İÇİNDEKİLER/CONTENTS

EGE KLİNİKLERİ TIP DERGİSİ
THE MEDICAL JOURNAL OF AEGEAN CLINICS

DANIŞMA KURULU/ADVISORY BOARD

YAZARLARA YÖNERGELER

GENEL BİLGİLER

Ege Klinikleri Tıp Dergisi, İzmir Hastanelerine Yardım ve Bilimsel Araştırmaları Teşvik Derneği'nin süreli yayın organıdır. Yılda üç sayı olarak yayımlanır. Basım ayları Nisan, Ağustos ve Aralık'tır. Dergide, tıbbın her dalı ile ilgili prospektif, retrospektif ve deneysel araştırmalar, olgu sunumu, editöre mektuplar ve derlemeler yayınlanır. Yayınlanan makalelerde konu ile ilgili en yüksek etik ve bilimsel standartlarda olması ve ticari kaygılarda olmaması şartı gözetilir. Yayın için gönderilen çalışmalar; orijinal, başka bir dergide değerlendirme sürecinde olmayan ve daha önce basılmamış olması koşullarıyla kabul edilir.

Dergiye gönderilen makale biçimsel esaslara uygun ise, baş editör ve en az yurt içi-yurt dışı iki danışman incelemesinden geçip gerek görüldüğü takdirde istenen değişiklikler yazarlar tarafından yapılıp hakemlerce kabul edildikten sonra yayımlanır.

BİLİMSEL SORUMLULUK

Tüm yazarlar çalışmaya direkt olarak katkıda bulunmalıdır. Yazar olarak tanımlanmış tüm kişiler çalışmayı planlamalı veya gerçekleştirmeli, çalışmanın yazılmasında, gözden geçirilmesinde ve son halin onaylanmasında rol almalıdır. Bilimsel kriterleri karşılayan bir metnin ortaya çıkması tüm yazarların sorumluluğudur.

ETİKSEL SORUMLULUK

İnsan çalışmaları ile ilgili tüm makalelerde 'yazılı onamım' alındığını, çalışmanın Helsinki Deklarasyonu'na

(World Medical Association Declaration of Helsinki http://www.wma.net/en/30/publications/10policies/b3/index.html) göre yapıldığı ve lokal etik komite tarafından onayın alındığını bildiren cümleler mutlaka yer almalıdır.

Etik Kurul Onamlarının kendisi (Etik Kurul Onam Belgesi) yayınla birlikte gönderilmelidir.

Hayvanlar üzerinde yapılan deneyleri bildirirken yazarlar; labaratuvar hayvanlarının bakım ve kullanımı konusunda kurumsal veya ulusal yönergelerin takip edilip edilmediğini mutlaka bildirmelidirler.

Ege Klinikleri Tıp Dergisi yazarların cümlelerinden sorumlu değildir. Makale bir kez kabul edildikten sonra derginin malı olur ve dergiden izinsiz olarak başka bir yerde yayınlanamaz.

İSTATİSTİKSEL DEĞERLENDİRME

Tüm retrospektif, prospektif ve deneysel çalışma makaleleri bioistatiksel olarak değerlendirilmeli ve uygun plan, analiz ve bildirimde bulunmalıdır. p değeri yazı içinde net olarak belirtilmelidir (örn, p=0.014).

YAZIM DİLİ

Derginin resmi dilleri Türkçe ve İngilizce'dir. Türkçe metinlerde Türk Dil Kurumu'nca (www.tdk.gov.tr)www.tdk.gov.tr yayınlanan Türkçe sözlük temel alınmalıdır. Gönderilmiş makalelerdeki tüm yazım ve gramer hataları sunulan verileri değiştirmeksizin editör tarafından düzeltilir. Yazım ve gramer kurallarına metin yazımı yazarların sorumluluğundadır.

TELİF HAKKI BİLDİRİMİ

Telif hakkı devrini bildirmek için kapak mektubunda 'Bu makalenin telif hakkı; çalışma, basım için kabul edilmesi koşuluyla Ege Klinikleri Tıp Dergisi'ne devredilir' şeklinde belirtilmelidir. Makaleler için yazarlara herhangi bir ücret ödenmez.

YAZI TİPLERİ

Derleme: Derlemeler yeni veya tartışmalı alanlara ışık tutar. Dergi editörü derleme yazımı için yazar veya yazarlardan istekte bulunur.

Orijinal makaleler: Orijinal makaleler temel veya klinik çalışmalar veya klinik denemelerin sonuçlarını bildirir". Orijinal makaleler 2500 kelime ve 25 kaynaktan fazla olmamalıdır.

Olgu Sunumları: Dergi, tıbbın her alanındaki belirgin öneme haiz olgu sunumlarını yayınlar. Yazar sayısı 6'yı, kaynak sayısı ise 5'i geçmemelidir.

Editör'e Mektup: Metin 400 kelimeyi geçmemeli ve kaynak sayısı ise en fazla 3 olmalıdır (kaynaklardan biri hakkında değerlendirme yapılan yayın olmalıdır)

YAZI GÖNDERİMİ

Tüm yazılar elektronik ortamda idhdergi@yahoo.com adresine gönderilmelidir.

Kapak mektubu: Kapak mektubu gönderilen makalenin kategorisini, daha önce başka bir dergiye gönderilmemiş olduğunu, çıkar ilişkisi bildirimini, yayın hakkı devri bildirimini ve varsa çalışmayı maddi olarak destekleyen kişi ve kurumların adlarını içermelidir.

Başlık sayfası: Bu sayfada çalışmanın tam ismi ve kısa başlığı (karakter sayısı ve boşluklar toplamı 55'i geçmemelidir) olmalıdır. Katkıda bulunanların adlarını ve çalıştıkları kurumları listeleyin. Yazışmaların yapılacağı yazar (yazışma yazarı) belirtilmelidir. Bu yazar yayının basım sürecinde dergi editörü ile iletişimde bulunacaktır. Öte yandan tüm yazarların ORCID numarası da eklenilmeli, ORCID numarası olmayan yazarlar en kısa zamanda edinilmelidir. http://orcid.org adresinden bireysel ORCID için **ücretsiz** kayıt oluşturulabilinir.

Öz ve Anahtar Kelimeler: Özet 250 kelimeyi geçmemelidir. Çalışmanın amacını, yöntemi, bulgu ve sonuçları özetlemelidir. İlaveten 3 adet anahtar kelime alfabetik sırayla verilmelidir.

Giriş: Giriş bölümü kısa ve açık olarak çalışmanın amaçlarını tartışmalı, çalışmanın neden yapıldığına yönelik temel bilgileri içermeli ve hangi hipotezlerin sınandığını bildirmelidir.

Gereç ve yöntemler: Okuyucunun sonuçları yeniden elde edebilmesi için açık ve net olarak yöntem ve gereçleri açıklayın. İlk vurgulamada kullanılan araç ve cihazların model numaralarını, firma ismini ve adresini (şehir, ülke) belirtin. Tüm ölçümleri metrik birim olarak verin. İlaçların jenerik adlarını kullanın.

Bulgular: Sonuçlar mantıklı bir sırayla metin, tablo ve görüntüler kullanılarak sunulmalıdır. Çok önemli gözlemlerin altını çizin veya özetleyin. Tablo ve metinleri tekrarlamayın.

Tartışma: Çalışmanın yeni ve çok önemli yönlerine, sonuçlarına vurgu yapın. Tartışma bölümü çalışmanın en önemli bulgusunu kısa ve net bir şekilde içermeli, gözlemlerin geçerliliği tartışılmalı, aynı veya benzer konulardaki yayınların ışığında bulgular yorumlanmalı ve yapılan çalışmanın olası önemi belirtilmelidir. Yazarlara, çalışmanın esas bulgularını kısa ve özlü bir paragrafla vurgu yapmaları önerilir.

Teşekkür: Yazarlar araştırmaya katkıda bulunan ancak yazar olarak atanmayan kişilere teşekkür etmelidir.

Kısaltmalar: Kelime veya söz dizinini ilk geçtiği yerde parantez içinde verilir. Tüm metin boyunca o kısaltma kullanılır.

Tablolar: Metin içinde tablolar ardışık olarak numaralandırılmalıdır. Her bir tabloya bir numara ve başlık yazın. Tablolar fotoğraf veya grafik dosyası olarak gönderilmemelidir.

Kaynaklar: Kaynaklar metin içinde alıntılanma sırasına uygun olarak doğal sayılar kullanılarak numaralandırılmalı ve cümlenin sonunda parantez içinde verilmelidir. " Uniform Requirements for Manuscript Submitted to Biomedical Journals" formatını kullanın. Yazar sayısı altı veya daha az ise hepsini, yedi veya daha fazla ise sadece ilk üç ismi yazın ve 've ark.'ı ilave edin. Dergi isimleri tam olarak verilmelidir. Kaynak ve kısaltılmış dergi adları yazımları Cumulated Index Medicus'a veya aşağıda verilen örneklere uygun olmalıdır.

Dergi makaleleri için örnek

*Sigel B, Machi J, Beitler JC, Justin JR**. Red cell aggregation as a cause of blood-flow echogenicity. Radiology 1983;148(2):799-802.*

Komite veya yazar grupları için örnek

The Standard Task Force, American Society of Colon and Rectal Surgeons: Practice parameters for the treatment of haemorrhoids. Dis Colon Rectum 1993; 36: 1118-20.

Kitaptan konu için örnek

Milson JW. Haemorrhoidal disease. In: Beck DE, Wexner S, eds. Fundamentals of Anorectal Surgery. 1 1992; 192-214. 1a ed. New York: McGraw-Hill

Kitap için örnek

Bateson M, Bouchier I. Clinical Investigation and Function, 2nd edn. Oxford: Blackwell Scientific Publications Ltd, 1981.

MAKALE GÖNDERİM KURALLARIMIZ

• Telif Hakkı Devir Formu tüm yazarlar tarafından imzalanılmalıdır.

• Makalenin tüm yazarları ORCID numaralarını göndermelidir. (Http://orcid.org adresinden ücretsiz olarak ORCID ID edinebilir ve kayıt olabilirsiniz. Dergimizin sayfa düzenine uygun olarak ; Yazının ilk sayfası.)

• Etik Kurul Onayı'nın kendisi (Etik Kurul Onay Belgesi) çalışma ile birlikte gönderilmelidir. Ayrıca çalışmanın başlığı Etik Kurul Belgesi'ndeki ile birebir aynı olmalıdır.

• Dergimizde yayınlanacak makaleler için etik kurul onayının alınması ve çalışmanın materyal-yöntem bölümünde çalışmanın etik kurul onayını aldığına dair bir açıklamanın bulunması zorunludur.

• Olgu sunumlarının dergimizde yayımlanabilmesi için hasta/hastaların onamının alınması ve olgu sunumunun giriş bölümünde 'hastadan/hastalardan onay alındığı'nı ifade eden bir cümle yer almalıdır.

• Makaleniz tek dosyada olmalıdır. Çalışma tasarımı sırası şu şekilde olmalıdır: Türkçe Başlık, İngilizce Başlık, Türkçe Özet ve Türkçe Anahtar Kelimeler, İngilizce Özet ve İngilizce anahtar kelimeler. Tablo/tablolar ve resim/resimler belirtilen yerde olmalıdır.

• Kapak sayfası ekteki örnekte olduğu gibi tasarlanılmalıdır.

EGE KLİNİKLERİ TIP DERGİSİ

TELİF HAKLARI DEVİR FORMU

Yazının Başlığı: |

Sorumlu Yazarlar:

Yazarların sorumlulukları:

- Yazı(lar) (sözlü veya poster sunum şekilleri hariç) başka hiçbir yerde yayınlanmamış ve şu anda başka bir dergi veya her hangi bir yayımcıda değerlendirme altında olmamalıdır.
- Makalenin yayınlanması ile ilgili diğer yazar onaylarından gönderen yazar sorumludur.
- Belirli bir kurum tarafından desteklenen yazılar için gerekli kurum onayının alınmasından yazarlar sorumludur.
- Yazıların bilimsel ve etik sorumluluğu yazarlara aittir.

| Yazar Adı Soyadı | İmza | Tarih |

Determinant Role of Magnetic Resonance Imaging in Transition of Clinical Isolated Syndrome to Multiple Sclerosis

Klinik İzole Sendromda Multipl Skleroza Dönüşümde Manyetik Rezonans Görüntülemenin Belirleyici Rolü

Ali BİGE*0000-0212-4446-0717

* Zonguldak Bülent Ecevit Üniversitesi, Tıp Fakültesi Hastanesi, Nöroloji Anabilim Dalı, Zonguldak

** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

*** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Yazışma Adresi: Ali BİGE

Zonguldak Bülent Ecevit Üniversitesi,

Tıp Fakültesi Hastanesi, Nöroloji Anabilim Dalı, ZONGULDAK

Gsm: 0532xxxxxx

e-mail adresi: alibige@gmail.com

INSTRUCTIONS FOR AUTHORS

GENERAL INFORMATION

The Medical Journal of Aegean Clinics is a periodical of the Society of Aid to Hospitals of İzmir and Fosterage of Scientific Investigations. The journal is published three times in a year. The printing months are April, August and December. The articles which could be prospective or retrospective on investigational studies, case reports, letter to the editor and reviews of every aspect of medicine are published. The studies should have paramount ethical and scientific standards as well as no commercial concerns. Articles are accepted for publication on the condition that they are original, are not under consideration by another journal, or have not been previously published.

The studies that are sent to the journal provided that the study is appropriate for formal principles are evaluated by the head editor and two peer reviewers.

The study is published once the approval of the reviewers have been taken. Hence, the authors should make the necessary changes in accordance with the reviewers comments.

SCIENTIFIC RESPONSIBILITY

All authors should have contributed to the article directly either academically or scientifically. All persons designated as authors should plan or perform the study, write the paper or review the versions, approve the final version. It is the authors' responsibility to prepare a manuscript that meets scientific criterias.

ETHICAL RESPONSIBILITY

Manuscripts concerned with human studies must contain statements indicating that informed, written consent has been obtained, that studies have been performed according to the World Medical Association Declaration of Helsinkihttp://www.wma.net/en/30/publications/10policies/b3/index.html) and that the procedures have been approved by a local ethics committee. The approval form of the ethics committee should be sent along with the manuscript. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.All Authors are responsible for the quality, accuracy, and ethics of the work. *The Medical Journal of Aegean Clinics* takes no responsibility for the Authors' statements. The manuscripts, once accepted, become property of the journal and cannot be published elsewhere without the written
permission of the Journal.

STATISTICALLY EVALUATION

All retrospective, prospective and experimental research articles must be evaluated in terms of biostatics and it must be stated together with appropriate plan, analysis and report. p values must be given clearly in the manuscripts (e.g. $p=0.014$).

LANGUAGE

The official languages of the Journal are Turkish and English. Turkish dictionary published by Turkish Language Institution (www.tdk.gov.tr) should be predicated on Turkish manuscripts. All spelling and grammar mistakes in the submitted articles, are corrected by the editor without changing the data presented.

It is the authors' responsibility to prepare a manuscript that meets spelling and grammar rules.

COPYRIGHT STATEMENT

A copyright transfer statement indicating that the ' *The copyright to this article is transferred to The Medical Journal of Aegean Clinics and will be effective if and when the article is accepted for publication'* should be sent in the content of cover letter. No payment is done to authors for their articles.

ARTICLE TYPES

Reviews: The reviews highlight or update new and/or controversial areas. The editor of the Journal invites author/authors for reviews.

Original articles: Original articles describe the results of basic or clinical studies or clinical trials. Original articles should not exceed 2500 words and 25 references.

Case Reports: The Journal publishes significant case reports related to the every aspect of medicine. The number of authors should not exceed 6 in the case reports.

Letter to the Editor: Text should not exceed 400 words, and include no more than 3 references (one of them should be the commenting article). Letters are selected for their importance, relevance, and originality; not all letters submitted can be published.

MANUSCRIPT SUBMISSION

All manuscripts must be submitted electronically to the idhdergi @yahoo.com

Cover letter: Cover letter should include statements about manuscript category designation, single-journal submission affirmation, conflict of interest statement, copyright transfer statement, sources of outside funding, equipments (if so).

Title Page: On the title page provide the complete title and a running title (not to exceed 55 characters and spaces). List each contributor's name and institutional affiliation. Corresponding Author is the contributor responsible for the manuscript and proofs. This is the person to whom all correspondence and reprints will be sent. The corresponding author is responsible for keeping the Editorial office updated with any change in details until the paper is published. All authors are also asked to submit their ORCID number, if they do not have it, it is kindly asked to be enrolled for the number form the webpage of http://orcid.org.

Abstract and Key Words: The abstract must not exceed 250 words. It should summarize the aim of the study and describe the work undertaken, results and conclusions. In addition, you should list up to three key words in alphabetical order.

INSTRUCTIONS FOR AUTHORS

Introduction: The Introduction should briefly discuss the objectives of the study and provide the background information to explain why the study was undertaken, and what hypotheses were tested.

Materials and methods: Clearly explain the methods and the materials in detail to allow the reader to reproduce the results. Equipment and apparatus should cite the make and model number and the company name and address (town, county, country) at first mention. Give all measurements in metric units. Use generic names of drugs.

Results: Results must be presented in a logic sequence with text, tables and illustrations. Underline or summarize only the most important observation. Tables and text should not duplicate each other.

Discussion: This section should be concise. Emphasize only the new and most important aspects of the study and their conclusions. The discussion should include a brief statement of the principal findings, a discussion of the validity of the observations, a discussion of the findings in light of other published work dealing with the same or closely related subjects, and a statement of the possible significance of the work. Authors are encouraged to conclude with a brief paragraph that highlights the main findings of the study.

Acknowledgements: Authors must acknowledge individuals who do not qualify as Authors but who contributed to the research.

Abbreviations: The abbrevation of a word or word sequence is given in the first appearance within a bracket after the word or word sequence. The abbrevation is used through the main text

Tables: Tables should be numbered consecutively within the text. Provide a number and title for each table.. Tables should not be submitted as photographs or graphics files.

Figure and table legends: Cite all tables and figures in the text, numbering them sequentially as they are cited. Each figure must have a corresponding legend. The legend must be numbered with a natural number

References: References in the text must be numbered in the order of citation and must be given with natural numbers within a bracket at the end of the sentence. Use of the form of the "Uniform requirements for manuscript submitted to biomedical journals" List all Authors when six or fewer; when seven or more, list only the first three and add 'et al'. Journal titles should be cited in full. The style of references and abbreviated titles of journals must follow that of cumulated Index Medicus or one of the examples illustrated below:

Format for journal articles:

Sigel B, Machi J, Beitler JC, Justin JR**.** Red cell aggregation as a cause of blood-flow echogenicity. Radiology 1983;148(2):799-802.

 Format for Committees and Groups of Authors:

The Standard Task Force, American Society of Colon and Rectal Surgeons: Practice parameters for the treatment of haemorrhoids. Dis Colon Rectum 1993; 36: 1118-20.

Format for Chapter from a book:

Milson JW. Haemorrhoidal disease. In: Beck DE, Wexner S, eds. Fundamentals of Anorectal Surgery. 1 1992; 192-214. 1a ed. New York: McGraw-Hill

Format for Books and Monographs:

Bateson M, Bouchier I. Clinical Investigation and Function, 2nd edn. Oxford: Blackwell Scientific Publications Ltd, 1981.

COMMUNICATION

Doç. Dr. Tuncay KIRIŞ

Head Editor

Izmir Hastanelerine Yardım ve Bilimsel

Araştırmaları Teşvik Derneği

Yeşilyurt, Izmir/TURKEY

Tel: 0 507 3114607

e-mail: idhdergi@yahoo.com

OUR ARTICLE SUBMITTING RULES

• Copyright Transfer Form must be signed by all authors.

• All authors of an article must submit their ORCID numbers.
(You can obtain and register for an ORCID ID from the website http://orcid.org for free of charge. In accordance with the layout of our journal; the author's ORCID ID must be written along with the author names and institution information in the first page of the study.)

• The Ethics Committee Consent itself (Ethics Committee Consent Document) must be sent with the study. Besides, the title of the study must be exactly the same in the Ethics Committee Document.

• The approval of ethics committe is a must for the articles to be published in our journal and a sentence denoting that the study has had ethics committee approval must be present in the material-method section of a study.

• The consent of patient/patients is a must for the case reports to be published in our journal and a sentence denoting that the case report has had 'consent from the patient/patients must be present in the introduction section of the study.

EGE KLİNİKLERİ TIP DERGİSİ

TELİF HAKLARI DEVİR FORMU

Yazının Başlığı:

Sorumlu Yazarlar:

Yazarların sorumlulukları:

- Yazı(lar) (sözlü veya poster sunum şekilleri hariç) başka hiçbir yerde yayınlanmamış ve şu anda başka bir dergi veya her hangi bir yayımcıda değerlendirme altında olmamalıdır.
- Makalenin yayınlanması ile ilgili diğer yazar onaylarından gönderen yazar sorumludur.
- Belirli bir kurum tarafından desteklenen yazılar için gerekli kurum onayının alınmasından yazarlar sorumludur.
- Yazıların bilimsel ve etik sorumluluğu yazarlara aittir.

Yazar Adı Soyadı   İmza   Tarih

Determinant Role of Magnetic Resonanceimaging in Transition of Clinical Isolated Syndrome to Multiple Sclerosis

Klinik İzole Sendromda Multipl Skleroza Dönüşümde Manyetik Rezonans Görüntülemenin Belirleyici Rolü

Ali BİGE*0000-0212-4446-0717

* Zonguldak Bülent Ecevit Üniversitesi, Tıp Fakültesi Hastanesi, Nöroloji Anabilim Dalı, Zonguldak

** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

*** xxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Yazışma Adresi: Ali BİGE

Zonguldak Bülent Ecevit Üniversitesi,

Tıp Fakültesi Hastanesi, Nöroloji Anabilim Dalı, ZONGULDAK

Gsm: 0532xxxxx

e-mail adresi: alibige@gmail.com

İÇİNDEKİLER/CONTENTS

KLİNİK ÇALIŞMALAR/ CLINICAL TRIALS

OLGU SUNUMLARI / CASE REPORTS

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Analyzing Public Interest in Secondary Prevention Practice in Cardiology: Google Trends Analysis

Kardiyolojide İkincil Önleme Uygulamasında Halkın İlgisini Analiz Etmek: Google Trends Analizi

Dogac Caglar GÜRBÜZ* 0000-0002-0517-8612

Eser VARİS* 0009-0005-5616-0550

*Department of Cardiology, Koc University, Istanbul, Turkey
**Department of Cardiology, Private Hospital, Istanbul, Turkey

Abstract

Introduction: To analyze public attention to secondary prevention practice in cardiology over 18 years using Google Trends (GT).

Methods: Two cardiologists identified 17 keywords (heart health, fluid intake, balanced diet, proper nutrition, lose weight, smoking cessation, alcohol intake, exercise, obesity, physical activity, management of stress, immunization, sodium intake, lipid profile, blood pressure monitoring, heart rate monitor, sleeping disorder) related to secondary prevention practice in the cardiology discipline. Terms were selected according to recommendations by the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. All terms were searched with using the 'web search', 'all categories', and 'worldwide' filters in GT. The last 18 years were equally divided into 3 periods (01.01.2005-31.12.2010, 01.01.2011-31.12.2016, and 01.01.2017-31.12.2022), and GT for all 17 terms were compared with three six-year periods.

Results: Public attention to 17 terms which were related with secondary prevention practices in cardiology discipline were significantly increased in the last 18 years (p= 0.001). Additionally, public interest in weight loss and sodium intake was significantly higher in 01.01.2011-31.12.2016 and 01.01.2017-31.12.2022 (p= 0.001 and p= 0.001). Public attention to heart health, exercise, and lipid profile was significantly higher between 01.01.2017 and 31.12.2022 (p= 0.001 for all three parameters). The GT score of fluid intake was significantly higher in last six-year period (p= 0.023). Public interest in smoking cessation and obesity keywords progressively increased from 01.01.2005-31.12.2010 to 01.01.2017-31.12.2022 (p= 0.001 and p= 0.001).

Conclusion: The present study found that public attention to terms which were related with secondary prevention practices in cardiology discipline were significantly increased in the last 18 years.

Keywords: Cardiology, google, google trends, secondary prevention, social media

Corresponding author: Dogac Caglar GÜRBÜZ
Department of Cardiology, Koc University, Istanbul, Turkey
E-mail: dogaccaglargurbuz@gmail.com

Öz

Amaç: Google Trends'i (GT) kullanarak 18 yılı aşkın bir süredir kardiyolojide ikincil koruma uygulamalarına yönelik kamuoyu ilgisini analiz etmek.

Yöntem: İki kardiyolog 17 anahtar kelime belirledi (kalp sağlığı, sıvı alımı, dengeli beslenme, doğru beslenme, kilo verme, sigarayı bırakma, alkol alımı, egzersiz, obezite, fiziksel aktivite, stres yönetimi, bağışıklama, sodyum alımı, lipid profili, kan basıncı) izleme, nabız monitörü, uyku bozukluğu) kardiyoloji disiplininde ikincil koruma uygulamasıyla ilgili. Terimler, Avrupa Kardiyoloji Derneği Kalp Yetmezliği Derneği Hasta Bakım Komitesi'nin tavsiyelerine göre seçilmiştir. Tüm terimler, GT'de 'web araması', 'tüm kategoriler' ve 'dünya çapında' filtreleri kullanılarak arandı.

Son 18 yıl eşit olarak 3 döneme (01.01.2005-31.12.2010, 01.01.2011-31.12.2016 ve 01.01.2017-31.12.2022) bölünmüş ve 17 dönemin tamamı için GT, altı yıllık üç dönemle karşılaştırılmıştır. dönemler.

Bulgular: Kardiyoloji disiplininde ikincil koruma uygulamaları ile ilgili 17 terime halkın ilgisi son 18 yılda önemli ölçüde arttı (p= 0.001). Ayrıca halkın kilo vermeye ve sodyum alımına olan ilgisi 01.01.2011-31.12.2016 ve 01.01.2017-31.12.2022 tarihlerinde anlamlı olarak yüksekti (p= 0.001 ve p= 0.001). Halkın kalp sağlığı, egzersiz ve lipid profiline olan ilgisi 01.01.2017 ile 31.12.2022 arasında anlamlı olarak daha yüksekti (her üç parametre için p= 0.001). Sıvı alımı GT skoru son altı yıllık dönemde anlamlı olarak yüksekti (p= 0,023). Sigarayı bırakma ve obezite anahtar kelimelerine halkın ilgisi 01.01.2005-31.12.2010'dan 01.01.2017-31.12.2022'ye kademeli olarak arttı (p= 0.001 ve p= 0.001).

Sonuç: Bu çalışma, kardiyoloji disiplininde ikincil koruma uygulamaları ile ilgili terimlere kamuoyunun ilgisinin son 18 yılda önemli ölçüde arttığını ortaya koymuştur.

Anahtar Kelimeler: Kardiyoloji, google, google trends, ikincil korunma, sosyal media

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality according to the World Health Organization. Scientific reports demonstrate that almost 20% of the world's population lose their life due to CVD (1). Despite advances in minimally invasive procedures and cardiovascular surgery, self-care management of cardiovascular risk factors is crucial to prevent CVD-related morbidity and mortality. The European Society of Cardiology suggest patients with CVD should optimize fluid and sodium intake, maintain ideal weight, stop smoking and prevent excessive alcohol usage, and maintain physical activity (2). However, in the EUROASPIRE IV study, Kotseva and colleagues found that most patients with CVD could not reach appropriate secondary prevention sources, and despite the high rate of medication use, the secondary prevention practice rate was not at the desired level (3).

Web sources have become an important tool for people to investigate their symptoms, treatment alternatives, and disease process because of their easily accessible character, free nature, and presence of many opinions (4). Search engines have a pivotal role in web searches, and despite numerous search engines available, nine out of ten internet users search with Google Search (Google Inc., California, USA). Google Trends (GT) was developed by Google Company to clarify how often a search is done in which language, in which geographic region, and in which time period, using Google search (5). Sevgili and Baytaroglu used GT to evaluate public interest in CVD during COVID-19, and the authors stated that public attention to CVD significantly decreased during COVID-19 (6). In another study, Teng and colleagues stated that GT was a useful tool for prediction of the Zika virus epidemic (7).

Although the role of GT in determining public interest in different medical conditions was evaluated in various studies, no study evaluated the public interest in secondary prevention practice in cardiology using GT. In the present study, we aimed to analyze public attention to secondary prevention practice in cardiology over 18 years using GT.

Material and Method

The study was performed between 1st January 2023 and 15th January 2023, and two cardiologists identified 17 keywords (heart health, fluid intake, balanced diet, proper nutrition, lose weight, smoking cessation, alcohol intake, exercise, obesity, physical activity, management of stress, immunization, sodium intake, lipid profile, blood pressure monitoring, heart rate monitor, sleeping disorder) related to secondary prevention practice in the cardiology discipline. Terms were selected according to recommendations by the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. All terms were searched with using the 'web search', 'all categories', and 'worldwide' filters in GT.

Google Trends (GT)

Google Trends provides information about how often any term is searched among similar keywords from all searches using Google in a particular time period. Additionally, GT give valuable data for reaching larger audiences during advertising and deciding on select words during website construction. The official web address of GT is 'https://trends.google.com', and results of any term searched is documented from this link. The score for any keyword according GT is rated between 0 and 100 (lowest search number to highest search number) (8).

To clarify public interest in secondary prevention practice in cardiology, the last 18 years were equally divided into 3 periods (01.01.2005-31.12.2010, 01.01.2011-31.12.2016, and 01.01.2017-31.12.2022), and the search rates for the 17 words mentioned above were recorded in these periods. Then, GT for all 17 terms were compared with three six-year periods. Due to not using patient data, ethics committee approval was not obtained for the present study.

Statistical Analysis

The Statistical Package for the Social Sciences version 26 (SPSS IBM Corp., Armonk, NY, USA) was used during statistical analysis. Relative search volume (RSV) data from the periods of 01.01.2005-31.12.2010, 01.01.2011-31.12.2016 and 01.01.2017-31.12.2022 were pooled, and the RSV means were calculated separately. Normality of variable distribution was checked with the Shapiro-Wilk test. Comparison of the RSV means between time periods was evaluated using the Kruskal Wallis test. The Tukey test was used for post hoc analysis between three groups. The data were analyzed at a 95% confidence level, and a p value of less than 0.05 was accepted as statistically significant.

Results

Total GT of the 17 terms related with secondary prevention practice in cardiology progressively increased from 01.01.2005-31.12.2010 to 01.01.2017-31.12.2022 (43.3 for 01.01.2005-31.12.2010, 48.9 for 01.01.2011-31.12.2016, and 53.9 for 01.01.2017-31.12.2022, p= 0.001). However, searches for keywords including 'balanced diet', 'proper nutrition', 'alcohol intake', 'physical activity', 'management of stress', 'immunization', 'blood pressure monitoring', 'hearth rate monitoring', and 'sleeping disorder' were similar between the three periods (p= 0.213, p= 0.782, p= 0.237, p= 0.788, p= 0.637, p= 0.329, p= 0.489, p= 0.119, and p= 0.725, respectively).

The public interest in weight loss and sodium intake was significantly higher in 01.01.2011-31.12.2016 and 01.01.2017-31.12.2022, and the GT score of weight loss and sodium intake was 38.4 and 58.3 in 01.01.2005-31.12.2010, 82.5 and 71.6 in 01.01.2011-31.12.2016, and 72.9 and 75.7 in 01.01.2017-31.12.2022 (p= 0.001 and p= 0.001).

Additionally, public attention to heart health, exercise, and lipid profile was significantly higher between 01.01.2017 and 31.12.2022 in comparison with the previous two six-year periods (p= 0.001 for all three parameters). Also, the GT score of fluid intake was 36.2 in 01.01.2005-31.12.2010, 34.3 in 01.01.2011-31.12.2016, and 42.1 in 01.01.2017-31.12.2022, and the difference was statistically significant in favor of the last six-year period (p= 0.023).Unlike other search terms, public interest in smoking cessation and obesity keywords progressively increased from 01.01.2005-31.12.2010 to 01.01.2017-31.12.2022. The GT score for smoking cessation was 24.1 in 01.01.2005-31.12.2010, 32.6 in 01.01.2011-31.12.2016, and 65.4 in 01.01.2017-31.12.2022 (p= 0.001). The GT score for obesity was 24.3 in 01.01.2005-31.12.2010, 34.3 in 01.01.2011-31.12.2016, and 58.2 in 01.01.2017-31.12.2022 (p= 0.001). The GT scores for all terms are summarized in Table 1.

Table 1: Comparison of terms related to protecting heart health in Google Trends data by year

	01.01.2005-31.12.2010	01.01.2011-31.12.2016	01.01.2017-31.12.2022	P value
Heart health	46.3±14.6[a]	42.2±12.3[a]	57.8±18.4[b]	***0.001***
Fluid intake	36.2±11.7[a]	34.3±10.8[a]	42.1±12.5[b]	***0.023***
Balanced diet	66.4±21.5	55.3±18.7	60.2±20.5	0.213
Proper nutrition	25.1±8.4	24.2±6.7	24.2±9.4	0.782
Lose weight	38.4±11.7[a]	82.5±24.2[b]	72.9±21.9[b]	***0.001***
Smoking cessation	24.1±7.8[a]	32.6±11.4[b]	65.4±22.4[c]	***0.001***
Alcohol intake	54.2±22.6	45.2±19.8	50.5±21.8	0.237
Exercise	53.4±18.2[a]	51.1±21.4[a]	65.2±19.7[b]	***0.001***
Obesity	24.3±9.2[a]	34.3±11.6[b]	58.2±21.9[c]	***0.001***
Physical activity	40.3±9.2	42.2±11.4	40.8±10.5	0.788
Management of stress	48.4±12.7	42.2±14.2	43.8±12.3	0.637
Immunization	58.3±18.2	50.5±24.2	55.2±21.3	0.329
Sodium intake	58.3±21.4[a]	71.6±23.5[b]	75.7±26.2[b]	***0.001***
Lipid profile	37.2±9.5[a]	39.2±10.4[a]	62.4±20.3[b]	***0.001***
Blood pressure monitoring	26.4±8.7	23.3±6.7	27.3±8.6	0.489
Heart rate monitor	61.3±24.5	60.5±20.4	51.9±18.3	0.119
Sleeping disorder	36.3±11.4	38.3±13.5	36.3±14.5	0.725
Total	43.3±8.5[a]	48.9±9.2[b]	53.9±11.5[c]	***0.001***

Lower-case letters are used to identify the group that makes the difference. The same letters (such as a-a) show that there is no difference, different letters (such as a-b) show that there is a difference.

The change in 'obesity' and 'smoking cessation' terms over time in Google Trends data is presented in Figure 1a and Figure 1b, respectively. In addition, popularity of the obesity term peaked in most countries in the last 6 years, especially in North America, Europe, Middle East and Pacific in 01.01.2017-31.12.2022. However, popularity of the term obesity has decreased in Sweden, Finland and, Poland in comparison with previous years (Figure 2a). In addition, popularity of 'smoking cessation' changed according to year, as shown in Figure 2b.

Figure 2a: Years in which the term 'obesity' was most popular by country

The popularity of the obesity term peaked in most countries in the last 6 years (yellow area). In some countries (red area: Sweden, Finland and, Poland), its popularity has decreased compared to previous years.

Figure 1a: Change in 'obesity' term over time in Google Trends data
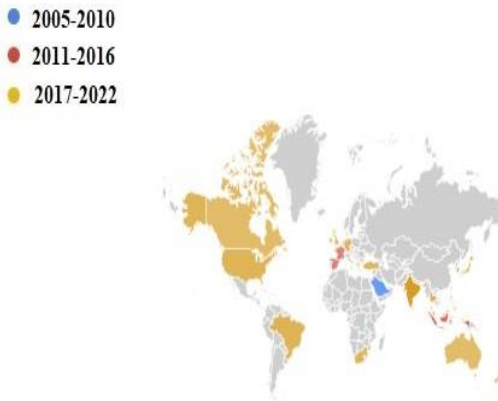
Figure 2b: Years in which the term 'smoking cessation' was most popular by country

The popularity of the term exercise peaked in most countries in the last 6 years (yellow area). In some countries (red area: Spain, France, and Indonesia; blue area: Saudi Arabia), its popularity has decreased compared to previous years.

Figure 1b: Change in 'smoking cessation' term over time in Google Trends data

Discussion

Web sources have become an important tool to obtain knowledge about various diseases, and many people decide on whether to attend a doctor, learn cons and pros about drugs, and which protection methods to use, according to search results on the internet (9). The role of secondary prevention practices has been proven in cardiology, and we believe that determining keywords which are searched more frequently using GT will be useful to increase the awareness and popularity of secondary prevention practices in the cardiology discipline, and in planning health policies. Thus, we conducted a study to analyze public attention to keywords about secondary prevention practices for the first time. We found that public interest in 'smoking cessation' and 'obesity' keywords steadily increased from 2005 to 2022, and public interest in 'weight loss' and 'sodium intake' significantly increased after 2011. In addition, public attention to 'heart health', 'fluid intake', 'exercise', and 'lipid profile' was significantly higher between 2017 and 2022.

Raising awareness of disease is critical for early diagnosis of disease and early treatment initiation. Placket and colleagues evaluated the importance of social media for cancer screening by analyzing 23 studies, and the authors concluded that social media sources had an important role in improving cancer screening and early diagnosis (10). In another review by Mandrola and Futyma, they stated that publication of knowledge and its translation practice takes 17 years, and emphasized that this time interval decreased after social media use (11). Additionally, Tanoue et al. analyzed the number of tweets on Twitter about cardiovascular scientific sessions between 2014 and 2016. The authors found that the number of tweets increased almost 2.5-times (12). In the present study, we found a steady increase in public interest for 17 keywords related to secondary prevention practices for CVD from 2005-2010 to 2017-2022.

Maintaining normal body mass index (BMI) and not gaining weight are critical for cardiac disease. Parks et al. used social media about weight management in severe obese patients, and the authors found that social media was an acceptable and feasible tool for weight management (13). Interestingly, Sui et al. found that although the number of scientific articles on 'weight loss' has increased in the last 20 years, public interest in this topic has not increased at the same rate (14). In the present study, we found a significant increase in public interest about the obesity term from 2005-2010 to 2017-2022. In addition, the terms 'exercise' and 'lose weight' were searched for significantly more in the last six years and in the last twelve years, respectively.

Dietary habits are important for the prevention and treatment of cardiovascular diseases. Theodoridis et al. evaluated the role of social media on dietary characteristics of patients with rheumatic disorders, and the authors concluded that patients who spent more time on social media had significantly higher compliance to recommended dietary habits (15).

Bot and colleagues investigated the role of social media on lifestyle behavior in patients with cardiovascular disease, and found significant positive correlations between higher vegetable consumption and maintaining normal BMI, and social media use (16). In the present study, public interest in fluid intake and lipid profile significantly increased in the last six years, and public attention to sodium intake significantly increased in the last 12 years. Additionally, queries about smoking cessation steadily increased from 2005-2010 to 2017-2022. Thus, we think that the production of social media content by health professionals using these words will have a positive effect on cardiac health.

Although the present study clarified public interest in secondary prevention practices in cardiology for the first time, our study has some limitations. Firstly, we are aware that many web search engines are available beyond Google search; however more than 90% of internet users choose Google during their searches on the web. Secondly, we conducted the study with only English keywords, and we believe that it would be difficult to evaluate the results and confusing for the reader if more than one language were used. Moreover, English is the most used language in Google. Lastly, some terms were not only related with cardiac disease, and these terms may be searched by individuals who wanted to improve general health, or by patients with other diseases such as kidney stone disease, lung cancer, deep vein thrombosis etc.

In conclusion, the present study found that public attention to terms which were related with secondary prevention practices in cardiology discipline were significantly increased in the last 18 years. Therefore, producing web content about secondary prevention practices in the cardiology discipline by using terms which are more frequently searched in Google will have a positive effect on public cardiac health.

References

1. Cetin HK, El Kilic H, Koramaz I, Demir T. The Evaluation of Cardiovascular Surgery-Associated Google Search Trends During COVID-19 Waves. Sisli Etfal Hastan Tip Bul. 2022;56:323-327.

2. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. Int J Cardiol. 2015;201:1-7.

3. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, Gyberg V, Amouyel P, Bruthans J, Castro Conde A, Cífková R. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. European journal of preventive cardiology. 2016;23:636-48.

4. Ergul A. Quality and Reliability of YouTube Videos on Surgical Treatment of Uterine Leiomyomas. Cureus. 2021;13:e20044.

5. Ikpeze TC, Mesfin A. Interest in Orthopedic Surgery Residency: A Google Trends Analysis. J Surg Orthop Adv. 2018;27:98-101

6. Sevgili E, Baytaroglu C. The role of Youtube as an information source about coronary artery disease during COVID-19 pandemic. Med Bull Haseki. 2021;1:1-6.

7. Teng Y, Bi D, Xie G, Jin Y, Huang Y, Lin B, An X, Feng D, Tong Y. Dynamic Forecasting of Zika Epidemics Using Google Trends. PLoS One. 2017; 6;12:e0165085.

8. Nuti SV, Wayda B, Ranasinghe I, Wang S, Dreyer RP, Chen SI, Murugiah K. The use of google trends in health care research: a systematic review. PloS one. 2014;9:e109583.

9. Yuksel B, Cakmak K. Healthcare information on YouTube: Pregnancy and COVID-19. International Journal of Gynecology & Obstetrics. 2020 Aug;150:189-93.

10. Plackett R, Kaushal A, Kassianos AP, Cross A, Lewins D, Sheringham J, Waller J, von Wagner C. Use of social media to promote cancer screening and early diagnosis: scoping review. Journal of medical Internet research. 2020;22:e21582.

11. Yuksel B, Cakmak K. Healthcare information on YouTube: Pregnancy and COVID-19. International Journal of Gynecology & Obstetrics. 2020 Aug;150:189-93.

12. Plackett R, Kaushal A, Kassianos AP, Cross A, Lewins D, Sheringham J, Waller J, von Wagner C. Use of social media to promote cancer screening and early diagnosis: scoping review. Journal of medical Internet research. 2020;22:e21582.

13. Mandrola J, Futyma P. The role of social media in cardiology. Trends in cardiovascular medicine. 2020;30:32-5.

14. Tanoue MT, Chatterjee D, Nguyen HL, Sekimura T, West BH, Elashoff D, Suh WH, Han JK. Tweeting the meeting: rapid growth in the use of social media at major cardiovascular scientific sessions from 2014 to 2016. Circulation: Cardiovascular Quality and Outcomes. 2018;11:e005018.

15. Parks EP, Renee'H M, Li Z, Bishop-Gilyard CT, Garrett AR, Hill DL, Bruton YP, Sarwer DB. Assessing the feasibility of a social media to promote weight management engagement in adolescents with severe obesity: pilot study. JMIR Research Protocols. 2018;7:e8229.

16. Sui Z, Raman J, Han B, Burchell T, Coogan SC, Brennan B, Sartoretto A. Recent trends in intensive treatments of obesity: Is academic research matching public interest?. Surgery for Obesity and Related Diseases. 2019;15:766-76.

17. Theodoridis X, Pittas S, Bogdanos DP, Grammatikopoulou MG. Social media as tools to study dietary habits of patients with rheumatic diseases: learning from relevant work on inflammatory bowel diseases. Mediterranean Journal of Rheumatology. 2020;31:382.

18. Bot SD, Mackenbach JD, Nijpels G, Lakerveld J. Association between social network characteristics and lifestyle behaviours in adults at risk of diabetes and cardiovascular disease. PLoS One. 2016 ;11:e0165041.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Kronik Migren Hastalarında GON Blokajının Özürlülük ve Migren İle İlişkili Durumlar Üzerine Etkisi

Effect Of GON Block On Disability And Migraine-Related Conditions in Choronic Migraine Patients

Buşra YILDIZ* 0000-0003-3235-9301

Zahide MAİL GÜRKAN* 0000-0002-8152-8311

Aygül TANTİK PAK* 0000-0002-7414-3800

Yıldızhan ŞENGÜL* 0000-0002-5087-9944

*Gaziosmanpaşa Eğitim Ve Araştırma Hastanesi, Nöroloji Kliniği, İstanbul

Öz

Amaç: Kronik migrende uygulanan profilaktik tedavi yöntemlerinden biri GON (büyük oksipital sinir) blokajıdır. Çalışmamızda GON blokajı uygulanan kronik migren hastalarında kutanöz allodini, uyku bozuklukları, depresyon ve anksiyete skorlarındaki değişimi ve tedavinin etkinliğini araştırmayı amaçladık.

Gereç ve yöntem: Prospektif olarak yapılan çalışmamıza, ICHD-3 kriterlerine göre kronik migren ve kronik migren zemininde gelişmiş İAB (ilaç aşırı kullanım başağrısı) olan, en az 3 aydır migren profilaksi ilacı kullanmayan 31 hasta dahil edildi. Hastalara yüz yüze görüşme yöntemi ile ağrı şiddetini belirlemek üzere Görsel Analog Skala (VAS), kutanöz allodiniyi ölçen Allodini Semptom Kontrol Listesi (ASK-12), Pittsburgh Uyku Kalitesi İndeksi (PUKİ), Beck Depresyon Ölçeği (BDÖ) ve Beck Anksiyete Ölçeği (BAÖ) GON blokajı öncesi ve sonrası 3. ayda uygulandı.

Bulgular: Çalışmaya dahil edilen 31 hastanın 20'si 3. ay kontrolünde değerlendirildi. Hastalarımızın yaş ortalaması 33,6±9, ortalama hastalık süresi 8,5±7 yıl idi. GON yapılan hastaların ASK-12, PUKİ, BDÖ, BAÖ skorlarında tedavi öncesine göre tedaviden sonraki üçüncü ayda istatistiksel olarak anlamlı bir düşüş bulundu (p=0,03; p=0,00; p=0,03; p=0,00 sırasıyla). Ayrıca tedavi öncesi başlangıç değerlerine göre tedavi sonrası birinci ve üçüncü aylarda VAS skorları, toplam ağrılı gün sayısı/ay, analjezik kullanım/ay ve ağrı sürelerinde istatistiksel olarak anlamlı azalma saptandı (p<0,001).

Sonuç: GON blokajı, kronik migrenli hastalarda allodini skorlarında ve eşlik eden uyku kalitesi, depresyon ve anksiyete skorlarında düşüşe katkı sağlayan, ilk sıralarda akla gelmesi gereken oldukça etkin bir tedavi yöntemdir.

Anahtar Kelimeler: Kronik Migren, GON blokajı, Allodini Semptom Kontrol Listesi

Yazışma Adresi: Buşra YILDIZ

Gaziosmanpaşa Eğitim Ve Araştırma Hastanesi,
Nöroloji Kliniği, İstanbul
E-mail adresi: busramumay88@gmail.com

Abstract

Aim: Greater occipital nerve (GON) block is one of the prophylactic treatment method in chronic migraine. We aimed to investigate the changes in cutaneous allodynia, sleep disorders, depression and anxiety scores and the effectiveness of the treatment in chronic migraine patients who underwent GON block.

Material and methods: Our prospective study included 31 patients who had chronic migraine and MOH (medication overuse headache) according to ICHD-3 criteria and who did not use migraine prophylaxis for at least 3 months. Visual Analogue Scale (VAS), Allodynia Symptom Checklist (ASC-12), Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) was applied before and 3 months after GON block.

Results: Twenty of the thirty one patients were evaluated three months after treatment. The mean age was 33.6±9 years and the mean disease duration was 8.5±7 years. A statistically significant difference was found in the ASC-12, PSQI, BDI and BAI scores at three months after treatment compared to pretreatment (p=0.03; p=0.00; p=0.03; p=0.00 respectively) In addition, a statistically significant difference was found in VAS scores, total number of painful days, analgesic use and duration of pain in the first and third months after treatment compared to pretreatment (p<0.001).

Conclusion: Greater occipital nerve block is a highly effective treatment method that contributes to the decrease in allodynia scores and accompanying sleep quality, depression and anxiety scores in patients with chronic migraine.

Keywords: Chronic Migraine, GON block, Allodynia Symptom Checklist (ASC-12)

Giriş

Kronik migren (KM), toplumda sık görülen ve maluliyete neden olma olasılığı yüksek bir hastalıktır. 3 aydan fazla süreyle ayda ≥15 gün ortaya çıkan, en az 8 gün/ay migren başağrısı özelliklerine sahip olan bir başağrısı olarak tanımlanır (1). Genel toplumda prevalansı yaklaşık %2 ve migren hastalarında prevalansı yaklaşık %8'dir (2,3). KM tedavisinde medikal tedaviye direnç, ilaç yan etkileri ve yüksek ilaç bırakma oranları nedeniyle son yıllarda periferik sinir blokajları daha sık gündeme gelmektedir (4). Öte yandan KM zemininde karşılaşılabilecek problemlerden biri olan ilaç aşırı kullanım başağrısı (İAB) tedavisinde de GON (büyük oksipital sinir) blokajı daha çok dikkat çekmeye başlamıştır (5,6).

KM profilaksisinde kullanılan tedavi yöntemlerinden biri olan GON blokajı güvenli, ilaç etkileşimi potansiyelinin düşük ve ucuz olması gibi avantajları nedeniyle ön plana çıkmaktadır (7). Oksipital bölgenin duyusunu alan GON, liflerinin çoğunu servikal (C2) dorsal kökten alır, C2 spinal sinirinden ve trigeminal sinirden gelen duyusal afferentlerin trigeminoservikal kompleks içindeki anatomik ve fonksiyonel yakınlığı tedavinin etkinliğindeki mantığın temelini oluşturur (8). GON'a lokal anestezik enjeksiyonu ile GON tarafından innerve edilen bölgelerden gelen afferent uyaranlar bloke edilerek ikinci sıra nöronların uyarılabilirliği modüle edilir ve sensitizasyon engellenir (9,10).

Migren hastalarında, profilaktik tedavilere yanıtı etkileyen uyku kalitesinde bozulma, depresyon ve anksiyete gibi psikiyatrik komorbiditeler oldukça sık görülmektedir (11). Öte yandan kutanöz allodini migrenin kronikleştiğini gösteren, disabilite yaratan etkenlerden biridir (12,13). Çalışmamızda GON blokajı tedavisinin etkinliğini, tedavinin bu komorbiditelerdeki olası değişime etkisini ve kronikleşmenin başka bir göstergesi olan kutanöz allodini üzerine etkisini araştırmayı amaçladık.

Gereç Ve Yöntem

Prospektif olarak yapılan çalışmamızda, Sağlık Bilimleri Üniversitesi Gaziosmanpaşa Eğitim Araştırma Hastanesi, Nöroloji polikliniğine Haziran 2021-Ağustos 2021 arasında başvuran, ICHD-3'e göre KM ve KM zemininde gelişen İAB tanısı konulan, 18-65 yaş arası, en az 3 aydır migren profilaksi ilacı kullanımı olmayan ve çalışmaya katılmayı kabul eden hastalar dahil edildi. Çalışmadan dışlanma kriterleri, psikiyatrik hastalık olması (depresyon ve anksiyete dışında), kranial MR' ın normal olmaması, KM ve İAB dışında başağrısı olması olarak belirlendi.

Hastaların demografik özellikleri ve hastalık ile ilişkili verileri, ağrı şiddeti (VAS'a göre), ağrılı gün sayısı/ay, ilaç kullanımı/ay, atak süresi (saat) not edildi. Yüz yüze görüşme yöntemi ile kutanöz allodiyi ölçen Allodini Semptom Kontrol Listesi (ASK-12), Pittsburgh Uyku Kalitesi İndeksi (PUKİ), Beck Depresyon Ölçeği (BDÖ) ve Beck Anksiyete Ölçeği (BAÖ) hastalara GON blokajı tedavisi öncesi ve tedavi sonrası 3. ayda uygulandı.

Çalışmaya alınması planlanan hasta sayısı power analize göre belirlendi fakat GON blokajı işlemini yapan hekimin görev yeri değişikliği nedeni ile istenilen sayıya ulaşılamadı ve 31 hastanın 11'i 3. ay kontrolünde değerlendirilemedi. Fakat azımsanamayacak hasta sayısı ve sonuçların anlamlı olması nedeni ile yazılmaya değer bulundu.

Görsel Analog Skala (VAS); 0'dan (ağrı yok) 10'a (en şiddetli ağrı) kadar numaralandırılmış olup başağrısı şiddetini belirlemek üzere geliştirilmiştir. (14).

ASK-12, Nicel Duysal Test (Quantitative Sensory Test) ile doğrulanmış olması ve iyi psikometrik özelliklere sahip olması nedeniyle güvenilir, hızlı ve uygulanması kolay bir ankettir. On iki sorudan oluşan bu anket, kutanöz allodininin tanımlanmasına ve ciddiyetine göre sınıflandırılmasına olanak sağlamaktadır. Türk popülasyonunda geçerli ve güvenilir olduğu Yalın ve arkadaşları tarafından yapılan validasyonu ile gösterilmiştir (15).

PUKİ, son bir aylık zaman dilimindeki uyku kalitesini ve uyku bozukluklarını değerlendiren bir ankettir, 19'u kişiye yönelik, 5'i eşi veya oda arkadaşı tarafından puanlanan toplam 24 sorudan oluşmaktadır. Toplam puan 0 ile 21 arasındadır ve puan yükseldikçe uyku kalitesi düşer. PUKİ skorunun > 5 olması zayıf uyku kalitesinin hassas ve spesifik bir ölçümü olarak kabul edilir (16). PUKİ'nin Türk nüfusunda iyi bir geçerlilik ve güvenilirliğe sahip olduğu gösterilmiştir (17).

BDÖ, depresyon şiddetini ölçmek için yaygın olarak kullanılan bir araçtır, her biri 0-3 puan verilen 21 maddeden oluşur. Toplam skor depresyon şiddetinin gösterir: 0–9 minimal, 10–16 hafif, 17–29 orta ve 30–63 ağır olarak belirlenmiştir. Türk popülasyonunda geçerli ve güvenilir olduğu Hisli tarafından yapılan validasyonu ile gösterilmiştir (18).

BAÖ, Beck ve arkadaşları tarafından geliştirilen bir öz değerlendirme ölçeğidir ve bireylerin yaşadığı anksiyete belirtilerinin sıklığını belirlemek amacıyla kullanılır. Hem kognitif hem de somatik anksiyete belirtilerini sorgulayan 0'dan 3'e kadar puanlanan 21 sorudan oluşmaktadır.

Toplam skor 0-7 arasında "minimum"; 8 - 15 "hafif"; 16 – 25 ''orta''; 26 - 63 "şiddetli" anksiyete düzeyi olarak yorumlanır (19). Türk toplumunda geçerlilik ve güvenilirlik çalışması Ulusoy ve arkadaşları tarafından yapılmıştır (20).

Hastalara 15 gün arayla birer kez, toplamda iki kez olacak şekilde, her hastaya aynı teknik kullanılarak aynı nörolog tarafından GON blokajı uygulandı. GON blokajı protuberantia occipitalis externa'nın 3 cm aşağısı, 1,5 cm lateraline bilateral olarak her bir enjeksiyon %0.5'lik 2 ml bupivakain içerecek şekilde uygulandı (21). Enjeksiyonlar 26-G (0.45 x 13 mm) iğne kullanılarak subkutan olarak yapıldı. Hastalar olası yan etkiler açısından 30 dakika gözlem altında tutuldu.

Bu çalışma Sağlık Bilimleri Üniversitesi, Gaziosmanpaşa Eğitim Araştırma Hastanesi etik kurulu tarafından onaylanmış olup 1964 Helsinki Deklarasyonu etik standartlarına uygun olarak düzenlenmiş ve yapılmıştır. Çalışmaya katılan tüm hastalardan yazılı onamları alınmıştır.

İstatistiksel Analiz

Veriler SPSS 24.0 (Statistical Package for the Social Sciences for Windows) programı kullanılarak analiz edildi. Dağılımın normalliği Shapiro-Wilk testi kullanılarak değerlendirildi. Normal dağılım gösteren değişkenler ortalama ± standart sapma, normal dağılım olmayan değişkenler ortanca [Interquartile range] ile ifade edildi. Kategorik değişkenler Pearson ki-kare testi veya Fisher exact test kullanılarak değerlendirildi. Normal dağılan verilerin karşılaştırılmasında bağımsız örneklem t testi, normal dağılmayan verilerde ise Wilcoxon T test kullanıldı. Korelasyon derecesi ise Pearson veya Spearman testleri kullanılarak değerlendirildi. $p < 0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya toplam 31 hasta dahil edildi; 29'u kadın (%93,5), 2'si (%6,5) erkekti. Katılımcıların yaş ortalaması 33,6±9 yıl idi. Hastalık süresi 8,5±7 olarak bulundu. Hastalarımızın %61,3'ünde(n=19) İAB bulunmaktaydı. Katılımcıların diğer demografik özellikleri ve hastalık ile ilişkili verileri Tablo 1'de sunulmaktadır.

Tablo 1: Demografik özellikler ve hastalık ile ilişkili veriler

Hastalar	n=31
Yaş (yıl)	33,6±9
Cinsiyet (Kadın/Erkek)	29/2
Eğitim Düzeyi, n(%)	
İlköğretim Mezunu	17(54,8)
Ortaokul/Lise Mezunu	6(19,4)
Ön Lisans/Üniversite Mezunu	8 (25,8)
Medeni Durum, n(%)	
Bekar	8 (25,8)
Evli	23 (74,2)
Günlük çay/kahve alımı, n(%)	
1-2 bardak/gün	5(16,1)
3-4 bardak/gün	10(32,3)
≥5 bardak/gün	16(51,6)
Hastalık süresi (yıl)	8,5±7
GON hassasiyeti, n(%)	15(48,4)
Aura varlığı	13(43,3)

GON: büyük oksipital sinir

Çalışmaya dahil edilen 31 hastanın 20 si 3.ay kontrolünde değerlendirildi. GON blokajı yapılan hastaların başlangıçtaki ASK-12 skor ortalaması 6,3±3,5 iken 3. ay kontrolünde bu değer 4 [0,2-8,5], başlangıçtaki PUKİ skorları 7,3±3 iken 3. ay kontrolünde bu değer 6,4±3,7, başlangıçtaki BDÖ ortalaması 16,2±9,8 iken 3. ay kontrolünde bu değer 10,3±7,3, başlangıçtaki BAÖ ortalaması 20,8±14,6 iken 3. Ay kontrolünde 17,7±10,4 olarak bulunmuş olup bu fark istatistiksel olarak anlamlıydı (p=0,03; p=0,00; p=0,03; p=0,00 sırasıyla) (Tablo 2). Ayrıca tedavi öncesi başlangıç değerlerine göre tedavi sonrası birinci ve üçüncü aylarda ağrı şiddetini belirlemek üzere yapılan VAS skorları, ağrılı gün sayısı/ay, ilaç kullanımı/ay, atak süresi (saat) değerlerinde belirgin azalma vardı (p<0,001) (Tablo 3, Tablo 4).

Tablo 2: GON blokajı öncesi ve sonrası 3. ayda anket verilerindeki değişimler

	Tedavi öncesi	3. ay	P değeri
ASK	6,3±3,5	4 [0,2-8,5]	0,03
PUKİ	7,3±3	6,4 ±3,7	0,00
BDÖ	16,2±9,8	10,3±7,3	0,03
BAÖ	20,8±14,6	17,7±10,4	0,00

Tablo 3: GON blokajı öncesi, sonrası 1. ve 3. ayda klinik özellikler

	Tedavi öncesi	1. ay	3. ay	P değeri
VAS skoru	8,4±1,3	5,2±2,6	5,5 [4-8,7]	0,00
Ağrılı gün sayısı/ay	17,7±7,1	2,5 [1-4,7]	4 [1,2-5,7]	0,00
İlaç kullanımı/ay	14,9±9,2	2 [0-6]	3 [0,2-5,7]	0,00

Tablo 4: GON blokajı öncesi, sonrası 1. ve 3. ayda atak süresi

Atak süresi	Tedavi öncesi	1.ay n(%)	3.ay n(%)	P değeri
<6 saat	0	9(45)	7(35)	0,00
6-12 saat	1(3,2)	3(15)	4(20)	0,00
12-24 saat	10(32,3)	6(30)	3(15)	0,00
>24 saat	20(64,5)	2(10)	6(30)	0,00

Tartışma

GON blokajı uygulanan KM hastalarında kutanöz allodini, uyku kalitesi, depresyon, anksiyete skorlarındaki değişimi ve tedavinin etkinliğini araştırmak üzere yaptığımız bu çalışmamızda GON blokajı yapılan hastaların ASK, PUKİ, BDÖ, BAÖ skorlarında tedavi öncesine göre tedaviden sonraki üçüncü ayda istatistiksel olarak anlamlı bir düşüş bulundu. Ayrıca tedavi öncesi başlangıç değerlerine göre birinci ve üçüncü aylarda ağrı şiddetini belirlemek üzere yapılan VAS skorları, ağrılı gün sayısı/ay, ilaç kullanımı/ay, atak süresi(saat) değerlerinde belirgin azalma saptandı.

Kutanöz alodini KM'li bireylerde epizodik migrenlilere göre daha yüksek oranda görülür ve santral sensitizasyonun bir göstergesi olarak kabul edilir (22). Tekrarlayan ağrı epizodları nosiseptif yollardaki 2. ve 3. sıra nöronlarda hipereksitabiliteye yol açarak santral sensitizasyona ve bunun sonucunda normalde ağrı oluşturmayacak uyaranlarla ağrı hissedilmesi olarak tanımlanan allodiniye yol açar (23). GON blokajı ikinci sıra nöron seviyesinde nöronal hipereksitabiliteyi azaltarak trigeminal bölgedeki ağrıyı hafifletebilir (24). Fonksiyonel görüntülemenin kullanıldığı bir çalışmada GON blokajının nosiseptif trigeminal aktivasyonu önemli ölçüde azalttığı, Nicel Duysal Test ile blokajla aynı tarafta oksipital anesteziyi indüklediği gösterilmiştir (25). GON blokajı ile kutanöz allodinin araştırıldığı diğer çalışmalara bakıldığında Cuadrado ve arkadaşlarının yaptığı çift kör plasebo kontrollü çalışmada GON bokajı yapılan KM'li hastalarda blokajdan 1 hafta sonra basınç ağrı eşiği/pressure pain tressold değerlendirilmiş, anlamlı şekilde yüksek olduğu bulunmuş ve GON blokajının trigeminal nucleus caudalise nosiseptif girdiyi azaltarak santral sensitizasyon üzerine ekili olduğunun bir göstergesi olabileceğini ifade etmişlerdir (21). Ashkenazi ve arkadaşları migren atağı sırasında lokal anesteziğe steroid eklenerek yapılan GON blokajından 20 dk sonra anket ve fizik muayene ile belirledikleri trigeminal ve servikal bölgede mekanik allodininin azaldığını göstermişler ve bunun blokaj sırasında uygulanan lokal anestetiğin etkisi veya enjeksiyonun kendisinin sinir üzerinde yaptığı ağrıyı kontrol eden inhibitör mekanizmaları etkilediğini düşünülebileceğini ifade etmişlerdir (26). Ertem ve arkadaşlarının yaptığı çalışmada lokal anesteziklerle tekrarlanan GON blokajı ile birlikte trigeminal dal sinir bloklarının KM'li hastalarda allodiniyi azalttığını göstermişler ve GON blokajının migren kronifikasyonunun tedavisine katkıda bulunabileceğini ifade etmişlerdir (27). Biz de çalışmamızda GON blokajı sonrasında ASK-12 skorlarının azaldığını dolayısıyla blokaj sonrası allodinin azaldığını saptadık. Bu sonuçlar trigeminoservikal kompleksi hedefleyen bu girişimsel tedavi yönteminin ağrı kontrol mekanizmaları üzerine olumlu etki ettiğini göstermektedir.

Migren hastalarında normal popülasyona göre uyku bozuklukları daha sık görülür ve en sık görülen uyku bozuklukları uykuya dalma ve sürdürme bozuklukları ile şekillenen insomnilerdir (28,29).

KM'li bireylerde GON blokajı uygulaması sonrası uyku kalitelerinin değerlendirildiği çalışmalara bakıldığında Saçmacı ve arkadaşlarının yaptığı GON sonrası uyku kalitelerinin değerlendirildiği çalışmamızla benzer sonuçlar bulunmuş ayrıca hastaların insomni skorlarında, uyku tutum ve davranışlarında iyileşme olduğunu göstermişlerdir (30). Ulusoy ve arkadaşları yaptıkları çalışmada GON blokajı tedavisi ile uyku kalitesi, uyku bozuklukları, eşlik eden depresyon ve anksiyete semptomlarının düzeldiğine dikkat çekmiştir (31). Biz de önceki çalışmalarla uyumlu olarak GON blokajı sonrası 3. ayda hastaların PUKİ skorlarının iyileştiğini saptadık. Uyku deprivasyonunun en sık migren tetikleyicilerinden biri olduğu düşünüldüğünde, atak sıklığında düşme ile beraber uyku kalitesinin artması GON blokajının migren kronifikasyonunu önlemede rol alabileceğini düşündürmektedir (32).

Kronik migren ile birlikte sık görülen psikiyatrik komorbiditelerden olan depresyon ve anksiyete varlığı baş ağrısı tedavisine yanıtı olumsuz etkilemektedir (33,34). Depresyon ve anksiyete migrenle çift yönlü bir ilişkiye sahiptir. Depresyon ve anksiyete migreni kötüleştirir, migren hastalarında depresyon ve anksiyete sık ortaya çıkar. Vigano ve arkadaşları yaptıkları çalışmada GON blokajı ile tedavi ettikleri hastalarda serotonin düzeylerinin plaseboya kıyasla önemli ölçüde arttığını göstermişlerdir (35). Ulusoy ve arkadaşları da yaptıkları çalışmada GON blokajı yapılan KM hastalarında BAÖ, BDÖ skorlarının anlamlı derecede düştüğünü bulmuş ve bu durumu azalan ağrı sıklığı ve şiddeti ile beraber artan serotonin seviyeleri ile ilişkilendirmişlerdir (31). Biz de çalışmamızda GON blokajı sonrası 3. ayda depresyon ve anksiyete skorlarının gerilediğini gösterdik. Skorlardaki bu düşüş hastalık yönetimi açısından dikkate değer bir bulgu olarak görünmektedir.

Kronik migrende GON blokajının etkili bir tedavi yöntemi olduğunu gösteren plasebo kontrollü çalışmalarda toplam ağrılı gün sayısı, ağrı süresi ve VAS skorlarında anlamlı düşüş olduğu belirlenmiş olup, yöntem konusunda belli bir standardizasyon bulunmamasının yanı sıra unilateral veya bilateral yapılmasının, lokal anestetik ile beraber steroid kullanılmasının veya kullanılmamasının etkinlik konusunda farklılığa neden olmadığını gösteren çalışmalar mevcuttur, yöntemin standardizasyonu için yeni çalışmalara ihtiyaç vardır (36). Biz de geçmişteki bu çalışmalarla uyumlu olarak GON blokajı sonrası hastaların toplam ağrılı gün sayısı, ağrı süresi ve VAS skorlarında anlamlı düşüş bulduk.

Kronik migrenli bireylerde atak sıklığının artması ile birlikte karşılaşılan en sık sorunlardan biri olan ilaç aşırı kullanımı KM tedavisini daha da komplike hale getirmektedir. Bizim çalışmamızda da 19 (%61,3) hastamızda ilaç aşırı kullanımı mevcuttu ve çalışmamızda GON blokajı ile ilaç kullanımının belirgin bir şekilde azaldığını gördük.

İlaç aşırı kullanım başağrısı olan hastalarda GON blokajının etkin olduğunu gösteren çalışmalar vardır (5,6). Öte yandan retrospektif bir çalışmada, semptomatik ilaç aşırı kullanımı, refrakter migren dahil olmak üzere karma bir başağrısı hasta grubunda GON blokajı başarısızlığı riskini neredeyse üç katına çıkardığı belirtilmiştir (37). Fakat özellikle çalışmamıza katılan hastalarımızda olduğu gibi KM zemininde gelişen ilaç aşırı kullanım başağrısında kullanılan nonsteroid antiinflamatuar veya triptan grubu ilaçları keserken atak sıklığında hızlı azalma sağlayabilecek olan GON blokajı iyi bir seçenek gibi görünmektedir.

Çalışmamız küçük bir vaka grubunu içermektedir. Bu konuda daha büyük hasta gruplarıyla yapılacak çalışmalara ihtiyaç vardır. Kontrol grubumuzun olmaması da kısıtlılıklarımızdan biridir.

Ayrıca takip süremiz 3 ay ile kısıtlıdır. Takip süresinin uzatılması GON blokajının uzun vadeli sonuçları ile ilgili bilgi verecektir.

Sonuç olarak GON blokajı tedavisi kronik migrende etkili bir tedavi yöntemidir ve allodini, uyku kalitesi, depresyon ve anksiyete üzerine de olumlu etki eder. Migren hastalarının yaşam kalitelerinin arttırılmasında tercih edilecek tedavinin migrene eşlik edebilecek komorbid durumlara da olumlu etkisinin gözetilmesi önemlidir.

Kaynaklar

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.

2. Buse DC, Manack AN, Fanning KM ve ark. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 2012;52:1456–1470.

3. Blumenfeld AM, Varon SF, Wilcox TK ve ark. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia 2011;31:301–315.

4. Afridi SK, Shields KG, Bhola R, Goadsby PJ. Greater occipital nerve injection in primary headache syndromes—prolonged effects from a single injection. Pain 2006;122:126–129.

5. Chowdhury D, Mundra A. Role of greater occipital nerve block for preventive treatment of chronic migraine: A critical review. *Cephalalgia Reports*. 2020;3.

6. Karadaş Ö, Özön AÖ, Özçelik F, Özge A. Greater occipital nerve block in the treatment of triptan-overuse headache: a randomized comparative study. Acta Neurol Scand 2017;135:426-433.

7. Gul HL, Ozon AO, Karadas O, Koc G, Inan LE. The efficacy of greater occipital nerve blockade in chronic migraine: a placebocontrolled study. Acta Neurol Scand 2017;136:138–144.

8. Goadsby PJ ve Bartsch T. The anatomy and physiology of the trigeminocervical complex. In: Ferna´ndez de las Pen˜as C, Arendt-Nielsen L and Gerwin RD (eds) Tension-type and cervicogenic headache: Pathophysiology, diagnosis and management. Sudbury: Jones and Barlett, 2010, pp.109–116.

9. Selekler MH. Greater occipital nerve blockade: Trigeminocervical system and clinical applications in primary headaches. Agri 2008; 20:6–13.

10. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain 2002;125:1496–1509.

11. Giannini G, Cevoli S, Sambati L, Cortelli P. Migraine: risk factor and comorbidity. Neurol Sci 2012;33:37–41.

12. Mathew NT. Pathophysiology of chronic migraine and mode of action of preventive medications. Headache 2011;51(Suppl 2): 84–92.

13. LoPinto C, Young WB, Ashkenazi A. Comparison of dynamic (brush) and static (pressure) mechanical allodynia in migraine. Cephalalgia 2006;26:852–856.

14. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17(1):45-56.

15. Yalin OÖ, Uludüz D, Sungur MA, Sart H, Özge A. Identification of Allodynic Migraine Patients with the Turkish Version of the Allodynia Symptom Checklist: Reliability and Consistency Study. Arch Neuropsychiatry 2017;54:260-266.

16. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

17. Agargün MY, Kara H, Anlar O. The validity and reliability of the Pittsburgh Sleep Quality Index. Turk Psikiyatr Derg 1996;7:107-15.

18. Hisli N. Reliability and validity of Beck Depression Inventory among university students. Turk Psikoloji Dergisi 1989;7(23):3-13.

19. Beck AT, Steer RA. Beck Anxiety Inventory Manual. San Antonio, TX: The Psychological Corporation Harcourt Brace & Company 1993.

20. Ulusoy M. Beck Anksiyete Envanteri: Geçerlik ve güvenirlik çalışması. Yayınlanmamış uzmanlık tezi. Bakırköy Ruh ve Sinir Hastalıkları Hastanesi, İstanbul. 1993.

21. Cuadrado ML, Aledo-Serrano Á, Navarro P ve ark. Short-term effects of greater occipital nerve blocks in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. Cephalalgia 2017;37(9):864-872.

22. LoPinto C, Young WB, Ashkenazi A. Comparison of dynamic (brush) and static (pressure) mechanical allodynia in migraine. Cephalalgia 2006;26:852–856.

23. Ashkenazi A, Young WB. The Effects of Greater Occipital Nerve Block and Trigger Point Injection on Brush Allodynia and Pain in Migraine. Headache 2005;45(4), 350–354.

24. Ashkenazi A,Levin M. Greater occipital nerve block for migraine and other headaches Is it useful?. Curr Pain Headache Rep 2007;11:231–235.

25. Hoffmann J, Mehnert J, Koo EM, Arne M. Greater occipital nerve block modulates nociceptive signals within the trigeminocervical complex. Journal of Neurology, Neurosurgery & Psychiatry 2021;92:1335-1340.

26. Ashkenazi A, Young WB. The effects of occipital nerve block on brush allodynia and pain in migraine. Headache 2005;45(4):350-354.

27. Ertem DH, Yalaz-Tekan Ü, Altunkaynak Y, Uluduz D. Repeated peripheral nerve blocks reduce cutaneus allodynia symptoms, headacherelated disability, depression, and anxiety in chronic migraine. Bakırköy dergisi 2019.

28. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache 2005;45:904–910

29. Sengul Y, Sengul HS, Bakim B, Yucekaya SK, Yucel S, Akgun M. Sleep disturbances and excessive daytime sleepiness in migraine: a comparison between comorbidities and disability. Sleep and Biological Rhythms. 2015;13(1):76-84.

30. Saçmacı H, Aktürk T, Tanık N, İnan LE. Clinical success of greater occipital nerve blockade in improving sleep quality of chronic migraineurs: a prospective observational study. Sleep Breath 2021;25(2):1003-1010.

31. Ulusoy EK, Bolatturk OF. The effect of greater occipital nerve blockade on the quality of life, disability and comorbid depression, anxiety, and sleep disturbance in patients with chronic migraine. Neurol Sci 2020;41:1829–1835.

32. Schoonman GG, Schytz HW, Ashina M. Migraine trigger factors. Oxford Textbook of Headache Syndromes 2020: p. 67.

33. Stewart WF, Wood GC, Manack A, Varon SF, Buse DC, Lipton RB. Employment and work impact of chronic migraine and episodic migraine. J Occup Environ Med 2010;52:8–14.

34. Chen YC, Tang CH, Ng K, Wang SJ. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. J Headache Pain 2012;13:311–319.

35.Vigano A, Torrieri MC, Toscano M ve ark. Neurophysiological correlates of clinical improvement after greater occipital nerve (GON) block in chronic migraine: relevance for chronic migraine pathophysiology. J Headache Pain 2018;19:73–82.

36. Inan LE, Inan N, Unal-Artık HA, Atac C, Babaoglu G. Greater occipital nerve block in migraine prophylaxis: Narrative review. Cephalalgia 2019;39(7):908-920.

37. Tobin JA, Flitman SS. Occipital nerve blocks: effect of symptomatic medication: overuse and headache type on failure rate. Headache 2009;49:1479–1485.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Splenektomi Yapılan Olguların Retrospektif Analizi

Retrospective Analysis of Splenectomy Cases

Zehra ÜNAL ÖZDEMİR* 0000-0002-4063-9402

Mehmet Onur GÜL** 0000-0001-9903-6246

* General Surgery, University of Health Sciences, Haydarpaşa Numune Training and Research Hospital, Istanbul, Türkiye
 ** Surgical Oncology, Malatya Training and Research Hospital, Malatya, Türkiye

Corresponding Author: Zehra Ünal ÖZDEMİR

E mail: drzehraunal@gmail.com

Haydarpaşa Numune Training and Research Hospital, Istanbul, Türkiye

Öz

Amaç: Splenektomi sıklıkla travma olguları, hematolojik bozukluklar, benign yada malign patolojiler nedeni ile yapılmaktadır. Bu çalışmada splenektomi yapılan olguların retrospektif analizi yapılarak sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2011-Aralık 2021 yılları arasında tek merkezde yapılan splenektomi olguları retrospektif olarak değerlendirildi. Toplam 227 splenektomi olgusu tespit edildi. Hastaların verileri hastane veri tabanından alınarak preoperatif görüntüleme yöntemleri, cerrahi bulguları ameliyat notları değerlendirildi ve splenektomi endikasyonları belirlendi.

Bulgular: Splenektomi uygulanan 227 hastanın kadın/erkek oranı 108/119 idi. Malignite sebebi ile planlı bir şekilde splenektomi yapılan hastalarda kadın/erkek oranı 29/34 idi. Bu hastaların 20 tanesine pankreas, 19'una mide, 16 tanesine kolon splenik fleksura tümörü nedeni ile cerrahi yapılırken ve kalan 8'ine de dalağa komşu diğer organların kanser invazyonu şüphesi veya metastatik malignite sebebi ile splenektomi yapıldığı belirlendi. Pankreas kanseri sebebi ile yapılan splenektomilerde dalak vasküler yapılarına invazyon şüphesi olan hastalardan sadece 2'sinde (%11.1) histopatolojik olarak invazyon varlığı saptanmıştır. Dalak parankim invazyon şüphesi olan 2 malignite olgusundan ise sadece 1 (%50) tanesinde histopatolojik incelemede invazyon varlığı saptanmıştır. Mide kanseri sebebi ile preopetatif dönemde splenektomi kararı verilen 19 (%3.7) hastanın 2 (%10.5) tanesinde histopatolojik incelemede metastatik hiler lenf nodu tespit edilmiş, 3 (%15.7) hastada ise vasküler invazyon şüphesi ile splenektomi yapılmış fakat herhangi bir vasküler invazyon varlığı histopatolojik incelemede gösterilememiştir. Yüz dört splenik fleksura tümörü içerisinde 12 (%11.53) hastada invazyon şüphesi ile yapılan splenektomilerin 1 (%8.3) tanesinde dalak parankim invazyon varlığı histopatolojik olarak tespit edilmiştir. Farklı bir hastada (%8.3) ise metastatik hiler lenf nodu tespit edilmiştir.

Sonuç: Bu çalışma sonuçları kılavuzluğunda, preoperatif dönemde dalağa komşu yapıların kanserlerinde dalak parankim invazyonu, vasküler invazyon veya metastaz şüpheli lenf nodu varlığının dikkatli bir şekilde değerlendirilmesinin splenektomi sayılarını azaltacağı düşündürmektedir.

Anahtar Kelimeler: Dalak, Malignite, Splenektomi

Abstract

Objective: Splenectomy is frequently performed in trauma cases, hematological disorders, and benign or malignant pathologies. This study aimed to evaluate the results of splenectomy cases by performing a retrospective analysis.

Materials and Methods: Splenectomy cases performed in a single center between January 2011 and December 2021 were evaluated retrospectively. A total of 227 splenectomy cases were identified. In addition, the patients' data were taken from the hospital database, preoperative imaging methods, surgical findings, and operative notes were evaluated, and splenectomy indications were determined.

Results: The female/male ratio of 227 patients who underwent splenectomy was 108/119. The female/male ratio was 29/34 in patients who underwent planned splenectomy due to malignancy. It was determined that 20 of these patients underwent surgery for pancreatic tumors, 19 for stomach tumors, 16 for colonic splenic flexure tumors, and the remaining eight patients underwent splenectomy due to suspected cancer invasion of other organs adjacent to the spleen or metastatic malignancy. Histopathologically, the invasion was detected in only 2 (11.1%) patients with suspected invasion of splenic vascular structures in splenectomies performed for pancreatic cancer. The invasion was found in only 1 (50%) of the two malignancies with suspected splenic parenchymal invasion in the histopathological examination. The metastatic hilar lymph node was detected in histopathological examination in 2 (10.5%) of 19 (3.7%) patients for whom splenectomy was decided preoperatively due to gastric cancer. Splenectomy was performed in 3 (15.7%) patients suspected of vascular invasion, but any vascular invasion could not be demonstrated histopathologically. Among 104 splenic flexure tumors, the splenic parenchymal invasion was detected histopathologically in 1 (8.3%) of splenectomies performed with suspicion of invasion in 12 (11.53%) patients. The metastatic hilar lymph node was detected in another patient (8.3%).

Conclusion: In light of the results of this study, it is thought that careful evaluation of the presence of splenic parenchymal invasion, vascular invasion, or metastasis suspected lymph nodes in cancers of structures adjacent to the spleen in the preoperative period would reduce the number of splenectomies.

Keywords: Spleen, Malignancy, Splenectomy

Introduction

Splenectomy is frequently performed in traumatic cases, hematological disorders, and benign or malignant spleen pathologies. It is frequently observed that the spleen is affected by pathologies originating from neighboring organs and tissues in addition to its pathologies. Splenectomy is performed primarily in gastric and pancreatic cancer cases to provide local control and R0 resection and to include lymph node station number 10 in the surgical specimen (1-4).

This study aimed to analyze the splenectomies performed in a single center over a 10-year period. It is also aimed to determine the frequency of lymph node involvement and parenchymal invasion in the splenic hilus in malignant cases.

Material Method

Splenectomy cases performed in a single center between January 2011 and December 2021 were evaluated retrospectively. A total of 227 splenectomy cases were identified. In addition, the patient's age, gender, surgical procedures, preoperative diagnoses, and diagnoses made after histopathological examination were taken from the hospital database and evaluated. Retrospective study approval was obtained for the study (2023-214578376).

Splenic flexure tumor was defined as the region from the distal third of the transverse colon to the descending colon. Cases that underwent splenectomy during colon tumor or other colon resections and those with a previous history of malignancy that underwent splenectomy due to recurrence or metastasis were analyzed. In addition, indications for splenectomy performed during gastric, colon, and pancreatic surgery were also examined. It aimed to evaluate the presence of invasion into the spleen and metastatic hilar lymph node in patients who underwent splenectomy in gastrointestinal system malignancies.

The patients' data were analyzed, and preoperative imaging results and preoperative findings were evaluated. The presence of suspected cancer invasion to the spleen in preoperative imaging and the presence of lymph node with suspected metastasis in the splenic hilum was evaluated with contrast-enhanced computed tomography, and what was done in this case was found by examining the epicrisis and surgical notes. In addition, invasion of the spleen and spleen artery-vein and the presence of suspected metastatic lymph nodes in the hilar region were evaluated by examining the post-operative histopathological findings. Although there was no suspicion of spleen invasion and metastatic hilar lymph node in the preoperative imaging and operative notes of 20 patients who underwent distal pancreatectomy, it was thought that splenectomy was performed to facilitate lymphatic dissection and to provide R0 resection.

Statistical analysis

Statistical data were analyzed using the SPSS (Statistical Package for the Social Sciences) 23.0 program. Categorical measurements were given as numbers and percentages. Continuous measurements were presented as mean and standard deviation (median and, when necessary, minimum-maximum).

Results

The female/male ratio of 227 patients who underwent splenectomy was 108/119. The mean age of the patients was found to be $53\pm13,24$ years. The female/male ratio was 29/34 in 63 patients who underwent splenectomy due to malignancy. The mean age of the tumor patients who underwent splenectomy was 58.3 ± 5.65 years. Splenectomy indications of the patients are shown in Table 1.

Planned splenectomy due to malignancy was the most common case of splenectomy.

It was determined that 20 patients underwent splenectomy due to pancreatic surgery, 19 gastric, 16 colonic splenic flexure tumor surgery, and the remaining eight due to suspected cancer invasion of other organs adjacent to the spleen or metastatic malignancy. Apart from gastrointestinal system surgeries, splenectomy was performed in 1 patient with suspected ovarian cancer metastasis and 2 patients in whom metastatic implants were detected in the spleen during cytoreduction for ovarian cancer. Splenectomy was performed in one patient with left retroperitoneal sarcoma, two during left adrenal mass operation, and one with lung cancer and left adrenal metastasis. A splenectomy was performed on a patient with peritoneal mesothelioma because he had an implant on the spleen. Indications for planned splenectomy due to malignancy are shown in Table 2.

Table 1: Splenectomy Indications

Indication	Patients (n)	Percent (%)
Malignancy Surgery	63	27.8
Iatrogenic Causes	38	16.7
Hematological Pathologies	34	15.0
Traumatic Causes	30	13.2
Spontaneous Spleen Rupture	16	7.0
Spleen Cyst	11	4.9
Spleen Masses	7	3.1
Spleen Abscess and Ischemia	5	2.2
Splenic Artery Aneurysm Rupture	3	1.3
Other Reasons	20	8.8

The second most common indication for splenectomy was iatrogenic injuries. When 38 patients who underwent splenectomy for iatrogenic reasons were examined, it was determined that splenic laceration developed in 11 colon surgery, 9 pancreatic surgery, 6 gastric surgery, 3 bariatric surgery, and 9 other abdominal surgeries. Splenectomy for iatrogenic reasons is shown in Table 3.

Table 2: Patients Undergoing Planned Splenectomy During Malignancy Surgery

Malignancy localization	Patients (n)	Percent (%)
Pancreas	20	31.7
Stomach	19	30.2
Colon	16	25.4
Other Abdominal Surgery	8	12.7
Retroperitoneal liposarcoma	1	
Lung cancer left adrenal metastasis	1	
Left adrenal mass	2	
Peritoneal mesothelioma	1	
Ovarian Cancer Metastasis	3	

Table 3: Patients who underwent splenectomy for iatrogenic reasons

Surgery localization	Patients (n)	Percent (%)
Colon Surgery	11	28.9
Pancreatic Surgery	9	23.7
Stomach Surgery	6	15.8
Bariatric Surgery	3	7.9
Other Organ Surgeries	9	23.7

Thirty cases who underwent splenectomy due to traumatic reasons were identified. It was determined that splenectomy was the most common cause of trauma due to falling from a height (n:11). The second most common cause of traumatic splenectomy was traffic accidents (n:10). Splenectomy was performed in 6 patients due to spontaneous rupture of the spleen. Splenectomy was performed in 3 patients due to splenic artery aneurysm rupture. Splenectomy was performed in 7 patients due to splenic infarction. Finally, splenectomy was performed in 11 cases due to splenic cyst, 7 cases due to splenic mass, and 5 cases because of splenic abscess.

Splenectomy was performed in 20 (8.2%) patients due to suspected parenchymal invasion, suspected vascular invasion, and suspicious hilar lymph node positivity at that 242 patients who underwent distal pancreatectomy for intraductal papillary neoplasia, mucinous pancreatic neoplasia, and pancreatic cancer. It was determined that invasion of the splenic artery or vein was suspected in 18 of these 20 pancreatic malignancies, and invasion of the spleen parenchyma was suspected in 2 cases, and therefore splenectomy was performed. Histopathologically, the invasion was detected in only 2 (11.1%) patients with suspected splenic artery and vein invasion. Histopathologically, invasion was detected in only 1 (50%) of the 2 patients with suspected splenic parenchymal invasion. In addition, the presence of metastatic lymph nodes in the spleen hilum was detected in only 1 of the patients who underwent surgery for pancreatic malignancy. Nine patients who underwent splenectomy for iatrogenic reasons during pancreatic surgery were identified. Splenectomy was performed in 7 of them due to spleen parenchymal injury and 2 of them due to vascular injury.

Splenectomy was performed in 19 (3.7%) of 501 patients who underwent total and subtotal gastrectomy due to gastric cancer, considering the presence of spleen invasion, lymph node metastasis, and vascular invasion. In 10 of these 19 patients, splenectomy was performed considering the presence of suspected metastasis lymph nodes in the splenic hilum.

However, metastatic hilar lymph node was detected in only 2 of them as a result of histopathological examination. Splenectomy was performed in 3 (15.7%) of these 19 patients suspected of vascular invasion, but any vascular invasion could not be demonstrated in the histopathological examination. Although the splenic parenchymal invasion was suspected in 6 patients, the presence of invasion could not be demonstrated in histopathological examination. During gastric surgery, splenectomy was performed in 9 patients for iatrogenic reasons. Splenectomy was performed in 3 of these patients due to splenic laceration during bariatric surgery. Splenectomy was performed due to spleen laceration developed in 5 of the other 6 patients during malignancy surgery and 1 during Nissen fundoplication.

It was found that splenectomy was the 3rd most frequent among malignancy surgeries, and it was performed during colon tumor surgery. Splenectomy was performed in 12 (11.53%) patients with suspicion of splenic parenchymal invasion among 104 splenic flexure tumors. The invasion was detected histopathologically in only one (8.3%) of them. The metastatic hilar lymph node was detected in another patient (8.3%). During colon tumor surgery, 11 patients underwent splenectomy for iatrogenic reasons. It was understood that 10 (90.9%) of the splenectomies performed due to iatrogenic spleen injury during colon surgery were performed during surgery for non-splenic flexure colon tumor, and 1 (9.1%) was performed during colon resection due to sigmoid volvulus.

It was determined that the patients who underwent splenectomy with the third frequency were those who underwent splenectomy due to hematological pathologies (n:34). It was determined that ITP (n:11) and lymphoma (n:11) were the most common indications for splenectomy performed due to hematological disorders. Later, hereditary spherocytosis was observed (n: 6). Hydatid cysts were detected in 7 of 11 patients who underwent splenectomy due to cystic lesions in the spleen.

Discussion

In this study, it was determined that the patients who underwent splenectomy were the patients who underwent the most common malignancy surgery. At the same time, it was mostly performed during surgeries performed for pancreatic malignancies. When the literature is examined, it is stated that splenectomy is a preferable method in tumors located in the body and tail of the pancreas, and lymph node station 10 is also removed with this method, allowing complete lymphatic dissection (5,6). It is emphasized that with a complete lymphatic dissection, R0 resection can be achieved by removing the metastatic lymph node in the hilum of the spleen. In contrast to this approach in the literature, spleen-sparing pancreatectomy cases during pancreatic malignancy surgeries and pancreatectomy cases that underwent splenectomy were compared, and no statistically significant difference was found in 5-year survival in both groups, and it was reported that the incidence of infection was statistically higher in the splenectomy group (2, 7).

It is also emphasized in the literature that this infection clinic, which develops in patients with splenectomy in pancreatic cancer surgery, has adverse effects on the quality of life (8). It is stated that the rate of metastatic lymph nodes in the spleen hilum is 4.7% in the pancreatic body and tail tumors (9). In our study, this rate was found to be 4%, which is compatible with the literature. In a study by Navez et al., they reported 10% invasion rates to vascular structures in the spleen hilum and spleen parenchyma in cancers located in the tail of the pancreas (10). In our study, the rate of vascular invasion was found to be 4.1%, and parenchymal invasion was 2.08% in patients who underwent splenectomy in distal pancreatic cancers.

Among the malignancy surgeries, the patients who underwent splenectomy were the second most common patients who underwent surgery due to gastric cancer. Although it has been stated that approximately % 9 of proximal gastric cancers metastasize to the lymph nodes in the splenic hilar region and splenectomy is required for a complete dissection, the benefit of splenectomy for lymphadenectomy on survival is still controversial (11,12). In a study by Kinoshita et al., it was stated that splenectomy should not be performed for the dissection of lymph node 10 unless gastric cancer invades the greater curvature (13). In the literature, it is stated that during gastric cancer surgery, the lymph nodes on the splenic artery can be removed with careful surgery without splenectomy and pancreatectomy, but splenectomy is inevitable in the presence of lymph nodes in the splenic hilum (1). In our study, metastatic hilar lymph nodes were detected at a rate of 10.5% in histopathological examinations in patients who underwent splenectomy for gastric cancer. The invasion was not demonstrated histopathologically in splenectomies performed with the suspicion of splenic parenchymal invasion. It is also stated in the literature that splenectomy has no effect on survival and increases post-operative complications in patients with gastric cancer who underwent splenectomy (14).

It has been reported in the literature that the rate of splenectomies due to splenic laceration during colorectal cancer surgery is less than 1%, but this rate is 6% for splenic flexure tumors (15). Cassar et al. reported in their study that 40% of splenectomies were performed for iatrogenic reasons (16). In the same study, it was reported that the operation that increased this risk the most was left hemicolectomy. In a study on splenic flexure tumors, it was stated that splenectomy was performed for tumors closer to 2 cm to the spleen, tumors suspected of parenchymal invasion, and patients with excessive bleeding during the surgical procedure. However, splenectomy had no effect on overall survival in these patients (17). At the same time, it was stated in this study that only two of 51 patients had metastatic lymph nodes in the splenic hilum, but no invasion of the spleen parenchyma was detected.

In another study, it was reported that tumor invasion to the spleen was observed in 10% of cases with splenic flexure tumors who underwent colectomy with splenectomy (18). It was seen that there are no current literature publications on the rates and presence of spleen invasion splenic colon cancer. In our study, 8.3% (n:1) of lymph node metastasis in the spleen hilum and parenchymal invasion were found at the same rate.

Conclusion

Since the splenic hilum is not an area where lymphatic dissection can be easily performed, splenectomy is frequently performed in malignant cases. Unfortunately, splenectomy does not affect overall survival in patients with malignancy but increases susceptibility to infection.

For this reason, it is thought that a detailed evaluation of the patient in the preoperative period and a surgical procedure that will be performed by paying attention to the spleen will reduce the splenectomy rates, especially in pancreatic, gastric, and colon splenic flexure tumors.

References

1. Faiz Z, Hayashi T, Yoshikawa T. Lymph node dissection for gastric cancer: Establishment of D2 and the current position of splenectomy in Europe and Japan. *Eur J Surg Oncol* 2021; 47(9):2233-2236.

2. Kwon J, Kim, SG, Chun JM, Hwang YJ, Kang MJ. Comparison of spleen-preserving distal pancreatectomy with and without splenic vessel preservation: A propensity score-matched analysis. *HPB* 2020; 22(12):1742-1750.

3. Sarıtaş AG, Altıok M, Dalcı K, Rencuzoğulları A, Gül MO, Yalav O, Eray İC. Non Hodgkin Lenfoma Nedeni İle Splenektomi Uygulanan Hastaların Retrospektif Analizi. *Ege Klinikleri Tıp Dergisi* 2020;*58*(3): 344-348.

4. Dalcı K, Sarıtaş AG, Gul MO, Ulku A, Gumus S, Kaycı Y, Atar C. Dalak İnfarktı: Tek Merkez Deneyimi. *Ege KlinTıp Derg* 2020;58 (2):182-186

5. Kimura W, Inoue T, Futakawa N, Shinkai H, Han I, Muto T. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. *Surgery* 2010; 128(6): 854-858.

6. Ferrone CR, Kattan MW, Tomlinson JS, Thayer SP, Brennan MF, Warshaw AL. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. *J Clin Oncol* 2005;23(30): 7529-35.

7. Fernández-Cruz L, Orduña D, Cesar-Borges G, López-Boado MA. Distal pancreatectomy: en-bloc splenectomy vs spleen-preserving pancreatectomy. *HPB (Oxford)* 2005;7(2): 93-98.

8. Şandra-Petrescu F, Tzatzarakis E, Mansour Basha M, et al. Impact of spleen preservation on the incidence of postoperative pancreatic fistula after distal pancreatectomy: Is less more?. *Pancreatology* 2022;22(7): 1013-1019.

9. Kim SH, Kang CM, Satoi S, Sho M, Nakamura Y, Lee WJ. Proposal for splenectomy-omitting radical distal pancreatectomy in well-selected left-sided pancreatic cancer: a multicenter survey study. *J Hepatobiliary Pancreat Sci* 2013;20: 375–381.

10. Navez J, Marique L, Hubert C, et al. Distal pancreatectomy for pancreatic neoplasia: is splenectomy really necessary? A bicentric retrospective analysis of surgical specimens. *HPB (Oxford)* 2020;22(11): 1583-1589.

11. Jeong O, Jung MR, Ryu SY. Clinicopathological features and prognostic impact of splenic hilar lymph node metastasis in proximal gastric carcinoma. *Eur J Surg Oncol* 2019;45(3): 432-438.

12. Wang F, Chang YC, Chen TH, Hsu JT, Kuo CJ, Lin CJ, et al. Prognostic significance of splenectomy for patients with gastric adenocarcinoma undergoing total gastrectomy: a retrospective cohort study. *International Journal of Surgery* 2014;12(6): 557e65.

13. Kinoshita T, Okayama T. Is splenic hilar lymph node dissection necessary for proximal gastric cancer surgery? *Annals of Gastroenterological Surgery* 2021;*5*(2): 173-182.

14. Kunisaki C, Sato S, Tsuchiya N, et al. Systemic Review and Meta-analysis of Impact of Splenectomy for Advanced Gastric Cancer. *In Vivo* 2020;34(6): 3115-3125.

15. McGory ML, Zingmond DS, Sekeris E, Ko CY. The significance of inadvertent splenectomy during colorectal cancer resection. *Arch Surg* 2007;142(7): 668-74.

16. Cassar K, Munro A. Iatrogenic splenic injury. *J R Coll Surg Edinb* 2002; 47(6): 731-41.

17. Kim, CW, Shin US, Yu CS, Kim JC. Clinicopathologic characteristics, surgical treatment and outcomes for splenic flexure colon cancer. *Cancer Research and Treatment: Official Journal of Korean Cancer Association* 2010;*42*(2): 69-76.

18. Khafagy MM, Stearns MW Jr. Carcinoma of the splenic flexure. *Dis Colon Rectum* 1973;16: 504-7.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Our Surgical Experience in Congenital Neck Masses

Konjenital Boyun Kitlelerinde Cerrahi Deneyimimiz

Mehmet Ekrem ZORLU[*] 0000-0003-0474-8094

Orçun DELİCE[**] 0000-0003-0569-2846

Ecem Sevim AKİ[***] 0000-0001-6256-2015

Fatih YILMAZ[**] 0000-0001-5303-961X

Abdullah DALGIÇ[**] 0000-0002-6958-4169

* Bakırçay University Faculty of Medicine, Çiğli Training and Research Hospital, Department of Otolaryngology and Head & Neck Surgery

** University of Health Sciences, Izmir Bozyaka Training and Research Hospital, Department of Otolaryngology and Head & Neck Surgery

*** Acibadem Şinasi Can (Kadıköy) Hospital

Corresponding author: Mehmet Ekrem ZORLU

Address: Bakircay University Faculty of Medicine, Ciğli Training and Research Hospital, Department of Otolaryngology and Head & Neck Surgery

Email: m_ekrem_zorlu@hotmail.com

Abstract

Objective: The study aims to present the congenital neck masses operated on in our clinic and to discuss the factors affecting the development of cancer arising from the cysts in the neck and recurrence after surgery.

Material and Methods: The study included patients operated on for congenital neck masses in our clinic between 2011 and 2022. Demographic characteristics, anamnesis, examination findings, radiological findings, operation notes, and pathological diagnoses were evaluated retrospectively.

Results: A total of 72 patients were included in the study. While 29 patients (40.3%) were operated on for thyroglossal duct cyst (TGDC), 37 patients (51.4%) were operated on for branchial cleft anomaly (BCA), 4 patients (5.5%) for dermoid cyst, and 2 patients for epidermoid cyst (2.8%). The mean age of all cases was 31.8 ± 16.1 years (min:5.0, max:70.0). Revision surgery was performed due to a recurrence in 1 patient (2.7%) operated on for BCA and in 4 patients (13.8%) operated on for TGDC. The risk factors affecting recurrence after the surgery for TGDC were the presence of infection and fistula before the operation (p:0.041, p:0.024). There were 3 patients (3.1%) with papillary thyroid cancer cystic metastasis in the lateral neck and 2 patients (6.9%) with papillary thyroid cancer arising from TGDC. The pathological lymph node on the radiological imaging was the most important factor increasing the risk of malignancy in cystic masses located in the lateral neck (p<0.001).

Conclusion: The treatment of congenital neck masses is surgical, and it is crucial to know the anatomy and embryology of the neck well in order to prevent complications and recurrences. Before the operation, especially for adult patients, a detailed head and neck examination should be performed, and possible metastases and malignancies should be excluded with appropriate imaging techniques and tests.

Keywords: Branchial cleft anomalies, congenital neck masses, thyroglossal duct cysts

Öz

Amaç: Kliniğimizde opere edilen konjenital boyun kitlelerinin sunulması ve cerrahi sonrası nüks ile kist zemininde kanser gelişimini etkileyen faktörlerin tartışılması amaçlandı.

Gereç ve yöntemler: Çalışmaya kliniğimizde 2011-2022 yılları arasında konjenital boyun kitlesi nedeniyle opere edilen olgular dâhil edildi. Hastaların retrospektif olarak demografik özellikleri, anamnezleri, muayene bulguları, radyolojik bulguları, operasyon notları, patolojik tanıları değerlendirildi.

Bulgular: Çalışmaya toplam 72 hasta dâhil edildi. 29 hasta (%40.3) tiroglossal duktus kisti (TGDK) nedeniyle opere edilirken 37 hasta (%51.4) brankial yarık anomalisi (BYA) nedeniyle, 4 hasta dermoid kist (%5.5), 2 hasta epidermoid kist (%2.8) nedeniyle opere edildi. Tüm olguların yaş ortalamasının 31.8 ± 16.1 (5.0-70.0) olduğu tespit edildi. BYA nedeniyle opere edilen 1 hastaya (%2.7) nüks nedeniyle cerrahi uygulanırken, TGDK nedeniyle opere edilen 4 hastaya (%13.8) nüks nedeniyle cerrahi uygulandı. TGDK cerrahisi sonrası nüksü etkileyen faktörler incelendiğinde operasyon öncesi enfeksiyon ve fistül varlığının nüksle ilişkili olduğu görülmektedir (p:0.041, p:0.024). BYA ön tanısıyla opere olan 3 hastada (%8.1) papiller tiroid kanseri kistik metastazı görülürken, 2 hastada (%6.9) TGDK zemininde gelişen papiller tiroid kanseri izlendi. Boyun lateralinde yerleşimli kistik kitlelerde malignite riskini arttıran en önemli faktörün görüntülemede patolojik görünümlü lenf nodu olduğu izlendi (p<0.001).

Sonuç: Konjenital boyun kitlelerinin tedavisi cerrahi olup komplikasyonların ve nükslerin önüne geçilebilmesi açısından boyun anatomisi ve embriyolojisinin iyi bilinmesi önem arz etmektedir. Operasyon öncesi özellikle erişkin hastalara ayrıntılı baş boyun muayenesi yapılmalı ve uygun görüntüleme teknikleri ve tetkikler ile olası metastazlar ve maligniteler ekarte edilmelidir.

Anahtar Kelimeler: Brankiyal yarık anomalileri, konjenital boyun kitleleri, tiroglossal duktus kistleri

Introduction

Congenital neck masses are the most common cause of non-inflammatory neck masses in the pediatric age group (1). Inflammatory, neoplastic, and traumatic masses are included in the differential diagnosis of congenital neck masses (2). The patient's age, history, location, size of the mass, symptoms, and physical examination are critical while evaluating pediatric neck masses. Imaging methods are also helpful in diagnosis, and the definitive treatment is usually surgery.

The location of the mass is important in the differential diagnosis of congenital neck masses, and it is classified as lateral neck masses, midline neck masses, and masses of the entire neck (3). Lateral neck masses include branchial cleft anomalies (BCA) (cyst, fistula, or sinus) and laryngoceles. The midline masses are thyroglossal duct cysts (TGDC) (including fistula and sinus), dermoid cysts, thymic cysts, and teratomas. Vascular and lymphatic malformations can be encountered anywhere in the entire neck (3). Although TGDC is the most common congenital neck mass in most of the case series, BCA is seen as the most common cause in some publications (4-6). While TGDC is most common in the midline, branchial cleft anomalies are most common in the lateral neck (1).

In this study, we aimed to present the patients operated on for non-vascular congenital neck mass in our clinic between January 2011 and January 2022 and to discuss the factors affecting cancer development arising from the cysts and recurrence after the surgery in light of current literature.

Materials and Methods

The study included patients from Izmir Bozyaka Training and Research Hospital's Department of Otolaryngology and Head & Neck Surgery Clinic who underwent surgery for congenital neck masses between January 2011 and January 2022. The study was approved by the ethics committee of our hospital with a decision dated 28.09.2022 and numbered 139, and it was conducted in accordance with the Declaration of Helsinki principles. A retrospective analysis of the database of our hospital was performed. Demographic characteristics, history, examination findings, radiological findings, operation notes, postoperative controls, and complications of the patients were recorded. The cases presenting with the preliminary diagnosis of a congenital neck mass were evaluated through neck ultrasonography and, if necessary, thyroid ultrasonography, contrast-enhanced computed tomography (CT), and contrast-enhanced neck magnetic resonance imaging (MRI) after a detailed head and neck examination. In case of clinical suspicion of malignancy in adults, ultrasound-guided fine-needle aspiration biopsy (FNAB) was performed by the radiology department.

Patients who underwent surgery with a preliminary diagnosis of a congenital neck mass were included in the study. In addition, patients with a prediagnosis of congenital neck mass whose definitive pathology result after the surgery was malignancy were also included in the study. Cases that underwent surgery for inflammatory neck masses, vascular lesions, and cystic neoplastic masses, which were diagnosed as malignancy preoperatively using imaging methods and FNAB, along with patients with missing data, were excluded from the study.

Preoperative consent was obtained from all patients. TGDCs were operated on with the modified Sistrunk procedure (7), in which the cyst or the fistula, the central portion of the hyoid bone, and the tract with a cuff of lingual musculature were excised up to the foramen cecum, but the tongue mucosa was preserved. Cyst excision was performed in branchial, dermoid, and epidermoid cysts. Superficial parotidectomy was performed in addition to fistula tract excision in a single case of Type 1 BCA.

Statistical Analysis

Statistical analysis was performed with IBM Statistical Package for the Social Sciences Statistics version 22.0. Whether the continuous variables were normally distributed or not was tested by Kolmogorov-Smirnov and Shapiro-Wilk tests. The Student T-test was used to compare the normally distributed continuous variables between the groups, and the Mann-Whitney U-test was used to compare the non-normally distributed continuous variables. Results were presented as mean ± standard deviation and median (min-max) values. Chi-square and Fisher's exact tests were used to compare categorical variables between groups. Binary logistic regression analysis was used to analyze the factors associated with recurrence and malignancy. P<0.05 was considered statistically significant.

Results

A total of 72 patients who were operated on between 2011 and 2022 were included in our study. 29 patients (40.3%) were operated on for TGDCs, 37 patients (51.4%) were operated on for BCAs, 4 patients (5.5%) for dermoid cysts, and 2 patients for epidermoid cysts (2.8%) (Figure 1).

Figure 1- Percentages of the congenital non-vascular neck masses within the study population

Percentages of the congenital neck masses within the study population.

- Thyroglossal duct cysts — 40.3%
- Branchial cysts — 51.4%
- Dermoid cysts — 5.5%
- Epidermoid cyst — 2.8%
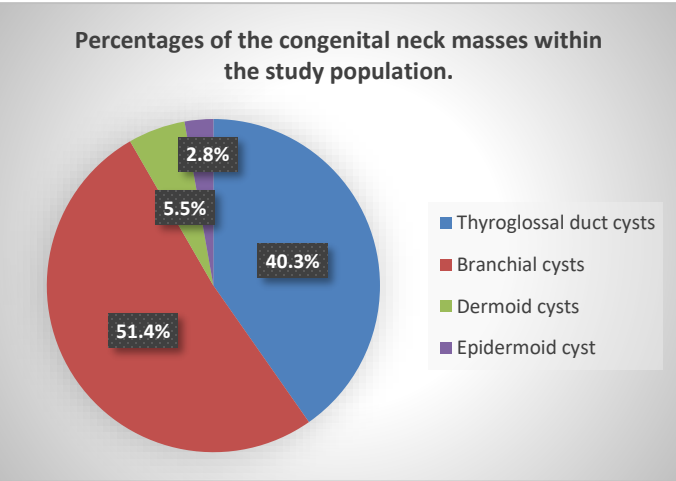
The mean age of all cases was 31.8 ± 16.1 (5.0-70.0) years. Figure 2 shows the distribution of the congenital neck masses by ages in decades. 36 patients were male (50%), and 36 (50%) were female. The mean follow-up period was 6.4 ± 3.5 (0.9-12.0) years. The most common symptoms were swelling, pain, and discharge in the neck. 66 patients presented with neck swelling (91.7%), 21 (30%) patients with tender fluctuant swelling, 12 patients (17.1%) with pain, and 5 patients with discharge (7.1%). One patient (1.4%) who had a thyroglossal cyst with intralaryngeal extension and a TGDC carcinoma had hoarseness before the surgery. Table 1 shows the clinical and demographic characteristics of all cases.

Figure 2- Distribution of the congenital neck masses by ages in decades

Distribution of neck masses according to age in decades.

Thyroglossal duct cysts | Branchial cysts | Dermoid cysts | Epidermoid cyst
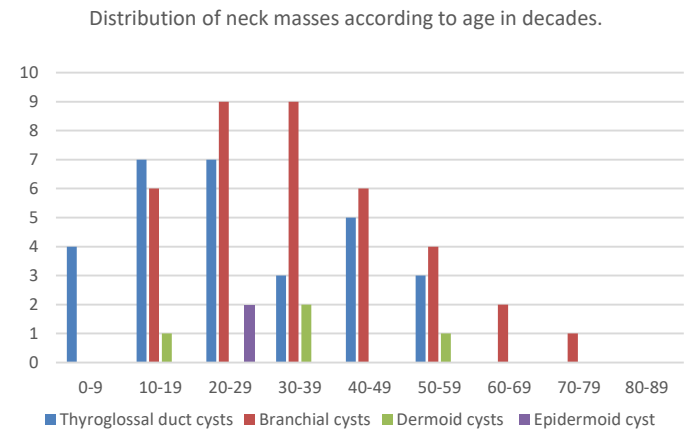
Table 1: Demographic data and clinical characteristics of all patients

Age	31.8 ± 16.1 (min:5.0, max:70.0)
Age in decades	
0-9	4 (5.6%)
10-19	14 (19.4%)
20-29	18 (25.0%)
30-39	14 (19.4%)
40-49	11 (15.3%)
50-59	8 (11.1%)
60-69	2 (2.8%)
70-79	1 (1.4%)
Sex	
Female	36 (50.0%)
Male	36 (50.0%)
Follow-up time (years)	6.4 ± 3.5 (min:0.9, max: 12.0)
Symptoms	
Swelling	66 (91.7%)
Tender fluctuant swelling	21 (30%)
Pain	12 (17.1%)
Discharge	5 (7.1%)
Hoarseness	1 (1.4%)
Size (mm)	34.8 ± 17.6 (min:4.0, max:80.0)
Diagnosis	
MRI	8 (11.4%)
MRI+CT	2 (2.9%)
USG	19 (27.1%)
USG+CT	10 (14.3%)
USG+MRI	25 (35.7%)
USG+CT+MRI	2 (2.9%)

While 23 (62.2%) of the patients who were operated on for a BCA were male, 14 (37.8%) were female. The mean age of these cases was 35.5 ± 15.8 (12.0-70.0) years. One patient (2.7%) was operated on for a first BCA, and 36 patients had a preliminary diagnosis of a second BCA (97.3%). The only BCA case with a fistula was a first BCA. The mean cyst size was 44.7 ± 15.5 mm (min: 13.0, max: 80.0). The definitive pathology result was papillary thyroid carcinoma in 3 (8.1%) patients and Warthin tumor in 1 (2.7%) patient. 32 (96.9%) of 33 patients with pathology results of BCA had a second BCA, and one patient (3.1%) had a first BCA. Three patients with cystic metastases of papillary thyroid carcinoma underwent total thyroidectomy and central and lateral neck dissections after the cyst excision. Of those, two patients were found to have a cystic lymph node metastasis due to thyroid papillary microcarcinoma. On the other hand, no tumor was observed in the thyroidectomy specimen in one patient, and it was hypothesized that papillary carcinoma developed from the thyroid tissue located within the branchial cyst.

Revision surgery was performed for a recurrence in one (2.7%) patient who was operated on for a second BCA. In the only patient who underwent revision surgery, incision and drainage were performed in the first operation with a preliminary diagnosis of abscess. Preoperative FNAB was performed in 11 patients (30.5%) who underwent branchial cyst excision. 2 of 3 patients with cystic metastases of papillary thyroid carcinoma underwent FNAB before the operation, but they were not diagnostic.

The factors associated with malignancy in cystic masses of the lateral neck are listed in Table 2. The most important factor increasing the risk of malignancy was the lymph node with a pathological appearance on imaging (p<0.001).

Table 2- Comparison of malignant and benign patients in lateral cystic neck masses

	Malignancy N=3	Benign N=34	p
Age (median) (min-max)	41.0 (39.0-44.0)	31.0 (12.0-70.0)	0.286

Sex n(%)
    Female
    Male
	
	1 (33.3%)
	2 (66.7%)
		
		13 (38.2%)
		21 (61.8%)
			0,867

Size (median) (min-max)	45.0 (25.0-50.0)	45.0 (13.0-80.0)	0.549
Swelling n(%)	3 (100.0%)	33 (97.1%)	1.000
Infection n(%)	0 (0.0%)	1 (2.9%)	1.000
Inflamation on the imaging n(%)	1 (33.3%)	13 (38.2%)	1.000
Pathological-appearing lymph node on the imaging n(%)	2 (66.7%)	0 (0.0%)	**<0.001**
Purely cystic appearance on the imaging n(%)	2 (66.7%)	24 (70.6%)	0.887

p<0.05 statistically significant

Of 29 patients operated on for TGDC, 19 were female (65.5%), and 10 were male (34.5%). The mean age of the patients who were operated on for TGDC was 27.3±16.1 (5.0-57.0) years. The location for TGDC was found to be suprahyoid region in 7 patients (24.1%), hyoid level in 8 patients (27.6%), and infrahyoid region in 14 patients (48.3%). Two patients (6.9%) had papillary thyroid carcinoma arising from TGDC.

Total thyroidectomy and central and lateral neck dissections were performed in one of the patients who had papillary thyroid carcinoma from the TGDC, and the other patient underwent only total thyroidectomy after the Sistrunk procedure.

The Sistrunk procedure was performed in all patients except for two patients who underwent a simple cyst excision in another hospital at the first operation and presented to our hospital with a recurrence. In addition, two patients (7.4%) had a recurrence after the primary Sistrunk procedure. As a result, a total of four patients (13.8%) had a recurrence, and all underwent the revision Sistrunk procedure. Revision surgery was performed two times for one patient.

Preoperative fistula was present in 4 patients (13.8%), and revision surgery was required in 2 (6.9%) of 4 patients with fistula. Postoperative wound infection and wound dehiscence were observed in one patient (3.4%) as a complication after the Sistrunk procedure. When the factors affecting the recurrence are examined, the presence of infection and fistula before the operation is associated with recurrence (Table 3) (p: 0.041, p: 0.024, respectively).

Table 3- Comparison of patients with and without recurrence in patients with a TGDC

	Recurrence N=4	No recurrence N=25	p
Age median (min-max)	16.0 (10.0-38.0)	25.0 (5.0-57.0)	0.311
Sex n(%)			0.667
Female	3 (75.0%)	16 (64.0%)	
Male	1 (25.0%)	9 (36.0%)	
Size (median) (min-max)	13.0 (4.0-21.0)	22.0 (5.0-67.0)	0.053
Infection n (%)	3 (75.0%)	6 (24.0%)	**0.041**
Fistula n (%)	2 (50.0%)	2 (8.0%)	**0.024**
Inflamation on the imaging n (%)	3 (75.0%)	8 (32.0%)	0.100
Multicystic appearance on the imaging n (%)	1 (25.0%)	3 (12.0%)	0.484
Midline n (%)	4 (100.0%)	20 (80.0%)	0.326
Surgery			0.999
Simple excision	2 (50%)	0 (0%)	
Sistrunk	2 (50%)	100 (100%)	
Location n(%)			0.670
Hyoid level	1 (25.0%)	7 (28.0%)	
İnfrahyoid	3 (75.0%)	11 (44.0%)	
Suprahyoid	0 (0.0%)	7 (28.0%)	

p<0.05 statistically significant

Dermoid cysts were found to be the 3rd with 4 patients (5.6%). Epidermoid cysts were the 4th, with 2 patients (2.8%). The mean age of the patients operated on for epidermoid cysts was 22 ± 1.4 years, and the mean age of those operated on for dermoid cysts was 33.7 ± 16.9 years. No recurrence was observed after the surgery in patients who had dermoid and epidermoid cysts.

Discussion

A detailed head and neck examination should be performed, and a precise history should be taken in all patients presenting with a neck mass.

The size, consistency (cystic, solid, or vascular), location, and growth rate of the mass are very useful in the differential diagnosis. Although the location of the lesion and physical examination often give an idea about the lesion, ultrasonography, contrast-enhanced CT, and MRI are frequently used. Imaging methods are helpful in differential diagnosis as well as in showing the boundaries of the mass and its relationship with critical neurovascular structures in the neck. FNAB is very useful, especially in adult patients, in distinguishing between cystic lymph node metastases of HPV+ oropharyngeal cancers and cystic lymph node metastases of thyroid masses (8, 9). However, the definitive diagnosis is made by histopathological examination of the mass.

Congenital neck masses can be seen at any age, and the mean age in our study was 31.8 ± 16.1 years. Brucoli et al. (2) found a mean age of 37 ± 17.6 years in their study consisting of 226 patients who were operated on for a congenital neck mass. On the other hand, Al-Khateeb et al. (3) reported the mean age as 16 in a similar retrospective case series. In our study, the mean age of patients presenting with TGDCs was lower than those presenting with branchial cysts (27.3 and 35.5, respectively). The mean age in the studies may vary according to the patient populations applying to the research centers. The ratio of women to men was equal in the total sample. However, the proportion of females (65.5%) was higher in the TGDC group, and the ratio of male patients (62.2%) was higher in the branchial cyst group.

In the present study, BCAs were the most common cause of congenital neck masses (51.4%). TGDCs are frequently seen as the most common cause of congenital neck masses in the literature (2, 6, 10). Having said that, BCAs are the most common cause of congenital neck masses when the studies conducted in centers with a predominantly adult patient group (5). The absence of a pediatric clinic in our hospital can explain the low TGDC rate in the present study.

At the end of the fourth week of gestation, there are 4 pairs of well-developed branchial arches of mesodermal origin and 2 pairs of rudimentary arches, each of which develops muscle, cartilage, bone, and neurovascular structures in specific regions of the head and neck (4). Branchial clefts and endodermal pharyngeal pouches are located between the branchial arches, and the branchial clefts disappear during embryogenesis. Branchial cleft anomalies occur as a result of insufficient involution of the branchial apparatus (6, 11) .

The differential diagnosis of BCAs includes cystic lymph node metastases, lymphatic malformations, abscesses, and laryngoceles. Although history and physical examination are beneficial in diagnosis, CT and MR are helpful in showing the relationship between neurovascular structures and the lesion and possible fistula tracts. The typical appearance of branchial cysts is uniloculated, with a non-contrast-enhancing cystic mass when uninfected. Second branchial cleft anomalies are usually seen as cystic masses that push the carotid sheath posteriorly and medially in the anteromedial of the sternocleidomastoid muscle (SCM).

Second branchial cleft anomalies are the most common BCAs, constituting approximately 95% of all BCAs (6, 12) . The frequency of first branchial cleft anomalies is approximately 1-4%, and third and fourth branchial cleft anomalies are infrequent. In our study, second BCAs were found with a rate of 96.9%, in accordance with the literature, while the rate of first BCAs was 3.1%. No patient had a third or fourth BCA in our case series. 96.9% of patients with a BCA presented with a cystic lesion, and 3.1% with a fistula. The only case presenting with a fistula was the patient who applied because of a first BCA.

In the treatment of first BCAs, in addition to excision of the fistula tract, dissection of the facial nerve and superficial parotidectomy are often required (10). When treating second BCAs, the cyst or fistula should be dissected from the surrounding tissues with a transverse cervical incision. If there is a fistula tract, it should be followed up to the tonsillar fossa (6). Care should be taken to protect the spinal accessory, hypoglossal, and vagus nerves during dissection (4). In the past, ipsilateral tonsillectomy was recommended in the presence of a fistula. However, nowadays, it is recommended to ligate the tract as high as possible since it is seen that ipsilateral tonsillectomy does not reduce recurrence (12, 13).

A single recurrence (3.1%) in branchial cysts was observed in a patient who previously underwent an incision and cyst drainage due to an infected cyst. This recurrence shows the importance of abscess–cyst distinction in congenital neck masses, and cyst drainage should be avoided whenever possible. Spinelli et al. (11) also reported revision rates in branchial cysts as 4%, and they encountered two recurrences in their case series in surgeries performed after infection.

Cancers that develop from branchial cysts are controversial, and there are still debates about the presence of primary cancer. It has been suggested that cystic lymph node metastases of squamous cell cancer in the neck are frequently caused by HPV+ oropharyngeal squamous cell cancers (9, 14). On the other hand, papillary thyroid carcinoma can also metastasize to the neck as a cystic lymph node, as well as a lymph node metastasis in a branchial cyst or carcinoma that develops from the thyroid tissue within the branchial cyst (8, 15-17). Since the treatment approach is quite different in malignant cystic lesions, it is important to distinguish between benign and malignant lesions before the operation. In 2 of the 3 cases whose pathology result was papillary thyroid carcinoma, cystic lymph node metastasis due to multifocal micropapillary thyroid carcinoma was found in the definitive pathology. However, no tumor was observed in the total thyroidectomy specimen in one patient. In this patient, it was thought that the cancer developed from the thyroid tissue within the branchial cyst. Cystic neck masses in adult patients should be considered as malignancy until proven otherwise(14). In different studies, the malignancy rate in patients over 40 years of age presenting with a lateral cystic neck mass varies between 22-80% (9, 18). In this respect, FNAB, detailed head and neck examination, endoscopic oropharyngeal examination, and evaluation of the thyroid gland are crucial in patients with a preliminary diagnosis of a branchial cyst.

The sensitivity of FNAB in detecting cystic SCC metastases varies between 0-66.7% (14). In cases with high suspicion of malignancy, HPV analysis in FNAB material and thyroglobulin assessments of the needle washout facilitate preoperative diagnosis (15, 16) . Yehuda et al. (17) recommends routine HPV and EBV analysis and thyroglobulin measurement from cysts in patients over 40 years of age or with high clinical suspicion .

The patient's age of over 40 and lymphadenopathy in the neck are the most important risk factors in predicting the lesion to be a malignancy rather than a branchial cyst (9, 15) . In our case series, the factor that increased the risk of malignancy the most was the presence of pathological lymph nodes in the neck on the imaging. The median age was 41.0 (min: 39.0, max:44.0) in the malignant group and 31.0 (min: 12.0, max: 70.0) in the branchial cyst group, but there was no statistically significant difference. (p: 0.286)

In the present study, TGDCs were the second most common congenital neck masses, with a rate of 40.3%. TGDCs develop due to insufficient involution of the thyroglossal duct, which occurs during the migration of the thyroid gland from the tongue base to its anatomical position during embryogenesis (6). TGDCs can be found in any localization between the tongue base and the thyroid gland. Generally, the most common localization for TGDCs was the thyrohyoid region with a rate of 61%, followed by suprahyoid (25%), suprasternal (13%), and intralingual (2%) regions (3).

In our case series, in 7 patients (24.1%), the TGDC location was found to be in the suprahyoid region, while in 8 patients (27.6%), it was at the hyoid level. For the remaining 14 patients (48.3%), the TGDC location was in the infrahyoid region. We observed that there was no relationship between TGDC's localization and recurrence.

Four patients (13.8%) had a recurrence, and all underwent the revision Sistrunk procedure. Of 4 patients with recurrence, simple cyst excision was performed in 2 (6.9%) of 4 patients (13.8%), and the Sistrunk procedure was performed in 2 other patients (6.9%) at the time of the first operation. Recurrence rates after the Sistrunk procedure vary between 2.6% to 5% (6). When simple cyst excision is performed in the treatment of TGDC, recurrence rates can reach up to 50% (18). In the present study, the recurrence rate was 7.4% in patients who underwent the primary Sistrunk procedure.

Considering the recurrences after TGDC surgery, different reasons come to the fore in different publications. Şahin et al. suggested that the patient's presentation with pain, the presence of a fistula, and the suprahyoid location of the lesion increased the recurrence (19). In their study with 251 patients, Gümüşsoy and Çukurova (20) stated that the age of the patients between 6-10 years old, history of infection, abscess formation, incision and drainage before surgery, and multicystic formation increase the recurrence of TGDCs. The factors affecting recurrence in the present study were the history of infection and fistula preoperatively.

Malignancy is seen in approximately 1% of thyroglossal duct cysts (21). More than 90% are papillary thyroid carcinoma, and squamous cell carcinoma is the second most common (21, 22). Papillary-type TGDC carcinomas are thought to arise from thyroid elements in the cyst (22). In our case series, papillary-type TGDC carcinoma was observed in 2 patients (3.8%).

Since there is little information in the literature about TGDC carcinomas, there is no clear consensus on the treatment. However, it is recommended not to perform a simple cyst excision and at least to perform the Sistrunk procedure (23). In the presence of papillary-type TGDC carcinoma, synchronous thyroid cancers may accompany at a rate of 20% (21).

Today, the common view is that TGDC carcinomas develop de novo with synchronous thyroid cancers, not metastases (22). In the presence of synchronous thyroid cancer, the treatment strategy should be determined according to the current established guidelines and to perform a total thyroidectomy, and if necessary, add central and lateral neck dissections (21). In our case series, total thyroidectomy and central and lateral neck dissections were performed in the second operation on one patient with multifocal papillary thyroid carcinoma due to suspicious lymph nodes in the neck. In contrast, only total thyroidectomy was performed in the second operation in the other patient because there were no suspicious lymph nodes.

Dermoid cysts are germ cell tumors that develop from the ectoderm and mesoderm. They arise from the inclusion of embryonic epithelial elements (6). They are painless, slow-growing, asymptomatic cysts in the submental region, the floor of the mouth, around the orbit, nose, and ear lobule. Cervical dermoid cysts constitute 20% of head and neck dermoid cysts and are frequently seen in the midline submental region. Dermoid cysts may be close to the hyoid and confused with TGDC. Simple cyst excision is usually sufficient, but in cases where the cyst is close to the hyoid, a Sistrunk procedure is recommended in order to prevent inadequate treatment of an atypical TGDC.

Epidermoid cysts develop from the ectoderm. They are generally seen in acne-prone areas of the face and neck after puberty (5). They contain squamous epithelium and keratin debris. Its treatment is surgical excision of the cyst.

The first of the limitations of our study is the relatively small number of patients due to the inaccessible records before 2011. The second is that our patients are mostly adults since our hospital has no pediatric clinic, and our patient group does not adequately reflect the entire population. Third, vascular lesions are often not operated on and followed up and are not included in the study due to the lack of outpatient records.

Conclusion

Surgery is the recommended approach for treating congenital neck masses. It is highly recommended to thoroughly examine the head and neck region before undergoing any surgical procedure, especially for adult patients. This will help to rule out any potential metastases or malignancies, and appropriate imaging techniques and tests should be utilized for this purpose.

References

1.Goins MR, Beasley MS. Pediatric neck masses. Oral Maxillofac Surg Clin North Am. 2012;24(3):457-68.

2.Brucoli M, Boffano P, Benech A, Rosa S, Garzaro M, Aluffi Valletti P. Congenital nonvascular neck masses: a retrospective analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129(3):192-9.

3.Al-Khateeb TH, Al Zoubi F. Congenital neck masses: a descriptive retrospective study of 252 cases. J Oral Maxillofac Surg. 2007;65(11):2242-7.

4.Acierno SP, Waldhausen JH. Congenital cervical cysts, sinuses and fistulae. Otolaryngol Clin North Am. 2007;40(1):161-76, vii-viii.

5.ÖzlügedİK S, Ant A. Konjenital Boyun Kitleleri: Bir Üçüncü Basamak Sağlık Merkezinin Retrospektif Çalışması. Kulak Burun Boğaz ve Baş Boyun Cerrahisi. 2019;27(2):57-62.

6.LaRiviere CA, Waldhausen JH. Congenital cervical cysts, sinuses, and fistulae in pediatric surgery. Surg Clin North Am. 2012;92(3):583-97, viii.

7.Sistrunk WE. Technique of removal of cysts and sinuses of the thyroglossal duct. Surg Gynecol Obstet. 46 (1928) 109–112.

8.Verge J, Guixa J, Alejo M, et al. Cervical cystic lymph node metastasis as first manifestation of occult papillary thyroid carcinoma: report of seven cases. Head Neck. 1999;21(4):370-4.

9.Koch EM, Fazel A, Hoffmann M. Cystic masses of the lateral neck - Proposition of an algorithm for increased treatment efficiency. J Craniomaxillofac Surg. 2018;46(9):1664-8.

10.Quintanilla-Dieck L, Penn EB, Jr. Congenital Neck Masses. Clin Perinatol. 2018;45(4):769-85.

11.Spinelli C, Rossi L, Strambi S, et al. Branchial cleft and pouch anomalies in childhood: a report of 50 surgical cases. J Endocrinol Invest. 2016;39(5):529-35.

12.Li W, Xu H, Zhao L, Li X. Branchial anomalies in children: A report of 105 surgical cases. Int J Pediatr Otorhinolaryngol. 2018;104:14-8.

13.Cheng J, Elden L. Management of pediatric second branchial fistulae: is tonsillectomy necessary? Int J Pediatr Otorhinolaryngol. 2012;76(11):1601-3.

14.Sira J, Makura ZG. Differential diagnosis of cystic neck lesions. Ann Otol Rhinol Laryngol. 2011;120(6):409-13.

15.Hammarstedt Nordenvall L, Jortso E, von Beckerath M, Tani E, Nordemar S, Bark R. Prevalence of cystic metastases in a consecutive cohort of surgically removed branchial cleft cysts. Acta Otolaryngol. 2022;142(1):100-5.

16.Wunderbaldinger P, Harisinghani MG, Hahn PF, et al. Cystic lymph node metastases in papillary thyroid carcinoma. AJR Am J Roentgenol. 2002;178(3):693-7.

17.Yehuda M, Schechter ME, Abu-Ghanem N, et al. The incidence of malignancy in clinically benign cystic lesions of the lateral neck: our experience and proposed diagnostic algorithm. Eur Arch Otorhinolaryngol. 2018;275(3):767-73.

18.Maddalozzo J, Alderfer J, Modi V. Posterior hyoid space as related to excision of the thyroglossal duct cyst. Laryngoscope. 2010;120(9):1773-8.

19.Şahin MM, Cebeci S, Uzunoğlu E, et al. Possible Risk Factors for Recurrence After Removal of Thyroglossal Duct Cysts with the Sistrunk Procedure. Kulak Burun Boğaz ve Baş Boyun Cerrahisi. 2020;28(3):275-81.

20.Gumussoy M, Cukurova I. Modified Sistrunk procedure in a pediatric population: Infected thyroglossal duct cysts as a risk factor for recurrence and review of the literature. Int J Pediatr Otorhinolaryngol. 2021;148:110837.

21.Rayess HM, Monk I, Svider PF, Gupta A, Raza SN, Lin HS. Thyroglossal Duct Cyst Carcinoma: A Systematic Review of Clinical Features and Outcomes. Otolaryngol Head Neck Surg. 2017;156(5):794-802.

22.Wood CB, Bigcas JL, Alava I, Bischoff L, Langerman A, Kim Y. Papillary-Type Carcinoma of the Thyroglossal Duct Cyst: The Case for Conservative Management. Ann Otol Rhinol Laryngol. 2018;127(10):710-6.

23.Plaza CP, Lopez ME, Carrasco CE, Meseguer LM, Perucho Ade L. Management of well-differentiated thyroglossal remnant thyroid carcinoma: time to close the debate? Report of five new cases and proposal of a definitive algorithm for treatment. Ann Surg Oncol. 2006;13(5):745-52.

The Effect of Hunger and Satiety on Heart Rate Variability Parameters During Ramadan

Ramazan Ayında Açlık ve Tokluğun Kalp Hızı Değişkenliği Üzerine Etkileri

Özgen ŞAFAK*0000-0001-8245-0117

Halil Lütfi KISACIK* 0000-0003-1102-8239

Tarık YILDIRIM*0000-0002-6314-7371

Eyüp AVCI*0000-0002-7790-8450

Didar Elif AKGÜN**0000-0001-6618-180X

Onur ARGAN* 0000-0001-7745-7736

Ayberk GÖRCAN*** 0000-0002-3840-7100

Eyyüp ERKİZ*0000-00017648-2884

* Balıkesir University Medicine Faculty, Department of Cardiology, Balikesir

** Kırklareli Training and Research Hospital, Department of Cardiology, Kirklareli

*** Balıkesir Balikesir City Hospital, Department of Cardiology, Balikesir

Corresponding author: Dr. Özgen ŞAFAK

Department of Cardiology, Balıkesir University, Balıkesir, Turkey

e-mail: ozgen_safak@yahoo.com

Abstract

Objective: The month of Ramadan is a holy month for Muslims who are ordered to fast. Heart rate variability (HRV) is a non-invasive method used to assess the effects autonomic nervous system. In this study, we evaluated the effects of fasting, fasting and postprandial time periods, in fasting and non-fasting patient groups in patients with rhythm holter for various reasons in our clinic during Ramadan 2019.

Methods: This study was carried out by retrospectively evaluating the heart rate variations at fasting and postprandial time periods of patients who applied to our clinic in Ramadan in 2019 and requested rhythm holter for various reasons. A total of 86 patients betweeen 18 and 86 years (mean age 59.0 ± 6.0) with 53 non-fasting group (mean age 61.68± 16.57) and 33 fasting group (mean age 55.58± 15.61) were included in this study. SPSS version 19 (SPSS Inc. Chicago, IL, USA) statistical package program was used for statistical analysis.

Results: When the groups were compared according to ECG Holter data, LF/HF after dinner was found higher in the fasting group (2,41 vs 3,26, *p*=0,031). LF/HF average was found higher in the fasting group (1,02 vs 1,53, *p*=0,006). There were no differences between the groups in terms of other ECG Holter parameters.

Conclusion: In Ramadan, the activity of the parasympathetic system increases during the period of hunger, and in the periods of satiety, the sympathetic system is activated and this is supported by parameters of heart rate variability. More careful and metered food consumption is especially important in terms of encountering cardiac events in iftar.

Keywords: Autonomic nervous system, fasting, heart rate variability, ramadan, hunger, satiety

Öz

Giriş: Ramazan ayı, Müslümanların oruç tuttuğu kutsal bir aydır. Kalp atış hızı değişkenliği (HRV), otonom sinir sisteminin etkilerinin non-invaziv değerlendirilmesini sağlayan bir yöntemdir. Çalışmamızda 2019 yılı Ramazan ayında kliniğimizde çeşitli nedenlerle ritim holteri olan hastalarda orucun açlık ve tokluk zaman dilimlerindeki etkilerini oruçlu olan ve olmayan hasta gruplarında değerlendirdik.

Gereç ve yöntemler: Bu çalışma, 2019 yılı Ramazan ayında kliniğimize başvuran ve çeşitli nedenlerle ritim holteri isteyen hastaların kayıtları retrospektif olarak incelenerek orucun açlık ve tokluk zaman dilimlerindeki etkileri değerlendirilmiştir. Bu çalışmaya yaşları 18 ile 86 arasında (ortalama yaş 59,0 ± 6,0), 53 oruçlu olmayan (ortalama yaş 61,68± 16,57) ve 33 oruçlu olan grup (ortalama yaş 55,58± 15,61) olmak üzere toplam 86 hasta dahil edildi. İstatistiksel analiz için SPSS version 19 (SPSS Inc. Chicago, IL, USA) istatistik paket programı kullanıldı.

Bulgular: EKG holter bilgilerine göre karşılaştırıldığında oruçlu grupta LF/HF değeri yemek sonrası dönemde daha yüksek saptandı (2,41 - 3,26, p=0,031). Ortalama LF/HF değeri oruçlu grupta daha yüksek saptandı (1,02-1,53, p=0,006). Diğer holter parametreleri açısından gruplar arasında fark yoktu.

Sonuç: Ramazan ayında açlık döneminde parasempatik sistemin aktivitesi artarken, tokluk dönemlerinde sempatik sistem devreye girer ve bu durum kalp atış hızı değişkenliği parametreleri ile desteklenir. Daha dikkatli ve ölçülü besin tüketimi özellikle iftarda kardiyak olaylarla karşılaşmamak açısından önemlidir.

Anahtar Kelimeler: Otonom sinir sistemi, oruç, nabız değişkenliği, ramazan, açlık, tokluk

Introduction

The month of Ramadan is a holy month for Muslims who are ordered to fast. During this month, all healthy adult Muslims around the world fast from dawn to sunset (absolute restriction of all solid and liquid food and beverage, sexual intercourse and smoking). Although the Qur'an exempts sick people from fasting, many people with chronic diseases, including cardiovascular disease, are fasting in Ramadan. Although Ramadan has over a billion Muslims fasting worldwide, there is no clear consensus on the effect of fasting on cardiovascular diseases (1). Since the Hijra calendar is 11 days shorter than the Gregorian calendar, Ramadan starts every year 11 days before. Therefore, the duration of fasting varies each year in different geographical regions. When it coincides with the summer months, there may be up to 18 hours of hunger. In recent years, interest in studies investigating the positive or negative effects of hunger and satiety on systems has increased. In particular, it focused on the positive or negative effects Ramadan fasting.

Heart rate variability (HRV), which is used as a non-invasive method to evaluate the effect of the autonomic nervous system (ANS), (2) is an independent indicator of increased mortality in patients with myocardial infarction and congestive heart failure (3-4). Autonomic changes have been found to be associated with ischemia in patients with coronary artery disease (5). Low parasympathetic activity was found to be a marker for poor prognosis in non ST-elevation acute coronary syndrome patients (6-7). Heart rate variables have been shown to be an important prognostic marker in patients with chronic heart failure with both ischemic and non-ischemic etiology (8-9).

Although a large number of Muslim population exists all over the world, to our knowledge, there is a lack of data on the effect of Ramadan fasting on HRV parameters, which has a prognostic significance of patients with heart failure and coronary artery disease. We evaluated the heart rate variations in fasting and postprandial time periods in in fasting and non-fasting patients who admitted to our clinic in Ramadan in 2019 and who had rhythm holter for various reasons.

Methods

This study was carried out by retrospectively evaluating the records of patients who applied to our clinic in Ramadan in 2019 and requested rhythm holter for various reasons. This study was approved by institutional Ethics Committee for human subjects.

A total of 86 patients betweeen 18 and 86 years (mean age 59.0 ± 6.0) with 53 non-fasting group (mean age 61.68± 16.57) and 33 fasting group (mean age 55.58± 15.61) were included in this study. Patients under 18 years of age, patients with unknown fasting status and patients with pacemakers were excluded.

Ramadan elapsed between May 06 and June 03 in 2019. During these months, daytime was longer than the night, so fasting time was in equipoise to average 17 hours. From the holter records, 86 of the patients who had rhythm holter between 06 May and 03 June, during the month of Ramadan in 2019, were detected. These patients were contacted by phone and it was questioned that whether they were fasting on the day of the device and other days or not. Patients were divided into 2 groups according to the results of the interrogation. The first group was composed of patients who did not fast during Ramadan and the second group was composed of patients who fasted during Ramadan.

HRV was determined by ambulatory 24-hour Holter recordings. Six-channel, ambulatory electrocardiographic recordings (BS6930-3 HolterReader; Prolinx GmbH, Dusseldorf, Germany) were obtained for 24 hours in all patients. Before automatic analysis of tapes with Holter program (İ Tengo Analysis System), all electrocar-diographic recordings were visually reviewed to delete artifacts. All data were reviewed by an analyst and edited. HRV was calculated using only normal-to-normal intervals. There had to be ±23 hours of analyzable data for the 24-hour recording to be accepted for study. Five time-domain measures were examined: between the 1st and 2nd hours after fasting begins, between the 7th and 8th hours, in the last 1 hour and between the 1st and 2nd hours after iftar; standart deviations (SD) of all analyzed RR intervals, mean±SDs of all RR intervals for 5-minute segments of the analysis (SDNNI), square root of the mean of the sum of the squares of differences between adjacent RR intervals (rMSSD),and percent differences between adjacent RR intervals ±50 ms for the entire analysis (pNN50). SDNN can be influenced by parasympathetic and sympathetic stimulation compared with rMSSD and pNN50, which are mostly related to vagal tone. Frequency domain HRV indices: the Fast Fourier Transform method was used for the spectral measurements. Heart rate spectrum between 0.003 and 0.40 Hz was defined as total power (ms2), combining the sum of all of the frequencies, is a global measure of ANS activity. This energy was divided into two components: low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.16-0.40 Hz). LF are affected by both vagal and sympathetic activity, whereas HF are affected by vagal tone. The low frequency/high frequency (LF/HF) ratio of heart rate variability power is used as a measure of cardiac sympathovagal balance in this study.

Statistical analyses

SPSS version 19 (SPSS Inc. Chicago, IL, USA) statistical package program was used for statistical analysis. The suitability of the data for normal distribution was analyzed by a Kolmogorov–Smirnov test. Student *t* test or Mann-Whitney *U* test were used to compare parametric values between the two groups. Mann-Whitney *U* test was used for nonparametric values. Chi-square test was used to compare nominal and categorical variables. The study group was divided into two groups: fasting group and nonfasting group. Two signed *p* values <0,05 were considered significant.

Results

Eighty-six patients who met the study criteria were included in the study. The mean age (years) was 61,7 ± 16 in the nonfasting group and 55,6 ± 16 in the fasting group. There was no difference between the groups in terms of age (*p*=0,093). 47.2% of the nonfasting group and 54,5% of the fasting group were female (*p*=0,329). Diabetes mellitus was present 18,9% of the nonfasting group and 21,2% of the fasting group (*p*=0,500). Hypertension was present 79,2% of the nonfasting group and 72,7% of the fasting group (*p*=0,329). COPD was present 17% of the nonfasting group and 6,1% of the fasting group (*p*=0,125). There were no differences between the groups in terms of lipid parameters (Table 1).

Table 1. Baseline characteristics of the groups

	Nonfasting (n=53)	Fasting (n=33)	P
Age, years ±SD	61,68±16,57	55,58 ±15,61	0,093
Female n, (%)	25 (47,2)	18 (54,5)	0,329
BMI, kg/m^2	23,1±1,7	23,2±1,8	0,279
DM, n (%)	10 (18,9)	7 (21,2)	0,500
HT, n (%)	42 (79,2)	24 (72,7)	0,329
KOAH, n %	9 (17)	2 (6,1)	0,125
TG, mean (min-max)	142 (43-498)	134 (26-360)	0,396
Total cholesterol, mean (min-max)	188 (92-271)	190 (109-264)	0,844
LDL-C, mean (min-max)	111 (36-190)	114 (40-178)	0,724
HDL-C, mean (min-max)	47 (20-82)	49 (31-76)	0,424

BMI: Body mass index, DM: Diabetes mellitus, HDL-C: High density lipoprotein cholesterol, HT: Hypertension, LDL-C: Low density lipoprotein cholesterol, TG: Triglyceride

When the groups were compared according to ECG Holter data, LF/HF after dinner was found higher in the fasting group (2,41 vs 3,26, *p*=0,031) (Table 2). LF/HF average was found higher in the fasting group (1,02 vs 1,53, *p*=0,006) (Table 3). There were no differences between the groups in terms of other ECG Holter parameters (Table 2-3-4).

Table 2. Comparison of HRV parameters 1 hour after Iftar (X_{after1});

	Nonfasting (n=53)	Fasting (n=33)	P
SDDN $_{after1}$ mean (min-max)	103 (9-912)	74 (14-328)	0,396
RMSSD $_{after1}$ mean (min-max)	108 (6-500)	75 (9-452)	0,250
NN50 $_{after1}$ mean (min-max)	61 (1-251)	44 (1-269)	0,817
PNN50 $_{after1}$ mean (min-max)	19,98 (0,25-164)	13,82 (0,19-67,42)	0,8110
LF $_{after1}$ mean (min-max)	501,38 (6,94-8446,81)	426,42 (6,55-2130,80)	0,190
HF $_{after1}$ mean (min-max)	602,19 (6,01-11470)	264,31 (13,17-2460)	0,849
LF/HF $_{after1}$ mean (min-max)	2,41 (0,06-10,27)	3,26 (0,24-14,99)	**0,031**

SDDN $_{after1}$: standard deviations of all analyzed RR intervals, rMSSD $_{after1}$: the sum of the squares of differences between adjacent RR intervals, pNN50 $_{after1}$: percent differences between adjacent RR intervals ±50 ms, LF $_{after1}$: Low frequency, HF $_{after1}$: High frequency

Table 3. Comparison of 24-hour average HRV parameters (X_{avr}) ;

	Nonfasting (n=53)	Fasting (n=33)	P
SDDN$_{avr}$ mean (min-max)	139 (21-295)	144 (71-327)	0,793
RMSSD$_{avr}$ mean (min-max)	98 (15-302)	78 (20-297)	0,199
NN50$_{avr}$ mean (min-max)	21786,2 (7-98470)	14985,4 (651-88619)	0,749
pNN50$_{avr}$ mean (min-max)	21,80 (0,36-88,38)	17,52 (0,71-80,10)	1,000
LF$_{avr}$ mean (min-max)	2294,27 (34,65-14950,03)	2771,07 (100,54-14864,35)	0,793
HF$_{avr}$ mean (min-max)	3570,98 (36,50-21078,70)	2308,78 (70,34-18947,15)	0,277
LF/HF$_{avr}$ mean (min-max)	1,02 (0,10-4,94)	1,53 (0,18-5,03)	**0,006**

SDDN$_{avr}$: standard deviations of all analyzed RR intervals, rMSSD$_{avr}$: the sum of the squares of differences between adjacent RR intervals, pNN50 $_{avr}$: percent differences between adjacent RR intervals ±50 ms, LF $_{avr}$: Low frequency, HF $_{avr}$: High frequency

Table 4. Comparison of HRV parameters in the 2nd hour (X_2);

	Nonfasting (n=53)	Fasting (n=33)	P
QT/QTc$_2$ mean (min-max)	0,90 (0,65-1,32)	0,96 (0,69-1,50)	0,114
SDDN$_2$ mean (min-max)	85 (5-271)	90 (24-490)	0,880
RMSSD$_2$ mean (min-max)	98 (3-428)	110 (15-914)	0,883
NN50$_2$ mean (min-max)	60 (0-291)	50 (1-242)	0,901
PNN50$_2$ mean (min-max)	20,13 (0-86,02)	19,64 (0,32-76,81)	0,807
LF$_2$ mean (min-max)	579 (0,45-4149,19)	578,50 (2,40-3499,93)	0,525
HF$_2$ mean (min-max)	654,63 (1,12-6113,26)	635,24 (1,05-3554)	0,561
LF/HF$_2$ mean (min-max)	2,07 (0,06-48,84)	0,97 (0,13-4,98)	0,713

SDDN$_2$: standard deviations of all analyzed RR intervals, rMSSD$_2$: the sum of the squares of differences between adjacent RR intervals, pNN50$_2$: percent differences between adjacent RR intervals ±50 ms, LF$_2$: Low frequency, HF$_2$: High frequency

Table 5. Comparison of HRV parameters at 7th hour (X_7) ;

	Nonfasting (n=53)	Fasting (n=33)	P
QT/QTc$_7$ mean (min-max)	0,91 (0,66-2,25)	0,91 (0,71-1,22)	0,660
SDDN$_7$ mean (min-max)	87 (9-503)	103 (18-884)	0,632
RMSSD$_7$ mean (min-max)	94 (8-357)	66 (1-294)	0,095
NN50$_7$ mean (min-max)	50 (0-290)	63 (0-262)	0,340
PNN50$_7$ mean (min-max)	21,57 (0-313)	13,77 (0-74,64)	0,525
LF$_7$ mean (min-max)	510,80 (1,60-4995,22)	520,23 (12,21-2873,40)	0,107
HF$_7$ mean (min-max)	475,56 (5,51-5834,86)	399,53 (9,69-3749,60)	0,363
LF/HF$_7$ mean (min-max)	3,06 (0,06-17,69)	3,38 (0,38-12,42)	0,445

SDDN$_7$: standard deviations of all analyzed RR intervals, rMSSD$_7$: the sum of the squares of differences between adjacent RR intervals, pNN50$_7$: percent differences between adjacent RR intervals ±50 ms, LF$_7$: Low frequency, HF$_7$: High frequency

Table 6. Comparison of HRV parameters in the last 1 hour (X_{last1});

	Nonfasting (n=53)	Fasting (n=33)	P
QT/QTc$_{last1}$ mean (min-max)	0,93 (0,64-2,10)	0,95 (0,80-1,50)	0,566
SDDN$_{last 1}$ mean (min-max)	80 (12-251)	95 (1-351)	0,434
RMSSD$_{last1}$ mean (min-max)	94 (6-345)	62 (0-256)	0,117
NN50$_{last1}$ mean (min-max)	66 (0-287)	42 (0-293)	0,118
PNN50$_{last1}$ mean (min-max)	19,71 (0-82,59)	17,68 (0-100)	0,255
LF$_{last1}$ mean (min-max)	427,60 (4,02-3165,09)	623,57 (2,32-4648,94)	0,680
HF$_{last1}$ mean (min-max)	488,52 (2,60-6099,55)	444,89 (1,36-4744)	0,543
LF/HF$_{last1}$ mean (min-max)	2,65 (0,25-17,89)	3,43 (0,26-12,84)	0,083
QT/QTc$_{after1}$	0,93 (0,76-1,25)	0,94 (0,74-1,37)	0,810

SDDN$_{last1}$: standard deviations of all analyzed RR intervals, rMSSD$_{last1}$: the sum of the squares of differences between adjacent RR intervals, pNN50$_{last1}$: percent differences between adjacent RR intervals ±50 ms, LF$_{last1}$: Low frequency, HF$_{last1}$: High frequency

Discussion

Ramadan is the ninth month in the Islamic calendar known as the Hijra calendar. During this month, which is holy for muslims, all healthy adult Muslims around the world fast from dawn to sunset (absolute restriction of all solid and liquid food and beverage, sexual intercourse and smoking). During Ramadan, there is a great motivation for fasting in Muslim societies. Sahur and iftar meals made with all family members, collective prayers, and a sense of helping with the whole society play an important role in the formation of this motivation. Children start fasting at an early age by being affected by this environment. Chronic diseases, which are gained with the advancement of age, may cause anxiety about fasting. Although the Qur'an prohibits sick people from fasting, these people continue to fast. To what extent are these patients fasting? Which situations are more risky for them? Intense efforts are made to find the answers to all these questions.

The incidence of acute cardiac diseases seen in Ramadan is not different from that seen in other months (9-16). However, unlike other months, acute cardiac events occur more frequently after iftar, breakdown of fasting, in Ramadan (17). Patients with stable heart disease can keep fasting in Ramadan without deteriorating their general condition. Significant improvements in blood pressure, lipid profile and body mass index have been shown in healthy individuals fasting (18-20).

In patients with diabetes after Ramadan, a marked deterioration was observed in the lipid profile (21-22). Could it be that the patients were divided into two groups as fasting and non-fasting, depending on the fasting timing in their heart rate variability parameters? Could there be a parallel to the timing of these differences, with the timing of these differences? With this in mind, we did this retrospective study. When we look at the results of our study, there was no statistically significant difference in comparing the heart rate variability parameters of fasting and non fasting groups at the 2nd hour, 7th hour, and the last 1 hour after fasting began (Tables 2-3 and 4). LF/HF ratio was higher in those who fasted in the 1 hour after iftar, compared to those who did not fast and this was statistically significant (Table 5). When we look at the average of 24-hour data again, there was a statistically significant elevation in those fasting in LF/HF (Table 6).

People fasting in Ramadan tend to eat more than usual times after breaking their fast in iftar. Excessive consumption of food after a prolonged fasting may also change the timing of cardiac events occurring in people fasting. In the study conducted by Al Suwaidi et al. (17), it was found that among the patients who came to the hospital with acute coronary syndrome, those who did not fast increase in the morning hours, and those who fast in the evening (after iftar).

In some other studies (23-26), fasting has been shown to reduce cardiac events. In our study, the increase of LF / HF ratio in 1 hour after iftar shows sympathetic system activation and this rate is associated with increased cardiac events (7). Hunger leads to catecholamine inhibition and reduced venous return. This results in a decrease in blood pressure, heart rate and cardiac output (23). Hussein et al. showed that the heart rate decreased due to catecholamine inhibition in those fasting (24).

It is observed that this effect will be more pronounced if moderate aerobic exercise is performed in Ramadan (25). Furthermore, another study has suggested that nutrition may have a role in cardiac events as a result of changes in circadian rhythm. For example, plasma levels of vitamin E and C were shown to exhibit a circadian pattern and hence nutrition timing changes may have a role (26). Hence it is not surprising to observe these changes in circadian pattern have an effect on the presentation acute cardiac events during fasting.

Conclusion

In Ramadan, the activity of the parasympathetic system increases during the period of hunger, and in the periods of satiety, the sympathetic system is activated and this is supported by parameters of heart rate variability. More careful and metered food consumption is especially important in terms of encountering cardiac events in iftar.

References

1. Chamsi-Pasha H, Ahmed WH, Al-Shaibe KF. The cardiac patient during ramadan and hajj. J Saudi Heart Assoc. 2014;26:212-15.

2. Buccelletti E, Gilardi E, Scaini E, et al. Heart rate variability and myocardial infarction: systematic literature review and metanalysis. Eur Rev Med Pharmacol Sci. 2009 Jul-Aug;13(4):299-307.

3. Balanescu S, Corlan AD, Dorobantu M, Gherasim L. Prognostic value of heart rate variability after acute myocardial infarction. Med Sci Monit. 2004 Jul;10(7):CR307-15. Epub 2004 Jun 29.

4. Kocaman SA, Taçoy G, Özdemir M, Açıkgöz SK, Çengel A. The preserved autonomic functions may provide the asymptomatic clinical status in heart failure despite advanced left ventricular systolic dysfunction. Anadolu Kardiyol Derg. 2010;10:519–25.

5. Coviello I, Pinnacchio G, Laurito M, Stazi A, Battipaglia I, Barone L, et al. Prognostic role of heart rate variability in patients with ST-segment elevation acute myocardial infarction treated by primary angioplasty. Cardiology. 2013;124:63–70.

6. Kudaiberdieva G, Görenek B, Timuralp B. Heart rate variability as a predictor of sudden cardiac death. Anadolu Kardiyol Derg. 2007;7:68–70.

7. Manfrini O, Pizzi C, Trerè D, Fontana F, Bugiardini R. Parasympathetic failure and risk of subsequent coronary events in unstable angina and non-ST-segment elevation myocardial infarction. Eur Heart J. 2003;24:1560–66.

8. Musialik-Lydka A, Sredniawa B, Pasyk S. Heart rate variability in heart failure. Kardiol Pol. 2003 Jan;58(1):10-6.

9. Al Suwaidi J, Bener A, Hajar HA, et al. Does hospitalization for congestive heart failure occur more frequently in Ramadan: a population-based study (1991–2001). Int J Cardiol 2004;96:217-21.

10. Al Suwaidi J, Bener A, Suliman A, et al. A population based study of Ramadan fasting and acute coronary syndromes. Heart 2004;90:695-6.

11. Temizhan A, Donderici O, Ouz D, et al. Is there any effect of Ramadan fasting on acute coronary heart disease events? Int J Cardiol 1999;70:149-53.

12. Bener A, Hamad A, Fares A, et al. Is there any effect of Ramadan fasting on stroke incidence? Singapore Med J 2006;47:404-8.

13. Chamsi-Pasha H, Ahmed WH. The effect of fasting in Ramadan on patients with heart disease. Saudi Med J 2004;25:47-51.

14. Al Suwaidi J, Zubaid M, Al-Mahmeed WA, et al. Impact of fasting in Ramadan in patients with cardiac disease. Saudi Med J 2005;26:1579-83.

15. Burazeri G, Goda A, Kark JD. Religious observance and acute coronary syndrome in predominantly Muslim Albania: a population-based case–control study in Tirana. Ann Epidemiol 2008;18:937-45.

16. Khafaji HA, Bener A, Osman M, et al. The impact of diurnal fasting during Ramadan on the lipid profile, hs-CRP, and serum leptin in stable cardiac patients. Vasc Health Risk Manag 2012;8:7-14.

17. Al Suwaidi J, Bener A, Gehani AA, et al. Does the circadian pattern for acute cardiac events presentation vary with fasting? J Postgrad Med 2006;52:30-3; discussion 33-4.

18. Norouzy A, Nematy M, Alinezhad-Namaghi M, et al. P155 Effects of Ramadan fasting on cardiovascular risk factors. Atherosclerosis Suppl 2010;11:48-9 (A).

19. Ibrahim O, Kamaruddin N, Wahab N, et al. Ramadan fasting and cardiac biomarkers in patients with multiple cardiovascular disease risk factors. Internet J Cardiovasc Res 2011;7(2). DOI: 10.5580/2717.

20. Nematy M, Alinezhad-Namaghi M, Mahdavi Rashed M, et al. Effects of Ramadan fasting on cardiovascular risk factors: a prospective observational study. Nutr J 2012;11:69.

21. Khatib FA, Shafagoj YA. Metabolic alterations as a result of Ramadan fasting in non-insulin-dependent diabetes mellitus patients in relation to food intake. Saudi Med J 2004;25:1858-63.

22. Khaled BM, Bendahmane M, Belbraouet S. Ramadan fasting induces modifications of certain serum components in obese women with type 2 diabetes. Saudi Med J 2006;27:23-6.

23. Stokholm KH, Breum L, Astrup A. Cardiac contractility, central hemodynamics and blood pressure regulation during semistarvation. Clin Physiol 1991;11:513-23.

24. Hussain R, Duncan MT, Cheah SH, Ching SL. Effects of fasting in Ramadan on tropical Asiatic Moslems. Br J Nutr 1987;58:41–8.

25. Ramdan JM, Barac-Nieto M. Cardio-respiratory responses to moderately heavy aerobic exercise during the Ramadan fasts. Saudi Med J 2000;21:238– 44.

26. Singh RB, Wedahl A, Otsuka K, Wantanabe Y, Yano S, Mori H, et al. Can nutrition influence circadian rhythm and heart rate variability? Biomed Pharma 2001;55:115s–24s.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Üçüncü Basamak Bir Sağlık Kuruluşunda Son Beş Yılda Hastane Enfeksiyonuna Neden Olan Etkenlerin İrdelenmesi

Evaluation of the Factors Causing Nosocomial Infection in the Last Five Years in a Tertiary Health Center

Selin ÖZDEMİR* 0000-0003-2298-4330

Şebnem ÇALIK*0000-0003-3798-4819

Selma TOSUN* 0000-0001-9844-9399

*Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim Araştırma Hastanesi, Enfeksiyon Hastalıkları kliniği

* Health Sciences University, Izmir Bozyaka Training and Research Hospital, Infectious Diseases Clinic

Yazışma Adresi: Selin ÖZDEMİR

Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim Araştırma Hastanesi,

Enfeksiyon Hastalıkları Kliniği

E-Mail: selingungor88@hotmail.com

Öz

Giriş ve Amaç: Hastane enfeksiyonları günümüzde klinisyen için tedavisi zor bir tablo oluşturmakta ve mortaliteyi ve sağlık sisteminin maddi yükünü artıran bir sebep olarak karşımıza çıkmaktadır. Çalışmamızda üçüncü basamak bir hastanede 5 yıllık süreçte gelişen hastane enfeksiyonlarının kliniklere ve organ sistemlerine dağılımının, etken çeşitliliğinin ve etkenlerin direnç profillerinin saptanması amaçlandı.

Bulgular: 5 yılda 1229 hastane enfeksiyonu vakası saptanmıştır. Popülasyonun yaş ortalaması 62,25 (±17,36) bulundu. Cinsiyet dağılımı %59,4 ile erkek ağırlıklı idi. Hastane enfeksiyonlarının %42,3' ü yoğun bakım ünitelerinde, %29,2si dahili servislerde, %28,5 i cerrahi servislerde saptandı. En sık görülen hastane enfeksiyonu %29,2 ile pnömoni iken, bunu %28 ile yumuşak doku enfeksiyonları %21,5 ile üriner sistem enfeksiyonları,%20,1 ile kan dolaşım enfeksiyonları ve %1,3 ile diğer enfeksiyonlar izlemekteydi. Vakaların %12,3 ünde etken saptanamadı. Etken saptanan 1077 vakada ise sırası ile *Klebsiella pneumoniae* (%23,9), *E. coli* (%18,3), *Acinetobacter spp* (%15,5), *Pseudomonas aerugınosa* (%14),*Enterecoc spp* (%7,2), *Candida spp* (%4) en sık üreyen mikroorganizmalardı.

Sonuç: Hastanemizde hastane enfeksiyon oran ve patojen dağılımları literatürel verilerle uyumlu izlenmiştir. Hastane enfeksiyonları etkenleri yıllar içinde benzer olsa da antibiyotik direnç oranları giderek arttığı için ve alternatif antibiyotik tedavileri aynı hızla yerine koyulamadığından bu enfeksiyonlarla tedaviyle başa çıkmak her zaman mümkün olamamaktadır. Bu da enfeksiyon kontrol önlemlerinin önemini ortaya koymaktadır.

Anahtar Kelimeler: Hastane enfeksiyonu, pnömoni, üriner sistem, kan-dolaşım sistemi

Abstract

Background and aim: Nosocomial infections create a difficult picture for the clinicians and it becomes a cause that increases mortality and the financial burden of the health system. In our study, it was aimed to determine the distribution of 5-year nosocomial infections to clinics and organ systems, the diversity of agents and the resistance profiles of agents in a tertiary hospital.

Results: 1229 nosocomial infections were detected in 5 years. The mean age of the population was 62.25 (±17.36) .

The gender distribution was male with 59.4%. 42.3% of hospital infections were found in intensive care units, 29.2% in internal services, and 28.5% in surgical services. The most common nosocomial infection was pneumonia with 29.2%, followed by soft tissue infections with 28%, urinary system infections with 21.5%, blood-stream infections with 20.1% and other infections with 1.3%. No causative agent was found in 12.3% of the cases. In 1077 cases with causative agents, Klebsiella pneumoniae (23.9%), E. coli (18.3%), Acinetobacter spp (15.5%), Pseudomonas aeruginosa (14%) ,Enterecoc spp (7.2%), Candida spp (4%) were the most common microorganisms.

Conclusion: In our hospital, nosocomial infections rate and pathogen distributions were observed in accordance with the literature data. Although the agents of nosocomial infections are similar over the years, it is not always possible to deal with these infections because antibiotic resistance rates are increasing and alternative antibiotic treatments cannot be replaced at the same rate. This reveals the importance of infection control measures.

Keywords: Hospital infection, pneumonia, urinary system, blood-stream system, nosocomial sinfections

Giriş

Hastane enfeksiyonları (HE) günümüzde özellikle mevcut antibiyotiklerle tedaviye dirençli mikroorganizmalarla meydana geldiği için yönetimi ve kontrolü zor, klinisyeni zaman zaman çaresiz bırakan ve yatış sürelerini uzattığı için de ülke ekonomisine ciddi maddi yük olabilen enfeksiyonlar haline gelmiştir(1). Hastane enfeksiyonlarının önüne geçilmesi için sarf edilen çabanın değeri yapılan çalışmalarla da ortaya konulmuştur(2). Bu nedenle hastane enfeksiyonların önlenmesi, oluştuğunda tanı ve tedavisinin kısa sürede yapılabilmesi için gerçekleştirilen hastane enfeksiyon kontrol programları önemli sağlık hizmetlerindendir (2).Gerekli kontrol önlemlerinin uygulanabilmesi için de düzenli sürveyans çalışmaları büyük öneme sahiptir. Hastane enfeksiyonlarının sürveyansı ile her merkez kendi enfekte hastalarını saptamakta, enfeksiyon sıklıklarını, enfeksiyona neden olan faktörleri ve enfeksiyon etkenlerini belirlemektedir(1). Böylece diğer merkezlerle kendi enfeksiyon hızlarını karşılaştırma, risk faktörlerine göre önlem alma ve etkenlerine göre tedavi planını oluşturma fırsatı yakalamaktadırlar. Bu çalışmayla 5 yıllık hastane enfeksiyonlarının kliniklere ve organ sistemlerine dağılımının, etken çeşitliliğin ve etkenlerin direnç profillerinin saptanması amaçlandı.

Gereç ve Yöntem

Çalışmamız yerel etik kuruldan 26.10.2022-2022/149 karar numarası ile onay almıştır. Üçüncü basamak bir devlet hastanesi olarak hizmet veren 580 yatak kapasiteli hastanemizde 01.01.2018 ile 31.12.2022 tarihleri arasındaki 5 yılda dahili/cerrahi servisler ve Yoğun Bakım Üniteleri(YBÜ)'nde yatarak tedavi alan hastalarda gelişen hastane enfeksiyonu (HE) tanısı alan vakaları inceleyen çalışmamız retrospektif bir çalışmadır.

Hastanemizde Anestezi, dahiliye, cerrahi, nöroloji, beyin cerrahisine ait YBÜ'lerine ek olarak yanık YBÜ ile birlikte 6 YBÜ bulunmaktadır. Dahili ana dal kliniklerinden kardiyoloji ve pediatri servisi yokken, palyatif, hematoloji, kemik iliği transplantasyon, gastroenteroloji ve nefroloji yan dallarının yataklı klinikleri mevcuttur. Cerrahi ana dal kliniklerinden kadın doğum yataklı kliniği bulunmazken özellikli birim olarak organ nakli, yanık ve stoma bakım servisleri bulunmaktadır. Vakalar Enfeksiyon Kontrol Komitesi (EKK) tarafından oluşturulan Hasta Takip Formları ve hastane bilgi yönetim sistemi üzerinden retrospektif olarak değerlendirildi. Hastane enfeksiyonu olarak ele alınan vakalar aşağıdaki kriterlere göre EKK hemşireleri ve Enfeksiyon Hastalıkları hekimleriyle beraber aşağıdaki kriterlere göre belirlendi.

1- Klinik materyallerinde pozitif üremesi olan ve bu etkene yönelik tedavi alan hastalar;

2-Pozitif üremesi olmadan 2017 Ulusal Hastane Enfeksiyonları Sürveyans Ağı (UHESA) Rehberi kriterlerine göre, hastane enfeksiyonu kriterlerini karşılayan hastalar

HE düşünülen vakalardan alınan kan kültürü ve enfeksiyon kaynağına göre idrar, yara, balgam, derin trakeal aspirat örneği ,BOS örnekleri hastanemiz mikrobiyoloji laboratuarı tarafından çalışıldı. Alınan kan kültürleri BACTEC Fx otomatize kan kültür sisteminde (Becton Dickinson, MD, USA) inkübe edildi. Diğer sistem örnekleri Mikrobiyoloji Laboratuarında standart manuel yöntemler kullanılarak çalışıldı. Bütün üremeler Phoenix 100 otomatize identifikasyon sistemi (Becton Dickinson MicrobiologySystems, MD, USA) ve bu sistemin kullanılamadığı izolatlarda standart manuel yöntemler kullanılarak değerlendirildi.

Bulgular

Araştırmanın kapsadığı tarih aralığındaki 5 yılda 1229 hastane enfeksiyonu vakası ele alındı. Vakaların yaş ortalaması 62,25 (±17,36) bulundu. Cinsiyet dağılımı %59,4 erkek,%40,6 kadın idi. Hastane enfeksiyonlarının %42,3' ü yoğun bakım ünitelerinde, %29,2si dahili servislerde, %28,5 i cerrahi servislerde saptandı. Yatış yerine göre alt gruplar incelendiğinde; hastane enfeksiyonlarına yoğun bakım birimi olarak en çok Anestezi Yoğun Bakım servisinde (%49),dahili servislerden en çok palyatif bakım (%34,7) ve hematoloji (28,8) servislerinde, cerrahi birimlerden ise genel cerrahi servisinde(%37,5) rastlandı. Vakaların altta yatan enfeksiyonu kolaylaştırıcı hastalıkları incelendiğinde %43,5'inde altta yatan hastalık bulunmazken,%10' unda iki ek hastalık, 3 hastada ise üç ek hastalığın bir arada olduğu görüldü. Diyabetus Mellitus(DM) en sık (%19,5) eşlikçi hastalık tanısıydı. Nörolojik hastalık %18,9'unda, kanser %17,6'sında (solid malignite %11,1;hematolojik malignite %6,5), kronik böbrek yetmezliği %8,7'sinde,yanık %4,3'ünde eşlik etmekteydi(Tablo-1).HE saptanan vakaların klinik gidişi incelendiğinde %53,5 'i taburcu olurken,%37,7 si kaybedilmiş, %0,8 i de başka merkeze sevk edilmişti.

Tablo 1 -Yüzdelerine göre altta yatan hastalıklar tablosu

Ek Hastalık	(n)	(%)
DM	240	19,5
SVO	128	10,4
Solid Malignite	136	11,1
Hematolojik Malignite	80	6,5
Otoimmun Hastalık	16	1,3
Yanık	53	4,3
KBY	107	8,7
Alzheimer/Demans	26	2,1
HIV	2	0,2

En sık görülen HE %29,2 ile pnömoni iken, bunu %28 ile yumuşak doku enfeksiyonları, %21,5 ile üriner sistem enfeksiyonları,%20,1 ile kandolaşım enfeksiyonları ve %1,3 ile diğer enfeksiyonlar izlemekteydi(Tablo-2). Vakaların %12,3 ünde etken saptanamadı. Etken saptanan 1077 vakada ise sırası ile *Klebsiella pneumoniae* (%23,9), *E. coli* (%18,3), *Acinetobacter spp* (%15,5), *Pseudomonas aerugınosa* (%14),*Enterecoc spp* (%7,2), *Candida spp* (%4) en sık üreyen mikroorganizmalardı(Tablo-3).Hastane enfeksiyonlarının sistemlere göre üreyen mikroorganizma dağılımı incelendiğinde pnömonide sırasıyla *K. pneumoniae* , (%33,3), *Acinetobacter spp*(%31,4);kan-dolaşım enfeksiyonlarında *K. pneumoniae* , (%24), *E.coli* (19,5); yumuşak doku enfeksiyonlarında *E.coli* (%24), *Pseudomonas aerugınosa* (%23,6); üriner sistem enfeksiyonlarında ise *K. pneumoniae* (%29,1),*E.coli* (%25,7) en sık etkenler olarak saptandı.
Hastane enfeksiyonlarına neden olan mikroorganizmaların antibiyotik duyarlılıkları Tablo 4 ve 5'de verildi.

Tablo 2 - Sistemlere göre Hastane Enfeksiyonlarının Dağılımı

Enfeksiyon	(n)	(%)
Pnömoni	359	29,2
Yumuşak Doku Enfeksiyonları	345	28
Üriner Sistem Enfeksiyonları	264	21,5
Kan-Dolaşım Enfeksiyonları	247	20,1
Diğer Enfeksiyonlar	14	1,2

Diğer: Santral sinir sistemi enfeksiyonları, protez enfeksiyonları, peritonit,orafarengeal enfeksiyon

Tablo 3-Üreme saptanan vakaların mikroorganizma dağılımı

Mikroorganizma	(n)	(%)
Klebsiella pneumoniae	258	24,0
E. coli	194	18
Acinetobacter spp.	169	15,7
Pseudomonas aeruginosa	152	14,1
Enterecoc spp	79	7,3
Candida spp	43	4,0
S.aureus	45	4,2
Proteus spp	37	3,4
Enterobacter spp	25	2,3
S.maltophilia	16	1,5
S.marsences	11	1,0
Koagülaz negatif stafilokoklar	10	0,9
Diğer	38	3,5

Diğer: *Streptococ spp,Citrobacter spp, Corynebacterium spp, Pseudomonas stutzeri,Myroides odatratus, Staphyococcus schleiferi, Staphylococcus saprophyticus, Providencia stuartii*

Tablo 4- Hastane Enfeksiyonu Etkeni Gram (+) İzolatların Antibiyotiklere Duyarlılıklar

Gram (+) Patojen / Antibiyotik	*S.aerıus* (Toplam:45) n,(%)	Koagulaz (-) Streptococ (Toplam: 18) n,(%)	*Enterococcus spp.* (Toplam: 79) n,(%)
Oksasilin	*22,(49)*	1,(5,5)	- -
Penisilin G	3,(10)	1,(5)	2,(18)
Ampisilin	- -	- -	44,(60)
Ciprofiloksasin	23,(61)	3,(17)	13,(39)
Levofiloksasin	19,(59)	2,(15)	11,(41)
TMP-SMZ	33,(89)	6,(46)	3,(8)
Vankomisin	*35,(100)*	15,(100)	72,(91)
Teikoplanin	28,(100)	15,(88)	59,(97)
Linezolid	32,(100)	13,(100)	51,(98)
Daptomisin	23,(100)	10 ,(91)	- -
Klindamisin	34,(97)	4,(33)	- -
Fusidik asit	25,(96)	2,(15)	- -
Tetrasiklin	19,(86)	4,(31)	- -

*Bir antibitogramda direnç paneli için birden fazla antibiyotik çalışmıştır.
Bazı panellerde bazı antbiyotikler ise çalışılmadığından yüzde dağılım kendi içinde değerlendirilmiştir.*

Tablo 5- Hastane Enfeksiyonu Etkeni Gram (-) İzolatların Antibiyotiklere Duyarlılıkları

Gram (-) Patojen / Antibiyotik	E.coli (Toplam:194) n, (%)	K.pneumoniae (Toplam:258) n, (%)	Acinetobacter spp. (Toplam:167) n, (%)	Pseudomonas spp. (Toplam:152) n, (%)
Amikasin	178,(97,3)	247,(45,4)	12,(7,2)	107,(72)
Gentamisin	105,(61,4)	237,(41)	8,(5)	65,(69,9)
Seftriakson	64 ,(37,2)	227,(8,4)	-	-
Seftazidim	51, (31,7)	227,(5,7)	1,(5,9)	50,(38,5)
Sefepim	44, (37,6)	157,(10,8)	-	28 ,(28)
Piperasilin-Tazobaktam	113 ,(68)	211,(15,6)	0,(0)	51,(37,5)
Ciprofiloksasin	58 ,(33,7)	229,(17,9)	2,(1,2)	56,(38,3)
Levofiloksasin	98, (39,8)	162,(14,8)	1,(1,1)	16,(22)
Ertapenem	125,(84,5)	188,(23,9)	0,(0)	-
Meropenem	164,(91,6)	241,(31,1)	7,(4,5)	55,(45)
Imipenem	171,(93)	241,(26,1)	1,(0,6)	35,(28,4)
Tigesiklin	101,(80)	95,(37,9)	1,(25)	-
Colistin	-	118 ,(68,6)	77,(82)	67,(91,8)
Seftazidim-Avibaktam	-	24 ,(45,8)	-	3,(75)
Fosfomisin	37,(97,3)	57,(70)	-	-
TMP-SMZ	-	-	50,(34,7)	1,(16,6)
Nitrofurontain	32, (97)	-	-	-
ESBL	126, (64,9)	226,(87,6)	-	

*Bir antibiyogramda direnç paneli için birden fazla antibiyotik çalışmıştır. Bazı panellerde bazı antbiyotikler ise çalışılmadığından yüzde dağılımı kendi içinde değerlendirilmiştir.

Tartışma

Hastane enfeksiyonları özellikle gelişmiş ve gelişmekte olan ülkelerde enfeksiyon hastalıklarının ilgi alanları içinde önemli bir yere sahiptir.Sosyo-ekonomik şartlar gelişip tıp alanında ilerleme kaydedildiğinde insan yaşam süresi uzamakta,bu da daha fazla ko-morbid hastalık,girişim ve daha fazla hastane yatış sayısı ve süresi anlamına geldiğinden karşılaşılan hastane enfeksiyonu sayısı artmaktadır(2)Ülke çapında hastane enfeksiyon hızlarının ve etkenlerin direnç profillerinin karşılaştırılmasının mutlak bir yararı olmakla birlikte aynı hastanede,birbirine daha yakın fiziki şartlar ve insani yaklaşımlar kaynak alınabileceğinden hastane içi sürveyansın takibi daha değerli hale gelmektedir(3)

Hastanemizde 2018-2022 yılları arası 5 yıllık, yıllara göre hastane geneli enfeksiyon hızları sırasıyla %2 ,%1,88, %1,85, %1,79, %2,14 şeklindedir. Türkiye geneli yapılan çalışmalarda HE hızı %1,3-16 arasında değişiklik göstermektedir(4).Hastanemiz HE hızları Türkiye verileriyle uyumlu olup son yıldaki artış Covid-19 pandemisinin ardından hastanenin tüm birimleriyle yeniden aktifleşmesi ve sağlık çalışanlarındaki kişisel enfeksiyon kontrol önlemlerinde azalma olmasıyla ilişkilendirilebilir.

Çalışmamızda hastane enfeksiyonlarının yarısına yakını (%42,3) yoğun bakım ünitelerinde saptanırken dahili (%29,2) ve cerrahi(%28,5)servislerde benzer oranda saptandı. Yapılan diğer çalışmalar da göstermiştir ki yoğun bakıma yatış oranı servislere yatış oranından düşük olduğu halde hastane enfeksiyonu görülme oranı YBÜ'lerinde daha yüksektir(5).YBÜ'leri arasından da Anesteziyoloji YBÜ'de en sıktı. Şahin ve ark. tarafından yapılan araştırmada da en sık HE Anestezi YBÜ' de saptanmış. Bunun nedeni hastanemiz YBÜ'leri arasında yatak sayısı bakımından en çok yatağa sahip olması, daha çok ventilatör ve invaziv işlem gerektiren, ağır klinik gidişli hastaların Anestezi YBÜ'de takip ediliyor olması olabilir(6). Dahili servislerden ise en yüksek HE oranı Palyatif Bakım(%34,7) ardından Hematoloji(%28,8) servislerinde görüldü. Kanser, SVO gibi altta yatan hastalığı mevcut olan ve uzun yatış süresine sahip hastaların bu servislerde takip edilmesi bu yüksek HE oranlarının nedeni olarak açıklanabilir. Çalışmamızda, vakaların sistemlere göre sıklıkları incelendiğinde en sık görülen HE pnömoni (%29,2) iken, bunu yumuşak doku enfeksiyonlarının (%28) izlediği görüldü. Üçüncü ve dördüncü en sık HE ise sırasıyla üriner sistem enfeksiyonları (%21,5) ve kan dolaşım enfeksiyonları (%20,8) idi. İngiltere'de 183 hastanenin incelendiği çok merkezli çalışmada da bizimle benzer şekilde ilk iki sırada pnömoni ve cerrahi alan enfeksiyonları en sık HE olarak saptanmış(7). Türkiye'de ise bu oranlar daha çok tek merkezli çalışmalarda hastanelerin özel şartlarına ve çalışmanın yapıldığı tarihlere göre değişiklik göstermektedir. Erdem ve arkadaşlarının 2013 tarihli çalışmasında(8) yine HE olarak pnömoni en sık saptanırken, daha önceki yıllara ait çalışmalarda üriner sistem enfeksiyonlarının ön plana geçtiği görülmüştür(9).Bunun sebebi günümüze yaklaştıkça ihtiyacı olan hastalara ventilatör desteği sağlamanın daha kolay olmasıyla ilgili olabilir. Bunun dışında, YBÜ'lerinde HE olarak pnömoni ön plana geçtiği için çalışmanın yapıldığı hastanenin yoğun bakım yatak sayısının YBÜ dışı yatak sayısına oranlarıyla bağlantılı olabilir (10).

Ülkemizde ve diğer ülkelerde yapılan çalışmalarda hastane enfeksiyonu etkenleri arasında gram negatif bakteriler ön sırada gelmektedir(3,11). Çalışmamızda da HE'ları genel olarak ele alındığında etkenler sıklık sırasına göre *Klebsiella pneumoniae* (%23,9), *E. coli* (%18,3), *Acinetobacter spp* (%15,5), *Pseudomonas aeruginosa* (%14) şeklinde sıralanmaktaydı. Karagün ve arkadaşlarının çalışmasında bizimkiyle uyumlu şekilde ilk 2 sırayı Klebsiella ve *E.coli* almaktaydı (12). Çalışmamız sonuçlarında sistemlere göre enfeksiyon etkenleri incelendiğinde pnömonide etken olarak ilk sıralarda *K. pneumoniae* , (%33,3), *Acinetobacter spp*(%31,4) gelmekteydi. Ülkemizde genellikle yoğun bakımlarda yapılan çalışmalarda(13) hastane kaynaklı pnömoni etkeni olarak *Acinetobacter spp* ilk sırayı almaktadır.Bizim çalışmamızda da sadece YBÜ'de gelişen pnömoniler ele alındığında *Acinetobacter* (%36,1), *Klebsiella Pneumoniae*'nin(%29,3) sıklık açısından öne geçmiş olarak bulundu.

Amerika'da yapılan geniş çaplı bir çalışmada yumuşak doku enfeksiyonları enfeksiyonlarında *S.aerıus* esas patojen olarak saptanmış olup çalışmamızda *Pseudomonas aerugınosa*'nın en sık etken olduğu gözlenmiştir(14). Bu farklılığın hastanemizin bölgesel hasta kabülü yapan, Yanık Ünitesine sahip, 3. basamak bir hastane olmasının etken olduğu düşünülmüştür(15). Üriner sistem enfeksiyonlarında Işıkgöz ve ark. tarafından yapılan ülkemizden çok merkezli bir çalışmada *E.coli*'nin esas etken olarak (%45.5) izlendiği saptanmış olup çalışmamızda bundan farklı olarak birinci patojen *K.pneumoniae* saptanmıştır(16). Çalışmamızdaki bu farklılık Flores-Mireles ve arkadaşlarının yaptığı çalışma ile açıklanabilir, bu çalışmada üriner sistem katateri olan hastalarda *K.pneumoniae* ön planda saptanmaktadır(17). Çalışmamıza alınan hastaların yoğun bakım hastaları ağırlıklı olması ve bu hastaların üriner kataterlerinin bulunması nedeniyle *K.pneumoniae* baskın etken olarak saptanmıştır. Dat ve arkadaşları tarafından 738 hastalık bir seride tanımlanan kan dolaşım enfeksiyonları etkenlerinde ilk sırada *K.pneumoniae* ikinci sırada *E.coli* bulunmuştur(18). Bizim çalışmamızda da kan-dolaşım sistemi enfeksiyonları (KDİ) etkenleri bu çalışmayla uyumlu izlenmiştir.

Çalışmamızda *S.aerıus* suşlarında metisilin dirençli S.aerıus(MRSA) oranı %51, Koagulaz Negatif Stafilokoklar(KNS)'da %95 saptanmış olup, Kılıç ve arkadaşları tarafından 2016-2021 yılları arasında 6 yıllık hastane enfeksiyonu etkeni olan *S.*aerıus'larda MRSA oranı çalışmamızla benzer olarak %48,5 olarak bulunmuş(19). Hastane kaynaklı 373 KDİ' nin incelendiği bir diğer çalışmada(20) KNS olarak tanımlanan 72 suşun metisilin direnci ise %79,2 bulunmuş, bizim sonuçlarımızda KNS üreyen vaka sayısının az olup (n:18) yalnız 1 suşun metisilin duyarlı saptanmasından kaynaklı olduğu düşünülmüştür. Türkiye'den hastane kaynaklı enfeksiyonlarda incelenen enterokoklarda vankomisin direnci %15,8 (21)olarak bildirilmiş, çalışmamızda %9 bulunmuştur. Bunun yanında bizim sonuçlarımızda *E.coli* ve *K.pneumoniae* için genişlemiş spektrumlu beta-laktamaz(GSBL) üreten suş oranı sırasıyla %64,9 ve% 87,6 olup, bu değerler 2021 yılı Ulusal SHİE özet raporunda belirtilen eğitim araştırma hastanelerindeki oranlarla karşılaştırıldığında *E.coli* (%61,2) için benzer olup *K. pneumoniae*(%68,5) için oldukça yüksektir.

Bunun nedeni 2022 yılında hastanemizde dirençli bir suş ile yaşanan *K.pneumoniae* salgını olabilir.Karbapenem dirençli *K.pneumoniae* oranı (%64,8) ve Karbapenem dirençli *Acinetobacter* oranı (%91,1) ise raporda eğitim ve araştırma hastaneleri için belirtilen oranlarla benzerdir(%64,9-%92,8)(22).Çalışmamızda *Acinetobacter* suşlarının en duyarlı olduğu antibiyotik colistin olup yine sık tercih edilen bu antibiyotiğe karşı da direnç oranlarında artış olduğu görülmüştür(%17) Ülkemizden son yıllarda yapılan çalışmalar incelendiğinde *A.baumanii* suşlarının colistin direnci %3,6-%11,7 arasında değişmektedir(23).Bizim direnç oranımızın yüksek olması colistin kullanılmasının sıklığına bağlı olabilir.Diğer tmp-smz ve tigesiklinle kombinasyonlar alternatif tedavi olarak akılda tutulabilir.

Pseudomonas aeurıgınosa suşlarının direnç profilleri incelendiğinde seftazidıme %61,5,meropeneme %55, ımıpeneme %72 oranında dirençli, colistine %91,8, gentamisine %69,9 oranında duyarlı olduğu görüldü. Yunanistan'da yapılan bir çalışmada hastane kaynaklı enfeksiyon etkeni olarak *P. aeurıgınosa* suşlarında seftazidım,karbapenemlere bizim çalışmamızla benzer direnç oranları saptanırken, colistine duyarlılık daha fazla(%97,4), gentamisine duyarlılık(%42,1) daha azdı (24).Bunun nedeni ülkemizde HE tedavisinde colistin kullanımının aminoglikozid kullanımna göre daha yoğun olmasıyla ilgili olabilir. Öyle ki ülkemizden yapılan bir çalışmada da *P.aeuriginosa* colistin duyarlılığı 93,3, gentamisine duyarlılık %80,3 olarak gösterilmiş(25).

Sonuç

Hastane enfeksiyonları etkenleri yıllar içinde benzer olsa da antibiyotik direnç oranlarının değişimi ile alternatif antibiyotik tedavilerinin aynı hızla yerine koyulma zorluğu nedenli bu enfeksiyonlarla başa çıkmak her zaman mümkün olamamaktadır. Bu da sağlıklı sürveyansın yapılıp doğru kontrol stratejileriyle hastane enfeksiyonlarının önlenerek sayısının azaltılmasının önemini ortaya koymaktadır. Merkezimize ait veriler literatürle uyuşmakla beraber bu konuda çok merkezli geniş çalışmalara ihtiyaç vardır.

Kaynaklar

1-İnan D. Hastane İnfeksiyonları. Klimik Dergisi, 2016; 2:148.

2- Allegranzi B, Nejad SB, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet, D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. The Lancet, 2011; 377.9761: 228-241.

3- Karahocagil MK, Yaman G, Göktaş U. et al. Hastane enfeksiyon etkenlerinin ve direnç profillerinin belirlenmesi.Van Tıp Derg.; 2011;18:27-32.

4- Ertek, M. Hastane enfeksiyonları: Türkiye verileri. İÜ Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri. 2008;60:9-14.

5- Akgül F, Gökler ME, Aksöz S, Tartar AS, Tekin R, Yıldız Y, Günay E. Yoğun bakım ünitelerindeki enfeksiyonların değerlendirilmesi: Çok merkezli nokta prevalans çalışması. Mikrobiyol Bul. 2019;53:364-373.

6- Şahin AR, YILDIZ BT, Aktemur A, Topal B, Nazik S, Ateş S. Bir üniversite hastanesi nöroloji yoğun bakım ünitesinde gelişen enfeksiyonların değerlendirilmesi. Çağdaş Tıp Dergisi. 2019;9(1): 43-47.

7- Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care–associated infections. New England Journal of Medicine. 2014;3701:1198-1208.

8- Erdem HA, Sipahi OR, Kepeli N, et al. Ege Üniversitesi Hastanesi'nde hastane infeksiyonları nokta prevalansı. Mediterranean Journal of Infection Microbes Antimicrobials. 2015; 4: 12-24.

9- Mamıkoğlu L, Günseren F, Özçelik F, et al. Akdeniz Üniversitesi Hastanesi'nde hastane infeksiyonları: 1994-1995. Hastane İnfeksiyonları Dergisi. 1998: 1; 42-45.

10- Şardan YÇ, Aşçıoğlu S, Büke Ç. Yoğun bakım ünitelerinde hastane infeksiyonlarının prevalansı: Çok merkezli bir nokta prevalans çalışması. Hastane İnfeksiyonları Dergisi. 2006;10:33.

11- Litwin, A, Fedorowıcz O, Duszynska W. Characteristics of microbial factors of healthcare-associated infections including multidrug-resistant pathogens and antibiotic consumption at the university intensive care unit in Poland in the years 2011–2018. International Journal of Environmental Research and Public Health. 2020; 17: 6943.

12- Karagun BŞ, AKYILDIZ Ö, Hilal ONAÇ. et al. Adana Acıbadem Hastanesinde hastane enfeksiyonları surveyansı: bir yıllık analiz sonuçları. Acıbadem Üniversitesi Sağlık Bilimleri Dergisi. 2020; 3:478-482.

13- Tomak Y, Ertürk A, Şen A, Erdivanlı B, Kurt A. Anestezi yoğun bakım ünitesinde ventilatör ilişkili pnömoni hızları ve etken mikroorganizmaların dağılımı. ŞEEAH Tıp Bülteni. 2012;46:115-119.

14-Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. BMC Infect Dis. 2013;30:252.

15-Vinaik R, Barayan D, Shahrokhi S, Jeschke MG. Management and prevention of drug resistant infections in burn patients. Expert Rev Anti Infect Ther. 2019;17:607-619.

16-Isikgoz Tasbakan M, Durusoy R, Pullukcu H, Sipahi OR, Ulusoy, S Turkish Nosocomial Urinary Tract Infection Study Group. Hospital-acquired urinary tract infection point prevalence in Turkey: differences in risk factors among patient groups. Annals of clinical microbiology and antimicrobials. 2013; 12: 1-8.

17-Flores-Mireles, A, Hreha T N, Hunstad DA . Pathophysiology, treatment, and prevention of catheter-associated urinary tract infection. Topics in spinal cord injury rehabilitation.2019; 25:228-240.

18-Dat VQ, Vu HN, Nguyen The H, et al. Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. BMC infectious disease. 2017; 17: 1-11.

19- Kılıç EK., Demircan ŞA, Kınıklı S, Cesur S, et al. Sağlık bakımı ilişkili enfeksiyonlarda Staphylococcus aureus dağılımının irdelenmesi: 6 yıllık deneyim. Journal of Medicine and Palliative Care. 2022; 3: 39-43.

20- Baştuğ A, Akıncı E, Aypak A, et al. The Evaluation of Healthcare Associated Bloodstream Infections at a Tertiary Care Hospital Between 2011 and 2015: Epidemiology and Mortality Risk Factors. Kafkas Journal of Medical Sciences. 2017; 7; 1-6.

21-Gümüş H. Vankomisine Dirençli Enterococcus faecium: Kısa Bir Derleme. Arşiv Kaynak Tarama Dergisi. 2023; 32: 1-9.

22- T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Bulaşıcı Hastalıklar ve Erken Uyarı Dairesi Başkanlığı. Ulusal sağlık hizmeti ilişkili enfeksiyonlar sürveyans ağı (USHİESA) özet raporu 2021. Erişim adresi: https://www.researchgate. net/publication/364113964_ULUSAL_SAGLIK_HIZMETI_ ILISKILI_ENFEKSIYONLAR_SURVEYANS_AGI_USHIESA_ OZET_RAPORU_2021/stats (Erişim tarihi: 25 Agustos 2023)

23- Karakoç E. , Ayyıldız A. , Yelken B. Antibiotic resistance of acinetobacter strains in our intensive care unit : a retrospective study. Acta Med Nicomedia. 2023; 6: 60-64.

24- Feretzakis G, Loupelis E, Sakagianni A, et al. A 2-year single-centre audit on antibiotic resistance of Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae strains from an intensive care unit and other wards in a general public hospital in Greece. Antibiotics. 2019; 8: 62.

25- Behçet M, Avcıoğlu F, Karabörk Ş, Kurtoğlu MG. Çeşitli Klinik Örneklerden İzole Edilen ID Pseudomonas aeruginosa Suşlarının Antimikrobiyal Direnç Oranları: Üç Yıllık Değerlendirme. ANKEM Derg 2019;33:43-48

KLİNİK ÇALIŞMA / CLINICAL TRIAL

YouTube Videolarında Psöriatik Artrit Tedavisinin Kalitesinin Analizi

Analysis of the Quality of Psoriatic Arthritis Treatment in YouTube Videos

Tuğba ÖZÜDOĞRU ÇELİK* 0000-0003- 0528-149X

Nadide KOCA** 0000-0002- 0839-5700

* Department of Physical Therapy and Rehabilitation, University of Health Sciences, Ankara Bilkent City Hospital, Ankara/TURKEY

** Department of Physical Therapy and Rehabilitation, University of Health Sciences, Ankara Training and Research Hospital, Ankara/TURKEY

Yazışma Adresi: Tuğba ÖZÜDOĞRU ÇELİK

Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, Ankara/TÜRKİYE

E-mail adresi: tugbaozudogru0626@gmail.com

Öz

Amaç: Psöriatik artrit (PsA), kompleks bir otoimmün hastalık olup, sinovyal eklemleri ve diğer dokuları etkiler. Bu çalışma, YouTube platformunda bulunan PsA tedavisi ile ilgili videoların kalitesini değerlendirmeyi amaçlamaktadır.

Gereçler ve Yöntemler: 01 Ağustos 2023 tarihinde YouTube' da "psöriatik artrit tedavisi", "psöriatik artrit tedavi yöntemleri", "psöriatik artrit tedavi seçenekleri" anahtar kelimeleri kullanılarak arama yapıldı. Videoların kalitesi ve doğruluğu Global Kalite Ölçeği (GQS), DISCERN ve Journal of American Medical Association (JAMA) puanlama sistemleri kullanılarak 2 fizik tedavi ve rehabilitasyon uzmanı tarafından değerlendirildi. Video özelliklerinden; video uzunluğu, yükleme kaynağı, video sunum şekli ve popülerlik gibi niceliksel veriler analiz edildi.

Bulgular: Toplamda 108 video değerlendirildi ve çalışmaya 50 video dahil edildi. Ortalama toplam DISCERN puanı 41,9±14,2 idi. YouTube videolarının 7'si (%14) çok zayıf, 15'i (%30) zayıf, 14'ü (%28) orta, 10'u (%20) iyi ve 4'ü (%8) mükemmel olarak sınıflandırıldı. Doktorlar tarafından yüklenen videolar en yüksek ortalama toplam DISCERN puanına (51,75) sahipti ve durum diğer üreticilerle karşılaştırıldığında istatistiksel olarak önemli (p<0,01) bulundu. GQS ve JAMA puanları da benzer sonuçları gösterdi. Doktorlar tarafından hazırlanan videoların %32 (16) ile en fazla yüklenen videolar olduğu görüldü. En sık video sunum şekli %40 konuşma ve %28 röportaj olarak saptandı. Video üreticileri ile video uzunluğu, izlenme sayısı, yorum sayısı, beğenme sayısı, takipçi sayısı ve video sunum şekli arasında istatistiksek fark saptanmadı (p=0.262, p=0.686, p=0.08, p=0.167, p=0.259, p=0.308). Günlük video güç indeksleri video üreticilerine göre karşılaştırıldığında istatistiksel olarak anlamlı bir fark bulundu (p<0,05).

Sonuçlar: Psöriatik artrit tedavisi ile ilgili YouTube videoları, hastalara doğru ve kaliteli sağlık bilgilerini sunma potansiyeline sahiptir. Bu çalışma sonuçları, doktorların nitelikli videolarla dijital platformlarda daha etkili bir şekilde bilgi paylaşmasının gerekliliğini vurgulamaktadır ve bu da hastaların daha iyi bir sağlık anlayışına sahip olmalarına yardımcı olabilir.

Anahtar Kelimeler: Psöriatik artrit tedavisi, YouTube, kalite

Abstract

Aim: Psoriatic arthritis (PsA) is a complex autoimmune disease affecting synovial joints and various tissues. This study aimed to evaluate the quality of videos related to Psoriatic Arthritis treatment available on the YouTube platform.

Materials and Methods: On August 1, 2023, searches were conducted on YouTube using the keywords "psoriatic arthritis treatment," "psoriatic arthritis treatment methods," and "psoriatic arthritis treatment options." The quality and accuracy of the videos were simultaneously assessed by two physical therapy and rehabilitation expert susing the Global Quality Scale (GQS), DISCERN, and Journal of American Medical Association (JAMA) scoring systems. Quantitative data, including video length, upload source, presentation style, and popularity were analyzed among video characteristics.

Results: A total of 108 videos were assessed, and 50 videos were included in the study. The average total DISCERN score was 41.9±14.2. Of the YouTube videos, 7 (14%) were rated as very poor, 15 (30%) as poor, 14 (28%) as fair, 10 (20%) as good, and 4 (8%) as excellent. Videos uploaded by doctors had the highest average total DISCERN score (51.75) and were found to be statistically significant compared to other producers ($p<0.01$). GQS and JAMA scores showed similar results. It was observed that videos prepared by doctors were the most uploaded videos, accounting for 32% (16). The most common video presentation styles were 40% speech and 28% interviews. There was no statistically significant difference between video producers and video length, views, comments, likes, followers, and video presentation style ($p=0.262$, $p=0.686$, $p=0.08$, $p=0.167$, $p=0.259$, $p=0.308$). There was a statistically significant difference in the daily video power index when compared among video producers ($p<0.05$).

Conclusions: YouTube videos on Psoriatic Arthritis treatment have the potential to provide patients with accurate and high-quality health information. The findings of this study underscore the importance of health care professionals sharing informative content effectively on digital platforms, which can contribute to patients having a beter understanding of their health.

Keywords: Psoriatic arthritis treatment, YouTube, quality

Giriş

Psöriazis, deride kızarıklık, pullanma ve kaşıntı gibi semptomlara yol açan bir hastalıktır. Psöriatik artrit (PsA), bu cilt hastalığına sahip hastalarının yaklaşık %30'unu etkileyen, kronik ve inflamatuar bir eklem hastalığıdır (1). PsA, eklemlerde ağrı, şişme, sertlik ve hareket kısıtlılığı gibi belirgin semptomlarla karakterize edilir. PsA, hem cilt hem de eklem problemlerini içeren bir hastalık olarak tedavi edilmezse eklemlerde kalıcı hasara yol açabilir (2,3). PsA' nın patogenezinin daha iyi anlaşılması, hastalığın ilerlemesini önleyebilen ve yaşam kalitesini artırabilen etkili biyolojik ve küçük moleküler ilaçların geliştirilmesine yol açmıştır. Tedavi seçenekleri bireysel hastalık özelliklerine ve hasta tercihlerine göre değiştiğinden, hastanın tüm klinik tablosunun gözden geçirilmesi zorunludur (1,3,4).

PsA' nın tedavisi, hastalığın şiddetine, hastanın semptomlarına ve genel sağlık durumuna bağlı olarak farklılık gösterebilir. Tedavi yaklaşımı hastadan hastaya farklılık göstereceğinden, hastaların bu konuda uzman bir doktorla işbirliği yapmaları ve özel bir tedavi planı oluşturmaları önemlidir (1, 5). Ayrıca, PsA' nın erken teşhisi ve tedaviye erken başlanması, uzun vadeli komplikasyonların önlenmesine yardımcı olabilir. Sonuç olarak bu hastalığın tedavisi multidisipliner bir tedavi yaklaşımını gerekir (1, 4, 5).

Günümüzde, sağlıkla ilgili bilgiye erişim için sosyal medya iletişimi giderek önem kazanmaktadır. Özellikle YouTube gibi video tabanlı sosyal medya platformları, sağlık konusunda önemli bir kaynak haline gelmiştir (6, 7). Videolar, sosyal medya platformlarında kullanıcılara yeni deneyimler ve bilgiler sunmanın yanı sıra kullanıcılar arasında etkileşimi artırmanın da etkili bir yoludur. YouTube, açık erişimli video içeriğine yönelik en büyük çevrimiçi platformdur (8, 9). Ancak, YouTube gibi açık kaynak platformlarda sunulan bu bilgilerin güvenilirliği ve kalitesi, ciddi bir endişe kaynağıdır. Bu kadar çok videoyla, henüz ilgili kurumlar tarafından onaylanmamış tedaviler, bilimsel olmayan tedaviler ve ilaçlar tanıtılabilmektedir. Bu da hastaların yanlış bilgiler öğrenme potansiyeline sahip olduğu anlamına gelir (10-12). Psöriatik artrit hastaları ve sağlık profesyonelleri, bu platformlar aracılığıyla tedavi seçenekleri hakkında bilgi edinirken, semptomları hafifletme ve yaşam tarzı değişiklikleri konusunda öneriler ararlar(13). YouTube videoların kalitesi değişebilir ve yanlış veya yanıltıcı bilgiler içerebilir (9-12). YouTube' da bulunan PsA tedavisi hakkındaki videoların kalitesini literatürde bildiğimiz kadarıyla ilk kez analiz edildiği bu makale, PsA tedavisi hakkında sunulan içeriğin doğruluğu, kalitesi ve güvenilirliğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem

Bu çalışma, kesitsel bir araştırma olarak tasarlanmıştır. Çalışma için veri toplama sürecinde "http://www.youtube.com" internet adresi kullanılmıştır. Tüm videoların çevrimiçi olarak halka açık olması ve insan katılımcıları veya hayvanlar içermemesi nedeniyle etik kurul onayı gerekmemiştir. Benzer çalışmalar literatürde mevcut olduğundan, bu protokol ile uyumlu bir şekilde çalışma yapılmıştır (14, 15).

Veri Toplama ve İşleme

Araştırma için, 1 Ağustos 2023 tarihinde YouTube platformunda "psöriatik artrit tedavisi", "psöriatik artrit tedavi yöntemleri", "psöriatik artrit tedavi seçenekleri" anahtar kelimeleri kullanılarak ingilizce dilinde sorgulama yapılmıştır. Tüm aramalarda web tabanlı tarayıcının önbelleği temizlenmiş ve çerezler silinmiştir. Veri analizi için; psöriatik artrit tedavisi ile ilgisi olmayan videolar, yinelenen videolar, ingilizce olmayan videolar, animasyonla hazırlanmış içerik ile sesi veya görüntülü anlatımı olmayan videolar hariç tutulmuş ve bunlar çalışma dışında bırakılmıştır. Ayrıca kısa videoların izleyici etkileşimini önemli ölçüde azalttığı göz önüne alındı, bu nedenle 2 dakikadan kısa videolar çalışmaya dahil edilmedi.

Araştırmalar, insanların arama sonuçlarının ilk üç sayfasındaki videolara daha fazla tıklama eğiliminde olduğunu göstermektedir. Bu nedenle, hariç tutma kriterleri uygulandıktan sonra YouTube platformundaki ilk 50 video, iki araştırmacı (TÖÇ ve NK) tarafından birlikte değerlendirildi ve sonuçlar ortak bir kararla kaydedildi.

Video Özellikleri ve Değerlendirmeler

Her video için aşağıdaki veriler kaydedilmiştir: Video uzunluğu (dakika), video yükleme süresi (ay olarak), toplam görüntülenme sayısı, yorum sayısı, yıllık yorum sayısı, beğeni sayısı, hesap aboneleri/takipçileri kaydedildi. Ayrıca, günlük izlenme oranı (görüntüleme sayısı/video yükleme süresi), günlük beğeni oranı (beğeni sayısı/video yükleme süresi x 30) ve günlük video popülerliği başına izlenme sayısı (günlük video güç indeksi [Günlük görüntüleme oranı x günlük beğeni oranı / 100]) her video için hesaplanmıştır.

Video kaynakları hekimler, sağlık kuruluşları/web siteleri, hastalar/bireysel kullanıcılar ve diğerleri olarak sınıflandırıldı. Video sunumları ise konuşma, röportaj, rapor ve karma sunum olarak belirlendi. Videolar aynı zamanda düşük, orta ve yüksek kalite olarak derecelendirildi.

Video Skorlama Kriterleri:

Çalışmamızda, video kalitesini değerlendirmek için JAMA (Amerikan Tabipler Birliği Dergisi) puanlama sistemi kullanılmıştır. Bu sistem, sağlıkla ilgili web sitesi içeriğinin kalitesini belirlemek amacıyla kullanılan bir derecelendirme sistemidir. JAMA puanlama sistemi, Yazarlık, Atıf, Açıklama ve Geçerlilik olmak üzere dört kriteri içerir, ve her biri 1 puanla değerlendirilir. Bu dört kriterin toplamı, toplam puanı 0 ile 4 arasında değiştiren bir sonuç verir. Daha yüksek puanlar, değerlendirilen bilginin kalitesinin arttığını gösterir.

Videoların güvenilirliği ve kalitesini değerlendirmek için iki araç kullanılmıştır: DISCERN anketi ve Küresel Kalite Ölçeği (GQS). DISCERN anketi, video bilgilerinin kalitesini, önyargısını ve güvenilirliğini değerlendiren 16 sorudan oluşur ve puanlama 1'den (zayıf) 5'e (iyi) kadar derecelendirilir. Toplam DISCERN puanı 0-80 arasında değişir ve bu puanlar çok zayıf (< 27), zayıf (27-38), orta (39-50), iyi (51-62) ve mükemmel (63-80) kategorilerine ayrılır.

Küresel Kalite Ölçeği (GQS), video bilgi akışını, kullanışlılığını ve eğitici değerini değerlendirmek için 5 puanlık bir ölçek kullanır. GQS puanları 1 ve 2'yi 'düşük kaliteli', 3'ü 'orta kalite', ve 4 ile 5'i 'yüksek kaliteli' olarak değerlendirir.

İstatistiksel Analiz

Toplanan araştırma verileri Windows sürüm 26.0 (SPSS, Inc, Chicago, Illinois) için SPSS yazılımı aracılığıyla bilgisayar ortamında analiz edilmiştir. Normal dağılmayan sürekli değişkenler ortanca (minimum-maksimum), ortalama artı-eksi standart sapma veya medyan ve çeyrekler arası aralıklar olarak sunuldu. Kategorik değişkenler sayı veya yüzde olarak sunuldu. Verilerin normalliği için Shapiro-Wilk testi kullanıldı, ve YouTube videolarının normal dağılmadığı belirlendi. Grupları karşılaştırmak için Mann-Whitney U testi ve kategorik verileri karşılaştırmak için ki-kare testi kullanıldı.

DISCERN, JAMA ve GQS puanlama sistemlerinin kategorileri Kruskal-Wallis testi ile karşılaştırıldı. Ayrıca, normal dağılıma uyan verilerde üç veya daha fazla bağımsız grup arasındaki farklar için Tek Yönlü Varyans Analizi (ANOVA) kullanıldı. Anlamlılık seviyesi olarak "p" değeri 0,05'ten küçük kabul edildi.

Bulgular

Çalışma kapsamında, YouTube platformunda toplamda 108 video incelendikten sonra dahil etme kriterlerine göre 50 video seçilmiştir (Şekil 1).
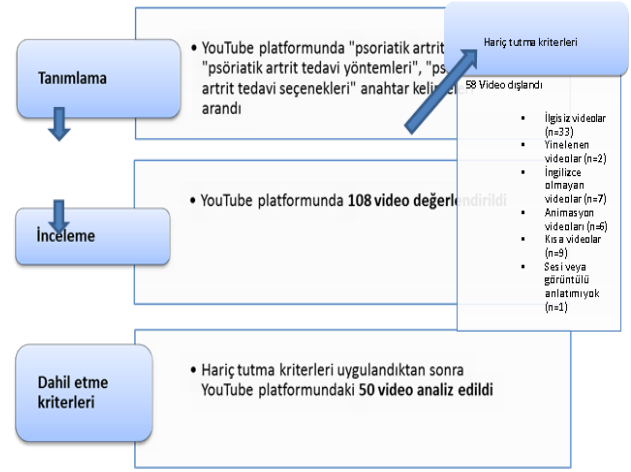
Şekil 1: YouTube' da psöriatik artrit tedavisi ile ilgili videoların tanımlama ve seçim işlemlerini gösteren akış şeması

Videolar, YouTube' a yüklendikten sonra ortalama 41.16±28.2 ay boyunca yayında kaldı. Ortalama video süresi 17±21.3 dakika oldu. Görüntülenme, takipçi ve beğeni ortalamaları sırasıyla 30,768.98±82,482, 87,594.36±222,142.9 ve 649.22±2,064.7 olarak hesaplandı. Yorum sayıları ortalama 73.54±241.7 iken, aylık yorum sayısı 33.99±121.4 oldu. Araştırmacılar tarafından yapılan değerlendirmeler sonucunda ortalama toplam DISCERN puanı 41.9±14.2, GQS skoru ortalama 2.74±1 ve ortalama JAMA skoru 2.26±1 olarak bulundu (Tablo 1).

Tablo 1: YouTube videolarının yükleme tarihinden analiz gününe kadar geçen süredeki tanımlayıcı istatistikleri.

Değişkenler (n=50)	Ortalama ± Standart Sapma
DISCERN Toplam güvenlik	22.64±6.9
DISCERN Toplam tedavi	16.34±6.6
DISCERN Yayın genel kalitesi	2.92±1.1
Toplam DISCERN	41.9±14.2
GQS Kriterleri	2.74±1
JAMA Kriterleri	2.26±1
Video süresi (dk)	17±21.3
Video yükleme zamanı (ay)	41.16±28.2
İzlenme sayısı	30768.98±82482
Yorum	73.54±241.7
Yıllık yorum	33.99± 121.4
Beğenme sayısı	649.22± 2064.7
Takipçi sayısı	87594.36± 222142.9
Günlük izlenme oranı	33289.31± 103534.4
Günlük beğenme oranı	782.64± 2591.8
Günlük video güç indeksi	2871667.74± 15904664.9
Aylık yorum oranı	3.33± 10.5

DISCERN anketi sonuçları, YouTube videolarını beş kategoriye ayırarak (çok zayıf, zayıf, orta, iyi ve mükemmel) değerlendirmektedir. Bu kategorilerden elde edilen veriler karşılaştırıldığında, DISCERN, JAMA ve GQS skorları arasında istatistiksel olarak anlamlı farklar tespit edilmiştir (p=0.0001). Bu sonuçlar, YouTube platformunda sunulan sağlıkla ilgili içeriklerin kalitesinin farklılık gösterebileceğini ve bu içeriklerin değerlendirilirken dikkate alınması gerektiğini göstermektedir. DISCERN kategorileri ile DISCERN toplam güvenlik, DISCERN toplam tedavi, DISCERN genel yayın kalitesi, toplam DISCERN ve JAMA kriterleri değişkenleri açısından istatistiksel olarak anlamlı farklar göstermiştir (p<0.0001). Ayrıca, YouTube videolarından elde edilen GQS kriterleri, video üreticisi ve video kalitesi ile DISCERN kategorileri karşılaştırıldığında da istatistiksel olarak anlamlı farklar bulunmuştur (p<0.01). Bununla birlikte, video yükleyen kişiler ve günlük beğeni oranı açısından istatistiksel olarak anlamlı bir fark saptanmamıştır (p>0.05) (Tablo 2).

YouTube videolarından elde edilen video süresi ile DISCERN kategorileri arasında istatistiksel olarak anlamlı bir fark tespit edilmiştir(p<0.001). Mükemmel kategorisindeki videoların ortalama süresi 41.84 (22.27-113.28) dakika ile en uzun videolar olarak belirlenirken, çok zayıf kategorisinde yer alan videolar ise ortalama 4.49 (2.27-16.29) dakika ile en kısa videolar olmuştur. Bu, videoların uzunluğu ile kalite arasında bir ilişkinin bulunduğunu göstermektedir, özellikle daha uzun videoların daha yüksek kaliteye sahip olduğu gözlenmiştir (Tablo 2).

DISCERN kategorileri ile diğer değişkenler arasındaki istatistiksel karşılaştırmalarda, video yükleme zamanı (p=0.134), izlenme sayısı (p=0.339), yorum (p=0.326), yıllık yorum (p=0.727), beğenme sayısı (p=0.301), takipçi sayısı (p=0.51), video sunumu (p=0.138), günlük izlenme oranı (p=0.272), günlük beğeni oranı (p=0.229), günlük video güç indeksi (p=0.227) ve aylık yorum oranı (p=0.846) arasında anlamlı bir fark bulunmamıştır.

Tablo 2: DISCERN kategorileri ile değerlendirme kriterleri ve videoların tanımlayıcı özellikleri arasındaki istatistiksel analizler

DISCERN Kategori	Çok zayıf (n=7) Ortanca/Ort. (Min-Maks.) veya n (%)	Zayıf (n=15) Ortanca/Ort. (Min-Maks.) veya n (%)	Orta (n=14) Ortanca/Ort. (Min-Maks.) veya n (%)	İyi (n=10) Ortanca/Ort. (Min-Maks.) veya n (%)	Mükemmel (n=4) Ortanca/Ort. (Min-Maks.) veya n (%)	p
DISCERN Güvenlik	12.71 (10-15)	18.2 (15-25)	24.07 (20-28)	29.3 (25-34)	35 (32-37)	0.0001**
DISCERN Tedavi	8 (7-9)	11 (8-16)	16 (14-20)	25,5 (21-28)	26 (26-27)	0.0001**
DISCERN Yayın genel kalitesi	1 (1-2)	2 (2-3)	3 (2-4)	4 (3-4)	5 (4-5)	0.0001**
Toplam DISCERN	22 (18-26)	31 (27-38)	44,5 (39-50)	60 (52-62)	66 (64-68)	0.0001**
GQS Kriterleri						
Düşük kalite	7 (100)	13 (86,7)	2 (14,3)	0 (0)	0 (0)	0.0001**
Orta kalite	0 (0)	2 (13,3)	9 (64,3)	3 (30)	0 (0)	
Yüksek kalite	0 (0)	0 (0)	3 (21,4)	7 (70)	4 (100)	
JAMA Kriterleri	1 (1-1)	2 (1-3)	2 (2-3)	3 (3-4)	4 (4-4)	0.0001**
Video süresi (dakika)	4.49 (2.27-16.29)	5.22 (2.2-39.44)	6.32 (3.2-54.53)	15.26 (5.01-59.32)	41.84 (22.27-113.28)	0.008**
Video Sunum						
Konuşma	2 (28.6)	7 (46.7)	6 (42.9)	4 (40)	1 (25)	0.138
Röportaj	3 (42.9)	3 (20)	6 (42.9)	1 (10)	1 (25)	
Rapor	0 (0)	4 (26.7)	0 (0)	1 (10)	2 (50)	
Karma	2 (28.6)	1 (6.7)	2 (14.3)	4 (40)	0 (0)	
Video Kalite						
Düşük	5 (71.4)	1 (6.7)	0 (0)	0 (0)	0 (0)	0.0001**
Orta	2 (28.6)	12 (80)	3 (21.4)	0 (0)	0 (0)	
Yüksek	0 (0)	2 (13.3)	11 (78.6)	10 (100)	4 (100)	

YouTube video üreticilerinin dağılımı şu şekildedir: Doktorlar (%32), Hastalar (%22), Medikal Kanallar (%30) ve Diğer Kaynaklar (%16). Video sunumu türlerine bakıldığında ise dağılım şu şekildedir: Konuşma (%40), Röportaj (%28), Rapor (%14) ve Karma (%18). Video içeriklerinin kalite düzeyi ise şu oranlarda bulunmuştur: Düşük Kalite (%12), Orta Kalite (%34) ve Yüksek Kalite (%54). Video üreticisi ile video kalitesi karşılaştırıldığında, aralarında istatistiksel olarak anlamlı bir fark saptanmıştır (p<0.001). Doktorlar tarafından üretilen videoların %87.5'i yüksek kaliteli olarak belirlenmiştir.

Tartışma

Bu çalışma, YouTube platformundaki psöriatik artrit tedavisi hakkındaki videoları inceleyen ilk araştırma olma özelliği taşımaktadır. Araştırmamızın sonuçları, YouTube platformunda PsA tedavisi ile ilgili videoların yükleme süresi, izlenme sayısı, yorum sayısı, beğeni sayısı ve takipçi sayısı gibi özelliklerde önemli farklılıklar göstermediğini göstermektedir. Video kaynakları incelendiğinde, hekimler tarafından hazırlanan videoların (% 32) en sık yüklendiği gözlemlenmiştir. Ayrıca, videoların YouTube' a yüklendikten sonra ortalama 41.16±28.2 ay boyunca yayında kaldığı ve ortalama video süresinin 17±21.3 dakika olduğu görülmüştür. Görüntülenme, takipçi ve beğeni ortalamalarının oldukça yüksek olduğu belirlenmiştir. Yorum sayılarının ortalama 73.54±241.7 ve aylık yorum sayısının 33.99±121.4 olduğu saptanmıştır, bu da videoların ilgi gördüğünü ve etkileşim aldığını göstermektedir.

Dijital çağın etkisiyle internet, sağlık bilgilerine erişmek için yaygın olarak kullanılan bir kaynağa dönüşmüştür. YouTube gibi video paylaşım platformları, hızla büyüyen bir kullanıcı kitlesi tarafından tercih edilmekte olup sağlık bilgilerine kolay erişim sağlamaktadır (5). Ancak, bu kolay erişim, güvensiz ve yanıltıcı sağlık bilgilerini de beraberinde getirmiştir. Bu nedenle, doğru ve yüksek kaliteli videolar gibi görsel materyaller, hastaların kendi sağlık durumlarını ve sağlık hizmeti ihtiyaçlarını daha iyi anlamalarına yardımcı olabilir (5, 16-19). YouTube gibi platformların sağlık bilgilerine erişim amacıyla kullanımının artması, videoların kalite ve içeriğini değerlendirmeyi gerektiren bir ihtiyacı ortaya koymuştur. Son yıllarda, birçok çalışma YouTube video içeriklerini incelemiş ve bu incelemelerde farklı puanlama sistemleri kullanılmıştır (20,21). Çalışmamızda DISCERN, JAMA ve GQS puanlama kriterlerini kullandık. Ortalama puanlar sırasıyla 41.9±14.2, 2.74±1 ve 17±21.3 olarak bulundu. Bu puanlar, videoların genel kalitesi ve bilimsel temeli hakkında önemli bilgiler sunar. DISCERN kategorileri ile diğer kriterler karşılaştırıldığında DISCERN, JAMA ve GQS puanları arasında istatistiksel olarak anlamlı farklar bulundu (p=0.0001). Bu sonuçlar, YouTube platformunda sunulan sağlıkla ilgili içeriklerin kalitesinin değişebileceğini ve bu içeriklerin değerlendirilirken dikkate alınması gerektiğini vurgular.

Çalışmamızın sonuçları, PsA tedavisi ile ilgili videoların YouTube' da yapılan diğer kalite değerlendirmeleriyle benzer sonuçlar sunduğunu göstermektedir (20, 22). Videoların kaynaklarına göre yapılan incelemeler, doktorlar tarafından hazırlanan videoların DISCERN, JAMA ve GQS puanlarının yüksek olduğunu ve bu farkın istatistiksel olarak anlamlı olduğunu ortaya koymaktadır. Bu sonuçlar, önceki araştırmalarla uyumlu bir şekilde bulunmuştur. Yine videoların uzunluğu ile kalite arasında bir ilişkinin bulunduğu da göstermekte olup, özellikle daha uzun videoların daha yüksek kaliteye sahip olduğu gözlenmiştir (22,23). Sağlık profesyonellerinin yüksek kalitede ve doğru bilgilere sahip videoları paylaşmaları, izleyicilerin güvenilir kaynaklara daha rahat erişmelerine yardımcı olabilir. Çalışmamızda, video süresi ile DISCERN kategorileri arasında istatistiksel olarak anlamlı bir ilişki bulunmuştur (p<0.001). Mükemmel kategorisindeki videoların ortalama süresi 41.84 (22.27-113.28) dakika ile en uzun videolar olarak belirlenirken, çok zayıf kategorisinde yer alan videolar ise, ortalama 4.49 (2.27-16.29) dakika ile en kısa videolar olmuştur.

Psöriatik artrit gibi kronik bir hastalığın etkili tedavisi, hem hastalar hem de sağlık profesyonelleri için hayati bir önem taşır. Yanlış tedavi veya eksik bilgi, hastalığın ilerlemesine ve yaşam kalitesinin düşmesine yol açabilir. Bu nedenle, PsA tedavisi hakkında doğru ve güncel bilgilere erişmek son derece önemlidir (3-5). Ancak videoların yüksek kaliteli olması, izleyici etkileşimini artırmayı garanti etmez (24). Bu araştırma, psöriatik artrit tedavisi ile ilgili sunulan videoların kalitesini inceleyerek, PsA hastaları ve sağlık profesyonelleri için güvenilir bir kaynak olup olmadığını değerlendirmiştir. Videoların kaynaklarına yönelik yapılan analiz sonuçları, sağlık profesyonelleri ve hastalar arasındaki iletişimde ne kadar önemli bir rol oynadığını göstermektedir. Özellikle hekimler tarafından hazırlanan videoların daha sık yüklenmiş olması, sağlık profesyonellerinin online platformları hasta eğitimi için etkili bir şekilde kullanabileceğini işaret etmektedir.

Çalışmamızın bazı sınırlamaları bulunmaktadır. İlk olarak, yalnızca İngilizce dilindeki videoları inceledik ve farklı dillerde araştırma yapılması daha kapsamlı bir sonuç verebilirdi. İkinci olarak, YouTube' un sürekli içerik güncellemesine izin veren dinamik yapısı, sonuçlarımızın zaman içinde değişebileceği anlamına gelir. Arama sonuçları coğrafi konuma bağlı olarak değişebilir. Değerlendirmeler için DISCERN, JAMA ve GQS gibi puanlama kriterleri kullanıldı, ancak farklı kriterler farklı sonuçlar doğurabilirdi. YouTube' daki video içeriği oldukça çeşitli olduğundan, her video ayrı ayrı analiz gerektirebilir (18, 23, 25). Bu sınırlamalar, çalışma sonuçlarını yorumlarken ve gelecekteki araştırmaları tasarlarken dikkate alınmalıdır. Gelecekteki araştırmalar, bu videoların PsA hastalarının bilgi edinme ve tedavi kararları süreçleri üzerindeki etkisini değerlendirmeye odaklanmalıdır.

Analizimiz, YouTube' da bulunan PsA tedavisi hakkındaki videoların kalitesinin değişken olduğunu gösterdi. Videoların çoğunun, PsA' nın nedenleri, belirtileri ve tedavisi hakkında genel bilgiler içerdiğini bulduk. Ancak, bazı videolar yanlış veya yanıltıcı bilgiler içeriyordu. Örneğin, bazı videolar, PsA' nın tedavisinde etkili olduğu kanıtlanmamış alternatif tedavileri öneriyordu. YouTube, PsA tedavisi hakkında bilgi almak için popüler bir kaynak olsa da, bu videoların kalitesi değişebilir. PsA tedavisi hakkında bilgi ararken, güvenilir kaynaklardan gelen bilgileri kullanmaya dikkat etmek önemlidir.

Sonuç olarak, bu çalışma, çevrimiçi kaynakların psöriatik artrit tedavisi konusundaki güvenilirlik ve kalitesine dair önemli bilgiler sunmaktadır. Bu sonuçlar, hastaların ve sağlık profesyonellerinin bu videoları değerlendirirken dikkatli olmalarını gerektirdiği ve sağlıkla ilgili doğru bilgilere erişimi desteklemek için çevrimiçi platformların daha etkili bir şekilde kullanılması gerektiğini vurgulamaktadır. Gelecekteki araştırmalar, bu konuda daha fazla bilgi sağlamak ve çevrimiçi sağlık bilgisi iletişimi alanındaki etkileri daha iyi anlamak için önemlidir.

Kaynaklar

1- Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology (Oxford) 2020;59(Suppl 1):i37-i46.

2- Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med (Lond) 2017;17(1):65-70.

3- Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391(10136):2273-2284.

4- Menter A. Psoriasis and psoriatic arthritis treatment. Am J Manag Care 2016;22(8 Suppl):s225-37.

5- Schemoul J, Poulain C, Claudepierre P. Treatment strategies for psoriatic arthritis. Joint Bone Spine 2018;85(5):537-544.

6- Chen J, Wang Y. Social Media Use for Health Purposes: Systematic Review. J Med Internet Res 2021;23(5):e17917.

7- Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, Gramopadhye AK. Healthcare information on YouTube: A systematic review. Health Informatics J 2015;21(3):173-94.

8- Afful-Dadzie E, Afful-Dadzie A, Egala SB. Social media in health communication: A literature review of information quality. Health Inf Manag 2023;52(1):3-17.

9- Yeung AWK, Tosevska A, Klager E, Eibensteiner F, Tsagkaris C, Parvanov ED, Nawaz FA, Völkl-Kernstock S, Schaden E, Kletecka-Pulker M, Willschke H, Atanasov AG. Medical and Health-Related Misinformation on Social Media: Bibliometric Study of the Scientific Literature. J Med Internet Res 2022;24(1):e28152.

10- Osman W, Mohamed F, Elhassan M, Shoufan A. Is YouTube a reliable source of health-related information? A systematic review. BMC MedEduc 2022;22(1):382.

11- Suarez-Lledo V, Alvarez-Galvez J. Prevalence of Health Misinformation on Social Media: Systematic Review. J Med Internet Res 2021;23(1):e17187. doi: 10.2196/17187.

12- Chou WS, Oh A, Klein WMP. Addressing Health-Related Misinformation on Social Media. JAMA 2018;320(23):2417-2418.

13- Hersh W. Social Media and its Impact on Rheumatology. Rheumatol Immunol Res 2022;3(4):151-152.

14- Onder ME, Zengin O. Quality of health care information on YouTube: psoriaticarthritis. Z Rheumatol 2023;82(Suppl 1):30-37.

15- Lenczowski E, Dahiya M. Psoriasis and the Digital Landscape: YouTube as an Information Source for Patients and Medical Professionals. J Clin Aesthet Dermatol 2018;11(3):36-38.

16- Kim K, Shin S, Kim S, Lee E. The Relation Between Health Literacy and Health-Related Behaviors: Systematic Review and Meta-analysis. J Med Internet Res 2023;25:e40778.

17- Bloch J, Duplain H, Rimoldi SF, et al. Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters. Pediatrics 2009;123(1):1-5.

18- Gabarron E, Fernandez-Luque L, Armayones M, Lau AY. Identifying Measures Used for Assessing Quality of YouTube Videos with Patient Health Information: A Review of Current Literature. Interact J MedRes 2013;2(1):e6.

19- Qi J, Trang T, Doong J, Kang S, Chien AL. Misinformation is prevalent in psoriasis-related YouTube videos. Dermatol Online J 2016;22(11):13030/qt7qc9z2m5.

20- Patel AA, Mulvihill L, Jin A, Patel A, Galiano RD. WebsitesorVideos: Which Offer Better Information for Patients? A Comparative Analysis of the Quality of YouTube Videos and Web sites for Cosmetic Injectables. PlastReconstrSurg 2022;149(3):596-606.

21- Mueller SM, Jungo P, Cajacob L, Schwegler S, Itin P, Brandt O. The Absence of Evidence is Evidence of Non-Sense: Cross-Sectional Study on the Quality of Psoriasis-Related Videos on YouTube and Their Reception by Health Seekers. J Med Internet Res 2019;21(1):e11935.

22- Idriss SZ, Kvedar JC, Watson AJ. The role of online support communities: benefits of expanded social Networks to patients with psoriasis. Arch Dermatol 2009;145(1):46-51.

23- Kocyigit BF, Akaltun MS, Sahin AR. YouTube as a source of information on COVID-19 and rheumatic disease link. ClinRheumatol 2020;39(7):2049-2054.

24- DeBord LC, Patel V, Braun TL, Dao H Jr. Socialmedia in dermatology: clinical relevance, academic value, and trends across platforms. J Dermatolog Treat 2019;30(5):511-518.

25- Atar E. Are YouTube Videos Beneficial for Patients Interested in Cervical Disc HerniationExercises? Ege Klin Tıp Derg 2022;60 (2): 131-136.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Clınıcal Sıgnıfıcance of HDL-C Values And Routıne Parameters Of Inflammatıon Such As Hs-Crp, Lenfocyte And Neutrofıl Ratıos In Covıd-19 Patıents

Covid-19 Hastalarında HDL-K Değerinin Rutin İnflamasyon Parametreleri Olan h-CRP,Lenfosit ve Nötrofil Oranlarının Klinik Önemi

Gül Şahika GÖKDEMİR* 0000-0002-8691-1504
Cemal NAS* 0000-0002-5616-8625

* Mardin Artuklu Üniversitesi,Tıp Fakültesi, Fizyoloji Anabilim Dalı, Mardin, Türkiye
** Gazi Yaşargil Eğitim Araştırma Hastanesi, Biyokimya Kliniği, Diyarbakır, Türkiye

Yazışma Adresi: Gül Şahika GÖKDEMİR
Mardin Artuklu Üniversitesi,Tıp Fakültesi, Fizyoloji Anabilim Dalı, Mardin,
E-mail: gulsahikagokdemir@gmail.com

Abstract

Objective: The study aimed to evaluate the prognostic significance of high-density lipoprotein cholesterol (HDL-C) levels, alongside markers including the neutrophil/HDL-C ratio (NHR) and lymphocyte/HDL-C ratio (LHR), on the mortality of COVID-19 patients. It also examined the potential clinical application of these biomarkers in the management of future healthcare crises, despite the end of the COVID-19 pandemic.

Materials and Methods: Patients diagnosed with COVID-19 were retrospectively analysed between March 2020 and August 2022. A total of 367 patients were categorised into two groups: survivors (group 2) and non-survivors (group 1). Patient demographics, biochemical and haematological parameters obtained from blood samples, high-sensitivity C-reactive protein (hs-CRP), neutrophil-to-lymphocyte ratio (NLR), monocyte/HDL-C ratio (MHR), NHR, LHR, platelet/HDL-C ratio (PHR) were calculated. Patient data were analysed using SPSS 26 and statistical differences of P<0.05 were considered significant.

Results: Among the patients analyzed in the study, the living group constituted 89.9% of individuals, while the deceased group represented 10.1%. The neutrophil levels were significantly higher in the deceased group, and NLR and NHR values were statistically significant (P<0.001 and P=0.001, respectively). There was no significant difference in HDL-C levels. Moreover, no significant differences in LHR, MHR, and PHR levels were observed between groups. The hs-CRP levels were significantly higher in the deceased (P<0.001). Correlation analysis indicated a negative correlation between HDL-C and LHR and NHR, and significant correlations were found for other markers. ROC analysis showed that LHR and NHR were significant in discriminating deceased patients.

Conclusion: Biochemical and haematological parameters, especially markers such as NLR and NHR, can potentially be used to assess the risk of death in COVID-19 patients. These markers may be valuable in predicting the prognosis of patients and could be used in future similar health crises.

Keywords: COVID-19, High-density lipoprotein (HDL-C), Neutrophil/HDL-C ratio, Lymphocyte/HDL-C ratio

Clınıcal Sıgnıfıcance of HDL-C Values And Routıne Parameters Of Inflammatıon Such As Hs-Crp, Lenfocyte And Neutrofıl Ratıos In Covıd-19 Patıents

Covid-19 Hastalarında HDL-K Değerinin Rutin İnflamasyon Parametreleri Olan h-CRP,Lenfosit ve Nötrofil Oranlarının Klinik Önemi

Öz

Amaç: Bu çalışma, nötrofil/HDL-C oranı (NHR) ve lenfosit/HDL-K oranı (LHR) gibi belirteçlerin yanı sıra yüksek yoğunluklu lipoprotein kolesterol (HDL-K) seviyelerinin COVID-19 hastalarının mortalitesi üzerindeki prognostik önemini değerlendirmeyi amaçlamıştır. Ayrıca, COVID-19 pandemisinin sona ermesine rağmen, bu biyobelirteçlerin gelecekteki sağlık krizlerinin yönetiminde potansiyel klinik uygulamalarını da incelemiştir.

Gereç ve Yöntemler: COVID-19 tanısı konan hastalar Mart 2020 ile Ağustos 2022 tarihleri arasında retrospektif olarak analiz edilmiştir. Toplam 367 hasta iki gruba ayrılmıştır: hayatta kalanlar (grup 2) ve hayatta kalmayanlar (grup 1). Hasta demografisi, kan örneklerinden elde edilen biyokimyasal ve hematolojik parametreler, yüksek hassasiyetli C-reaktif protein (hs-CRP), nötrofil-lenfosit oranı (NLR), monosit/HDL-K oranı (MHR), NHR, LHR, trombosit/HDL-K oranı (PHR) hesaplanmıştır. Hasta verileri SPSS 26 kullanılarak analiz edildi ve P<0.05 olan istatistiksel farklılıklar anlamlı kabul edildi.

Bulgular: Çalışmada analiz edilen hastalar arasında yaşayan grup bireylerin %89,9'unu oluştururken, vefat eden grup %10,1'ini temsil etmektedir. Nötrofil düzeyleri ölen grupta anlamlı olarak daha yüksekti ve NLR ve NHR değerleri istatistiksel olarak anlamlıydı (sırasıyla P<0,001 ve P=0,001). HDL-K düzeylerinde herhangi bir farklılık yoktu. LHR, MHR ve PHR değerlerinde gruplar arasında anlamlı bir farklılık gözlenmedi. Hs-CRP düzeyleri ölenlerde anlamlı olarak daha yüksekti (P<0.001). Korelasyon analizi HDL-K ile LHR ve NHR arasında negatif korelasyon olduğunu gösterirken, diğer belirteçler için anlamlı korelasyonlar bulunmuştur. ROC analizi LHR ve NHR'nin ölen hastaları ayırt etmede anlamlı olduğunu göstermiştir.

Sonuçlar: Biyokimyasal ve hematolojik parametreler, özellikle NLR ve NHR gibi belirteçler, COVID-19 hastalarında ölüm riskini değerlendirmek için potansiyel olarak kullanılabilir. Bu belirteçler hastaların prognozunu tahmin etmede değerli olabilir ve gelecekteki benzer sağlık krizlerinde kullanılabilir.

Anahtar Kelimeler: COVID-19, Yüksek yoğunluklu lipoprotein (HDL-C), Nötrofil/HDL-C oranı, Lenfosit/HDL-C oranı

Introduction

Coronavirus disease 2019 (COVID-19) went down in history as a pandemic that spread rapidly around the world, severely impacting health systems, economies and societies. Thanks to the development of treatment options and widespread vaccination, the spread of the pandemic was brought under control (1). Although the pandemic has ended, it is important to remember that new mutations of COVID-19 may have the potential to spread. The SARS-CoV-2 virus, first described in 2019, causes a range of symptoms and complications characterizing this virus-induced respiratory disease, including pneumonia (2). In severe cases, organ dysfunction (such as shock, acute heart and kidney damage) and death have occurred (3). Some patients with pneumonia may deteriorate rapidly and require mechanical ventilation.

The mortality rate in these patients is quite high, reaching up to 60% (4). Therefore, identification of high-risk individuals and prevention of their infections may reduce mortality from the disease.

Recently, there has been an increased interest in new, practical and inexpensive markers of inflammation, especially in inflammatory diseases. Haemogram and biochemistry analysis is the most widely used test in the clinic in almost all laboratories, large and small. In this context, haematological markers such as neutrophil-to-lymphocyte ratio (NLR) has recently gained attention as new parameters associated with chronic inflammatory conditions and disease severity (5). Several studies demonstrate that HDL-C is capable of predicting mortality in individuals with COVID-19 (6). Additionally, recent studies have identified new haematological parameters associated with HDL-C, including the neutrophil to high-density lipoprotein cholesterol ratio (NHR), monocyte to high-density lipoprotein cholesterol ratio (MHR), lymphocyte to high-density lipoprotein cholesterol ratio (LHR) and platelet to high-density lipoprotein cholesterol ratio (PHR) as indicators of inflammation. Prognostic markers have been established for NHR, MHR, and LHR regarding cardiovascular events, diabetes, neurological diseases, and metabolic syndrome (7,8). The NHR ratio, which provides insight into inflammation and lipid metabolism, has been proposed as a predictive factor for clinical outcomes in patients diagnosed with acute ischemic stroke and acute myocardial infarction. Although studies are still limited, these biomarkers have been identified in a number of lung diseases (9). However, the predictive value of these serological biomarkers for mortality in COVID-19 remains unclear.

The objective of this study was to investigate the prognostic effect of markers such as HDL-C levels, NHR and LHR ratios on mortality in individuals diagnosed with COVID-19 and to determine the most valuable diagnostic indicators. At the same time, the applicability of these biomarkers for the clinical management of similar health crises in the future should be evaluated, even though the COVID-19 pandemic has ended.

Materials And Methods

Study Design:

The study included patients who tested positive for Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) between March 27, 2020, and August, 2022 at Diyarbakır Training and Research Hospital. The patients' clinical symptoms, findings, and laboratory data were obtained from the hospital's medical records. The diagnosis of COVID-19 was confirmed by the positive result of the RT-PCR test performed on the patients' nasal and throat swab samples from the hospital data. A total of 367 patients diagnosed with COVID-19 were included in the study. The study participants were categorized into two groups: Group 1, consisting of deceased patients, and Group 2, consisting of those who were alive.

Patients under 18 years of age, pregnant women, steroid users, patients with malignancy, hyperlipidaemia and haematological diseases were not were not included in the study. In our study, written consent was obtained from participants in accordance with the Helsinki Declaration, and it was conducted with the approval of the local ethics committee. This study was approved by the local ethics committee of Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (date: 09.09.2022, number: 164).

Analysis of Clinical and Laboratory Data:

Demographic data including age, sex and survival were obtained from hospital medical records. Levels of HDL-C, lymphocytes, neutrophils, monocytes, platelets, high-sensitivity C-reactive protein (hs-CRP) and NLR (neutrophil-lymphocyte ratio), MHR (ratio of monocyte count to HDL-C level), NHR (ratio of neutrophil count to HDL-C level), LHR (ratio of lymphocyte count to HDL-C level), PHR (ratio of platelet count to HDL-C level) were calculated.

Statistical analysis

Analysis of the results was performed using SPSS version 26. The Student T test was used for continuous variables and the Mann-Whitney U test for categorical variables. Pearson correlation analysis was used to assess the relationship between the outcomes. Results were expressed as arithmetic mean±standard deviation for continuous variables and as number (percentage) for categorical data. Receiver operating characteristic (ROC) curve analyses were performed to assess the diagnostic accuracy of certain parameters. The estimated area under the ROC curve was calculated together with sensitivity and specificity values. Significance was accepted at P<0.05.

Results

A total of 367 patients, 198 (54%) female and 169 (46%) male, were included in the study. Among the patients included in the study, 89.9% of the individuals constituted the living group, while the rate of the deceased group was determined to be 10.1%. The mean age of the deceased patients was 64.00±11.23 years and the mean age of the living patients was 64.54±12.65 years (t=0.396, P=0.803). While no significant difference was found in the gender distribution (χ²=2.154, P=0.142), no difference was observed in the age distribution (t=0.396, P=0.803) (Table 1).

All biochemical parameters are shown in Table 1.The mean HDL cholesterol level was 30.19 ± 10.71 in the deceased and 32.96 ± 13.81 in the survivors (P=0.238). The mean neutrophil level was 9.05 ± 6.195 in the deceased and 5.89 ± 3.68 in the survivors; this difference was significantly higher (P<0.001). No significant difference was found between lymphocyte, monocyte and platelet levels.

Table 1. Distribution of Gender, Age and Biochemical Parameters in Deaths and Survivors Patient.

Parameters	Deaths (n=37,10%) [N,% or Mean±SD]	Survivors (n=330,90%) [N,% or Mean±SD]	P
Gender(Men/ Women)	20 (11.8%)/ 17 (8.6%)	149(88.2%)/ 181(91.4%)	
Age (year)	64.00±11.23	64.54±12.65	0.803
HDL-C (mg/dl)	30.186±10.71	32.96 ± 13.81	0.238
LYM (10*3/uL)	1.35±2.195	1.76±1.34	0.101
NEUT (10*3/uL)	9.05±6.195	5.89±3.68	<0.001
MONO (10*3/uL)	0.44±0.30	0.49±0.27	0.367
PLT (10*3/uL)	224.68±88.06	238.72±111.82	0.461
NLR	16.36±27.04	4.93±5.23	<0.001
LHR	0.05 ±0.08	0.06±0.06	0.104
NHR	0.33±0.21	0.22±0.19	0.001
MHR	0.02±0.01	0.02±0.01	0.755
PHR	8.26±4.57	8.42±5.58	0.867
hs-CRP (mg/L)	84.92±80.76	36.40±49.34	<0.001

**. Correlation is significant at the 0.01 level (2-tailed).*. Correlation is significant at the 0.05 level (2-tailed).

HDL-C: High density lipoprotein cholesterol, LYM: Lymphocyte, NEUT: Neutrophil, MONO: Monocyte, PLT: Platelet, NLR: Neutrophil lymphocyte ratio LHR: Lymphocyte to high-density lipoprotein cholesterol ratio, NHR: Neutrophil to high-density lipoprotein cholesterol ratio, MHR: Monocyte to high-density lipoprotein cholesterol ratio , PHR: Platelet to high-density lipoprotein cholesterol ratio, hs-CRP: High-sensitivity C-reactive protein

The NLR value was 16.36 ± 27.04 in the deceased and 4.93 ± 5.23 in the living, and this difference was statistically significant (P<0.001). The NHR ratio was 0.33 ± 0.21 in the deceased and 0.22 ± 0.19 in the living, and this difference was statistically significant (P=0.001). No statistically significant difference was found between the groups in LHR, MHR and PHR ratios. The mean hs-CRP level was 84.92 ± 80.76 in the deceased and 36.40 ± 49.34 in the living, and this difference was found to be significantly higher (P<0.001).

Clınıcal Sıgnıfıcance of HDL-C Values And Routıne Parameters Of Inflammatıon Such As Hs-Crp, Lenfocyte And Neutrofıl Ratıos In Covıd-19 Patıents

Covid-19 Hastalarında HDL-K Değerinin Rutin İnflamasyon Parametreleri Olan h-CRP,Lenfosit ve Nötrofil Oranlarının Klinik Önemi
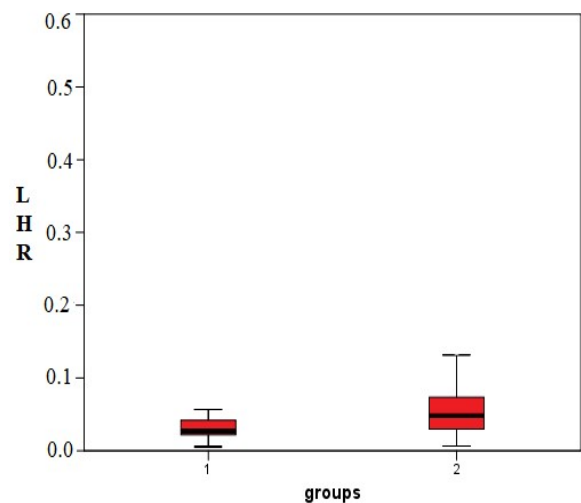
Figure 1. LHR Level Comparison in COVID-19 Patient Groups (group 1: non-survivors group 2: survivors).
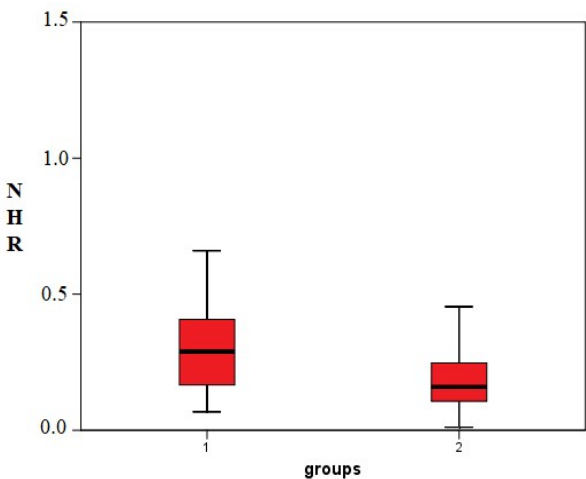
Figure 2. NHR Level Comparison in COVID-19 Patient Groups (group 1: non-survivors group 2: survivors).

Our results showed that LHR was positively correlated with MHR (R=0.498, P<0.001) ,and PHR (R=-0.459, P<0.001). In addition, LHR negatively correlated with HDL-C(R=-0.403,P<0.001) and NLR(R=-0.232,P<0.001) (Table 2).

Table 2. Correlation relationship of LHR and NHR with other parameters

Parameters	LHR	NHR
MHR	R=0.498*,P<0.001	R=0.447*,P<0.001
PHR	R=0.459*,P<0.001	R=0.363*,P<0.001
HDL-C	R=-0.403*,P<0.001	R=-0.459*,P<0.001
NLR	R=-0.232*,P<0.001	R=0.479*,P<0.001
hs-CRP	R=0.012,P=0.821	R=0.322*,P<0.001

R:Pearson correlation coefficient. *Correlation is significant at the 0.01 level (2-tailed).

LHR: Lymphocyte to high-density lipoprotein cholesterol ratio, NHR: Neutrophil to high-density lipoprotein cholesterol ratio, MHR: Monocyte to high-density lipoprotein cholesterol ratio , PHR: Platelet to high-density lipoprotein cholesterol ratio, HDL-C: High density lipoprotein cholesterol , NLR: Neutrophil lymphocyte ratio hs-CRP: High-sensitivity C-reactive protein

In the ROC analysis, the under the curve values of HDL-C, hs-CRP, LHR and NHR of deceased and living COVID-19 patients are shown in Figure 1 and 2. ROC analyses showed significant results for LHR and NHR in deceased COVID-19 patients (Figure 3). In deceased patients, LHR had a sensitivity of 51.4% and a specificity of 22% at a cut-off value of 0.027 and NHR had a sensitivity of 73% and specificity of 64% at a cut-off of 0.206. In living patients, LHR had a sensitivity of 76% and a specificity of 60% at a cut-off of 0.029 and NHR had a sensitivity of 50% and a specificity of 24% at a cut-off of 0.216.

Figure 3. ROC analyses of HDL-C, hs-CRP, LNR and NHR levels by groups

Discussion

Significant relationships between COVID-19 results and some clinical and biochemical parameters were found in our study. Our results showed that HDL-C levels were similar in deceased and living COVID-19 patients, whereas LHR and NHR rates were significantly higher in deceased patients.

The fact that approximately 40% mortality was observed during the COVID-19 pandemic shows the critical importance of early diagnosis and treatment in reducing mortality (10). It is therefore important to identify easily accessible and inexpensive markers for early diagnosis of cases that are likely to become clinically severe.

Acute inflammation triggered by viral infections can lead to dyslipidaemia in patients. At the same time, it is recognized that lipid metabolism plays a crucial part in the host's immune response (11). Furthermore, inflammatory responses and lipid irregularities have been observed to be associated with negative clinical results effects in diseases such as COVID-19.

It is therefore important to identify more reliable and sensitive biomarkers. This is because they have the potential to more accurately portray inflammatory status and lipid metabolism. Leukocyte subsets and HDL-C, which are regularly monitored, are cost-effective and easily accessible markers that can be used for this purpose with a simple calculation. These biomarkers may help us to better assess patients' immune responses and health status and to develop effective treatment strategies.

Ninety per cent of lung surfactant is made up of lipids, and the fact that most lung cholesterol comes from plasma suggests that lipids play an important role in respiratory infections (12). Low HDL-C levels have been linked to the seriousness of illness and fatalities in COVID-19 patients.

HDL-C plays a crucial part in host defence against various infections because of its anti-inflammatory, anti-thrombotic, and antioxidant characteristic (13). HDL-C and apolipoprotein A-1 (apoA-1) in its structure exert direct anti-inflammatory effects by neutralising lipopolysaccharide and lipoteic acid, inhibiting peripheral blood monocyte activation and reducing TNF-α and IL-1β production. Changes in serum lipid levels during COVID-19 infection resulted in decreased HDL-C levels. This process leads to a loss of anti-inflammatory properties and a further decrease in HDL-C levels during infection (14). Many studies have shown a link between COVID-19 infection and low HDL-C levels (14-16). In our study, individuals who succumbed to COVID-19 exhibited lower levels of serum HDL-C compared to those who survived. However, this disparity failed to demonstrate statistical significance.

High CRP levels may serve as an early indication for potential disease progression in non-severe COVID-19 patients (15). Furthermore, hihg CRP levels have been linked to mortality among COVID-19 patients (16). Low HDL-C levels have been shown to be associated with high CRP levels in many diseases, such as cardiovascular disease (17). This suggests that HDL-C has anti-inflammatory properties and may have a significant role in modulating inflammation during infection (18).

Clınıcal Sıgnıfıcance of HDL-C Values And Routıne Parameters Of Inflammatıon Such As Hs-Crp, Lenfocyte And Neutrofıl Ratıos In Covıd-19 Patıents

In our study, we observed a significantly higher NLR rate in deceased individuals compared to those who were alive. Additionally, our study revealed a weak negative correlation between NLR and LHR. This suggests that HDL-C may have a positive effect on the immune system and that the lymphocyte/neutrophil ratio may be a determinant in predicting the course of the disease.

In their research, Wang et al. showed a robust association between reduced HDL-C levels, elevated NHR and unfavorable clinical consequences in COVID-19 patients. This may suggest that NHR is an effective predictor of adverse outcomes in COVID-19. Elevated NHR levels may indicate an overactive inflammatory response leading to multiple organ damage and mortality (7). However, elevated NHR is linked with various illnesses, such as metabolic health issues and heart-related illnesses, which are COVID-19 risk factors (19,20). There is limited literature on the use of NHR as a parameter for atherosclerosis and cardiovascular disease. Recent studies indicate that NHR is a negative predictor of prognosis in patients diagnosed with myocardial infarction and is elevated in patients with metabolic syndrome (21,22). Huang et al. reported that it was a good marker in acute myocardial infarction (21). The research conducted by Koseoglu et al. proposes that a lack of vitamin D may increase inflammation and can be linked to higher cardiovascular risk. Additionally, the NHR ratios might serve as a measure to forecast cardiovascular disease in cases where vitamin D levels are low (23). MHR constitutes a crucial indicator for inflammatory processes, although the available studies on MHR and its role in assessing the severity of COVID-19 exhibit incongruous findings. Coşkun et al. showed that high MHR levels correlated with disease severity in their study (24). However, Wang et al.'s study data was inconclusive in confirming the potential predictive impact of LHR, MHR, and PHR on the severity of COVID-19 (7). Similarly, in this study, there was no significant difference in LHR, MHR, and PHR between those who died and those who survived due to COVID-19. However, the NHR ratio was significantly higher in those who died compared to those who survived.

At the same time, in our study, LHR and NHR rates showed a negative association with HDL-C in COVID-19 patients. As HDL-C levels increase, LHR and NHR decrease. In our study, NHR had higher sensitivity and specificity in the deceased patient group, while LHR had higher sensitivity and specificity in the living patients.

The clinical significance of our study demonstrated the need to monitor HDL-C levels and evaluate its relationship with inflammatory parameters in the management of COVID-19 patients. Elevated HDL-C levels may reduce patients' inflammation levels, which may have a beneficial effect on the course of the disease.

Our study undoubtedly has some limitations. A specific patient population was studied in a single centre, and it is difficult to establish cause-effect relationships. We acknowledge that the retrospective nature of our study represents another limitation. In the future, larger sample sizes and randomised controlled trials may make a better contribution.

Conclusions

Our research shows that clinical outcomes can be derived from biochemical and haematological parameters in COVID-19 patients. Lower HDL-C concentrations and higher levels of NHR and hs-CRP were observed in deceased COVID-19 patients compared to living COVID-19 patients, which can be considered as potential markers for assessing the mortality risk of individuals. These results may help to improve clinical therapies in the management of COVID-19 patients.

Acknowledgments

Reference

1. Soylu M, Taşbakan M, Zeytinoğlu A, et al. Evaluation of a SARS-CoV-2 antigen test in the rapid diagnosis of COVID-19 suspected patients. Ege Tıp Dergisi. 2023; 62(2): 234-239.
2. Tuncar A, Sanmak E, Canbaz H, Beştemir A. Decision to Close a Factory in the COVID-19 Pandemic: Only One Hour of Work. Eurasian J Emerg Med. 2023;22(2): 88-92.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506.
4. Arabi YM, Murthy S, Webb S. COVID-19: a novel coronavirus and a novel challenge for critical care. Intensive care medicine. 2020:1-4.
5. Kaya O, Mermutlu IS. Monocyte-to-HDL cholesterol ratio as a new parameter of systemic inflammation and disease severity in treatment-resistant chronic spontaneous urticaria. J Basic Clin Health Sci 2023; 7: 501-506.
6. Sun JT, Chen Z, Nie P, et al. Lipid Profile Features and Their Associations With Disease Severity and Mortality in Patients With COVID-19. Front Cardiovasc Med (2020) 7:584987. doi: 10.3389/fcvm.2020.584987.
7. Wang Y, Zhang J, Li H, et al. Prognostic Value of Leucocyte to High-Density Lipoprotein-Cholesterol Ratios in COVID-19 Patients and the Diabetes Subgroup. Front Endocrinol (Lausanne). 2021;12:727419. doi: 10.3389/fendo.2021.727419.
8. Shi K, Hou J, Zhang Q, Bi Y, Zeng X, Wang X. Neutrophil-to-high-density-lipoprotein-cholesterol ratio and mortality among patients with hepatocellular carcinoma. Front Nutr. 2023;10:1127913. doi: 10.3389/fnut.2023.1127913.
9. Huang Y, Jiang B, Miao X, et al. The Relationship of Lymphocyte to High-Density Lipoprotein Ratio With Pulmonary Function in COPD. Int J Chron Obstruct Pulmon Dis .2020;15:3159–69.
10. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782–793.
11. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. Cardiovasc Res. 2014 ;103(3):372-83.
12. Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. Ann Am Thorac Soc. 2015;12:765. doi: 10.1513/ANNALSATS.201411-507FR.
13. Tanaka S, Couret D, Tran-Dinh A, et al. High-density lipoproteins during sepsis: from bench to bedside. Crit Care. 2020;24(1):134. doi: 10.1186/s13054-020-02860-3.
14. Chidambaram V, Shanmugavel Geetha H, Kumar A, et al. Association of Lipid Levels With COVID-19 Infection, Disease Severity and Mortality: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2022;9:862999. doi: 10.3389/fcvm.2022.862999.
15. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol. 2020; 92(11):2409-2411.
16. Stringer D, Braude P, Myint PK, et al. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol. 2021;50(2):420-429.
17. Calle MC, Vega-López S, Segura-Pérez S, Volek JS, Pérez-Escamilla R, Fernandez ML. Low Plasma Hdl Cholesterol and Elevated C Reactive Protein further Increase Cardiovascular Disease Risk in Latinos with Type 2 Diabetes. J Diabetes Metab. 2010;1:109. doi: 10.4172/2155-6156.1000109.
18. Verma S, Husain M, Madsen CM, et al. Neutrophil to lymphocyte ratio predicts cardiovascular events in people with type 2 diabetes: Post hoc analysis of the SUSTAIN 6 and PIONEER 6 cardiovascular outcomes trials. Diabetes Obes Metab. 2023;25(8):2398-2401.
19. Ren H, Zhu B, Zhao Z, et al. Neutrophil to high-density lipoprotein cholesterol ratio as the risk mark in patients with type 2 diabetes combined with acute coronary syndrome: a cross-sectional study. Sci Rep. 2023;13(1):7836. doi: 10.1038/s41598-023-35050-6.
20. Jiang M, Sun J, Zou H, et al. Prognostic Role of Neutrophil to High-Density Lipoprotein Cholesterol Ratio for All-Cause and Cardiovascular Mortality in the General Population. Front Cardiovasc Med. 2022;9:807339. doi: 10.3389/fcvm.2022.807339.
21. Huang JB, Chen YS, Ji HY, et al. Neutrophil to high-density lipoprotein ratio has a superior prognostic value in elderly patients with acute myocardial infarction: a comparison study. Lipids Health Dis. 2020;19(1):59. doi: 10.1186/s12944-020-01238-2.
22. Tong C, Chen H, Xiao H, et al. Comparison of the value of neutrophil to high-density lipoprotein cholesterol ratio and lymphocyte to high-density lipoprotein cholesterol ratio for predicting metabolic syndrome among a population in the Southern Coast of China. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020;13:597-605.
23. Köseoğlu D, Özdemir Başer Ö, Çetin Z, Çatlak M. Monocyte and neutrophil to high density lipoprotein cholesterol ratios are elevated in patients with vitamin D deficiency. J Health Sci Med. 2022;5(1):119-123.
24. Coşkun B, Ayhan M, Sarıcaoğlu EM, et al. The Evaluation of Relationship Between Monocyte/High-Density Lipoprotein Ratio (MHR) and COVID-19. Konuralp Medical Journal. 2022;14(2):386-390.

Evaluation of the Performance of Sentinel Lymph Node and Imaging Methods, USG, MRI, and PET CT in Breast Cancer

Meme Kanserinde Sentinel Lenf Nodu ve Görüntüleme Yöntemleri Olan USG, MR ve PET CT' nin Performanslarının Değerlendirilmesi

Ferdi CAMBAZTEPE* 0000-0003-4754-776X

Müfide Nuran AKÇAY** 0000-0001-8470-1741

Metin YILDIZ*** 0000-0002-8180-2827

* İstanbul Sağlık Bilimleri üniversitesi Haydarpaşa Numune Eğitim ve Araştırma hastanesi Genel Cerrahi Kliniği

**Atatürk Üniversitesi Tıp Fakültesi Genel cerrahi Ana Bilim Dalı

*** Atatürk Üniversitesi Tıp Fakültesi Genel cerrahi Ana Bilim Dalı

Yazışma Adresi: Ferdi CAMBAZTEPE

İstanbul Sağlık Bilimleri Üniversitesi Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği

E-mail adresi: drferdictepe@gmail.com

Öz

Amaç: Meme kanserinde metastatik lenf nodu tutulumu, hastalığın genel evresi ve prognozunun önemli bir belirleyicisidir. Aksillanın değerlendirilmesinde görüntüleme yöntemleri yeterli olmayabilir. Sentinel lenf nodu örneklemesi (SLNS), nod negatif meme kanserli hastalarda aksiller evreleme için yaygın olarak kullanılmaktadır. Metilen mavisi yöntemiyle sentinel lenf bezi örneklemesi, uygulama kolaylığı ve düşük maliyeti nedeniyle önem kazanmıştır.

Yöntemler: 2016-2021 yılları arasında 238 meme kanserli hastanın ameliyat öncesi görüntüleme yöntemleri ve metilen mavisi yöntemiyle sentinel lenf nodu örneklemesi sonuçları analiz edildi.

Sonuçlar: Metilen mavisi yöntemiyle Sentinel lenf nodu örneklemesinin duyarlılığı %98, özgüllüğü ise %98 idi. Ameliyat öncesi aksiller görüntülemede ultrasonografinin duyarlılığı %48, özgüllüğü %75 idi. Ameliyat öncesi aksiller görüntülemede manyetik rezonans görüntülemenin duyarlılığı %50, özgüllüğü %61 idi. Ameliyat öncesi aksiller görüntülemede pozitron emisyon bilgisayarlı tomografinin duyarlılığı %52, özgüllüğü %70 idi.

Tartışma: Aksillaya cerrahi yaklaşımda preoperatif ve perioperatif değerlendirme çok önemlidir. Görüntüleme yöntemleri henüz yeterince hassas değildi. Metilen mavisi yöntemi ile sentinel lenf nodu örneklemesi koltuk altı için yeterli duyarlılık ve özgüllüğe sahiptir.

Anahtar Kelimeler: Metilen mavisi,sentinel lenf nodu,meme kanseri

Abstract

Purpose Metastatic lymph node involvement in breast cancer's a key determinant of the overall stage of disease and prognosis. Imaging methods may not be sufficient to evaluate the axilla. Sentinel lymph node sampling (SLNS) is widely used for axillary staging in patients with node-negative breast cancer. Sentinel lymph node sampling with the methylene blue method has gained importance due to its ease of application and low cost.

Methods The results of preoperative imaging methods and sentinel lymph node sampling with methylene blue method of 238 patients with breast cancer between 2016-2021 were analyzed.

Results Sentinel lymph node sampling with methylene blue method had a sensitivity of 98% and a specificity of 98%. In preoperative axillary imaging, the sensitivity of ultrasonography was 48% and the specificity was 75%.

Evaluation of the Performance of Sentinel Lymph Node and Imaging Methods, USG, MRI, and PET CT in Breast Cancer

Meme Kanserinde Sentinel Lenf Nodu ve Görüntüleme Yöntemleri Olan USG, MR ve PET CT' nin Performanslarının Değerlendirilmesi

In preoperative axillary imaging, the sensitivity of magnetic resonance imaging was 50% and the specificity was 61%. In preoperative axillary imaging, the sensitivity of positron emission computed tomography was 52% and the specificity was 70%.

Conclusions

Preoperative and perioperative evaluation is very important for the surgical approach to the axilla. Imaging methods were not yet sensitive enough. Sentinel lymph node sampling with methylene blue method has enough sensitivity and specificity for axilla.

Keywords: Methylene blue- Sentinel lymph node- Breast cancer

Introduction

Breast cancer is the most common malignancy in women today [1]. Detection of axillary lymph node metastasis is very important for the staging, treatment and prognosis of the disease, as it is a locoregional disease that spreads through the lymphatic route. Axillary lymph node dissection leads to complications by disrupting the axillary anatomy. The most important complications of axillary lymph node dissection include pain, lymphedema and nerve damage. Sentinel lymph node sampling (SLNS) has reduced the need for axillary lymph node dissection [2,3]. Sentinel lymph node sampling is currently the most accurate method for axillary lymph node staging [4]. Sentinel lymph node can be sampled using the blue dye method, the gamma probe method or both methods.

Yang S. et al. stated in their study that only the blue dye method is sufficient for sentinel lymph node sampling. Emphasized its applicability in every institution because it does not require special equipment [5]. The purpose of imaging methods is to detect the presence of metastatic disease in palpable or nonpalpable axillary lymph nodes before surgery. Ultrasonography (USG), magnetic resonance imaging (MRI), and positron emission tomography (PET CT) can be used to visualize axillary adenopathy. Although different techniques are used, mainly morphological features are kept in the foreground. Ultrasonography is the most preferred method for evaluating axillary lymph nodes and performing image-guided lymph node interventions [6]. The present study aimed to provide a comprehensive overview of preoperative axillary lymph node status with sentinel lymph node sampling and imaging modalities.

Methods

Participants

We retrospectively reviewed 238 patients who were diagnosed with breast cancer and planned for surgery by us between January 2016-June 2021 at Atatürk University Faculty of Medicine, Department of General Surgery. The patients included in the study also had 4 criteria. These criteria were (1) being female, (2) histopathologically confirmed, diagnosed with in situ or invasive breast cancer, (3) breast-conserving surgery or mastectomy accompanied by sentinel lymph node sampling with methylene blue method. In addition, USG, MRI, PET CT images from preoperative imaging methods were scanned retrospectively.

Axillary lymph node involvement was evaluated. The sensitivity and specificity of the imaging methods were evaluated according to the pathology results after surgery.

Sentinel lymph node sampling surgical procedure

Sentinel lymph node sampling was performed with methylene blue method in all patients included in the study. In the method we applied, 5 ml of 1% isosulfan blue was given intraparenchymal in the lower-upper-medial-lateral of the areola. Massage was applied from the injection site to the axilla and waited for 5 minutes. An incision was made along the lower border of the axillary hairs, the outer edge of the pectoralis major, and the anterior edge of the latissimus dorsi. Then, the blue stained lymph vessels were observed by going deep into the axillary fascia. If a blue stained lymph node was detected during the procedure, it was considered successful.

Sentinel lymph node sampling and pathological evaluation

The SLNS procedures were standardized according to the College of American Pathologists (CAP) recommended techniques [7]. According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th Edition),[8] the total number of SLNs detected should be <6. A positive SLN was defined as a macrometastatic (maximum diameter of metastatic lesion >2.0 mm) or micrometastatic SLN (maximum diameter of metastatic lesion >0.2 and ≤2.0 mm and/or >200 tumor cells in a section). A negative SLN was defined as one lacking tumor cells or with isolated tumor cells (maximum diameter of metastatic lesion ≤0.2 mm and ≤200 tumor cells in a section).

Imaging methods

The files of the patients were scanned retrospectively. Axillary evaluations of the patients who were evaluated with USG, MRI, and PET CT were compared with the results of sentinel lymph node biopsy.

Ethical approval

Approval for this study in accordance with Declaration of Helsinki was obtained from the Ethics Committee of Erzurum Atatürk University Faculty of Medicine (No: B.30.2.ATA.0.01.00/837).

Statistical analysis

Categorical variables were presented as numbers (percentages) and analyzed using Chi-squared test or Chi-squared test with Yates' continuity correction. SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A two-sided $p<0.05$ was considered statistically significant.

166 patients did not receive neoadjuvant therapy, 72 patients received neoadjuvant therapy. Mastectomy was performed in 162 patients and breast-conserving surgery was performed in 76 patients. USG was performed in 143 patients, MRI was performed in 127 patients and PET CT was performed in 152 patients preoperatively.

When the pathologies of the patients were examined, ductal carcinoma in situ 11, invasive ductal carcinoma 156, invasive lobular carcinoma 20, mixed type carcinoma 22, epithelial tumor 2, cribriform tumor 2, mucinous type tumor 3, papillary type tumor 2, metastatic tumor 2, no tumor tissue 18 the patient has been identified.

Sentinel lymph node sampling was evaluated peroperatively with frozen section. Axillary lymph node dissection was performed in patients with lymph nodes compatible with macrometastases. Axillary dissection was not performed on patients with lymph nodes compatible with micrometastasis and isolated tumor cells. For sentinel lymph nodes that could not be clearly evaluated in the frozen section, the decision was made according to the final pathology result. Axillary lymph node dissection was performed as the second session in patients who were compatible with macrometastasis.

Results

We retrospectively analyzed 238 female patients who were diagnosed with breast cancer in the last 5 years and underwent surgical methylene blue and sentinel lymph node sampling. Mastectomy or breast conserving surgery was performed in the same session. The mean age of the patients was 53±11, the youngest age was 23, the oldest was 84, and the median age was 52. The mean age of patients with positive sentinel lymph nodes was 52.93, and the mean age of patients with sentinel lymph nodes was 53.3. Neoadjuvant therapy was not applied to 166 patients (69.7%), and 72 patients (30.3%) received neoadjuvant therapy. Of the patients who did not receive neoadjuvant therapy, 143 (86.1%) sentinel lymph nodes were negative, and 23 (13.9%) sentinel lymph nodes were positive. Sentinel lymph node was positive in 18 (25%) of 72 patients who received neoadjuvant therapy. Sentinel lymph node was negative in 54 (75%) of 72 patients who received neoadjuvant therapy. Mastectomy was performed in 162 patients (68.1%), and breast-conserving surgery was performed in 76 patients (31.9%).

When the pathologies of the patients were examined, ductal carcinoma in situ 11 (4.6%), invasive ductal carcinoma 156 (65.5%), invasive lobular carcinoma 20 (8.4%), mixed type carcinoma 22 (9.2%), epithelial tumor 2 (0.8%). cribriform tumor 2 (0.8%), mucinous type tumor 3 (1.3%), papillary type tumor 2 (0.8%), metastatic tumor 2 (0.8%). 18 patients (7.6%) had no tumor tissue as a result of pathology.

An average of 2.1 lymph nodes were removed in sentinel lymph node sampling. In 41 (17.2%) patients, macrometastasis was detected in the sentinel lymph node frozen section and axillary lymph node dissection was performed. An average of 17.2 lymph nodes were removed in axillary lymph node dissections. The mean number of metastatic lymph nodes removed was 3.06.

Metastasis was not detected as a result of axillary dissection in 1 of 41 patients who underwent sentinel lymph node sampling and whose results were positive. Micrometastases were detected in 9 of 197 patients who were evaluated as negative in sentinel lymph node sampling, and isolated tumor cells were detected in 5 of them. Axillary lymph node dissection was not performed in these patients.

Macrometastasis was detected in the sentinel lymph node as a result of the final pathology of 3 patients who were accepted as sentinel lymph node negative on frozen section. Axillary dissection was performed in the second session in 2 patients with macrometastases. Axillary dissection was not performed on her own request and one patient was followed up. According to these results, the sensitivity and specificity of sentinel lymph node sampling with the methylene blue method was 98% and 98%.

Preoperatively, USG was performed in 143 patients, MRI was performed in 127 patients, and PET CT was performed in 152 patients to evaluate the breast and axilla before surgery.

Sentinel lymph node was evaluated as positive in 10 of 41 patients with axillary metastases as a result of USG. Sentinel lymph node was positive in 11 of 101 patients whose axilla was evaluated as negative as a result of USG. According to these results, the sensitivity of USG was 48% and the specificity was 75%. The results of statistical analyzes for USG are shown in Table-1.

Sentinel lymph node was evaluated as positive in 10 of 52 patients with axillary metastases detected by MRI. Sentinel lymph node was positive in 10 of 75 patients whose axilla was evaluated as negative in MRI. According to these results, the sensitivity of MR was 50% and the specificity was 61%. The results of statistical analyzes for MRI are shown in Table-1.

Sentinel lymph node was evaluated as positive in 13 of 51 patients with axillary metastases as a result of PET CT. Sentinel lymph node was positive in 12 of 101 patients whose axilla was evaluated as negative as a result of PET CT. According to these results, the sensitivity of Pet CT was 52% and the specificity was 70%. The results of statistical analyzes for PET CT are shown in Table-1.

Evaluation of the Performance of Sentinel Lymph Node and Imaging Methods, USG, MRI, and PET CT in Breast Cancer

Meme Kanserinde Sentinel Lenf Nodu ve Görüntüleme Yöntemleri Olan USG, MR ve PET CT' nin Performanslarının Değerlendirilmesi

Table 1. Diagnostic value of imaging methods

	Status of sentinel lymph node							
	Positive	Negative						
			Sensitivity (%)	Specificity (%)	PPV	NPV	LR+	LR-
USG Positive	10	31	48%	75%	0.24	0.89	1.87	0.70
USG Negative	11	91						
MRI Positive	10	42	50%	61%	0.19	0.87	1,27	0.82
MRI Negative	10	65						
PET CT Positive	13	38	52%	70%	0.25	0.88	1.74	0.68

LR+ positive likelihood ratio, LR- negative likelihood ratio, PPV Positive predictive value, NPV negative predictive value USG ultrasonography, MRI magnetic resonance imaging, PET CT positron emission tomography

1 patient had positive axilla in USG, MR, Pet CT and sentinel lymph node sampling were evaluated as negative. However, the sentinel lymph node was evaluated as positive in the final pathology of the patient and axillary dissection was performed in the second session for the patient. 1 patient had positive axilla in MRI and Pet CT evaluation, and sentinel lymph node sampling was negative. however, her axilla was evaluated as positive in the final pathology result and axillary dissection was performed in the second session.

Discussion

Axillary lymph node involvement affects both prognosis and staging in breast cancer. Therefore, preoperative evaluation of the axilla is very important today. Guidelines implemented by the National Comprehensive Cancer Network (NCCN) and the Chinese Anti-Cancer Society generally adopted SLNB as the standard procedure for evaluating axillary lymph nodes [9]. As seen in the AMAROS and ACOSOG studies, the rate of axillary dissection decreased with sentinel lymph node sampling [10-11]. Methylene blue method or gamma probe marking methods are frequently used among sentinel lymph node sampling methods.

In our study, we applied sentinel lymph node sampling with the methylene blue method as a standard. In the literature, Gupta et al. found that the sensitivity and specificity of sentinel lymph node sampling with only methylene blue were 75% and 95.45% [12]. Brahma et al. conducted a similar study with 92% sensitivity and 100% specificity in a study they conducted on 96 patients in 2017 [13].

In our study, we evaluated the sensitivity of the sentinel lymph node sampling with the methylene blue method as 98% and the specificity as 98%. These results were found in agreement with the literature. We argue that the methylene blue method is more advantageous because of its practicality, fast learning process and cost-effectiveness compared to other methods.

The use of USG in preoperative imaging of the axilla can detect suspicious lymph nodes in clinically node-negative patients. Kim WH et al. stated that preoperative axillary USG is a frequently performed procedure in patients diagnosed with primary breast cancer [14]. Cools-Lartigue et al. in their study, they evaluated the sensitivity of axillary node metastases as 55% and the specificity as 88% by using axillary USG alone [15]. Singh SP et al. according to the results of his study, after the evaluation of the axilla with preoperative USG, its sensitivity was 50% and its specificity was 100% [16]. In the literature, the sensitivity of axillary USG has been evaluated between 48.8%-87.1% and the specificity between 55.6-97.3% [17]. In our study, the sensitivity and specificity of preoperative axillary USG was 48% and 75%. When we look at the literature, it is thought that the accuracy of USG is moderate. However, in clinical use, percutaneous biopsy with USG and evaluation of blood flow with doppler are advantageous. The disadvantage is that it is highly dependent on the person doing it and the learning process is long. It requires experience.

Evaluation of the axilla with MRI in breast cancer has been shown to improve its accuracy with the use of a special axillary MRI array [17]. Schipper RJ et al. In the study, it was reported that the sensitivity of the axilla was evaluated by MRI as 64% and the specificity was 94% [18]. Yamaguchi K et al. In his study, it was seen that the sensitivity of MRI in the evaluation of the axilla was 85% and the specificity was 81%. In the literature, the sensitivity of axillary MRI has been evaluated between 75%-80% and specificity between 89-91% [17]. In our study, the sensitivity and specificity of axillary MRI performed preoperatively were 50% and 61%. Differences in MRI systems, differences with or without contrast injection, and the histological subtypes of metastatic lymph nodes examined change the sensitivity of MRI evaluation of the axilla. In breast cancer, MRI is a method that can show the anatomy of the breast and axilla and the localization of the pathology. In addition, MRI allows evaluation of the inner breast and full visualization of the entire axilla with contralateral axilla comparison. Disadvantages include high cost, difficulty in accessing, length of examination time and necessity of being suitable for the patient (claustrophobia, use of contrast material, patient with metallic implants). The use of contrast agents that are more specific to axillary lymph nodes will allow MRI to be more specific and sensitive to metastases.

Axillary metastasis is also evaluated with PET CT, which is also used preoperatively in terms of distant metastases. In the study conducted by Kutluturk K et al, the sensitivity of PET CT in detecting axillary metastases was 72%, and the specificity was 77% [20]. In the study of Assi HI et al, the sensitivity of PET CT in detecting axillary metastases was 86%, and the specificity was 63% [21]. In our study, the sensitivity and specificity of PET CT performed preoperatively in axillary metastases was 52% and 70%. In the literature, the sensitivity of axillary PET CT has been evaluated between 59% and 69%, and the specificity between 90-95% [17]. In our study, it was seen that the number of patients was sufficient according to the literature, but metastasis dimensions were not specified. Tumor size is an important factor in detecting metastasis in PET CT. For the use of PET CT in the evaluation of the axilla, further studies with a large number of patients and the size of the lymph node with axillary metastases are required.

In conclusion, sentinel lymph node sampling with methylene blue method is seen to be more specific and sensitive than imaging methods such as USG, MRI, PET CT, both in our study and in other studies in the literature. Unnecessary axillary lymph node dissection can be performed in patients who are evaluated with preoperative imaging methods without sentinel lymph node sampling. In addition, treatment of metastatic axillary lymph nodes may be inadequate due to false negative results. We recommend sentinel lymph node sampling with the methylene blue method, which is inexpensive and easy to apply, in patients with breast cancer with negative axillary lymph nodes.

Evaluation of the Performance of Sentinel Lymph Node and Imaging Methods, USG, MRI, and PET CT in Breast Cancer

Meme Kanserinde Sentinel Lenf Nodu ve Görüntüleme Yöntemleri Olan USG, MR ve PET CT' nin Performanslarının Değerlendirilmesi

References

1-Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;**68**(6):394–424. doi:10.3322/caac.21492

2- Veronesi P, Corso G. Standard and controversies in sentinel node in breast cancer patients. *Breast*. 2019;48 Suppl 1:S53-S56. doi:10.1016/S0960-9776(19)31124-5

3- Land SR, Kopec JA, Julian TB, Brown AM, Anderson SJ, Krag DN, et al. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32 [published correction appears in J Clin Oncol. 2010 Dec 20;28(36):5350]. *J Clin Oncol*. 2010;28(25):3929-36. doi:10.1200/JCO.2010.28.2491

4- Garcia-Etienne CA, Ferrari A, Della Valle A, Lucioni M, Ferraris E, Di Giulio G, et al. Management of the axilla in patients with breast cancer and positive sentinel lymph node biopsy: An evidence-based update in a European breast center. *Eur J Surg Oncol*. 2020;46(1):15-23. doi:10.1016/j.ejso.2019.08.013

5- Yang S, Xiang HY, Xin L, Zhang H, Zhang S, Cheng YJ, et al. Retrospective analysis of sentinel lymph node biopsy using methylene blue dye for early breast cancer. *Chin Med J (Engl)*. 2021;134(3):318-25. Published 2021 Jan 11. doi:10.1097/CM9.0000000000001359

6- Singh R, Deo SVS, Dhamija E, Mathur S, Thulkar S. To Evaluate the Accuracy of Axillary Staging Using Ultrasound and Ultrasound-Guided Fine-Needle Aspiration Cytology (USG-FNAC) in Early Breast Cancer Patients-a Prospective Study. *Indian J Surg Oncol*. 2020;11(4):726-34. doi:10.1007/s13193-020-01222-3

7-Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*. 2009;133(10):1515-38. doi:10.5858/133.10.1515

8-Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-9. doi:10.3322/caac.21388

9- National Health Commission Of The People's Republic Of China. Chinese guidelines for diagnosis and treatment of breast cancer 2018 (English version). *Chin J Cancer Res*. 2019;31(2):259-77. doi:10.21147/j.issn.1000-9604.2019.02.02

10- Donker M, van Tienhoven G, Straver ME, Meijnen, P., van de Velde, C. J., Mansel, R. E., et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303-1310. doi:10.1016/S1470-2045(14)70460-7

11- Giuliano AE, Ballman KV, McCall L, Beitsch, P. D., Brennan, M. B., Kelemen, P. R., et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA*. 2017;318(10):918-26. doi:10.1001/jama.2017.11470

12- Gupta V, Raju K, Rao TS, Naidu, C. K., Goel, V., Hariharan, N., et al. A Randomized Trial Comparing the Efficacy of Methylene Blue Dye Alone Versus Combination of Methylene Blue Dye and Radioactive Sulfur Colloid in Sentinel Lymph Node Biopsy for Early Stage Breast Cancer Patients. *Indian J Surg Oncol*. 2020;11(2):216-22. doi:10.1007/s13193-019-01023-3

13- Brahma B, Putri RI, Karsono R, Andinata B, Gautama W, Sari L, et al. The predictive value of methylene blue dye as a single technique in breast cancer sentinel node biopsy: a study from Dharmais Cancer Hospital. *World J Surg Oncol*. 2017;15(1):41. Published 2017 Feb 7. doi:10.1186/s12957-017-1113-8

14-Kim WH, Kim HJ, Jung JH, Park HY, Lee J, Kim WW, et al. Ultrasound-Guided Fine-Needle Aspiration of Non-palpable and Suspicious Axillary Lymph Nodes with Subsequent Removal after Tattooing: False-Negative Results and Concordance with Sentinel Lymph Nodes. *Ultrasound Med Biol*. 2017;43(11):2576-81. doi:10.1016/j.ultrasmedbio.2017.07.011

15- Cools-Lartigue J, Sinclair A, Trabulsi N, Meguerditchian A, Mesurolle B, Fuhrer R, et al. Preoperative axillary ultrasound and fine-needle aspiration biopsy in the diagnosis of axillary metastases in patients with breast cancer: predictors of accuracy and future implications. *Ann Surg Oncol*. 2013;20(3):819-27. doi:10.1245/s10434-012-2609-7

16-Singh SP, Mishra SP, Gupta V, Singh SP, Gupta P, Verma RL, et al. To assess the feasibility and diagnostic accuracy of preoperative ultrasound and ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in patients of breast carcinoma. *J Family Med Prim Care*. 2022;11(1):133-38. doi:10.4103/jfmpc.jfmpc_2521_20

17-Marino MA, Avendano D, Zapata P, Riedl CC, Pinker K. Lymph Node Imaging in Patients with Primary Breast Cancer: Concurrent Diagnostic Tools. *Oncologist*. 2020;25(2):e231-e242. doi:10.1634/theoncologist.2019-0427

18- Schipper RJ, Smidt ML, van Roozendaal LM, Castro CJ, de Vries B, Heuts EM, et al. Noninvasive nodal staging in patients with breast cancer using gadofosveset-enhanced magnetic resonance imaging: a feasibility study [published correction appears in Invest Radiol. 2013 May;48(5):332]. *Invest Radiol*. 2013;48(3):134-139. doi:10.1097/RLI.0b013e318277f056

19- Yamaguchi K, Schacht D, Nakazono T, Irie H, Abe H. Diffusion weighted images of metastatic as compared with nonmetastatic axillary lymph nodes in patients with newly diagnosed breast cancer. *J Magn Reson Imaging*. 2015;42(3):771-778. doi:10.1002/jmri.24829

20- Kutluturk K, Simsek A, Comak A, Gonultas F, Unal B, Kekilli E. Factors affecting the accuracy of ^{18}F-FDG PET/CT in evaluating axillary metastases in invasive breast cancer. *Niger J Clin Pract*. 2019;22(1):63-68. doi:10.4103/njcp.njcp_198_18

21- Assi HI, Alameh IA, Khoury J, Bou Zerdan M, Akiki V, Charafeddine M, et al. Diagnostic Performance of FDG-PET/CT Scan as Compared to US-Guided FNA in Prediction of Axillary Lymph Node Involvement in Breast Cancer Patients. *Front Oncol*. 2021;11:740336. Published 2021 Oct 1. doi:10.3389/fonc.2021.740336

Evaluation Of The Relationship Between Epicardial Adipose Tissue Thickness And Extensity Of Coronary Artery Disease

Epikardiyal Yağ Dokusu Kalınlığı İle Koroner Arter Hastalığı Yaygınlığı Arasındaki İlişkinin Değerlendirilmesi

Elif ERGÜL* 0000-0003-3192-4719
Ali Gökhan ÖZYILDIZ** 0000-0003-0679-9434
Hüseyin DURAK* 0000-0002-8248-5966
Mustafa ÇETİN* 0000-0001-6342436X

* Department of Cardiology, Recep Tayyip Erdoğan University Faculty of Medicine, Rize, Turkey
** Department of Cardiology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Turkey

Abstract

Aim: The relationship between coronary artery disease (CAD) and epicardial adipose tissue (EAT) thickness has been demonstrated in many studies. In the present study, we evaluated the relationship between CAD extensity and the EAT using a newly developed formula.

Materials and Methods: The study population comprised stable angina pectoris patients with ischemic findings detected in non-invasive tests. Coronary angiography was performed to all patients and 53 patients with 20% or more stenosis in at least one coronary artery were included in the study.

Results: We found a significant correlation between EAT thickness with total CAD extensity score and coronary lesion length (p<0.01).

Conclusion: The EAT is associated with the extensity and severity of CAD, and measurement of it by transthoracic echocardiography may contribute to daily practice.

Keywords: Epicardial adipose tissue, coronary artery disease, scoring systems

Öz

Amaç: Koroner arter hastalığı (KAH) ile epikardiyal yağ dokusu (EAT) kalınlığı arasındaki ilişki birçok çalışmada gösterilmiştir. Bu çalışmada KAH yaygınlığı ile EAT arasındaki ilişkiyi yeni geliştirilen bir formül kullanarak değerlendirdik.

Gereç ve Yöntem: Çalışma popülasyonunu invaziv olmayan testlerde iskemik bulguları saptanan stabil anjina pektoris hastaları oluşturdu. Tüm hastalara koroner anjiyografi yapıldı ve en az bir koroner arterde %20 ve üzerinde darlığı olan 53 hasta çalışmaya dahil edildi.

Bulgular: Epikardiyal yağ dokusu kalınlığı ile KAH yaygınlığı skoru ve koroner lezyon uzunluğu arasında anlamlı bir korelasyon bulduk (p<0.01).

Sonuç: Epikardiyal yağ dokusu, KAH'ın yaygınlığı ve ciddiyeti ile ilişkilidir ve bu dokunun transtorasik ekokardiyografi ile ölçülmesi günlük pratiğe katkı sağlayabilir.

Anahtar Kelimeler: Epikardiyal yağ dokusu, koroner arter hastalığı, skorlama sistemleri

Corresponding Author: Ali Gökhan ÖZYILDIZ
Department of Cardiology, Recep Tayyip Erdoğan University
Training and Research Hospital, Rize, Turkey
Email: aligokhanozyildiz@gmail.com

Introduction

Coronary artery disease (CAD) is caused by decreased blood flow in the coronary arteries and is a potent cause of morbidity and mortality affecting millions of people. (1,2) It has association with cardiovascular risk factors such as hypertension, hyperlipidemia, smoking, obesity, gender, age, and family history. (3)

Recent studies have focused more on organ-specific adiposity rather than general obesity. Epicardial adipose tissue (EAT) is a visceral adipose tissue located between the myocardium and the inner layer of the pericardium. Due to the proximity between the myocardium and EAT, adipokines and proinflammatory molecules secreted by EAT can directly affect the metabolism of the heart and coronary arteries. Enlarged EAT in CAD patients has been reported in the literature. (4) Therefore, it has been suggested that EAT plays a role in the development and progression of cardiovascular diseases. (5)

The complexity of CAD and lesion features are predictors of periprocedural complications and long-term mortality. (6) Scoring systems and laboratory parameters are used to determine the severity of CAD. Syntax score and Gensini score are the most frequently used scoring systems and can predict prognosis and the necessity for revascularization. (7) Considering that these scores are insufficient to determine the total atherosclerotic burden, we used a formula developed for a study in which the relationship between carotid and brachial artery intima-media thickness and the extensity of CAD was evaluated (8). We aimed to examine the relationship between the extensity of CAD and EAT using the mentioned formula.

Methods

The present research is a cross-sectional single-center study. The study population comprised stable angina pectoris patients with ischemic findings detected in non-invasive tests. Coronary angiography was performed on all patients and 53 patients with 20% or more stenosis in at least one coronary artery were included in the study. The study was conducted under the principles of the Helsinki Declaration and was approved by the local ethics committee.

Acute coronary syndrome and a history of percutaneous coronary angioplasty or coronary artery bypass surgery were determined as exclusion criteria. Hypertension and hyperlipidemia were defined according to current guidelines. Body mass index (BMI) was calculated with the formula weight/height (cm)^2. Smoker was defined as smoking at least one cigarette per day.

Echocardiographic examination: Transthoracic echocardiography images of the patients were obtained with GE-Vingmed Vivid S5 (GE-Vingmed Ultrasound AS, Horten, Norway) device using a 2.5-3.5 MHz transducer. To determine the EAT thickness, the distance between the myocardium and visceral pericardium was measured parallel to the line passing through the aortic annulus and perpendicular to the right ventricular free wall in the parasternal long axis view. Measurements were made in the parasternal long axis, adjacent to the right ventricular free wall and close to the ventricular baseline, by freezing the image at the end of the diastole post three cardiac cycles. (9) To increase the analysis, acuity magnification was used in the measurements, and the EAT thickness was calculated in millimeters (Figure 1).
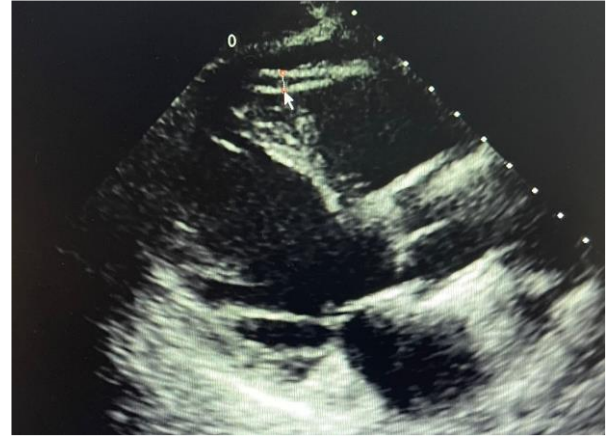
Figure 1: Long-axis parasternal view from transthoracic echocardiogram showing the epicardial fat over the free wall of the right ventricle

Coronary Angiography: Coronary angiography was performed by the Judkins method after femoral artery puncture. The extensity of CAD (CVI) was calculated using the newly developed formula (Figure 2). First, the length and osteal diameters of the three main coronary arteries were calculated. The lesion length, reference diameter, and narrowest diameter of the lesion were then measured for all lesions. The CVI for each coronary artery was calculated with the following formula; CVI LAD, CX, RCA = L1 (MNL x CLL x RD) + L2 +...+ Ln/COD x CVL (L, lesion; MNL, mean lesion stenosis; CLL, coronary lesion length; RD, reference diameter; COD, coronary osteal diameter; CVL, coronary artery length).

The total CVI was calculated with the following formula:

Total CVI = LAD (L1 + L2 +...+ Ln)/CVL LAD + CX (L1 + L2 +...+ Ln)/CVLCX + RCA (L1 + L2 +...+ Ln)/CVLRCA/COD LAD + CX + RCA.
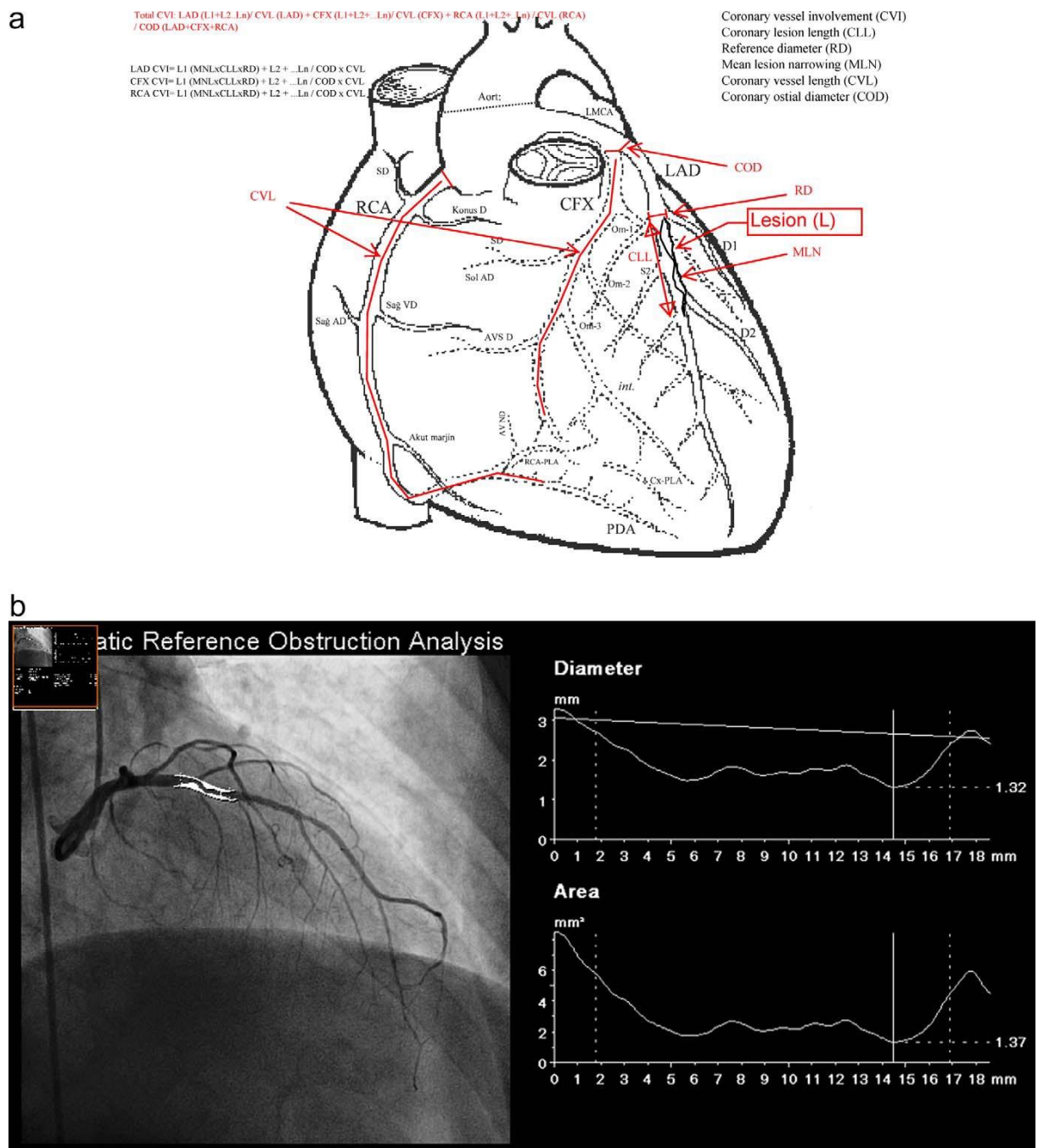
Figure 2. A: The calculation of diffuse coronary involvement score on coronary angiography. B: The calculation of mean coronary artery narrowing.

Statistical Analysis: SPSS (Statistical Package for Social Sciences) for Windows (Version 19.0, SPSS, Inc., Chicago, IL) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation) were used for evaluating the study data. Variables were analyzed using analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to determine the normal distribution of the data. Categorical variables were expressed as numbers and percentages, continuous variables were presented as mean±standard deviation.

Spearman's rho and Pearson correlation tests were used to examining the relationships between continuously variable parameters. Significance was defined as $p < 0.005$.

Results

The study included 53 patients (%26.4 of them were women) with a mean age of 61.7 years. The mean BMI was 29.42±4.39 kg/m^2, and the mean EAT thickness was 5.03±2.14 mm (Table 1).

Table 1: Demographic characteristics table

		Min-max	Mean±SD
Age		40-83	61,77±10,88
EAT (mm)		2,6-12,4	5,03±2,14
		n	%
Gender	Women	14	26,4
	Men	39	73,6
Hypertension	Var	36	67,9
	Yok	17	32,1
Smoker	Var	28	52,8
	Yok	25	47,2
Hyperlipidemia	Var	26	49,1
	Yok	27	50,9

EAT: Epicardial adipose tissue

There was no relation between EAT thickness with gender, smoking, hypertension, and low-density lipoprotein (LDL) levels. The EAT thickness was correlated with age (p<0.05) and significantly correlated with BMI and waist circumference (p<0.01, Figure 3).

There was a significant correlation between the CVI score with age (p<0.05) and waist circumference (p<0.01). The correlation associated with EAT thickness and CVI score is shown in Table 2 (Figure 4).
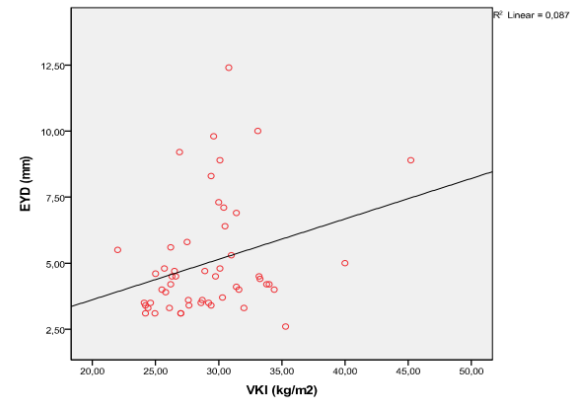
Figure 3: EAT thickness and BMI correlation graph
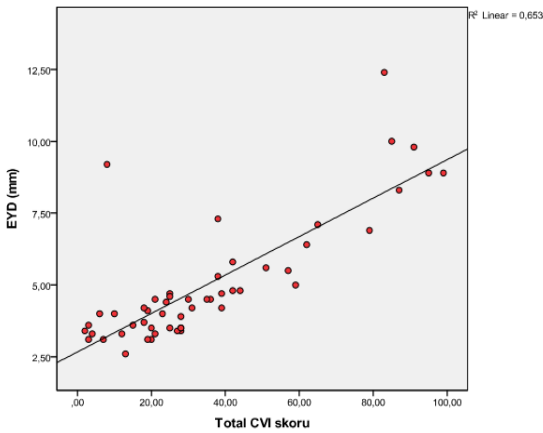
Figure 4 : EAT thickness and total CVI score correlation graph

Table 2: Correlations associated with EAT and Total CVI score

	EAT thickness (mm)		Total CVI score	
	r	p	r	p
Age	0.350	0.011*	0.441	0.001**
Body-mass index (kg/m2)	0.305	0.028*	0.238	0.086
LDL (mg/dl)	0.24	0.867	0.122	0.388
Waist circumference (mm)	0.405	0.003**	0.314	0.022*

r: Spearman's rho correlation test
*p<0.05 significancy level ** p<0.01 significancy level
LDL: Low-density lipoprotein

A significant correlation was found between EAT thickness with total CVI score and coronary lesion length (p<0.01, Table 3, Figure 5).

Table 3: Correlations associated with EAT and coronary artery involvement

	EAT thickness (mm)	
	r	p
LAD lesion	0.376	0.018*
Cx lesion	0.495	0.01*
RCA lesion	0.516	0.004*
Total CVI	0.785	0.000**

r: Spearman's rho correlation test
*p<0.05 significance level ** p<0.01high significancy level

LAD: Left anterior descending artery, Cx: Circumflex, RCA: Right coronary artery, CVI: Coronary vessel involvement
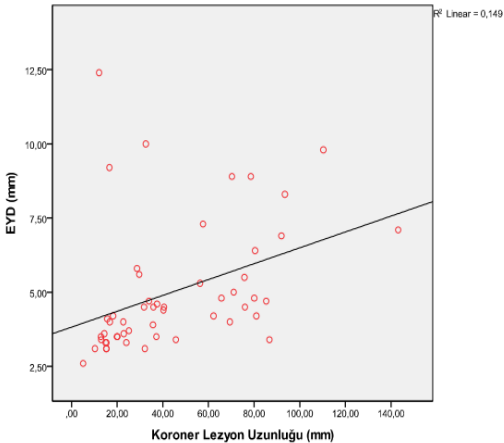
Figure 5: Correlation graph of EAT thickness and coronary lesion length

Discussion

We found a significant correlation between the CVI score and EAT thickness. This result supports the well-known relationship between EAT thickness and CAD. In addition, EAT thickness was associated with diffuse involvement in the coronary arteries rather than focal lesions.

The main cause of CAD is atherosclerosis, an inflammatory process that occurs with the accumulation of low-density lipoproteins in the arterial wall, and it remains the leading cause of mortality and morbidity worldwide. (10,11)

Epicardial adipose tissue acts as an endocrine organ to influence adjacent blood vessels via paracrine and endocrine signaling. (12,13) This tissue can cause atherosclerosis via mechanisms such as inflammation, oxidative stress, endothelial damage, adipocyte stress, lipid accumulation, and glucotoxicity. (14) The thicker the EAT, the more severe the coronary atherosclerosis, as the inflammatory activity would increase. (15)

In a large case-control study, MESA (Multi-Ethnic Study of Atherosclerosis), increased EAT thickness was associated with a higher risk of CAD in an adult without a history of cardiovascular disease. (16) This result supports the findings of our study.

Previous studies have reported correlations between EAT and commonly used scoring systems, such as Syntax and Gensini. (17,18) Erkan et al. showed that EAT was independently associated with the extensity and complexity of CAD, and predicted CAD, as indicated by Gensini and Syntax scores. (19) In a study conducted with the newly developed scoring system, a positive correlation was observed between the carotid and brachial artery intima-media thickness and the extensity of CAD. (8) In our study, based on the mentioned correlation, we showed a similar relationship between CAD extensity and EAT thickness.

There is a significant relationship between CAD, increased EAT, and Gensini scores in patients with positive exercise tests. Echocardiographic measurement of EAT predicts the severity and prevalence of CAD. (20) Picard et al. angiographically showed that EAT is associated with the presence and extensity of CAD in stable angina pectoris patients. (21)

Visceral obesity is one of the major risk factors for CAD. An increase in visceral adipose tissue is associated with accelerated atherosclerosis. (22) Among the available anthropometric measurements, waist circumference shows intra-abdominal adiposity ideally. Since EAT is not affected by subcutaneous adipose tissue, it is considered a good indicator of visceral adiposity and metabolic and cardiovascular risk associated with adiposity. (23) In the present study, a significant correlation was found between waist circumference with EAT and total CVI. This finding supports the reliability of EAT in demonstrating visceral adiposity, as previous researchers have reported. (24)

Current research has shown a significant correlation between age and EAT. (25) In our study, a significant correlation was found between age and CAD. This link between age and EAT may be due to the increased incidence of CAD with aging. Although previous studies have shown a correlation between LDL and EAT thickness, no relation was observed in the present study. (24) The reason for this may be the medical treatments used by the patients.

Limitations: Limited number of patients, operator-dependent transthoracic echocardiographic analyses, and not including other imaging methods in EAT measurement are the limitations of the study.

Conclusion

EAT is correlated with the extensity and severity of CAD, as assessed by coronary angiography. Measurements obtained by echocardiography, which is a non-invasive method, seem to be a practical method for estimating the extensity of CAD and lesion type in routine usage.

References

1. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A: Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016, 4:256. 10.21037/atm.2016.06.33 2.

2. Khera, A.V.; Kathiresan, S. Genetics of Coronary Artery Disease: Discovery, Biology and Clinical Translation. Nat. Rev. Genet. 2017, 18, 331–344

3. Wang Y, Li J, Zheng X, et al.: Risk factors associated with major cardiovascular events 1 year after acute myocardial infarction. JAMA Netw Open. 2018, 1:e181079. 10.1001/jamanetworkopen.2018.1079

4. Hajsadeghi, F.; Nabavi, V.; Bhandari, A.; Choi, A.; Vincent, H.; Flores, F.; Budoff, M.; Ahmadi, N. Increased Epicardial Adipose Tissue Is Associated with Coronary Artery Disease and Major Adverse Cardiovascular Events. Atherosclerosis 2014, 237, 486–489.

5. Camarena, V.; Sant, D.; Mohseni, M.; Salerno, T.; Zaleski, M.L.; Wang, G.; Iacobellis, G. Novel Atherogenic Pathways from the Differential Transcriptome Analysis of Diabetic Epicardial Adipose Tissue. Nutr. Metab. Cardiovasc. Dis. 2017, 27, 739–750

6. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219-227.

7. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. 1983;51(3): 606.

8. Çanga A, Kocaman SA, Durakoglugil ME, Çetin M, Erdogan T, Çiçek Y, Şatıroglu Ö. Increased carotid and brachial intima-media thickness is related to diffuse coronary involvement rather than focal lesions. Angiology. 2013 Jul;64(5):356-63. doi: 10.1177/0003319712445373. Epub 2012 May 13. PMID: 22584246.

9. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr. 2009;22(121):1311-1319.

10. Kalampogias A, Siasos G, Oikonomou E, Tsalamandris S, Mourouzis K, Tsigkou V, et al. Basic mechanisms in atherosclerosis: The role of calcium. Med Chem 2016; 12(2): 103-13.

11. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S: A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019, 234:16812-16823. 10.1002/jcp.28350

12. Gabriela, B.; Miksztowicz, V.; Morales, C.; Barchuk, M. Epicardial Adipose Tissue in Cardiovascular Disease. Adv. Exp. Med. Biol. 2019, 1127, 131–143

13. Gaborit, B.; Venteclef, N.; Ancel, P.; Pelloux, V.; Gariboldi, V.; Leprince, P.; Amour, J.; Hatem, S.N.; Jouve, E.; Dutour, A.; et al. Human Epicardial Adipose Tissue Has a Specific Transcriptomic Signature Depending on Its Anatomical Peri-Atrial, Peri-Ventricular, or Peri-Coronary Location. Cardiovasc. Res. 2015, 108, 62–73

14. Iacobellis, G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat. Rev. Endocrinol. 11, 363–371 (2015).

15. Mazurek, T. et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 108, 2460–2466 (2003).

16. Ding, J.; Hsu, F.-C.; Harris, T.B.; Liu, Y.; Kritchevsky, S.B.; Szklo, M.; Ouyang, P.; Espeland, M.A.; Lohman, K.K.; Criqui, M.H.; et al. The Association of Pericardial Fat with Incident Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis (MESA). Am. J. Clin. Nutr. 2009, 90, 499–504.

17. Wang T, Liu Q, Liu C, et al. Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease in patients with acute myocardial infarction. Echocardiography. 2014;31(10):1177-1181.

18. Kim SH, Chung JH, Kwon BJ, Song SW, Choi WS. The associations of epicardial adipose tissue with coronary artery disease and coronary atherosclerosis. Int Heart J. 2014;55(3): 197-203.

19. Erkan AF, Tanindi A, Kocaman SA, Ugurlu M, Tore HF. Epicardial adipose tissue thickness is an independent predictor of critical and complex coronary artery disease by Gensini and Syntax scores. Tex Heart Inst J. 2016;43(1):29-37.

20. Katlandur H, Ulucan Ş, Özdil H, Keser A, Kaya Z, Özbek K, Ülgen MS. Evaluation of Echocardiographic Epicardial Fat Thickness as a Sign of Cardiovascular Risk in Positive Exercise Test Patients. Acta Cardiol Sin. 2016 Nov;32(6):684-689. doi: 10.6515/acs20160110a. PMID: 27899855; PMCID: PMC5126446.

21. Picard FA, Gueret P, Laissy JP, et al. Epicardial adipose tissue thickness correlates with the presence and severity of angiographic coronary artery disease in stable patients with chest pain. PLoS One 2014;9:e110005.

22. Lakka TA, Lakka HM, Salonen R et al. Abdominal obesity associated with accelerated progression of carotid atherosclerosis in men. Atherosclerosis 2001; 154(2): 497-504.

23. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005;2:536-43.

24. Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, Yoon MH, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart 2008, 94:e7.

25. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003, 88:5163-5168.

KLİNİK ÇALIŞMA / CLINICAL TRIAL

Initial Experiences In The Novel Cryoablation System: From An Experience Of A Tertiary Center

Yeni Cryoablasyon Sisteminde 3. Basamak Bir Merkezin Ilk Deneyimleri

Muhammet Mucahit TIRYAKI* 0000-0003-4882-9072
Ugur KOCABAS** 0000-0001-9868-206X
Tuncay KIRIS** 0000-0001-9793-718X
Fatma KAYAALTI ESIN** 0000-0002-5129-4606
Mustafa KARACA** 0000-0002-5060-1045

* Department of Cardiology, Bulanik State Hospital, Bulanik, Mus, Turkiye
** Department of Cardiology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkiye

Corresponding Author: Muhammet Mucahit TIRYAKI
Department of Cardiology, Bulanik State Hospital, Bulanik, Mus, Turkiye Zafer, Yeni Hastane Caddesi, 49530 Bulanik, Mus
E-mail: mchttryk@gmail.com

Abstract

Background: The main approach to the ablation of atrial fibrillation (AF) is complete isolation of the pulmonary veins (PVs). Today, a new cryoablation system, known as the POLARx system (Boston Scientific), has started to be used for AF ablation. In this study, we compared the procedural efficacy and biophysical properties of the POLARx system and the Arctic Front Advance PRO (AFA-Pro)(Medtronic) system, which is currently used worldwide, in the experience of a tertiary center.

Methods: A total of 48 patients undergoing first-time cryoablation from January 2021 to May 2022 in our center were included in this study (POLARx: n = 26; AFA-Pro: n = 22).

Results: Acute success was achieved in all patients in both groups. POLARx was associated with a lower cryoballoon ablation (CBA) count per patient than AFA-Pro (6.1 vs 5, p = 0.003), and a lower ablation duration per patient (22.3 vs 17.2 min, p = 0.002). POLARx was also associated with a shorter time to balloon temperatures -30°C and -40°C, and a longer thawing time to 0°C for each pulmonary vein (each p < 0.05).

Conclusion: This study showed that the POLARx cryoablation system is comparable to AFA-Pro in terms of efficacy and safety and may be used for PVI.

Keywords: Atrial fibrillation, Cryoballoon, Cryoballoon ablation

Öz

Amaç: Atriyal fibrilasyonun (AF) ablasyonunda temel yaklaşım pulmoner venlerin (PV) tam izolasyonudur. Günümüzde AF ablasyonu için POLARx sistemi (Boston Scientific) olarak bilinen yeni bir kriyoablasyon sistemi kullanılmaya başlanmıştır. Bu çalışmada, POLARx sisteminin ve şu anda dünya çapında kullanılan Arctic Front Advance PRO (AFA-Pro) (Medtronic) sisteminin prosedürel etkinliğini ve biyofiziksel özelliklerini üçüncül bir merkezin deneyimi olarak karşılaştırdık.

Method: Merkezimizde Ocak 2021-Mayıs 2022 tarihleri arasında ilk kez kriyoablasyon uygulanan toplam 48 hasta çalışmaya dahil edildi (POLARx: n= 26; AFA-Pro: n = 22).

Bulgular: Her iki gruptaki tüm hastalarda akut başarı elde edildi. POLARx, hasta başına AFA-Pro'dan daha düşük kriyobalon ablasyon (CBA) sayısı (6.1'e karşı 5, p = 0.003) ve hasta başına daha düşük ablasyon süresi (22.3'e karşı 17.2 dakika, p = 0.002) ile ilişkiliydi. POLARx ayrıca -30 °C ve -40 °C balon sıcaklıklarına daha kısa bir sürede ulaşmakta ve her bir pulmoner ven için daha uzun bir çözülme süresinde 0 °C'ye ulaştığı tespit edildi. (her p < 0.05).

Sonuç: Bu çalışma, POLARx kriyoablasyon sisteminin etkinlik ve güvenlik açısından AFA-Pro ile karşılaştırılabilir olduğunu ve PVI için kullanılabileceğini göstermiştir.

Anahtar Kelimeler: Atrial fibrilasyon, Cryobalon, Cryobalon ablasyon

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia worldwide. Owing to the number of patients affected, it is the most common arrhythmic cause of morbidity and mortality. According to data from the Framingham Heart Study, the prevalence of AF has increased 3-fold over the last 50 years (1). Many studies have shown that AF is directly related to impaired quality of life, cerebrovascular events, and increased mortality and morbidity (2). Numerous studies have shown that catheter ablation is superior to antiarrhythmic drugs in reducing AF-related mortality and morbidity (3, 4).

The main approach to AF ablation is complete pulmonary vein isolation (PVI). Cryoballoon ablation has been shown to be as effective and safe as point-by-point radiofrequency (RF) ablation (5, 6). In addition, cryoballoon ablation has a lower processing time and is much less dependent on operator experience (7). The Arctic Front Advance PRO (AFA-Pro) (Medtronic) system is accepted as a reference system of cryoablation, owing to its many years on the market and successful results. Recently, however, the POLARx (Boston Scientific) cryoablation system has started to be used all over the world. According to the first experiences, this cryoballoon system seems as effective and safe as the AFA-Pro system; however, data on its biophysical parameters are limited (8-10). Indeed, parameters such as processing time, nadir balloon temperature, time to nadir temperature and thawing time are important predictors of successful intervention.

This study aimed to compare the procedural success, biophysical parameters and efficacy of the POLARx system with those of the currently established fourth-generation Arctic Front Advance Pro system.

Methods

Study population

This study was conducted by retrospective evaluation of symptomatic paroxysmal and persistent AF patients who underwent ablation with AFA-Pro system or POLARx system in a tertiary care center between January 2021 and May 2022.

We collected the clinical and procedural characteristics of the patients from the hospital's medical records and cryoballoon system records. Finally, 48 patients were included in the present study. These patients were divided into two groups: patients who underwent AF ablation with the AFA-Pro system (n = 22) and those who underwent AF ablation with the POLARx system (n = 26). Patients with a history of AF ablation were excluded from the study, as this may affect biophysical parameters. To exclude left atrial thrombi, we performed transesophageal echocardiography in all patients within 24 hours before ablation.

The primary end-point was defined as successful electrical isolation of all four veins during the procedure. Secondary outcomes were: ablation time, time-to-isolation (TTI), lowest temperature reached, number of veins isolated by means of a single cryoablation cycle, and complication rate.

Procedural Management

All ablation procedures were performed by the same operators, under local anesthesia and, if necessary, under sedation and analgesia. We used the standard femoral vein approach. A decapolar catheter was inserted into the coronary sinus and standard fluoroscopy-guided transseptal puncture was performed. The position of the transseptal sheath was controlled by means of iso-osmolar contrast after the puncture. After confirmation that the sheath was in the left atrium, intravenous unfractionated heparin was administered (100 UI/kg) in order to achieve an activated clotting time (ACT) of ≥300 s. The balloon system was advanced to the left atrium through a steerable sheath (15 F FlexCath, Medtronic; or 15.9 F POLARSHEATH™, Boston Scientific). The pulmonary veins were occluded consecutively. Vein occlusion was checked by means of contrast dye injection and classified by means of a grading system (Fig. 1) (11).

Figure 1: _Pulmonary veins' occlusion grades. A. Left Superior Pulmonary Vein B. Left Inferior Pulmonary Vein C. Right Superior Pulmonary Vein D. Right Inferior Pulmonary Vein_

When optimal PV occlusion had been achieved, cryoablation was initiated. During the ablation process, vein potentials were recorded in real time, whenever possible, by a circular wire catheter (Achieve™ or POLARMAP™). During cryoablation of the right-sided PVs, the phrenic nerve was paced by the diagnostic catheter, and diaphragmatic movements were closely monitored by palpation of the upper abdomen or, if the POLARx was used, by the motion sensor. When diaphragmatic movement was found to be reduced or the diaphragmatic movement sensor (DMS) was found to have fallen below a certain percentage (65%), cryoablation was stopped.

The duration of ablation was 180 s if the TTI was less than 60 s; otherwise, 240 s ablation was applied.

During ablation, real-time pulmonary vein recordings were examined. Mostly, pulmonary vein signals were dissociated with pulmonary vein isolation. However, in some procedures where this situation could not be observed, intrapulmonary vein records and atrial activity were evaluated by pacing over the right atrium, CS and appendix to distinguish between far-field recordings and pulmonary vein potencials. Entrance and exit block were checked to evaluate pulmonary vein isolation after ablation. The exit block was confirmed by the absence of atrial capture when the vein was stimulated by maximal outflow, and the entrance block was confirmed by the absence of simultaneous vein potentials when the atrium was stimulated.

All patients were checked for atrial fibrillation in the first and third months. In the third month of control, 24-hour Holter monitoring of rhythm was performed. All patients in both the AFA-Pro group and the POLARx group were followed up at least for 6 months after the ablation procedure.

This study was approved by the Ethics Committee of Izmir Katip Celebi University Ataturk Training and Research Hospital (374-25/08/22) and complied with the Declaration of Helsinki. This is a retrospective study and informed consent was waived.

Statistical Analysis

Statistical tests were carried out by means of SPSS version 26 (SPSS Inc., Chicago, IL, USA). Continuous variables were recorded as the mean ± minimum and maximum value, and categorical variables as the number of subjects and percentage of the total number. Either the Student's t-test or the Mann-Whitney U test was used to compare parametric values between the two groups, as appropriate. The Chi-square test was used to compare categorical variables.

Results

The dimension of the left atrium evaluated by 2D echocardiography was larger in the POLARx group than in the AFA-Pro group (POLARx: 43 mm vs. AFA-P: 39 mm, p = 0.034). Other baseline variables - age, sex, hypertension, diabetes mellitus, coronary artery disease, previous stroke, smoking, type of AF, left ventricular ejection fraction, CHA2DS2-VASc score, use of NOAC, use of antiarrhythmic agents and recurrence were similar between the groups (Table 1).

Table 1. Baseline patient characteristics

Variables	AFA-Pro n:22	POLARx n:26	P-value
Age mean (min-max)	56 (26-68)	59 (51-68)	0.520
Male gender n (%)	14 (64)	13 (50)	0.343
Hypertension n (%)	11 (50)	11 (50)	0.594
Diabetes mellitus n (%)	3 (14)	5 (19)	0.604
Coronary artery disease n (%)	2 (9)	2 (8)	0.861
Previous stroke n (%)	4 (18)	2 (8)	0.274
Smoking n (%)	5 (23)	2 (8)	0.309
Type of AF			0.158
Paroxysmal AF n (%)	15 (68)	14 (54)	
Chronic AF n (%)	5 (22.7)	10 (39)	
New-onset AF n (%)	2 (9)	2 (8)	
LVEF (%) (min-max)	59 (40-70)	58 (30-65)	0.700
LA dimension, mm mean (min-max)	39 (32-47)	43 (30-65)	0.034
CHA2DS2-VASc score mean (min-max)	1.7 (0-5)	1.8 (0-4)	0.800
Vitamin K antagonist n (%)	1 (5)	5 (19)	0.125
DOAC n (%)	10 (46)	13 (50)	0.450
Antiarrhythmic agents n (%)	20 (91)	19 (73)	0.112
Recurrance n (%)	2 (9)	3 (12)	0.826

Note: Variables are presented as mean value and minimum and maximum value or count (%)
Abbreviations: AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; NOAC, novel oral anticoagulants

All patients were undergoing their first AF ablation procedure. There was only one left common trunk; this was in an AFA-Pro patient. The primary end-point, namely acute success, was achieved in all patients in both groups. Complications were similar in both groups. POLARx was associated with a lower CBA count per patient than AFA-Pro (6.1 vs 5, p = 0.003) and a lower ablation duration per patient (22.3 vs 17.2 min, p = 0.002) (Fig 2).
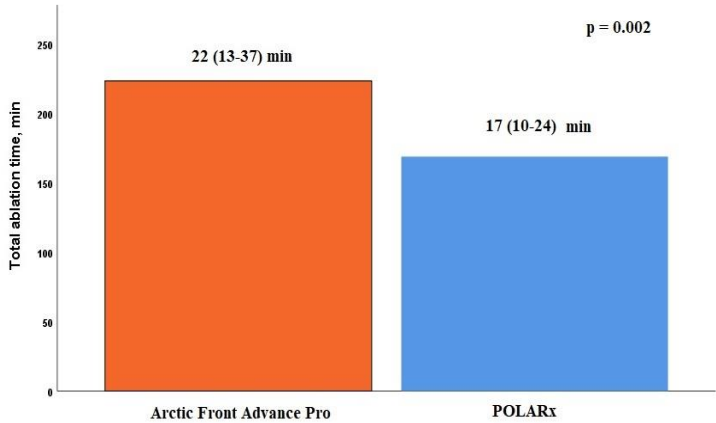
Figure 2: Total ablation times of the groups.

On comparing the procedures carried out on each pulmonary vein separately, POLARx was associated with a lower CBA count (1.9 vs 1.3, p = 0.036) per patient in the left inferior pulmonary vein. In terms of complications, no significant difference emerged between the two groups. One pericardial tamponade and two phrenic nerve palsies occurred in the AFA group. The patient with pericardial effusion underwent surgical intervention. Both phrenic nerve palsy patients recovered within 24 hours. In the POLARx group, pericardial tamponade occurred in one patient; no phrenic nerve palsy occurred. The pericardial effusion patient underwent percutaneous pericardiosynthesis. Procedural outcomes are presented in Table 2**.**

Figure 4 : EAT thickness and total CVI score correlation graph

Variables	AFA-Pro	POLARx	P-value
	n:22	n:26	
Total number of CBA n	135	123	
Number of CBA per patient mean (min-max)	6.1 (4-9)	5 (3-6)	0.003
Ablation time, minute mean (min-max)	22,3 (12,6-37,4)	17,2 (10-24)	0.002
Fluoroscopy time, min	15 (12,2-18,1)	14 (9,6-17,3)	0.576
Radiation dose, cGy*cm2	550 (392-785)	510 (312-696)	0.429
Contrast agent, ml	55 (37-62)	43 (27-61)	0.736
Left common ostium PV n (%)	1 (4.5)	0	
Number of CBA per patient mean (min-max)			
LSPV	1.4 (1-3)	1.2 (0-2)	0.479
LIPV	1.9 (1-5)	1.3 (0-2)	0.036
RSPV	1.3 (1-3)	1.4 (0-2)	0.718
RIPV	1.6 (1-3)	1.3 (0-2)	0.246
LCPV	2	0	
Ablation time, minute mean (min-max)			
LSPV	329 (255-550)	271 (87-480)	0.129
LIPV	392 (135-1032)	302 (180-480)	0.155
RSPV	296 (120-755)	266 (70-480)	0.485
RIPV	323 (75-696)	300 (180-480)	0.624
LCPV	523	0	
Complication			0,782
Pericardial Effusion n (%)	1 (5)	1 (4)	
Phrenic Nerve Palsy n (%)	2 (1)	0	

Note: Variables are presented as mean value and minimum and maximum value or count (%)
Abbreviations: CBA, cryoballoon ablation; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; RIPV, right inferior pulmonary vein; RSPV; right superior pulmonary vein

The balloon nadir temperature was lower in the POLARx group than in the AFA-Pro group. However, the difference was statistically significant only in left pulmonary veins (LSPV -58 vs -49°C, p < 0.001) (LIPV -55 vs -47°C, p = 0.002).

On the other hand, POLARx was associated with a shorter time to balloon temperatures -30°C and -40°C than AFA-Pro, and a longer thawing time to 0°C for each pulmonary vein (Table 3, each p < 0.05, Fig 3, 4).

Table 3. Comparison of procedural and biophysical parameters between POLARx and AFA-Pro

Variables	AFA-Pro n:22	POLARx n:26	P-value
Total number of CBA n	135	123	
Balloon nadir temperature (°C) mean (min-max)			
LSPV	-49 (-57/-37)	-58 (-69/-42)	< 0.001
LIPV	-47 (-68/-33)	-55 (-67/-47)	0.002
RSPV	-52 (-67/-35)	-57 (-69/-45)	0.084
RIPV	-48 (-70/-31)	-53 (-62/-44)	0.131
LCPV	-44	-	
Time to balloon temperature −30°C, s mean (min-max)			
LSPV	59 (33-108)	28 (22-35)	< 0.001
LIPV	60 (26-91)	29 (25-36)	< 0.001
RSPV	53 (31-86)	28 (24-35)	< 0.001
RIPV	58 (25-141)	30 (25-50)	< 0.001
LCPV	52	-	
Time to balloon temperature −40°C, s mean (min-max)			
LSPV	88 (49-248)	33 (24-50)	< 0.001
LIPV	104 (29-253)	35 (29-43)	< 0.001
RSPV	74 (43-131)	33 (27-47)	< 0.001
RIPV	92 (28-231)	39 (28-80)	0.001
LCPV	106	-	
Thawing time to 0°C, s mean (min-max)			
LSPV	11 (4-25)	23 (13-34)	< 0.001
LIPV	10 (4-29)	19 (13-25)	< 0.001
RSPV	11 (3-24)	22 (13-39)	< 0.001
RIPV	9 (4-28)	20 (11-35)	< 0.001
LCPV	8	-	
Grade of PV occlusion mean (min-max)			
LSPV	3.8 (3-4)	3.8 (3-4)	0.838
LIPV	3.5 (2-4)	4 (3-4)	0.441
RSPV	3.8 (3-4)	3.6 (3-4)	0.143
RIPV	3.6 (2-4)	3.4 (3-4)	0.278
LCPV	3	-	
TTI, s	44 (26-66)	37 (28-62)	0.218

Note: Variables are presented as mean value and minimum and maximum value or count (%)
Abbreviations: CBA, cryoballoon ablation; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein; RIPV, right inferior pulmonary vein; RSPV; right superior pulmonary vein
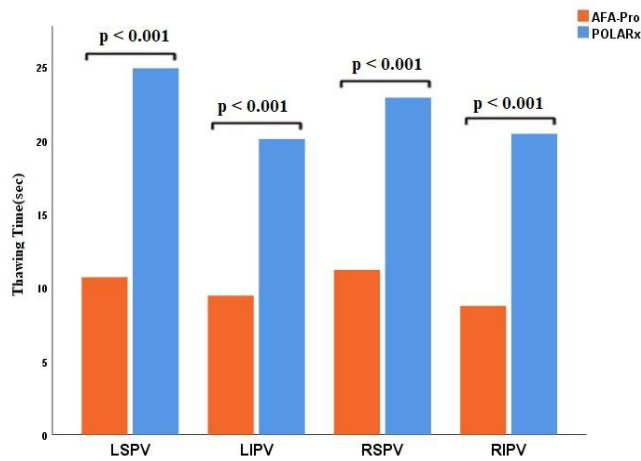
Figure 3: Thawing times of the groups.

Figure 4: The time it takes for the balloon temperature of the groups to reach -40 degrees

Discussion

In this study, the new POLARx cryoablation system was compared with the AFA-Pro system. We found that the POLARx system was similar to the AFA system in terms of efficacy and safety.

In cryoballoon ablation, balloon-tissue contact is important in order to achieve the desired effect. Therefore, pulmonary vein occlusion is an important factor in ensuring successful isolation in this technique. It is usually desirable to start ablation after grade 4 occlusion (12). In our study, there was no statistically significant difference between the 2 groups in terms of the degree of PV occlusion before ablation. Although the balloon characteristics of both systems look similar, there is a fundamental difference between the two systems, in that the POLARx system ensures an equal and consistent balloon size during the freezing phase. Therefore, only minimal thrust is required to ensure adequate balloon-to-tissue contact, which can protect from small slips of the balloon during the ablation phase. Accordingly, catheter manipulations during freezing and high forward push are not advised by the manufacturer of POLARx. Additionally the POLARx system the POLARx system is offered with a more flexible sheath compared to the AFA-Pro system. The greater flexibility of the POLARSHEATH™ introducer may facilitate vein cannulation and crossing of the interatrial septum. On the other hand, the caliber of the sheath is larger, so this may be safer in the AFA-Pro group for small vessels.

It is thought that the POLARx system may cause prolongation of the procedures during the learning period due to its features such as the new console system, more flexible sheath, foot pedal etc. However, contrary to what was predicted, it was determined that this situation did not cause any procedural prolongation.
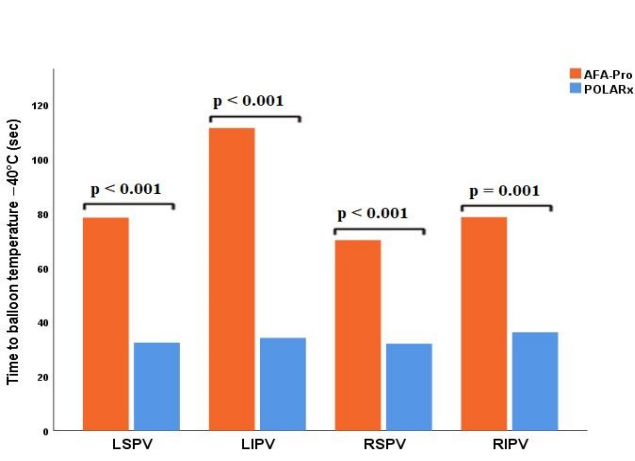
We found that, although all vessels were 100%isolated, the CBA count for each vein was lower in the POLARx group than in the AFA-Pro group. Likewise, the total ablation time was shorter in the POLARx group. Similarly, Tilz et al. and Mojica et al. found a shorter procedure time with POLARx (13, 14).

This may have been because the POLARx group had a shorter TTI but the difference was not statistically significant. Prospective studies involving a larger number of patients may be needed to elucidate this condition.

The POLARx system reached effective ablation temperatures in a shorter time and reached a lower minimum temperature. Although there was a difference between the groups in terms of these parameters, TTI was similar in both groups, as reported in other studies (8, 10). Other studies have shown that TTI is the most important predictor of durable PV isolation (12). As a result of these findings, similar tissue damage is thought to occur at similar times. Although the position of the thermocouple is similar in the two systems, it is located differently during the freezing phase, perhaps owing to the balloon complaint. On the other hand, it is matter to understand that the measured balloon inner temperature is not the same as the surface balloon temperature. Moreover, previous studies have shown that the POLARx system has a longer thawing time to 0°C, as found in our study (8-10). A longer thaw time may predict more tissue damage and more effective CBA (12). This may not show direct success, however, it may be a marker of more effective ablation.

After the introduction of a new technology, it is one of the first concerns to know whether the device is safe or not all over the world. In a meta-analysis, the frequency of phrenic nerve palsy was found to be similar in both systems. Another new feature of the POLARx system is the DMS. This sensor enables the movement of the diaphragm to be displayed as a percentage on the ablation monitor, which is not the case in conventional techniques. This may enable the number of diaphragmatic palsies to be reduced.

Limitations

Our study has several limitations. Firstly, as it was a single-center retrospective study, its findings should be interpreted in the light of the common limitations of retrospective studies. Secondly, the follow-up period was short.

Moreover, there were few patients in both groups. Finally, as esophageal temperatures during the freezing phase could not be measured, we cannot provide insight into how the POLARx system affects the esophagus at the lowest balloon temperatures.

Conclusions

This study showed that the POLARx cryoablation system is comparable to AFA-Pro in terms of efficacy and safety and may be used for PVI. However, these findings need to be investigated through further studies.

Abbreviations
AF: Atrial fibrillation
ACT: Activated clotting time
AFA-Pro: Arctic Front Advence PRO
CBA: Cryoballoon ablation
DMS: Diaphragmatic movement sensor
LA: Left atrium
LCPV: Left common pulmonary vein
LIPV: Left inferior pulmonary vein
LSPV: Left superior pulmonary vein
LVEF: Left ventricular ejection fraction
NOAC: Novel oral anticoagulants
PV: Pulmonary vein
PVI: Pulmonary vein isolation
RF: Radiofrequency
RIPV: Right inferior pulmonary vein
RSPV: Right superior pulmonary vein
TTI: Time to isolation

References

1. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet. 2015; 386:154–162. https://doi.org/10.1016/S0140-6736(14)61774-8

2. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014 Jun 16;6:213-20. https://doi.org/10.2147/CLEP.S47385.

3. Packer DL, Mark DB, Robb RA, et al. CABANA Investigators. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 Apr 2;321(13):1261-1274. https://doi.org/10.1001/jama.2019.0693.

4. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012 Oct 25;367(17):1587-95. https://doi.org/10.1056/NEJMoa1113566.

5. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021 Feb 1;42(5):373-498. https://doi.org/10.1093/eurheartj/ehaa612.

6. Andrade JG, Deyell MW, Verma A, et al. The Cryoballoon vs Irrigated Radiofrequency Catheter Ablation (CIRCA-DOSE) Study Results in Context. Arrhythm Electrophysiol Rev. 2020 Jun 3;9(1):34-39. https://doi.org/10.15420/aer.2019.13. PMID: 32637118; PMCID: PMC7330729.

7. Providencia R, Defaye P, Lambiase PD, et al. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? Europace. 2017 Jan;19(1):48-57. https://doi.org/10.1093/europace/euw080.

8. Assaf A, Bhagwandien RE, Szili-Torok T, et al. Comparison of the acute outcome of two cryoballoon technologies for pulmonary vein isolation: An updated systematic review and meta-analysis. Int J Cardiol Heart Vasc. 2022 Sep 5;42:101115. https://doi.org/10.1016/j.ijcha.2022.101115.

9. Guckel D, Lucas P, Isgandarova K, et al. News from the Cold Chamber: Clinical Experiences of POLARx versus Arctic Front Advance for Single-Shot Pulmonary Vein Isolation. J Cardiovasc Dev Dis. 2022 Jan 8;9(1):16. https://doi.org/10.3390/jcdd9010016.

10. Yap SC, Anic A, Breskovic T, et al. Comparison of procedural efficacy and biophysical parameters between two competing cryoballoon technologies for pulmonary vein isolation: Insights from an initial multicenter experience. J Cardiovasc Electrophysiol. 2021 Mar;32(3):580-587. https://doi.org/10.1111/jce.14915.

11. Neumann T, Vogt J, Schumacher B, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008 Jul 22;52(4):273-8. https://doi.org/10.1016/j.jacc.2008.04.021.

12. Aryana A, Mugnai G, Singh SM, et al. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm. 2016 Feb;13(2):424-32. https://doi.org/10.1016/j.hrthm.2015.10.033.

13. Tilz RR, Meyer-Saraei R, Eitel C et al. Novel Cryoballoon Ablation System for Single Shot Pulmonary Vein Isolation - The Prospective ICE-AGE-X Study. Circ J. 2021 Jul 21;85(8):1296-1304. doi: 10.1253/circj.CJ-21-0094. Epub 2021 Apr 13. PMID: 33854004.

14. Mojica J, Lipartiti F, Al Housari M et al. Procedural Safety and Efficacy for Pulmonary Vein Isolation with the Novel Polarx™ Cryoablation System: A Propensity Score Matched Comparison with the Arctic Front™ Cryoballoon in the Setting of Paroxysmal Atrial Fibrillation. J Atr Fibrillation. 2021 Jun 30;14(1):20200455. doi: 10.4022/jafib.20200455. PMID: 34950358; PMCID: PMC8691321.

Evaluation Of Attention And Perception Test In Patients Diagnosed With Acute Lymphoblastic Leukemia Who Have Completed Treatment

Akut Lenfoblastik Lösemi Tanısı İle Tedavisi Biten Hastaların Dikkat Ve Algı Testi İle Değerlendirilmesi

Ömer AKÇAL* 0000-0002-3046-7133

Gönül AYDOĞAN**0000-0002-3805-531X

*Istanbul Biruni Univesity Medicine Faculty Hospital, Istanbul, Turkey

Department of Pediatrics, Division of Immunology and Allergy Clinic, Istanbul, Turkey

** İstanbul Kanuni Sultan Süleyman Training and Research Hospital Department of Pediatrics, Division of Hematology and Oncology Clinic, İstanbul, Turkey

Corresponding Author: **Ömer AKÇAL**

Department of Pediatrics, Division of Allergy and Immunology, Istanbul Biruni Univesity Medicine Faculty Hospital,Istanbul, Turkey

E-mail: omerakcal@hotmail.com

Abstract

Background: Acute lymphoblastic leukemia (ALL) is one of the childhood malignancies. The classification of ALL patients into risk groups may highlight different risk factors among patients receiving diverse treatment protocols. Attention deficit hyperactivity disorder (ADHD) is a mental disorder of the neurodevelopmental type, characterized by core symptoms such as excessive impulsivity, difficulty in maintaining attention, and age-inappropriate hyperactivity.

In this prospective study, we aimed to determine the prevalence of attention deficiency in ALL patients who were treated with ALL-BFM 2000 protocol.

Materials And Methods: The study included 64 patients with ALL in the 8-14 age group who were treated in the Pediatric Hematology Clinic of the İstanbul Kanuni Sultan Süleyman Training and Research Hospital. The control group consisted of 30 healthy children in the same age group. The patients' records were reviewed to record their demographic data, risk group, chemotherapy protocol, and type of radiotherapy. Both patient and control groups underwent Benton Visual Retention Test. Results were statistically analyzed.

Results: There were 36 females and 28 males in the patient group with a median age of 10.63 ± 2.06 years while control group consisted of 21 females and 9 males with a median age of 10.80 ± 1.95 years. The prevelance of attention deficit was 32% vs. 13% in patient and control groups, respectively.

Discussion: The prevelance of attention deficit was higher in patients with ALL compared to control group. Among ALL patients with attention deficit, presence of T-ALL phenotype, *cerebrospinal fluid* involvement, and administration of high-dose methotrexate were significantly higher.

Keywords: Acute Lymphoblastic Leukemia, Chemotherapy, Attention Deficit

Öz

Giriş: Akut lenfoblastik lösemi (ALL), çocukluk çağında görülen kanser hastalıkları arasında yer almaktadır. ALL hastalarında belirlenen risk grubuna göre sınıflanması, farklı tedavi protokolü alan hastalar arasında farklı risk faktörlerini ön plana çıkartabilmektedir. Dikkat eksikliği hiperaktivite bozukluğu (DEHB) ise, gelişim düzeyine uygun olmayan aşırı hareketlilik, dikkati sürdürmede güçlük ve yetersiz dürtü kontrolü gibi temel belirtilerin gözlendiği bir bozukluktur. Prospektif yapılan bu çalışmada, ALL-BFM 2000 Protokolü ile tedavi edilen ve tedavisi başarılı bir şekilde tamamlanan ALL hastalarında dikkat eksikliği sıklığının saptanması amaçlanmıştır.

Evaluation Of Attention And Perception Test In Patients Diagnosed With Acute Lymphoblastic Leukemia Who Have Completed Treatment

Akut Lenfoblastik Lösemi Tanısı İle Tedavisi Biten Hastaların Dikkat Ve Algı Testi İle Değerlendirilmesi

Gereç Ve Yöntemler: İstanbul Sağlık Bilimleri Üniversitesi Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Çocuk Hematoloji Kliniğinde tedavisi tamamlanmış olup, 8-14 yaş grubunda toplam 64 ALL hastası çalışmaya dahil edildi. Kontrol grubu olarak, yine aynı yaş grubunda olan toplam 30 sağlıklı çocuk çalışmaya alındı. Hastaların dosyaları gözden geçirildi, demografik verileri, risk grubu, aldığı kemoterapi protokolü, radyoterapi alıp-almadığı değerlendirilerek kaydedildi. Hasta ve kontrol grubu Benton Görsel Dikkat Algı Testi ile değerlendirildi. Sonuçlar istatistiksel olarak analiz edildi.

Bulgular: Hasta grubunun 36 'sı kız, 28 'i erkekti ve yaş ortalaması 10,63±2,06 idi. Kontrol grubunun ise, 21 'i kız, 9 'u erkekti ve yaş ortalaması 10,80±1,95 idi. ALL hastalarında dikkat eksikliği oranı %32 olarak saptandı. Kontrol grubunda ise %13 olarak saptandı.

Tartışma: Çalışmamızda, ALL hastalarında dikkat eksikliği sıklığı, kontrol grubuna göre yüksek olduğu saptandı. Dikkat eksikliği olan ALL hastalarında; T-ALL fenotipi varlığı, beyin omurilik sıvısı tutulumu, yüksek doz methotreksat alımı istatistiksel olarak anlamlı saptandı.

Anahtar Kelimeler: Akut Lenfoblastik Lösemi, Kemoterapi, Dikkat Eksikliği, Algı Bozukluğu

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. It is the second most common cause of death in children aged 1 to 15 years in the USA and Europe, with accidents being the first. In our country, the causes of death in the 1-15 age group include infectious diseases, cardiac diseases and accidents, respectively, which are followed by acute leukemias (1). While treatment response and cure rates in acute lymphoblastic leukemia did not even reach 10% in 1960s, treatment of patients with ALL with multiple chemotherapy and radiotherapy can result in nearly 80% complete cure rate at present. Transition to multiple chemotherapy combinations, central nervous system (CNS) prophylaxis and identification of risk groups for adjustment of treatment intensity based on the patient have led to significant improvements in survival in recent years (2,3,4). However, the success achieved in the treatment of leukemia is accompanied with secondary malignancies, infertility, growth retardation, endocrinological problems such as obesity and, specifically, psychosocial problems in the long term (5). With advancements in its diagnosis and treatment, it has been found that specific clinical and laboratory findings are significant for prognosis, emphasizing the individualized treatment based on the existing risk. Clinical, laboratory, cytogenetic and biological characteristics such as immunophenotype have been taken into consideration in determining risk groups, and thus therapeutic approaches (6,7). As a result, treatment strategies have been tailored to treat leukemia patients at low risk of recurrence with mild intensity regimens and less toxic effects and those at high risk of recurrence with high intensity regimens (8).

Attention deficit hyperactivity disorder (ADHD) is a condition characterized by basic symptoms such as age-inappropriate hyperactivity, difficulty in maintaining attention and impulsivity. The prevalence of ADHD in school-age children is reported to range from 3% to 5% (9,10). A study conducted in the urban areas found that the prevalence of ADHD is 6.2% in Turkey (11). The development of ADHD is attributed to various factors, mainly to neurobiological and psychological factors. It is very difficult for children with ADHD to direct their attention to activities or school work during a certain period of time. These children are more likely to present with hasty work styles, distraction, lack of planning, excessive motor activity and risky behaviors (11,12,13,14).

In this study, we aimed to investigate the development of ADHD, a significant factor in school failure during primary school years in patients with ALL who had been treated with modified TRALL-BFM 2000 Protocol.

Material And Method

Our study recived ethical approval from clinical research ethics committee (2012,310). The study included a total of 64 patients with ALL in the 8-14 age group who received the Turkish ALL-BFM 2000 (TRALL-BFM 2000) protocol at the Pediatric Hematology Clinic of the Istanbul SBU Kanuni Sultan Süleyman Training and Research Hospital at Health Sciences University. The control group included a total of 30 healthy children from the same age group.

We conducted one-on-one meetings with the parents of patients who completed the treatment with TRALL-BFM 2000 protocol and met the inclusion criteria in order to explain the aim of our study. We recorded information about their age, gender, risk group, FAB classification, CSF involvement, and chemotherapy and radiotherapy treatments received. The Benton Visual Retention Test was administered to all patients under the supervision of a pediatric psychologist. The same test was also administered to a total of 30 healthy children of the same age who had no active complaint and had a normal physical examination as the control group.

Inclusion criteria for the study group

Being 8-14 years old

No known neurological pathology at the start of treatment

No active complaints on the day of the assessment

Normal physical and laboratory findings on the day of assessment

Parents' consent for test administration

The patients were divided into 3 groups as standard-, medium - and high-risk groups according to the TRALL-BFM 2000 protocol.

Risk Group Classification

Group I = Standard Risk Group (SRG): Patients aged 1 to 6 years old with a baseline leukocyte count below 20,000 /mm³, periphreal leukaemic cell count below 1000/mm³ on day 8 following a 7-day daily course of treatment with prednisone, no T- immunology, complete remission on day 33, and no t (9;22) and t(4;11) translocations.

Group II = Medium Risk Group (MRG): Patients with peripheral leukeamic cell count below 1000/mm³ on day 8, and those who achieved remission on day 33 and had negative translocations, if any of the specified other conditions for SRG was positive.

Group III = High Risk Group (HRG): Patients with peripheral leukaemic cell count > 1000 / mm³ on day 8 or those who did not achieve complete remission on day 33 or had positivity in either of the t (9;22) or t (4;11) translocations.

Table 1. ALL-BFM 2000 Chemotherapy Protocol

Treatment Regimen	Dose	Day(s) of Administration
Induction (Protocol I)		
Prednisone, PO	60 mg/m2	1-28
Vincristin, IV	1.5 mg/m2	8, 15, 22, 29
Daunorubicin, 1-h infusion	30 mg/m2	8, 15, 22, 29
L-Asparaginase, 1-h infusion	10.000 IU/m2	12, 15, 18, 21, 24, 27, 30, 33
Cyclophosphamide, 1-h infusion	1.000 mg/m2	36, 64
Cytarabine, IV	75 mg/m2	38-41, 45-48, 52-55, 59-62
6-Mercaptopurine, PO	60 mg/m2	36-63
Methotrexate, intrathecal	12 mg	1, 45, 59
Consolidation (Protocol M; only for SRG and MRG)		
6- Mercaptopurine	25 mg/m2	1-56
Methotrexate, 36-h infusion	† 1 g/m2	8, 22, 36, 50
Methotrexate, 24-h infusion	† 5 g/m2	8, 22, 36, 50
Methotrexate, intrathecal	12 mg	8, 22, 36, 50
Reinduction (Protocol II)		
Dexamethasone, PO	10 mg/m2	1-21
Vincristin, IV	1.5 mg/m2	8, 15, 22, 29
Adriamycin	30 mg/m2	8, 15, 22, 29
L-Asparaginase, 1-h infusion	10,000 IU/m2	8, 11, 15, 18
Cyclophosphamide, 1-h infusion	1,000 mg/m2	36
Cytarabine, IV	75 mg/m2	38-41, 45-48
6-Thioguanine, PO	60 mg/m2	36-49
Methotrexate, intrathecal	12 mg	38, 45
Intense Consolidation (only for HRG) (HR1/HR2/HR3)x2		
HR1		
Dexamethasone, PO	20 mg/m2	1-5
6- Mercaptopurine, PO	100 mg/m2	1-5
Vincristin, IV	1.5 mg/m2	1, 6
Methotrexate, 36-h infusion	1 g/m2	1
Cytarabine, 3-h infusion, q 12 h	2 g/m2	5
L-Asparaginase, IM	25,000 IU/m2	6
Methotrexate/Citarabin/Prednisone, intrathecal	Per age	1
HR2		
Dexamethasone ,PO	20 mg/m2	1-5
6-Thioguanine, PO	100 mg/m2	1-5
Vindesine ,IV	3 mg/m2	1
Methotrexate, 36-h infusion	1 g/m2	1
Iphosphamide, 1-h infusion	400 mg/m2	1-5
Daunorubicin, 24-h infusion	50 mg/m2	5
L-Asparaginase, IM	25,000 IU/m2	6
HR3		
Dexamethasone, PO	20 mg/m2	1-5
Cytarabine, 3-h infusion, q 12 h	2 g/m2	1-2
Etoposide, 1-h infusion	150 mg/m2	3-5
L-Asparaginase, IM	25,000 IU/m2	6
Methotrexate/Cytarabine/Prednisone, intrathecal	Per age	6

Evaluation Of Attention And Perception Test In Patients Diagnosed With Acute Lymphoblastic Leukemia Who Have Completed Treatment

Akut Lenfoblastik Lösemi Tanısı İle Tedavisi Biten Hastaların Dikkat Ve Algı Testi İle Değerlendirilmesi

Benton Visual Retention Test

It is a test that can be administered to individuals aged 8 years and above. It involves the presentation of shapes at different time intervals, requiring the drawing of shapes while viewing them, delayed drawing of shapes or recognition of shapes among others. Benton Visual Retention Test can evaluate shape memory instantaneously and with a delay; moreover, it can distinguish visual memory from visual perception and motor skills.

Upon administration of the test, we examined the relationship between ALL patients who completed their treatment and healthy children. We also examined the association between the attention deficit and the ALL risk group, FAB classification, CSF involvement, radiotherapy and high-dose methotrexate treatment within the study group.

Results

Of the 64 patients, 36 (56.25%) were female, and 28 (43.75%) were male. In the control group of 30 healthy children, 21 (70%) were female, and 9 (30%) were male (Table 2). No statistically significant difference was found in distribution of gender between the study and control groups (p=0.203). The mean age of the study group was 10.63±2.06 years versus 10.80±1.95 years in the control group. No statistically significant difference was found in mean age between the control and study groups (p=0.710).

Table 2. Comparison Between Control and Study Groups

		Control Group		Study Group		P
Age, years		10.80±1.95		10.63±2.06		0.710
Gender	Male	9	30.00%	28	43.75%	0.203
	Female	21	70.00%	36	56.25%	
Benton Test	Low score	26	86.70%	43	67.20%	0.046
	High score	4	13.30%	21	32.80%	

In the Benton Visual Retention Test, the test result was high score(HS) in 21 (32.80%) vs. 43 (67.2%) of 64 patients. In the control group, the test result was HS in 4 (13.30%) vs. 26 (86.7%) of 30 children. The Benton Visual Test high scoredf was statistically significantly higher (p=0.046). The presence of T-ALL was significantly higher in patients with Benton HS compared to those with Benton low score (LS) (p=0.001). When evaluated according to the CSF involvement, CSF involvement was positive in 0 of patients (0%) with Benton LS test result vs. 43 (100%) patients with Benton HS result. In patients with positive Benton test, CSF involvement was positive in 4 (19.05%) and negative in 17 (80.95%) patients. CSF involvement was statistically significantly higher in patients with HS Benton compared to those with LS Benton (p=0.003).

When evaluated according to high-dose MTX, 1 (2.33%) patient with LS Benton test received high-dose methotrexate and 42 (97.67%) received normal dose methotrexate. In patients with HS Benton test, 7 (33.33%) received high-dose methotrexate, and 14 (66.67%) received normal dose methotrexate.

Discussion

Acute lymhoblastic leukemia is the most common oncological disease in childhood, and complete cure can be achieved by multiple chemotherapy and radiotherapy. Throughout the course of this disease and its treatment, patients often face various challenges, resulting from both complications of the disease and problems caused by the treatment itself. For this reason, it is not uncommon for these patients to manifest psychological problems.

In this study, we compared the prevalence of attention deficit in children with acute leukemia who achieved complete cure with that of healthy children. Additionally, we compared the factors that might have played an etiological role in attention deficit in patients with acute lymphoblastic leukemia. In children with ALL who received BFM 2000 protocol, attention deficit was more common compared to the healthy children. No significant correlation was found between FAB classification and attention deficit in patients with ALL. No statistically significant difference was found in the incidence of attention deficit among the SRG, MRG, and HRG patient groups. A statistically significant difference was observed beween phenotype and attention deficit in patients with ALL, with predominance of T-ALL in patients with attention deficit. There was a statistically significant relationship between CSF involvement and attention deficit in patients with ALL, who also had a statistically significant relationship between attention deficit and administration of high- and normal-doses of methotrexate according to the patient protocol. There are studies in the literature showing a significant relationship with the cumulative dose of methotrexate (15). However, we found no statistically significant relationship between radiotherapy and attention deficit. Attention deficit, which is one of the leading psychological problems in childhood in our country, often occurs during the primary school age. Although it may not manifest as a severe illness, attention deficit may affect the entire lifespan of a person starting from childhood. Our study demonstrated that it would be rational to evaluate patients receiving chemotherapy for diseases such as ALL in the long-term follow-up for attention deficit.

References

1. Brunning RD. Classification of acute leukemias. Semınars In Dıagnostıc Pathology. 2003 Aug;20(3):142-53. doi: 10.1016/s0740-2570(03)00031-5. PMID: 14552428.

2. Pui CH, Relling MV, Downing JR. Mechanism of disease: Acute lymphoblastic leukemia. New England Journal Of Medıcıne. 2004;350:1535-48.

3. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. Blood 2000;95:3310-22.

4. Devine SM, Larson RA. Acute leukemia in adults: recent developments in diagnosis and treatment. CA-A Cancer Journal For Clınıcıans. 1994 Nov-Dec;44(6):326-52. doi: 10.3322/canjclin.44.6.326. PMID: 7953914.

5. Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. Journal Of Clinical Oncology. 2007;25(24):3649–56.

6. Reaman GH, Sposto R, Sensel MG, et al. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia on two consecutive trials of the Children's Cancer Group. Journal Of Clınıcal Oncology 1999;17(2): 445-455

7. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin oncol 1996;14(1): 18-24

8. Pui C-H, Crist WM, Biology and treatment of acute lymphoblastic leukemia. The Journal Of Pediatrics. 1994;124: 491-503

9. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I (2009) Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. British Journal Of Psychiatry 194: 204–11.

10. Rajaprakash M, Leppert ML. Attention-Deficit/Hyperactivity Disorder. Pediatr Rev. 2022 Mar 1;43(3):135-147. doi: 10.1542/pir.2020-000612. PMID: 35229109.

11. Vesile Senol, Demet Unalan, Raziye Peksen Akca, Mustafa Basturk Prevalence of attention-deficit/hyperactivity and other disruptive behaviour disorder symptoms among primary school-age children in Kayseri, Turkey J Int Med Res. 2018 Jan; 46(1): 122–134

12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed (DSM-5). Arlington VA: American Psychiatric Association; 2013.

13. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. Arch Dis Child 2005;90 Suppl 1:i2-7.

14. Krull KR, Khan RB, Ness KK, et al. Symptoms of attention-deficit/hyperactivity disorder in long-term survivors of childhood leukemia. Pediatric blood & cancer. 2011;57(7):1191–6.

15. Jacola LM, Edelstein K, Liu W, et al. Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. Lancet Psychiatry. 2016;3(10):965–72.

OLGU SUNUMU /CASE REPORT

Hydrocele of the Canal of Nuck in Adult Females: A Case Report and Systematic Review

Erişkin Kadınlarda Nuck Kanalının Hidroseli: Bir Olgu Sunumu ve Sistematik Derleme

Örgün GÜNEŞ * 0000-0002-0576-6086

Seyfi EMİR   0000-0002-5117-599X

Selim SÖZEN* 0000-0003-2006-9198

*Atatürk Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye.

**Reyap Hastanesi, Genel Cerrahi Kliniği, Tekirdağ, Türkiye.

***Sözen Surgery Clinic, İstanbul, Türkiye.

Yazışma Adresi: Örgün GÜNEŞ

Atatürk Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye

E-mail adresi: orgungunes@hotmail.com

Abstract

Hydrocele of the canal of Nuck is a very rare condition in female population and can be defined as invagination of the parietal peritoneum into the canal of Nuck. Here, a woman operated for an inguinal mass and diagnosed to have a cyst of Canal of Nuck will be evaluated with respect to clinical picture, diagnosis, treatment and differential diagnosis as well.

Keywords: Canal of nuck, inguinal mass, processus vaginalis.

Öz

Nuck kanal kisti kadın populasyonunda çok nadir görülen bir durum olup, pariyetal peritonun Nuck kanalına invajinasyonu olarak tanımlanır. Bu makalede, kasıkta kitlesi nedeniyle ameliyat edilen ve Nuck kanal kisti saptanan hasta klinik yaklaşım, tanı, tedavi ve ayırıcı tanı açısından değerlendirildi.

Anahtar Kelimeler: Nuck kanalı, inguinal kitle, processus vaginalis

Introduction

Cyst of the canal of Nuck is a very rare condition in female population and can be defined as invagination of the parietal peritoneum into the canal of Nuck (1). The intraabdominal peritoneal extensions accompany the round ligament thereby attaching to the labia majora, in females. Typically, this peritoneal fold obliterates into a fibrous band in early stage life. Any defect that will occur in the obliteration contributes to the canal of Nuck to be left open and the formation of hydrocele or hernia in the following years. The fluid inside a Nuck's cyst results from an imbalance between the production and absorption of fluid produced by the parietal peritoneum. A patient who was operated for an inguinal mass and diagnosed with cyst of the canal of Nuck will be addressed here clinically and in terms of diagnosis, treatment and differential diagnosis.

Patient consent was obtained for the study.

Case

A 26-year-old female patient was admitted to our clinic with complaints of pain and swelling in the right groin for 6 months. Upon her physical examination, an irreducible mass measuring 5*4 cm was found in the right inguinal region. Upon her ultrasonography, a lobule-contoured septal cystic mass measuring 52*33*33 mm (cyst of Nuck) was observed in the right inguinal region (Fig. 1).

Figure 1. Ultrasound image of the right groin with the patient supine, showing the anechoic cystic structure
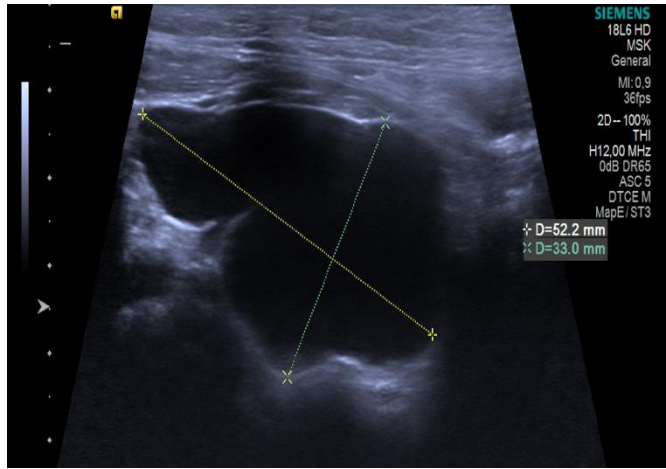

On a pelvic MRI, a cystic lesion with peripheral contrast enhancement measuring 52*33*23 mm in diameter (cyst of Nuck) was observed in the right inguinal canal (Fig. 2).

Figure 2. Axial T2 weighted image depicts that the lesion is hyperintense
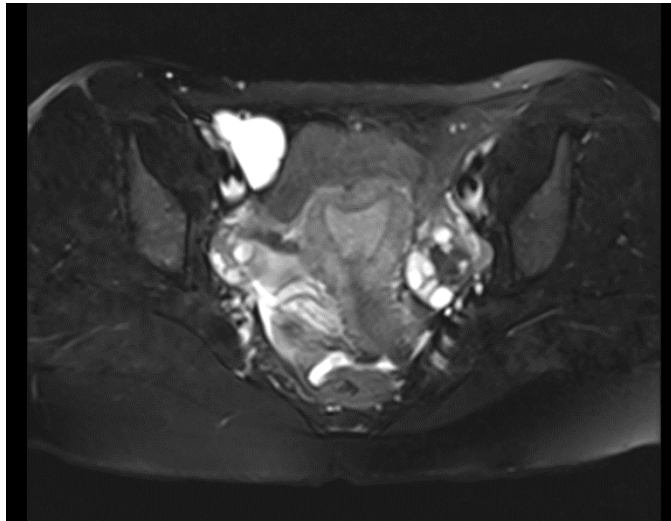
During the operation performed under spinal anesthesia, a cystic mass measuring 5*3 cm with connected to the round ligament and entrance to the internal inguinal ring was found in the inguinal canal (Fig. 3).

Figure 3. Cystic structure was detected in the surgery.
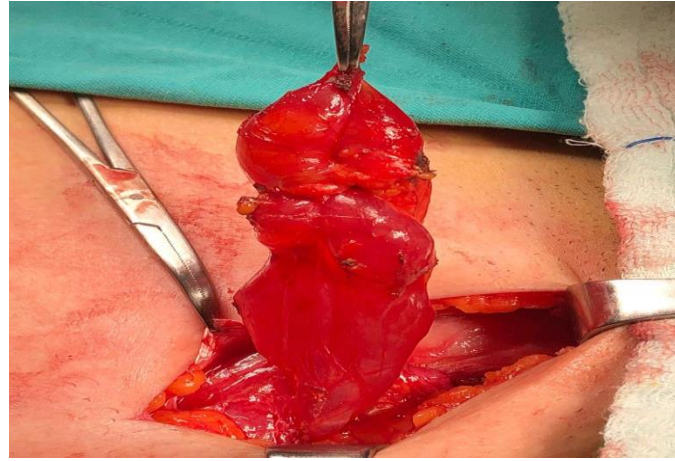
Also, there was a hernia sac proximal to the cystic mass. The cystic mass was resected with the hernia sac. Inguinal hernia repair was performed using the Lichtenstein method. Histopathological examination revealed a mesothelial walled nuck cyst filled with fluid and lined with single-layer cuboidal cells.

The patient was discharged 1 day after surgery without any problem. There was no swelling or recurrence on the operated side at 6 weeks and 6 months after surgery.

Discussion

A periodontal pocket similar to the processus vaginalis is seen to extend into the inguinal canal by the round ligament. This is called Nuck's diverticulum. This formulation corresponds to the processus vaginalis (PV) in men. PV and Nuck's diverticulum are potential hernias. If the patent processus vaginalis is small enough to allow only the passage of fluid, pathologies such as hydrocele or cord cyst occur; if it is large enough to allow the passage of abdominal organs, then an inguinal hernia occurs. The cyst of the canal of Nuck, which was first described by the Dutch anatomist Anton Nuck Van Leiden in 1691 (2). Nuck cyst is a rare condition. Although the incidence is not exactly known, it is estimated to be 1% in young girls in the literature (3). However, this may be somewhat lacking since the cyst can be misdiagnosed. The canal of Nuck is the female analogue of the male patent processus vaginalis. During the first postnatal year, it regresses by separating from the peritoneal cavity. Non-obliteration of this duct causes Nuck's cyst or hydrocele. This condition, which is mostly seen in pediatric population and in males, is called hydrocele of the canal of Nuck. This is called spermatic cord cyst in boys. This condition is very rare in females and the patient consults a physician with complaints of swelling in the groin and a palpable mass in symptomatic cases.

Pathophysiology has suggested some theories for pathologies obliteration of processus vaginalis. Tanyel et al (4) have stated that programmed cell death by increased afferent neurotransmitter via androgen receptors due to parasympathetic tone dominance and sympathetic tone decrease thereby the obliteration of processus vaginalis, and they have also said that at this stage, the absence or insufficiency of the parasympathetic dominant effect, inappropriate location or inappropriate timing influence calcium release, thus rendering apoptosis insufficient and resulting in hydrocele. There are also some people who argue that upon the immunohistochemical examinations of hernia sacs, apoptotic nuclei were observed in the vascular and mesothelial structures of the sac wall, but failure to observe these nuclei in smooth muscle cells may be due to insufficient apoptosis of smooth muscle cells in the PV wall (5). The differential diagnosis includes soft tissue tumors such as inguinal hernia, enlarged lymph nodes, and lipoma, leiomyoma, and endometriosis of the round ligament. It should also include indirect inguinal hernia, hernia of ovarian tissue, cystic lymphangiomas, inflammatory or malignant lymphadenopathy, abscess formation, and vascular formations (aneurysm) (5).

Ultrasonographic evaluation is of great importance in today's practice. Several previous reports suggested excluding jejunoileal atresia, volvulus, meconium ileus, Hirschsprung disease, enteric duplications, anorectal atresia, congenital salt loss diarrhea, Bartter syndrome, and MVID from differential diagnosis when dilated intestines are detected on prenatal ultrasound (Chih-Ping Chen 2010, Langer J.C. et al.1991, Kennea et al 2010). Fetuses with MVID may present with multiple dilated bowel loops and polyhydramnios mimicking intestinal obstruction in the early third trimester (Chih-Ping Chen 2010).

Congenital chloride and sodium diarrheas may also present with polyhydramnios multiple dilated bowel loops, fluid-filled intestinal obstruction on prenatal ultrasound, and elevated amniotic fluid electrolyte concentrations (Langer J.C. et al.1991; Colombani et al 2010).

Kennea et al. (2001) reported that polyhydramnios accompanied by dilated large and small bowel loops which resembled an intestinal obstruction on an antenatal ultrasound could lead to a postnatal diagnosis of MVID (Kennea et al 2010). The authors stated that bowel obstruction and congenital enteropathy should be considered if a prenatal ultrasound showed dilated bowel loops and polyhydramnios. In the present case, amniocentesis was helpful to rule out the diagnosis of congenital sodium and chloride diarrheas in the prenatal period. Currently, there is no curative treatment for MVID. Although long-term TPN or bowel and liver transplantation are treatment options, MVID-related complications and reduced longevity are common. Novel genome editing technologies, such as CRISPR/Cas9, hold promise for MVID treatment. However, further studies are needed to shed light on this. (Vogel et al. 2016). In conclusion, when dilated bowel loops are detected regardless of the presence of polyhydramnios in prenatal ultrasound examination, MVID should be considered as a differential diagnosis. Prenatal genetic molecular studies should be performed to confirm the diagnosis of MVID.

Disclosure of interest

The authors report no conflict of interest.

References

1. Badak B, İhtiyar E. Nuck Kanal Hidroseli. Osmangazi Tıp Dergisi. 2019; 41(4): 421-424.
2. Qureshi NJ, Lakshman K. Laparoscopic excision of cyst of canal of Nuck. J Minim Access Surg. 2014;10(2):87-9.
3. Sarkar S, Panja S, Kumar S. Hydrocele of the Canal of Nuck (Female Hydrocele): A Rare Differential for Inguino–Labial Swelling. J Clin Diagn Res. 2016; 10(2): PD21– PD22.
4. Tanyel FC, Okur HD. Autonomic nervous system appears to play a role in obliteration of processus vaginalis. Hernia. 2004; 8(2):149-154.
5. Hosgor M, Karaca I, Ozer E, Erdag G, Ulukus C, Fescekoglu O, et al. The role of smooth muscle cell differentiation in the mechanism of obliteration of processus vaginalis. J Pediatr Surg. 2004; 39(7):1018-1023.

Revaccination in a Patient With Anaphylaxis to 9-Valent Human Papillomavirus: To Vaccinate Or Not To Vaccinate?

9-Valanlı İnsan Papilloma Virüsüne Karşı Anafilaksisi Olan Bir Hastada Yeniden Aşılama: Aşılamalı mı, Aşılamamalı mı?

Şeyma ÖZDEN* 0000-0002-6646-9894

Fatma Merve TEPETAM* 0000-0002-9794-5662

Özge ATİK* 0000-0003-2219-0039

*University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, İstanbul, Turkey.

Abstract

Objective: Vaccines have been recognized as one of the most effective public health interventions With the widespread use of vaccination, a significant reduction in vaccine-preventable infectious diseases and related deaths can be achieved. Vaccine-associated hypersensitivity reactions are not infrequent . In this case, we wanted to share the desensitization protocol that we developed and successfully applied in the 2nd dose in a patient who developed anaphylaxis after the first dose of 9-valent human papillomavirus (9vHPV) vaccine.

Material and Methods: We successfully administered the second dose of 9vHPV vaccine with a 5-step desensitisation protocol lasting 150 minutes in total to a 29-year-old female patient who developed anaphylaxis immediately after the first dose of 9vHPV vaccine.

Results and Conclusion: As health professionals, we should always draw attention to the importance of vaccination and try alternative methods to vaccinate patients who develop or are at risk of developing hypersensitivity reactions. It should not be forgotten that vaccines are still the most powerful weapon of modern medicine in preventing infectious diseases and related deaths.

Keywords: Vaccination, human papillomavirus, anaphylaxis

Correspondence: Şeyma ÖZDEN

University of Health Sciences Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy Basi buyuk Mahallesi.Maltepe 34854, Istanbul, Turkey E-mail:seymaglhn@hotmail.com

Öz

Amaç: Aşılar, en etkili halk sağlığı müdahalelerinden biri olarak kabul edilmiştir Aşılamanın yaygın kullanımı ile aşı ile önlenebilir bulaşıcı hastalıklarda ve buna bağlı ölümlerde önemli bir azalma sağlanabilir. Aşı ile ilişkili aşırı duyarlılık reaksiyonları çok da nadir olmayan durumlardır. Bu vakada 9 valanlı insan papilloma virüsü (9vHPV) aşısının ilk dozundan sonra anafilaksi gelişen bir hastada geliştirdiğimiz ve 2. dozda başarıyla uyguladığımız desensitizasyon protokolünü paylaşmak istedik.

Materyal ve Metod: 9vHPV aşısının ilk dozundan hemen sonra anafilaksi gelişen 29 yaşındaki bir kadın hastaya toplam 150 dakika süren 5 aşamalı bir duyarsızlaştırma protokolü ile 9vHPV aşısının ikinci dozunu başarıyla uyguladık.

Bulgular ve Sonuç: Sağlık profesyonelleri olarak aşılamanın önemine her zaman dikkat çekmeli ve aşırı duyarlılık reaksiyonu gelişen veya gelişme riski olan hastaları aşılamak için alternatif yöntemler denemeliyiz. Unutulmamalıdır ki aşılar, bulaşıcı hastalıkların ve buna bağlı ölümlerin önlenmesinde hala modern tıbbın en güçlü silahıdır.

Anahtar Kelimeler: Aşılama, insan papilloma virüsü, anafilaksi

Introduction

Human papillomavirus (HPV) is associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both females and males (1). On 10 December 2014, the FDA approved the use of the 9vHPV vaccine (for women between 9 and 26 years of age; for men between 9 and 15 years of age) (2). At its February 2015 meeting, the Advisory Committee on Immunisation Practices (ACIP) recommended the 9-valent human papillomavirus (HPV) vaccine (9vHPV) (Gardasil 9®, Merck and Co., Inc.) as one of three HPV vaccines available for routine vaccination.

Vaccine-associated hypersensitivity reactions are not infrequent . Howerver, most of the reported hypersensitivity reactions associated with vaccination are not serious. However, very serious cutaneous and severe anaphylaxis reactions may occur, although rare. Vaccines, like drugs, have the potential to cause allergic reactions. Vaccines contain an active component (the antigen) and additional components. Vaccine antigens may contain whole organisms or parts of organisms, or they may contain inactivated toxins (toxoids). Some vaccines may contain both components. 9vHPV is a noninfectious, virus-like particle (VLP) vaccine (3). The vaccine antigens themselves rarely cause hypersensitivity reactions. Excipients such as egg protein, gelatine, etc. are usually responsible for hypersensitivity reactions following vaccination.

Gardasil 9® contains the following: HPV Type 6 L1 protein, HPV Type 11 L1 protein, HPV Type 16 L1 protein, HPV Type 18 L1 protein, HPV Type 31 L1 protein, HPV Type 33 L1 protein, HPV Type 45 L1 protein, HPV Type 52 L1 protein, HPV Type 58 L1 protein; Amorphous aluminium hydroxyphosphate sulphate adjuvant, sodium chloride, L-Histidine, polysorbate 80, sodium borate, water for injection (3).

Since there is no standard desensitisation protocol for 9vHPV vaccine in the literature, we wanted to share the patient in whom we performed successful desensitisation with the protocol we developed ourselves. The patient's consent was obtained and patient information was presented.

Case Report

29-year-old female patient, no active complaints. HPV positivity was detected in cervical smear test during routine gynaecological controls and 9vHPV vaccination was recommended. The patient had no previous hypersensitivity reaction to any medication or vaccine in her medical history, nor did she have a history of asthma, food allergy (egg, etc.) or any other atopic disease. Approximately 30 minutes after the administration of Gardasil 9®, she developed generalised urticaria throughout the body and shortness of breath. Adrenaline 0,3 mg inramuscular (IM), pheniramine 45,5 mg/2 ml Intravenous (IV) and methylprednisolone 40 mg IV administration were made. The patient was observed in the emergency department for about 2 hours and was externed when her complaints regressed.

The patient was referred to an allergist for a second dose of 9vHPV vaccine.Since it is known that polysorbate 80, an excipient in Gardasil 9®, may cause hypersensitivity reactions and cross-react with polyethylene glycol (PEG), the patient underwent skin tests with PEG and polysorbate 80.[6] Skin tests with PEG and polysorbate 80 were negative. Aluminum hydrofastate, another excipient in Gardasil 9®, was not considered as the agent responsible for anaphylaxis because it causes more contact allergy (4). The reaction that occurred after the first dose of vaccination was evaluated as anaphylaxis. Since serum tryptase level could not be studied in our centre, serum tryptase level could not be measured. However, mast cell disease was not considered because the patient had no history of atopic disease or drug hypersensitivity in her medical history. It was decided to perform desensitization for the 2nd dose of vaccination. In a recent study on PEG-containing covid-19 vaccines, vaccines were administered without premedication regardless of the previous reaction (5) Since there is no desensitisation protocol for 9vHPV vaccine in the literature, we performed desensitisation without premedication with our clinical experience in this patient.

A 5-step rapid desensitisation protocol developed by us was applied without premedication (Table 1). After vaccination, the patient was observed for 2 hours. No hypersensitivity reaction occurred during or after vaccination.

Table 1: 5-step rapid 9vHPV desensitization protocol		
	Dose (mL)	Total Dose (mL)
Step 1	0.05	0.05
Step 2	0.05	0.10
Step 3	0.10	0.20
Step 4	0.15	0.35
Step 5	0.15	0.50
30 minutes between steps		

Discussion

Vaccines have been recognized as one of the most effective public health interventions With the widespread use of vaccination, a significant reduction in vaccine-preventable infectious diseases and related deaths can be achieved (6). Although vaccine-associated hypersensitivity reactions are not uncommon, severe hypersensitivity reactions such as anaphylaxis are extremely rare. IgE-mediated anaphylaxis against quadrivalent HPV vaccine has been reported with a rate of 2.6/100 000 [10]. There are no studies indicating the rate of IgE-mediated anaphylaxis against 9vHPV vaccine. The 9vHPV vaccine, like the quadrivalent HPV vaccine, contains polysorbate 80, a stabiliser that can trigger anaphylaxis (3). Therefore, we We know that serum mast cell tryptase level has an important role in confirming the diagnosis of anaphylaxis. We did skin tests with polysorbate 80 before desensitization and found it negative.

However, there is no established cut off value for serum tryptase value in vaccine-associated anaphylaxis reactions. But, measurement of serum tryptase levels in the first 2 hours after the reaction and 48 hours after the reaction is recommended. A significantly increased serum tryptase level compared to baseline serum tryptase level is a strong indicator of a systemic mast cell-mediated hypersensitivity reaction (4). Since our patient had received the first dose at another healthcare institution and presented to us approximately 3 months after the reaction, serum tryptase level could not be measured during or after the reaction.

If the patient is thought to have developed a hypersensitivity reaction to the vaccine, it is very important to identify the allergy causing this condition. This may provide guidance for avoiding this allergy in subsequent doses of the vaccine or using alternative agents that do not contain this allergen. To the best of current knowledge, there is no test that can predict severe hypersensitivity reactions following vaccination. Patients with severe allergic reactions after vaccination are considered high risk for the next vaccination and require special precautions

Patients who have been sensitized to a vaccine or its components and have developed a severe hypersensitivity reaction, such as anaphylaxis, should be revaccinated only if absolutely indicated. In this case, if possible, a vaccine that does not contain the allergen that causes hypersensitivity should be preferred. .Where this is not possible, two pragmatic (not evidence-based) approaches have been used: split-doze vaccination (1/10, remaining 9/10 if no reaction after 30 minutes) and desensitization (6). In our patient, we decided to administer the vaccine with desensitization because the second dose of vaccination was absolutely necessary and the patient developed anaphylaxis after the previous vaccination.

Although the clearest recommendations for vaccine allergy are in the presence of egg allergy, studies for other components are very limited. The ease of access to information about adverse events of vaccines on the internet can sometimes mislead patients and cause them to hesitate about vaccination. As health professionals, we should always draw attention to the importance of vaccination and try alternative methods to vaccinate patients who develop or are at risk of developing hypersensitivity reactions. HPV vaccines have been shown to significantly prevent cervical cancer, especially cervix cancer, oropharyngeal and anal tumours and genital warts, even if the patient has previously been exposed to the HPV virüs (7,8). It should not be forgotten that vaccines are still the most powerful weapon of modern medicine in preventing infectious diseases and related deaths.

References

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B: a review of human carcinogens. IARC Monographs Eval Carcinog Risks Hum 2012;100(Pt B):1–441.

2. Food and Drug Administration. December 10, 2014 Approval letter—GARDASIL 9. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426520.htm.

3. Petrosky E, Bocchini JA Jr, Hariri S, et all. Centers for Disease Control and Prevention (CDC). Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2015 Mar 27;64(11):300-4. PMID: 25811679; PMCID: PMC4584883.

4. Bergfors E, Trollfors B, Inerot A. Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. *Vaccine*. 2003; **22**: 64- 69.

5. Özden Ş, Tepetam FM, Atik Ö. COVID-19 aşılarına alerjik reaksiyon gösteren veya alerjik reaksiyon gelişme riski olan hastalarda aşılama yaklaşımı [Vaccination approach in patients with an allergic reaction to COVID-19 vaccines or at risk of developing allergic reactions]. Tuberk Toraks. 2023 Jun;71(2):166-175.

6. National Vaccine Advisory Committee. Protecting the public's health: critical functions of the Section 317 Immunization Program—a report of the National Vaccine Advisory Committee. Public Health Rep 2013;128:78–95. [PubMed: 23450872]

7. Villa LL, Costa RLR, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005; 6: 271-278.

8. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus type 16 and 18 in young women: a randomised controlled trial. Lancet 2004; 364: 1757-1765