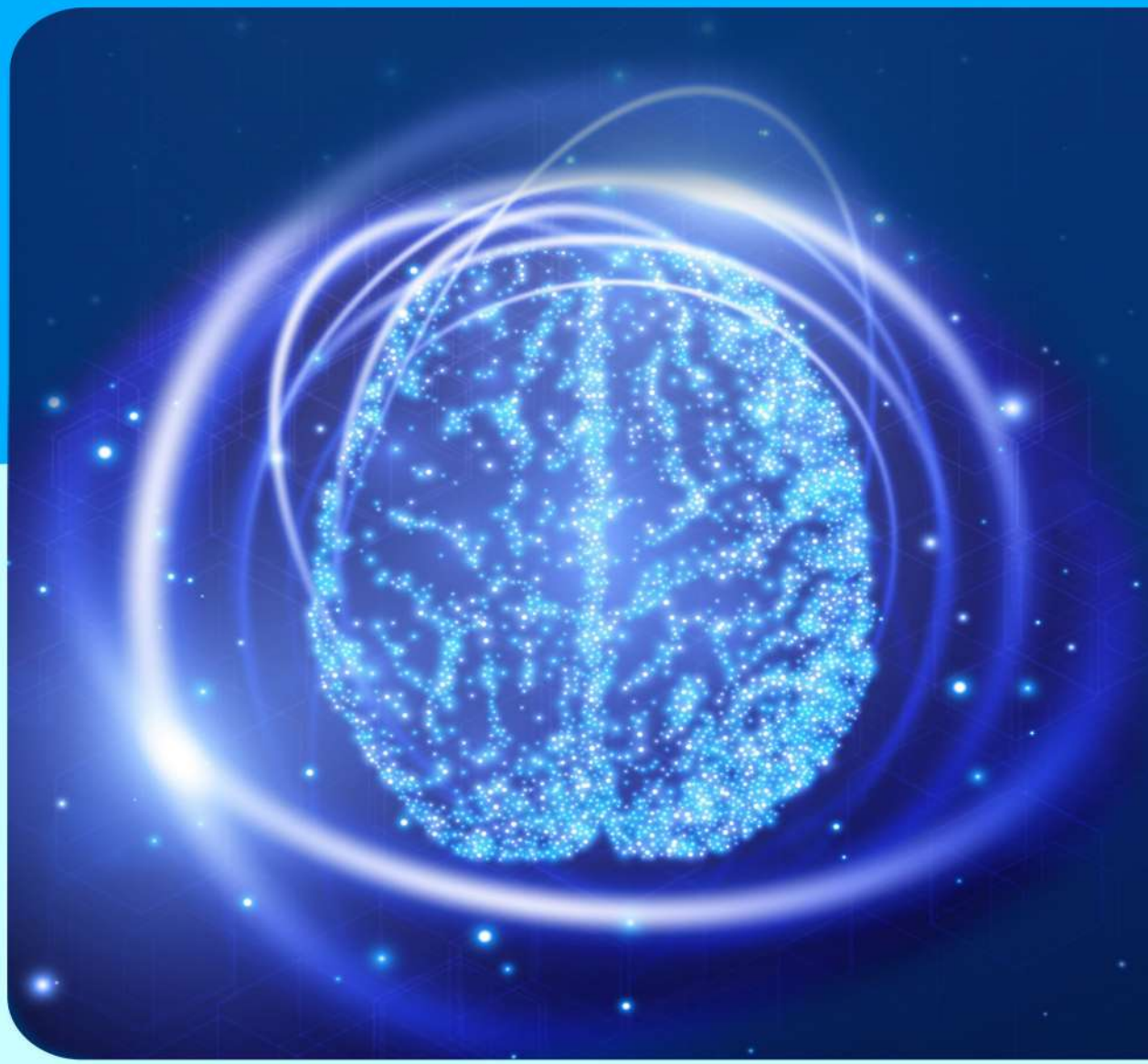

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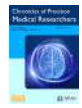

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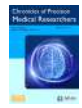

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INSTRUCTIONS FOR AUTHORS

AIM AND SCOPE

The Journal will not consider manuscripts any that have been published elsewhere, or manuscripts that are being considered for another publication, or are in press. Studies previously announced in the congresses are accepted if this condition is stated. If any part of a manuscript by the same author(s) contains any information that was previously published, a reprint or a copy of the previous article should be submitted to the Editorial Office with an explanation by the authors

A technical review is performed to confirm that all of the required documentation has been submitted and to conduct a preliminary evaluation of the manuscript and supplementary files to assess suitability for the Journal. The manuscript will be returned to the Author in the event of any deficiency.

Chronicles of Precision Medical Researchers operates a blind review process. Contributions deemed suitable are then typically sent to a minimum of two independent expert reviewers in the field of study to assess the scientific quality of the paper.

The Editor/Editors are responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. If necessary, author(s) may be invited to submit a revised version of the manuscript. This invitation does not imply that the manuscript will be accepted for publication. Revised manuscripts must be sent to the Editorial Office within 4 (four) weeks, otherwise they will be considered as a new application. The corresponding author will be notified of the decision to accept or reject the manuscript for publication.

Statements and suggestions published in manuscripts are the authors' responsibility and do not reflect the opinions of the Editor, Associate Editors and the Editorial Board members.

The manuscript will not be returned to the authors whether the article is accepted or not. Copyright fee is not paid for the articles published in the journal. A copy of the journal will be sent to the corresponding author.

Language of the Journal

The official languages of the Journal are Turkish and English. The manuscripts that are written in Turkish have abstracts in English, which makes the abstracts available to a broader audience.

Authorship Criteria

After accepted for publication, all the authors will be asked to sign "Coyright Transfer Form" which states the following: " This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by the ethics committee. " All authors should agree to the conditions outlined in the form.

Chronicles of Precision Medical Researchers has agreed to use the standards of the International Committee of Medical Journal Editors. The author(s) should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. It is available at www.icmje.org.

Ethical Responsibility

The protocol of clinical research articles must be approved by the Ethics Committee.

In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the Helsinki Declaration of Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/).

It should be stated in the text that all persons included in the study signed the am Informed Consent Form ".

The articles submitted to the Chronicles of Precision Medical Researchers will be deemed to have been conducted in accordance with the Helsinki Declaration of Principles, and have received ethical and legal permissions and will not be held responsible.

If the "Animal" item was used in the study, the authors stated that in the Material and Method section of the article, they protect the animal rights in their studies in accordance with the principles of Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) and that they have received approval from the ethics committees of their institutions. must specify.

In case reports, Informed Consent a should be obtained from patients regardless of the identity of the patient.

If the article includes the institution (directly or indirectly) providing financial support for the commercial connection or work, the authors; the commercial product used, the drug, the company has no commercial relationship with, or if there is any relationship (consultant, other agreements, etc.), the editor must inform the presentation page.

If Ethics Committee Approval is required in the article; the received document should be sent with the article.

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The manuscript should be submitted to the Academic Plagiarism Prevention Program by the authors.

It is the authors' responsibility to ensure that the article complies with the ethical rules.

Policy of Screening for Plagiarism

The manuscripts are scanned by the Journal using the iThenticate program for determination of plagiarism and non-ethical situations. Chronicles of Precision Medical Researchers will immediately reject manuscripts leading to plagiarism.

TYPES OF MANUSCRIPT

Manuscripts should be submitted online via www.chronpmr.com

Original Articles should not exceed 3000 words and should be arranged under the headings of Abstract (not more than 300 words), Introduction, Materials and Methods, Results, Discussion, Conclusion and References.

Case Reports should not exceed 1000 words and 10 references, and should be arranged as follows: Abstract, Introduction, Case Report, Discussion and References. It may be accompanied by only one figure or table.

Letter to the Editor should not exceed 500 words. Short relevant comments on medical and scientific issues, particularly controversies, having no more than five references and one table or figure are encouraged. Where letters refer to an earlier published paper, authors will be offered right of reply.

Reviews are not accepted unless written on the invitation of the Editorial Board.

PREPARATION OF MANUSCRIPTS

All articles submitted to the Journal must comply with the following instructions:

a) Submissions should be doubled-spaced and typed in Arial 10 points.

b) All pages should be numbered consecutively in the top right-hand corner, beginning with the title page.

c) The title page should not include the names and institutions of the authors.

d) The manuscript should be presented in the following order: Title page, Abstract (English, Turkish), Keywords (English, Turkish), Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgements (if present), References, Figure Legends, Tables (each table, complete with title and foot-notes, on a separate page) and Appendices (if present) presented each on a separate page.

Title

The title should be short, easy to understand and must define the contents of the article.

Abstract

Abstract should be in both English and Turkish and should consist "Aim, Materials and Methods, Results and Conclusion". The purpose of the study, the setting for the study, the subjects, the treatment or intervention, principal outcomes measured, the type of statistical analysis and the outcome of the study should be stated in this section (up to 300 words). Abstract should not include reference. No abstract is required for the letters to the Editor.

Keywords

Not more than five keywords in order of importance for indexing purposes should be supplied below the abstract and should be selected from Index Medicus Medical Subject Headings (MeSH), available at www.nlm.nih.gov/meshhome.html.

Text

Authors should use subheadings to divide sections regarding the type of the manuscript as described above. Statistical methods used should be specified in the Materials and Methods section.

References

In the text, references should be cited using Arabic numerals in parenthesis in the order in which they appear. If cited only in tables or figure legends, they should be numbered according to the first identification of the table or figure in the text. Names of the journals should be abbreviated in the style used in Index Medicus. The names of all authors should be cited when there are six or fewer; when seven or more, the first three should be followed by et al. The issue and volume numbers of the referenced journal should be added.

References should be listed in the following form:

Journal article

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

Supplement

Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002; 19(Suppl 25): 3-10.

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Online article not yet published in an issue

Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Book

Sample1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Sample 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

An organization as an author

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

Figures

All illustrations (including line drawings and photographs) are classified as figures. Figures must be added to the system as separate .jpg or .gif files (approximately 500x400 pixels, 8 cm in width and at least 300 dpi resolution). Figures should be numbered consecutively in Arabic numbers and should be cited in parenthesis in consecutive order in the text.

Figure Legends

Legends should be self-explanatory and positioned on a separate page. The legend should incorporate definitions of any symbols used and all abbreviations and units of measurements should be explained. A letter should be provided stating copyright authorization if figures have been reproduced from another source.

Measurements and Abbreviations

All measurements must be given in metric system (Système International d'Unités, SI). Example: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, etc. Statistics and measurements should always be given in numerals, except where the number begins a sentence. When a number does not refer to a unit of measurement, it is spelt out, except where the number is greater than nine.

Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc.

Drugs should be referred to by their generic names, rather than brand names.

Editorial Correspondence

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Checklist for Manuscripts

Review guide for authors and instructions for submitting manuscripts through the electronic submission, website at

http://www.chronpmr.com

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YAZARLARA BİLGİ

AMAÇ ve KAPSAM

Chronicles of Precision Medical Researchers Dergisi, dört ayda bir yayımlanır ve üç sayı ile bir cilt tamamlanır. Dergi; pediatri ile ilgili tüm nitelikli klinik ve deneysel araştırmaları, olgu sunumlarını ve editöre mektupları yayımlar.

Chronicles of Precision Medical Researchers Dergisi, bilimsel yayınlara açık erişim sağlar. Dergi basımından hemen sonra, makalelerin tam metinlerine ücretsiz ulaşılabilir.

Dergide yayımlanmak üzere gönderilen yazıların daha önce başka bir yerde yayımlanmamış veya yayımlanmak üzere gönderilmemiş olması gerekir. Daha önce kongrelerde sunulmuş çalışmalar, bu durum belirtilmek koşuluyla kabul edilir. Makale, yazar(lar) ın daha önce yayımlanmış bir yazısındaki konuların bir kısmını içeriyorsa bu durum belirtilmeli ve yeni yazı ile birlikte önceki makalenin bir kopyası da Yayın Bürosu'na gönderilmelidir.

Gerekli tüm belgelerin sunulduğunu teyit etmek ve dergiye uygunluğunu değerlendirmek için makale ve ek dosyaların ön değerlendirmesini yapmak üzere teknik bir inceleme yapılır. Herhangi bir eksiklik olması halinde makale yazara iade edilecektir. Chronicles of Precision Medical Researchers Dergisi kör bir inceleme süreci yürütmektedir. Uygun görülen yazılar daha sonra makalenin bilimsel kalitesini değerlendirmek için çalışma alanında en az iki bağımsız uzmana gönderilir. Editör / Editörler makalelerin kabulü veya reddi ile ilgili nihai karardan sorumludur.

Editörün kararı kesindir. Gerekli olduğu durumlarda, yazar(lar) dan düzeltme istenebilir. Yazardan düzeltme istenmesi, yazının yayımlanacağı anlamına gelmez. Bu düzeltmelerin en geç 21 gün içinde tamamlanıp dergiye gönderilmesi gereklidir. Aksi halde yeni başvuru olarak değerlendirilir. Sorumlu yazara yazının kabul veya reddedildiğine dair bilgi verilir.

Dergide yayımlanan yazıların etik, bilimsel ve hukuki sorumluluğu yazar(lar)a ait olup Editör, Editör Yardımcısı ve Yayın Kurulu'nun görüşlerini yansıtmaz.

Dergide yayımlanması kabul edilse de edilmese de, yazı materyali yazarlara geri verilmez. Dergide yayımlanan yazılar için telif hakkı ödenmez. Bir adet dergi, sorumlu yazara gönderilir.

Derginin Yazı Dili

Derginin yazı dili Türkçe ve İngilizcedir. Dili Türkçe olan yazılar, İngilizce özetleri ile yer alır. Yazının hazırlanması sırasında, Türkçe kelimeler için Türk Dil Kurumundan (www.tdk.gov.tr), teknik terimler için Türk Tıp Terminolojisinden (www.tipterimleri.com) yararlanılabilir.

Yazarlık Kriterleri

Dergide yayınlanması uygun bulunan tüm yazıların araştırma ve yayın etiğine uygun hazırlandığı, varsa sağlanan fonun kaynağının tanımlandığı, başka yerde yayımlanmadığı veya yayımlanmak üzere gönderilmediği, çalışmaya katılan tüm yazarlar tarafından yazının son halinin onaylandığı, yayımlanacak yazı ile ilgili telif haklarının dergiye devredildiği, tüm yazarların imzaları ile "Yayın Hakkı Devir Formu"nda belirtilmesi gerekir.

Chronicles of Precision Medical Researchers Dergisi, Uluslararası Tıp Dergileri Editörleri Kurulu'nun (International Committee of Medical Journal Editors) "Biyomedikal Dergilere Gönderilen Makalelerin Uyması Gereken Standartlar: Biyomedikal Yayınların Yazımı ve Baskıya Hazırlanması (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication)" standartlarını kullanmayı kabul etmektedir. Bu konudaki bilgiye www.icmje.org adresinden ulaşılabilir.

Etik Sorumluluk

Etik Sorumluluk / Kurallar: Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır.

İnsanlar üzerinde yapılan tüm çalışmalarda "Gereç ve Yöntem" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonu'na (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır.

Çalışmaya dahil edilen tüm kişilerin Bilgilendirilmiş Onam Formu'nu imzaladığı metin içinde belirtilmelidir.

Chronicles of Precision Medical Researchers Dergisi'ne gönderilen makalelerdeki çalışmaların Helsinki İlkeler Deklarasyonu'na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır.

Makalede ticari bağlantı veya çalışma için maddi destek veren kurum (doğrudan veya dolaylı) mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar vs.), editöre sunum sayfasında bildirmek zorundadır.

ISSN: 2757-6124

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Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir.

Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir.

Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

İntihal Taraması Politikası

Makaleler, intihal ve etik olmayan durumların belirlenmesi için iThenticate programı kullanılarak Journal tarafından taranır. Chronicles of Precision Medical Researchers Dergisi intihallere yol açan makaleleri derhal reddedecektir.

YAZI TÜRLERİ

Yazılar, elektronik ortamda www.chronpmr.com adresine gönderilir.

Orijinal makaleler, 3000 sözcük sayısını aşmamalı, "Öz (en fazla 300 kelime), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar" bölümlerinden oluşmalıdır.

Olgu Sunumu, "Öz, Giriş, Olgu Sunumu, Tartışma, Kaynaklar" şeklinde düzenlenmelidir. En fazla 1000 sözcük ile sınırlıdır. Sadece bir tablo veya şekil ile desteklenebilir.

Editöre Mektup, yayımlanan metinlerle veya mesleki konularla ilgili olarak 500 sözcüğü aşmayan ve beş kaynak ile bir tablo veya şekil içerecek şekilde yazılabilir. Ayrıca daha önce dergide yayınlanmış metinlerle ilişkili mektuplara cevap hakkı verilir.

Yayın Kurulu'nun daveti üzerine yazılanlar dışında derleme kabul edilmez.

MAKALENİN HAZIRLANMASI

Dergide yayınlanması istenilen yazı için aşağıdaki kurallara uyulmalıdır.

a) Yazı; iki satır aralıklı olarak, Arial 10 punto ile yazılmalıdır.

b) Sayfalar başlık sayfasından başlamak üzere, sağ üst köşesinde numaralandırılmalıdır.

c) Online makale sistemine yüklenen word dosyasının başlık sayfasında (makalenin adını içeren başlık sayfası), yazarlara ait isim ve kurum bilgileri yer almamalıdır.

d) Makale, şu bölümleri içermelidir: Her biri ayrı sayfada yazılmak üzere; Türkçe ve İngilizce Başlık Sayfası, Öz, Abstract, Anahtar Sözcükler, Keywords, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Açıklamalar (varsa), Kaynaklar, Şekil Alt Yazıları, Tablolar (başlıkları ve açıklamalarıyla beraber), Ekler (varsa).

Yazının Başlığı

Kısa, kolay anlaşılır ve yazının içeriğini tanımlar özellikte olmalıdır.

Özetler

Türkçe (Öz) ve İngilizce (Abstract) olarak yazılmalı, Amaç, Gereç ve Yöntem, Bulgular ve Sonuç (Aim, Materials and Methods, Results, Conclusion) olmak üzere dört bölümden oluşmalı, en fazla 300 sözcük içermelidir. Araştırmanın amacı, yapılan işlemler, gözlemsel ve analitik yöntemler, temel bulgular ve ana sonuçlar belirtilmelidir. Özette kaynak kullanılmamalıdır. Editöre mektup için özet gerekmemektedir.

Anahtar Sözcükler

Türkçe Öz ve İngilizce Abstract bölümünün sonunda, Anahtar Sözcükler ve Keywords başlığı altında, bilimsel yazının ana başlıklarını yakalayan, Index Medicus Medical Subject Headings (MeSH)'e uygun olarak yazılmış en fazla beş anahtar sözcük olmalıdır. Anahtar sözcüklerin, Türkiye Bilim Terimleri'nden (www.bilimterimleri.com) seçilmesine özen gösterilmelidir.

Metin

Yazı metni, yazının türüne göre yukarıda tanımlanan bölümlerden oluşmalıdır. Uygulanan istatistiksel yöntem, Gereç ve Yöntem bölümünde belirtilmelidir.

Kaynaklar

Chronicles of Precision Medical Researchers Dergisi, Türkçe kaynaklardan yararlanmaya özel önem verdiğini belirtir ve yazarların bu konuda duyarlı olmasını bekler.

Kaynaklar metinde yer aldıkları sırayla, cümle içinde atıfta bulunulan ad veya özelliği belirten kelimenin hemen bittiği yerde ya da cümle bitiminde noktadan önce parantez içinde Arabik rakamlarla numaralandırılmalıdır. Metinde, tablolarda ve şekil alt yazılarında kaynaklar, parantez içinde Arabik numaralarla nitelendirilir. Sadece tablo veya şekil alt yazılarında kullanılan kaynaklar, tablo ya da şeklin metindeki ilk yer aldığı sıraya uygun olarak numaralandırılmalıdır. Dergi başlıkları, Index Medicus'ta kullanılan tarza uygun olarak kısaltılmalıdır. Kısaltılmış yazar ve dergi adlarından sonra nokta olmamalıdır. Yazar sayısı altı veya daha az olan kaynaklarda tüm yazarların adı yazılmalı, yedi veya daha fazla olan kaynaklarda ise üç yazar adından sonra et al. veya ve ark. yazılmalıdır. Kaynak gösterilen derginin sayı ve cilt numarası mutlaka yazılmalıdır.

Kaynaklar, yazının alındığı dilde ve aşağıdaki örneklerde görüldüğü şekilde düzenlenmelidir.

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Dergilerdeki yazılar

Teke Z, Kabay B, Aytekin FO et al. Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. Am J Surg 2007;194(6):255-62.

Ek sayı (Supplement)

Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002;19(Suppl 25):3-10.

Henüz yayınlanmamış online makale

Butterly SJ, Pillans P, Horn B, Miles R, Sturtevant J. Off-label use of rituximab in a tertiary Queensland hospital. Intern Med J doi: 10.1111/j.1445-5994.2009.01988.x

Kitap

Örnek 1: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.
Örnek 2: Sümbüloğlu K, Akdağ B. Regresyon Yöntemleri ve Korelasyon Analizi. Hatiboğlu Yayınevi: Ankara; 2007.

Kitap bölümü

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

İnternet makalesi

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Web Sitesi

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Yazar olarak bir kuruluş

The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Açıklamalar

Varsa finansal kaynaklar, katkı sağlayan kurum, kuruluş ve kişiler bu bölümde belirtilmelidir.

Tablolar

Tablolar metni tamamlayıcı olmalı, metin içerisinde tekrarlanan bilgiler içermemelidir. Metinde yer alma sıralarına göre Arabik sayılarla numaralandırılıp tablonun üstüne kısa ve açıklayıcı bir başlık yazılmalıdır. Tabloda yer alan kısaltmalar, tablonun hemen altında açıklanmalıdır. Dipnotlarda sırasıyla şu semboller kullanılabilir: *, †, ‡, §, ¶.

Şekiller

Şekil, resim, grafik ve fotoğrafların tümü "Şekil" olarak adlandırılmalı ve ayrı birer .jpg veya .gif dosyası olarak (yaklaşık 500x400 piksel, 8 cm eninde ve en az 300 dpi çözünürlükte) sisteme eklenmelidir. Şekiller metin içinde kullanım sıralarına göre Arabik rakamla numaralandırılmalı ve metinde parantez içinde gösterilmelidir.

Şekil Alt Yazıları

Şekil alt yazıları, her biri ayrı bir sayfadan başlayarak, şekillere karşılık gelen Arabik rakamlarla çift aralıklı olarak yazılmalıdır. Şeklin belirli bölümlerini işaret eden sembol, ok veya harfler kullanıldığında bunlar alt yazıda açıklanmalıdır. Başka yerde yayınlanmış olan şekiller kullanıldığında, yazarın bu konuda izin almış olması ve bunu belgelemesi gerekir.

Ölçümler ve Kısaltmalar

Tüm ölçümler metrik sisteme (Uluslararası Birimler Sistemi, SI) göre yazılmalıdır. Örnek: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min, mmHg, vb. Ölçümler ve istatistiksel veriler, cümle başında olmadıkları sürece rakamla belirtilmelidir. Herhangi bir birimi ifade etmeyen ve dokuzdan küçük sayılar yazı ile yazılmalıdır.

Metin içindeki kısaltmalar, ilk kullanıldıkları yerde parantez içinde açıklanmalıdır. Bazı sık kullanılan kısaltmalar; iv, im, po ve sc şeklinde yazılabilir.

İlaçların yazımında jenerik isimleri kullanılmalıdır.

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CONTENTS

ORIGINAL ARTICLES

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Amino Acid Levels in Patients with Fibromyalgia Syndrome

Fibromiyalji Sendromlu Hastalarda Amino Asit Düzeyleri

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ABSTRACT

Aim: Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterised by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive symptoms, making the patients seek long-term healthcare. While it is more common in females, the exact aetiopathogenesis of the disease is not clear, and current biomedical and psychosocial treatments are insufficient for many patients. This study aimed to examine the amino acid profile levels of patients with FMS to identify the amino acids that can potentially be used in the diagnosis and treatment of FMS.

Material and Method: Ninety participants (female patients diagnosed with FMS: n=45, mean age= 42.80±11.78 years; healthy controls: n=45, mean age=39.60±12.35 years) who applied to the Physical Medicine and Rehabilitation Clinic were recruited. Blood samples were drawn from all participants, and their plasma amino acid profiles were measured using an 8045 LC-MS/MS device. Multivariate analysis of the amino acid profile parameters was performed.

Results: The mean plasma levels of alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, alloisoleucine, phenylalanine, proline, serine, tyrosine, valine, alpha aminopimelic acid, hydroxy proline, serotonin, 5-hydroxytryptamine, taurine, glutamine, and glutamic acid were significantly lower in the FMS patients group ($p < 0.001$). In contrast, tryptophan, cystine, anserine, argino succinic acid, and gamma amino butyric acid levels were significantly higher among the patients with FMS ($p < 0.001$).

Conclusion: There were obvious differences in the amino acid profiles of patients with FMS and their corresponding healthy controls. These findings indicate the role of amino acids in elucidating the pathophysiology of FMS and as potential biomarkers in its prognosis, treatment, and follow-up.

Keywords: Fibromyalgia, Amino acids, LS-MS/MS

ÖZ

Amaç: Fibromiyalji sendromu (FMS), yaygın kas-iskelet ağrısı, yorgunluk, uyku bozuklukları ve kognitif semptomlarla karakterize kronik bir ağrı sendromudur ve hastaları uzun süreli sağlık hizmeti almak zorundadır. Kadınlarda daha sık görülmekle birlikte, hastalığın kesin etiyopatogenezi net değildir ve mevcut biyomedikal ve psikososyal tedaviler birçok hasta için yetersizdir. Bu çalışmada FMS'li hastaların amino asit profil düzeylerinin incelenmesi ve FMS'nin tanı ve tedavisinde potansiyel olarak kullanılabilecek amino asitlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Fiziksel Tıp ve Rehabilitasyon Kliniği'ne başvuran doksan katılımcı (FMS tanılı kadın hastalar: n=45, ortalama yaş= 42.80±11.78 yıl; sağlıklı kontroller: n=45, ortalama yaş=39.60±12.35 yıl) çalışmaya dahil edildi. Tüm katılımcılardan kan örnekleri alındı ve plazma amino asit profilleri 8045 LC-MS/MS cihazı kullanılarak ölçüldü. Amino asit profil parametrelerinin çok değişkenli analizi yapıldı.

Bulgular: Alanin, arginin, aspartik asit, sitrülin, glutamin, glutamik asit, glisin, histidin, lösin, izolösin, alloizolösin, fenilalanin, prolin, serin, tirozin, valin, alfa aminopimelik asit, hidroksi prolin, serotonin, 5-hidroksitriptamin, taurin, glutamin ve glutamik asit ortalama plazma düzeyleri FMS hasta grubunda anlamlı olarak daha düşüktü ($p < 0.001$). Buna karşılık, triptofan, sistin, anserin, argino süksinik asit ve gama amino bütirik asit düzeyleri FMS'li hastalarda anlamlı olarak daha yüksekti ($p < 0.001$).

Sonuç: Anlamlı olan amino asitlerin FMS'nin patofizyolojisinin aydınlatılmasında; prognozu, tedavisi ve takibinde potansiyel biyobelirteç rolü olabileceğini göstermektedir.

Anahtar Kelimeler: Fibromiyalji, Amino asitler, LS-MS/MS

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic disease of unknown aetiology with symptoms affecting multiple body systems. It is typically characterised by widespread body pain and the development of tender points. Essentially, FMS is a central desensitization syndrome in which the central processing of pain is impaired (1). Patients with FMS often require symptomatic care for years (2). However, current medical and psychosocial treatments are inadequate for many patients. Due to the lack of a clear understanding of the pathophysiology of FMS, little progress has been made in the treatment options for FMS (3).

Physiologically, amino acids play a vital role in maintaining immunity, regulating redox homeostasis, and serving as substrates for protein synthesis (4, 5). Functional amino acids, including glutamine, arginine, glycine, glutamic acid, and tryptophan, improve inflammatory disorders. Lately, extensive research has been done to understand how dietary amino acids affect growth, development, and immune response in mammals (6), Which has expanded our understanding of the activity of amino acids.

Tryptophan, phenylalanine, and tyrosine are classified as aromatic amino acids due to the presence of benzyl-based aromatic groups. Apart from acting as the building blocks of proteins, aromatic amino acids are critical in the body's metabolic and immune processes (6). Consequently, disturbances in their metabolism are associated with several hereditary diseases and neurological symptoms, especially those involving damage or deficiency of a cellular enzyme.

The amino acid aspartate is a critical precursor for protein synthesis, especially in pyrimidine and purine production, and primarily functions as a neurotransmitter, apart from its role in hormone secretion, neuronal protection, and reproductive regulation (7). Blachier et al. stated that aspartate triggers metabolic reprogramming and activation of hypoxia inducible factor-1α (HIF-1α) and NOD-like receptor protein-3 (NLRP3) in peritoneal macrophages, thus causing severe pain (8). Asparagine, an aspartate derivative, triggers this cellular metabolic reprogramming and HIF-1α activation, leading to increased interleukin-1β production from M1 macrophages (8).

In this context, the current study aims to define the relationship between different amino acids and FMS to reveal the mechanisms underlying the beneficial activities of these amino acids.

MATERIAL AND METHOD

Female patients with FMS (n=45) and healthy female controls (n=45) in the same age group, not having an existing chronic disease, and not taking any medication who applied to have widespared pain the Harran University Faculty of Medicine Physical Medicine and Rehabilitation Polyclinic were included in this study. FMS diagnosis was made according to the ACR's 2010 diagnostic criteria (9). Written consent for participation was obtained from all participants. Ethical approval for the study was obtained from the Harran University Clinical Research Ethics Committee (approval number: 23/10/04; dated: 05.06.2023).

A 5-cc blood samples were taken from all participants at 08.00 AM and stored at -80°C until the time of the study. The blood was centrifuged at 4000 rpm for 10 min, and the plasma section was separated. The plasma samples were analysed using the JASEM amino acid kit at the Biochemistry Laboratory of the Harran University Faculty of Medicine Research and Application Hospital. For analysis, 45 different amino acid parameters were studied by placing them in the tray section of the HPLC section of the LC-MS/MS device (Shimadzu 8045, Japan).

Statistical Analysis

For descriptive analysis, mean±standard deviation and range were computed for numerical variables, and frequency and percentages for categorical variables. Normality of the distribution of the data was examined using the Kolmogorov-Smirnov test; accordingly, Student's t-test for normally distributed features and the Mann-Whitney U test for non-normally distributed. Relationships between categorical variables were analysed using Pearson's chi-square or Fisher's exact tests. SPSS for Windows (version 20, IBM Corp., Armonk, NY, USA) was used for statistical analysis; a p-value of <0.05 was considered statistically significant.

RESULTS

The AA's between groups data are presented in Table 1. In patients with FMS, plasma levels of free amino acids–alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, allo-isoleucine, lysine, phenylalanine, proline, serine, tryptophan, tyrosine, hydroxyproline, cystine, homocysteine, serotonin, and taurine were statistically significantly lower compared to the control group (p <0.001 each).

Likewise, a statistically significant difference was found in the levels of branched chain amino acids (BCAAs) valine, leucine, and isoleucine in the patient group compared to the control group (p <0.001 each). However, there were no statistically significant differences in the plasma levels of asparagine, ornithine, methionine, and threonine between the two groups.

Table 1. The AA's between groups

	Control Group			Patient Group			p
	Min	Max	Mean±SD	Min	Max	Mean±SD	
Alanine	222.72	768.49	483.07±186.27	153.98	524.12	274.73±83.43	<0.001
Argjnine	177.19	605.43	303.61±112.90	21.32	111.12	68.49±22.42	<0.001
Asparagine	16.04	76.18	41.07±20.96	26.59	66.31	43.93±11.42	0.628
Aspartic Acid	42.33	158.22	95.67±39.24	1.21	44.62	10.49±10.83	<0.001
Citrulline	10.37	44.67	31.52±9.97	5.57	31.67	19.04±7.21	<0.001
Glutamin	161.55	709.45	348.77±147.97	66.09	312.70	139.17±65.15	<0.001
Glutamic Acit	131.56	505.25	310.92±112.74	19.76	264.65	78.31±47.00	<0.001
Glisine	148.38	419.94	306.34±77.34	116.15	340.66	198.01±50.47	<0.001
Histidine	97.92	255.56	170.51±48.14	30.69	87.42	57.52±12.48	<0.001
Leucine	101.99	381.01	220.73±85.66	20.00	149.43	95.27±27.06	<0.001
İsoleucine	54.62	195.51	120.87±45.54	10.27	91.51	59.96±15.95	<0.001
Allosoleucine	0.63	2.74	1.43±0.60	0.06	1.13	0.36±0.20	<0.001
Lysine	148.40	464.60	297.29±104.64	43.47	228.72	132.56±36.88	<0.001
Methionine	13.07	47.89	29.51±12.01	11.50	37.21	24.25±6.27	0.129
Ornithine	16.72	106.14	59.91±29.70	40.41	136.72	67.51±22.88	0.441
Phenylalanine	68.01	210.37	132.91±44.47	33.82	72.58	51.10±10.20	<0.001
Proline	147.08	646.15	318.48±144.44	101.68	249.54	155.49±40.28	<0.001
Serine	143.16	404.89	236.52±69.05	90.10	193.18	130.52±31.19	<0.001
Threonine	78.64	215.22	154.46±48.23	74.82	203.54	132.52±37.08	0.098
Tryptophan	49.22	155.76	83.72±30.58	26.15	81.56	56.44±14.93	0.002
Tyrosine	60.39	170.36	102.33±35.34	33.55	112.31	68.62±16.83	0.003
Valine	150.76	432.52	266.94±88.49	48.62	285.22	174.70±47.57	0.001
Alpha Amino Adipic Acid	0.10	2.25	1.03±0.65	0.18	2.92	0.94±0.57	0.904
Anserine	0.04	0.44	0.18±0.12	0.09	8.82	2.11±2.31	<0.001
Arginino Succinic Acid	0.02	0.44	0.10±0.11	0.01	0.62	0.19±0.14	0.006
Alpha Amino Butyric Acid	5.85	20.07	11.29±4.43	2.21	25.04	13.32±6.12	0.261
Beta Amino İsobutyric Acid	0.04	10.90	3.68±3.28	1.00	4.05	2.66±0.90	0.116
Gamma Amino Butyric Acid	20.13	63.21	40.05±14.06	0.32	7.72	4.89±1.70	<0.001
Beta Alanine	2.03	8.61	4.81±2.08	0.15	6.34	3.04±1.05	0.005
Cystathionine	0.01	0.19	0.09±0.06	0.01	0.50	0.12±0.12	0.981
Thiaproline	0.02	0.47	0.15±0.14	0.00	0.23	0.08±0.06	0.135
1-Methylhistidine	0.63	3.45	1.86±0.85	0.62	1.92	1.30±0.37	0.026
3-Methylhistidine	0.12	4.10	1.22±1.06	0.09	4.85	0.66±1.15	0.002
Hydroxylysine	0.03	0.42	0.16±0.13	0.01	0.60	0.15±0.14	0.463
Hydroxyproline	37.54	142.68	79.21±32.05	1.16	41.45	25.67±10.39	<0.001
Homocystin	1.25	1.90	1.18±0.43	0.41	0.74	0.17±0.18	<0.001
Serotonin	0.01	1.99	0.48±0.57	0.00	1.09	0.10±0.25	<0.001
Histamine	0.01	0.03	0.02±0.01	0.00	0.08	0.02±0.02	0.019
Ethanolamine	1.15	18.19	10.96±5.02	1.16	35.41	7.26±6.21	0.007
Phosphoethanol Amine	20.47	122.39	67.66±34.67	0.00	85.20	28.38±24.45	0.001
5-OH Tryptophan	0.05	0.57	0.23±0.15	0.00	0.50	0.04±0.09	<0.001
Taurine	208.37	1514.27	688.51±394.13	11.93	161.03	78.29±37.28	<0.001

DISCUSSION

Patients with FMS have significantly reduced levels of serum amino acids compared to healthy controls, which concurs with the existing literature.

Small molecules, such as peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, drugs, and human bacterial products, with molecular weights below 1, 500 Da, are considered metabolites (10). Metabolomics uses high-throughput technologies for the detection, quantification, and identification of these small molecule metabolites arising from lipids, carbohydrates, vitamins, hormones, and other cell components in tissues and physiological fluids over a certain period of time. It is well known that abnormalities in amino acid uptake and metabolism occur in many diseases, highlighting the role of specific amino acids in disease pathology. At the cellular level, aerobic physical activity increases the amount and quality of muscle mitochondria, which results in increased muscle oxidation capacity and exercise tolerance (11). As amino acids play an important role in genotoxicity, oxidative stress, and nutritional stress, abnormalities in amino acid levels presumably affect the physiology of patients with FMS (12).

Previous studies have reported that long-term and vigorous physical activities are associated with low blood levels of valine, leucine, and isoleucine, and blood glucose metabolism; accordingly, it is proposed as an

indicator of fatty acid oxidation in lipid metabolism. Furthermore, blood levels of glutamate and 2-hydroxybutyrate amino acids are inversely related to physical activity. These amino acids are involved in critical mechanisms in energy regulation and protein synthesis, such as the metabolism of glutamate and cysteine, and in the tricarboxylic acid (TCA) cycle (13-16).

Decreased values of some amino acids have been reported in patients with pancreatic, thyroid, or gastrointestinal diseases, and FMS (17, 18). In our study, the patient group had significantly reduced levels of the following free amino acids–alanine, arginine, aspartic acid, citrulline, glutamine, glutamic acid, glycine, histidine, leucine, isoleucine, alloisoleucine, lysine, phenylalanine, proline, serine, tryptophan, tyrosine, hydroxyproline, cystine, homocysteine, serotonin, and taurine.

In living organisms, many cellular proteins are constantly degraded and resynthesised to ensure that they are available as sources of energy and amino acids in the case of nutritional deficiency. Presumably, the pathophysiology of FMS causes a decrease in the body's amino acid pool. Amino acids are key elements in the maintenance of a constant cycle of protein synthesis and degradation and are essential to sustaining the body's protein balance (20, 21). In our study group comprising patients with FMS, there were significant changes in the amino acid profiles of phenylalanine and citrulline, and for 3-MMH only in the amino acid phenylalanine, compared to the control group. Additionally, the patient group showed significant lower in glycine, and glutamate amino acids compared to the control group.

BCAAs (valine, leucine and isoleucine) are alternative sources of organic molecules that can also fuel the TCA cycle (20, 21). We observed a statistically significant difference in the levels of BCAAs in patients with FMS compared to the healthy control group; however, no such difference was observed between the groups regarding the amino acid's asparagine, ornithine, methionine, and threonine. Like bioenergetic pathways, biosynthetic pathways are also based on various amino acid contributions (22, 23). The catabolism of BCAAs can mediate lipogenesis through acetyl-CoA synthesis. Likewise, nucleotide synthesis, which can be divided into purine and pyrimidine biosynthesis, is another amino acid-dependent process in which glycine, glutamine, and aspartate serve as carbon and nitrogen donors for purine biosynthesis.

Essential and nonessential amino acids are important for the development of all cells and the biosynthesis of lipids and nucleotides (24). Aa's are especially involved in reducing the effect of oxidative stress, producing glutathione, and adjusting the balance of oxidation and reduction. Furthermore, the formation of nonessential amino acids occurs through the catabolism, transamination, and chemical reactions of essential amino acids (25, 26). In the central nervous system, serotonin (5-hydroxytryptamine, 5-HT) is synthesised from tryptophan, an essential amino acid. Presynaptic autoreceptors on serotonergic neurons control the release of 5-HT in terminal areas, which inhibits serotonergic signalling (27). The low tryptophan in our study supports the disorder in the functional activity of brain structures in patients with FMS.

Recent research has shown that amino acids play an important role in immunity against viral, bacterial, and fungal infections (28, 29). Additionally, amino acids regulate immune activation and suppress inflammation resulting from infection. Therefore, amino acids, especially tryptophan, play a crucial role in protecting host tissues against infections by reducing excessive inflammatory reactions (30). It is well known that FMS may be triggered secondarily to the body's inflammatory response to infection. The low rate in our study supports this.

The most important limitation of our study is that only female patients were included, the disease is more common in women, thus ensuring homogeneity between groups and eliminating gender-related variables. There is a need for studies with larger participation including men.

CONCLUSION

We obtained data supporting central nervous system changes and inflammatory pathogenesis in the etiopathogenesis of FMS.

Patients with FMS have significantly reduced levels of serum amino acids compared to healthy controls. The pathophysiology of FMS remains unclear; consequently, no definitive treatment is available. We believe that our findings will contribute to the development of diagnostic and therapeutic strategies for FMS; nevertheless, further research is warranted on this subject..

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for the study was obtained from the Harran University Clinical Research Ethics Committee (approval number: 23/10/04; dated: 05.06.2023).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Developmental Hip Dysplasia Screening Results in a Children Hospital in Konya: A Large Cohort Study

Konya'da Bir Çocuk Hastanesinde Gelişimsel Kalça Displazisi Taraması Sonuçları: Geniş Bir Kohort Çalışması

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ABSTRACT

Aim: Developmental hip dysplasia (DHD) is the most common congenital hip pathology in babies. The aim of this study is to evaluate the incidence of DHD in Konya region using the ultrasonography(USG) and to emphasize the importance of early detection of DHD.

Material and Method: The study was a retrospective study which was designed between June 2016 and March 2022 in Konya region. Hip ultrasonography was used for detection of DHD according to Graf method. Babies who were referred to the pediatric outpatient clinic of our hospital by their family physicians for hip ultrasonography or who applied to the outpatient clinic for any reason and were asked to have hip USG to screen for DHD were included in the study.

Results: A total of 2074 infants who met the inclusion criteria were included in the study. The mean duration of the first hip USG was 8.4 (4-18) weeks. In 1946 infants, the hip USG result was found to be bilateral type 1. We found the incidence of DHD to be 1.35% in our series.

Conclusion: In our study, the incidence in our series was similar to other studies in which ultrasonography technique was used. In addition, the incidence of 1.35% we found is the same with the study conducted in Konya in 1992 and shows that the incidence for Konya has not changed in the last 20 years. Prospective multicenter studies should be organized to obtain a clearer picture of the incidence of DHD at the national level.

Keywords: Developmental hip dysplasia, ultrasonography, baby, incidence

ÖZ

Amaç: Gelişimsel kalça displazisi (GKD) bebeklerde en sık görülen konjenital kalça patolojisi olup, kalça usg ile erken saptanabilirve geç saptanmasıyla ortaya çıkabilecek komplikasyonlar önlenebilir. Hastalığın görülme sıklığı genetik, tarama teknikleri ve kültürler arası farklılıklara bağlı olarak değişmektedir. Çalışmanın amacı, Konya bölgesinde ultrasonografi kullanılarak GKD insidansını değerlendirmek ve GKD'nin erken teşhisinin önemini vurgulamaktır.

Gereç ve Yöntem: Çalışma, Haziran 2016 ile Mart 2022 tarihleri arasında Konya bölgesinde tasarlanmış retrospektif bir çalışmadır. GKD'nin tespiti için Graf yöntemine göre kalça ultrasonografisi kullanıldı. Çalışmaya hastanemiz çocuk polikliniğine aile hekimleri tarafından kalça ultrasonografisi (USG) için yönlendirilen veya herhangi bir nedenle polikliniğe başvuran ve GKD taraması için kalça USG çekilen bebekler dahil edildi.

Bulgular: Çalışmaya dahil edilme kriterlerini karşılayan toplam 2074 bebek değerlendirildi. Bunların 1036'sı erkek, 1038'i kız bebekti. Bebeklerimizin ortalama ilk kalça USG zamanı 8,4 (4-18) hafta idi. 1946 bebekte ilk kalça ultrasonu sonucu normaldi ve 27 bebekte bilateral tip 2a vardı. Serimizde DHD insidansını %1.35 olarak bulduk.

Sonuç: Çalışmamızda serimizdeki insidans ultrasonografi tekniğinin kullanıldığı diğer çalışmalarla benzerdi. Ayrıca bulduğumuz %1.39'luk insidans 1992 yılında Konya'da yapılan çalışma ile aynıdır ve Konya için insidansın son 20 yılda değişmediğini göstermektedir. Ülke düzeyinde DHD insidansını daha net bir şekilde elde etmek için prospektif çok merkezli çalışmalar düzenlenmelidir.

Anahtar Kelimeler: Gelişimsel kalça displazisi, ultrasonografi, bebek, insidans

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INTRODUCTION

Developmental hip dysplasia (DHD) is the most common congenital hip pathology. In 1988, instead of the term "Congenital Hip Dislocation", the term "Developmental Hip Dysplasia" began to be used all over the world (1). Although the exact incidence in the world is not known, it is estimated to be between 1 and 34 per thousand (2,3). While the incidence of physiological immature hips in newborns in Europe is between 3 and 13%, actual dysplasia rates have been reported to be between 1 and 3% (4,5). The reasons for the different reported incidences are genetic predisposition to DHD, differences in screening techniques, and cross-cultural differences in baby-raising habits (6-9) Differences between studies conducted at different times and in different regions in our country (0.047-17%) also support this conclusion (9-22).

The initial pathology is abnormal laxity in the hip joint, causing the femoral head to displace and displace from the acetabulum. Dislocation or permanent subluxation of the femoral head causes permanent degeneration in the acetabulum over time (23). DHD cases that cannot be detected and treated early face serious hip problems in the following years. It has been reported that 9% of patients who underwent hip replacement surgery in Norway had DHD sequelae (24). While DHD can be treated successfully with conservative methods without sequelae when detected at an early stage, surgical interventions become mandatory in late cases and also treatment costs increase (25,26).Genetic, hormonal, mechanical and developmental elements are shown in etiology. Foot deformities, congenital anomalies such as torticollis, female gender, breech presentation, multiple births, birth weighing over 4500 g and a positive family history are known risk factors for DHD (2,27,28). While many advanced stage DHD cases can be detected by physical examination, borderline cases may not be detected. In a study that is of particular importance because it was conducted in our country, it is recommended that all newborns should undergo ultrasonoraphy in the first two weeks (16). The most common recommendation among radiodiagnostic specialists is to perform the procedure every 2-8 weeks. Ultrasonography examination should be performed more later weeks in premature babies. Since most of the upper end of the femur consists of cartilage in babies under three months of age, radiographic examinations may contain diagnostic findings but do not give definitive results. For this reason, hip ultrasonography has become a common diagnostic tool with higher sensitivity and specificity than physical examination and radiography in the diagnosis of DHD and it is the gold standard in screening (2,3,10-12,29). While in some countries such as Germany and Austria, all babies are screened for DHD with hip ultrasonography, in the USA and the UK, only babies with risk factors are screened.

Hip utrasonography is not included in the routine screening program in our country. In the guide prepared by the Ministry of Health for family physicians, screening with ultrasonography is recommended for risk groups and cases with positive examination findings (30).

Hip ultrasonography was first described by Reinhard Graf in 1978 and this method is static ultrasonography. In the static method, the placement of the femoral head is evaluated by measuring the morphological structure and angular values of the acetabulum (31).

The aim of this study is to draw attention to the fact that hip ultrasonograhic evaluation should be included in the routine for screening purposes in our country and to emphasize the importance of early detection of DHD.

MATERIAL AND METHOD

Our study was a retrospective study which was performed between June 2016 and March 2022. Babies who were referred to the pediatric outpatient clinic of our hospital by their family physicians for hip ultrasonography (USG) or who applied to the outpatient clinic for any reason and were asked to have hip USG to screen for DHD were included in the study. Ultrasonograhy was requested for premature babies with a corrected week of at least 4 weeks. Since borderline cases may be missed by physical examination, hip USG is requested for screening purposes in all cases aged between 4 weeks and 4 months who apply to our outpatient clinic for any reason, if hip USG has not been requested yet. The data was accessed from the hospital database. All USG results were examined and recorded digitally. All USG examinations were performed with the method described by Graf, by taking standard sections in the coronal plane, with the baby lying in the lateral decubitus position, the hip and knee in semi-flexion, and the hip joint in 15-20°C internal rotation (**Figure 1**). Ultrasonography was performed using a 7.5 Mhz linear probe USG device (Mindray Digi Prince Dp-9900) by experienced radiology specialists in our hospital. Angular measurements are taken twice for each hip in the same session for confirmation purposes. The angular values noted in the USG reports by our radiologists and were classified using the method described by Graf (31) (**Table 1**). While the cases whose USG result was Type 1 at the first admission were considered normal, double spacer cloth was recommended for cases 2a and 2b, and the patient was called for a follow-up check after 4 weeks. The results of our patients who underwent control USG were also documented in the hospital database. At the second follow-up, the cases whose USG results were other than Type 1 were referred to orthopedics. The cases whose first USG results were Types 2c, 2d, 3 and 4 were referred to orthopedics without a control USG.

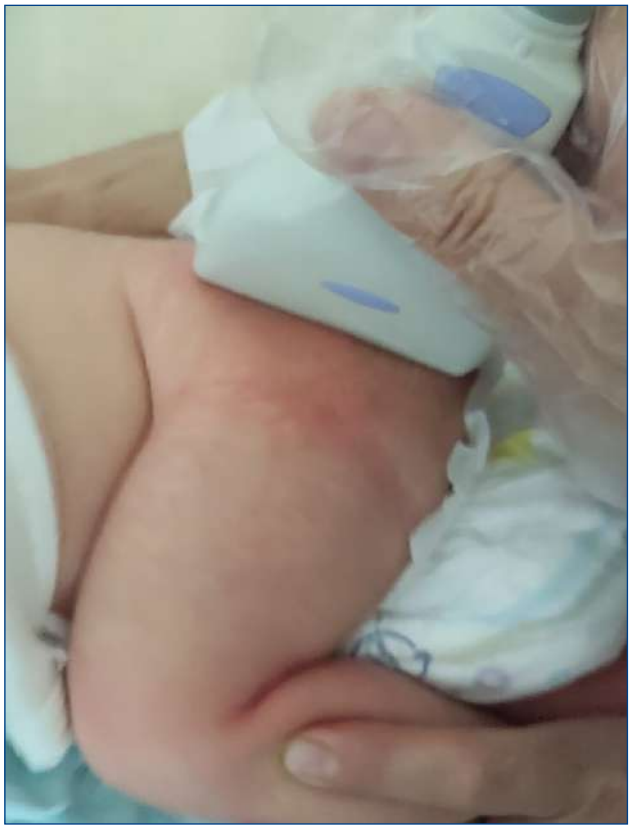

Figure 1. The ultrasonographic examinationof a baby which was performed with the method described by Graf.

Table 1: Ultrasonographic classification of developmental hip dysplasia based on the Graf Method.

Type	Alpha angle (bone roof)	Beta angle/age (cartilage roof)	Definition
1	>60	<55	Normal hip
2a	50-60	55-75/<3 month	Physiologically immature hip
2b	50-60	55-77/>3 month	Stable centralized hip
2c	43-49	>77	Unstabil centralized hip
2d	43-49	>77	Decentralized hip
3	<43	>77	Excentric hip
4	Unmeasurable	-	Dislocated hip

Statistical Analysis

The data were analyzed using SPSS (Statistical Package or Social Sciences) Program 15.0. Chi-square test was used to evaluate categorical variables (such as age, gender). A p value of <0.05 was taken for statistical significance. The results were expressed as numbers and percentages.

RESULTS

Hip USG was performed on 2074 babies in our pediatric clinic between June 2016 and March 2022. Of these, 1036 were male babies and 1038 were female babies. The average time in our babies' for first hip USG was 8.4 (4-18) weeks.

The distribution of the initial hip USG results when classified according to the Graf method is shown in **Table 2**. The patients with type 1 initial USG results were considered normal, while the patients with type 2a and 2b results were recommended to use double spacer and were called for follow-up after one month. All other cases were referred to orthopedics after the first USG. 121 patients were called for control USG. Of these, 36 patients did not come for follow-up. The results of the patients who underwent USG for the second time are shown in **Table 3**. Dysplasia was detected and referred to orthopedics in a total of 28 cases who were found to have type 2a and 2b dysplasia that did not improve in the control USG performed one month after double spacer application and type 2c or more advanced dysplasia in the first USG. Of these 28 babies, 23 were girls and 5 were boys. 6 of 28 patients had bilateral dysplasia. Of the 85 patients who were offered double diapers and who came for follow-up, 64 had normal control USG. According to the first USG result, 7 patients were referred to orthopedics.

Table 2: The results of initial hip ultrasonography of patients.

Ultrasonography results	Number of patients
Bilateral type 1	1946
Bilateral type 2a	27
Bilateral type 3	1
Bilateral type 4	2
Left type1 / right type 2a	33
Left type 2a / right type 1	59
Left type 2c / right type 2a	1
Left type 2b /right type 1	1
Left type 2b / right type 2c	2
Left type2a / right type 2b	1
Left type2c / right type 1	1

Table 3: The results of second control of hip ultrasonography of patients.

Ultrasonography results	Number of patients
Bilateral type 1	64
Bilateral type 2a	6
Left type 1 / right type 2a	5
Left type 2a / right type 1	10

DISCUSSION

Developmental hip dysplasia, which is thought to develop before or after birth as a result of a dynamic process, is seen at a high rate in our country, especially in regions where swaddling is common. The disease affects around 15.000 newborns per year in our country. Some of the cases may resolve spontaneously, but lack of improvement leads to serious morbidity. For this reason, DHD is a process that must be recognized early and managed appropriately. Delays in diagnosis lead to longer treatment times, the need for more invasive interventions, and decreased treatment success rates.

This situation negatively affects not only the patient, but also his family and the country's economy. For this reason, especially the first 2-3 months of life are the golden period in the treatment of DHD (32).

In our study, the hip USG examination results performed with the Graf method of 2074 babies who were referred to the pediatric outpatient clinic of our hospital by their family physicians for hip ultrasonography (USG) between June 2016 and March 2022, or who applied to the polyclinic for any reason and asked for hip USG to screen for DHD, were evaluated. In our study dysplasic hips were detected in 28 (1.35%) babies, so, our result is compatible with dysplasia rates in Europe (4,5,32) There are many studies published on the incidence of DHD in our country, and in these reports, the incidence has been reported at very different levels such as 0.047-17% due to differences in the number of cases included and the method of case selection (9-23,33,34). In a review, the incidence of DHD detected only by clinical examination was found to be between 0.047 and 1%.[19] In the study conducted by Kutlu et al. in 1992, the frequency of DHD in the Konya region was reported as 1.34% (15). Karapınar et al. conducted a three-year study between 1993 and 1996, in which 15.000 newborns in the Izmir region were screened only by clinical examination without USG, and the incidence of DHD was reported as 0.5% (21). In another study of Karapınar et. al. with USG guidance in 2002, the incidence was reported as 5.2% (12). This difference in incidence between USG scan and physical examination indicates that many DHD cases can be missed with physical examination. Soyuncu et al. examined 447 cases in the Antalya region in 1999 and stated the incidence as 6.2% (20). In the study conducted by Karapınar et al. in Izmir region, where 327 babies were examined with hip joint USG, the incidence of DHD that required treatment was reported as 5.2% (12). On the other hand, Sahin et al. reported the results of the screening of 5798 babies in the Ankara region, and found the incidence as 0.17% in 2004 (35). In another study published by Köse et al. the incidence of DHD in the Eskişehir region was reported as 1.2% (22). Additionally, Doğruel et al. reported the incidence of DHD by ultrasonography screening and clinical examination, as 5.3% in 3541 babies in Ankara region (11). Also, in another study conducted in Ankara in 2009, type 2b hips were detected in three cases (1%) as a result of hip examination using the Graf method among 300 babies who applied to the well-child clinic (14). Can et al. reported the frequency of DHD as 0.3% in the hip USG examination performed in the first month of 258 babies in Istanbul in 2010 (10). However, Tosun et al. reported the frequency of dysplasia in the Elazığ region as 14.7% (36). In this study, only 310 patients who were referred to the orthopedic outpatient clinic were evaluated, and this may be one of the reasons for the high incidence. In the study of Duramaz et al. which was conducted in Istanbul in 2014 and examined 1316 cases, the DHD rate was reported as 0.5% that was similar to the literature (9).Also, Çekiç et al. reported the incidence of DHD in the Western Mediterranean region as 1.34% (37). In the study conducted by Ceylan et al., dysplasia could be detected in seven (0.46%) of 1491 babies who underwent hip ultrasonography examination in Istanbul (38). However, Batu et al. reported the incidence of DHD by hip ultrasonography as 1.5% in the same region (33). It has been shown that even some of the cases with completely dislocated hips cannot be detected by physical examination alone (31). Sensitivity of physical examination alone has been reported at levels of 13% to 60% (11). In a study conducted by Dorn and Neumann on 8221 newborns, it was reported that 1.3% of patients with normal physical examination had pathological changes (type 2c, 2d and 3) on ultrasonography (39). Also, in another study, it was determined that only 40% of the patients with positive findings on ultrasonography had positive examination findings (16). For this reason, methods with better sensitivity should be used. Ultrasonography allows the evaluation of the femoral epiphysis and labral cartilage, which cannot be distinguished on direct radiography in babies younger than three months. Additionally, it is radiation-free and frequently repeatable (6). Control of the hip joint and recognition of possible DHD with hip ultrasonograhy, which is a non-invasive, safe and simple method in the early period, significantly increases the success of treatment (40). Although there is no clear data on timing, the general opinion is to perform hip ultrasonographic evaluation between 4-6 weeks (31). In some European countries, screening examination is performed in the first days following birth (4,5,32)

In the Graf method, control with ultrasonography is recommended on the 40th day (31). In our series, the mean time of ultrasonograhic evaluation of DHD was 8.4 weeks.

The relationship between female gender and DHD has been shown in all studies (3,11,15,22,33,34). In the study of Köse et al. which was conducted on 975 babies, it was observed that girls were affected six times more than boys (22). Also, Doğruel et al. reported this rate as 3.6 times (11) Similarly, Kutlu et al. reported that female babies were three times more likely to be diagnosed with DHD than boys (15) In our study, 23 of 28 babies diagnosed with dysplasia were girls, and the number of girls was approximately 5 times more than boys. So, the difference between the male and female ratio was statistically significant ($p<0.05$). Additionally, only the right side was affected in 5 of 28 babies with hip dysplasia and the remaining 23 patients were either left unilateral or bilateral. It has been emphasized that the left hip being affected more frequently than the right, so it may be due to the intrauterine position (39).There

are other studies supporting that isolated right hip involvement is less common (40,41).In our study, 12 of the 28 cases who were diagnosed as DHD had bilateral involvement. Since our study was retrospective and limited recorded data, the relationship between risk factors, physical examination and DHD frequency could not be evaluated.

CONCLUSION

As a result, in our study, ultrasonography results of all babies who applied for screening examination were discussed, instead of cases with suspicious clinical conditions or additional problems. In this respect, we think that the incidence obtained as a result of our study is close to reality. The fact that the 1.35% incidence that we found is the same as the study conducted in Konya in 1992 and it shows that the incidence for Konya has not changed in the past 20 years. Prospective multicenter studies should be organized to more clearly obtain the incidence of DHD at the country level..

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the ethics committee of Republic of Türkiye, Ministry of Health, Konya Provincial Health Directorate (No:E86737044-806,01,03).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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ORİJİNAL ARAŞTIRMA
ORIGINAL ARTICLE

Annelerin Hasta Çocukları için Üniversite Hastanesini Tercih Etmesini Etkileyen Faktörler

Factors Affecting Mothers' Preference for University Hospitals for Their Sick Children

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ÖZ

Amaç: Bu araştırma bir üniversite hastanesi çocuk sağlığı ve hastalıkları (ÇSH) klinik ve polikliniklerine başvuran hastaların annelerine üniversite hastanesini tercih nedenlerini ve bunu etkileyen faktörlerin belirlenmesi ve sonrasında hastane hizmetlerinin kalitesinin geliştirilmesi için yapılabilecekler konusunda önerilerde bulunmak amacı ile planlanmıştır.

Gereç ve Yöntem: 1 Nisan- 31 Mayıs 2015 tarihlerinde, hastalara refakat eden annelere demografik bilgiler ve üniversite hastanesini tercih nedenini belirlemeye yönelik araştırmacıların oluşturduğu anket uygulandı.

Bulgular: 17-59 yaş aralığındaki (yaş ortalaması=32,7 ± 6,9 yıl) 385 anneye uygulanan anketlerin verileri analiz edilmiştir. Hastaların 188'ini (%48,8) kızlar oluşturmakta ve tüm hastaların yaş ortalaması= 6,7 ± 4,9 yıldı. Üniversite hastanesini tercih etmede en önemli etmen Kariyer yapmış, tecrübeli uzman hekimlerin fazla olması en düşük etmen ise radyolojik testlerin fazla olması olarak işaretlenmesiydi.

Sonuç: Araştırma, kişisel, kurumsal ve toplumsal faktörler tarafından yönlendirilen hastane seçiminin karmaşıklığını vurgulayarak sağlık hizmetlerinin iyileştirilmesi ve politika planlaması için değerli içgörüler sağlamaktadır. Elde edilen bulgular, sağlık hizmeti sağlayıcılarının hizmetleri geliştirirken veya yeni tesisler kurarken hasta merkezli iyileştirmelere öncelik vermeleri, beklentileri yönetmeleri ve coğrafi ve finansal yönleri stratejik olarak dikkate almaları gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Hastane tercihi, hastaların tercihleri, 3. basamak sağlık kuruluşu, çocuk sağlığı ve hastalıkları

ABSTRACT

Aim: This study aimed to identify the reasons why mothers of patients who visited the pediatric clinics and polyclinics of a university hospital chose the university hospital and to examine the factors influencing this decision.

Material and Method: A survey prepared by the researchers was applied to the mothers accompanying the patients between April 1 and May 31, 2015 to determine demographic information and the reason for preferring the university hospital.

Results: Data from the surveys applied to 385 mothers between the ages of 17-59 (mean age=32.7 ± 6.9 years) were analyzed. 188 (48.8%) of the patients were girls and the mean age of all patients was=6.7 ± 4.9 years. The most important factor in choosing a university hospital was the high number of experienced specialist physicians who have made a career, and the lowest factor was the high number of radiological tests.

Conclusion: The study highlights the complexity of hospital selection, driven by personal, institutional and societal factors, providing valuable insights for improving healthcare services and policy planning. The findings highlight the need for healthcare providers to prioritize patient-centered improvements, manage expectations and strategically consider geographical and financial aspects when developing services or establishing new facilities.

Keywords: Hospital preference, patient preferences, level 3 healthcare institution, child health and diseases

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GİRİŞ

Sağlık hizmetleri, bireylerin yaşam kalitesini doğrudan etkileyen kritik unsurlardan biridir. Sağlık hizmetlerine erişim ve bu hizmetlerin kalitesi, bireylerin genel sağlık durumunu ve yaşam memnuniyetini belirleyen temel faktörler arasında yer almaktadır. Hastaların sağlık hizmetlerinden beklentileri ve bu hizmetlere erişim şekilleri, sağlık kurumlarının tercih edilmesinde belirleyici rol oynamaktadır. Bu bağlamda, hastaların hastane tercihlerini etkileyen faktörlerin belirlenmesi, sağlık hizmetlerinin kalitesinin artırılması ve hasta memnuniyetinin sağlanması açısından büyük önem taşımaktadır

Hastaların hastane tercihlerinde etkili olan faktörler, çeşitli sosyal ve ekonomik değişkenlerle şekillenmektedir. Gelir seviyesi, hastaların sağlık hizmetlerine erişimini ve tercihlerini doğrudan etkileyen en önemli faktörlerden biridir. Yüksek gelir seviyesine sahip bireyler, genellikle daha iyi hizmet sunan özel hastaneleri tercih etme eğilimindedirler. Bu durum, özel hastanelerin sunduğu hizmet kalitesi ve teknolojik altyapının daha yüksek olmasıyla ilişkilendirilebilir (1-3).

Hastaneye ulaşım kolaylığı, hastanenin konumu ve hastanenin bulunduğu bölgeye olan yakınlık, hastaların tercihlerini doğrudan etkileyen unsurlar arasındadır. Özellikle acil durumlarda, hastaların en yakın ve en hızlı ulaşabilecekleri hastaneleri tercih ettikleri gözlemlenmektedir (4). Bu nedenle, sağlık kurumlarının konumlandırılması ve ulaşım imkanlarının iyileştirilmesi, hasta memnuniyetinin artırılması açısından kritik öneme sahiptir (1).

Sağlık hizmetlerinin kalitesi; doktorların uzmanlığı, hastane personelinin ilgisi, teknolojik altyapı ve genel hasta memnuniyeti gibi unsurları içermektedir. Hastalar, kendilerine en iyi hizmeti sunabilecek, güvenilir ve donanımlı hastaneleri tercih etmektedirler. Hizmet kalitesinin yüksek olduğu hastaneler, hasta memnuniyetini artırarak, hastaların tekrar tercih etme olasılığını yükseltmektedir (1,5).

Kısa bekleme süresi ve hızlı hizmet sunumu, hastalar tarafından tercih edilen hastanelerin özelliklerindendir (6). Özellikle acil durumlarda, hızlı ve etkili hizmet sunan hastaneler, hastalar tarafından daha fazla tercih edilmektedir (1).

Yaş, cinsiyet, eğitim seviyesi gibi demografik faktörler, bireylerin sağlık hizmetlerine yönelik beklentilerini ve tercihlerini şekillendirmektedir (3). Örneğin, yaşlı bireyler genellikle daha fazla sağlık hizmetine ihtiyaç duyarken, genç bireyler daha az sıklıkla sağlık hizmetlerine başvurmaktadır. Eğitim seviyesi de sağlık hizmetlerine erişim ve kullanımda önemli bir rol oynamaktadır; daha yüksek eğitim seviyesine sahip bireyler, sağlık hizmetleri konusunda daha bilinçli ve talepkâr olabilmektedirler (7).

Üçüncü basamak sağlık hizmeti, en yüksek uzmanlık ve teknoloji gerektiren sağlık bakımını ifade eder. Bu hizmet, genellikle nadir görülen veya karmaşık sağlık sorunlarının tedavisi için hastaneler ve tıp merkezlerinde sunulur. Bu hizmet kapsamında yer alan alanlar, özel cerrahi işlemler, organ nakilleri, yoğun bakım hizmetleri ve ileri teşhis teknolojilerinin kullanımını içerir. Üçüncü basamak sağlık hizmeti, nüfusun sınırlı bir kısmına hizmet veren, oldukça pahalı ve yüksek maliyetli bir sağlık hizmetidir (8-10).

Türkiye Cumhuriyeti'nde hastalar, tercih ettikleri sağlık hizmetini diledikleri sağlık kuruluşundan herhangi bir kısıtlama olmaksızın alabilmekte ve birinci basamak sağlık kuruluşlarından sevk almadan doğrudan ikinci ve üçüncü basamak sağlık kuruluşlarına başvurabilmektedirler. Ayrıca, bireyler aile hekimini seçme konusunda da özgürdürler (11,12).

Birinci basamak sağlık hizmeti sunan kurumlar, hastaların sağlık hizmeti talebiyle ilk başvurdukları yerlerdir. Ancak bu basamakta sunulan hizmetin yetersiz olması ya da vatandaşlar tarafından eksik veya yetersiz olarak algılanması durumunda, hastalar sevk zincirine tabi olmadan doğrudan ikinci veya üçüncü basamak sağlık hizmeti sunan kurumlara başvurabilmektedirler (13).

Hastaların hastane tercihlerini etkileyen faktörler çok yönlü ve karmaşıktır. Gelir seviyesi, kuruma erişim imkânı, hizmet kalitesi, bekleme süresi ve sosyal-demografik faktörler, hastaların sağlık hizmetlerine yönelik tercihlerini belirleyen başlıca unsurlar arasında yer almaktadır. Bu çalışmada, annelerin hasta çocukları için 3. Basamak bir hastane olan Tokat Gaziosmanpaşa Üniversitesi Sağlık Uygulama ve Araştıra Merkezini tercihlerinde etkili olan faktörler incelenmesi ve elde edilen bulgular doğrultusunda sağlık hizmetlerinin iyileştirilmesine yönelik girişimlere ışık tutulması amaçlanmıştır.

GEREÇ VE YÖNTEM

Anket

Hastalara refakat eden annelere demografik bilgiler ve üniversite hastanesini tercih nedenini belirlemeye yönelik araştırmacıların oluşturduğu anket uygulandı. Örnekler Tokat Gaziosmanpaşa Üniversitesi Sağlık Uygulama ve Araştırma Merkezi Çocuk Sağlığı ve Hastalıkları polikliniğine 1 Nisan- 31 Mayıs 2015 tarihlerinde başvuran ardışık, ayırt edilmeksizin, hastaların anneleri olarak belirlendi. Anket formları randevusunu bekleyen hastanın annesine verildi ve muayene için poliklinik odasına alındığında doldurulmuş formlar teslim alındı. Değişkenler arasında hastanın cinsiyeti, yaş, sevk durumu, yaşanılan yer, kimin tavsiye ettiği, annenin yaşı ve eğitim durumu gibi veriler yer aldı.

Bulgular kısmında sunulan hastanenin tercih nedeni olarak düşünülen modern testler ve ekipman; kariyerli uzman hekim varlığı, idari basitlik, bekleme süresi gibi 7 sorunun da verileri alınmıştır. Çok önemli görülmüşse 1- önemsiz görülmüşse 5 puan olacak şekilde puanlandırılmıştır.

Veriler SPSS 22.0 statistics program for Windows® (SPSS Inc., Chicago, Illinois, ABD) ile değerlendirildi. Sürekli değişkenler ortalama ± standart sapma (SD), kesikli değişkenler ise sayı ve yüzde olarak sunuldu. Karşılaştırmalarda ki-kare testi kullanıldı ve $p < 0.05$ anlamlılık düzeyi olarak kabul edildi.

BULGULAR

17-59 yaş aralığındaki 385 anneye uygulanan anketlerin verileri analiz edilmiştir. Anneler ve hastalara ait demografik ve genel özellikler **Tablo 1**'de verilmiştir.

İstatistiksel analizin uygulanması için çok önemli ve önemli yanıtları birleştirilmiş ayrıca orta -az önemli ve önemsiz grupları birleştirilmiş ve 2 Grup oluşturulmuştur. Böylece anne yaşının, eğitim durumunun tercih nedenlerine etkisinin araştırılmasına imkan tanınmıştır.

Hastaların %29,8'ini kronik hastalığa sahip bireyler oluşturmaktadır. Kronik hastalık varlığının tercih nedeni olabilecek 7 soruya yanıt etkisi için yapılan Chi-Kare testinde her bir soru için p>0.05 saptanmış ve kronik hastalık varlığının bu tercih nedenleri ile istatistiksel ilişkisi bulunmamıştır. Aynı şekilde yaşanılan yer ile de bir istatistiksel anlamlılık saptanmamıştır (p>0,05).

Tablo 1. Demografik ve Genel özellikler

	n	%
Hastanın yaşı (yıl)	6,7 ± 4,9 (0-17)	
Cinsiyet		
Kız	188	48,8
Erkek	197	51,2
Hastanın yaşadığı yer		
Köy	74	19,2
Belde	19	4,9
İlçe	124	32,2
Şehir merkezi	168	43,6
Sevk Durumu		
Yok	272	70,5
Aile sağlığı merkezinden	5	1,1
Devlet hastanesinden	108	28,4
Annenin yaşı (ort ± SS) (Range)	32,7 ± 6,9 (17-59)	
Anne eğitim durumu		
Okuryazar değil	8	2,1
İlkokul	4	,9
Ortaokul	204	53,1
Lise	68	17,5
Lisans- önlisans	63	16,3
Yüksek lisans	11	3,0
Doktora	27	7,1

Tablo 2. Hastane tercih nedenlerinin önem puanlaması

	Çok önemli	Önemli	Orta önemli	Az önemli	Önemsiz
Hasta başına muayene için ayrılan süre uzunluğu	193	160	18	5	4
Laboratuvar testlerinin daha fazla olması	144	190	34	9	4
Radyoloji tetkiklerinin daha fazla olması	114	192	41	23	6
Diğer ileri test ve tekniklerin bulunması	158	183	28	7	3
Kariyer yapmış, tecrübeli uzman hekimlerin fazla olması	260	109	9	2	1
Muayene için sıra beklemenin daha kısa sürmesi	159	173	34	8	8
Tetkik sonuçlarının değerlendirilmesi için geçen sürenin daha kısa sürmesi	159	180	29	5	6

Tablo 3. Anne eğitim durumu ile tercih ilişkisi tablosu

	Annenin Eğitim Durumu		Total (n=385)	P
	Orta öğrenim (n=248)	Yüksek öğrenim (n=137)		
Laboratuvar testlerinin daha fazla olması				0,638
Çokönemli + önemli	217 (87,5)	117(85,4)	334 (100)	
Orta->önemsiz	31(12,5)	20 (14,6)	51 (100)	
Hasta başına muayene için ayrılan süre uzunluğu				0,467
Çokönemli + önemli	225(90,7)	128(93,4)	353 (100)	
Orta->önemsiz	23 (9,3)	9 (6,6)	32 (100)	
Radyoloji tetkiklerinin daha fazla olması				0,069
Çokönemli + önemli	204 (82,3)	102 (74,5)	306 (100)	
Orta->önemsiz	44 (17,7)	35 (25,5)	79 (100)	
Diğer ileri test ve tekniklerin bulunması				0,342
Çokönemli + önemli	223 (89,9)	118 (86,1)	341 (100)	
Orta->önemsiz	25 (10,1)	19 (13,9)	44 (100)	
Kariyer yapmış, tecrübeli uzman hekimlerin fazla olması				0,667
Çokönemli + önemli	239 (96,4)	130 (94,9)	369 (100)	
Orta->önemsiz	9 (3,6)	7 (5,1)	16 (100)	
Muayene için sıra beklemenin daha kısa sürmesi				0,674
Çokönemli + önemli	212 (85,5)	120 (87,6)	332 (100)	
Orta->önemsiz	36 (14,5)	17 (12,4)	53 (100)	
Tetkik sonuçlarının değerlendirilmesi için geçen sürenin daha kısa sürmesi				0,540
Çokönemli + önemli	216 (87,1)	123 (89,8)	339 (100)	
Orta->önemsiz	32 (12,9)	14 (10,2)	46 (100)	

Tablo 4. Anne yaşı ile hastane tercih ilişkisi tablosu

	Anne yaşı gruplaması		Total(n=385)	P
	40 yaş ve altı (n=299)	40 yaş üzeri (n=86)		
Hasta başına muayene için ayrılan süre uzunluğu				0,044
Çokönemli + önemli	279 (93,3)	74 (86)	353 (100)	
Orta->önemsiz	20 (6,7)	12 (14)	32 (100)	
Laboratuvar testlerinin daha fazla olması				0,262
Çokönemli + önemli	263 (88)	71 (82,6)	334 (100)	
Orta->önemsiz	36 (12)	15 (17,4)	51 (100)	
Radyoloji tetkiklerinin daha fazla olması				0,387
Çokönemli + önemli	241 (80,6)	65 (75,6)	306 (79,5)	
Orta->önemsiz	58 (19,4)	21(24,4)	79 (20,5)	
Diğer ileri test ve tekniklerin bulunması				0,003
Çokönemli + önemli	273 (91,3)	68 (79,1)	341 (88,6)	
Orta->önemsiz	26 (8,7)	18 (20,9)	44 (11,4)	
Kariyer yapmış, tecrübeli uzman hekimlerin fazla olması				0,367
Çokönemli + önemli	288 (96,3)	81(94,2)	369 (95,8)	
Orta->önemsiz	11 (3,7)	5 (5,8)	16 (4,2)	
Muayene için sıra beklemenin daha kısa sürmesi				0,345
Çokönemli + önemli	261 (87,3)	71 (82,6)	332 (86,2)	
Orta->önemsiz	38 (12,7)	15 (17,4)	53 (13,8)	
Tetkik sonuçlarının değerlendirilmesi için geçen sürenin daha kısa sürmesi				0,644
Çokönemli + önemli	265 (88,6)	74(86)	339 (88,1)	
Orta->önemsiz	34 (11,4)	12 (14)	46 (11,9)	

TARTIŞMA

Hastaların ve hastanelerin farklı özellikleri hastane seçimlerini etkileyen unsurları içerir, bu da farklı sağlık sorunlarına sahip farklı hastaların yine farklı hastaneleri tercih etmesine yol açar (14,15). Özel hastaneler uzman doktor ve cerrah kadrosu nedeniyle tercih edilirken, bazı hastaneler ise sunduğu fiziksel olanaklara göre seçilir (16,17). Araştırmalar, hastaların hastane tercihlerini demografik, sosyokültürel ve psikolojik faktörlerin etkilediğini göstermiştir (18). Hastane seçimi, hizmet kalitesinin altyapıya dair özelliklerinden (sağlık kurumunun varlığı, ulaşılabilirliği, büyüklüğü ve türü, çalışanların tecrübe ve uzmanlığı, sağlık hizmetinin maliyeti, doktorların sosyodemografik özellikleri), süreçten (kişisel faktörler, hekimin hastaya bilgi verilmesi, tedavinin sürekliliği, muayene ve tetkikler için bekleme süresi ve tedavinin kalitesi) ve sonuçtan etkilenir (19). Hastalar genellikle uzun mesafeler kat etmeyi tercih etmedikleri için evlerine yakın hastaneleri seçebilirler (20), daha iyi hizmet almak veya daha konforlu olmak amacıyla hastane değiştirebilirler (21). Örneğin, yaşlı veya düşük eğitim seviyesine sahip hastalar, yönlendirildikleri polikliniklere ulaşımı kolaylaştıran tabelalara dikkat edilmesini isterken, zamanı kısıtlı olan hastalar randevularda yaşanan gecikmeler hakkında bilgilendirilmek isteyebilirler (22). Yaşlandıkça, bekleme sürelerinin uzunluğu nedeniyle devlet hastaneleri daha az tercih edilir. Ev hanımları, evlerine yakın aile sağlık merkezlerini seçerken, erkek hastalar devlet hastanelerini tercih eder. Ülkemizde kırsal bölgelerde yaşayan hastalar, ulaşım zorlukları nedeniyle üniversite ve özel hastaneler yerine, birinci ve ikinci basamak sağlık kuruluşlarını tercih etmektedir (1).

Dijs-Elsinga ve ark. (23) yaptıkları çalışmada, hastanenin tanınırlığı ve atmosferinin hastaların tercihlerini önemli ölçüde etkilediğini bulmuşlardır. Benzer şekilde, hastanenin temizliği ve hijyeninin yanı sıra tanınırlığının da hastane seçiminde etkili olduğu belirlenmiştir (24). Her ne kadar günümüzde bilgi arayışında ilk akla gelen kaynak internet olsa da araştırmalarda, hastaların hastane seçiminde aile hekimleri ile aile ve arkadaşlarının daha önceki deneyimlerinin hala önemli bir rol oynadığı gösterilmiştir (25). Hastaların genellikle evlerine yakın hastaneleri tercih ettiklerini ve karar verme süreçlerinde hastanelerin reklam ve tanıtım faaliyetlerinin önemli olduğu ortaya konulmuştur (26). Diğer bir araştırmada ise tedavi kalitesi, tavsiyeler, ulaşım kolaylığı, maliyetler, güvenlik ve hastanede sunulan hizmetlerin, hastaların hastane seçimlerinde etkili olduğu sonucuna varılmıştır (27).

Hastane tercihlerine etki eden faktörlere yönelik ulusal literatürde de birçok araştırma bulunmaktadır. Tengilimoğlu (28) yaptığı araştırmada, özellikle özel hastaneler bağlamında, sağlık kuruluşunun yakınlığının hastaların hastane tercihlerinde birinci derecede etkili olduğunu tespit etmiştir. Aynı çalışmada, sağlık kuruluşunda kullanılan teknolojinin seviyesi (modern cihaz ve ekipmana sahip olma) ve sağlık kuruluşunun fiziksel koşulları (bina yapısı, temizliği, asansör ve otopark gibi) hastane tercihinde ikinci en önemli faktör olarak belirtilirken, hastanenin hastalar ve toplum üzerinde bıraktığı imaj üçüncü en önemli etken olarak ortaya konulmuştur. Hastaların bir hastaneyi seçme nedenleri arasında öncelikle doktorlarına duydukları güven, ardından hastanenin randevu sisteminin bulunması

ve son olarak hastaneye sevk edilme ya da başkaları tarafından yönlendirilme ile hastanenin yakınlığının eşit öneme sahip olduğu tespit edilmiştir (29).

Hastaların demografik özellikleri ile hastane seçimleri arasındaki ilişkinin incelendiği çalışmada, yaş, eğitim, gelir ve medeni durumun hastane tercihlerini etkilediği sonucuna varılmıştır (30). Hastanenin temizliği, kayıt işlemlerinin hızlı ve kolay olması, her türlü hizmet ve uzman personelin bulunması, ve hastaların hastalıkları hakkında yeterli bilgilendirilmeleri, hastane seçiminde etkili olan başlıca faktörler olarak belirlenmiştir (31).

Türkiye örnekleminde hastaların hastane seçimlerinde hangi faktörleri dikkate aldıklarını incelemek amacıyla 1996-2017 yıllarını kapsayan 102 çalışma üzerinden bir sistematik derleme gerçekleştirilmiştir (32). Bu derlemede, hastane tercihinde etkili olan toplamda 46 farklı neden tespit edilmiştir. Bu nedenler arasında hastalar için en önemli beş faktör sırasıyla; mesafe, yakın çevre tavsiyesi, fiyat, alternatifsizlik/mecburiyet ve sahip olunan sağlık güvence türü olarak belirlenmiştir. En az etkili olan unsurlar ise, sağlık personelinin cinsiyeti ve bireylerin başvuracakları hastane hakkında bizzat yaptıkları araştırma ve incelemeler olarak saptanmıştır.

Boscarino ve Steiber tarafından gerçekleştirilen araştırmada, bireylerin hastane tercihinde etkili olan ilk üç unsurun sırasıyla mesafe (eve yakınlık/ulaşım kolaylığı) olduğu, hekim tavsiyesi ve hastanede uzman hekimin varlığı olduğu bildirilmiştir (33). Bu çalışmamızda, Boscarino ve Steiber'in bulgularında 3. sırada yer alan hastanede uzman hekim varlığının "spesifik bir uzmanlık alanı olan ve akademik unvana sahip hekimlerin mevcudiyeti" şeklinde ilk sırada yer aldığı sonucuna varılmıştır. Fakat çalışmamızda mesafe faktörü araştırılmamıştır. Hastane tercihinde tavsiyenin etkisi diğer hekimler- sağlık personeli ve diğerleri (arkadaş, akraba ve yakın çevre gibi) biçiminde iki ayrı kategoride belirlenmiş ve %53 oranında tavsiyeye rastlanmazken %22 hekim-sağlık personeli %24 oranında ise diğerlerinin tavsiyesinin olduğu bulunmuştur.

Malik ve Sharma (34) tarafından yapılan bir araştırmada, hastaların hastane seçimi sırasında en çok önem verdikleri üç faktörün sırasıyla; sağlık personelinin mesleki yetkinliği, hastanenin klinik etkililiği ve hastaların kişisel tercihleri olduğu belirlenmiştir. . Bizim çalışmamızda ise profesyonel anlamda tanınmış ve işinin ehli hekimlerin mevcudiyeti faktörünün en önemli faktör olduğu ortaya çıkmıştır.

Bir başka araştırmada, hastaların hastane seçimini etkileyen faktörler incelenmiş ve hem kamu hem de özel hastanelerde, hizmet sunucusuna ait özelliklerin (doktorun deneyimi, uzmanlığı ve ilgisi) kurumsal özelliklerden daha etkili olduğu sonucuna varılmıştır (35). Bu bulgu, doktorlar ve genel olarak tüm sağlık personelinin hem tıbbi hem de hasta ilişkileri açısından iyi bir eğitim almasının hasta memnuniyeti üzerinde olumlu etkiler yaratacağını göstermektedir.

Hasta memnuniyetini etkileyen başlıca faktörlerden biri sağlık kuruluşlarında yaşanan bekleme süresidir. Araştırmalar, uzun bekleme sürelerinin hasta memnuniyeti üzerinde olumsuz bir etkiye sahip olduğunu sürekli olarak göstermiştir. Journal of Management Information and Decision Sciences'da yayınlanan bir çalışmada, acil servislerde uzun bekleme sürelerinin sadece hasta memnuniyetini azaltmakla kalmayıp aynı zamanda ölüm oranı ve hastaneye tekrar yatış gibi olumsuz sonuç riskini de artırdığı belirtilmektedir (36). Benzer şekilde, Kaliforniya'nın acil servislerindeki bekleme sürelerinin, özellikle daha fakir mahallelerde bulunan hastanelerde kabul edilebilir sınırları aştığı gösterilmiş olup, bu da hasta memnuniyeti üzerindeki olumsuz etkiyi daha da vurgulamaktadır (37).

Ek olarak, *Medicine* dergisinde yayınlanan bir ampirik çalışma, beklenen bekleme süresi ve algılanan bekleme süresi gibi öznel bekleme sürelerinin hasta memnuniyeti üzerinde önemli bir etkiye sahip olduğunu keşfetti. İlginç bir şekilde, çalışma gerçek bekleme süresinin hasta memnuniyeti üzerinde önemli bir doğrudan etkiye sahip olmadığını buldu. Bunun yerine, hastaların bekleme süresine ilişkin öznel algıları aracılığıyla memnuniyeti dolaylı olarak etkiledi (38). Bu, hastaların bekleme süresiyle ilgili beklentilerini ve algılarını yönetmenin gerçek bekleme süresini azaltmak kadar önemli olabileceğini göstermektedir.

Randevu planlama sistemleri, bekleme sürelerine ek olarak hasta memnuniyeti ve hastane seçimi konusunda önemli bir rol oynar. *Journal of Patient Experience* dergisinde yayınlanan bir çalışma, İsrail'in kamu sağlık sistemindeki hastaları inceledi ve planlamanın zamanında yapılması ve belirli bir doktoru seçebilme olanağının hastalar için önemli hususlar olduğunu buldu (39). Çalışma ayrıca, uzun bekleme sürelerinin bazı hastaları randevu almaktan caydırdığını ve bunun yerine özel bakım veya acil tedavi aramalarına yol açtığını belirtti. Çalışmamızda, hastane tercihini belirleyen faktörler arasında muayene ve test için bekleme süresinin, kariyer uzmanı bir hekimin varlığından sonra ikinci sırada yer aldığı bulundu.

Gelişmiş laboratuvar ve teknik olanakların mevcudiyeti, bir hastane seçerken önemli bir faktördür. Bu olanaklar yalnızca klinik sonuçları ve hasta güvenliğini iyileştirmekle kalmaz, aynı zamanda genel hasta deneyimini de geliştirir. Son teknolojiye yatırım yapan ve kanıta dayalı tasarım ilkelerini izleyen hastanelerin hastaları çekme olasılığı daha yüksektir, çünkü bu özellikler hasta algıları ve memnuniyeti üzerinde önemli bir etkiye sahiptir (40,41).

Kronik hastalığı olan hastaların hastane bakımı için tercihi, sağlık hizmetlerinin erişilebilirliği, maliyeti ve algılanan bakım kalitesi gibi çeşitli faktörlerden etkilenir. Araştırmalar, birden fazla kronik rahatsızlığı olan hastaların, cepten yapılan harcamaların artmasına ve evden daha uzun mesafelere rağmen, kapsamlı hizmetleri nedeniyle genellikle üçüncül hastaneleri tercih ettiklerini vurgulamaktadır (42). Buna karşılık, hasta deneyimi ve memnu-

niyeti kronik hastalıklardan olumsuz etkilenebilir, çünkü bunlar genellikle daha karmaşık bakım koordinasyonu ve yeterince ele alınamayabilecek duygusal destek ihtiyaçlarını içerir (43). Kronik hastalığı olan yaşlı hastalar prognozlarını tartışırken sözlü iletişimi ve yazılı özetleri tercih ederler ve bakımlarıyla ilgili ortak karar alma süreçlerine katılmaya isteklidirler (44). Araştırmamızda kronik hastalıkları olan ve olmayan çocukları olan annelerin hastane tercihinde önemli faktörleri puanlaması açısından bir fark görülmemiştir. Mevcut durumda yaşanılan yerde tek 3. Basamak sağlık kuruluşu üniversite hastanesidir ve annelerin başka bir seçeneği de bulunmadığından bu sonuçların alınması muhtemeldir.

Ek olarak, anne yaşı hastane uygulamalarının nasıl algılandığını ve alındığını önemli ölçüde etkiler. Genç anneler, yaşlı annelere kıyasla farklı zorluklarla karşılaşabilir ve farklı beklentilere sahip olabilir. Örneğin, genç anneler, özellikle emzirme ve doğum sonrası bakım gibi alanlarda daha kişiselleştirilmiş bakım ve destek sunan hastanelere değer verebilir (45). Buna karşılık, yaşlı anneler, olası doğum komplikasyonlarını ele almak için gelişmiş sağlık tesisleri ve deneyimli personel ile donatılmış hastaneleri tercih edebilir (46).

Genel hastane deneyimi söz konusu olduğunda, hastane seçiminde tedavi kalitesi, temizlik ve hastane itibarı gibi faktörler çok önemlidir (46,47). Bu faktörler, çeşitli yaşlardaki anneler tarafından farklı şekilde görülebilir. Daha fazla deneyime veya daha yüksek beklentilere sahip olabilecek yaşlı anneler, mükemmel tıbbi bakım ve olanaklarıyla bilinen hastanelere öncelik verebilir. Tersine, genç anneler daha çok destekleyici hizmetlerin mevcudiyetine ve besleyici bir ortama odaklanabilir.

Araştırmamızda ise genç annelerin hastane tercihinde hasta başına ayrılan muayene süresi ve kurumda ileri testlerin uygulanmasını daha önemli buldukları ortaya konmuştur. Ebeveynler sağlık kurumuna başvurmadan önce internetten semptom ve bulguları sorgulayıp bir önbilgi edinmekte ve başvurmaktadır (48). İleri testlerin nerelerde yapıldığı da araştırılmaktadır. Gençlerin internet kullanımı yaşlılara göre daha fazladır. Daha yaşlı anneler ise daha önceki tecrübelerine dayanarak hastane tercihini yapabilmektedir. Hasta başına ayrılabilecek sürenin ne kadar olduğu bilindiğinden bu unsur çok dikkate alınamayabilir.

Her çalışmada olduğu gibi elbette bu çalışma da birtakım sınırlılıklara sahiptir. Dolayısıyla bu çalışmanın en önemli sınırlılığını; nispeten küçük bir il merkezinde, yalnızca bir adet 3. Basamak sağlık kuruluşunda ve annelere uygulanan anket ile gerçekleştirilmiş olmasıdır. Ataerkil bir toplumda babanın da tercihleri çok önemli olacaktır. Ayrıca araştırmacıların belirlediği tercih nedenlerinin sayısının da düşük olması ise bir diğer sınırlılığı teşkil etmektedir ve bir ön çalışma olarak görülmeli ve daha kapsayıcı sorular ve daha fazla katılımcı ile veriler desteklenmelidir.

SONUÇ

Gaziosmanpaşa Üniversitesi Sağlık Uygulama ve Araştırma Merkezi'nde yapılan bu çalışma, hastaların üniversite hastanesi seçimini etkileyen çok yönlü faktörlerin kapsamlı bir analizini sunmaktadır. Deneyimli doktorların varlığı, erişim kolaylığı, gelişmiş tesislerin mevcudiyeti ve hizmet kalitesi gibi kilit belirleyiciler önemli faktörler olarak ortaya çıkarken, ikamet yerinin ve kronik hastalığın varlığının daha az etkili olduğu bulundu. Bu araştırma yoluyla toplanan içgörüler, demografik ve sosyoekonomik faktörlerin yanı sıra kişisel tercihlerin hastane seçimini şekillendirmedeki önemli rolünü vurgulamaktadır. Bu bulgular, sağlık hizmeti sağlayıcılarının hizmetleri geliştirirken veya yeni tesisler kurarken hasta merkezli iyileştirmelere öncelik vermeleri, beklentileri yönetmeleri ve coğrafi ve finansal yönleri stratejik olarak dikkate almaları gerekliliğini vurgulamaktadır. Bu öncü araştırma, sağlık hizmetlerini hasta tercihleriyle daha iyi uyumlu hale getirmeyi ve genel hasta memnuniyetini artırmayı amaçlayan sağlık hizmetlerini iyileştirme stratejileri için değerli rehberlik sunmaktadır.

ETİK BEYANLAR

Etik Kurul Onayı: Araştırma Helsinki Bildirgesi'ne uygun şekilde hareket ederek ve İyi Klinik Uygulamalarına ilişkin ulusal ve uluslararası standartları takip edilerek yürütülmüş, kişi mahremiyetine özen gösterilmiştir.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Effect of Fluid Biochemistry on Bleomycin Pleuredesia in Non-mesothelioma Malign Pleural Effusions

Mezotelyoma Dışı Malign Plevral Efüzyonlarda Sıvı Biyokimyasının Bleomisin Plöredezisine Etkisi

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ABSTRACT

Aim: Malignant pleural effusions (MPE) often signal terminal-stage malignancy, with limited survival and quality of life prospects. This study aimed to evaluate whether fluid biochemistry influences recurrence after bleomycin pleurodesis in patients diagnosed with MPE through VATS pleural biopsy and fluid cytology.

Material and Method: A total of 23 patients diagnosed with MPE due to primary lung carcinoma or pleural metastasis, and treated with bleomycin pleurodesis at our institution, were included. All diagnoses were confirmed via VATS pleural biopsy.

Results: The mean age of patients with recurrence was 52.5 years. Their mean pleural fluid values were: LDH 569.75 U/L, pH 7.5, protein 4.53 g/dL, glucose 81 mg/dL, and albumin 3.13 g/dL. The average drainage time was 10.5 days. Recurrence occurred in 20% of men and 12.5% of women, with a 20% recurrence rate on the right side and 12.5% on the left. Recurrence in pulmonary adenocarcinoma patients was 33.3%, while the overall recurrence after bleomycin pleurodesis was 17.4%. General anesthesia had a higher recurrence rate (25%) compared to local anesthesia (9.1%).

Conclusion: Recurrent pleural effusion in MPE presents a clinical challenge. VATS is a crucial tool in diagnosing and managing MPE. Bleomycin is readily available for pleurodesis in our country, but the treatment should be personalized to balance quality of life and hospitalization time. International guidelines offer valuable insights but need to be adapted to individual cases.

Keywords: Malignant pleural effusions, video-assisted thoracoscopic surgery, quality of life, adenocarcinoma, pleurodesis

ÖZ

Amaç: Malign plevral efüzyonlar (MPE), genellikle terminal evredeki kontrolsüz malign hastalığı işaret eder ve bu hastalarda yaşam süresi ve yaşam kalitesi genellikle sınırlıdır. Bu çalışmada, VATS plevra biyopsisi ve sıvı sitolojisi ile MPE tanısı konmuş hastalarda, bleomisin plöredezisi sonrası sıvı biyokimyasının rekürrens gelişimini etkileyip etkilemediğini araştırmayı amaçladık.

Gereç ve Yöntem: Kurumumuzda VATS plevra biyopsisi ile MPE tanısı konan ve bleomisin ile plöredezi uygulanan 23 hasta çalışmaya dahil edildi. Primer akciğer karsinomu ve plevral metastaza bağlı MPE tanısı almış ve bleomisin ile plöredezi yapılmış hastalar çalışmaya alındı.

Bulgular: Rekürrens görülen hastaların ortalama yaşı 52,5 idi. Ortalama plevra sıvısı değerleri: LDH 569,75 U/L, pH 7,5, protein 4,53 g/dL, glukoz 81 mg/dL ve albümin 3,13 g/dL olarak saptandı. Ortalama drenaj süresi 10,5 gündü. Erkeklerde rekürrens oranı %20, kadınlarda %12,5 idi. Sağ tarafta rekürrens oranı %20, sol tarafta %12,5 olarak bulundu. Pulmoner adenokarsinom tanısı alanlarda rekürrens oranı %33,3 iken, bleomisin ile plöredezi sonrası genel rekürrens oranı %17,4 idi. Genel anestezi uygulananlarda rekürrens oranı %25, lokal anestezi uygulananlarda ise %9,1 olarak tespit edildi.

Sonuç: MPE'da rekürren plevral efüzyon tanı ve uzun dönem yönetimi açısından zorluklar oluşturur. VATS, malign efüzyonların tanı ve tedavisinde önemli bir rol oynar. Bleomisin, malign efüzyonlarda ülkemizde kolay erişilebilir bir ajandır. Klinik yaklaşım, yaşam kalitesi ve hastanede geçirilen süre dikkate alınarak bireyselleştirilmelidir. Uluslararası kılavuzlar klinik karar vermede önemli rol oynasa da, takip ve tedavi bireysel hasta özelliklerine göre belirlenmelidir.

Anahtar Kelimeler: Malign plevral efüzyonlar, video yardımlı torakoskopik cerrahi, yaşam kalitesi, adenokarsinom, plöredez

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INTRODUCTION

Malignant pleural effusions (MPE) are often indicative of uncontrolled terminal-stage malignant disease. Therefore, survival and quality of life after them are not promising. One of the most common causes of exudative effusions encountered in the clinic is malignant pleural effusions. The presence of malignant pleural effusion indicates advanced-stage disease. The mean survival after diagnosing malignant pleural effusion is 3–12 months. However, survival varies depending on the organ of origin of the primary tumour, histological type and the stage of the disease. Lung cancer has the shortest survival, while ovarian cancer has the longest survival (1).

The most common findings in patients with malignant pleural effusion are shortness of breath and cough. These occur in more than 50% of patients. The severity of dyspnea depends on the amount of effusion. Since pleural metastasis is often an indicator of advanced disease, patients may experience fatigue, loss of appetite, and significant weight loss. Chest pain may occur due to metastatic parietal pleura, ribs, or chest wall involvement. Approximately 25% of patients are asymptomatic. In physical examinations, decreased breath sounds due to pleural effusion are frequently observed (2).

Chest X-ray indicates the amount and location of pleural fluid and can be between 500 and 4000 millilitres of liquid. While the fluid is below 500 ml in 10% of the cases, there is massive pleural effusion in the other 10% (3). Thorax computed tomography (CT) is required in malignant pleural effusions. Computed tomography provides information about whether the MPE is loculated, the status of the primary disease, and the anatomy of other organs within the thorax. Pleural thickening, atelectasis in the parenchyma, solitary or multiple nodules, hilar or mediastinal lymphadenopathy, lymphangiitis carcinomatosis, lytic or sclerotic lesions on the ribs, and pericardial effusion can be observed (4). Positron emission tomography (PET–CT) is frequently used to detect metastatic findings in other organs (5).

Malignant pleural effusions are almost always exudate. There is usually lymphocyte predominance. Protein concentration is around 4 g/dl and can vary between 1.5 and 8.0 g/dl. Malignant effusions can be serous, serosanginous or hemorrhagic. The average erythrocyte count is around 40.000/mm3. An excessively hemorrhagic (>100.000 mm3) effusion should be interpreted in favour of malignancy (6).

Malignant pleural effusions are an indicator of poor prognosis and are the second most common cause of exudative pleural fluid encountered in clinical practice. The aim of MPE management is palliation and relieving symptoms. The treatment approach should remain minimally invasive and avoid repetitive procedures as much as possible. In case of recurrent fluids, repeated thoracentesis, pleurodesis with tube thoracostomy, pleurodesis with a permanent tunnelled catheter, thoracoscopy and video-assisted thoracoscopic surgery (VATS) may be preferred depending on the clinic. In MPE, the recommended method is to choose talc as a sclerosing agent and apply it with VATS (7). Within the scope of this research, we aimed to elucidate whether fluid biochemistry affected the development of recurrence after bleomycin pleurodesis in patients diagnosed with MPE by VATS pleural biopsy and fluid cytology.

MATERIAL AND METHOD

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was granted from our institution on 04/06/2024 with protocol number 2024–312, and informed consent was obtained from all participants.

A total of 23 patients who were diagnosed with MPE as a result of VATS pleural biopsy in our institution between January 2018 and June 2023 and underwent pleurodesis with bleomycin were enrolled in the study. Among 200 patients whose pleural effusion was determined to be exudate by thoracentesis and who underwent VATS biopsy between these dates, 23 patients who were diagnosed with MPE due to primary lung carcinoma and pleural metastasis and developed pleurodesis with Bleomycin were included in the study (**Figure 1, Figure 2**). Recurrence was defined as the detection of pleural effusion on the chest X-ray taken during the first-month outpatient follow-up after the chest tube was removed in patients who underwent pleurodesis with bleomycin, specifically if the effusion was detected on the same side (**Figure 3**).

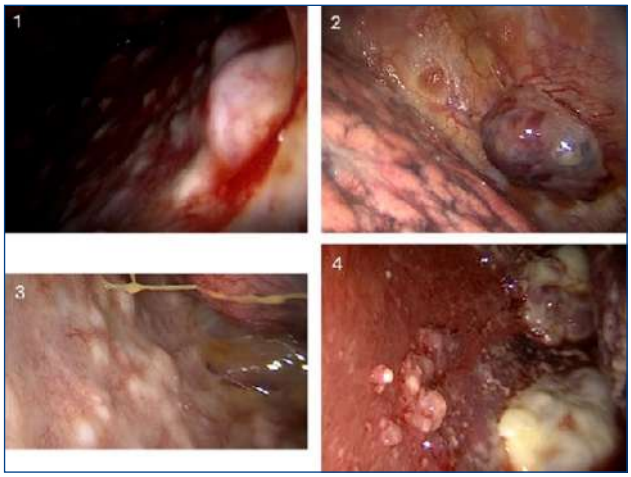

Figure 1: (1) Adenocarcinoma in the parietal plavra , (2) Adenocarcinoma nodüle in the parietal pleura, (3) Adenocarcinoma in the parietal pleura, (4) Adenocarcinoma sarcomatoid type in te parietal pleura

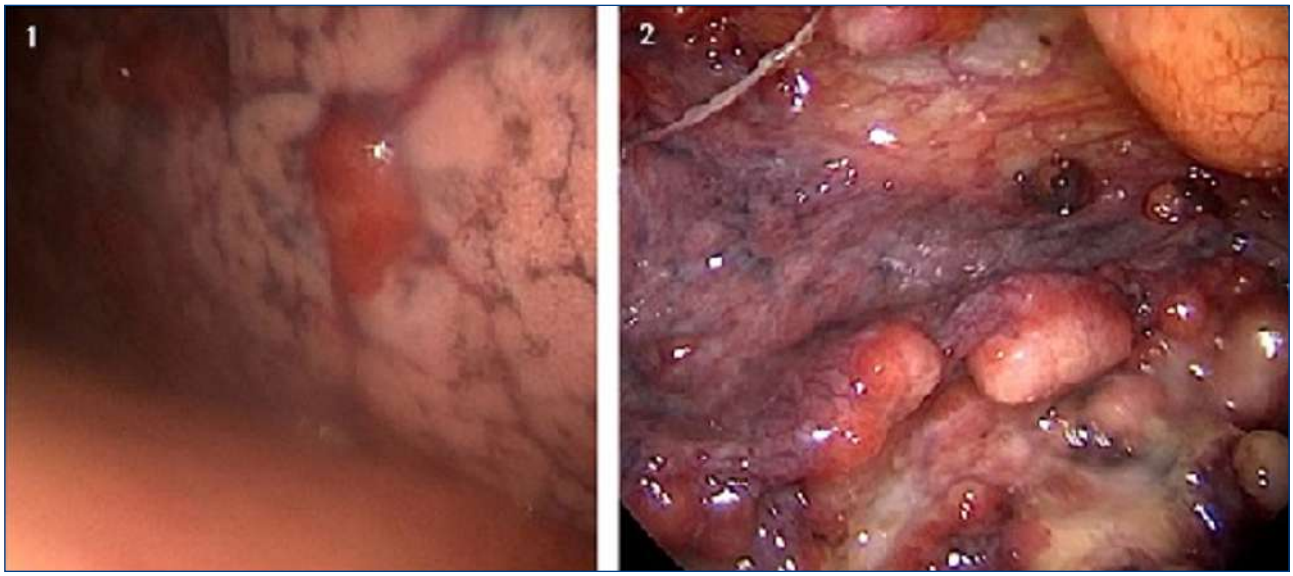

Figure 2: (1) Renal cell carcinoma of the visceral pleura, (2) Renal cell carcinoma metastasis in the parietal pleura

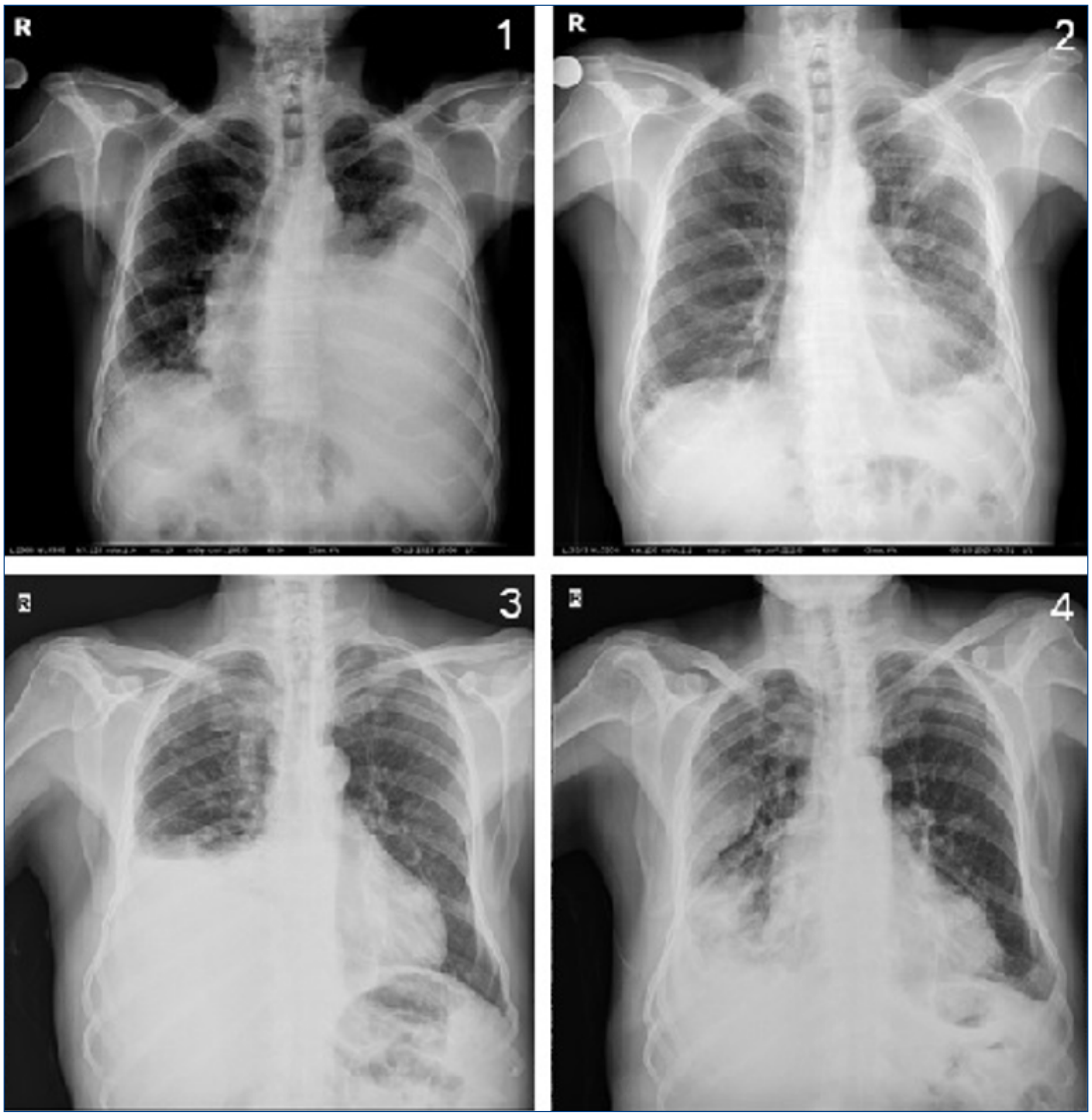

Figure 3: (1) The pre-operative X-ray of a 74-year-old male adenocarcinoma patient, (2) The post-operative X-ray of a 74-year-old male adenocarcinoma patient, (3) The pre-operative X-ray of a 75-year-old male renal cell carcinoma, (4) The post-operative X-ray of a 75-year-old male renal cell carcinoma patient,

Mesotheliomas and benign effusions were excluded from the study. All patients had unilateral fluid. All patients underwent thoracentesis before the operation. VATS pleura biopsy pathologies, fluid cytology, biochemistry results of fluids, and patient information were examined retrospectively.

Statistical Analysis

Patient data collected within the scope of the study were analysed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 29.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T-test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. Binary Logistic Regression Analysis (BLRA) examined independent risk factors. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Risk factors affecting recurrence were examined with Binary Logistic Regression Analysis. When the model was examined univariately, variables such as age, thoracentesis (T)-LDH, T-Ph, T-Protein, T-Glucose, T-Albumin, and number of days of follow-up with drains, gender, localisation, and type of anaesthesia were not found as statistical risk factors on recurrence (p>0.050).

The mean age of those with recurrence was 52.5, the mean T-LDH value was 569.75 U/L, the mean T-PH value was 7.5, the mean T-protein value was 4.53 g/dL, the mean T-glucose value was 81 mg/dL, the mean T-albumin value was 3.13 g/dL, and the mean number of days we monitored with drains was found to be 10.5 (**Table 1**).

Table 1. Investigation of risk factors affecting recurrence by Binary Logistic Regression Analysis

	Recurrent effusion		Univariate	
	No	Yes	OR (95% CI)	p-value
Age	62.68±12.72	52.5±6.25	0.897 (0.767-1.048)	0.172
T-LDH	879.11±919.78	569.75±137.11	0.999 (0.997-1.001)	0.514
T-PH	8±0.29	7.5±0.5	0.015 (0-3.46)	0.130
T-Protein	4.31±0.93	4.53±0.6	1.33 (0.384-4.613)	0.653
T-Glucose	111.59±95.73	81±12.99	0.995 (0.978-1.011)	0.519
T-Albumin	2.71±0.82	3.13±0.32	2.055 (0.402-10.511)	0.387
Drain day	9.26±6.16	10.5±4.36	1.035 (0.87-1.232)	0.695
Gender				
Male	12 (80)	3 (20)	1.75 (0.151-20.231)	0.654
Female	7 (87.5)	1 (12.5)	Reference	
Localization				
Right	12 (80)	3 (20)	1.75 (0.151-20.231)	0.654
Left	7 (87.5)	1 (12.5)	Reference	
Primary diagnosis				
Pulmonary adenocarcinoma	6 (66.7)	3 (33.3)	---	---
Squamous cell lung cancer	1 (100)	0 (0)	---	---
Small cell lung cancer	1 (100)	0 (0)	---	---
Breast cancer	2 (100)	0 (0)	---	---
Renal cell carcinoma	1 (100)	0 (0)	---	---
Tubal serous carcinoma	0 (0)	1 (100)	---	---
None	8 (100)	0 (0)	---	---
Adenocarcinoma	0 (0)	1 (100)	---	---
Pre-operative diagnosis				
Adenocarcinoma	6 (75)	2 (25)	---	---
Small cell lung cancer	1 (100)	0 (0)	---	---
Malignity	1 (100)	0 (0)	---	---
Breast cancer	2 (100)	0 (0)	---	---
Renal cell carcinoma	1 (100)	0 (0)	---	---
Squamos cell lung cancer	1 (100)	0 (0)	---	---
Tubal serous carcinoma				
None				
Post-operative diagnosis				
Adenocarcinoma	0 (0)	1 (100)	---	---
Adenocarcinoma metastasis	1 (100)	0 (0)	---	---
Pulmonary adenocarcinoma	6 (75)	2 (25)	---	---
Pulmonary adenocarcinoma infiltration	4 (80)	1 (20)	---	---
Squamos cell lung cancer	1 (100)	0 (0)	---	---
Small cell lung cancer	4 (100)	0 (0)	---	---
Breast cancer metastasis	1 (100)	0 (0)	---	---
Metastasis	1 (100)	0 (0)	---	---
Renal cell carcinoma metastasis	1 (100)	0 (0)	---	---
Pleurodesis				
Bleomycine	19 (82.6)	4 (17.4)	---	---
Anesthesia				
General anesthesia	9 (75)	3 (25)	3.333 (0.292-38.082)	0.333
Local anesthesia	10 (90.9)	1 (9.1)	Reference	

The recurrence rate in men was 20% and 12.5% in women. While the recurrence rate was 20% on the right side and 12.5% on the left. The recurrence rate in patients whose primary diagnosis was pulmonary adenocarcinoma in 33.3% of the cases. The recurrence rate in patients who underwent pleurodesis with bleomycin was 17.4%. The recurrence rate was 25% in those with general anesthesia (GA) as the type of anesthesia applied. This rate was 9.1% in those with local anesthesia (LA) (**Table 1**).

DISCUSSION

Medical thoracoscopy and video-assisted thoracoscopic surgery enabled a large pleural surface area to be evaluated and large tissue samples to be taken. In addition to having high diagnostic value, they provide the opportunity to perform diagnosis, drainage and pleurodesis in a single procedure. Diagnostic success in malignant pleural effusions with thoracoscopy is over 90%, sensitivity is 100%, and operative mortality is below 0.5% (8). VATS has increasingly replaced thoracotomy. The effectiveness of VATS in the diagnosis and management of malignant pleural effusions has been emphasized once again in this study. The minimally invasive nature of VATS, along with its advantages of shortening hospital stay and reducing postoperative pain, contributes to improving quality of life in the treatment of malignant pleural effusions.

VATS biopsy and pleurodesis are typically performed under general anesthesia using double-lumen intubation. However, these procedures can also be carried out with single-lumen intubation or under sedation with local anesthesia, depending on the patient's condition and the surgeon's preference (9). In the study, we made the procedure more feasible for patients by applying local anesthesia to those who were not suitable for general anesthesia. As a result, the recurrence rate of 25% in patients who received general anesthesia suggests that local anesthesia should be preferred as a less invasive option in the treatment of MPE. According to the results of our study, we found that local anesthesia can increase the success of pleurodesis with a lower risk of complications. Therefore, this information will be important in clinical practice.

In the multicenter Cancer and Leukemia Group B (CALGB) study, VATS was 82% successful after 30 days of follow-up in patients with over 90% lung expansion, while the success rate of talc administered as a slurry via tube remained at 67%. In addition to providing tissue diagnosis, VATS increases success in sclerosis by removing adhesions and loculations and visualising the pleural surfaces (10). On the other hand, in the study of Yim et al. (11), no significant difference was found between the two techniques. Publications stating that the patient's manoeuvres/rotations (lateral decubitus, prone, supine and reverse lateral decubitus positions) to ensure a uniform distribution after talc is given in the form of slurry do not change the result and are not recommended (12).

Surgical options such as video-assisted thoracoscopic partial pleurectomy were compared to 'physician-performed' talc pleurodesis in the MesoVATS study (n=175 mesothelioma patients). VATS was associated with longer hospital stays, was more expensive and associated with more complications without any difference in fluid control or quality of life. There is insufficient evidence as to whether surgical pleurodesis or decortication is better than talc slurry pleurodesis, and it suggests that, in selected patients considered fit enough for both modalities and where accessibility is not a barrier, both techniques should be discussed to individualize treatment choice (13).

Although the exact mechanism of action is unknown, chemical pleurodesis is understood to generate an inflammatory reaction leading to fibrosis and symphysis between the parietal and visceral pleural layers. Elayouty et al. (14) mentioned in their comparative study that bleomycin resulted in effective pleurodesis in (89%). Mesothelial cells are the main structural axis of pleurodesis. Another important factor involved in angiogenesis is VEGF. This inflammatory mediator is secreted by a wide range of cells in the pleural cavity, including mesothelium, inflammatory and cancer cells (15). Vascular endothelial growth factor is released during inflammatory pleural processes. Higher VEGF concentrations have been observed in complicated pleural effusions and pleural empyema. Pleural thickening, low pH and glucose levels correlate with VEGF secretion into the pleural cavity (18). There is no data on pH's influence on VEGF production (16). In our study, the recurrence rate in patients who underwent pleurodesis with bleomycin was found to be 17.4%, which is consistent with the rates reported in the literature and supports the efficacy of this agent.

Factors associated with decreased survival in patients newly diagnosed with MPE include low pleural fluid (PF) pH, low pleural fluid glucose, high pleural fluid neutrophil count, elevated lactate dehydrogenase (LDH), a high serum neutrophil-to-lymphocyte ratio, primary malignant cell type, and poor performance scores (therefore indicating worse functional status) (17,18). Prognostic scores based on readily available clinical testing can help guide clinical decisions in the treatment of MPE. Both the LENT (lactate dehydrogenase, ECOG, neutrophil-to-lymphocyte ratio, and tumour type) and PROMISE scoring systems have been validated as risk stratification scores to predict survival and help guide clinicians in the care of patients diagnosed with MPE (19,20).

As reported previously, MPE with neutrophilic inflammation (elevated neutrophil percent of cell count, LDH, and total protein) found within the pleural space may be associated with decreased survival after index thoracentesis. In contrast, PF lymphocytosis is associated with improved survival (21). Neither neutrophil nor lymphocyte counts remained significantly associated with survival in multivariate regression modelling. These findings are consistent with studies evaluating the serum neutrophil to lymphocyte ratio, in which patients with MPE and a higher neutrophilic ratio had decreased survival (22). Conversely, improvement in survival reported in MPE patients with high PF lymphocyte count is thought to be the exact mechanism behind the improvement in survival in patients with elevated tumour-infiltrating lymphocytes (23). In our study, age, thoracentesis (T)-LDH, T-Ph, T-Protein, T-Glucose, T-Albumin, and number of days of follow-up with drains, gender, localisation, and type of anaesthesia were not found as statistical risk factors on recurrence.

One of the limitations of this study is the relatively small sample size. Additionally, the lack of long-term outcome evaluation has resulted in a gap in data regarding the quality of life of patients following pleurodesis. In future studies, larger sample sizes and long-term outcome assessments will contribute to determining the best approach for the treatment of malignant pleural effusion.

In conclusion, VATS and bleomycin pleurodesis are proven, reliable, and accessible methods in the treatment of malignant pleural effusion. However, treatment should be tailored to each patient, taking into account factors such as quality of life and length of hospital stay. Our study emphasizes the need for patient-specific decisions in determining the methods to be used in MPE treatment.

CONCLUSION

This study highlights the effectiveness of VATS and bleomycin pleurodesis in the management of malignant pleural effusion (MPE). Our findings demonstrate that these methods are reliable, with low recurrence rates, especially when local anesthesia is used as a less invasive alternative for patients unsuitable for general anesthesia. The results also suggest that tailoring treatment plans to individual patient needs, with a focus on improving quality of life and reducing hospital stay, is essential. Future studies with larger sample sizes and long-term follow-up are necessary to further refine treatment strategies and optimize outcomes in MPE management.

Abbreviations

BLRA: Binary Logistic Regression Analysis, **CALGB**: Cancer and Leukemia Group B Study, **CT**: computed tomography, **GA**: general anaesthesia, **LA**: local anesthesia, **LDH**: lactate dehydrogenase, MPE: malignant pleural effusions, SCLC: small cell lung cancer, **PET–CT**: positron emission tomography, **PF**: pleural fluid, **RCC**: renal cell carcinoma, **SPSS**: Statistical Package for the Social Sciences, **VATS**: video-assisted thoracoscopic surgery

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval for the study was obtained from Selçuk University Local Ethics Committee (Date: 04/06/2024 Decision No: 2024-312).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

AI Statement: The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work. Still, they did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Role of Procalcitonin in Differentiating Between Gram-Negative and Gram-Positive Sepsis

Gram-Negatif Sepsis ve Gram-Pozitif Sepsis Ayrımında Prokalsitoninin Rolü

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ABSTRACT

Aim: Detecting the agent group in sepsis patients with culture positivity is crucial in determining our treatment scheme. We aimed to evaluate the diagnostic accuracy of procalcitonin (PCT) levels in distinguishing between different pathogen groups in sepsis patients with proven bacteremia.

Material and Method: Records of patients hospitalized in ICU were retrospectively investigated over 28 months were retrospectively investigated confirmed microbiologically to have a positive blood culture result. The patients were evaluated in two groups regarding gram-negative (GN) and gram-positive bacteria based on the findings of blood culture and Gram staining. Age, gender, APACHE II score, hospital stay, mortality, and laboratory parameters were compared in both groups. Of 894 patients followed up in ICU during 28 months, 56 sepsis patients confirmed microbiologically to have blood culture positivity were included.

Results: While GN bacteria grew in the blood cultures of 26 (46.4%) patients, 30 (53.6%) patients were found to have GP bacteria. The level of PCT was significantly higher in the GN group, compared to that of the GP group (p=0.003). There were no significant differences in CRP values and APACHE II scores between the GN and GP groups (p=0.147 and p=0.633, respectively). Additionally, no statistically significant difference was determined between the GN and GP groups regarding the mortality rate (p=0.712). Leukocyte, neutrophil, lymphocyte, platelet, and albumin values of both groups were also similar.

Conclusion: PCT was found to be a useful marker in predicting the pathogen groups in early treatment management of patients diagnosed with sepsis.

Keywords: C-reactive protein, Gram-positive bacteria, Gram-negative bacteria, procalcitonin, sepsis

ÖZ

Amaç: Sepsis, yoğun bakım ünitelerindeki hastalarda morbidite ve mortalitenin en önemli nedenlerindendir. Kültür pozitifliği saptanan sepsis hastalarında etken grubunu belirlemek tedavi şemamızı belirlemede önemlidir. Çalışmamızda bakteriyemi kanıtlanmış sepsis tanısı alan hastalarda prokalsitonin (PCT) seviyesinin farklı patojen gruplarını ayırmada tanısal doğruluğunun değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Yoğun bakım ünitesinde (YBÜ) yatan hastaların kayıtları 28 aylık süreçte retrospektif olarak incelendi. Sepsis tanısı alan, mikrobiyolojik olarak (pozitif kan kültürü sonuçları) doğrulanan tüm hastalar dahil edildi. Hastalar kan kültürü ve Gram boyama sonuçlarına göre Gram negatif (GN) grup ve Gram pozitif (GP) grup olmak üzere iki grupta değerlendirildi. Bu iki grupta yaş, cinsiyet, APACHE II skoru, hastanede kalış süresi, mortalite ve laboratuvar parametleri karşılaştırıldı.

Bulgular: Hastaların 26 (%46,4)'sının kan kültüründe GN, 30 (%53,6) unun kan kültüründe GP bakteri saptandı. PCT düzeyi GN grubunda GP grubuna göre anlamlı derecede yüksekti (p=0,003). GN ve GP grupları arasında CRP değerleri ve APACHE II skorları açısından anlamlı fark yoktu (sırasıyla p=0,147 ve p=0,633). Ayrıca GN ve GP grupları arasında mortalite açısından istatistiksel olarak anlamlı fark saptanmadı (p=0,712). Her iki grubun lökosit, nötrofil, lenfosit, trombosit ve albümin değerleri de benzerdi.

Sonuç: Sepsis tanısı alan hastalarda erken tedavi yönetiminde, patojen gruplarının tahmin edilebilmesinde prokalsitoninin faydalı bir belirteç olduğu saptandı.

Anahtar Kelimeler: C-reaktif protein, Gram-pozitif bakteri, Gram-negatif bakteri, prokalsitonin, sepsis

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INTRODUCTION

Sepsis is among the most important causes of morbidity and mortality in patients admitted to intensive care units (ICU). The rates of mortality can be seen at a rate of 30% in sepsis patients and 50% in septic shock patients (1). It is important to choose appropriate antibiotic therapy and predict the causative pathogen in sepsis in terms of survival (2). It is critical to identify the causative pathogen in blood culture; however, bacteremia is confirmed in only 30% of the patients diagnosed with sepsis (3). When evaluated in terms of Gram-negative (GN) and Gram-positive (GP) bacteria, there are significant differences between the types of sepsis. Such differences arise from the wall structure of the cells of microorganisms (4). While procalcitonin (PCT) is detected at normal levels in patient groups with no infection, PCT appears to be quite reliable, compared to most biomarkers in patients with suspected bacterial infection (5). When the clinical status of the patient suggests the suspicion of sepsis, PCT is a rapid and inexpensive biomarker that can provide insight into the causative pathogen group in indicating the presence of bacteremia. PCT is also significantly elevated in patients with GN bacteremia, demonstrating that PCT can be used to distinguish GN sepsis from GP sepsis (6-8). Therefore, in our study, it was aimed to evaluate the diagnostic accuracy of the PCT level in distinguishing between different pathogen groups in patients diagnosed with sepsis with proven bacteremia.

MATERIAL AND METHOD

Approval was obtained from the local ethics committee of the Faculty of Medicine at Karatay University (Reg. number: 2024/006 and date: 7th June 2024) for our study. The study was conducted in accordance with the principles stated in the Declaration of Helsinki. The medical records of the patients (>18 years of age) hospitalized in the ICU of Meram State Hospital in Konya for 28 months between January 2022 and May 2024 were retrospectively examined. All patients diagnosed with sepsis whose blood culture results were microbiologically confirmed to be positive were included in the study. Coagulase-negative staphylococci, *Corynebacterium* spp., and other skin flora components were considered contaminants when grown in a single bottle. Skin flora pathogens were considered causative pathogens if they grew in blood cultures taken from two different sites. Depending on the pathogen identified in the blood, bacteremia was classified as GP or GN sourced. PCT is examined on every patient with suspected sepsis in the ICU. Non-infectious causes considered to affect the PCT level, such as trauma, surgery, burns, or advanced renal failure, were ruled out from the study. The patients were evaluated in two groups, the GN and GP groups, based on the findings of blood culture and Gram staining. Age, gender, APACHE II score, hospital stay, mortality, and such laboratory parameters as leukocyte, neutrophil, lymphocyte, platelet, PCT, C-reactive protein (CRP), and albumin were recorded in the two groups. In the patients developing sepsis more than once, the first attack of sepsis was recorded. In each patient, the mortality rates within the first 28 days were also recorded. Blood cultures were analyzed using the BACTEC 9240 fully automatic blood culture device (Becton Dickinson, Diagnostic Device System, Spark, USA). The colonies of isolated bacteria were identified through the VITEK 2 Compact® system (BioMérieux, France).

Statistical analysis

Statistical analyses of the study findings were evaluated with the Statistical Package for the Social Sciences software for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA). While the nominal data were described as ratios and percentages, mean and standard deviation (±, SD) were used to describe continuous numerical data. Additionally, median and interquartile ranges were used to describe non-normally distributed continuous numerical data. The presence of normal distribution was evaluated using statistical tests and graphical methods. While the Pearson chi-square test was used to compare the categorical data, the Mann-Witney U test was utilized to compare non-normally distributed numerical data in pairs, and the student's t-test was used in independent groups to compare normally distributed continuous numerical variables. In evaluating the ability of laboratory tests to predict that the sepsis-causing bacterium is a GN bacterium and to predict death, the receiver-operating characteristic (ROC) analysis was applied. A value of $p < 0.05$ was accepted to be statistically significant.

RESULTS

During the study for 28 months, a total of 894 patients were followed up in the ICU. Among 894 patients followed up in ICU, 63 diagnosed with sepsis and confirmed microbiologically to have blood culture positivity were included in the study. Of 63 patients included, two patients seen multiple microorganisms in their blood culture, two diagnosed with chronic kidney failure (CKD), and three where skin flora was detected in their blood culture were determined and excluded from the study. Therefore, a total of 56 patients were included in the study. Of 56 patients, 48.2% (n=27) and 51.8% (n=29) were female and male, respectively. The age of the patients also ranged between 35-97 years (average age, 75.45±11.7 years). Twenty-six (46.4%) patients were found to have GN bacteria in the blood cultures while 30 (53.6%) had GP bacteria in their blood cultures. The level of PCT was significantly higher in the GN group than that in the GP group (p=0.003). Even so, no significant difference was found between the GP and GN groups in terms of the CRP value (p=0.147). There was also no significant difference between the APACHE II scores of

the GN and GP groups (p=0.633). Given the mortality rate, no statistically significant difference was determined between the GN and GP groups (p=0.712). The values of leukocyte, neutrophil, lymphocyte, platelet, and albumin were similar in both groups (**Table 1**).

Table 1. Data for the groups with gram-positive and gram-negative sepsis

	Gram (-)	Gram (+)	p
	Median (Q1-Q3)	Median (Q1-Q3)	
Gender (M/F), n (%)	11 (42.3)/15 (57.7)	12 (40)/18 (60)	[a]0.186
Age (years), mean±SD	79±13	74.5±22	[c]0.464
Leukocyte $\times 10^9$/L	11920±13383	13593±8440	[c]0.755
Neutrophil $\times 10^9$/L	8630±11798	11300±8475	[c]0.588
Lymphocyte $\times 10^9$/L	850±1150	965±1175	[c]1
Platelet $\times 10^9$/L	186±163	187±123	[c]0.475
Albumin	23.8±5.5	25.35±6.5	[c]0.224
PCT (ng/mL)	4.83±15.76	1.25±2.53	[c]0.031*
CRP (mg/L)	126.5±120.5	158.5±113.9	[b]0.633
Apache II score	28±7	28±9	[b]0.147
Hospital stay (days)	46±76	24±37	[c]0.57
Mortality, n (%)	17 (65.4)	21 (70.0)	[a]0.712

[a]Pearson chi-square test, [b]Student's t-test, [c]Mann-Whitney U test, *p <0.05; p <0.001. Q1: First quartile, 25th percentile, Q3: Third quartile, 75th percentile, CRP: C-reactive protein, F: Female, M: Male, PCT: Prokalsitonin

The sensitivity and specificity values were evaluated for PCT at different cut-off levels in distinguishing the cases with the GN and GP origins. The threshold value for PCT was determined as 2.5, with a sensitivity of 61.5% and a specificity of 76.7%. The area under the ROC curve (AUC) for the PCT value was calculated as 0.66 [95% confidence interval (CI): 0.520-0.816, p<0.001] (**Figure 1**), and the AUC obtained for the PCT value was found to be significant. Even so, the AUC for the CRP value was calculated as 0.629 (95% CI: 0.481-0.776, p=0.099) (**Figure 2**). It was determined that the AUC obtained for the CRP value was not significant.

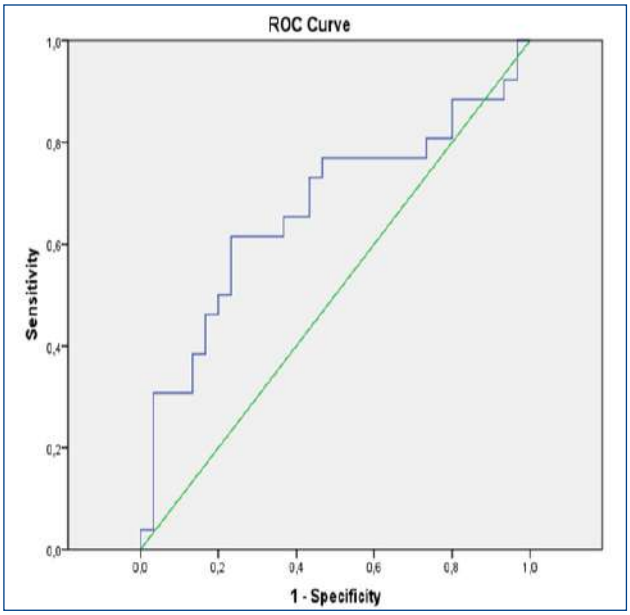

Figure 1. ROC curve for procalcitonin values

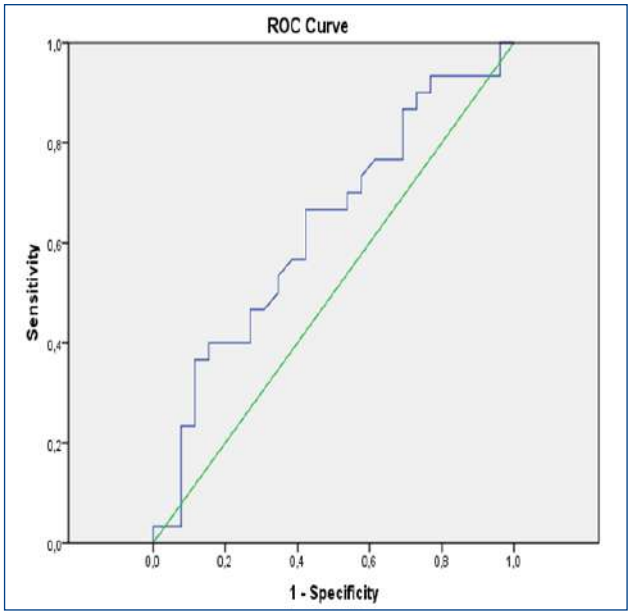

Figure 2. ROC curve for CRP values

DISCUSSION

Early diagnosis is important since sepsis still causes on high morbidity and mortality in ICUs. Among the main pathogens leading to sepsis are bacteria, and there are different mechanisms in the sepsis pathogenesis of GN and GP bacteria. The response given by the host to GN and GP bacteria stems from the structural differences of the pathogens (9). PCT is more significant than other biomarkers of sepsis in predicting whether systemic inflammation is of infectious origin and in evaluating the response to the treatment (10). The inflammatory response has been reported to develop more in the group of patients developing GN sepsis and the issue has been associated with high PCT values (11). In the present study, we evaluated the role of sepsis biomarkers in distinguishing between GN and GP bacterial growths in those diagnosed with sepsis and detected that the PCT value plays a crucial role in differentiating between GN sepsis and GP sepsis.

In our study, the sensitivity and specificity values were calculated at different cut-off levels for PCT in distinguishing between the patients with GN and GP bacterial sepsis. The PCT value was found to be higher in those with GN sepsis [4.8 ng/mL, interquartile range (IQR): 15.76] than in those having GP sepsis (1.25 ng/mL, IQR: 2.53). The threshold value for PCT was determined as 2.5 ng/mL, with a sensitivity of 61.5% and a specificity of 76.7%. The AUC value for PCT was also calculated as 0.66 (95% CI: 0.520-0.816). Positive predictive value (PPV) and negative predictive value (NPV) were found to be 69.5 and 69.70%, respectively.

In the current study where a total of 1.949 samples obtained from those with suspected bloodstream infections were examined, the median PCT values in bacteremia of GN (13.8 ng/mL, IQR: 3.4-44.1) were determined to be higher, compared to the infections GP (2.1 ng/mL, IQR: 0.6-7.6). In the ROC analysis, for a threshold value of 10.8 ng/mL, AUC for PCT in the GN and GP groups was detected to be 0.765 (95% CI: 0.725-0.805) (12).

According to blood culture classifications consisting of a total of 262 cases, the PCT value was found to be higher in the GN sepsis group (26.7 ng/mL, 0.09-188.3) than in the GP bacteria sepsis group (0.84 ng/mL, 0.05-18.79). The threshold value of 3.39 ng/mL for PCT, sensitivity of 80% in identifying GN bacteremia, specificity of 71%, PPV of 35%, NPV of 91%, and 0.73 of AUC were calculated. In 122 cases with blood culture positivity, however, the threshold value of 6.47 ng/mL for PCT, sensitivity of 74% in identifying GN bacteremia, specificity of 81%, NPV of 75%, PPV of 82% and AUC of 0.81 were calculated (13).

In 124 sepsis cases, the threshold value for PCT in differentiating between the cases caused by GN and GP bacteria was determined as 1.3, with a sensitivity and specificity of 70.83% and 84.21%, respectively. The AUC for the PCT value was calculated as 0.80 (95% CI: 0.722-0.887) (14).

In another study including 501 cases and carried out in our country, in which the GN and GP bacteria groups were distinguished, the sensitivity and specificity were calculated at different threshold values for PCT and CRP. In the study, while the optimal threshold value for PCT was found as 1.45 ng/mL, sensitivity as 75%, and specificity as 53%, the AUC was also determined as 0.675 (95% CI: 0.623-0.726) (15).

In another study where 147 patients were evaluated, the PCT value was found to be significantly higher in those in the GP sepsis group, compared to the GN sepsis group; however, no significant increase was detected in the CRP value. In the study, the values of AUC for PCT and AUC for CRP were found as 0.73 (95% CI: 0.65-0.81) and 0.52 (95% CI: 0.43-0.62) respectively, and these findings were different from those in our study; additionally, the serum PCT value was also found to be significantly higher in the GP sepsis group in the study, and no significant difference was found in CRP levels (16).

In the study conducted by Alıcı et al. in our country, the median values of CRP in GN and GP sepsis groups were determined as 167.72 mg/L (94.37-265.81), 145.49 mg/L (81.31-235.23) respectively, and the values were seen to be statistically similar in the GN-GP groups (p=0.73) (15).

In addition to some studies investigating serum PCT levels, there are also others reporting that CRP levels were significantly higher in GN sepsis groups (17,18). In a study, while the PCT values were calculated significantly higher, the values of platelets were reported to be lower in the GN sepsis group, compared to the GP sepsis group (19). In our study, low platelet value was observed to be associated with mortality in sepsis. In a meta-analysis where 45 studies were examined, the levels of CRP, PCT, and TNF-α were found to be higher in the GN sepsis group than those in the GP sepsis group. In our study, while the levels of PCT were observed to be significantly beneficial in the early diagnosis in the GN sepsis group, CRP levels were not helpful in the early diagnosis in the GN sepsis group. In the same study reporting similar findings to those in our study, the researchers stated no significant difference in leukocyte, platelet count, and length of stay in ICU in the GN sepsis group (20). However, it was observed that long hospital stay was associated with higher mortality within all sepsis group patients in our study. In the same meta-analysis, the difference between the GN and GP sepsis groups regarding the APACHE II score was seen not to be significant, similar to our study findings (20).

In our study, while only microbiologically proven cases of sepsis were included, the clinical cases of sepsis were not included, and the retrospective design is among the limitations of our study.

CONCLUSION

PCT was found to be significantly higher in sepsis caused by GN bacteria than in sepsis caused by GP bacteria. PCT was also detected to be a useful marker in predicting pathogen groups in the early management of patients diagnosed with sepsis. However, there was no significant difference between GN and GP groups in terms of the values of hospitalization time, APACHE II score, leukocyte, neutrophil, lymphocyte, platelet, and albumin.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the local ethics committee of the Faculty of Medicine at Karatay University (Reg. number: 2024/006 and date: 7th June 2024) for our study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Sonographic Head Circumference on Delivery Mode and Perineal Laceration

Ultrasonografik Baş Çevresinin Doğum Şekli ve Perine Yırtığı Üzerine Etkisi

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ABSTRACT

Aim: The present study aimed to determine the role of head circumference for delivery mode and perineal laceration both in primiparous and multiparous patients and compare this role with estimated fetal weight.

Material and Method: A total of 866 patients, who delivered in our clinic were divided into two groups: vaginal delivery (n=604) and cesarean section (n=262). Demographic characteristics, sonographic head circumference, estimated fetal weight, birth week and weight, presence of severe perineal laceration, gender, neoatal head circumference, Apgar scores were compared between groups.

Results: The median head circumference was 339 (302-384) milimeter in vaginal delivery and 347 (314-384) milimeter in cesarean section (p<0.001). Sonographic head circumference was positively correlated with estimated fetal weight (r=0.561,p<0.001), birth weight (r=0.446,p<0.001) and neonatal head circumference (r=0.396,p<0.001). Head circumference >35.4 predicted cesarean section with 36.3% sensitivity and 84.8% specificity (AUC=0.637,p<0.001) and >35.2 predicted perineal laceration with 78.6% sensitivity and 85.4% specificity (AUC=0.853,p<0.001). Head circumference was superior for cesarean section as compared to estimated fetal weight (p=0.003) whereas no difference was found for perineal laceration (p=0.64).Head circumference >34.9 predicted cesarean section with 60% sensitivity and 73.8% specificity (AUC=0.692,p<0.001) in primiparous while >35.4 predicted cesarean section with 34.3% sensitivity and 84.5% specificity in multiparous women (AUC=0.624,p<0.001).

Conclusion: Considering large head circumference was more strongly associated with cesarean delivery and perineal lacerations than estimated fetal weight, we suggest that measuring head circumference would be an appropriate approach for determining delivery mode and complications.

Keywords: Cesarean section, estimated fetal weight, head circumference, perineal tear, vaginal delivery

ÖZ

Amaç: Bu çalışmanın amacı, hem primipar hem de multipar hastalarda baş çevresinin doğum şekli ve perine yırtığı üzerindeki rolünü belirlemek ve bu rolü tahmini fetal ağırlıkla karşılaştırmaktır.

Gereç ve Yöntem: Kliniğimizde doğum yapan toplam 866 hasta iki gruba ayrıldı: vajinal doğum (n=604) ve sezaryen (n=262). Demografik özellikler, ultrasonografik baş çevresi, tahmini fetal ağırlık, doğum haftası ve ağırlığı, şiddetli perine yırtığı varlığı, cinsiyet, neonatal baş çevresi, Apgar skorları gruplar arasında karşılaştırıldı.

Sonuçlar: Ortanca Baş çevresi vajinal doğum grubunda 339 (302-384) milimetre ve sezaryen doğumda 347 (314-384) milimetre idi (p<0,001). Ultrasonografik baş çevresi, tahmini fetal ağırlık (r=0,561, p<0,001), doğum ağırlığı (r=0,446, p<0,001) ve yenidoğan baş çevresi (r=0,396, p<0,001) ile pozitif korelasyon gösterdi. Baş çevresinin >35,4 olması sezaryen doğumu %36,3 duyarlılık ve %84,8 özgüllükle (AUC=0,637, p<0,001) ve >35,2 olması perine yırtığı %78,6 duyarlılık ve %85,4 özgüllükle (AUC=0,853, p<0,001) öngördü. Baş çevresi sezaryen için tahmini fetal ağırlığa göre daha üstündü (p=0,003) ancak perineal laserasyon için fark bulunamadı (p=0,64). Baş çevresi >34,9 primipar kadınlarda %60 duyarlılık ve %73,8 özgüllükle sezaryen doğumu tahmin ederken (AUC=0,692, p<0,001) >35,4 multipar kadınlarda %34,3 duyarlılık ve %84,5 özgüllükle sezaryen doğumu tahmin etti (AUC=0,624, p<0,001).

Sonuç: Büyük baş çevresinin sezaryen doğum ve perineal laserasyonlarla tahmini fetal ağırlığa göre daha güçlü bir şekilde ilişkili olduğu düşünüldüğünde, baş çevresinin ölçülmesinin doğum şeklini ve komplikasyonları belirlemek için uygun bir yaklaşım olabilir

Anahtar Kelimeler: Sezaryen, tahmini fetal ağırlık, baş çevresi, perine yırtığı, vajinal doğum

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INTRODUCTION

Cesarean section is the most common surgical procedure performed in obstetric practice. Although it is life-saving in some circumstances, like other surgeries, it has some complications. Perioperative complications such as aspiration, adjacent organ injury, hemorrhage, wound infections and future complications such as placenta accreata spectrum and pelvic adhesions are some of associated perinatal morbidities (1,2). There is an increasing trend to find preventive strategies all around the world to reduce cesarean section rates. On the other hand, pelvic lacerations, operative births, shoulder dystosia and asphyxia are some of the complications of vaginal birth (3,4). Thus, obstetricians are torn between the pressure to reduce the cesarean section rate on the one hand, and the desire to ensure perinatal well-being on the other. Therefore, it is crucial to give appropriate caesarean section decision is of vital importance.

Considering that the harmony between the passage and the passenger has a critical role for vaginal birth, the role of anthropometric measurements were started to be investigated (5). Fetal weight estimation has shown to be a gold standard approach to decide delivery mode for many years (6). Recent studies have focused especially on the fetal head (7). These studies claimed that head circumference has been a good predictor for operative deliveries, cesarean section, perineal laceration and is better than the birth weight for adverse obstetric outcomes (6,8-10). Other studies defined an equal role for head circumference and estimated fetal weight (5,8,11). Similar to the confliction in the comparative role of two parameters, there is no clear results for the correlation with neonatal features and the cut-off levels predicting these outcomes. Then, the researchers made an effort to determine cut-off levels for head circumference to predict operative deliveries and cesarean section. But, there was a conflicting results about this issue and the studies were lack of the categorization for parity (5,6,12).

Here, we aimed to determine the correlation between sonographic head circumference, neonatal head circumference and birth weight. Secondary aim was to determine the predictive role of sonographic head circumference for delivery mode and severe perineal laceration in vaginal birth. Additionally, the predictive role of sonographic head circumference was determined for primiparous and multiparous patients and aimed to be compared with estimated fetal weight.

MATERIAL AND METHOD

The present study was designed as a retrospective case control study. It was performed at University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Department of Obstetrics and Gynecology between April 2018 and September 2019. The local ethics committee approved the study (2011-KAEK-25 2019/10-17) and also it was in accordance with Helsinki declaration. For using medical records of study participants, written informed consent was taken from all patients.

Study Population

A total of 866 patients, who delivered in our clinic were admitted to the study. The participants were divided into two groups: vaginal delivery (n=604) and cesarean section (n=262) groups. The inclusion criteria were as follows: having term (37 to 42 weeks of gestation), viable, singleton pregnancy with vertex presentation, being 18 to 45 years old, having available perinatal records and sonographic measurements within 1 week of delivery. Exclusion criteria of the study consists of having fetal anomaly, preterm births, multiple pregnancy, previous uterine surgery, conditions leading to fetal growth restriction, malpresentations and elective cesarean section patients.

Demographic characteristics such as age, gravida, parity, height, weight, body mass index, sonographic head circumference and estimated fetal weight, birth week and mode, presence of severe perineal laceration (stage 3 and 4), birth weight, gender, head circumference of the baby, Apgar scores of neonates were recorded from hospital medical records.

In sonographic evaluation, we routinely use Hadlock formula for estimated fetal weight which use the biparietal diameter, head circumference, abdominal circumference and femur length for calculation. Biparietal diameter refers the measurement between outer and inner borders at the level of cavum septum pellucidum while head circumference presents elipsed-shape perimeter around fetal kranium. Perimeter of the fetal abdomen at the level of umbilical vein is defined as abdominal circumference. Fetal femur length refers to the distance between the diaphysis of femoral bones (13,14). Additionally, neonatal birth weight and head circumference are measured by widwifes in delivery room. Neonatal head circumference presents the maximal horizontal plane above eyebrows, ears and two occipital prominenses (15).

Statistical Analysis

The normality of variables were tested with Shapiro Wilk test. The Student t-test was used to compare normally distributed continuous variables whereas Mann Whitney-U test was performed for non-normally distributed variables. Categorical variables were compared with Chi-square or Fisher's Exact test. Data were presented as mean±standard deviation or median (minimum-maximum) values for continuous variables and frequency (percentages) for categorical variables. Spearman correlation coefficient was applied to assess the relationship between sonographic head circumference, estimated fetal weight, birth weight and neonatal head circumference. The predictive role

of sonographic head circumference and estimated fetal weight for delivery mode was assessed by ROC analysis. SPSS version 22.0 and MedCalc 18 programs were used for statistical analysis. An alfa value ≤0.05 was considered as statistically significant.

RESULTS

The demographic, sonographic and perinatal features of patients were presented in **Table 1**. There was no significant difference between vaginal delivery and cesarean section groups in terms of body mass index, parity, birth week, Apgar fifth minutes scores and neonatal intensive care unit admission rates. Statistically significant difference was present in according to age, sonographic head circumference, estimated fetal weight, neonatal head circumference, birth weight, fetal gender and first minutes Apgar scores.

The box-plot graph showing the distribution of head circumference and estimated fetal weight was presented in **Figure 1**. The median head circumference was 339 (302-384) milimeter in vaginal delivery group and 347 (314-384) milimeter in cesarean section group which was statistically significant. Similarly, estimated fetal weight, neonatal head circumference and birth weight were smaller in vaginal delivery group.

Spearman correlation coefficient was applied to assess the relationship between sonographic head circumference, estimated fetal weight, birth weight and neonatal head circumference. The correlation analysis was demonstrated in **Table 2**. Sonographic head circumference was found to be positively correlated with estimated fetal weight (r=0.561, p<0.001), birth weight (r=0.446, p<0.001) and neonatal head circumference (r=0.396, p<0.001).

Table 1. The demographic, sonographic and perinatal features of patients

	Vaginal delivery (n=604)	Cesarean section (n=262)	p
Age (years)	22 (18-42)	24 (18-42)	<0.001
Body mass index (kg/m2)	27 (21-37)	27 (23-36)	0.051
Parity (n,%)			
Primiparous	145 (24%)	55 (21%)	0.334
Multiparous	459 (75%)	207 (79%)	
Head circumference (mm)	339 (302-384)	347 (314-384)	<0.001
Estimated fetal weight (gram)	3156 (2001-4079)	3263 (2208-4439)	0.002
Neonatal head circumference (mm)	34 (32-38)	34 (32-39)	0.018
Birth week (week)	39 (37-41)	39 (37-41)	0.674
Birth weight (gram)	3154.64 ± 397.2	3239.05 ± 470.39	0.011
Fetal gender (n,%)			
Female	314 (52%)	116 (44.3%)	0.037
Male	290 (48%)	146 (55.7%)	
Apgar first minutes score	9 (2-9)	9 (1-9)	0.046
Apgar fifth minutes score	10 (6-10)	10 (4-10)	0.064
NICU requirement (n,%)	25 (4.1%)	19 (7.3%)	0.081

NICU: neonatal intensive care unit

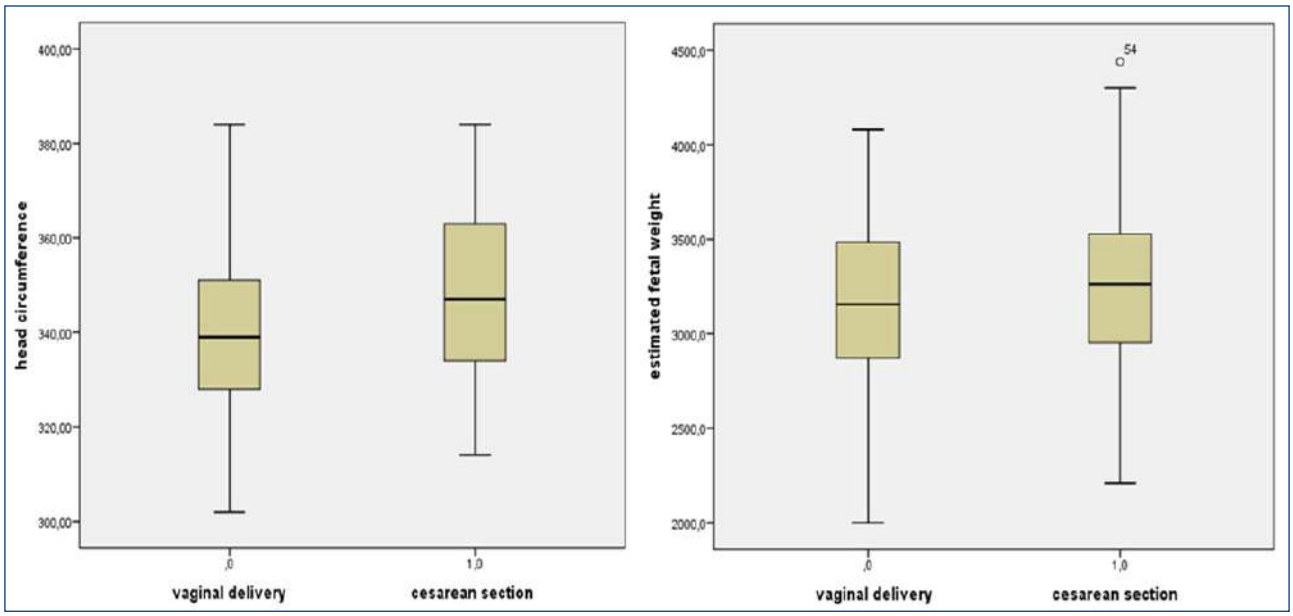

Figure 1. The box-plot graphs showing the distribution of head circumference (left) and estimated fetal weight (right)

Table 2. The correlation analysis for sonographic head circumference, estimated fetal weight, birth weight and neonatal head circumference

	Correlations			
	Head Circumference	**Estimated fetal weight**	**Birth weight**	**Neanatal head Circumference**
Spearman's rho				
Head circumference				
Correlation coefficient	1000	.561**	.446**	.369**
Sig. (2-tailed)	.	.000	.000	.000
N	866	866	866	866
Estimated fetal weight				
Correlation coefficient	.561**	1.000	.524**	.344**
Sig. (2-tailed)	.000	.	.000	.000
N	866	866	866	866
Birth weight				
Correlation coefficient	.466**	.524**	1.000	.597**
Sig. (2-tailed)	.000	.000	.	.000
N	866	866	866	866
Neanatal head circumference				
Correlation coefficient	.369**	.344**	.597**	1.000
Sig. (2-tailed)	.000	.000	.000	.
N	866	866	866	866

**: Correlation is significant at the 0.01 level (2-tailed)

Severe perineal laceration was detected in 14 patients (2.3%) in vaginal delivery group. The predictive role of sonographic head circumference and estimated fetal weight for delivery mode and perineal laceration was assessed by ROC analysis and demonstrated in **Figure 2**.

Sonographic head circumference >35.4 centimeter was found to predict cesarean section with 36.3% sensitivity and 84.8% specificity (AUC=0.637, p<0.001). Also, sonographic head circumference >35.2 centimeter was found to predict perineal laceration with 78.6% sensitivity and 85.4% specificity (AUC=0.853, p<0.001).

The comparison of the predictive role of sonographic head circumference and estimated fetal weight for delivery mode and perineal laceration was shown in **Figure 3**.

Head circumference was found to be superior for cesarean section as compared to estimated fetal weight (p=0.003) whereas no difference was found between head circumference and estimated fetal weight for perineal laceration (p=0.64).

The predictive role of sonographic head circumference for delivery mode in primiparous and multiparous patients were presented in **Figure 4**. Sonographic head circumference was found to predict cesarean section with a cut-off value 34.9 centimeter, 60% sensitivity and 73.8% specificity (AUC=0.692, p<0.001) in primiparous women while a cut-off value 35.4 centimeter predicted cesarean section with 34.3% sensitivity and 84.5% specificity in multiparous women (AUC=0.624, p<0.001).

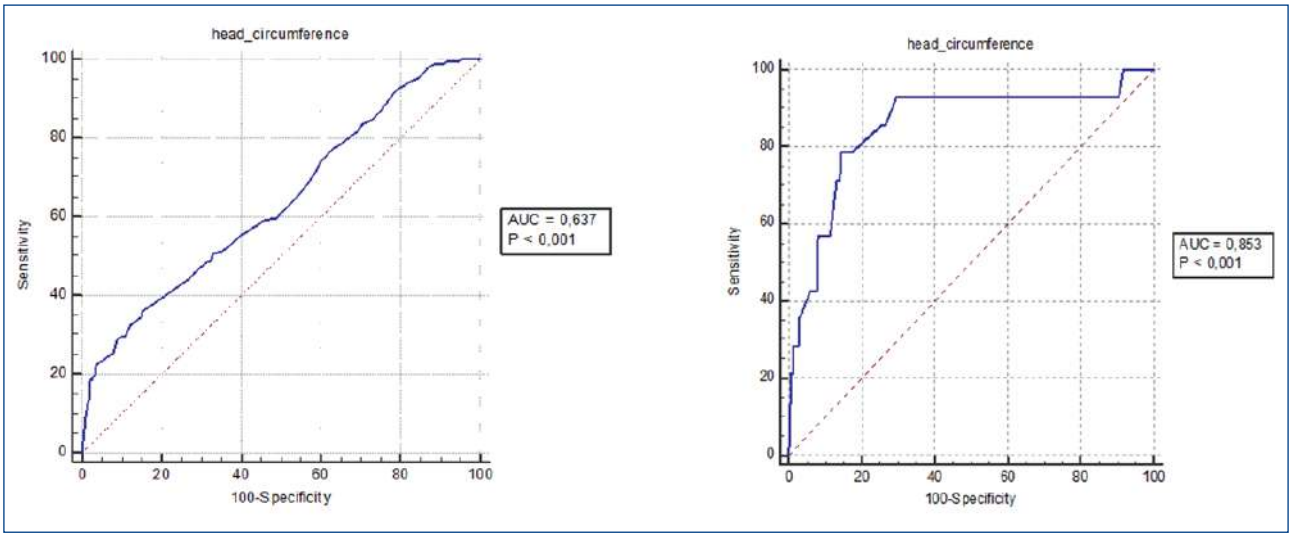

Figure 2. The ROC analysis of sonographic head circumference for delivery mode (left) and perineal laceration (right)

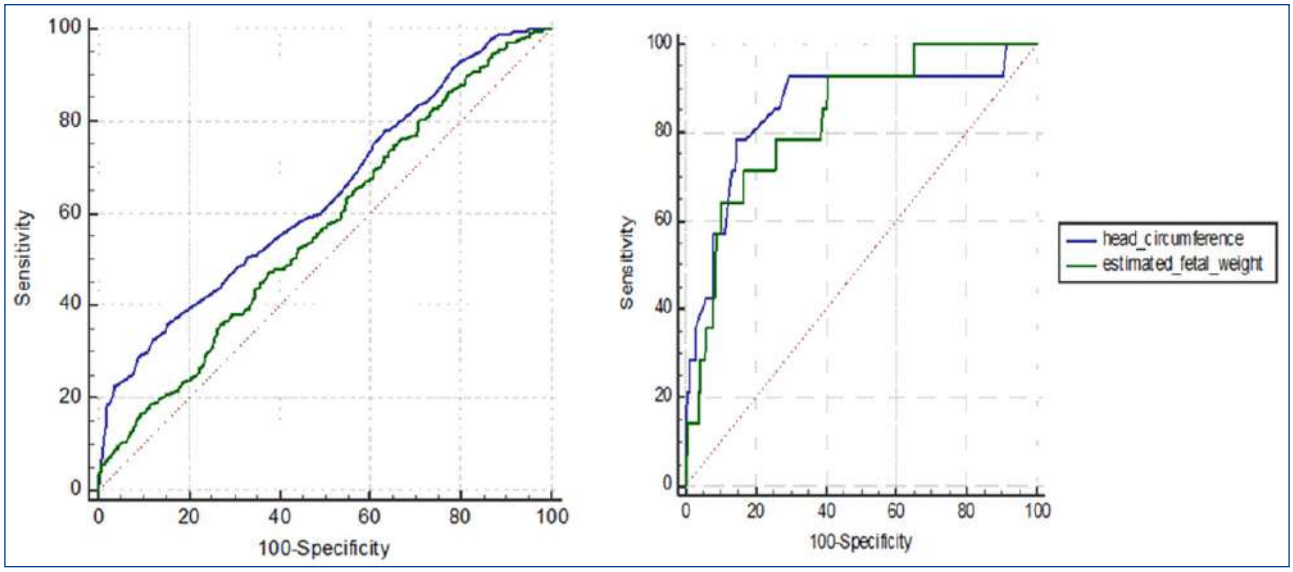

Figure 3. The comparative ROC analysis of sonographic head circumference and estimated fetal weight for delivery mode (left) and perineal laceration (right)

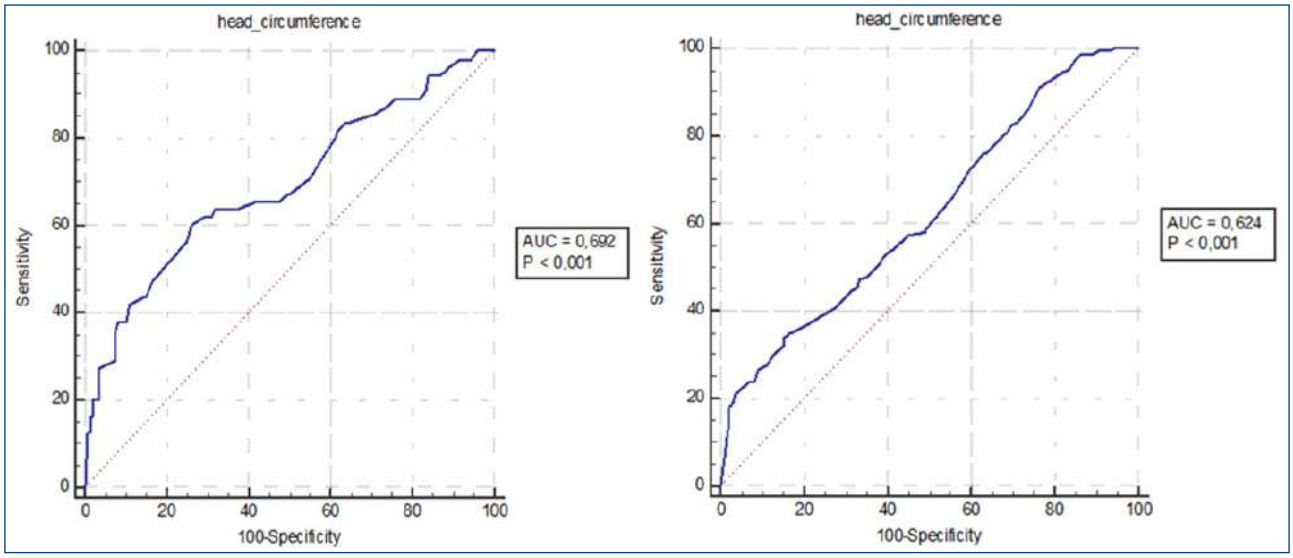

Figure 4. The predictive role of sonographic head circumference for delivery mode in primiparous (left) and multiparous (right) patients

DISCUSSION

Influence of fetal anthropometric measurements has been studied in previous studies. Estimated fetal weight which is the determinator of fetal macrosomia has been claimed to be a good predictor for adverse perinatal outcomes and obstructed labor (16-18). Similar to increased estimated fetal weight, large head circumference was found to be related to the increased rates of unplanned cesarean section, operative delivery, prolonged second stage, neonatal asphyxia and perineal lacerations (12). In 2015, Lipschuetz et al. demonstrated that large head circumference is associated with nearly 2.13 fold increased risk for operative delivery and 2.58 fold increased risk for unplanned cesarean section. This risk was more prominent in primiparae patients. Moreover, infants who have large head circumference and normal birth weight were more prone to cesarean section and instrumental delivery as compared to infants with normal head circumference and normal birth weight. Interestingly, infants with normal head circumference and high birth weight combination was not associated with cesarean section. In this study, large head circumference was defined as being above 95th persentile and no cut-off was determined (19). Similarly, Passerini et al. showed that large head circumference is associated with increased risk of instrumental delivery and cesarean section independent of fetal real weight (12). In another study, head circumference was related to the unplanned cesarean section independent from maternal height and epidural analgesia (20). In the

literature, a few studies are present comparing the role of estimated fetal weight and head circumference in predicting delivery mode. In our study, similar to study of Lipschuetz et al, we found that head circumference was superior for cesarean section as compared to estimated fetal weight. In contrast, other studies claimed that estimated birth weight and head circumference have an equal role for successful vaginal delivery (8,11,19).

The cut-off value of head circumference for adverse perinatal outcomes is controversial. Lipschuetz et al. reported that sonographic head circumference ≥35 centimeter is an independent risk factor for cesarean section. Furthermore, head circumference ≥35 centimeter combined with estimated fetal weight greater than 3900 gram increases the risk of prolonged second stage (5). Kennelly et al. claimed that head circumference >37 centimeter is associated with prolonged labor (8). For the same cut-off values, Ayinde and Mujugira reported elevated risk for cesarean section and instrumental delivery (21,22). In a study of Elvander et al, increased instrumental delivery rate was reported in a group with head circumference between 38-41 centimeter as compared to 35 centimeter group (23). Passerini et al. presented 63.6% sensitivity and 47.7% specificity for a cut-off value of 35 centimeter, 37.3% sensitivity and 81% specificity for a cut-off value of 36 centimeter and 11.6% sensitivity and 95.3% specificity for a cut-off value of 37 centimeter (12). In a study of Rabei et al, head circumference ≥36.8 centimeter was associated with an increased risk of instrumental delivery with 44.7% sensitivity and 91.9% specificity (6). In our study, sonographic head circumference >35.4 centimeter was found to predict cesarean section with 36.3% sensitivity and 84.8% specificity.

Another issue about head circumference is the correlation with neonatal head circumference. We found correlation between neonatal and sonographic head circumference. Likewise, Lipschuetz et al. showed this correlation (19). In the literature, due to the skin, hair and edema in postnatal period, 1 centimeter difference is acceptable for head circumference (24,25).

Different from previous studies, we evaluated the predictive role of sonographic head circumference for delivery mode both in primiparous and multiparous patients. Sonographic head circumference >34.9 centimeter was found to predict cesarean section with 60% sensitivity and 73.8% specificity in primiparous women while a cut-off value 35.4 centimeter predicted cesarean section with 34.3% sensitivity and 84.5% specificity in multiparous women. Leading to this result, we suggest that measurement of head circumference is more beneficial in primiparous women to determine the delivery mode.

Head circumference has been widely studied in perineal laceration. In a study of Nelson et al, sonographic head circumference was found to be associated with mode of delivery but not with the risk of anal sphincter injury (26). Similarly, Meyer et al. demonstrated that head circumference and estimated fetal weight was not associated with anal sphincter injury in unassisted vaginal births (27). In another study of Meyer et al, significant relationship was reported between anal sphincter injury and head circumference above 90 percentile on vacuum deliveries in primiparous women and this association was stronger than fetal weight (9). Chill et al. demonstrated a correlation between large head circumference and the severity of anal sphincter injury (28). In our study, sonographic head circumference >35.2 centimeter was found to predict severe perineal laceration with 78.6% sensitivity and 85.4% specificity (AUC=0.853, $p<0.001$). But the number of patients with perineal laceration was small in our study. These conflicting results can be due to the confounding factors such as primiparity, instrumental delivery and prolonged labor. Another reason can be the acceptance of head circumference as categorical or continuous variables in different studies.

Limitations

The present study has some limitations. It has a small sample size and retrospective design leading to selection and information biases. Sonographic measurements were not done by same researchers. All infants with large head circumference did not have high birth weight, and vice versa. Thus, stratification and multinominal regression analysis may be appropriate for the analysis.

CONCLUSION

Although the importance of estimated fetal weight can not be ignored, our study demonstrated that head circumference has an essential role for predicting unplanned cesarean section and severe perineal lacerations. Even, large head circumference was more strongly associated with cesarean delivery and perineal lacerations than estimated fetal weight. Thus, we suggest that measuring head circumference would be an appropriate approach for determining delivery mode and complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The local ethics committee approved the study (University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital; 2011-KAEK-25 2019/10-17) and also it was in accordance with Helsinki declaration.

Informed Consent: For using medical records of study participants, written informed consent was taken from all patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Comparison of Volumetric Arc Therapy (VMAT) and Helical Intensity Modulated Radiotherapy (Hel-IMRT) in Lung Cancer Radiotherapy

Akciğer Kanseri Radyoterapisinde Volümetrik Ark (VMAT) Terapi Tekniği ile Helikal Yoğunluk Ayarlı Radyoterapi (Hel-IMRT) Tekniğinin Karşılaştırılması

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ABSTRACT

Aim: Definitive radiotherapy is significant in the treatment of locally advanced lung cancer. Various radiotherapy techniques have been developed to preserve critical organ doses while providing better dose coverage to improve the therapeutic index. The aim of this study was to evaluate the differences between VMAT and Hel-IMRT techniques in the treatment of locally advanced lung cancer.

Material and Method:This study was planned to use VMAT and Hel-IMRT techniques with simulation computed tomography data of 15 patients who underwent definitive chemoradiotherapy for locally advanced lung cancer between 01.01.2022 and 01.04.2022. It was planned to compare two different radiotherapy techniques in which continuous irradiation was performed circularly in the treatment of lung cancer. The same user created the plans according to the same dose limitation goal. Target volume coverage and critical organ doses of the patients were recorded.

Results: In the Hel-IMRT technique, the D 95% value for target volume dose coverage was found to be significantly higher (p=0.001). In terms of CI (p=0.001), more optimal values were found with the VMAT technique. There was no significant difference between the two techniques for HI (p=0. 916) and GI (p=0.069).In the data obtained for critical organs, the maximum dose to the spinal cord was found to be statistically significantly lower in the Hel-IMRT technique (p=0.011), the lung dose parameters (V20, V5 and mean dose) in the VMAT technique (p=0.002, p=0.01, p=0.01), and the heart mean dose was lower in the VMAT technique (p=0.002, p=0.01, p=0.01) and the mean heart dose was found to be lower (p=0.012). There is no significant difference between the two techniques for esophageal mean dose and hot spot dose in the plan.

Conclusion: There are different points at which the two different techniques are superior to each other. For this reason, the choice of techniques in treatment planning should be based on patient and clinical factors.

Keywords: Lung cancer, volumetric arch therapy, helical tomotherapy, radiotherapy, toxicity

ÖZ

Amaç: Lokal ileri akciğer kanserinin tedavisinde definitif radyoterapinin önemi büyüktür. Tümör dokusuna yeterli radyasyon dozunu verirken, çevre kritik organları korunmak terapötik indeksi sağlamak ana hedeftir. Bu amaçla farklı radyoterapi teknikleri geliştirilmiştir.

Gereç ve Yöntem: Bu çalışmada Ankara Şehir Hastanesi Radyayon Onkolojisi Kliniğinde 01.01.2022 ile 01.04.2022 tarihleri arasında lokal ileri akciğer kanseri nedeniyle definitifkemoradyoterapi uygulanmış olan 15 hastanın simülasyon bilgisayarlı tomografi verileri kullanılarak iki farklı radyoterapi tekniği karşılaştırılmıştır. Bu amaçla önceden planlama amacıyla çekilmiş GE Discovery marka bilgisayarlı tomografi (BT) verileri kullanılarak Accuray®-Tomotherapy® H™ tedavi planlama sistemi ile Helikal Yoğunluk Ayarlı Radyoterapi (Hel-IMRT) planı, Eclipse™ tedavi planlama sistemiyle Volümetrik Ark Terapi (VMAT) planı oluşturulmuştur. Her iki plan da tez öğrencisi tarafından oluşturulmuş olup PTV D%95 değerinin 5700cGy (Hedef hacim volümünün %95'nin prescribe dozun % 95'ini alması) üzerinde almasına özen gösterilerek kritik organlarda istenilen doz sınırlamaları sağlanmaya çalışılmıştır. Hastane elektronik sistem verileri, hasta dosya bilgileri ve DVH bilgileri kullanılmıştır. Hastalık evresi, tümör lateralizasyonu (sağ-sol), karinaya göre yerleşimi (üst-alt) bigileri kaydedilmiştir.

Bulgular: Tekniklerin karşılaştırılmasında planda oluşan sıcak nokta 0,01cc maksimum doz değeri, kritik organlardan kalp (ortalama dozu), özefagus (ortalama doz, maksimum doz (0,03cc), V60Gy), spinalkord (maksimum doz (0,03cc)) doz bilgileri, hedef hacim sarımı (coverage) değerlerinin yanısıra, gradientindex (GI), homojeniteindex (HI), ve konformalitelndex (CI) değerleri kullanılmıştır.Verilerin analizinde SPSS Package Program version 23.0 (IBM Corporation, Armonk, NY, USA) kullanılmıştır.Aynı hasta için yapılan iki farklı planının doz verileri karşılaştırılmış olup, bağımlı iki grup analizi için Wilcoxon-SignedRank test kullanılmıştır. İstatistiksel olarak anlamlılık sınır 0.05 'in altı kabul edilmiştir. Hel-YART tekniğinde hedef hacim doz sarımı için bakılan D%95 değeri anlamlı olarak daha yüksek (p=0.001) saptanmıştır. CI (p=0.001) açısından VMAT tekniği ile daha optimale yakın değerler bulunmuştur. HI (p=0.916) ve GI (p=0.069) iki teknik açısından anlamlı farklılık yoktur. Kritik organlar için elde edilen verilerdespinalkord maksimum doz Hel-YART tekniğinde istatistiksel anlamlı daha düşük (p=0.011) saptanmış, VMAT tekniğinde akciğer doz parametreleri (V20, V5 ve ortalama doz) (p=0.002,p=0.01,p=0.01), ve kalp mean dozu daha düşük bulunmuştur (p=0.012). Özefagusdozu ve planda oluşan sıcak nokta dozu için iki teknikte anlamlı farklılık yoktur.

Sonuç: İki farklı tekniğin birbirine üstünlük sağladığı farklı noktalar vardır. Bu nedenle tedavi planlamasında teknik seçiminde hastaya ve kliniğe ait faktörler göz önünde bulundurularak tercih yapılmalıdır.

Anahtar Kelimeler: Akciğer kanseri, helikaltomoterapi, radyoterapi, toksisite, volümetrik ark tedavi

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INTRODUCTION

Despite effective and evolving treatments, lung cancer is the leading cause of cancer-related deaths. GLOBOCAN 2020 data show that 19.3 million people will be diagnosed with cancer and approximately 10 million people will die from cancer (1). Current treatment modalities for lung cancer are more complex than in the past, including radiotherapy, immunotherapy, targeted drugs, chemotherapy, and current surgical techniques. In parallel with better identification of molecular markers and biomarkers than in the past, immunotherapy and personalized treatments have been developed and overall patient survival has improved (2). Despite new agents and changing protocols, RT maintains its place in the treatment of NSCLC. RT can be used for curative and palliative purposes in the treatment of NSCLC and is one of the essential elements of treatment. In 77% of all lung cancer patients, RT is required during treatment (3). Many technological advances have been made in the simulation, treatment planning and delivery phases to improve the application of RT. Modern techniques make it easier to calculate uncertainties in the movement of the tumor. These developments have made it possible to reduce the safety margins allowed for movement. As a result, critical organ doses and side effects have been reduced (4).

Recent advances in computer technology have had a major impact on imaging and the delivery of radiation (5). IMRT provides a more appropriate distribution depending on the tumor and organ at risk (OAR). This is done using a computer-controlled MLC attached to the linear accelerator gantry and treatment planning system (TPS) algorithms. Optimization algorithms are used to find the most appropriate dose distribution.

Volumetric arc therapy uses multiple arcs for each intensity level, and each arc contains multiple MLC segments. The MLC segments move dynamically during the gantry cycle (6,7,8). VMAT differs from IMRT in that the gantry rotates around the patient axis with a cyclic motion during irradiation. The main advantages of VMAT over IMRT are that treatment can be completed in a much shorter time, patient movement is minimized depending on the treatment speed, and treatment accuracy is increased. VMAT uses three variables to modulate the dose. These are gantry speed and dose rate. This technique has been reported to reduce treatment time by 75-80% compared to standard IMRT techniques (7-9).

RT is rapidly moving towards fewer side effects, more effective tumor control, shorter and more targeted treatment programs. After the 2D and 3D treatments used in the past; thanks to technological advances, new and modern techniques have begun to replace these traditional treatments. The main current techniques are IMRT, IGRT, VMAT, helical tomotherapy and SRT. For better RT applications, techniques such as 4D CT, deep breathing inspiration, and simulation CT scans have also been developed. With 3D treatments, treatment times are shorter but may not be sufficient for dose wrap and surrounding critical organ doses. With PTV, IMRT can achieve better dose delivery, but treatment times are longer and there is an increase in low-dose regions. Helical IMRT (Hel-IMRT) is a type of IMRT used in treatments with helical tomotherapy. With Hel-IMRT, rotational dosing is used. Modern techniques have made it easier to understand the uncertainties of tumor movement, resulting in a reduction in the margins that can be achieved. In parallel, a reduction in normal tissue doses has led to a reduction in side effects (10,11). Optimal simulation and RT are still ongoing research topics, and many studies are being conducted.

The aim of this study was to evaluate the dosimetric differences between VMAT and Hel-IMRT techniques in the treatment of locally advanced lung cancer.

MATERIAL AND METHOD

The study used planning and tomography data of 15 patients who underwent definitive chemoradiotherapy for locally advanced lung cancer at the Radiation Oncology Department of Ankara City Hospital between 01.01.2002 and 01.04.2002. Patient records and information from the electronic planning system were used to obtain data. Virtual planning was performed separately. Disease stage, laterality (right-left) and tumor location relative to the carina (up-down) were defined. VMAT and Hel_IMRT techniques were compared for target volume coverage and critical organ doses. (Eclipse and Accuray®-Tomotherapy® H™).

Creation of VMAT plans

The Eclipse™ software used to create VMAT plans. The planning system provides the ability to control dose to target volumes and OARs, while also displaying three-dimensional dose distributions and generating dose volume histograms (DVHs). It uses the Pencil Beam Convolution (PBC) and Analytical Anisotropy Algorithm (AAA) algorithms for photon beams and the Monte Carlo (MC) algorithm for electron beams.The optimization process can be observed and interfered with if necessary while a process algorithm is used to generate the plan (10). In the VMAT treatment plan, the necessary virtual structures were drawn for the target volume and critical organs intersecting the target volume. Two partial arcs were created according to the tumor locations. The 6MV photon was used in the plans and a dose of 60 Gy in 30 fractions was given.

Hel-IMRT plan creation

In the Accuray®-Tomotherapy® H™ treatment planning system, target structures and OARs are assigned to the

second tab. Anatomical proximity is ranked in order of importance, taking into account the target dose and dose constraints for OARs (for example, because the heart is closer to the mass in the left lung, it is ranked higher in importance than the right lung). If there is no overlap, the order may vary depending on the user. In tomotherapy plans, target volumes and critical organs were listed and calculated in order of importance (batch beamlet). A treatment plan was then generated according to the desired dose values for the target volume and organs at risk according to the protocol in **Table 1**.

Table 1. Dose constraints used in planning

Structures	Metric	Target value
PTV	V60Gy Mean dose(D99%) Maximum dose (0.03cc)	≥95% ≥57% ≤72%
Spinalcord	Maximum dose (0.03cc)	≤ 50.0Gy
Lung-GTV	V20Gy V5Gy Mean dose	≤34% ≤60% ≤18%
Heart	Mean dose	≤20Gy
Esophagus	Mean dose (0.03cc) Mean dose V60Gy	≤60Gy ≤34Gy Along the entire wall

Targeted Common Parameters

In both plans, the D95 value for PTV was attempted to be 5700 cGy and (95% of the target volume takes 95% of the prescribed dose) and the desired dose limits were attempted to be provided in the critical organs. Calculations were performed using the AAA algorithm in the newly created plans. The two plans generated for each case (VMAT and Hel-YART) were compared in terms of the following parameters.

Conformity Index (CI): CI Paddick=([(TV²]_PIV))/(PIV×TV))

Homogeneity Index (HI)=(D_(%2)-D_(%98))/D_(%50)

Gradient index (GI)=[PTV]_(%50)/[PTV]_(%100)

PTV coverage: Isodose curve covering the planned target volume.
V5: Lung volume receiving 5 Gy
V20: Lung volume receiving 20Gy
Mean lung dose: Mean lung dose.
Spinal cord _0.03cc and maximum dose: The dose received by the spinal cord in 0.03cc and the maximum dose received by the spinal cord.
Esophagus average and maximum 0.03cc dose: The average dose received by the oesophagus and the dose received in 0.03cc.
Heart mean: The mean dose received by the heart.

Table 2. Results of V5, V20 and PTV_Volume, PTV_Coverage_dose, CI, GI and HI calculated in the helical intensity modulated radiotherapy and volumetric arc therapy plans of the patients.

Patient	Technique	V5	V20	PTV_ Volume	PTV_coverage_dose	CI	GI	HI
1	Hel-YART VMAT	22.30 3.95	7.70 50.55	484.12 348.80	6013.00 5818.00	1.21 0.75	4.44 3.1	0.02 0.09
2	Hel-YART VMAT	53.00 20.85	25.20 45.97	289.32 1228.20	6015.00 6000.00	1.26 1.01	5.10 4.7	0.03 0.07
3	Hel-YART VMAT	53.00 17.28	33.70 45.90	406.24 1067.70	6016.00 5857.77	1.39 0.82	5.03 3.2	0.03 0.08
4	Hel-YART VMAT	49.40 17.27	23.10 45.90	231.77 1067.70	6001.00 5703.09	1.43 1.66	6.81 12.0	0.05 0.08
5	Hel-YART VMAT	58.50 15.96	23.40 56.65	541.87 1191.00	5965.00 5705.21	1.31 1.03	3.76 3.2	0.11 0.07
6	Hel-YART VMAT	62.70 17.62	23.00 49.87	271.70 991.60	5974.00 5893.00	1.21 0.81	3.97 3.5	0.07 0.05
7	Hel-YART VMAT	50.80 13.86	23.60 42.68	257.76 827.40	5918.00 5720.00	1.86 0.58	6.80 3.4	0.08 0.08
8	Hel-YART VMAT	72.70 16.55	22.60 65.12	224.03 1139.20	6005.00 5706.20	1.95 0.87	5.30 3.7	0.44 0.18
9	Hel-YART VMAT	55.90 15.90	18.80 33.06	163.04 886.10	5967.00 5710.77	1.18 1.01	4.20 5.2	0.11 0.05
10	Hel-YART VMAT	51.80 16.47	27.10 45.08	412.18 1029.10	6018.00 5705.19	1.53 1.06	4.97 3.8	0.08 0.18
11	Hel-YART VMAT	63.20 9.90	19.60 64.15	823.91 1031.00	6028.00 5696.60	1.35 0.88	4.05 3.8	0.05 0.05
12	Hel-YART VMAT	58.90 23.54	30.10 54.62	696.57 1425.30	5965.00 5701.39	1.39 1.98	4.52 3.4	0.12 0.12
13	Hel-YART VMAT	58.40 29.15	31.60 60.77	572.85 1767.20	5941.00 5711.79	1.62 1.11	4.78 3.7	0.12 0.06
14	Hel-YART VMAT	56.30 28.74	23.90 51.75	177.19 1094.00	5938.00 5718.53	1.40 1.04	6.13 4.3	0.14 0.08
15	Hel-YART VMAT	55.40 19.12	19.20 51.98	225.95 1110.90	5978.00 5704.02	1.14 1.03	3.71 4.3	0.09 0.06

Table 3. Critical organ dose values calculated in two different planning technique

Patient	Technique	Spinal Cord Max dose (Gy)	Heart Mean dose(Gy)	Esophagus Max dose(Gy)	Esophagus Mean dose(Gy)	Esophagus V60Gy
1	Hel-YART	3803.00	54.00	5352.00	1454.00	0
	VMAT	4040.00	38.30	5586.50	910.30	
2	Hel-YART	1486.00	925.00	4500.00	948.00	0
	VMAT	2030.00	739.10	4395.00	1589.80	
3	Hel-YART	2911.00	365.00	6160.00	1936.00	0
	VMAT	3939.00	176.70	6265.00	1222.90	
4	Hel-YART	2899.00	112.00	2899.00	1076.00	0
	VMAT	3984.00	176.70	5720.00	880.40	
5	Hel-YART	3601.00	558.00	6480.00	1955.00	0
	VMAT	4281.00	626.80	6281.00	2114.70	
6	Hel-YART	4751.00	955.00	6222.00	1453.00	0
	VMAT	3384.00	677.20	6040.00	1836.70	
7	Hel-YART	1295.00	1716.00	4059.00	1486.00	0
	VMAT	4302.00	1088.40	2517.93	830.70	
8	Hel-YART	3315.00	1272.00	5991.00	1061.00	0
	VMAT	4472.38	1085.50	5693.03	1482.30	
9	Hel-YART	2968.00	508.00	5841.00	623.00	0
	VMAT	2989.86	483.00	6210.28	836.10	
10	Hel-YART	4048.00	153.00	6277.00	3028.00	0
	VMAT	4353.03	119.00	6100.00	2514.10	
11	Hel-YART	3505.00	1541.00	6303.00	3584.00	0
	VMAT	2894.59	1343.00	6268.73	2013.20	
12	Hel-YART	929.00	1089.00	5652.00	873.00	0
	VMAT	2386.40	855.10	6066.07	3167.80	
13	Hel-YART	2891.00	1609.00	6283.00	3069.00	0
	VMAT	4348.17	1163.80	6066.07	3167.80	
14	Hel-YART	1095.00	306.00	2966.00	572.00	0
	VMAT	2519.76	183.70	5483.41	1210.70	
15	Hel-YART	1969.00	306.00	5550.00	512.00	0
	VMAT	4042.26	533.90	6289.73	1402.10	

Statistical analysis

In this study, planning data were entered using SPSS Package Program version 23.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used for continuous (quantitative) variables; mean, standard deviation, minimum and maximum values were expressed, whereas categorical variables were expressed as numbers (n) and proportions (%). Data from two different schedules for the same patient were compared. The Wilcoxon signed rank test was used for dependent group analysis. For the results of these tests, $p \leq 0.05$ was considered to be significant.

RESULTS

The plans were prepared using the same criteria and VMAT and Hel-IMRT techniques were compared. The results of the prepared plans were compared according to the target volumes (GI, CI, HI, V5, V20 and PTV _coverage_volume) and the values specified in the protocol for the organs at risk (Tables 2, 3). The median age of patients was 61 years (range 52-78). Regarding the gender distribution of the patients, 4 (26.7%) were female and 11 (73.3%) were male. The stage of the patients was stage IIB in 4 patients, stage IIIA in 5 patients, stage IIIB in 3 patients, stage IIIC in 1 patient and stage IVA in 2 patients.

In terms of lateralization, seven (46.7%) patients were in the left lung and eight (53.3%) in the right lung. Based on the level of the carina, the tumor localization was divided into 2 groups as upper localization and lower localization. It was observed that most tumors (13 patients 86.7%) were located above the level of the carina. The median planned tumor volume (PTV) of the patients was 289.3 cc (range 163.0-823.9 cc).

When comparing the two plans in terms of target volume dose wrapping, the D value of 95% was significantly higher for the Hel-IMRT technique (p=0.001). On the other hand, the VMAT technique was more advantageous in terms of CI (Conformity Index) (p=0.001). There was no significant difference between the two techniques in terms of Plan HI (p=0.916) and GI (p=0.069) values (**Table 4**).

When comparing the critical organ dose parameters using the Wilcoxon sum rank test, while the maximum spinal cord dose was statistically significantly lower in the Hel-IMRT plans (p=0.011), the dose parameters for the lung (V20, V5 and mean dose) and VMAT with respect to mean heart doses were statistically significantly lower (respectively; p=0. 002, p=0.01, p=0.01 and p=0.012). There was no difference between VMAT and Hel-IMRT techniques in terms of dose parameters (maximum and average dose) and hot spot (0.01cc maximum dose) for the esophagus.

Table 4. Analysis of the difference between the two plans in terms of PTV coverage, HI, CI and GI (PTV: Planned Target Volume, HI: Homogeneity Index, CI: Conformity Index, GI: Gradient Index, Z: score value, P: probability value)

		Hel-IMRT Plan		VMAT Plan		P	Z
PTV_coverage_D95	Mean Median (Range)	5982.80 cGy 5978	33.90 5918-6028 cGy	5756 5710	92.13 5701-6012 cGy	.001	-3.408
PTV_HI	Mean Median (Range)	0.10 0.08	0.10 0.2-0.44	0.08 0.08	0.33 0.05-0.18	.916	-.105
PTV_CI	Mean Median (Range)	1.41 1.39	0.24 1.14-1.95	0.97 1.01	0.23 0.58-1.66	.001	-3.238
Gradient Index	Mean Median(Range)	4.90 4.78	1.00 3.71-6.81	4.40 3.77	2.19 3.19-12.06	.069	-1.818

Table 5. Differential analysis of the values obtained in plans prepared with two different techniques in terms of critical organ dose parameters (Hel-IMRT: helical intensity modulated radiotherapy, VMAT: volumetric arc therapy).

		Hel-IMRT Plan		VMAT Plan		P	Z
Spinal Cord maximum dose (0,03cc)	Mean Median (Range)	2764 cGy 2911	1161 929-4751	3597 3984	824 2030-4472 cGy	0.011	-2.556
Lung-PTV V20	Mean Median (Range)	23.50% 23.4	6.16 7.70-33.70	17.74% 17.27	6.39 3.95-29.15	0.002	-3.067
Lung-PTV V5	Mean Median (Range)	54.86 55.9	10.74 22.30-72.70	49.03 50.55	12.15 17.34-65.12	0.01	-3.181
Lung-PTV Mean dose	Mean Median (Range)	1354 cGy 1362	303 558-1916 cGy	1080 1067	302 348-1767 cGy	0.01	-3.408
Heart Mean dose	Mean Median (Range)	777 cGy 558	581 54-1716 cGy	619cGy 626	424 38-1343 cGy	0.012	-2.499
Esophagus maximum dose (0,03cc)	Mean Median (Range)	5369 cGy 5841	1200 2899-6480 cGy	5679 6066	1007 2517-6289 cGy	0.478	-.710
Esophagus Mean dose	Mean Median (Range)	1575 cGy 1453	968 512-3584 cGy	1601cGy 1482	679 830-3167 cGy	0.820	-.227
Hot point (0.01cc)	Mean Median (Range)	6616 cGy 6562	281 6260-7268	6510cGy1 6500	150 6302-6816	0.427	-.795

DISCUSSION

In this thesis study, using CT images of 15 NSCLC patients who completed their treatment in Ankara City Hospital Radiation Oncology Clinic, Hel-YART and VMAT planning techniques were used by the thesis student with the aim of the same plan objectives. The aim here is to determine the advantages and disadvantages of two different techniques in radiotherapy for lung cancer. According to the results of the study, the two different techniques have different dosimetric advantages. However, the clinical significance of this dosimetric difference in target and critical tissues is unknown.

Tomotherapy uses a different technology to linear accelerators. Thanks to the movement of the tomotherapy table and the 360-degree rotating gantry, the radiation is delivered helically. The VMAT technique is based on the use of more treatment angles, which allows the dose at any point on the target edge to be the same as the dose at the center of the field.

The reduction in treatment time is due to the higher dose rate when using arc techniques and the avoidance of unnecessarily complex MLC positions with the mathematical optimization solution. New treatments for lung cancer include radiotherapy, immunotherapy, targeted agents, chemotherapy and current surgical techniques and are more complex than in the past. In parallel with better identification of molecular markers and biomarkers compared to the past; targeted therapies have been developed and overall survival of patients has improved (11). Despite new agents and changing protocols, the role of RT in the treatment of locally advanced NSCLC remains. RT can be used for both curative and palliative purposes in the treatment of NSCLC. 77% of all lung cancer patients require RT during their treatment course (12). In an article evaluating all lung cancers, an 8.3% increase in local control and a 4% increase in overall survival over 5 years are achieved with the use of RT in the local control of lung cancer (13).

RT is rapidly moving towards fewer side effects, more effective tumor control, shorter and more targeted treatment programs. After the 2D and 3D treatments used in the past; thanks to technological advances, new and modern techniques have begun to replace these traditional treatments. The main current techniques are IMRT, IGRT, VMAT, helical tomotherapy and SRT. For better RT applications, techniques such as 4D CT, deep inspiration breathing, and simulation CT scans have also been developed. With 3D treatments, treatment times are shorter, but may not be sufficient for dose wrap and surrounding critical organ doses. With PTV, IMRT can achieve better dose delivery, but treatment times are longer and there is an increase in low-dose regions. Helical IMRT (Hel-IMRT) is a type of IMRT used

in treatments with helical tomotherapy. With Hel-IMRT, rotational dosing is used. Modern techniques have made it easier to understand the uncertainties of tumor movement, resulting in a reduction in the margins that can be achieved. In parallel, a reduction in normal tissue doses has led to a reduction in side effects (14). Optimal simulation and RT are still an ongoing research topic and many studies are being conducted.

Dosimetric studies comparing different techniques have been performed to evaluate which technique is more beneficial in different patient populations. Lung cancer is one such patient population.

In a study by Tang et al. (15); it was found that using a certain number of beam angles in IMRT planning can be effective in providing optimal dose distribution, but the choice of angle is important for the optimal plan. In the IMRT technique, dose adjustment is performed using MLC movements only, whereas in the VMAT technique, dose rate and gantry speed parameters reduce the load on the MLC during dose adjustment, providing fewer MLC movements and thus increasing the accuracy of the calculated plan in practice.

Another area of study is the combined use of different techniques in a single treatment, known as hybrid treatment planning. In a dosimetric study comparing 3D-VMAT hybrid planning and Hel-IMRT, both techniques produced plans that met current guidelines. However, shorter treatments with lower MU were achieved with the hybrid plan; better counter lung, heart and oesophageal doses were achieved (16).

In another comparison of VMAT and IMRT plan, Zhao et al; compared 3 different plans in 15 stage IIIB patients. These; 1. a VMAT plan created with 2 partial arcs, 2. an IMRT plan created with 5 different planes, and finally 3. a hybrid plan created by combining these two plans (17). As expected, lower lung doses at V5, V10, V20 and mean lung were obtained with the hybrid plan compared to the VMAT plan; on the other hand, better critical organ dose protection and lower MU values were obtained compared to the IMRT plan. The researchers argued that the superiority achieved with IMRT was achieved with minimal increases in V5 and V10, and therefore hybrid planning may be beneficial in these cases.

CONCLUSION

The rationale for creating a hybrid plan is to combine the dose conformity provided by VMAT and its advantage in critical organ dose protection with the advantage of low dose area volume reduction achieved with IMRT. This technique can be used in challenging cases. Our study compared two different techniques with continuous irradiation, and the advantage that can be achieved in low dose areas is limited for both techniques compared to static field IMRT plans. The difference in low-dose areas depends on the different planning algorithms, helical and cross-sectional irradiation, and especially on the experience of the physicist who made the plan. The variable depending on the experience of the physicist was tried to be reduced by the PhD student by making both plans and setting specific targets. At the end of the study, significantly lower doses were obtained in the lung low dose area regions and lung-heart mean doses with the VMAT technique. However, no conclusions can be drawn about their clinical significance.

In our study, each patient received a total dose of 60 Gy in 30 fractions. Our results showed that at least 98% of the PTV volume received 95% of the prescribed dose in both techniques. Comparison of the two schedules in terms of dose delivery

The D value of 95% is significantly higher in the Hel-IMRT technique when the time is higher. VMAT was found to be superior in terms of CI. There was no significant difference between the two techniques in terms of HI and GI values. Each technique has its own advantages and disadvantages. For this reason, the choice of technique in treatment planning should be based on patient and clinic factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No: 1 Clinical Research Ethics Committee (Date: 29.12.2021, Decision No: E1-21-2198).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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ORİJİNAL ARAŞTIRMA
ORIGINAL ARTICLE

COVID-19 Hastalarında Biyokimyasal, İnflamatuar ve Hematolojik Parametrelerin Değerlendirilmesi

Evaluation of Biochemical, Inflammatory, and Hematological Parameters in COVID-19 Patients

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ÖZ

Amaç: Bu çalışma, COVID-19 hastalarında yaş ve cinsiyet gibi demografik faktörlerin rutin laboratuvar parametreleri üzerindeki etkilerini değerlendirmeyi amaçlamaktadır. COVID-19 hastalığı, hafif semptomlardan kritik çoklu organ yetmezliğine kadar geniş bir yelpazede klinik bulgular sergileyebilir. Bu bağlamda, biyokimyasal belirteçlerin hastalığın prognozunu tahmin etmedeki rolü oldukça önemlidir.

Gereç ve Yöntem: Çalışmada, COVID-19 hastalarında yaş ve cinsiyete bağlı olarak karaciğer, böbrek ve kalp fonksiyonlarını değerlendiren biyokimyasal parametreler ile inflamasyon belirteçleri analiz edilmiştir.

Bulgular: Ürik asit, Blood urea nitrogen (BUN), Laktat dehidrogenaz (LDH), Potasyum, C-reaktif protein (CRP), CRP/Lenfosit oranı (CLR) ,Nötrofil/Lenfosit oranı (NLR), D-Dimer, Monosit sayısı (MONO) Fibrinojen, Hematokrit (HCT), Beyaz kan hücreleri (WBC), Nötrofil sayısı (NEU) ve Platelet dağılım genişliği (PDW) parametreleri ile yaş arasında pozitif korelasyon görülmüştür. Ayrıca De Ritis oranı (AST/ALT), sodyum, Gromerular filtrasyon oranı (EFGR), Kırmızı kan hücreleri (RBC), Hemoglobin (HBG) ve Eozinofil sayısı (EOS)'nın yaş ile negatif korelasyon gösterdiği görülmüştür. Ayrıca, trombositopeni ve hiperkoagülasyon gibi trombozla ilişkili belirteçlerde de yaşla birlikte artış görülmüştür.

Sonuç: Çalışmamız, COVID-19 hastalarında yaşla birlikte inflamatuar belirteçler ve organ fonksiyonlarındaki bozulmaların belirgin hale geldiğini ortaya koymaktadır. Yaşlı hastaların yakından izlenmesi gerektiği ve bu grupta hastalığın prognozunu değerlendirmek için bulgular kısmında çok önemli korelasyon gösteren parametrelerin belirteç olarak kullanılabileceği sonucuna varılabilir.

Anahtar Kelimler: COVID-19, yaş, cinsiyet, laboratuvar parametreleri

ABSTRACT

Aim: This study aims to evaluate the effects of demographic factors such as age and gender on routine laboratory parameters in COVID-19 patients. COVID-19 disease can exhibit a wide range of clinical findings, from mild symptoms to critical multiorgan failure. In this context, the role of biochemical markers in predicting the prognosis of the disease is very important.

Material and Method: In the study, biochemical parameters evaluating liver, kidney and heart functions and inflammation markers were analyzed in COVID-19 patients depending on age and gender.

Results: Uric acid, Blood urea nitrogen (BUN), Lactate dehydrogenase (LDH), Potassium, C-reactive protein (CRP), CRP/Lymphocyte ratio (CLR), Neutrophil/Lymphocyte ratio (NLR), D-Dimer, Monocyte count (MONO), Fibrinogen, Hematocrit (HCT), White blood cells (WBC), Neutrophil count (NEU) and Platelet distribution width (PDW) parameters were positively correlated with age. In addition, De Ritis ratio (AST/ALT), sodium, Gromerular filtration rate (EFGR), Red blood cells (RBC), Hemoglobin (HBG) and Eosinophil count (EOS) were negatively correlated with age. In addition, thrombosis-related markers such as thrombocytopenia and hypercoagulation increased with age.

Conclusion: Our study reveals that inflammatory markers and organ function deteriorations become evident with age in COVID-19 patients. It can be concluded that elderly patients should be closely monitored and that parameters that show very significant correlation in the findings section can be used as markers to evaluate the prognosis of the disease in this group.

Keywords: COVID-19, age, gender, laboratory parameters

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GİRİŞ

COVID-19, 2019'un sonlarında Çin'in Vuhan kentinde ortaya çıkan ve hızla dünya genelinde yayılan yeni bir koronavirüs türü olan SARS-CoV-2'nin neden olduğu bulaşıcı bir hastalıktır. İlk olarak 31 Aralık 2019'da Çin'de tespit edilen bu virüs, hızla uluslararası boyutta bir tehdit haline gelmiştir. Dünya Sağlık Örgütü (DSÖ), 11 Mart 2020'de COVID-19'u pandemi olarak ilan etmiş ve bu tarihten itibaren dünya genelinde alınan önlemler hızla artmıştır. 2022 Ekim ayı itibarıyla, dünya genelinde 622 milyondan fazla vaka kaydedilmiş ve 6,5 milyondan fazla kişi COVID-19 nedeniyle hayatını kaybetmiştir. Türkiye'de ise 16,9 milyon vaka ve 101 binden fazla ölüm gerçekleşmiştir (1,2).

COVID-19, özellikle solunum yollarını etkileyen bir hastalık olarak bilinse de, yapılan araştırmalar virüsün birçok organ sistemini etkileyebileceğini göstermektedir. Özellikle ACE-2 reseptörleri yoluyla vücuda giriş yapan SARS-CoV-2, bu reseptörlerin bulunduğu akciğerler, böbrekler, kalp, bağırsaklar ve damar endotelyumu gibi birçok farklı organda hasara yol açabilmektedir (3,4). Bu durum, hastalığın çoklu organ yetmezliği ile sonuçlanabilen ciddi komplikasyonlara neden olabileceğini göstermektedir. COVID-19'un semptomları genellikle ateş, kuru öksürük, yorgunluk ve nefes darlığı gibi solunum yolu semptomlarıdır, ancak ileri vakalarda zatürre, akut solunum sıkıntısı sendromu (ARDS), sepsis ve septik şok gibi hayatı tehdit eden komplikasyonlar gelişebilmektedir (5,6).

COVID-19'un klinik seyri bireyden bireye değişiklik göstermekte olup, hastalığın şiddeti büyük ölçüde bireyin yaşı, cinsiyeti ve eşlik eden kronik hastalıklarına bağlıdır. Özellikle yaşlı bireyler, bağışıklık sistemi zayıflamış olanlar ve diyabet, hipertansiyon, kalp hastalıkları gibi komorbiditeleri olan kişiler COVID-19 enfeksiyonu sonucunda daha ciddi semptomlar ve komplikasyonlar yaşamaktadırlar (7,8). DSÖ'nün verilerine göre, enfekte olan bireylerin %80'i hafif semptomlar gösterirken, %20'si ciddi veya kritik hastalık geliştirmekte ve bu hastaların %6'sı yoğun bakım tedavisine ihtiyaç duymaktadır (9). Ayrıca, yaş arttıkça mortalite oranları da yükselmektedir; 70 yaş üzeri bireylerde mortalite oranı %8, 80 yaş üzeri bireylerde ise %14,8'e kadar çıkmaktadır (10).

COVID-19 hastalığının patofizyolojisi tam olarak anlaşılmamış olsa da, enflamasyonun önemli bir rol oynadığına dair artan kanıtlar bulunmaktadır. SARS-CoV-2 enfeksiyonu, vücudun bağışıklık yanıtını tetikleyerek ciddi bir sitokin fırtınasına yol açabilmektedir. Bu durum, özellikle akciğerlerde aşırı enflamasyona, alveol hasarına ve sonunda ARDS gelişimine neden olabilmektedir (11). Ayrıca, enfeksiyon sırasında artan pro-enflamatuar sitokinler, damar endotelinde hasar ve pıhtılaşma eğilimini artırarak tromboembolik olayların gelişimine zemin hazırlayabilir (12). Bu nedenle, COVID-19 hastalarında biyokimyasal ve hematolojik parametrelerdeki değişikliklerin incelenmesi, hastalığın seyrinin anlaşılmasında ve komplikasyonların öngörülmesinde kritik bir öneme sahiptir.

COVID-19 hastalarında yapılan çalışmalar, çeşitli biyokimyasal belirteçlerin hastalığın şiddetiyle ilişkili olduğunu ortaya koymuştur. CRP), interlökin-6 (IL-6) gibi enflamatuar belirteçlerin, ciddi vakalarda daha yüksek seviyelerde bulunduğu ve bu parametrelerin prognozun öngörülmesinde önemli rol oynadığı gösterilmiştir (13). Ayrıca, lenfosit sayısında azalma (lenfopeni), trombosit sayısında değişiklikler ve D-dimer gibi pıhtılaşma göstergelerinde artış, COVID-19'un seyrini öngörmede kullanılabilecek potansiyel biyomarkerlar arasında yer almaktadır (14).

COVID-19'un etkilediği diğer önemli sistemlerden biri de kardiyovasküler sistemdir. Enfeksiyon sırasında kalp kası hasarı, miyokardit, aritmi ve tromboembolik olaylar gibi çeşitli kardiyak komplikasyonlar ortaya çıkabilmektedir. Yapılan bir çalışmada, COVID-19 hastalarının %12'sinde akut miyokard hasarı tespit edilmiştir ve bu durum, özellikle hastalığın ilerleyen evrelerinde mortalite riskini artırmaktadır (15). Ayrıca, SARS-CoV-2 enfeksiyonu damar endotelyumunu doğrudan etkileyerek damar içi pıhtılaşmaya neden olabilmekte ve bu da venöz tromboembolizm gibi komplikasyonların gelişmesine yol açabilmektedir (16).

Bu çalışma, COVID-19 hastalarında biyokimyasal ve hematolojik parametrelerin değerlendirilmesi ve bu parametrelerin hastalığın şiddeti üzerindeki etkilerinin incelenmesini amaçlamaktadır. Özellikle, CRP, IL-6, lenfosit sayısı, D-dimer gibi biyokimyasal belirteçlerin hastalığın prognozunu belirlemedeki rolü araştırılmıştır. Bu çalışma, COVID-19'un patofizyolojisine dair bilgi sağlayarak, hastalığın yönetimi ve tedavi stratejilerinin geliştirilmesine katkıda bulunmayı hedeflemektedir.

GEREÇ VE YÖNTEM

Retrospektif bu çalışma Ankara Pursaklar Devlet Hastanesi'nde yapıldı. Çalışmaya 1 Mart 2020 ile 31 Ocak 2021 tarihleri arasında gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) ile tanısı 18 yaş ve üstü erişkin 1036 hasta dahil edildi. Çalışma sadece hastanede pozitif COVID-19 servisine yatışı yapılan COVID-19 pozitif hastalarla yapılmış, yoğun bakıma alınan hastalar çalışmaya dahil edilmemiştir. Hastaların yaş ve cinsiyet gibi demografik verileri, biyokimyasal parametreleri, inflamasyon ve koagulasyon faktörleri ve hematolojik verileri hastane bilgi işletim sisteminden geriye dönük olarak taranmıştır. Ayrıca nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLT) ve CRP/lenfosit oranı (CLR) hesaplanmıştır.

Hastaların Aspartat transaminaz (AST), Alanin transaminaz (ALT), De-Tiris oranı (AST/ALT), total bilirubin, ürik asit, BUN, kreatinin, EGFR, LDH, CK-MB, troponın I, glikoz, sodyum, potasyum, kalsiyum, klor'u kapsayan biyokimyasal parametreleri; CRP, CLR oranı, D-Dimer, ferritin, fibrinojen, Prokalsitonin (PCT), INR, APTT değerlerini kapsa-

yan inflamasyon ve koagulasyon faktörleri ve RBC, HGB, demir, HCT, Ortalama hücre hacmi,(MCV), MCH, MCHC, RDW, WCB, LYM#, NEU#, NLR, MON#, BAS#, EOS#, PLT, Platelet/Lenfosit oranı(PLR), Ortalama platelet hacmi(MPV) ve PDW'den oluşan hematolojik verileri değerlendirilmiştir.

Çalışma İzinleri

Bu çalışma için ilk olarak Sağlık Bakanlığı COVID-19 Bilimsel Çalışma Platformundan izin alınmıştır. Ardından Amasya Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan etik kurul onayı (karar no: 55/4-2021) alınmıştır.

Araştırmadan elde edilen veriler, IBM SPSS Version 22.0. (IBM Corp.) programı kullanılarak analiz edilmiştir. Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testi ile kontrol edilmiştir. Kategorik değişkenler sayı (n) ile ve sürekli değişkenler ortalama (mean) şeklinde gösterilmiştir. Gruplu karşılaştırmalarda Ki Kare testi, normal dağılıma uygun olmayan sürekli veriler ile iki grubun karşılaştırılmasında Mann Whitney U t esti, normal dağılıma uygun olan sürekli veriler ile iki grubun karşılaştırılmasında student t testi kullanılmıştır. Normal dağılıma uygun olmayan sürekli verilerde Kruskal-Wallis testi, Normal dağılıma uygun sürekli verilerde ise Tek Yönlü ANOVA kullanılmıştır. Biyokimyasal parametreler ile İnflamasyon ve Koagulasyon Faktörleri arasında anlamlı bir ilişki olup olmadığı korelasyon katsayılarına bakılarak incelenmiştir.

BULGULAR

Çalışmaya alınan hastaların sayısı 1036 olup; hastaların %57,4'ü (595 kişi) erkek %42,6'sı (441) kadındır. Hastaların yaşları incelendiğinde toplam 1036 hastanın %28,2'si (292 kişi) 18-45 yaş aralığında, %41,2'si (427 kişi) 46-64 yaş aralığında ve %30,6'sı (317 kişi) 65 yaş ve üzerindedir. Çalışmaya alınan hastaların ortalama yaşı ise 55 olarak bulgulanmıştır (**Tablo 1**).

Tablo 1. Hastaların yaş, cinsiyete göre gruplandırılması ve dağılımı

	n	%
Yaş		
18-45	292	28.2%
46-64	427	41.2%
65 >	317	30.6%
Cinsiyet		
Erkek	595	57.4%
Kadın	441	42.6%

Yaş grupları incelendiğinde biyokimyasal parametreler arasında AST/ALT oranı açısından anlamlı bir farklılık olduğu görülmektedir (p<0.0001). 18-45 yaş aralığındaki hastalarda ortalama değer 0.40 olup 46-64 yaş aralığında ortalama değer 0.18 ve 65 yaş üzerindeki hastalarda ise ortalama değer 0.14 olarak görülmektedir. T. bilirubin değerleri açısından yaş grupları arasında anlamlı bir farklılık olduğu söylenebilir (p=0.016). 18-45 yaş arası hastaların değer ortalaması 0.60 iken 65 yaş üzeri hastaların ortalama değeri 0.72'dir. Ürik asit. BUN. EGFR. LDH. troponin I. sodyum ve potasyum değerleri açısından yaş grupları arasında anlamlı bir farklılık olduğu görülmektedir (p<0.0001). CK-MB değeri açısından yaş grupları arasında anlamlı bir farklılık olduğu söylenebilir (p=0.013). 18-45 yaş arası hastaların ortalama değeri 13.19 iken 65 yaş üzeri hastaların ortalama değeri 22'dir. Glikoz değerleri açısından yaş grupları arasında anlamlı bir farklılık olduğu görülmektedir (p<0.0001). 18-45 yaş arasındaki hastaların ortalama glikoz değeri 123.03 iken 46-64 yaş arası hastaların ortalama değeri 160.33 ve 65 yaş üzeri hastaların ortalama değeri 161.85'dir (**Tablo 2**).

Tablo 2. Yaş grupları arasında biyokimyasal parametreler açısından farklılığın değerlendirilmesi

	Yaş Grupları						p
	18-45 Yaş		46-64 Yaş		65 Yaş ve Üzeri		
	Ortalama	Standart Sapma	Ortalama	Standart Sapma	Ortalama	Standart Sapma	
SGOT (AST)	26.51	12.41	36.27	43.86	31.20	14.91	0.108
SGPT (ALT)	34.66	58.28	40.15	33.21	39.85	32.70	0.183
AST/ALT oranı	0.40	0.60	0.18	0.46	0.14	0.57	<0.0001
T. BİLİRUBİN	0.60	0.34	0.59	0.29	0.72	0.48	0.016
ÜRİK ASİT	3.31	3.60	6.11	22.31	17.73	84.68	<0.0001
BUN	14.16	9.91	16.92	8.05	28.33	18.43	<0.0001
KREATİNİN	8.69	2.03	8.28	2.46	8.19	6.57	0.361
EGFR	111.26	16.57	93.45	17.02	73.51	21.71	<0.0001
LDH	201.47	109.35	252.23	168.85	279.24	156.36	<0.0001
CK-MB	13.19	5.10	18.18	13.12	22.00	16.06	0.013
TROPONİN I	3.31	3.60	6.11	22.31	17.73	84.68	<0.0001
GLİKOZ	123.03	74.24	160.33	96.48	161.85	83.27	0.001
SODYUM	130.00	25.09	125.05	40.52	114.78	42.90	<0.0001
POTASYUM	4.09	0.41	4.22	0.50	4.30	0.63	<0.0001
KALSİYUM	8.71	0.88	8.83	0.69	8.68	0.57	0.906
KLOR	99.00	1.41	98.84	2.76	100.12	6.34	0.810

Yaş grupları arasında inflamasyon ve koagulasyon faktörlerinden CRP. CLR oranı. D-dimer. fibrinojen. PCT. INR ve APTT değerleri açısından anlamlı bir farklılık olduğu görülmektedir (p<0.0001). CRP değerleri incelendiğinde 18-45 yaş arası hastaların CRP değerleri ortalaması 11.15 iken 46-64 yaş arası hastaların ortalaması 14.25 ve 65 yaş üzeri hastaların ortalama değeri 21.15'dir. CLR oranı incelendiğinde 18-45 yaş arası hastaların CLR oranı ortalaması 7.37 iken 65 yaş ve üzeri hastalarda bu oran 14.67'dir. Fibrinojen değeri incelendiğinde 18-45 yaş arası hastalarda ortalama değer 343.09 iken 46-64 yaş arası hastalarda 390.75 ve 65 yaş üzeri hastalarda ise ortalama değe 478.80'dir. Ferritin değeri açısından yaş grupları arasında anlamlı bir farklılık olmadığı söylenebilir (p=0.174) (**Tablo 3**) .

Yaş grupları arasında hematolojik parametrelerden RBC. HBG. HCT. WBC. NEU#. NLR oranı. MON# ve PDV değerlerinin çok anlamlı düzeyde (p<0.0001) farklılık gösterdiği görülmektedir. Ayrıca MCH. MCHC. BAS#. EOS#. PLT ve MPV parametrelerinin de belirgin şekilde farklılık (p<0.05) gösterdiği görülmektedir (**Tablo 4**).

Tablo 3. Yaş grupları arasında inflamasyon ve koagulasyon faktörleri açısından farklılığın değerlendirilmesi

	Yaş Grupları						p
	18-45 Yaş		46-64 Yaş		65 Yaş ve Üzeri		
	Ortalama	Standart Sapma	Ortalama	Standart Sapma	Ortalama	Standart Sapma	
CRP	11.15	7.80	14.25	6.91	21.15	13.11	<0.0001
CLR oranı	7.37	7.36	9.29	7.53	14.67	13.41	<0.0001
D-DİMER	0.73	1.57	0.80	1.14	1.79	4.00	<0.0001
FERRİTİN	421.82	407.59	574.14	457.26	548.22	461.55	0.174
FİBRİNOJEN	343.09	362.07	390.75	365.75	478.80	390.92	<0.0001
PCT	0.21	0.07	0.23	0.09	0.22	0.08	<0.0001
INR	1.09	0.23	1.10	0.38	1.14	0.33	<0.0001
APTT	23.15	2.93	24.35	3.73	23.56	5.53	<0.0001

Tablo 4. Yaş grupları arasında hematolojik veriler açısından farklılığın değerlendirilmesi

	Yaş Grupları						p
	18-45 Yaş		46-64 Yaş		65 Yaş ve Üzeri		
	Ortalama	Standart Sapma	Ortalama	Standart Sapma	Ortalama	Standart Sapma	
RBC	4.93	0.52	4.81	0.53	4.62	0.56	<0.0001
HGB	14.19	1.70	13.83	1.69	13.47	1.68	<0.0001
DEMİR	29.00	24.57	43.56	46.42	28.00	18.15	0.766
HCT	84.27	47.28	112.63	77.95	117.50	78.70	<0.0001
MCV	87.25	6.10	86.76	6.13	87.92	6.46	0.197
MCH	28.84	2.38	28.81	2.38	29.25	2.48	0.012
MCHC	33.03	1.11	33.19	1.01	33.24	1.02	0.014
RDW	13.63	1.69	13.73	1.70	13.92	2.02	0.212
WCB	5.88	2.93	6.53	2.81	7.29	3.86	<0.0001
LYM#	1.85	1.05	1.93	1.02	1.98	1.31	0.547
NEU#	3.53	2.35	4.21	2.38	4.68	2.88	<0.0001
NLR oranı	2.40	2.32	2.82	2.48	3.33	3.32	<0.0001
MON#	0.43	0.27	0.51	0.36	0.61	0.54	<0.0001
BAS#	0.04	0.16	0.04	0.20	0.03	0.02	0.041
EOS#	39.67	54.84	30.03	44.83	26.50	37.12	0.028
PLT	227.89	80.95	236.27	103.94	258.18	97.09	0.001
PLR oranı	147.89	82.40	165.54	116.64	161.20	113.80	0.132
MPV	9.15	0.81	9.18	0.78	9.33	0.81	0.012
PDW	16.08	2.36	16.16	2.26	16.76	2.40	<0.0001

Tablo 5. Yaş ile biyokimyasal parametreler. inflamasyon ve koagülasyon faktörleri ve hematolojik veriler arasındaki korelasyon katsayılarının incelenmesi

	r	p
Biyokimyasal Parametreler		
SGOT (AST)	0.113	0.124
SGPT (ALT)	0.038	0.241
AST/ALT oranı	-0.196	<0.0001
T. BİLİRUBİN	0.148	0.002
ÜRİK ASİT	0.317	<0.0001
BUN	0.434	<0.0001
KREATİNİN	-0.050	0.203
EGFR	-0.686	<0.0001
LDH	0.217	<0.0001
CK-MB	0.282	0.017
TROPONİN	0.127	0.002
GLİKOZ	0.153	0.005
SODYUM	-0.170	<0.0001
POTASYUM	0.143	<0.0001
KALSİYUM	-0.137	0.318
KLOR	0.240	0.179
İnflamasyon Ve Koagulasyon Faktörleri		
CRP	0.397	<0.0001
CLR oranı	0.313	<0.0001
D-DİMER	0.186	<0.0001
FERRİTİN	0.055	0.436
FİBRİNOJEN	0.153	<0.0001
PCT	0.051	0.103
INR	0.014	0.716
APTT	-0.070	0.056
Hematolojik Veriler		
RBC	-0.238	<0.0001
HGB	-0.188	<0.0001
DEMİR	-0.139	0.397
HCT	0.150	<0.0001
MCV	0.038	0.226
MCH	0.060	0.056
MCHC	0.070	0.025
RDW	0.077	0.014
WCB	0.174	<0.0001
LYM#	0.048	0.122
NEU#	0.171	<0.0001
NLR oranı	0.146	<0.0001
MON#	0.163	<0.0001
BAS#	-0.026	0.413
EOS#	-0.122	<0.0001
PLT	0.033	0.295
PLR oranı	0.059	0.058
MPV	0.086	0.006
PDW	0.113	<0.0001

Yaş ile biyokimyasal parametreler. inflamasyon ve koagulasyon faktörleri ve hematolojik veriler arasında korelasyon katsayıları incelenmiş olup tabloda gösterilmiştir. Biyokimyasal parametrelerden t. bilirubin. ürik asit. BUN. LDH. CK-MB. Troponin I. glukoz ve potasyum arasında 0.01 anlamlılık düzeyinde pozitif yönde bir ilişki olduğu söylenebilir. Yani yaş arttıkça bu parametrelerde artış gözlemlenmiştir. Buna karşın AST/ALT oranı. EFGR ve sodyum (korelasyon katsayıları sırası ile =-0.196; -0.686 ve -0.170; p<0.0001) yaşla negatif korelasyon göstermişlerdir. Diğer bir ifade ile bu parametreler yaşla birlikte çok anlamlı bir şekilde azalma göstermişlerdir. İnflamasyon ve Koagulasyon faktörlerinden CRP. CLR. D-dimer ve Fibrinojen (korelasyon katsayıları sırası ile =0.397; 0.313; 0.186 ve 0.153; p<0.0001) ile yaş arasında çok anlamlı düzeyde pozitif korelasyon bulunmuştur. Yaşla birlikte bu parametrelerde artışlar görülmüştür. Hematolojik verilerden HCT. WBC. NEU#. NLR. MON#. MPV ve PDV parametreleri ile yaş arasında p<0.0001düzeyinde çok anlamlı pozitif korelasyon görülmüştür. Yaş ile birlikte bu hematolojik parametrelerde de artış görülmüştür. Ancak RBC. HBG ve EOS# parametrelerinde negatif korelasyon görülmüştür (korelasyon katsayıları sırası ile =-0.238; -0.188 ve -0.122; p<0.0001) (**Tablo 4**).

TARTIŞMA

Her ne kadar COVID-19 ile ilgili yayınların sayısı hızla artsa da. yaş ve cinsiyet gibi demografik faktörlerin rutin laboratuvar parametreleriyle ilişkisi henüz tam olarak açıklığa kavuşturulmamıştır. COVID-19 şiddeti asemptomatik vakalardan kritik sistemik ve çoklu organ patolojilerine kadar geniş bir yelpazede değişkenlik göstermektedir. Bu nedenle hastalığın seyri ve sonuçlarını tahmin edebilecek biyokimyasal belirteçlerin tanımlanması büyük önem taşır. COVID-19 hastalarına yaygın olarak istenen testler arasında tam kan sayımı (CBC). pıhtılaşma testleri INR. aPTT) ve inflamasyon belirteçleri (NLR. IL-6. CRP) yer alır. Aynı zamanda ALT. AST. kreatinin ve LDH gibi organ fonksiyon parametreleri de sıkça takip edilir (17).

COVID-19. birçok hayati organa ciddi şekilde zarar verebilir ve organ fonksiyonlarını takip etmek için biyokimyasal belirteçlerin izlenmesi çok önemlidir. Örneğin. LDH. COVID-19 hastalarında genellikle yükselir ve akciğer hasarını gösterir (18). Ayrıca. trombositopeni. trombosit sayısının 50.000'in altına düşmesi durumunda. mortalitenin arttığı bir durumu ifade eder. Trombositopeni. COVID-19'un akciğerdeki megakaryositlerin olgunlaşmasını etkilemesi ve SARS-CoV-2'nin ACE2 reseptörlerine bağlanarak endotel hasarı oluşturmasıyla ilişkilidir. Bu süreç. trombosit agregasyonuna ve tromboza yol açarak yaygın damar içi pıhtılaşma (DIC) ve trombositopeni ile sonuçlanır (19).

Karaciğer COVID-19'dan sıklıkla etkilenir ve ALT ile AST seviyelerindeki yükselme hepatosellüler hasarın bir göstergesidir (20). ALT. karaciğerde daha spesifik bir belirteçken. AST birçok dokuda bulunduğundan karaciğer hasarı için daha az spesifik bir belirteçtir. COVID-19'un karaciğeri doğrudan etkileyebileceği düşünülmektedir; özellikle ACE2 reseptörü bakımından zengin olan kolanjiyositler virüs tarafından enfekte olabilir ve bu da karaciğer fonksiyon bozukluğuna neden olabilir (21). COVID-19 hastalarının %14 ila %53'ü arasında karaciğer fonksiyon bozukluğu bildirilmiştir (22). Ayrıca. yaşlı COVID-19 hastalarında sodyum dengesizlikleri (hiponatremi ve hipernatremi) ciddi pnömoni ile ilişkilendirilmiştir (23).

CRP. COVID-19 şiddetinin erken bir göstergesi olabilir ve hastaneye başvuru anında değerlendirilerek erken müdahale fırsatı sağlayabilir (24). Benzer şekilde. fibrinojen seviyeleri şiddetli hastalığı olanlarda daha yüksek bulunmuş ve D-Dimer ile fibrinojenin mortaliteyi öngörmede önemli faktörler olduğu bildirilmiştir (25-26).

Yaşla birlikte karaciğer enzimlerindeki değişiklikler gözlemlenmiştir. En yüksek AST ve ALT seviyeleri 45-64 yaş grubunda bulunmuş. ancak De Ritis oranının (AST/ALT) yaşla birlikte azaldığı gözlenmiştir. Yaşa bağlı karaciğer hasarını değerlendirmek için AST/ALT oranı yaygın olarak kullanılmaktadır. Bulgularımız. önceki araştırmalarla uyumlu olarak yaşa bağlı olarak AST ve ALT seviyelerinin arttığını göstermektedir (27). Bununla birlikte. bazı çalışmalar COVID-19 hastaları arasında bu enzimlerde yaşa bağlı anlamlı bir fark bulmamıştır (18).

Kalp hasarı. özellikle yaşlı hastalarda daha sık gözlemlenen bir komplikasyon olup. yaşlılarda LDH seviyeleri belirgin şekilde yüksektir. Bu durum. yaşla birlikte miyokardiyal hasarın arttığını düşündürmektedir (28-29). Böbrek fonksiyonları da yaşla birlikte kötüleşmektedir. Çalışmamızda. BUN ve ürik asit seviyelerinin yaşla birlikte artarken EGFR değerlerinin düştüğü gözlenmiştir. Bu bulgular. yaşlı hastalarda akut böbrek hasarı (AKI) insidansının daha yüksek olduğunu desteklemektedir [30]. COVID-19'a bağlı böbrek hasarının başlıca nedenleri arasında sepsis. sitokin fırtınası ve virusün doğrudan böbrek hücrelerine saldırması yer alır (31).

CRP. CLR. D-Dimer ve fibrinojen gibi inflamatuar belirteçlerin yaşla birlikte arttığı gözlenmiştir. Özellikle yaşlı hastalarda COVID-19'un pıhtılaşma bozukluklarına yol açabileceği düşünülmektedir. Yaşlanma ile bazı pıhtılaşma faktörlerinin artması. yaşlı hastalarda hiperkoagülasyon durumuna yol açabilir (32). Bulgularımız. CRP seviyelerinin yaşla birlikte önemli ölçüde arttığını göstermektedir; bu da yaşlı hastalarda daha yüksek inflamatuar yanıtlarla ilişkilendirilebilir (33).

Kan parametreleri açısından. yaşla birlikte RBC. HGB. BAS ve EOS düzeylerinde azalma. buna karşılık WBC. NEU. NLR ve PLT düzeylerinde artış görülmüştür. Yüksek NLR. COVID-19 hastalarında mortaliteyi öngörmede önemli bir belirteç olarak kabul edilir (34). Eozinofil sayısındaki azalma ise. virüs kaynaklı enfeksiyonlarda beklenen bir durumdur ve kötü prognoza işaret edebilir (35). Eozinofiller enfekte olmuş dokularda birikerek enfeksiyonla savaşır ve bu süreçte kan dolaşımında azalır (35).

SONUÇ

Bu çalışma COVID-19 hastalarında yaşa bağlı olarak inflamatuar ve hematolojik belirteçlerdeki farklılıkları ortaya koymuştur. Yaşlı hastalar. daha şiddetli inflamatuar yanıtlar. çoklu organ yetmezliği ve daha kötü sonuçlarla karşı karşıya kalmaktadır. Bu bulgular. özellikle yaşlı hastaların yakından izlenmesi gerektiğini ve CRP. D-Dimer. LDH ve BUN gibi belirteçlerin COVID-19'un seyrini öngörmede önemli olduğunu vurgulamaktadır.

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