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SDÜ Tıp Fak Derg / Med J SDU

Yılda dört sayı (Mart, Haziran, Eylül, Aralık) yayınlanan 'peer review' yöntemiyle çalışan hakemli dergidir.
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Süleyman Demirel Üniversitesi Tıp Fakültesi Dergisi Yazım Kuralları

Hakkında

SDÜ Tıp Fakültesi Dergisi (SDÜ Tıp Fak Derg) Süleyman Demirel Üniversitesi Tıp Fakültesi'nin yayın organıdır. Dergi; yılda dört sayı olarak Mart, Haziran, Eylül ve Aralık aylarında yayınlanır. Bağımsız, tarafsız ve çift-kör değerlendirme ilkelerine sahip uluslararası, bilimsel, açık erişimli (Open Access), çevrimiçi/basılı bir dergidir.

SDÜ Tıp Fakültesi Dergisinde; sağlık bilimleri alanındaki özgün klinik ve deneysel araştırmalar, derlemeler, vaka takdimleri, editöre mektuplar, dergimizde yayınlanan yazılarla ilgili görüşler ve tecrübeleri içeren yazılar yayınlanabilir. Derginin dili Türkçe ve İngilizcedir.

SDÜ Tıp Fakültesi Dergisi uluslararası (DOAJ, EBSCO, Index Copernicus) ve ulusal (TR Dizin) hakemli dergi statüsündedir.

SDÜ Tıp Fakültesi Dergisi'ne gönderilen ve dergide yayınlanan makalelerden hiçbir ücret talep edilmemektedir. Dergide yayınlanan makaleler için yazarlara veya üçüncü kişilere telif ücreti ödenmemektedir. Yazarların kimlik bilgileri ve e-posta adresleri hiçbir şekilde başka amaçlar için kullanılmamaktadır.

Derginin yayın ve editöryal süreçleri Uluslararası Tıp Dergileri Editörler Kurulu (ICMJE) yönergesine göre yürütülmektedir. Dergi, bilimsel süreli yayınların şeffaflık ve mükemmellik ilkelerine uyar (doaj.org/bestpractice).

Bir yazının yayın için kabul edilmesinde en önemli kriterler özgünlük, yüksek bilimsel kalite ve alıntı potansiyelinin varlığıdır. Dergide yayınlanmak üzere gönderilen yazılar, daha önce başka bir yerde yayınlanmamış ve yayınlanmak üzere gönderilmemiş olmalıdır. Bir kongrede tebliğ edilmiş ve özeti yayınlanmış çalışmalar organizasyonun adı, yeri ve tarihi belirtilmek şartı ile kabul edilebilir.

Etik İlkeler

Deneysel, klinik ve ilaç çalışmaları ile bazı vaka raporlarının araştırma protokollerinin Etik Kurullar tarafından uluslararası sözleşmelere uygun olarak onaylanması (Ekim 2013'te güncellenen Dünya Tıp Birliği Deklarasyonu "İnsan Denekleri ile İlgili Tıbbi Araştırmalar İçin Etik İlkeler"ine göre, www.wma.net) gereklidir. İlgili etik kurul raporu veya bu rapora eşdeğer olan resmi bir yazı dergipark sistemine yüklenmelidir.

• Üzerinde deneysel çalışma yapılan gönüllü kişilere ve hastalara uygulanan prosedürler ve sonuçları anlatıldıktan sonra onaylarının alındığını ifade eden bir açıklama (bilgilendirilmiş onam) yazının içinde bulunmalıdır.

• Bilgilendirilmiş onam ve etik kurul onayı (etik kurulun adı, etik kurul toplantı tarihi ve onay numarası ile ilgili bilgiler) makalenin Gereç ve Yöntem bölümünde ve makalenin en sonunda kaynaklardan önce ayrı alt başlıklar ile belirtilmelidir.

• Hastaların gizliliğini korumak, yazarların sorumluluğundadır. Hasta kimliğini ortaya çıkarabilecek fotoğraflar için, hasta ve/veya yasal temsilcileri tarafından imzalanan onayların alınması ve yazılı onay alındığının metin içerisinde belirtilmesi gereklidir.

• Hayvanlar üzerinde yapılan araştırmalarda acı ve rahatsızlık verilmemesi için yapılan uygulamalar ve alınan tedbirler açık olarak belirtilmelidir. **İlgili etik kurullardan alınan onaylar makalenin Gereç ve Yöntem bölümünde ve makalenin en sonunda kaynaklardan önce ayrı alt başlıklar ile belirtilmelidir.**

Dergimize gönderilen tüm yazılar intihal tespit etme programı (iThenticate) ile değerlendirilmektedir. **Benzerlik oranının %25 ve altı olması gerekmektedir.**

Derginin Yayın Kurulu, tüm itirazları Yayın Etik Komitesi (COPE) kuralları çerçevesinde ele alır. Bu gibi durumlarda, yazarlar temyiz ve şikayetleri ile ilgili olarak yayın kuruluyla doğrudan iletişime geçmelidir. Gerektiğinde, dahili olarak çözülemeyen sorunları çözmek için bir ombudsman atanabilir. Baş Editör, tüm temyiz ve şikayetler için karar verme sürecindeki nihai otoritedir.

Yazarlar, SDÜ Tıp Fakültesi Dergisine bir makale gönderirken makalelerinin telif hakkını dergiye vermeyi kabul etmiş sayılır. Eğer yazarın çalışmasının basılması reddedilirse, yazının telif hakkı yazarlara geri verilmiş sayılır.

SDÜ Tıp Fakültesi Dergisine gönderilen her makale, adı geçen yazarların tümünün imzaladığı yayın hakları devir formu (erişim adresi: https://dergipark.org.tr/tr/download/journal-file/22117) ile birlikte dergi şablonuna (erişim adresi: https://dergipark.org.tr/tr/download/journal-file/24521) uygun olarak gönderilmelidir. Gönderilmesi gereken zorunlu belgelere https://dergipark.org.tr/tr/pub/sdutfd adresinden ulaşılabilir.

Şekiller, tablolar veya hem basılı hem de elektronik formatlardaki diğer materyaller de dahil olmak üzere başka kaynaklardan alınan içeriği kullanan yazarların telif hakkı sahibinden izin almaları gerekir. Bu hususdaki hukuki, mali ve cezai sorumluluk yazarlara aittir. SDÜ Tıp Fakültesi Dergisinde yayınlanan yazılarda belirtilen ifadeler veya görüşler yazarlara aittir. Editörler, editörler kurulu ve yayıncı, bu yazılar için herhangi bir sorumluluk kabul etmemektedir. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir. Ön kontrol aşamasında düzeltme istenen makaleler için 15 gün, değerlendirme sonrası düzeltme istenen makaleler için 30 gün süre verilir, bu sürelerin aşılması halinde makale reddedilir.

Makalenin Yayına Hazırlığı

Makaleler yalnızca çevrimiçi olarak https://dergipark.org.tr/tr/pub/sdutfd adresinden gönderilebilir. Başka bir yolla gönderilen yazılar değerlendirilmez. Dergiye gönderilen yazılar, öncelikle yazının dergi kurallarına uygun olarak hazırlanmasını ve sunulmasını sağlayacakları teknik değerlendirme sürecinden geçer. Derginin kurallarına uymayan yazılar, teknik düzeltme talepleri ile gönderen yazara iade edilir. Editör, ana metni değiştirmeden düzeltme yapılabilir. Editör, istenilen şartlara uymayan makaleleri reddetme hakkını saklı tutar.

Yazarların aşağıdaki belgeleri göndermeleri gerekir:

•Yayın Hakkı Devir Formu
•Başlık Sayfası (Tüm kısımlar eksiksiz ve detaylı olarak doldurulmalıdır)
•Ana belge (Şablona göre hazırlanmalıdır, bölümlendirilmiş türkçe ve ingilizce öz ile türkçe ve ingilizce başlıkları da içermelidir)
•Şekiller (JPEG formatında, en az 300 DPI, en fazla 6 adet)
•Tablolar (Microsoft word dosyası formatında, en fazla 6 tablo)
•Etik Kurul Kararları (Gerekliyse)
•Yazar Katkı Formu (CRediT sistemine göre, Bknz: Şablon)

Ana Belgenin Yayına Hazırlığı

Yazılar bilgisayar ile çift aralıklı olarak 12 punto büyüklüğünde ve Times New Roman karakteri ile yazılmalıdır. Her sayfanın bütün kenarlarında 2.5 cm boşluk bırakılmalıdır. **Özgün makaleler bölümlendirilmiş bir Öz (abstract) içermelidir (Amaç, Gereç ve Yöntem, Bulgular, Sonuç, Anahtar Kelimeler).** Olgu sunumları ve derlemeler için bölümlendirilmiş öz gerekmez. Öz bölümü 300 kelime ile sınırlandırılmalıdır. Özde kaynaklar, tablolar ve atıflar kullanılamaz. Özün bittiği satırın altında sayısı 3-5 arasında olmak üzere anahtar kelimeler verilmelidir. Türkiye dışındaki ülkelerden yazı gönderen ve Türkçe bilmeyen yazarlar için Başlık, Öz, Anahtar Kelimeler ve yazıyla ilgili diğer bazı temel bölümlerin Türkçe olarak gönderilmesi zorunlu değildir. Makalede kullanılan tüm kısaltmalar, ilk kullanımda tanımlanmalıdır. Kısaltma, tanımı ardından parantez içinde verilmelidir. Ana metinde bir ilaç, ürün, donanım veya yazılım programından bahsedildiğinde, ürünün adı, ürünün üreticisi, üretim şehri ve üreten şirketin ülkesi de dahil olmak üzere ürün bilgileri parantez içinde verilmelidir.

Tüm kaynaklara, tablolara ve şekillere ana metinde atıfta bulunulmalı ve kaynaklar, ana metinde geçen sıraya göre numaralandırılmalıdır. Kullanılan semboller, sembollerin standart kullanımlarına uygun olmalıdır.

Özgün araştırma yazıları **en fazla 4000 kelime** olmalı ve aşağıdaki başlıkları içermelidir;

• Başlık (hem Türkçe hem İngilizce)
• Öz (hem Türkçe hem İngilizce)
• Anahtar Kelimeler (hem Türkçe hem İngilizce)
• Giriş
• Gereç ve yöntemler
• Bulgular
• Tartışma
• Sonuçlar
• Beyanlar (Çıkar çatışması vb. Bknz: Şablon)
• Kaynaklar
• Şekil ve tablo açıklamaları (gerekirse)

Olgu sunumları **en fazla 2000 kelime** olmalı ve aşağıdaki başlıkları içermelidir;

• Başlık (hem Türkçe hem İngilizce)
• Öz (hem Türkçe hem İngilizce)
• Anahtar Kelimeler (hem Türkçe hem İngilizce)
• Giriş
• Olgu sunumu
• Tartışma ve Sonuç
• Beyanlar (Çıkar çatışması vb. Bknz: Şablon)
• Kaynaklar
• Şekil ve tablo açıklamaları (gerekirse)

Derleme yazıları **en fazla 5000 kelime** olmalı ve aşağıdaki başlıkları içermelidir;

• Başlık (hem Türkçe hem İngilizce)
• Öz (hem Türkçe hem İngilizce)
• Anahtar Kelimeler (hem Türkçe hem İngilizce)
• Ana metin
• Sonuç
• Beyanlar (Çıkar çatışması vb. Bknz: Şablon)
• Kaynaklar
• Şekil ve tablo açıklamaları (gerekirse)

Editöre Mektuplar **en fazla 1000 kelime** olmalı ve aşağıdaki başlıkları içermelidir;

• Başlık (hem Türkçe hem İngilizce)
• Öz (hem Türkçe hem İngilizce)
• Anahtar kelimeler (hem Türkçe hem İngilizce)
• Editöre Mektup
• Beyanlar (Çıkar çatışması vb. Bknz: Şablon)
• Kaynaklar
• Şekil ve tablo açıklamaları (gerekirse)

Şekillerin ve Tabloların Yayına Hazırlığı

• Şekiller, grafikler ve fotoğraflar, makale yükleme sistemi aracılığıyla ayrı dosyalar (JPEG formatında) halinde sunulmalıdır.

• Dosyalar bir Word belgesine veya ana belgeye gömülmemelidir.

• Şeklin alt birimleri olduğunda; alt birimler tek bir görüntü oluşturmak için birleştirilmemelidir. Her alt birim, başvuru sistemi aracılığıyla ayrı ayrı sunulmalıdır.

• Şekil alt birimlerini belirtmek için görüntüler Arabik rakamlarla (1,2,3...) numaralandırılmalıdır.

• Gönderilen her bir şeklin en düşük çözünürlüğü 300 DPI olmalıdır.

• Şekiller, basılı hali rahatça okunacak şekilde yüksek çözünürlükte olmalı ve en fazla 6 adet ile sınırlandırılmalıdır.

• Şekillerin açıklamaları ana belgenin sonunda listelenmelidir.
• Bilgi veya resimler hastaların tanımlanmasına izin vermemelidir. Kullanılan herhangi bir fotoğraf için hastadan ve/veya yasal temsilcisinden yazılı bilgilendirilmiş onam alınmalıdır.

• Tablolar Microsoft Word dosyası formatındaayrı dosyalar halinde sunulmalıdır. Tablo sayısı en fazla 6 adet olmalıdır. Tüm tablolar, ana metinde kullanıldığı sırayla art arda numaralandırılmalıdır. Tablo açıklamaları ana belgenin sonunda listelenmelidir.

Kaynaklar

Tüm referanslar Vancouver tarzında ana metinde atıfta bulunuldukları sırayla numaralandırılmalıdır. Metin içinde ikiden fazla ardışık kaynak kullanılıyorsa yalnızca ilk ve son kaynak numaraları belirtilmelidir (örn; 2-6). Dergi isimleri Index Medicus'taki dergi kısaltmalarına uygun olarak kısaltılmalıdır. Altı veya daha az yazar olduğunda, tüm yazarların ismi yazılmalıdır. Yedi veya daha fazla yazar varsa, ilk 6 yazarın isminin arkasından 've ark. (et al.)' yazmalıdır. Farklı yayın türleri için kaynak yazım stilleri aşağıdaki örneklerde sunulmuştur:

Dergi için;
Neville K, Bromberg A, Bromberg S, Hanna BA, Rom WN. The third epidemic multidrug resistant tuberculosis. Chest 1994;1(4):45-8.

Kitap için;
Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Kitap bölümü için;
Collins P. Embryology and development, Neonatal anatomy and growth. In: Williams PL, Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE, Ferguson MWJ. Gray's Anatomy (38th Ed) London, Churchill Livingstone, 1995; 91-342.

Web sitesi için;
Gaudin S. How moon landing changed technology history [Internet]. Computerworld UK. 2009 [cited 15 June 2014]. Available from: http://www.computerworlduk.com/in-depth/it-business/2387/how-moon-landing-changed-technology-history/

Bildiriler için;
Proceedings of the Symposium on Robotics, Mechatronics and Animatronics in the Creative and Entertainment Industries and Arts. SSAISB 2005 Convention. University of Hertfordshire, Hatfield, UK; 2005.

Tez için;
Ercan S. Venöz yetmezlikli hastalarda kalf kası egzersizlerinin venöz fonksiyona ve kas gücüne etkisi. Süleyman Demirel Üniversitesi Tıp Fakültesi Spor Hekimliği Anabilim Dalı Uzmanlık Tezi. Isparta: Süleyman Demirel Üniversitesi. 2016.

Geri Çekme veya Reddetme

Yazıyı Geri Çekme: Gönderilen yazının değerlendirme sürecinde gecikme olması vb. gibi gerekçelerle yazıyı geri çekmek ve başka bir yerde yayınlatmak isteyen yazarlar yazılı bir başvuru ile yazılarını dergiden geri çekebilirler.

Yazı Reddi: Yayınlanması kabul edilmeyen yazılar, gerekçesi ile geri gönderilir.

Kabul Sonrası

Makalenin kabul edilmesi durumunda, kabul mektubu dergipark sistemi üzerinden sorumlu yazara gönderilir. Makalenin baskıdan önceki son hali yazarın son kontrolüne sunulur. Dergi sahibi ve yayın kurulu, kabul edilen makalenin derginin hangi sayısında basılacağına karar vermeye yetkilidir. Yazarlar, yazılarının basılmasının ardından makalelerini kişisel veya kurumsal web sitelerinde, uygun alıntı ve kütüphane kurallarına bağlı kalarak yayınlayabilirler.

Medical Journal of Süleyman Demirel University Authors Guidelines

About Med J SDU

Medical Journal of Süleyman Demirel University (Med J SDU) is a journal published by Süleyman Demirel University and is published quarterly in March, June, September and December. Med J SDU is an international, scientific, open access, online/printed journal in accordance with independent, unbiased, and double-blinded peer-review principles.

Med J SDU publishes the researches in the fields of health sciences including original clinical and experimental studies, reviews on current topics, case reports, editorial comments and letters to the editor. The journal's publication language is Turkish and English.

Med J SDU is indexing in both international (DOAJ, EBSCO, Index Copernicus) and national (TRDizin) indexes.

There is no charges for publishing or publishing process. No copyright price are payable to the authors or other third parties for the articles published in the journal. Med J SDU has adopted the policy of providing open access with the publication. Authors' credentials and e-mail addresses are in no way used for other purposes.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Ethical Principles

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. Ethics committee approvals or an equivalent official documents must be uploaded into the dergipark system.

• For manuscripts concerning experimental researches on humans, a "Written Informed Consent to Participate and Publish" statement should included in the text.

• Written Informed Consent to Participate Publish statement and Ethics Committee approval details (name of the committee, date and number) should included in the Materials and Methods section and in the end of the article (before references) with separate sub-headings.

• It is the authors responsibility to carefully protect the patients anonymity. For photographs that may reveal the identity of the patients, releases signed by the patient or their legal representative should be enclosed.

• For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. **Ethics Committee approval details (name of the committee, date and number) should included in the Materials and Methods section and in the end of the article (before references) with separate sub-headings.**

All submissions are screened by a **similarity detection software (iThenticate) and the similarity limitation is 25%**. The Editorial Board of the journal handles all appeal and complaint cases within the scope of Committee on Publication Ethics (COPE) guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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Manuscript Preparation

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/tr/pub/sdutfd. Manuscripts submitted via any other medium will not be evaluated. Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests. The editor reserves the right to reject manuscripts that do not comply with the above-mentioned requirements. Corrections may be done without changing the main text. The editor reserves the right to reject the articles that do not meet the required conditions.

Authors are required to submit the following:

• Copyright Transfer Form,
• Title Page (including Title of Manuscript, Running title, authors' name, title and institution, corresponding author's contact information, ORCID addresses, name of the organization supporting the research and ethical approvals)
• Main document (It should be prepared according to the template and should include a sectioned abstract.).
• Figures (Jpeg format, at least 300 DPI, up to 6 figures)
• Tables (Microsoft Word format, up to 6 table)
• Ethical Approvals (If applicable)
• Author Contributions (according to CRediT, please see Template)

Preparation of the Main Document

The articles should be written with double-spaced in 12 pt, Times New Roman character and at least 2.5 cm from all edges of each page. The main text should not contain any information about the authors' names and affiliations. **Original articles should have a structured abstract (Objective, Material and Methods, Results, Conclusion, Keywords).** For case reports and reviews, the structured abstract is not used. Limit the abstract to 300 words. References, tables and citations should not be used in an abstract. Authors must include relevant keywords (3-5) on the line following the end of the abstract. For the Non-Turkish authors, submission of Turkish

title, Turkish abstracts and Turkish keywords are not required. All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition. When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company, should be provided in parentheses.

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively. The symbols used must be in nomenclature standards.

Original Research Articles should be **maximum of 4000 words** and include subheadings below;

• Title
• Abstract
• Keywords
• Introduction
• Material and Methods
• Results
• Discussion
• Conclusions
• Statements (Please See: Template)
• References
• Figure and Table Legends (if necessary)

Case Reports should be **maximum of 2000 words** and include subheadings below;

• Title
• Abstract
• Keywords
• Introduction
• Case Presentation
• Discussion and Conclusion
• Statements (Please See: Template)
• References
• Figure and Table Legends (if necessary)

Reviews should be **maximum of 5000 words** and include subheadings below;

• Title
• Abstract
• Keywords
• Main text
• Conclusion
• Statements (Please See: Template)
• References
• Figure and Table Legends (if necessary)

Letters to Editor should be **maximum of 1000 words** and include subheadings below;

• Title
• Abstract
• Keywords
• Letter to Editor
• Statements (Please See: Template)
• References
• Figure and Table Legends (if necessary)

Preparation of the Figures and Tables

• Figures, graphics, and photographs should be submitted as separate files (in JPEG format) through the submission system.
• The files should not be embedded in a Word document or the main document.
• When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system.
• Images should be numbered by Arabic numbers to indicate figure subunits.
• The minimum resolution of each submitted figure should be 300 DPI.
• Figures should be in high resolution so that the printed version can be read easily and should be limited to a maximum of 6 figures.
• Figure legends should be listed at the end of the main document.
• Information or illustrations must not permit identification of patients, and written informed consent for publication must be sought for any photograph.
• Tables should be submitted as separate Microsoft Word files and are limited with six pieces. All tables should be numbered consecutively. Table legends should be listed at the end of the main document.

References

All references should be numbered consecutively in Vancouver style. If more than two consecutive resources are used, only the first and last source numbers should be specified (for example; 2-6). Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus. When there are 6 or fewer authors, all authors should be listed. If there are 7 or more authors, the first 6 authors should be listed followed by “et al.” The reference styles for different types of publications are presented in the following examples:

For journals;
Neville K, Bromberg A, Bromberg S, Hanna BA, Rom WN. The third epidemic multidrug resistant tuberculosis. Chest 1994;1(4):45-8. 555For books; Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

For book section;
Collins P. Embryology and development, Neonatal anatomy and growth. In: Williams PL, Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE, Ferguson MWJ. Gray’s Anatomy (38th Ed) London, Churchill Livingstone, 1995; 91-342.

For website;
Gaudin S. How moon landing changed technology history [Internet]. Computerworld UK. 2009 [cited 15 June 2014]. Available from: http://www.computerworlduk.com/in-depth/it-business/2387/how-moon-landing-changed-technology-history/

For conference proceeding;
Proceedings of the Symposium on Robotics, Mechatronics and Animatronics in the Creative and Entertainment Industries and Arts. SSAISB 2005 Convention. University of Hertfordshire, Hatfield, UK; 2005.

For Thesis;
Ercan S. Venöz yetmezlikli hastalarda kalf kası egzersizlerinin venöz fonksiyona ve kas gücüne etkisi. Suleyman Demirel University Faculty of Medicine Sports Medicine Department Thesis. Isparta: Suleyman Demirel University. 2016.

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İçindekiler

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EDİTORYAL EDITORIAL

Med J SDU / SDÜ Tıp Fak Derg ▶ 2022:29(2):149-151 doi: 10.17343/sdutfd.1092180

SÜLEYMAN DEMİREL ÜNİVERSİTESİ HASTANESİNDE COVID-19 YÖNETİMİ: BİR PANDEMİNİN İKİNCİ YIL KRONOLOJİSİ

COVID-19 MANAGEMENT IN SULEYMAN DEMIREL UNIVERSITY HOSPITAL: THE SECOND YEAR CHRONOLOGY OF A PANDEMIC

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Öz

Pandemi henüz bitmiş değildir, pandeminin ikinci yılı özellikle delta ve omicron varyantlarının, özellikle ikinci yarısı da normalleşme kararlarının etkisi altında geçti. Toplumsal uyumun bu süreçteki tartışmasız tek doğru olduğu gerçeği hem Türkiye hem de Dünya için değişmedi.

Anahtar Kelimeler: Covid-19, Yönetim, Hastane

Abstract

The pandemic is not finish yet. The second year of the pandemic passed under the influence of especially delta and omicron variants, and especially the second half of passed the normalization decisions. The fact that compliance of the society to the rules is the only undisputed truth in this process both for Türkiye and the world.

Keywords: Covid-19, Management, Hospital

"Dünya, 2020 yılında 'Pandemi' ifadesinin tüm anlamı ve gerçekliği ile yüzleşti ve pandemi ile mücadelenin ancak toplumsal uyum ile sağlanabileceği gerçeği bu sürecin değişmez tek doğrusu oldu" ifadeleri ile başladığımız, Covid-19'un düşündürdüklerinden, Covid-19 pandemi sürecinde hastanemizde yapılan yönetsel ve fiziksel değişikliklerden, Covid-19 pandemi sürecinin hastanemizdeki yönetim kronolojisinden bahsettiğimiz ve tüm insanlığa pandeminin olmadığı bir Dünya diliyoruz temennisi ile bitirdiğimiz 'Süleyman Demirel Üniversitesi hastanesinde Covid-19 yönetimi: bir pandeminin birinci yıl kronolojisi' başlıklı çalışmamızın ardından (1) bir yıl daha geçti ve pandeminin 11 Mart 2022 tarihi itibariyle ikinci yılını da tamamlamış bulunmaktayız. Bu makalenin amacı pandeminin ikinci yıl kronolojisini sizlerle paylaşmaktır ancak pandeminin bütünlüğünün anlaşılması açısından öncelikle birinci yıl kronolojisinden bahsetmiş olduğumuz makalemizi (1) okumanız faydalı olacaktır.

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Süleyman Demirel Üniversitesi Hastanesi süreci yine olması gerektiği gibi bu dönemde de çok dinamik ve dikkatli bir şekilde takip etti. Hastanemizin verilerini, pandemi hastaları ile diğer hastalıklardan dolayı başvuran hastalar arasındaki dengeyi, Isparta ili ve Türkiye'deki pandemi vaka sayısı ve aşılanma oranlarını yakından takip ederek hastane içerisinde pandemi hastalarının hizmetine yönelik alanların planlamaları dinamik bir şekilde gerçekleştirildi.

Covid-19 Pandemi sürecinin Türkiye'de alınan kararların etkisi altında hastanemizdeki ikinci yıl yönetim kronolojisi aşağıda sıralanmıştır;

11 Mart 2021: Pandeminin ikinci yılına 11 Mart 2021 tarihi itibariyle girildi. Henüz pandemi bütün gerçekliği ile hayatımızdadır. Özellikle İngiltere, Brezilya ve Güney Afrika varyantları gündemde yer almaktadır.

15 Mart 2021: Sayın Cumhurbaşkanımız Recep Tayyip Erdoğan tarafından kabine toplantısı ardından daha önce açıklanan illere göre risk haritası uygulamasını bir süre daha sürdürme ve gelişmeleri yakın takip etme kararı alındığı açıklandı.

26 Mart 2021: Isparta İl Sağlık Müdürlüğü'nde genel durum değerlendirme toplantısı yapıldı.

29 Mart 2021: Sayın Cumhurbaşkanımız Recep Tayyip Erdoğan tarafından kabine toplantısı ardından "yeni önlemler" açıklandı.

05 Nisan 2021: Tüm personelimize maske, mesafe ve temizlik kurallarına uymaları ile ilgili bilgilendirme ve hatırlatma mesajı gönderildi.

13 Nisan 2021: Sayın Cumhurbaşkanımız Recep Tayyip Erdoğan tarafından kabine toplantısı ardından "kısmi kapanma uygulaması" başlatıldığı açıklandı.

14 Nisan 2021: On yedinci Hastane Pandemi Kurulu toplantısı yapıldı.

26 Nisan 2021: 29 Nisan 2021 Perşembe günü saat 19.00'dan 17 Mayıs 2021 Pazartesi günü saat 05.00'e kadar sürecek olan "tam kapanma" dönemi ilan edildi.

28 Nisan 2021: T.C. Sağlık Bakanı Sayın Dr. Fahrettin Koca tarafından "İstanbul'da 5 vatandaşımızda Hindistan varyantı (Delta) gözlendi. Bu varyant ilk kez görüldü ve vakalar izolasyon altında takip ediliyor" açıklaması yapıldı.

29 Nisan 2021: 29 Nisan 2021 Perşembe günü saat 19.00'dan 17 Mayıs 2021 Pazartesi günü saat 05.00'e kadar sürecek olan "tam kapanma" uygulaması başladı.

17 Mayıs 2021: Tam kapanmanın ardından "Kısmi kapanma" uygulamasına devam edildi.

01 Haziran 2021: Sayın Cumhurbaşkanımız Recep Tayyip Erdoğan tarafından kabine toplantısı ardından "kademeli normalleşme" ve "yeni normal" dönemi açıklandı.

09 Haziran 2021: On sekizinci Hastane Pandemi Kurulu toplantısı yapıldı.

01 Temmuz 2021: T.C. İçişleri Bakanlığı tarafından 1 Temmuz normalleşme genelgesi yayınlandı.

01 Temmuz 2021: Sağlık personellerine yönelik 3. doz aşılama işlemleri başladı.

04 Temmuz 2021: T.C. Sağlık Bakanlığı Covid-19 Bilgilendirme Platformu'nda tablo bilgilendirmesinde değişikliğe gidildi ve tablodan "toplam" ifadesi ile belirtilen parametreler (toplam vaka, toplam vefat vb.) çıkartıldı.

20 Ağustos 2021: On dokuzuncu Hastane Pandemi Kurulu toplantısı yapıldı.

06 Eylül 2021: Tam zamanlı yüz yüze eğitime başlandı.

02 Kasım 2021: Yirminci Hastane Pandemi Kurulu toplantısı yapıldı.

24 Kasım 2021: Güney Afrika'dan Dünya Sağlık Örgütü'ne ilk omicron varyantı rapor edildi.

11 Aralık 2021: Türkiye'de ilk omicron varyantı vakası ilan edildi.

31 Aralık 2021: 2 doz Sinovac, 2 doz BioNTech aşısı yaptıranlar için beşinci doz aşı uygulaması başladı.

01 Şubat 2022: Türkiye'de pandeminin başından bu yana vaka sayısı ilk kez 100.000 sınırının üzerine çıktı.

04 Şubat 2022: Türkiye'de pandeminin başından bu yana bir günde 111.157 vaka ile en yüksek vaka sayısının tespit edildiği gün oldu.

02 Mart 2022: Sağlık Bakanı Sayın Dr. Fahrettin Koca ve Bilim Kurulu üyelerinin toplantısı sonrası salgının

düşüşe geçtiği realitesine dayanarak, hayatımızın ihtiyaç duyduğu psikolojik rehabilitasyon da amaçlanarak alındığı belirtilen kararlar açıklandı. Bu kararlar; açık havada maske kullanma zorunluluğunun kaldırılması, kapalı ortamlarda havalandırma yeterliyse mesafe kuralına uyum gösteriliyorsa maske şartının kaldırılması, HES (Hayat Eve Sığar) kodu uygulamasının kaldırılması, hastalık şüphesi olmayan kişilerden test istenmemesi, okullarda 2 vaka çıkması halinde sınıfın kapatılması şeklindeki uygulamanın kaldırılması.

11 Mart 2022: itibariyle Dünya Sağlık Örgütü'nün Covid-19'u pandemi olarak ilanının ve T.C. Sağlık Bakanlığı'nın Türkiye'de ilk vaka tespit edildiğini ilanının üzerinden 2 yıl geçmiş oldu.

11 Mart 2022: Bugün 25.401 vaka tespit edildi.

11 Mart 2022: tarihi itibariyle Dünya Sağlık Örgütü'nün resmî web sayfasında Dünya genelinde doğrulanmış toplam 452 milyondan fazla vaka ve 6 milyondan fazla ölüm bildirildi (2).

11 Mart 2022: Bu makale, pandeminin ikinci yılının hastanemizdeki yönetim sürecini kapsamaktadır. Bir yıl boyunca özellikle T.C. Cumhurbaşkanlığı, T.C. Sağlık Bakanlığı, T.C. İçişleri Bakanlığı, T.C. Milli Eğitim Bakanlığı ve Isparta İl Hıfzıssıhha Kurulları tarafından çok sayıda genelge ve talimatlar yayınlandı. Bu genelgeler içerisinde hastanemizi ilgilendiren uygulamalar oldu, bu genelgeler ve talimatlar bütün personellerimiz ile çok hızlı bir şekilde paylaşıldı ve hastane yönetimi olarak uygulanması gerekenler vakit kaybetmeden hayata geçirildi.

11 Mart 2022: Artık pandeminin üçüncü yılına 11 Mart 2022 tarihi itibariyle girmiş bulunuyoruz. Henüz pandemi bütün gerçekliği ile hayatımızdadır, özellikle omicron varyantı tüm dünyada etkisini göstermeye devam etmektedir.

Bu süreç doğruların yanlışların sürekli tartışıldığı çok dinamik bir süreçti, yukarıda bahsedilen kronoloji içerisinde kurum disiplinini, dinamizmini ve bilimselliğini pandeminin ikinci yılında da 4 kez düzenlediğimiz ve 14 farklı karar alarak uygulamaya geçirdiğimiz Hastane Pandemi Kurulu toplantıları ile sürdürdük. Bu toplantılar günlük, haftalık ve aylık gelişmelerin, Süleyman Demirel Üniversitesi Hastanesi, Isparta ve Türkiye dinamiklerinin, bilimsel ve toplumsal verilerin bütün yönleri ile değerlendirilerek çok yakından takip edildiği ve kararların alındığı toplantılardı.

Pandemi henüz bitmiş değildir, pandeminin ikinci yılı özellikle delta ve omicron varyantlarının, yeni önlemlerin, kısmi kapanma, tam kapanma, normalleşme kararlarının ve aşılama uygulamalarının yaygınlaştırılmasına yönelik çalışmaların etkisi altında geçmiştir, Dünya Sağlık Örgütü'nün 11 Mart 2021 ve 11 Mart 2022 toplam vaka ve toplam ölüm sayıları karşılaştırılır ise pandeminin ikinci yılında birinci yılına kıyasla çok daha fazla vaka ve ölüm sayısına ulaşıldığı görülmektedir (2). Bu dönemde bütün insanlık pandemi ile yaşamaya daha da alıştı, süreç toplumun olağan yaşama isteği, tedbirleri reddediş ve unutmaya yönelik yaklaşımı, kurallara ve yeni yaşam biçimine uyumunun ve uyumsuzluğunun olduğu, pandeminin bir an önce son bulması ve olağan hayata geri dönme beklentisinin daha da arttığı bir süreç oldu. Ancak değişmeyen tek gerçek toplumsal uyumun bu süreçteki tartışmasız tek doğru olduğu gerçeğiydi, bu gerçek hem Türkiye hem de Dünya için değişmedi, bu sürecin son bulması için önlemlere toplumsal olarak azami ölçüde dikkat edilmesi, özen gösterilmesi ve aşılama oranının arttırılması gerekmektedir.

Son söz; pandeminin ikinci yılı, aşılamanın yaygınlaştırılma çabasının en önemli hedef olduğu, içerisinde tam kapanmayı da tedbirleri hafiflettiğimiz kararları da yaşadığımız bir dönemdi. Ancak pandeminin birinci yılının sonunda yer alan temennimiz güncelliğini korudu, üçüncü yıl içerisinde pandeminin son bulmasını temenni ederek tüm insanlığa pandeminin olmadığı bir Dünya diliyoruz.

Çıkar Çatışması Beyanı
Herhangi bir çıkar çatışması yoktur.

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Kaynaklar

1. Yazkan R, Şengeze N, Zihni İ, Erdoğan M, Şenol N, Ergün O, İbrişim E. Covid-19 Management in Suleyman Demirel University Hospital: The First Year Chronology of a Pandemic. Med J SDU 2021;28(ozelsayi-1):1-10.
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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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EVALUATION OF ORAL AND MAXILLOFACIAL SURGEONS' AND RESEARCH ASISSTANTS' ATTITUDES OF DEFENSIVE DENTISTRY

AĞIZ, DİŞ VE ÇENE CERRAHLARI VE ARAŞTIRMA GÖREVLİLERİNİN DEFANSİF DİŞ HEKİMLİĞİ TUTUMLARININ DEĞERLENDİRİLMESİ

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Öz

Amaç

Defansif tıp uygulamaları kavramı, klinik karar süreçlerinde öncelikle hekimlerin olası hukuki işlemlerden korunmayı amaçlaması olarak tanımlanmaktadır. Günümüzde gelinen noktada sağlık uygulamalarını konu edinen yasal süreçlerin artması hekimlerin klinik uygulamalarında defansif tıp uygulamalarını daha sık kullanmalarına neden olmaktadır. Bu çalışmanın amacı ağız, diş ve çene cerrahları ve araştırma görevlilerinin defansif diş hekimliği tutumlarını ve bu tutumları etkileyen faktörleri araştırmaktır.

Gereç ve Yöntem

Ocak-Şubat 2021 tarihleri arasında çeşitli kurumlarda görev yapan 146 ağız, diş ve çene cerrahisi (ADÇC) uzmanı/araştırma görevlisine çevrimiçi anket formu ulaştırıldı, anket formunu eksiksiz dolduran ve çalışmaya dahil edilme kriterlerini karşılayan 63 diş hekimi (%43,1) çalışmaya dahil edildi. Katılımcıların yaşı, cinsiyeti, faaliyet gösterdikleri kurum veya özel kuruluş, hekim-hasta ilişkisinde geçirdikleri süre, malpraktis davası geçmişi, önümüzdeki 10 yıl içinde malpraktis davasıyla karşılaşıp karşılaşmayacaklarına ilişkin düşünceleri ve defansif diş hekimliği konusundaki bilgi düzeyleri sorgulandı. Çalışmaya dahil edilme kriterleri ADÇC alanında en az 1 yıl hizmet vermiş olmak ve halen bu alanda hasta-hekim ilişkisi içerisinde olmak olarak belirlendi.

Bulgular

Çalışmaya katılan hekimlerin %47,6'sının çok yüksek düzeyde, %41,3'ünün yüksek düzeyde ve %11,1'inin orta düzeyde defansif diş hekimliği uyguladıkları saptanmış olup, ortalama defansif diş hekimliği skoru 46,25 ± 7,42 olarak bulunmuştur. Ortalama defansif diş hekimliği skorlarının çalışılan kurum, dava geçmişi ve gelecek 10 yıldaki dava beklentisine bağlı olarak değişim gösterdiği saptanmıştır. (p<0,05)

Sonuç

ADÇC uzmanları ve araştırma görevlilerinin yaygın şekilde defansif diş hekimliği uyguladığı sonucuna ulaşılmıştır. Öte yandan çalışmamızda ADÇC uzmanlarının ve araştırma görevlilerinin defansif diş hekimliği kavramı hakkında yeterli bilgiye sahip olmadığı tespit edilmiş olup, mezuniyet öncesi müfredatta defansif diş hekimliği kavramına yer verilmesinin faydalı olacağını düşünmekteyiz.

Anahtar Kelimeler: Ağız,Diş ve Çene Cerrahisi, Defansif Diş Hekimliği, Sağlık Hukuku

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Abstract

Objective
The concept of defensive medicine practices can be described as the physicians primarily aiming to protect themselves from possible legal actions in clinical decision processes. At the point reached today, the increase in legal processes dealing with health practices causes physicians to use defensive medical practices more frequently in their clinical practice. The aim of this study is to investigate the defensive dentistry attitudes of oral and maxillofacial surgeons (OMFS) and research assistants and the factors affecting these attitudes.

Materials and Methods
146 OMFS specialists/research assistants working in various institutions were contacted between January-February 2021, and 63 dentists (43.1%), who responded by filling out the survey and met the inclusion criteria, were included in the study. The participants' age, gender, institution or private establishment where they operate, time spent in the physician-patient relationship, history of malpractice lawsuits, thoughts on whether they will face malpractice lawsuits in the next 10 years, and their level of knowledge on defensive dentistry were recorded. Inclusion criteria for the study were determined as having served at least 1 year in the field of OMFS and still being in a patient-physician relationship in this field.

Results
It was concluded that 47.6% of the physicians participating in the study applied defensive dentistry at a very high level, 41.3% at a high level, and 11.1% at a moderate level, while the mean defensive dentistry score was found as 46.25 ±7.42. It has been determined that the mean defensive dentistry scores vary depending on the institution, litigation history and the anticipation of litigation in the next 10 years.

Conclusion
OMFS specialists and research assistants commonly practice defensive dentistry. On the other hand, it has been determined that OMFS specialists and research assistants do not have sufficient knowledge about the concept of defensive dentistry, therefore we think that including training on the concept of defensive dentistry in graduate or post-graduate programs would be beneficial.

Keywords: Oral and Maxillofacial Surgery, Defensive Dentistry, Health Law

Introduction

The concept of defensive medicine practices can be described as the physicians primarily aiming to protect themselves from possible legal actions in clinical decision processes (1). This concept is essentially divided into two as positive and negative defensive medicine practices (2). Positive defensive medicine practices are defined as requiring additional examination, imaging, or consultation from patients solely for the purpose of protection from legal processes, without seeking medical benefit, while negative defensive medicine practices are defined as physicians refraining from applying treatment procedures with high complication rates and avoiding treatment of patients with complicated problems (3).

At the point reached today, beside the increase in the number of health law cases, especially in developed countries, the number of studies carried out in this field is expanding at an increasing pace (4,5). On the other hand, the increase in legal processes dealing with health practices causes physicians to use defensive medical practices more frequently in their clinical practice, consequently leading to an inevitable increase in medical expenses (6,7). While the estimated cost of malpractice lawsuits filed against physicians in the USA in 2002 was reported to be about 6.3 billion dollars, defensive medical practices were estimated to cause a burden of 60 to 108 billion dollars to the health system (4).

As expected, surgical branches frequently face such cases. The retrospective study of Jena et al. conducted between 1991 and 2005, including 40,916 physicians working in 25 different specialties, reported that the rate of facing legal proceedings in a year was 19.1% for physicians providing services in the branch of neurosurgery, followed by cardiovascular surgery with 18.9% and general surgery with 15.3% (5).

Malpractice cases in the field of dentistry make up approximately 7-8% of medical malpractice cases (8). Dentistry practices are in the low-medium risk group in terms of malpractice and legal processes (9). Dentistry practices are legally treated under the title of medical practices in our country, just as well as

the whole world, so the concept of defensive dentistry is seen as a sub-title of the concept of defensive medicine practices (10).

Oral and maxillofacial surgery (OMFS) practices need to be performed with utmost care and attention, as they are the most invasive operations of dentistry and the mistake that may occur is usually irreversible. Compared to general dentistry practices and other branches, OMFS can be considered as the riskiest branch in terms of complications, malpractice, and permanent tissue damage. In the study carried out by Perea-Perez et al. in Spain between 2000-2010, 4149 claims that led to legal processes were reviewed and 415 claims that met the inclusion criteria were examined. 40% of these claims were classified as complications, 40% as malpractice, and the remaining 20% as accidents, and the distribution by branches revealed that 50.3% (n: 209) was OMFS practices (problems related to local anesthesia, implantology and oral surgery) followed by endodontics with 20.76%, and prosthetic dental treatment with 12.53% (11).

According to the 27648 numbered ‘’Communiqué on the procedures and principles regarding the institutional contribution in the compulsory liability insurance for medical malpractice’’ published by the Ministry of Health of the Republic of Turkey on July 21, 2010, in the Official Gazette, general dentistry practices are in the 2nd level risk group, oral and dentoalveolar surgery practices are in the 3rd level, and maxillofacial surgery operations are in the 4th level risk group (12). For this reason, the branch of Oral and Maxillofacial Surgery can be evaluated to be in the medium-high risk group since it performs the most invasive operations of dentistry, including maxillofacial surgical operations. Reviewing the previous studies on this subject revealed that general dentistry and specialties were examined, but there were no accessible studies considering oral and maxillofacial surgeons. This study aims to determine the defensive dentistry attitudes of oral and maxillofacial surgeons and research assistants who perform the riskiest operations in terms of complications and malpractice among dentistry practices and to reveal which factors are affected by these attitudes.

Materials and Methods

In our study, a 5-point Likert-type survey prepared by Başer et al. (10), whose validity-reliability tests were carried out, consisting of 4 questions about demographic data, 4 questions about malpractice case history, and knowledge level about defensive dentistry, and 12 propositions about positive and negative defensive dentistry attitudes was applied online. The ethics committee approval required for the study was obtained from the Suleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 30.12.2020 and numbered 407.

Within the scope of the study, 146 OMFS specialists/ research assistants working in various institutions were contacted between January-February 2021, and 63 clinicians (43.1%), who responded by filling out the survey and met the inclusion criteria, were included in the study. Total scores were determined for each participant by scoring the propositions that measure the defensive dentistry attitudes of the participants as “Strongly disagree” (1 point), “Disagree” (2 points), “Undecided” (3 points), “Agree” (4 points), "Strongly agree" (5 points). The total scores were categorized as very high (60-48 points), high (47-36 points), moderate (35-24 points), low (23-12 points) and the attitude levels of the participating physicians about defensive medicine practices were tried to be determined. The participants' age, gender, institution or private establishment where they operate, time spent in the physician-patient relationship, history of malpractice lawsuits, thoughts on whether they will face malpractice lawsuits in the next 10 years, and their level of knowledge on defensive dentistry were recorded. Inclusion criteria for the study were determined as having served at least 1 year in the field of OMFS and still being in a patient-physician relationship in this field.

SPSS 22.0 (IBM®, Chicago, Illinois, US) program was used for data analysis. First of all, the percentage distributions of the answers given to the statements questioning the defensive dentistry attitudes of the participants were determined separately for each question using descriptive statistical methods. Whether the variables fit the normal distribution was assessed with the Kolmogorov-Smirnov test, and the homogeneity of the variances was evaluated with the Levene test. The Student's t-test was used to determine the relationship between demographic data and the mean total scores, while the Kruskal Wallis and Mann Whitney U tests were used to evaluate the data with non-normal distribution, that is the relationship between the institution and the time spent in the patient-physician relationship and the total scores. The level of statistical significance was set as $p<0.05$. Obtained results were presented as mean ± standard deviation or number (n) and percentage (%).

Results

A total of 63 oral and maxillofacial surgeons/research assistants with a mean age of 30.98 ± 4.27, 25 of whom were women (39.7%), were included in our study. It was concluded that 47.6% of the physicians participating in the study applied defensive dentistry at a very high level, 41.3% at a high level, and 11.1% at a moderate level, while the mean defensive dentistry score was found as 46.25 ±7.42.

The mean defensive dentistry score was 45.96 ±7.7 in female dentists and 46.44 ±7.32 in male dentists participating in our study, and there was no statistically significant difference between the two groups (p>0.05). When the participants were asked “Have you been sued for malpractice during your medical profession?", the mean defensive dentistry score of 7 physicians who answered "Yes" was 49.66 ±5.38, while the mean score of dentists who answered "No" was 45.41 ±7.64. It was determined that there was a statistically significant difference between the two groups (p<0.05). On the other hand, when the participant dentists were categorized according to their answers to the question "Do you think you will be sued for malpractice in the next 10 years?" , the mean defensive dentistry score of the physicians who answered "Yes" (n: 35, 55.5%) was 48.37 ± 6.46, and of the dentists who answered "No" (n: 28, 44.5%) was 43.6 ± 7.79, unveiling a statistically significant difference between the two groups (p<0.05) (Table 1).

The distribution of the answers given to the propositions, in which positive and negative defensive dentistry attitudes were questioned, in the survey is presented in Table 2.

Evaluation of the participating physicians' patient-physician relationship duration showed that 14 physicians (22.2%) had a patient-physician relationship for "1-3 years", 26 physicians (41.2%) "4-7 years", 11 physicians (17.4%) "8-10 years", and 12 physicians (19%) for 10 years or more. When the comparison between the physician-patient relationship and the defensive dentistry scores was examined, it was found that the defensive dentistry scores increased as the time spent in the physician-patient relationship increased, but there was no statistically significant difference between the groups (p>0.05) (Table 3).

Classification of the participating physicians according to the institutions they worked in pointed out that 28 physicians were university staff, 18 physicians were employed in the ministry of health, and 17 physicians in private clinics. While the mean defensive dentistry score of the physicians working as university staff was found to be 42.53 ±7.01, it was determined as 50.5 ±6.93 in the physicians employed in the ministry of health, and 47.88 ±5.65 in the physicians working in private clinics. The difference between the mean of the categorical data was found to be statistically significant, and the Mann - Whitney U test was applied to determine from which groups the present

Table 1 Mean defensive dentistry scores by gender, litigation history and anticipation of litigation in the next 10 years.

		N (%)	Mean score	Standard deviation	Standard error	p value
Gender	Female	25(%39.7)	45.96	7.70	1.54	**0.803**
	Male	38(%60.3)	46.44	7.32	1.18	
Litigation history	Yes	7 (%11.1)	49.66	5.38	1.55	**0.046***
	No	56(%88.9)	45.41	7.64	1.07	
Anticipation of litigation in the next 10 years	Yes	35(%55.5)	48.37	6.46	1.09	**0.010***
	No	28(%44.5)	43.60	7.79	1.47	

*:p<0,05

Table 2 The distribution of the answers given to the propositions.

	Proposition number	Strongly disagree(1)	Disagree(2)	Undecided(3)	Agree(4)	Strongly agree (5)	Total
Positive Propositions	1	3 (%4.8)	1 (%1.6)	8 (%12.7)	15 (23.8)	36 (%57.1)	63
	2	1 (%1.6)	1 (%1.6)	4 (%6.3)	22 (%34.9)	35 (%55.6)	63
	3	0 (%0.0)	1 (%1.6)	7 (%11.1)	14 (%22.2)	41 (%65.1)	63
	4	18 (%28.6)	7 (%11.1)	5 (%7.9)	18 (%28.6)	15 (%23.8)	63
	5	0 (%0.0)	0 (%0.0)	7 (%11.1)	16 (%25.4)	40 (%63.5)	63
	6	4 (%6.3)	7 (%11.1)	8 (%12.7)	20 (%31.7)	24 (%38.1)	63
	7	0 (%0.0)	4 (%6.3)	14 (%22.2)	9 (%14.3)	36 (%57.1)	63
Negative Propositions	8	1 (%1.6)	5 (%7.9)	22 (%34.9)	12 (%19)	23 (%36.5)	63
	9	12 (%19)	11(%17.5)	20 (%31.7)	7 (%11.1)	13 (%20.6)	63
	10	9 (%14.3)	8 (%12.7)	16 (%25.4)	12 (%19)	18 (%28.6)	63
	11	8 (%12.7)	5 (%7.9)	14 (%22.2)	18 (%28.6)	18 (%28.6)	63
	12	6 (%9.5)	5 (%7.9)	17 (%27.0)	8 (12.7)	27 (%42.9)	63

Table 3 Mean defensive dentistry scores of dentists according to the time spent in patient-physician relationship.

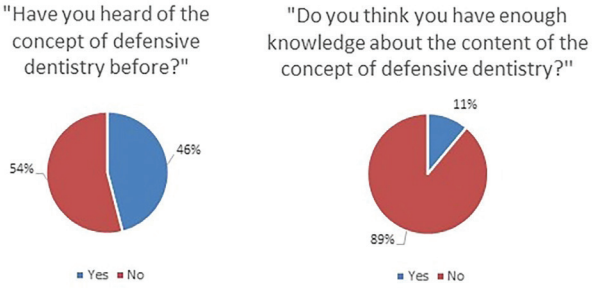
Patient-physician relationship duration	N	Meanscore	Standard deviation	Standard error	p value
1-3 year(s)	14 (%22.2)	42.42	8.20	2.19	0.196
4-7 years	26 (%41.2)	47.03	7.13	1.39	
8-10 years	11 (%17.4)	47.32	8.61	2.59	
10+ years	12 (%19)	48.58	4.64	1.33	
Total	63 (%100)	46.25	7.42	.93	

Table 4 Average defensive dentistry scores of dentists working in different institutions.

Institutions	N	Mean score	Standard deviation	Standard error	p value
University	28	42.53	7.01	1.32	0.001*
Ministry of Health	18	50.50	6.93	1.63	
Private clinics	17	47.88	5.65	1.37	
Total	63	46.25	7.42	.93	

*:p<0,05

Graphic 1
The knowledge levels of the participants about defensive dentistry.



difference originated. According to the results of this test, the defensive dentistry scores of the physicians working in university hospitals were statistically significantly lower than the scores of physicians working in the ministry of health and private clinics (p<0.05), while there was no statistically significant difference between the scores of physicians working in the ministry of health and private clinics (p>0.05) (Table 4).

In the study, the knowledge levels of the participants about defensive dentistry were also questioned. In response to the question "Have you heard of the concept of defensive dentistry before?", 29 participants (46%) answered "Yes", while 34 participants (54%) answered "No". In response to the question "Do you think you have enough knowledge about the content of the concept of defensive dentistry?" 7 participants (11.1%) answered "Yes", while 56 participants (88.9%) answered "No" (Graphic 1).

Discussion

Dentists providing services in the field of OMFS perform many different surgical procedures, especially dentoalveolar surgical operations and dental implantology, carrying risks for permanent or temporary neurosensory disorders, aesthetic dissatisfaction, permanent hard and soft tissue losses, facial scarring, and iatrogenic injury (13). In this respect, OMFS specialization differs from general dentistry and other dentistry branches, therefore, defensive attitudes in this field should be evaluated separately, as in other surgical branches.

There are many studies in the literature examining the defensive attitudes of different surgical branches. In their study published in 2007, Upadhyay et al. reported that among orthopedics and traumatology specialists who performed knee arthroplasty, 78% of physicians faced at least one malpractice lawsuit during their professional life (14). In the survey conducted by Yan et al. in 2017, a questionnaire was sent to 136 neurosurgeons, and 45 physicians who provided feedback were included in the study. In this study, the rate of physicians who faced complaints in the last 3 years was reported as 71.1%, while the rate of physicians who requested additional imaging with a defensive attitude was 64%, and the rate of physicians who referred patients to higher centers for defensive reasons was reported as 28.9% (15). In the study published by Çalıkoğlu et al. in 2020, in which they examined the defensive attitudes of physicians serving in various surgical disciplines, the

rate of participants who exhibited at least 1 defensive attitude was reported as 94.2%, while the rate of participants who had at least one lawsuit process in the past was reported as 24.7% (16). Studdert et al. reported in their study on high-risk branches (emergency medicine, general surgery, neurosurgery, gynecology, orthopedics and traumatology, and radiology) that 87% of the participants had an experience of complaints or lawsuit, and 93% of the physicians showed defensive attitudes. In this study, the most used method among defensive attitudes was reported as an additional imaging request (43%) (2).

Non-evidence-based examination and imaging requests, spending more time on complicated procedures, providing detailed information about the procedure to be performed, keeping patient records in more detail are some of the positive defensive medicine practices (17). In our study, the rate of participation in the proposition "I prescribe most of the drugs I can to my patients within the indications in order to be protected from legal problems", which is one of the suggestions of positive defensive dentistry, was 90.5%, whereas "I request examinations other than those I deem necessary in order to be protected from legal problems (X-ray request, etc.)" was 80.9%. While the rate of agreement with the proposition "I want more consultation about complications that may develop in my patients in order to be protected from legal problems" in our study was determined as 88.9%, the rate of the participants who answered "I agree" and "I totally agree" to the proposition "I refer my patients to more high-level health institutions in order to be protected from legal problems." was determined as 52.4%. While the rate of agreement with the proposition "I explain the surgical procedures in more detail to my patients in order to be protected from legal problems" was 88.9%, 69.8% of the participating physicians agreed with the proposition "I spend more time with my patients in order to be protected from legal problems". The rate of agreement with the proposition "I keep patient records (consent form, etc.) in more detail in order to be protected from legal problems"' was 71.4%. The rate of additional imaging requests we obtained in our study is higher than the rates reported in the studies of Studdert et al. and Yan et al. It can be considered that this result may be due to the fact that radiological imaging is used in almost every patient since the majority of operations and pathologies in the OMFS field occur in hard tissues such as bones and teeth. In the study of Başer et al. (10), in which 66 dentists working in the Ministry of Health participated, the rate of dentists who refer to a higher level health institution due to their defensive attitudes was reported as 87.9%, while this rate was 52.4% in our study. It can be assumed that as a natural result of OMFS specialists and research assistant physicians being in the last link of the referral chain, they apply less to the alternative of referral to a higher level health institution.

The behaviors of avoiding complicated patients or complicated procedures due to defensive attitudes of physicians are defined as negative defensive medicine practice (18). In our study, the rate of agreement with the proposition "I avoid patients with a high probability of litigation in order to protect myself from legal problems", which is one of the propositions questioning the level of negative defensive dentistry, was determined as 55.5%. While the rate of agreement with the proposition "I refrain from patients with complex medical problems in order to avoid legal problems" was 31.7%, the rate of agreement with the proposition "I refrain from treatment protocols with high complication rates in order to avoid legal problems" was 47.6%. While the rate of agreement with the proposition "I tend to prefer non-interventional protocols instead of interventional treatment protocols in order to avoid legal problems" was 57.2%, the rate of agreement with the proposition "I feel apprehension in my practice as malpractice gets more coverage in the media" was found to be 55.6%. The rate of participation in the negative defensive dentistry statements obtained in the study is lower than the rates reported by Başer et al. It may have arisen due to the fact that specialist physicians frequently encounter complicated cases and patients during their residency training in tertiary healthcare institutions, and therefore they are experienced in the management of complicated cases.

It was concluded that 88.9% of the OMFS specialists and research assistants participating in our study practiced defensive dentistry at high and very high levels. In the study of Başer et al., this rate was reported as 78.8% in dentists. In the light of this information, it can be stated that OMFS specialists and research assistants have a higher level of defensive dentistry compared to dentists, and they have a very common defensive attitude, similar to the rates reported in studies on high-risk medical surgery branches (2,16).

In our study, it is seen that 7 participants (11.1%) answered "Yes" to the question "Have you been sued due to malpractice during your medical profession?" This rate was reported as 1.5% among dentists participating in the study of Başer et al. Based on these results, it can be said that the risk of malpractice lawsuits that may be faced during OMFS applications is high compared to general dentistry and low

compared to medical surgery branches. This result is compatible with the definition of "3rd level high-risk branch" for OMFS experts and research assistants, stated in the "Communiqué on the procedures and principles regarding the institutional contribution in the compulsory liability insurance for medical malpractice". On the other hand, a statistically significant difference was found between the defensive dentistry scores of the participating physicians with and without a litigation history ($p<0.05$). This result supports the view that past lawsuits affect the defensive attitude of physicians (5).

In the current literature, there are very few studies dealing with the defensive attitudes of dentists. The study conducted by Başer et al. on 66 dentists in 2014 reported that 45.5% of dentists applied very high, 33.3% high, 15.2% moderate, and 6.1% poor defensive dentistry. (10) The mean defensive dentistry score of the dentists participating in this study was 44.96. ±10.07. In our study, it was concluded that 47.6% of the participant dentists applied very high, 41.3% high, 11.1% moderate defensive dentistry, and the mean defensive dentistry score was 46.25 ± 7.42. Although OMFS specialists and research assistant dentists have higher defensive dentistry scores compared to the dentists working in the ministry of health, it is seen that the mean defensive dentistry scores are similar.

The study published by Saruhan et al. in 2018, which included 120 dentists, reported that defensive dentistry attitudes are common among dentists. In this study, the question "What is your risk of encountering a medical malpractice lawsuit?" was answered "high" by 39% of the participants, "very high" by 13%, and "extremely high" by 20% (19). In our study, 55.5% of the participants answered “Yes” to the question “Do you think you will be sued for malpractice in the next 10 years?” In addition, it was concluded that physicians who expect litigation in the future have statistically significantly higher defensive dentistry scores. Considering that the primary purpose of defensive attitudes is to be protected from legal processes, it can be said that this result is not surprising.

Analysis of the defensive dentistry scores of the physicians working in different institutions revealed that the physicians working as university staff have statistically significantly lower defensive dentistry scores compared to the physicians working in the ministry of health and private clinics, and there was no statistically significant difference between physicians working in the ministry of health and working in private clinics. It can be said that this difference may be due to the fact that the faculty of dentistry is a tertiary health care institution, and the consultant physicians/faculty members can be consulted within the institution instead of referral to a different institution. Moreover, analysis of the relation between the time spent in the patient-physician relationship and the defensive dentistry scores of the participating physicians showed that the defensive dentistry scores of the physicians increased as the time spent in the patient-physician relationship increased, but this difference was not statistically significant. Along with this finding, considering that the majority of the physicians working as university staff (71.4%) are research assistants, it can be said that the shorter time spent in patient-physician relationships compared to specialist physicians may also have contributed to this situation.

When the participants' level of knowledge on defensive dentistry was assessed with the question "Have you heard of the concept of defensive dentistry before?" , 29 of them (46%) answered "Yes", 34 of them (54%) answered "No". In response to the question "Do you think you have enough knowledge about the content of the concept of defensive dentistry?" , 7 participants (11.1%) answered "Yes", while 56 participants (88.9%) answered "No". Based on these results, it can be asserted that awareness and knowledge levels about defensive dentistry should be improved.

Conclusion

As in all surgical branches, malpractice and complications are frequently encountered in the OMFS branch. It is an expected situation that the defensive attitudes of "high risk" branches, where malpractice and complications are more common, will increase in direct proportion to the risk that they face. In our study, we concluded that since the OMFS branch is riskier than general dentistry, OMFS specialists and research assistants commonly practice defensive dentistry. On the other hand, it has been determined that OMFS specialists and research assistants do not have sufficient knowledge about the concept of defensive dentistry, therefore we think that including training on the concept of defensive dentistry in graduate or post-graduate programs would be beneficial.

Ethical Approval

The ethical committee approval was obtained from the Suleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 30.12.2020 and numbered 407.

Conflict of Interest

The authors have no conflicts of interest to declare.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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THE ASSOCIATION OF TYPE D PERSONALITY AND PREMENSTRUEL SYNDROME

PREMENSTRUEL SENDROM İLE TİP D KİŞİLİK İLİŞKİSİ

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Öz

Amaç
Negatif duygulanım ve Sosyal içe dönüklük olmak üzere iki kişilik karakterinin varlığı olarak tanımlanan D tipi kişiliğin, çeşitli hastalıklarla ilişkili olduğu bilinmektedir. Çalışmamızın amacı, Tip D kişilik ile premenstruel sendrom (PMS) arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem
Çalışmaya toplam 286 kadın (PMS:86; kontrol:200) dahil edildi. Yaş ortalamaları 21,28 ± 0,12 di. Veriler Premenstrüel Sendrom Ölçeği, Beck Depresyon Envanteri (BDI-21), D Tipi kişilik Ölçeği (DS14) sonuçlarından elde edildi. Verilerin değerlendirilmesi için SPSS 22 (Statistical Package for Social Sciences) programı kullanıldı. İstatistiksel anlamlılık düzeyi p<0,05 olarak kabul edildi. Sürekli değişkenlerin karşılaştırılmasında t testi, kategorik verilerin karşılaştırılmasında ki-kare testi, sürekli değişkenler arasındaki ilişkileri belirlemek için pearson korelasyon testi kullanıldı.

Bulgular
Depresyon ve D Tipi kişilik, PMS grubunda kontrol grubuna göre anlamlı olarak daha yaygın bulundu. (p<0.0001). D tipi kişilik ile, PMS ve BDI-21 arasında pozitif korelasyon tespit edildi (r=0,434 p<0.0001,r=0,621 p<0.0001).

Sonuç
PMS ile depresyon ve D Tipi kişilik arasında pozitif ilişki tespit edildi. Altta yatan mekanizmaları daha iyi anlayabilmek için ileriye dönük, çok hasta sayılı çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: Depresyon, Kişilik, Premenstruel sendrom

Abstract

Objective
Type D personality, defined as the presence of two personality characters -negative affectivity (NA) and social inhibition (SI), is associated with various disorders. The aim of our study was to investigate the association between Type D personality and premenstruel syndrome (PMS).

Material and Methods
A total of 286 female (86 with PMS and 200 control) were recruited for the study. The mean age of the participants was 21.28 ± 0.12 years. Data were

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obtained from the Premenstrual Syndrome Scale, Beck Depression Inventory (BDI-21) and Type D Personality Scale (DS14). SPSS 22 (Statistical Package for Social Sciences) program was used to evaluate the data. Statistical significance level was accepted as $p<0.05$. T test was used to compare continuous variables, chi-square test was used to compare categorical data, and pearson correlation test was used to determine the relationships between continuous variables.

Results
Depression and Type D personality were found to be significantly more common in the PMS group than in the control group ($p<0.0001$). Type D personality was positively correlation with PMS and BDI-21 ($r=0.434$, $p<0.0001$; OD ($r=0.621$, $p<0.0001$).

Conclusion
A positive relationship was found between PMS and depression and Type D personality. Prospective studies with a large number of patients are needed to better understand the underlying mechanisms.

Keywords: Depression, Personality, Premenstrual syndrome.

Introduction

Premenstrual syndrome (PMS) is a cyclical late luteal phase disorder of the menstrual cycle whereby the daily functioning of woman is affected by emotional and physical symptoms substantially interfering with her quality of life (1). Globally, 50%-80% of women experience PMS and 30%-40% of them present with severe symptoms that affect physical, psychological as well as mental health which require treatment (2).

The etiopathogenesis of PMS is not fully understood. Recent evidence from research studies suggests that reproductive hormone release patterns are normal in women with PMS but women with PMS have a heightened sensitivity to cyclical variations in the levels of reproductive hormones which predisposes them to experience mood and behavioral alterations, and somatic symptoms (3). Gonadal steroid fluctuations may modulate serotonergic transmission and dysregulation of the serotonin system in women with PMS has been demonstrated (4). The probable role of aforementioned mechanisms, PMS causes important behavioral changes in a way that disrupts social relations and daily activities. There is also a relationship between PMS and negative psychological effects such as depression, anxiety, and emotional stress (5).

Type D personality is a personality type characterized by negative affectivity (NA) and social inhibition (SI). It is a general tendency to experience emotional distress characterized by the inhibition of the expression of emotions or behaviors in social relations (SI) and the predisposition to negative mood (NA). People with SI tend to experience inhibition, stressful and insecure social relations due to the fear of rejection and disapproval by other individuals (6). People with NA tend to feel negative emotions in the face of situations and time and these individuals often report feelings of dysphoria, depression, anxiety, tension, irritability, worry, and unhappiness. Type D personality has been reported to be associated with the presence of chronic disorders (7) and the clinical outcomes of various disorders such as cardiac disorders (8), chronic pain (9), fibromyalgia (10). However, there is no study investigating the role of Type D personality on PMS.

Common incidence of PMS, its' relation with physiological well-being, behavioral changes, and disruption of daily activities resulting as well as the paucity of the investigations in this field, we aimed to investigate the relationship between PMS and Type D personality.

Material and Methods

Study Design
This was a cross-sectional study conducted at the Family Medicine outpatient clinic of a tertiary center, six months from July and December 2018. All participants provided written informed consent before enrolling in this study.

Sampling Methods and Sample Size
A total of 286 young female patients (18-23 years), 86 diagnosed as a premenstrual syndrome -the PMS group, and 200 age and body mass index (BMI) matched healthy females without PMS -the control group, were recruited to the study. PMS diagnosis was made by Premenstrual Syndrome Scale (PMSS) (11). The PMSS is a Likert scale consisting of 9 subgroups and 44 items, totally. Scores of PMSS varies between 44 and 220 points, and the cut -off score was 102. As the score increases, the symptoms of PMS are considered to be increased (11).

The exclusion criteria for all participants were a history of any psychiatric disorder, pregnancy, presence of chronic diseases, and chronic medication use.

Data Collection

A self-administered questionnaire including demographic features -age, weight, height, age at menarche, cycle characteristics (duration, volume, regularity, etc.), habits (smoking, alcohol use), presence of sporting activity (≥3 days per week), the requirement of an analgesic drug, herbal medication and traditional method (heat and coffee, etc.) for dysmenorrhea of the participants were used for data collection. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2).

Depression was evaluated using the 21-item Beck Depression Inventory (BDI-21) which is a self-report inventory that measures the severity of depression. These scales were administered to all participants at their enrollment and the scores were noted. Each item in BDI-21 describes a specific behavioral, emotional, and somatic manifestation of depression. The scores range from 0 to 3. Having more than 17 points was considered depression. Mild depression was considered for a total of 17-20 points, moderate depression was considered for 21-30 points and severe depression was accepted as having more than 30 points (12).

Type D personality was evaluated using the DS-14 scale. This 14-item questionnaire comprises two 7-item subscales: NA (e.g. 'I take a gloomy view of things') and SI (e.g. 'I often feel inhibited in social interactions'). Two positively worded items on the SI subscale (e.g. 'I often talk to strangers') were reverse scored. Responses to each item were made on a five-point scale ranging between 0 and 4, yielding a total score of between 0 and 28 for each subscale. Women with a score ≥10 points on NA and SI subscales were considered as Type D personality (6).

Statistical Analyses

Statistical Package for Social Sciences (SPSS) version 22 was used to evaluate the data obtained from the participants. Statistical significance level was accepted as $p < 0.05$. Student t-test and Mann Whitney-U test were used for the comparison of the continuous variables on the basis of their distribution. The Chi-square test was used for the comparison of the categorical data and shown as frequencies. The Pearson correlation tests were performed to determine the relationships between continuous variables for parametric and nonparametric data, respectively.

Permission and Approval of the Ethics Committee

The study was conducted in accordance with the principles of the Helsinki Declaration related to conducting clinical trials on humans, and the research proposal was approved by the Ethics Committee of the Süleyman Demirel University with the number 140 in 04 July 2018.

Results

A total of 286 subjects (86 female in the PMS group and 200 female in the control group) were included in the study. The mean age of the participants was 21.28 ± 0.12 years. There were no significant differences in terms of age, BMI, age at menarche, duration of cycle and menstruation, menstrual regularity, smoking and alcohol use, sporting activity (>3 days per week). The volume of menstrual bleeding was significantly higher in the PMS group (3.55 ± 1.31 pad/day) compared to the controls (3.16 ± 1.25, p=0.01). Dysmenorrhea was also significantly more prevalent in the PMS group (90.7%) than the controls (78.5%, p<0.01), as expected. The requirement of analgesic during menstruation was higher in the PMS group (60.5%) compared to the controls (45.5%, p=0.02). However, the type, duration, and the number of analgesic use were distributed homogenously between two groups (p=0.8, p=0.6, and p=0.2, respectively). The use of herbal medicine for dysmenorrhea was similar between the groups (p=0.07), however, the use of a traditional methods (such as coffee, heat) was significantly higher in the PMS group (52.3%) than the controls (38.5%, p=0.03). Comparison of demographic features of the participants are given in Table 1.

BDI-21 score was higher in the PMS group compared to the controls with a significant difference (p<0.0001). Depression was found in 26.9% (77/286) of the participants. Of those with depression, 10.1% (29/77) had mild depression, 9.1% (26/77) had moderate depression, and 7.7% (22/77) had severe depression. 54.7% (47/86) of the PMS group had depression, and depression was found to be significantly more prevalent in the PMS group compared to the controls (15.5%, p<0.0001). When the severity of depression was compared between the groups, it was found to be severe in22.1% (19/46) of the PMS group and 1.5% (3/31) of the control group.

54.5% (156/286) of the participant had Type D personality. The scores of the NA and SI subscales were higher in the PMS group than in the controls (p<0.0001 and p=0.04, respectively). In the PMS group, 83.7% (72/86) of patients had NA and 87.2%

Table 1 Baseline demographic features of premenstrual syndrome group and control group

	Control group (n=200)	PMS group (n=86)	p value
Age (years)	21.3 ± 2.2	21.17 ± 2.07	0.1
BMI (kg/m²)	21.67 ± 3.01	21.46 ± 2.85	0.3
Age at menarche (years)	12.92 ± 1.09	12.6 ± 1.07	0.05
Duration of cycle (days)	28 ± 1.23	29 ± 2.1	0.6
Duration of menstruation (days)	5.79 ± 1.21	5.98 ± 1.22	0.7
Volume of menstrual bleeding (pad/day)	3.16 ± 1.25	3.55 ± 1.31	**0.01**
Menstrual irregularity (n, %)	16/200 (8%)	8/86 (9.3%)	0.8
Dysmenore (n, %)	157/200 (78.5%)	78/86 (90.7%)	**0.01**
Habits (n,%) **Smoking** **Alcohol use**	 21 (10.5%) 30 (15%)	 8 (9.3%) 9 (10.5%)	 0.7 0.3
Sportic activity (n,%) (≥3 days per week)	75 (%37.5)	32 (%37.2)	0.9
Requirement of analgesic (n, %)	91 (45.5%)	52 (60.5%)	**0.02**
Type of analgesic use (n, %) **Nonsteroid antiinflamatuar drug** **Antispasmotic**	 77/91 (84.6%) 14/91 (15.4%)	 4/52 (82.7%) 9%52 (17.3%)	0.8
Duration of analgesic use (day) **2 day (before mens and day 1)** **1 day (day 1)** **During menstruation**	 3/91 (3.3%) 80/91 (87.9%) 8/91 (8.8%)	 3/52 (5.8%) 46/52 (88.5%) 3/52 (5.8%)	0.6
The number of analgesic use (n)	1.98 ± 1.35	2.36 ± 2.83	0.2
Use of herbal medicine (n, %)	27 (13.5%)	19 (22.1%)	0.07
Use of traditional method (n, %)	77/200 (38.5%)	45/86 (52.3%)	**0.03**
Type of traditional method used (n, %) **Heat** **Coffee**	 76/77 (98.7%) 1/77 (1.3%)	 45 (100%) 0	 1

BMI: Body mass index.
PMS: Premenstrual syndrome

(75/86) had SI. NA and SI were significantly more prevalent in the PMS group than the control group (p<0.0001, and p=0.03, respectively). In the PMS group, 75.6% (65/86) had Type D personality, whereas 45.5% (91/200) of the control group had Type D personality. Type D personality was also significantly more prevalent in the women with PMS compared to the women without PMS (p<0.0001). Comparison of Type D personality and depression scores and rates for the groups are given in Table 2.

Correlation analysis showed a positive correlation between PMS score, depression and Type D personality Table 3.

Table 2 Comparison of Type D personality and depression scores and rates between the groups

	Control group (n=200)	PMS group (n=86)	p value
BDI score (points)	9.19 ± 6.8	18.87 ± 11.38	**<0.0001**
Depression, present (n, %)	29 (14.5%)	46 (53.5%)	**<0.0001**
Severity of depression (n, %) **Mild (17-20 point)** **Moderate (21-30 points)** **Severe (>30 points)**	 17/29 (58.6%) 10/29 (34.5%) 2/29 (6.9%)	 14/46 (30.4%) 14/46 (30.4%) 18/46 (39.1%)	**0.005**
NA score (points)	10.95 ± 6.02	15.66 ± 6.73	**<0.0001**
NA (n, %)	111/200 (55.5%)	72/86 (83.7%)	**<0.0001**
SI score (points)	11.77 ± 4.06	14.17 ± 4.67	**0.04**
SI (n, %)	142/200 (71%)	75/86 (87.2%)	**0.03**
Type D personality. present (n, %)	91/200 (45.5%)	65/86 (75.6%)	**<0.0001**

BDI: Beck depression inventory; NA: Negative affectivity; SI: Social inhibition.

Table 3 Correlation between PMS, Type D personality and depression.

	PMS	Type D personality	NA	SI
BDI	0,434**	0.621**	0.623**	0.430**
PMS		0.362**	0.359**	0.259**
Type D personality			0.922**	0.818**

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

Discussion

Herein, we investigated the relationship between Type D personality and PMS in 286 women (200 in the control group and 86 in the PMS group). Our results suggest that Type D personality may affect the PMS status of women. We found significantly higher rates of NA, SI, and Type D personality in the PMS population than in the controls. Depression and the severity of depression were also more prevalent in the women with PMS compared to the women without PMS. Positive association between Type D personality, PMS and depression

Premenstrual symptoms include a constellation of mood, behavioral, and physical indications that occur in a cyclic pattern prior to menstruation and then decrease after the menstrual period in women of reproductive age (4). During the premenstrual period, onset of a depressive episode may be observed. Approximately, 65% of women with unipolar depression experienced PMS (13). It is evident that women are twice as likely as men to develop the major depressive disorder during their reproductive years across different countries and different settings (14). Research studies found that a significant relationship between the risk of depression and PMS in studies in which they evaluated the presence of depression using different scales (15). Similar results of increased rates of depression in those suffering from PMS have been found by other authors (16-19). Our results concur with previous findings as we observed the presence of depressive symptoms to be associated with PMS. Depression was also found to be more severe in the PMS group compared to the controls in the recent research. The medical literature

and the results of our research indicate that persons who have PMS should be evaluated in terms of the risk of depression.

Type D personality refers to individuals with a joint propensity toward negative affectivity (NA) as well as social inhibition (SI). Recently, the relationship between Type D personality and health in the general population is beginning to receive more attention. Previous studies showed a prevalence range of 21–33% of Type D personality in the general population (20). This personality trait is linked to biological and behavioral mechanisms which may affect health. Neuroendocrine and immunologic pathways have been investigated to explain the negative clinical outcomes for patients with Type D personality and increased pro-inflammatory immune activation (21), oxidative stress (22), and cortisol levels (23) found to be related to Type D personality. Type D personality is related to depression, anxiety, somatization (20), dysregulated stress reactivity (24), sleep problems, psychosomatic symptoms, musculoskeletal pain (25), lower subjective quality of life (26), adverse health behaviors (27). Most of the studies have evaluated the relationship between depression and PMS; however, the present study is the first that evaluates the role of Type D personality on PMS. In the recent study, a positive association between Type D personality and the presence of PMS even after the adjustment of the parameters that were different between the PMS and the control group and correlated with PMSS score and could affect PMS. The scores for the NA and SI were also strongly correlated with the scores for the PMSS.

Research studies showed that the prevalence of PMS and PMDD (Premenstrual dystrophic disorder) were higher among younger women, women with higher BMI, women whose age at menarche was 12 years or younger, and women who are physically inactive (28-30). In contrast, PMS was not associated with age, BMI, and women who do sportic activity in our study. Small sample size and the definition of ‘physically inactive’ person could be the reason of discrepancy in the results with the previous studies In the literature, PMS also increases in women with menstrual irregularities (31), long menstrual duration, and cycles (32). In our research, no significant relationship was determined between characteristics of the menstrual cycle with PMS, however, the volume of menstrual bleeding was significantly higher in the PMS group compared to the controls. A strong association between the duration of the menstrual period and volume of bleeding could explain the discrepancies in the results with the previous studies (3, 33). Smoking and alcohol use during the adolescent period has been found to be a risk factor for PMS (3, 33) We could not found any differences in terms of smoking and alcohol use between PMS and control groups. Longitudinal studies evaluating the association between age, obesity, exercise, and PMS should be conducted.

The main limitation of our research is its’ cross-sectional design. A longitudinal study would better explain the association between PMS and Type D personality. The other limitation that should be taken into account when interpreting the results is the bi-directional relationship between personality type and PMS. Because Type D personality could be a risk factor for PMS or PMS could create Type D personality. The third limitation is that the data of this study were obtained from participants through a self-reported questionnaire, which may reflect bias in self-reporting (i.e. participants may have underestimated or overestimated their level of PMS and PMDD symptoms). Further large sample-sized investigations should be performed to investigate the underlying cause for the pathogenetic mechanism of the relationship between Type D personality and PMS. Despite the aforementioned limitations, an association between Type D personality and PMS was shown for the first time.

Conclusion

There is a positive relationship between PMS, depression and Type D personality. Large sample-sized studies are required to further understand the mechanisms underpinning the now well-documented relationship. Knowing the personality type in patients with PMS may be beneficial for the treatment of PMS. It can also improve the patient's quality of life and well-being.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval

The study was conducted in accordance with the principles of the Helsinki Declaration related to conducting clinical trials on humans, and the research proposal was approved by the Ethics Committee of the Süleyman Demirel University with the number 140 in 04 July 2018.

Consent to Participate and Publish

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ISPARTA İLİNDE AKUT SOLUNUM YOLU ENFEKSİYONU ÖN TANISI OLAN HASTALARDA MULTİPLEKS PCR YÖNTEMİYLE VİRAL VE BAKTERİYEL ETKENLERİN SIKLIĞININ ARAŞTIRILMASI

INVESTIGATION OF THE PREVALENCE OF VIRAL AND BACTERIAL AGENTS BY MULTIPLEX PCR METHOD IN PATIENTS WITH A PRE-DIAGNOSIS OF ACUTE RESPIRATORY TRACT INFECTION IN ISPARTA PROVINCE

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Öz

Amaç
Solunum yolu enfeksiyonları, tüm yaş gruplarında en sık karşılaşılan hastalıklardan olup etkenlerin görülme sıklığı ve mevsimsel dağılımı coğrafi bölgeler arasında farklılıklar gösterebilmektedir. Bu çalışmada, Süleyman Demirel Üniversitesi Araştırma ve Uygulama Hastanesi'ne başvuran hastalarda solunum yolu etkenlerinin prevalansı ve mevsimsel dağılımının belirlenmesi amaçlanmıştır.

Gereç ve Yöntem
Tıbbi Mikrobiyoloji Laboratuvarı'na 1 Ocak 2019-31 Aralık 2019 tarihleri arasında akut solunum yolu enfeksiyonu ön tanısı alan hastalardan gönderilen solunum yolu örnekleri, multipleks gerçek zamanlı polimeraz zincir reaksiyonu (MRT-PCR) yöntemi (FTD Respiratory Pathogens 21 plus, Fast Track Diagnostics, Luxembourg) ile viral ve bakteriyel etkenlerin varlığı açısından araştırıldı. Yirmisi çocuk, 100'ü erişkin toplam 120 hastanın sonuçları retrospektif olarak incelendi.

Bulgular
Örneklerin 71 (%59.2)'inde bir veya birden fazla etken pozitifliği saptanırken, 49 (%40.8)'unda etken saptanmadı. Çocuk hastaların 9'unda (%45), erişkinlerin 62'sinde (%62) pozitiflik saptandı. Enfeksiyona en sık yol açan viral ve bakteriyel etkenler sırasıyla rinovirüs ve *Streptococcus pneumoniae* olarak belirlendi. Rinovirüs (n=20) ve *S.pneumoniae* (n=16) yıl boyunca saptanırken, koronavirüslerin (n=15) kış ve ilkbahar aylarında, influenza virüsleri (n=9) ve solunum sinsityal virüs (RSV) A/B'nin (n=8) kış aylarında daha sıklıkla enfeksiyona neden oldukları gözlendi.

Sonuç
Solunum yolu patojenlerinin moleküler yöntemlerle tanımlanmasına yönelik ilimizde yapılan ilk araştırma özelliğini taşıyan bu çalışmada, çocuklarda ve erişkinlerde en sık saptanan etkenlerin sırasıyla RSV A/B ve rinovirüs olduğu görülmüştür. Solunum yolu enfeksiyonlarından sorumlu viral ve bakteriyel etkenlerin MRT-PCR yöntemiyle eş zamanlı, hızlı ve duyarlı bir şekilde tespiti, gereksiz antibiyotik kullanımının önlen-

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mesi ve enfeksiyon kontrolü açısından klinisyenlere yol gösterici olacaktır.

Anahtar Kelimeler: Solunum yolu enfeksiyonları, Multipleks polimeraz zincir reaksiyonu, Solunum virüsleri, Prevalans

Abstract

Objective
Respiratory tract infections are among the most common diseases in all age groups, and the prevalence and seasonal distribution of the agents may differ between geographical regions. This study aimed to determine the prevalence and seasonal distribution of respiratory tract agents in patients admitted to Süleyman Demirel University Research and Practice Hospital.

Material and Methods
Respiratory tract samples sent to the Medical Microbiology Laboratory from patients with a prediagnosis of acute respiratory tract infection between January 1, 2019 and December 31, 2019 were investigated for the presence of viral and bacterial agents by multiplex real-time polymerase chain reaction (MRT-PCR) method (FTD Respiratory Pathogens 21 plus, Fast Track Diagnostics, Luxembourg). The results of a total of 120 patients, 20 children and 100 adults, were analyzed retrospectively.

Results
One or more agent positivity was detected in 71 (59.2%) of the samples, while no agent was detected in 49 (40.8%) of the samples. Positivity was detected in 9 (45%) of the pediatric patients and 62 (62%) of the adults. The most common viral and bacterial agents causing infection were determined as rhinovirus and *Streptococcus pneumoniae*, respectively. While rhinovirus (n=20) and *S.pneumoniae* (n=16) were detected throughout the year, it was observed that coronaviruses (n=15) caused infection more frequently in winter and spring months, influenza viruses (n=9) and respiratory syncytial virus (RSV) A/B (n=8) in winter months.

Conclusion
In this study, which is the first research conducted in our province for the identification of respiratory tract pathogens by molecular methods, the most common agents in children and adults were found to be RSV A/B and rhinovirus, respectively. Simultaneous, rapid and sensitive detection of viral and bacterial agents responsible for respiratory tract infections by MRT-PCR method will guide clinicians in terms of preventing unnecessary antibiotic use and infection control.

Keywords: Respiratory tract infections, Multiplex polymerase chain reaction, Respiratory viruses, Prevalence

Giriş

Solunum yolu enfeksiyonları, tüm yaş gruplarında en yaygın görülen hastalıklar arasındadır ve dünya genelinde ciddi bir halk sağlığı sorunudur (1,2). Klinik tablo sağlıklı bireylerde genellikle hafif belirtiler ile seyrederken, enfeksiyon özellikle beş yaş altı çocuklarda, yaşlılarda ve immünsüprese kişilerde ciddi oranda morbidite ve mortalite ile sonuçlanabilmektedir (1,3). Yapılan araştırmalar, solunum yolu enfeksiyonlarının yol açtığı iş gücü kaybı ve tedavi maliyetleri ile ulusal sağlık harcamaları açısından ülke ekonomilerine ağır bir yük getirdiğini göstermektedir (2,4).

Akut solunum yolu enfeksiyonlarının %60-80'inin virüs kaynaklı olduğu bildirilmekle birlikte, etkenlerin görülme sıklığı ve mevsimsel dağılımı ülkeler hatta bölgeler arasında farklılıklar gösterebilmektedir (5,6). Genellikle en sık saptanan virüsler influenza virüs (INF)'ler, insan rinovirüsü (human rhinovirus; HRV), solunum sinsityal virüs (respiratory syncytial virüs; RSV), insan koronavirüs (human coronavirus; HCoV)'leri ve parainfluenza virüs (PIV)'lerdir. Enfeksiyonların çoğu kuzey yarımkürede yılın soğuk aylarında görülmekte, özellikle INF'ler Aralık-Nisan aylarında epidemiler yapmaktadır (1,5-7).

Klinik ve radyolojik açıdan virüs ve bakteri kaynaklı akut solunum yolu enfeksiyonlarının birbirinden ayırt edilmesi güçtür. Etkene özgü klinik belirtiler yok denilecek kadar azdır. Kesin tanı büyük ölçüde mikrobiyolojik tanı testlerine dayanmaktadır. Bununla birlikte, solunum yolu enfeksiyonlarına yol açan etkenlerin hızlı ve doğru tanımlanması, antiviral tedaviye zamanında başlanması ve gereksiz antibiyotik kullanımının önlenmesinin yanı sıra hastanede kalma süresi, nozokomiyal bulaş riski ve tedavi masraflarının azaltılması açısından da büyük öneme sahiptir (2,4,8,9).

Son yıllarda, solunum yolu enfeksiyonlarına neden olan solunum virüslerini aynı anda saptayabilen çok sayıda nükleik asit amplifikasyon testleri geliştirilmiş ve yaygın olarak kullanılmaya başlanmıştır. Multipleks gerçek zamanlı polimeraz zincir reaksiyonu (multip-

lex real-time polymerase chain reaction; MRT-PCR) yönteminin konvansiyonel yöntemler olan hücre kültürü ve direkt floresan antikor testinden daha kısa sürede sonuç verdiği ve daha yüksek duyarlılığa ve özgüllüğe sahip olduğu bildirilmektedir (5,6,10,11). MRT-PCR tekniğinde, aynı solunum yolu örneğinde tek reaksiyonda birden fazla solunum virüsü ve bakteri eş zamanlı saptanabilmektedir. Ayrıca bu yöntem klasik solunum virüslerinin yanı sıra hücre kültürü yapılamayan veya güç üreyen insan metapnömovirüsü (human metapneumovirus; HMPV), HCoV-NL63, HCoV-HKU1, insan bokavirüsü (human bocavirus; HBoV) gibi daha yeni etkenlerin de tanımlanmasına olanak sağlamaktadır (11-13). Viral yükün az olduğu örneklerde veya antimikrobiyal tedavi gören hastaların örneklerinde bile viral veya bakteriyel etkenler hassas bir şekilde saptanabilmektedir. Bu avantajlarının yanında test maliyetinin yüksek olması ve deneyimli personel gerektirmesi yöntemin en önemli kısıtlayıcı unsurlarıdır (13,14).

Bu çalışmada, hastanemize başvuran ve akut solunum yolu enfeksiyonu ön tanısı alan hastalarda solunum yolu etkenlerinin prevalansı ve mevsimsel dağılımının belirlenmesi amaçlanmıştır.

Gereç ve Yöntem

Akut solunum yolu enfeksiyonu semptomlarıyla 1 Ocak 2019-31 Aralık 2019 tarihleri arasında Süleyman Demirel Üniversitesi Araştırma ve Uygulama Hastanesi'ne başvuran hastaların solunum yolu örneklerine ait MRT-PCR sonuçları retrospektif olarak incelendi. Çalışma öncesinde Süleyman Demirel Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan onay alındı (Tarih: 18.08.2021, Karar No: 264).

Akut solunum yolu enfeksiyonu olan hastalardan alınan solunum yolu örnekleri (nazofarengeal sürüntü, bronkoalveoler lavaj), soğuk zincir kurallarına uyularak viral taşıma besiyeri (UTM, Copan Diagnostics, İtalya) içinde Tıbbi Mikrobiyoloji Laboratuvarı'na ulaştırıldı. Klinik örneklerden nükleik asit ekstraksiyonu, EZ1 Virus Mini Kit v2.0 (Qiagen, Almanya) kullanılarak üretici firmanın önerileri doğrultusunda EZ1 Advanced XL (Qiagen, Almanya) cihazında gerçekleştirildi. Solunum yolu örneklerinde virüs ve bakterilere ait nükleik asitlerin (DNA veya RNA) varlığı, FTD Respiratory Pathogens 21 plus (Fast Track Diagnostics, Luxembourg) kiti ile araştırıldı. MRT-PCR tekniğine dayanan bu sistemde, solunum yolu enfeksiyonu etkeni olan 20 virüs ve 5 bakterinin varlığı aynı anda saptanabilmektedir. Kullanılan solunum paneli kiti ile tespit edilebilen etkenler; INF-A, INF-A H1N1, INF-B, HRV, RSV A/B, HCoV-229E, HCoV-HKU1, HCoV-OC43, HCoV-NL63, PIV-1, PIV-2, PIV-3, PIV-4, enterovirus (EV), adenovirüs (AdV), insan parekovirüsü (human parechovirus; HPeV), HMPV A/B, HBoV, *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* tip b, *Mycoplasma pneumoniae* ve *Chlamydophila pneumoniae*'dir. Amplifikasyon, floresan ışımanın ölçülmesi ve verilerin analizi Rotor-Gene Q 5Plex HRM (Qiagen, Almanya) ısı döngü cihazında üretici firmanın talimatları doğrultusunda gerçekleştirildi.

Çalışmada elde edilen verilerin istatistiksel analizi için Statistical Package for the Social Sciences (SPSS) programı versiyon 20.0 kullanıldı. Verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testi kullanılarak değerlendirildi. Gruplar arasında kategorik değişkenlerin karşılaştırılmasında ki-kare testi kullanıldı. İstatistiksel değerlendirmede $p<0.05$ değeri anlamlı kabul edildi.

Bulgular

Yirmisi (%16.7) çocuk (<18 yaş), 100'ü (%83.3) erişkin, 0-93 yaş (ortalama yaş=42.2) aralığında bulunan toplam 120 hastanın (54 kadın; %45, 66 erkek; %55) sonuçları değerlendirildi. Solunum yolu örneklerinin (118 nazofarengeal sürüntü, 2 bronkoalveoler lavaj) 40 (%33.3)'ı poliklinik, 80 (%66.7)'i yatan hastalardan alındı. Örneklerin kliniklere göre dağılımı Tablo 1'de gösterilmiştir.

Örneklerin 71 (%59.2)'inde bir veya birden fazla etken pozitifliği saptanırken, 49 (%40.8)'unda etken saptanamadı (Tablo 2). Çocuk hastaların 9'unda (%45), erişkinlerin 62'sinde (%62) pozitiflik tespit edildi. Kadın ve erkeklerdeki pozitiflik oranı sırasıyla %57.4 (31/54) ve %60.6 (40/66), poliklinik ve yatan hastalardaki pozitiflik oranı ise sırasıyla %70 (28/40) ve %53.8 (43/80) olarak belirlendi. Gruplar arasında (çocuk-erişkin, kadın-erkek ve poliklinik-yatan hastalar) etken pozitifliği açısından istatistiksel olarak anlamlı farklılık saptanmadı (sırasıyla; p=0.158, p=0.723 ve p=0.088).

Yetmiş bir örnekten izole edilen toplam 86 patojenin 60'ını (%69.8) viral etkenler, 26'sını (%30.2) bakteriyel etkenler oluşturdu. Saptanan etkenler sıklık sırasıyla HRV (n=20, %23.3), *S. pneumoniae* (n=16, %18.6), HCoV'lar (n=15, %17.4), INF'ler (n=9, %10.4), *S. aureus* (n=9, %10.4), RSV A/B (n=8, %9.3), PIV-3 (n=5, %5.8), HMPV A/B (n=2, %2.4), EV (n=1, %1.2) ve *C. pneumoniae* (n=1, %1.2) olarak belirlendi. Solunum yolu patojenlerinin çocuk ve erişkin hastalara göre dağılımı Tablo 3'te gösterilmiştir. Çocuklarda en sık RSV A/B'nin (n=4; %36.4), erişkinlerde ise en sık HRV'nin (n=17; %22.7) solunum yolu enfeksiyonlarına yol

Tablo 1 Solunum yolu örneklerinin kliniklere göre dağılımı [n (%)]

Klinik	Örnek sayısı
Enfeksiyon Hastalıkları	43 (35.8)
İç Hastalıkları	24 (20)
Anestezi YBÜ	14 (11.7)
Çocuk Sağlığı ve Hastalıkları	12 (10)
Çocuk YBÜ	8 (6.7)
Organ Nakli	8 (6.7)
Diğer klinikler	11 (9.1)
Toplam	**120 (100)**

Tablo 2 Olguların çocuk ve erişkin hastalara ve cinsiyete göre dağılımı [n (%)]

	Çocuk	Erişkin	Toplam
Etken saptanan olgular	9 (45)	62 (62)	71 (59.2)
Etken saptanmayan olgular	11 (55)	38 (38)	49 (40.8)
Toplam	**20 (100)**	**100 (100)**	**120 (100)**
Etken saptanan kadın olgular	4 (44.4)	27 (43.5)	31 (43.7)
Etken saptanan erkek olgular	5 (55.6)	35 (56.5)	40 (56.3)
Toplam	9 (100)	62 (100)	71 (100)

açan etkenler olduğu görüldü. Bakteriyel etkenler arasında en sık *S. pneumoniae* (n=16) saptandı. HRV, hem kadınlarda (n=9) hem de erkeklerde (n=11) en sık saptanan etken olarak belirlendi. Poliklinik hastalarında en sık HRV (n=9), yatan hastalarda ise en sık *S. pneumoniae* (n=12) tespit edildi.

Koenfeksiyonların (n=13; %10.8) çocuk ve erişkin hastalara göre dağılımı Tablo 4'te sunulmuştur. On bir örnekte iki etken, 2 örnekte ise üç etken varlığı eş zamanlı saptandı. En sık HRV ve *S. pneumoniae* (n=3) birlikteliği görüldü. Çocuk hastalarda koenfeksiyon görülme sıklığı %10 (2/20), erişkin hastalarda ise %11 (11/100) olarak tespit edildi. Koenfeksiyonların görülme oranı, kadın ve erkek hastalarda sırasıyla %5.6 (3/54) ve %15.2 (10/66), poliklinik ve yatan hastalarda ise sırasıyla %15 (6/40) ve %8.8 (7/80) olarak belirlendi. Gruplar arasında (çocuk-erişkin, kadın-erkek ve poliklinik-yatan hastalar) koenfeksiyon varlığı açısından istatistiksel olarak anlamlı farklılık saptanmadı (sırasıyla; p=0.895, p=0.092 ve p=0.299).

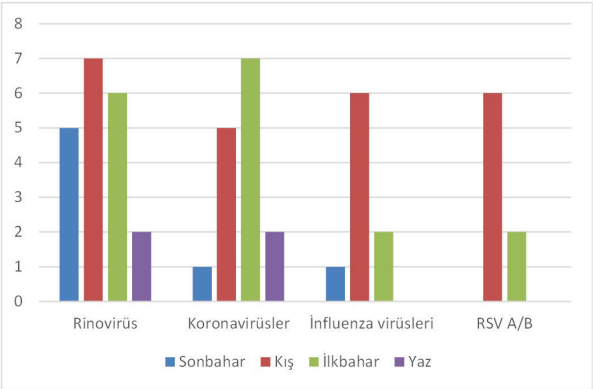
Solunum yolu patojenlerinin mevsimlere göre dağılımı incelendiğinde, sıklık sırasıyla kış (n=31), ilkbahar (n=30), sonbahar (n=18) ve yaz (n=7) mevsiminde izole edildikleri tespit edildi (Tablo 3). HRV, HCoV'lar ve *S. pneumoniae* yıl boyunca saptanırken, INF'lerin ve RSV A/B'nin özellikle kış ve ilkbahar aylarında daha sıklıkla enfeksiyona yol açtıkları gözlendi. En sık saptanan solunum virüslerinin mevsimsel dağılımı Şekil 1'de gösterilmiştir.

Tablo 3 Solunum yolu etkenlerinin çocuk ve erişkin hastalara ve mevsimlere göre dağılımı (n)

Etken	Çocuk	Erişkin	Toplam	Sonbahar	Kış	İlkbahar	Yaz
HRV	3	17	20	5	7	6	2
HCoV-229E	2	8	10	-	3	5	2
HCoV-HKU1	-	3	3	1	2	-	-
HCoV-OC43	-	1	1	-	-	1	-
HCoV-NL63	-	1	1	-	-	1	-
INF-A	-	3	3	-	3	-	-
INF-A H1N1	-	1	1	1	-	-	-
INF-B	-	5	5	-	3	2	-
RSV A/B	4	4	8	-	6	2	-
PIV-3	1	4	5	1	-	4	-
HMPV A/B	-	2	2	-	-	2	-
EV	-	1	1	1	-	-	-
S. pneumoniae	1	15	16	7	4	2	3
S. aureus	-	9	9	2	3	4	-
C. pneumoniae	-	1	1	-	-	1	-
Toplam	11	75	86	18	31	30	7

Tablo 4 Koenfeksiyonların çocuk ve erişkin hastalara göre dağılımı (n)

Koenfeksiyonlar	Çocuk	Erişkin	Toplam
HRV + *S. pneumoniae*	-	3	3
HRV + HCoV-229E	1	1	2
HRV + INF-B	-	1	1
HRV + EV	-	1	1
RSV A/B + HCoV-229E	1	-	1
RSV A/B + *S. pneumoniae*	-	1	1
INF-B + HCoV-229E	-	1	1
HCoV-HKU1 + *S. pneumoniae*	-	1	1
HRV + HCoV-229E + PIV-3	-	1	1
HCoV-OC43 + HCoV-NL63 + *S. pneumoniae*	-	1	1
Toplam	**2**	**11**	**13**



Şekil 1:
En sık saptanan solunum virüslerinin mevsimsel dağılımı

Tartışma

Solunum yolu enfeksiyonlarında, patojen mikroorganizmaların zamanında tespit edilmesi ve uygun antimikrobiyal tedavinin başlatılması, morbidite ve mortaliteyi önemli ölçüde azaltmaktadır. Farklı solunum yolu etkenleri ile enfekte hastalar benzer klinik ve radyolojik bulgulara sahip olduğundan etyolojik etkenin spesifik olarak tanımlanması ancak mikrobiyolojik tanı yöntemlerinin uygulanması ile mümkündür. Son yıllarda yaygın olarak kullanılmaya başlanan ve solunum yolu enfeksiyonlarına yol açan etkenleri aynı anda yüksek duyarlılıkla saptayabilen MRT-PCR yöntemleri, viral ve bakteriyel enfeksiyon ayırımını sağlayarak doğru ve etkin tedaviye karar verilmesinde büyük rol oynamış ve aynı zamanda bu etkenlerin dağılımı ile ilgili epidemiyolojik verilerin daha iyi anlaşılmasını sağlamıştır (6,8,9,13,15). Solunum yolu etkenlerinin moleküler yöntemlerle tanımlanmasına yönelik ilimizde yapılan ilk araştırma özelliğini taşıyan bu çalışmada, Coronavirus Disease 2019 (COVID-19) pandemisinden önce bir yıllık süre içinde akut solunum yolu enfeksiyonu ön tanısı alan hastalarda etkenlerin sıklığı araştırılmış ve mevsimsel dağılımı belirlenmiştir.

Moleküler yöntemlerin kullanıldığı çalışmalarda etken saptama oranlarının, kullanılan kite, hasta popülasyonuna ve çalışmanın yapıldığı zaman aralığına bağlı olmak üzere %30.9 ila %96.1 arasında değiştiği bildirilmektedir (8,16). Sunulan araştırmada incelenen örneklerin %59.2'sinde en az bir viral veya bakteriyel etken pozitifliği saptanırken, %40.8'inde herhangi bir etken saptanamamıştır (Tablo 2). Bununla beraber, yaş (çocuk-erişkin), cinsiyet (kadın-erkek) ve klinik (poliklinik-yatan) dağılım açısından pozitiflik oranlarının erişkinlerde (%62), erkeklerde (%60.6) ve poliklinik hastalarında (%70) daha yüksek olduğu gözlenmiştir. Ülkemizde Çiçek ve ark. (6) tarafından yapılan çalışmada, pozitiflik oranlarının erkeklerde (%33.9) ve poliklinik hastalarında (%40.2) daha yüksek olduğu, ancak çocuk hastalarda (%35.4) etken saptama oranının erişkinlere (%27.3) göre daha yüksek olduğu bildirilmiştir. Özellikle virüs kaynaklı solunum yolu enfeksiyonlarının çocuklarda daha sık görüldüğü belirtilmekle birlikte (2,3,16), sunulan araştırmada çocuklarda (%45) erişkinlere (%62) göre etken saptama oranının (istatistiksel olarak anlamlı olmasa da) daha düşük bulunmuş olması, bir yıllık süreçte araştırmaya dahil edilen çocuk hasta sayısının (n=20) az olması nedeniyle olabilir.

Solunum yolu enfeksiyonlarına bakteri, virüs, mantar ve parazitler neden olabilmekle birlikte, enfeksiyonların büyük bir çoğunluğundan virüslerin sorumlu olduğu bilinmektedir (5,6). Bu çalışmada, solunum yolu örneklerinden izole edilen patojenlerin %69.8'ini viral etkenler oluşturmuş ve en sık saptanan virüsler sırasıyla HRV (%23.3), HCoV'lar (%17.4), INF'ler (%10.4), RSV A/B (%9.3), PIV-3 (%5.8), HMPV A/B (%2.4) ve EV (%1.2) olarak belirlenmiştir (Tablo 3). Çocuklarda en sık rastlanılan etken RSV A/B, erişkinlerde ise HRV olmuştur. Etkenlerin dağılımı açısından elde edilen verilerin yurt dışında ve ülkemizde yapılan araştırma verileri ile benzerlik gösterdiği görülmektedir (3,6,8-13,15-20). İstanbul'da Kuşkucu ve ark. (15) tarafından 788 erişkin hasta örneğinin incelendiği bir çalışmada, en fazla saptanan etkenlerin sırasıyla INF'ler (%16.9), HRV (%14.9), HCoV'lar (%8.6) ve RSV A/B (%6.9) olduğu belirtilmiştir. İzmir'de yapılan ve 5102 örneğin araştırıldığı bir çalışmada, erişkin hastalarda en sık saptanan virüslerin sırasıyla INF'ler (%53.8), AdV (%11), RSV (%7.1) ve PIV (%7.1), çocuk hastalarda ise RSV (%24.5), INF'ler (%22.9), PIV (%14.4) ve HRV (%8.6) olduğu tespit edilmiştir (6).

Özdamar ve ark.'nın (13) Kocaeli ve İstanbul illerini kapsayan çalışmasında, incelenen 283 örnek (251 çocuk, 32 erişkin) arasında en sık sırasıyla HRV, AdV, INF'ler ve RSV A/B izole edilmiştir. Bursa'da nötropenik 50 erişkin hastanın dahil edildiği bir çalışmada, en sık görülen etkenler sırasıyla HCoV'lar (%49.1), PIV (%24.5), INF'ler (%11.3) ve RSV A/B (%5.7) olarak belirlenmiştir (21).

Ülkemizde moleküler yöntemlerin kullanıldığı çalışmalarda, solunum yolu örneklerinden en sık tespit edilen bakteriyel etkenin *S. pneumoniae* olduğu belirtilmektedir (14,22-24). Benzer şekilde, bu çalışmada elde edilen bulgular (sırasıyla en sık izole edilen bakteriyel etkenler; *S. pneumoniae*, *S. aureus*, *C. pneumoniae*) bu bilgiyi desteklemektedir. İzmir'de Kanberoğlu ve ark. (22) tarafından yapılan çalışmada, en sık saptanan bakteriyel etkenlerin sırasıyla *S. pneumoniae* (n=23), *S. aureus* (n=12) ve *M. pneumoniae* (n=5) olduğu bildirilmiştir. Yurt dışında yapılan çalışmalar incelendiğinde, sıklık dağılımı ülkelere göre değişkenlik göstermekle birlikte, en sık saptanan etken *S.pneumoniae'*yı genellikle atipik etkenlerin (*M. pneumoniae*, *C. pneumoniae*, *Legionella pneumophila*), *H. influenzae* veya *S. aureus'*un izlediği görülmektedir (19,25-27). Bununla birlikte, özellikle nazofarengeal sürüntü örneklerinde *S. aureus* saptanan hastalarda, solunum yolu enfeksiyonu tanısı konulmadan önce nazal kolonizasyon olasılığı göz önünde bulundurularak moleküler test sonuçları mutlaka klinik bulgular ile birlikte değerlendirilmelidir.

Birçok klinik araştırmada bir solunum yolu örneğinde aynı anda birden fazla patojen varlığının klinik tabloyu etkilemediği öne sürülmüşse de, koenfeksiyon ile hastalığın şiddeti arasındaki ilişki hala tartışmalı bir konudur (3,16,28). Bununla birlikte, literatür incelendiğinde, yapılan çalışmalarda koenfeksiyon saptama oranları ve koenfeksiyonlarda yer alan etkenlerin dağılımı açısından farklı sonuçların elde edildiği görülmektedir. On dokuz farklı araştırmaya ait verilerin değerlendirildiği bir meta-analizde, koenfeksiyon oranlarının %5 ile %62 arasında değiştiği bildirilmiştir (16). Daha çok çocuk hastaları kapsayan araştırmaların dahil edildiği bu analizde, koenfeksiyonlarda en sık RSV'ye rastlanıldığı ve RSV'ye en fazla eşlik eden etkenlerin AdV, HBoV ve INF-A olduğu belirtilmiştir. Çin'de Zhang ve ark. (20) tarafından yürütülen çok merkezli bir çalışmada, koenfeksiyonlarda en yaygın görülen etkenlerin INF'ler ve HRV olduğu bildirilmiştir. Ülkemizde Çolak ve ark. (29), koenfeksiyonlarda HCoV'lara en sık eşlik eden etkenin HRV olduğunu belirtmişlerdir. Yurt içinde yapılan başka bir çalışmada, koenfeksiyon olgularının çoğunun pediatrik yaş grubunda olduğu ve ilk sırada RSV, ikinci sırada HRV'nin yer aldığı bildirilmiştir (30). Bu çalışmada ise literatür verilerine benzer şekilde, incelenen örneklerin 13'ünde (%10.8) iki veya üç etken varlığı eş zamanlı saptanmıştır. En sık HRV ve *S. pneumoniae* (n=3) birlikteliği tespit edilmekle birlikte, koenfeksiyonlarda en fazla yer alan etkenlerin sırasıyla HCoV'lar (n=7), HRV (n=5), *S. pneumoniae* (n=4), INF-B (n=2), RSV A/B (n=2), PIV-3 (n=1) ve EV (n=1) olduğu görülmüştür (Tablo 4). HCoV'lar ve HRV'nin genellikle soğuk algınlığı şeklinde enfeksiyonlara neden olduğu, ancak diğer solunum yolu etkenleriyle birlikte özellikle yenidoğanlar, yaşlılar, kronik hastalığı olanlar ve immünsüpresif hastalarda alt solunum yolu hastalıklarına da yol açabildiği bildirilmektedir (4,5,29).

Solunum virüslerine bağlı olarak gelişen akut solunum yolu enfeksiyonlarının özellikle ılıman iklime sahip coğrafi bölgelerde mevsimsel özellik gösterdiği bilinmektedir. Yapılan çalışmalarda, solunum virüslerinin kuzey yarımkürede kış ve erken ilkbahar aylarında özellikle Aralık-Nisan ayları arasında daha etkin oldukları belirtilmektedir (1,3-7,12,15,17,18,29-31). Bu çalışmada da bölgemizde, solunum virüslerinin çoğunlukla kış ve ilkbahar aylarında etken olarak saptandığı ve yaz aylarında ise etken pozitifliğinin en düşük seviyelere gerilediği görülmüştür (Tablo 3, Şekil 1). HRV ve HCoV'lar, özellikle kış ve ilkbahar aylarında pik yapmakla birlikte tüm yıl boyunca akut solunum yolu enfeksiyonlarından izole edilmiştir. INF'ler ile birlikte RSV A/B'nin de özellikle kış ve ilkbahar aylarında daha sıklıkla enfeksiyona yol açtıkları gözlenmiştir.

Sunulan çalışmanın retrospektif ve tek merkezli olması, nispeten sınırlı sayıda örnek içermesi ve klinik değerlendirme yapılamamış olması gibi birtakım kısıtlayıcı yönlerinin bulunmasına rağmen epidemiyolojik veri açısından literatüre katkı sağlayacağı düşünülmektedir.

Sonuç

Sonuç olarak, solunum yolu etkenlerinin prevalansı ve mevsimsel dağılımı açısından elde edilen veriler ülkemizde farklı coğrafi bölgelerde yapılan çalışmalar ile benzerlik göstermektedir. Akut solunum yolu enfeksiyonu olan hastalardan gönderilen örneklerin %59.2'inde bir veya birden fazla etken pozitifliği saptanmış ve çocuklarda en sık rastlanılan etkenin RSV A/B, erişkinlerde ise HRV olduğu görülmüştür. Bölgemizde solunum virüslerinin mevsimsel farklılıklar gösterdikleri ve kış ve ilkbahar aylarında daha aktif oldukları belirlenmiştir. Solunum yolu örneklerinde MRT-PCR ile viral ve bakteriyel etkenlerin taranması, akut solunum yolu enfeksiyonu olan hastalarda etyolojiyi ortaya koymada hızlı ve etkili bir yöntem olarak düşünülmüştür.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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FACTORS AFFECTING THE FALL RISK AND ASSISTIVE WALKING DEVICE USE OF PATIENTS WITH KNEE OSTEOARTHRITIS

DİZ OSTEOARTRİTLİ HASTALARDA DÜŞME RİSKİNİ VE YARDIMCI YÜRÜME CİHAZI KULLANIMINI ETKİLEYEN FAKTÖRLER

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Öz

Amaç

Bu çalışmada, ileri evre diz osteoartriti olan hastalarda düşme riskini ve yardımcı yürüme cihazı kullanım oranlarını ve bu hastalarda bu cihazların kullanımını etkileyen faktörleri araştırmayı amaçladık.

Gereç ve Yöntem

Bu prospektif, kesitsel, gözlemsel çalışmaya Mart 2020 ile Eylül 2020 arasında polikliniğimize başvuran ve ileri evre diz osteoartriti olan 79 hastayı (72 kadın, 7 erkek; medyan yaş 60; dağılım, 40-75) dahil ettik. Hastaların denge durumunu Berg Denge Ölçeği ile ağrı düzeylerini Sayısal Derecelendirme Ölçeği ile kişi beyanına dayanan dizabilite skorlarını ise Western Ontario and McMaster Universities Osteoarthritis Index ile değerlendirdik. Birincil sonlanım noktası hastaların denge durumu ve yardımcı yürüme cihazı kullanım oranlarıydı. İkincil sonlanım noktaları ise yaş, obezite, hastalık şiddeti, ağrı düzeyleri, sakatlık skorları ve düşme öyküsüydü.

Bulgular

Berg Denge Skalasına göre 40 (% 50,6) hastada düşme riski saptandı. Yardımcı yürüme cihazı kullanım oranları tüm hastalarda ve düşme riski olan hastalarda sırasıyla % 21.5 ve % 42.5 idi. Düşme riski olanlar ile olmayanlar arasında yardımcı yürüme cihazı kullanımı açısından istatistiksel olarak anlamlı fark vardı (p<0,001). Artan düşme riski ile obezite, yüksek hastalık şiddeti ve yüksek özürlülük skorları arasında anlamlı bir ilişki bulundu. Ancak düşme riski olan kişilerde yaş dışında (p<0,001) yardımcı yürüme cihazı kullanımını etkileyen herhangi bir faktör bulamadık.

Sonuç

Çalışmamızın sonuçları ileri evre diz osteoartriti olan hastalarda düşme riskinin arttığını ve bu hastalarda yardımcı yürüme cihazı kullanımının düşme riski ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: Diz osteoartriti, düşme riski, yardımcı yürüme cihazı

Abstract

Objective

In this study, we aimed to investigate the risk of falling in patients with advanced-stage knee osteoarthritis and the rates of assistive walking device use, and the factors affecting the use of these devices in such patients.

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Materials and Methods
In this prospective, cross-sectional, observational study, we included 79 patients (72 females, 7 males; median age 60 years; range, 40 to 75) with advanced-stage knee osteoarthritis. We assessed the balance status of the patients with the Berg Balance Scale, pain levels with the Numeric Rating Scale, self-reported disability scores with the Western Ontario and McMaster Universities Osteoarthritis Index. Our primary outcome measurements were balance status, and assistive walking device usage rates of the patients. Secondary outcome measures were age, obesity, disease severity, pain levels, disability scores, and fall history.

Results
According to Berg Balance Scale, 40 (50.6 %) patients had a risk of fall. Assistive walking device usage rates were 21.5 % and 42.5 % for the total of the patients and for the patients at risk of falling, respectively. There was a statistically significant difference in assistive walking device use between those at risk of falling and those without (P<0.001). A significant correlation was found between increased risk of falling and obesity, high disease severity, and high disability scores. However, we did not find any factors other than age (P<0.001) that affect assistive walking device use in people at risk of falling.

Conclusion
The results of our study showed that the risk of falling is increased in patients with advanced-stage knee osteoarthritis and that the use of an assistive walking device is associated with the risk of falling in these patients.

Keywords: Knee osteoarthritis, Risk of falling, Assistive walking device

Introduction

Osteoarthritis (OA) is the most common form of arthritis. Among all joints, OA of the knee is one of the most frequent debilitating and life-altering joint diseases causing pain and disability. The lifetime risk of developing symptomatic knee OA is approximately 40 % in men and 47 % women and the likelihood of knee OA increases with age [1, 2].

Falls in the elderly are a major problem and attenuated balance control is an important cause of falls in this group [3]. The prevalence of falls in people over 60 years of age with knee OA is significantly higher than the others without knee OA, with a rate of 50-60 % [4]. Elderly and people with difficulty in walking demand assistive walking devices (AWDs), such as canes (walking sticks), crutches, and walkers, to maintain their balance and move independently. The use of an AWD in people with knee OA takes part in guidelines with strong recommendations [5, 6].

Even though the prevalence of falls is high in patients with knee OA, the mechanism, certain causes, and prevention methods of falling in this group are unclear. Thus more excessive studies are needed to comprehend the magnitude of balance attenuation in this group [4, 7].

Albeit biomechanical and clinical studies have exposed that AWD can help individuals to maintain balance and to improve their mobility, it remains a lack of understanding of the effectiveness of these devices [8]. Furthermore, when these devices are used improperly, on the contrary of expected effect, they can decrease the control on the balance and ability of walking and can cause falls [7, 9].

According to limited studies of understanding the mechanism of the main causes of falls in patients with knee OA and the necessity of AWD use in such group; we aimed to reveal the fall risk of these patients and the rate of assistive walking device use and the relationship between these two factors.

Materials and Methods

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Suleyman Demirel University, Faculty of Medicine Ethical Committee on March 5, 2020 (number 72867572.050.01.04). All participants included in the study signed a consent form.

Study Design
Our study was a prospective, cross-sectional, observational study, consisted of 79 patients with knee OA, who consulted our outpatient clinic between March 2020 and September 2020. The primary outcome of our study was the association between risk of fall and use of AWD among patients with grade 3 and grade 4 knee OA. Secondary outcome measures were the association between fall risk and AWD usage with age, body mass index (BMI), pain, disease severity, self-reported disability scores, and fall history.

The patients, who were between the ages of 40 and 75, had the ability of walking and had radiographic disease severity of grade 3 and grade 4 knee OA according to the Kellgren-Lawrence (KL) scale, were admitted to the study. The exclusion criteria were the following: (1) another lower extremity disease contributing to a disability, (2) significant cognitive disorder, (3) visual problems, (4) upper extremity disorders that interfere with the usage of AWD, (5) severe respiratory and cardiovascular disease.

All participants were assessed by the same examiner. Demographic characteristics of the patients consisting of age, gender, body mass index (BMI) (data were collected as obese and non-obese), educational status, smoking habit, comorbidities were recorded.

Clinical Data

Clinical data collected were disease-related features including disease duration, pain, previous fall history, serum acute phase reactant (erythrocyte sedimentation rate (ESR), c-reactive protein (CRP)) levels, and therapy-related factors including use of an AWD, drug therapy for OA. Knee radiographs were assessed by the same experienced clinician according to the KL scale. The numeric rating scale (NRS) was used to evaluate the pain severity, the disability was assessed with a self-reported functional questionnaire: Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. The patients' holistic balance status was assessed with the Berg Balance Scale (BBS).

Assessment Tools

KL grading scale is a radiographic classification system for OA of the knee joint [10]. The scale uses plain radiographs and is graded between 0 and 4. Radiographic images according to the KL grading scale are the following: grade 0: no radiographic features of OA, grade 1: possible joint space narrowing and osteophyte formation, grade 2: definite osteophyte formation with possible joint space narrowing, grade 3: multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity, grade 4: large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity.

NRS is a pain severity scale. The numerical scale is 0 to 10. Zero refers to "no pain" while 10 refers to "the most intense pain that the patient can imagine". The patient can express the pain severity either verbally or written [11].

WOMAC OA index is a widely used self-reported functional questionnaire [12]. The WOMAC measures totally 24 items; 5 for pain (score range 0-20), 2 for stiffness (score range 0-8) and 17 for functional limitation (score range 0-68). Symptom severity is directly proportional to high scores in the knee.

BBS is a measurement tool used for determining holistic balance and fall risk of elderly individuals [13]. The scale consists of 14 items. Each item is scored from 0 to 4, while the maximum score is 56. Scores between; 0-20 indicate severe balance impairment and a high risk of fall, 21-40 indicates moderate balance impairment and a moderate risk of fall, 41-56 indicates normal balance status and a low risk of fall. The assessment takes about 15-20 minutes.

Statistical Analysis

The statistical analysis was performed using SPSS for IBM version 21. Data are presented as a percentage, median (range), or mean±Standard deviation as appropriate. All the continuous variables were evaluated for normality by Kolmogorov-Smirnov and Shapiro-Wilk test. The comparisons between the risk of fall groups and also walking aid usage groups were made using the Chi-square or Fisher's exact tests for nominal and categorical variables and the Mann-Witney U test for continuous variables. Logistic regression analysis was performed to evaluate the risk factors that may affect the fall situation in the previous year. We considered the p value less 0.05 statistically significant.

Results

Patients

A total of 79 patients, 7 (8.9 %) male, and 72 (91.1 %) female met the inclusion criteria and enrolled in the study. The median age of all patients was 64 (40-75). The baseline characteristics of the patients including age, gender, body mass index, education level, smoking habit, and clinical features were detailed in Table 1.

Clinical Evaluations

The median scores of all patients for NRS, WOMAC OA index, and BBS were 6 (0-9), 42.7 (4-80.2), 40 (5-56), respectively. According to BBS, 40 (50.6 %) patients had a risk of fall, 7 (17.5 %) of which had a high risk. AWD usage rates were 21.5 % and 42.5 % for the total of the patients and for the patients at risk of falling, respectively. An AWD was recommended and prescribed for 31 (77.5 %) patients all of which were among those who have a risk of fall. Of these 31 patients, 17 (54.8%) used the recommended device, while 14 (45.2%) did not. Among these 14 patients, 7 patients have tried to use the prescribed AWD but

Table 1 The baseline characteristics of all patients(n=79)

	Number	Percentage
Gender		
Male	7	8.9 %
Female	72	91.1 %
Age		
<65	41	51.9 %
≥65	38	48.1 %
Body mass index (kg/cm$^{2)}$		
<30	38	48.1 %
≥30	41	51.9 %
Education		
Primary	54	68.4 %
High school	15	19 %
Graduate	10	12.6 %
Smoking		
Yes	14	17.7 %
No	65	82.3 %
Regular drug use		
Yes	34	43 %
No	45	57 %
Other chronic disease		
Yes	61	77.2 %
No	18	22.8 %
Pain		
Yes	76	96.2 %
No	3	3.8 %
	Median	Range
Time from diagnosis(year)	4	1-20
C-reactive protein (mg/l)	3.23	0.04-68
Erythrocyte sedimentation rate (mm/h)	12.5	2-38
	Mean	**Standart Deviation**
Uric acid (mg/l)	5.09	±1.31

had to stop using due to increasing pain severity and further impairment of their walking skills. Despite professional recommendation four of the other seven people never used an AWD for cosmetic reasons and three did not believe they had an imbalance. The walking aids used were standard canes (12), Canadian crutches (3), and simple wooden sticks (2). All AWD users had been using AWD for more than a year, except for one patient who had been using Canadian crutch for two months. Walker and custom-made walking sticks were neither advised nor prescribed for any of the patients. None of the patients without fall risk were using an AWD. 37 (46.8 %) patients had a fall in the one last year, and 20 of them fell two or more times.

The clinical findings of the patients with and without risk of fall are compared in Table 2. There were no statistically significant differences between the two groups for age and pain (P=0.454, P=0.541 respectively). Only 3 of our patients did not suffer from pain and 65.8 % of those suffering, were describing severe pain. The rate of obesity (62.5 % vs 41 %) and grade 4 knee OA (40 % vs 7.7 %) were statistically

Table 2 The comparison of clinical findings of patients who have a risk of fall and have not.

	Risk of fall(n=40)	No risk of fall(n=39)	p value
Age			
< 65	20(50%)	21 (53.8%)	0.454
≥ 65	20(50%)	18(46.2%)	
Obesity			
Yes	25(62.5%)	16(41%)	0.046
No	15(37.5%)	23(59%)	
Pain			
Yes	39(97.5%)	37(94.9%)	0.541
No	1 (2.5%)	2(5.1%)	
KLGS			
Grade 3	24(60%)	36(92.3%)	0.001
Grade 4	16(40%)	3(7.7%)	
Use of an AWD			
Yes	17(42.5%)	0	<0.001
No	23(57.5%)	39(100%)	
Fall in the previous year			
Yes	30(75%)	7(17.9%)	<0.001
No	10(25%)	32(82.1%)	
NRS score	6.5 (0-9)	6 (1-9)	0.151
WOMAC score	55.2(21.8-73.95)	31.25(4-80.2)	<0.001

AWD: Assistive walking device, KLGS: Kellgren Lawrence grading system, NRS: Numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Table 3 The comparison of clinical findings and falling status of patients at risk of fall (n=40), with and without AWD

	Using a walking aid (n:17)	No walking aid (n:23)	p value
Age			
< 65	2 (11.8 %)	18 (78.3 %)	<0.001
≥ 65	15 (88.2 %)	5 (21.7 %)	
Obesity			
Yes	8 (47.1 %)	17 (73.9 %)	0.107
No	9 (52.9 %)	6 (26.1 %)	
Pain			
Yes	16 (94.1 %)	23 (100.0 %)	0.425
No	1 (5.9 %)	0 (0.0 %)	
KLGS			
Grade 3	9 (52.9 %)	15 (65.2 %)	0.522
Grade 4	8 (47.1 %)	8 (34.8 %)	
NRS score	7 (0-9)	6 (3-9)	0.381
WOMAC score	66.6 (27-73.95)	53.12 (21.8-71.8)	0.122
Fall in the previous year			
Yes	13 (76.5%)	17 (73.9%)	0.853
No	4 (23.5%)	6 (26.1%)	
Falling number			
0	4(23.5%)	6(26.1%)	0.720
1	5(29.4%)	9(39.1%)	
≥2	8(47.1%)	8(34.8%)	

AWD: Assistive walking device, KLGS: Kellgren Lawrence grading system, NRS: Numerical rating scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis İndex

significantly high in the group of fall risk, WOMAC scores were statistically significantly different between the two groups (all P values <0.001). The rate of falling in the one last year was noticeably higher in the patients at risk of fall (75 % vs 17.9 %, P<0.001)

The clinical findings of the patients at risk of falls with or without using an AWD are compared in Table 3. There was a statistically significant difference between the two groups for age (P<0.001). There were no statistically significant differences for obesity, pain, pain scores, and WOMAC scores (all P values >0.005). To investigate the effect of using a walking aid on falls, the fall status in the last year and the number of falls were compared between the patients at risk of fall who used and did not use an AWD. The number of falls and falling status in the last year were similar in the patients who used and did not use a walking aid (Table 3) (P=0.853 and P=0.720 respectively).

Logistic regression analysis was performed to evaluate the risk factors that may affect the fall situation in the previous year. We examined age, gender, obesity, presence of pain, pain scores, disease severity, and self-reported functional scores of WOMAC for disability as risk factors. Only high scores of WOMAC were associated with fall history in the last year (OR: 1.068, 95 % CI: 1.029-1.109, p=0.001).

Discussion

The main findings of our study are the fall risk of the patients with moderate to severe knee OA and their AWD usage rates. Our secondary findings were the relationship between fall risk and use of an AWD with age, obesity, pain, the severity of the disease, disability, and fall history.

We used the BBS tool to determine the fall risk of the participants. Such performance-oriented functional tests are widely used in clinical practice to assess the mobility and balance problems of the elderly. BBS has been claimed to have a ceiling effect in patients with mild knee OA who are functioning well [3]. To our knowledge, a similar relationship has not been demonstrated in moderate to severe (grade 3-4) knee OA. Furthermore, in a systematic review, published in 2017, it is reported that the BBS score (≤50 points) is one of the most evidence-based functional measures in determining the risk of future falls [14].

We found that 50.6 % of the patients had a risk of fall and 21.5 % of total patients were using an AWD. The AWD usage rates among patients at risk of falling were 42.5 %. The amount of fall risk in our study is in accordance with the literature while the AWD usage rates among individuals with knee OA are much lower than the estimated rates of 40-70 % [9, 15, 16]. In an analytical systematic review, it is put forward that people with knee OA have a higher risk of falling and more than half of them express a fall history in the previous year [7, 17]. Similar to such knowledge, 46.8 % of our patients had a fall experience in the last year, and according to our results, the fall history of the participants in the previous year was an important predictor of fall risk in our participants.

In our study, we could not find any relationship between age, pain score, and fall risk. But there was a statistically significant association between obesity, disease severity, and self-reported disability scores. Although 48.1 % of our patients were over 65 years old, contrary to the literature [18] we found no relationship between age and fall risk. This might be caused by our patients who had advanced stage knee OA regardless of age. We could not find a relationship between pain and fall risk unlike Kim et al. and results reported in a systematic review [7, 19]. This may be because almost all of our patients suffer from pain and a large percentage of them have a high pain score. On the other hand, our findings suggest a close relationship between fall risk with disease severity and self-reported disability scores (WOMAC) like that of Kim et al. [19] and Adegoke et al., respectively [20]. Since the gait pattern of obese adults is similar to the elderly, obesity is linked to both static and dynamic stability and thus to higher rates of fall risk [21, 22]. Our results were consistent with these reported results in obesity-related fall risk in patients with knee OA.

According to our results, age was the only factor that was contributing to the use of an AWD among patients with knee OA who were at risk of falls. We could not correlate pain, pain score, obesity, disease severity, and disability with AWD use. Walking sticks are used not only to increase balance but also to reduce pain with a weight-bearing effect. The factors contributing to the possession of an AWD were determined as age, disability, and pain [15, 23]. The reason why we could not associate device use with pain may be that our patients who were at risk of falling had similar pain intensity. A similar inference can be made for disease severity and disability. Because both of the factors were associated with falling risk, and patients at risk of falling had similar disease severity and disability scores. On the other hand, Van Hook et al. reported that standard canes would not be sufficient to reduce pain and they offered that offset walking sticks should be used in such expectation especially in patients with knee OA. Furthermore to

increase the base of support they put forward that custom-made devices, fitted to the patients, should be prescribed [24]. Although all of our patients took the professional opinion of a clinician, the majority of them were using simple and non-custom fitted canes. Additionally, in accordance with nonuse reasons of our patients, Akinbo et al. found that nonuse is related to a negative outcome, negative effects on walking, and no need [23]. Contrary to the relationship with the risk of falling, fall history did not affect AWD use. Use of walking aids were specified as the only extrinsic risk factor for fall risk in a recent comprehensive review [7]. However, considering that these devices are generally prescribed for patients at high risk of falling, we believe that more comprehensive studies are needed to fully reveal this relationship. A fact that should not be overlooked is the adaptation process to AWD use, which is included in the OARSI 2014 recommendations [25]. It was stated in this report that at the end of the second month of use, compliance would not be a further concern.

We would like to point out that our study has some limitations. First, the sample size was small due to being a single-center study and our sample group was not homogenous for gender which has been previously shown to influence pain perception and expression [26]. Only 7 of the 79 participants were male. Therefore, we could not perform any statistical comparisons between male and female participants. Second, BBS is an objective measurement tool, but to a certain extent, it depends on the opinion of the patient and the clinician.

In conclusion, we found that about half of the participants with moderate to severe knee OA have fall risk and the rate of acquiring and using walking devices of such patients is well below than expected. We think that it is important to prescribe the right device for the right purpose and to inform the patient about the intended use of the device and the adaptation period. We believe that more comprehensive disease-specific studies will shed light on scientific literature.

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

Ethical Approval
The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Suleyman Demirel University, Faculty of Medicine Ethical Committee on March 5, 2020 (number 72867572.050.01.04).

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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IL-18 AND ADROPIN LEVELS IN PATIENTS WITH ACUTE ISCHEMIC STROKE

AKUT İSKEMİK İNMELİ HASTALARDA IL-18 VE ADROPİN DÜZEYLERİ

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Öz

Amaç

İnmeli hastalarda disfonksiyonel vasküler olaylara yol açan önde gelen faktörlerden bir tanesi olan ateroskleroz; endotelyal disfonksiyon ve vasküler inflamasyonun önemli bir rol oynadığı çok faktörlü ve kompleks bir süreçtir. Biz bu çalışmada endotel disfonksiyonu ve inflamatuar süreçlerle ilişkisi gösterilmiş olan IL-18 ve adropininin akut iskemik inme hastalarındaki serum düzeyleri ile epidemiyolojik, klinik, radyolojik bulgular ve inme şiddeti arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem

Çalışmamıza akut iskemik inme tanısı konulan 61 hasta ve kontrol grubu olarak 30 sağlıklı birey alındı. Hasta grubunda etiyolojik ve klinik olarak inme alt grupları ve inme şiddeti belirlendi. Hasta grubundan ilk 24 saatte, kontrol grubundan herhangi bir zamanda venöz kan örnekleri alınarak serumları ayrıldı ve -80^{0}C'de saklandı. ELISA yöntemi kullanılarak IL-8 ve adropin düzeyleri belirlendi. Hasta ve kontrol gruplarının IL-18 ve adropin düzeyleri ile iskemik inme arasındaki ilişkiler istatistiksel olarak analiz edildi.

Bulgular

Adropin düzeyi hasta grubunda kontrol grubuna göre istatistiksel olarak anlamlı derecede düşüktü (sırasıyla 398.01±403.51 ve 509.42±1492.89; p=0.041). Çalışma ve kontrol gruplarının IL-18 düzeyleri benzerdi (sırasıyla 24.87±14.26 ve 21.11±14.93; p=0.112). İnme risk faktörleri, inme alt grupları ve inme şiddeti ile belirlenen IL-18 ve adropin düzeyleri arasında ilişki yoktu.

Sonuç

Bu bulgular, düşük adropin düzeylerinin ateroskleroz göstergesi olarak iskemik inme risk tahmini ölçeklerinde kullanılabileceğini göstermiştir. Akut iskemik inmeli hasta grubu ile kontrol grubu arasında ortalama serum IL-18 düzeyi açısından fark olmaması, IL-18'in iskemiye bağlı inflamasyonda geç dönem bir sitokin olarak rol oynayabileceğini düşündürmüştür.

Anahtar Kelimeler: İskemik inme, Adropin, IL-18, İnflamasyon, Endotel disfonksiyonu

Abstract

Objective

Atherosclerosis, one of the prominent factors causing dysfunctional vascular events in stroke patients, is a multi-factorial and complex process in which endothelial dysfunction and vascular inflammation play significant roles. This study aimed to investigate the relationships between serum levels of IL-18 and adropin, associated with endothelial dysfunction and

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inflammatory processes in acute ischemic stroke patients, with epidemiological, clinical, radiological findings and stroke severity.

Materials and Methods
Sixty-one patients diagnosed with acute ischemic stroke and 30 healthy individuals were included in the study as the patient and control groups. In the patient group, the stroke sub-groups and severity were determined etiologically and clinically. Venous blood samples were obtained within the first 24 hours in the patient group, and at any time in the control group, their serums were separated and stored at -80°C. IL-8 and adropin levels were determined using the ELISA method. The relationships between patient and control groups' IL-18 and adropin levels and ischemic stroke were analyzed statistically.

Results
The adropin level was statistically significantly lower in the patient group than the control group (398.01±403.51 and 509.42±1492.89, respectively; p=0.041). The IL-18 levels of the study and control groups were similar (24.87±14.26 and 21.11±14.93, respectively; p=0.112). There was no relationship between the IL-18 and adropin levels determined with stroke risk factors, stroke sub-groups, and stroke severity.

Conclusion
These results showed that low adropin levels could be used to indicate atherosclerosis in the risk prediction scales of ischemic stroke. The absence of a difference between the patient group with acute ischemic stroke and the control group regarding the first 24-hour mean serum IL-18 level suggested that IL-18 could play a role as a late-stage cytokine in ischemia-related inflammation.

Keywords: Ischemic stroke, adropin, IL-18, inflammation, endothelial dysfunction

Introduction

Stroke is an acute clinical syndrome due to vascular causes and characterized by rapidly developing symptoms and signs of focal neurologic deficit (1). Strokes that develop as a result of decreased cerebral blood flow due to local arterial pathology (mostly atherosclerosis), embolism or hemodynamic reasons and that are pathologically characterized by infarction are called ischemic strokes (2). In addition to many well-known classical risk factors, mechanisms such as free radical formation, lipid peroxidation, excitotoxicity, increased intracellular calcium, and inflammation play a role in the pathophysiology of cerebral ischemia (3). Inflammatory mechanisms play roles in both the stroke development risk and the pathophysiology of cerebral ischemia. In recent years, many inflammatory markers have been defined in ischemic stroke-related studies. Some of these markers have been shown to be helpful to determine the stroke risk, whereas some others were helpful for diagnosis and prognosis (4).

IL-18 is a proinflammatory cytokine considered to play a part in the pathophysiology of acute ischemic stroke like the other proinflammatory cytokines (5, 6). Experimental studies demonstrated that IL-18 was closely linked with atherosclerotic plaque formation and instability (7). Besides, IL-18 is an independent predictor of coronary events in healthy males and a predictor of cardiovascular mortality in patients with coronary artery disease (8). In various studies related to ischemic stroke etiology, it has been hypothesized that the proinflammatory profile due to increased IL-18 level created a pro-thrombotic and pro-atherosclerotic process (9). Even though an increased IL-18 level was not determined in stroke patients, multiple pieces of evidence showed that the IL-18 level could predict stroke development (9, 10, 11, 12).

Atherosclerosis is a principal factor causing cerebrovascular diseases. Atherosclerosis development is a complex process depending on multiple factors such as endothelial dysfunction, vascular inflammation, and thrombus formation (13). Adropin is a newly discovered peptide that plays a role in energy homeostasis and lipid metabolism (14). Adropin, which regulates glucose and fatty acid metabolism, is also associated with endothelial cell function and endothelial nitric oxide synthase (eNOS) bioactivity (15). Adropin can play a protective role by increasing nitric oxide (NO) release through eNOS activation (16). Impairment of endothelial functions brings about the loss of vasomotor control, decreased NO production, formation of a pro-coagulant surface, and increased inflammation. Subsequently, aforementioned events can cause destabilization of atherosclerotic plaques and initiate acute coronary syndromes (17). Another recently conducted study has revealed that decreased serum adropin level would be a coronary

atherosclerosis-related independent determiner and a new predictor (18). Because endothelial dysfunction plays a significant role in atherosclerosis development and progression, besides its favorable metabolic profile, adropin has been predicted to be a new target to limit endothelial dysfunction-related diseases (16). These results have shown adropin would be a novel and convenient determiner for the non-invasive assessment of endothelial functions (19).

The study aimed at examining the relationships between the first 24-hour serum levels of adropin and IL-18, which play significant roles in atherosclerosis and inflammatory processes that have a place in ischemic stroke pathophysiology, with the subtypes and severity of the ischemic stroke.

Materials and Methods

The study included 61 patients admitted between May 2016 and October 2016 to the Neurology Clinic of Medical Faculty Hospital of Atatürk University within the first 24 hours after the onset of their complaints and diagnosed with acute ischemic stroke and 30 age/gender-matched healthy individuals. The approval of the head of the Ethics Committee of Atatürk University Medical Faculty was taken for the study (on April 26th, 2016: 4/29), and ethical principles were observed over the course of the study. Both groups participating in the study gave their consent. Volunteer patients over the age of 18 years and diagnosed with acute ischemic stroke within the first 24 hours were included. Patients with stroke history, brain tumor, or systemic malignancy, severe infection in the last three months, those with autoimmune, rheumatic, hematologic, or immunosuppressive disorders, patients treated with anti-inflammatory drugs during the past six months, those with severe renal or hepatic failure, history of myocardial infarction within the last one year, patients with peripheral arterial disease or deep venous thrombosis, history of major trauma or surgery within the last one year, psychiatric disorders, malnutrition, and intoxication were excluded from the study.

Clinics, Laboratory, and İmaging

Epidemiologic data of the patients in the study, such as age, gender, personal medical, and family histories, were questioned. A detailed history of vascular risk factors (HT, DM, AF, coronary arterial disease (CAD), congestive heart failure (CHF), hyperlipidemia, and smoking was obtained in every patient. Systemic and neurological examinations of all patients were performed. In all patients with no contraindication for MRI, the diffusion MRI was performed within the first 24 hours, following the stroke protocol. Routine hematologic and biochemical tests, complete urinalysis, chest X-ray, electrocardiography, echocardiography, carotid-vertebral artery Doppler ultrasonography, cranial MRI, and MR angiography were carried out in all the study group patients.

Ischemic stroke subtypes in the patient group were determined in accordance with the Bamford classification as the total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), lacunar infarct (LACI), and according to the TOAST classification as large- artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), the stroke of undetermined etiology, and the stroke of other determined etiology. The control group was divided into two sub-groups: those with two or more risk factors (age included) and those with less than two risk factors (age only). In the National Institute of Health Stroke Scale (NIHSS), the NIHSS levels were divided into three groups: an NIHSS score of 0-6 as mild, 7-15 as moderate, and over 16 as severe.

Demographic and clinical data, laboratory and imaging results of all patients were recorded in the forms arranged on an individual basis for every patient.

Blood Collection and Serum Preparation

Approximately five ml of blood was drawn into 10-ml biochemistry tubes with jelly through the antecubital veins of the patients within the first 24 hours following symptom onset, was kept at room temperature for approximately 30 minutes, and then the serum was separated by centrifuging at 4000 rpm for ten minutes. The serum samples were placed in two separate 1.5-ml Eppendorf tubes and stored at -80^{0}C until the analysis day. The IL-18 level was quantitatively measured employing the Human Interleukin 18 (IL-18) ELISA Kit (Cat. No: CK-E10092, China) with the brand name of EASTBIOPHARM. The adropin level was quantitatively measured using the Human Adropin (AD) ELISA Kit (Cat. No: CK-E90267, China) with the brand name of EASTBIOPHARM. The serum IL-18 and adropin concentrations were presented in ng/L.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS)-Windows software, version #17, performed the statistical analysis. The Shapiro Wilks test evaluated the normal distribution of data, and all continuous variables in the study were determined not to have a normal distribution. The numerical variables having a normal distribution were shown as mean±standard deviation, whereas the ones with no normal distribution as median (min-max). The categorical variables were

presented as numbers and percentages. The Mann-Whitney U test determined the factors related to 2-category risk groups (numerical variables with no normal distribution). The Kruskal Wallis test was used to determine the factors related to 3-category risk groups (numerical variables with no normal distribution). The Chi-square and Fisher's Exact Chi-square tests were employed to compare the categorical data. The relationships among the numerical variables were analyzed employing Spearman's correlation analysis. The value for statistical significance was considered as $p<0.05$.

Results

The study included 91 individuals in total involving 61 patients with acute ischemic stroke and 30 controls. The demographic and clinical data obtained from the patient and control groups were presented in the table (Table 1). No statistically significant differences were observed between the patient and control groups regarding age and gender ($p>0.05$). By comparison of the patient group diagnosed with acute ischemic stroke with the control group, a significantly lower mean adropin level was found in the patient group (398.01±403.51 and 509.42±1492.89, respectively; $p=0.041$). No statistically significant difference was established between the mean IL-18 values of the patient and control groups (24.87±14.26 and 21.11±14.93, respectively; $p=0.112$) (Table 1).

When the distributions of risk factors in the stroke subtypes (TOAST) were analyzed, HT was most frequent (87.5%) in the group with small vessel

Table 1 Demographic, clinical and laboratory characteristics in patients and healthy controls.

	Patients (n=61)	Controls (n=30)	p
Age (years, mean±SD)	71.47±11.67	70.00±11.86	0.254
Gender (female)	38 (62.3%)	18 (60%)	0.832
Stroke risk factors			
Hypertension	41 (67.2%)	12 (40%)	
Diabetes	20 (32.8%)	5 (16.7%)	
Atrial fibrillation	21 (34.4%)	2 (6.7%)	
Coronary artery disease	11 (18%)	2 (6.7%)	
Congestive heart failure	13 (21.3%)		
Hyperlipidemia	17 (27.9%)	3 (10%)	
Smoking	17 (27.9%)	2 (6.7%)	
TOAST			
LAA	15 (24.6%)		
CE	15 (24.6%)		
SVO	16 (26.2%)		
UD	11 (18%)		
OD	4 (6.6%)		
Bamford			
TACI	11 (18%)		
PACI	18 (29.5%)		
LACI	22 (32.8%)		
POCI	12 (19.7%)		
NIHSS			
Hafif (0-6)	26 (42.6%)		
Orta (7-15)	18 (29.5%)		
Ağır (>16)	17 (27.9%)		
IL 18 (ng/L)	24.87±14.26	21.11±14.93	0.112
Adropin (ng/L)	398.01±403.51	509.42±1492.89	**0.041**

TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: Large-artery atherosclerosis, CE: Cardioembolism, SVO: Small vessel occlusion, UD: undetermined etiology, OD: Other determined etiology, TACI: Total anterior circulation infarcts, PACI: Partial anterior circulation infarcts, LACI: Lacunar infarcts, POCI: Posterior circulation infarcts

occlusion (SVO), which was considered to be statistically significant (p=0.038). AF was most common in the cardioembolism group (66.7%) as expected, being statistically significant (p=0.012). DM was most common in the SVO group; however, there was no correlation (p=0.113). No significant relationships were determined among the other risk factors and the stroke subtypes (Table 2).

The adropin and IL-18 levels were not correlated with age in the patient group (p=0.557, and p=0.649, respectively). The adropin and IL-18 levels of the control group were not correlated with age (p=0.666, and p=0.408, respectively), and not with gender (p>0.05) (Table 3).

Among ischemic stroke sub-groups (according to the TOAST classification), the adropin level was highest in the CE subgroup (536.34±558.09), whereas the lowest in the stroke subgroups of undetermined and other determined etiologies (238.60±64.15 and 299.17±183.25, respectively; p=0.946). The IL-18 level was highest in the SVO subgroup (30.89±17.57), whereas lowest in the CE subgroup (18.95±12.47) (p=0.172) (Table 4).

Table 2 Distribution of risk factors in ischemic stroke subtypes (TOAST).

	LAA	CE	SVO	OD	UD	p
n	15	15	16	4	11	
Hypertension (%)	66.7	46.7	87.5	25	81.8	**0.038**
Diabetes (%)	33.3	13.3	50	0	45.5	0.113
Atrial fibrillation (%)	40	66.7	12.5	0	27.3	**0.012**
Coronary artery disease (%)	13.3	26.7	12.5	0	27.3	0.587
Congestive heart failure (%)	33.3	26.7	18.8	0	9.1	0.452
Hyperlipidemia (%)	40	20	31.3	25	18.2	0.703
Smoking (%)	40	33.3	31.3	25	0	0.224

TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: Large-artery atherosclerosis, CE: Cardioembolism, SVO: Small vessel occlusion, UD: undetermined etiology, OD: Other determined etiology

Table 3 Relationship between gender and adropine and IL-18 levels.

		Gender	n	Mean±SD	p
Patients	**Adropin**	Male	23	363.09±270.96	>0.05
		Female	38	419.14±468.15	
	IL 18	Male	23	28.94±18.30	
		Female	38	22.40±10.69	
Control	**Adropin**	Male	12	218.50±73.36	
		Female	18	703.37±1923.25	
	IL 18	Male	12	21.95±12.20	
		Female	18	20.54±16.82	

Table 4 Adropine and IL 18 levels in ischemic stroke subtypes (TOAST).

		n	Mean±SD	p
Adropin	LAA	15	342.19±364.73	0.946
	CE	15	536.34±558.09	
	SVO	16	454.96±424.29	
	UD	11	238.60±64.15	
	OD	4	299.17±183.25	
IL18	LAA	15	24.63±7.47	0.172
	CE	15	18.95±12.47	
	SVO	16	30.89±17.57	
	UD	11	24.34±16.79	
	OD	4	25.30±15.15	

TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: Large-artery atherosclerosis, CE: Cardioembolism, SVO: Small vessel occlusion, UD: undetermined etiology, OD: Other determined etiology

Table 5 Adropin and IL 18 levels in healthy controls and controls with risk factors.

	Risk faktörü	n	Ortalama	p
Adropin	<2	13	203.10±97.34	0.170
	≥2	17	743.67±1974.31	
IL18	<2	13	17.80±11.77	0.341
	≥2	17	23.63±16.87	

No statistically significant differences were determined between ischemic stroke risk factors and NIHSS scores and adropin and IL-18 levels in both the patient and control groups.

The control group included 13 individuals (43.3%) with less than two risk factors (no risk factor other than age). Any significant difference concerning the IL-18 and adropin levels was not ascertained between the healthy controls and the controls under risk (having risk factors other than age) (p=0.341, and p=0.170, respectively) (Table 5).

Discussion

The study investigated the relationships of acute ischemic stroke, in which the inflammatory and atherosclerotic processes play significant etiological roles, with IL-18 and adropin. Despite the similar IL-18 levels of the patient and control groups, the serum adropin level of the group with acute ischemic stroke was found to be significantly lower than the control group.

Detailed molecular-level and cellular-level identification of intertwined toxic mechanisms, emerging with sudden interruption of the blood flow and leading to brain cells' irreversible death, is essential for improving diagnostic and therapeutic approaches.

Atherosclerosis, having a significant role in the pathophysiology of ischemic stroke, is a multi-factorial and complex process. Endothelial dysfunction is one of the primary mechanisms in the atherosclerotic

process. The conventional and newly described risk factors cause a chronic injury that leads to impairment of the endothelial vasodilator response. Thus, events such as the vasoconstriction in the endothelium, piling up of inflammatory cells, migration of smooth muscle cells, and enhanced cytokine production lead to atherosclerotic plaque formation. Endothelial dysfunction is not only the first step of the atherosclerotic process that causes plaque formation but also leads the formed plaque to enlarge, crack, triggering the thrombogenic events (20). NO, released from the endothelium, enhances reparative vasculogenesis and acts as an anti-atherosclerotic, anti-inflammatory, and anti-thrombotic factor. Adropin, which modulates eNOS expression, has been considered to play a protective role for the endothelium (16).

The serum adropin level of the patient group with acute ischemic stroke was ascertained to be significantly lower than that of the control group. Few clinical studies were conducted on adropin in patients with acute ischemic stroke. In the conducted studies, the low plasma adropin level reported to be linked with obesity-related insulin resistance, atherogenesis, diabetes, aging, pediatric obstructive apnea, and many other metabolic disorders (16). In their study on diabetic patients, Topuz et al. determined that the group with endothelial dysfunction had lower adropin level (19). In their study analyzing the correlation of serum adropin level with coronary artery disease (CAD) in 356 patients, Zhang et al. determined that the serum adropin level of the CAD group was significantly lower than that of the control group, and adropin was an independent risk factor for CAD (21). Yu et al., in their study on patients with stable angina pectoris and acute myocardial infarction (AMI), reported that the serum adropin level decreased in AMI patients (22). In their study, Wu et al. showed that the adropin level was independently and negatively correlated with the angiographic severity of coronary atherosclerosis, and the serum adropin level could be a new indicator of coronary atherosclerosis (18). In the recent study, Günaydın et al. reported a significantly lower adropin level in ischemic stroke patients compared with the controls and that adropin could be an independent predictor of acute ischemic stroke (23). Our study results supported the studies on both ischemic stroke and CAD, which have similar risk factors and etiologies. Even though adropin is known to reduce the paracellular permeability in brain endothelial cells in ischemic conditions, little is known about adropin's effects on the brain. Adropin has been considered to provide neuroprotection by activating endothelial nitric oxide synthase (eNOS) / NO signal pathway and reducing blood-brain barrier injury (24). Yang et al., in their study, claimed that adropin deficiency in the brain increased neurovascular dysfunction and thus the severity of stroke damage and that over-expression of this peptide reduced the cerebral ischemic damage (25). In our study, low adropin level was found to be related to ischemic stroke. When the studies reporting that low adropin levels could be an indicator of atherosclerosis were considered, it was shown that adropin could be used in ischemic stroke risk prediction scales and could be a novel and useful determiner for the evaluation of endothelial functions. When all these results are considered, it can be suggested that adropin can be used as a biomarker for diagnosing ischemic stroke and is a promising therapeutic agent in the light of more extensive clinical studies that will be performed. Even though adropin seems like a new target to prevent vascular disorders because of its known impacts on metabolic regulation, further studies should be conducted to explain the unique mechanism forming the base for the relationship between adropin and cerebrovascular diseases.

Ischemic stroke causes a severe inflammatory reaction, and cytokines, expressed mainly in the glial cells and neurons, are produced (26). Besides inducing IFN- γ, IL-18 induces the synthesis of cytokines TNF-α and IL-10 that can inhibit the inflammatory process and cause instability of atherosclerotic plaques and thrombosis (27). The studies investigating the relationship between the IL-18 level and ischemic stroke found inconsistent outcomes. In the study, even though the mean serum IL-18 level within the first 24 hours in acute ischemic stroke patients was higher than in the control group, no statistically significant difference was observed between them.

IL-18 is considered to play a part in the pathophysiology of acute ischemic stroke like the other proinflammatory cytokines (6). The relationship between acute ischemic stroke and IL-18 was first shown in a study published by Zaremba et al. in 2003. They studied the IL-18 levels in serum samples obtained within the first 24 hours and determined significantly higher IL-18 levels in the patient group (10). In their study published in 2007, Yuen et al. reported significantly higher IL-18 levels in the patients' venous blood samples obtained at the 48th hour following the acute ischemic stroke onset (27). In their study conducted in 2011, Ormstad et al. determined significantly high IL-18 levels in the group with acute ischemic stroke (28). In their cross-sectional study followed by meta-analysis in 2019, Hao et al. showed that the IL-18 level of the stroke patients was higher than that of the

controls (29). However, unlike these studies, in the studies conducted with animal models, it was shown that the intracerebral IL-18 levels had not increased in the early period (within the first 24 hours) (30, 31). In their study on mice, Wheeler et al. claimed that IL-18 played a minor part in acute ischemic processes, could be induced in the late stage of cerebral infarct, and could change the repair and healing status (31). In their study investigating whether IL-18 was induced after focal ischemia in the rat brain, Jander et al. determined a delayed increase of IL-18 level starting at 48 hours and reaching its maximal level 7-14 days after ischemia (30). In the study conducted by Gürkaş et al., no significant difference was reported between the serum IL-18 levels of ischemic stroke patients within the first 24 hours and the control group, similar to our study (6). After demonstrating the inflammation's role in the pathogenesis of ischemic stroke, numerous studies have been conducted on inflammatory markers such as IL-1β, TNF-α, IL-6, and IL-18. The IL-18-related studies in animal models revealed that IL-18 played a role in the late stage of ischemic cerebral inflammatory response.

On the other hand, while no increase was determined in IL-18 level within the first 24 hours in some studies, other studies reported increases in both the early and late periods. Because IL-18 levels were studied in samples obtained within the first 24 hours (mostly at admission) in our study, the elevation of IL-18 level might not have been determined. Because of the different results of these clinical studies, new studies investigating the IL-18 levels in both the early and late periods on larger sample-sized patient groups are required.

Conclusion

The serum adropin level of the patient group with acute ischemic stroke was significantly lower than the level of the control group; however, the IL-18 levels of the patient and control groups were similar. It can be suggested that adropin can be used as a biomarker for diagnosing ischemic stroke and is a promising therapeutic agent in the light of more extensive clinical studies that will be performed.

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

Ethical Approval
The approval of the head of the Ethic Committee of Atatürk University Medical Faculty was taken for the study (on April 26th, 2016: 4/29), and ethical principles were observed during the study.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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THE EFFECT OF PICO GAME ON NURSING DIAGNOSIS AND PROBLEM-SOLVING SKILLS OF STUDENTS

PİCO OYUNUNUN ÖĞRENCİLERİN HEMŞİRELİK TANILARI VE PROBLEM ÇÖZME BECERİLERİ ÜZERİNE ETKİSİ

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Öz

Amaç
Bu araştırma, PICO oyununun öğrencilerin hemşirelik sürecinde tanı ve planlamayı belirleme ve problem çözme becerilerine olan etkisinin belirlenmesi amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem
Araştırma Şubat-Mart 2020 tarihinde yapılan yarı-deneysel tipte bir araştırmadır. Araştırmanın örneklemini hemşirelik bölümünde hemşirelik süreci dersine devam eden 40 ikinci sınıf öğrencisi oluşturmuştur. Araştırmanın verileri sosyodemografik özellikler anketi, memnuniyeti değerlendirmeye yönelik görsel analog ölçeği, problem çözme envanteri ve hemşirelik süreç planlama tablosu ile toplanmıştır.

Bulgular
Öğrencilerin PICO oyunu öncesi ve sonrası Problem Çözme Becerileri Ölçeği toplam ve alt ölçekleri puan ortalamaları arasında anlamlı bir fark bulunmamıştır. Öğrencilerin dersin işlenişi ile ilgili memnuniyet puan ortalaması 10 üzerinden 9.38±1.19 olarak belirlenmiştir.

Sonuç
Araştırma sonucunda, öğrencilerin PICO senaryolarına özgü etkili klinik soru sorma ve hemşirelik tanılarını ve bu tanılara özgü girişim ve hasta sonuçlarını doğru bir şekilde belirledikleri saptanmıştır.

Anahtar Kelimeler: PICO, Oyuna Dayalı Öğrenme, Hemşirelik, Hemşirelik Süreci, Problem Çözme Becerisi

Abstract

Objective
This research was conducted to determine the effect of the PICO game on students' problem-solving skills as well as their ability to determine the diagnosis and planning in the nursing process.

Materials and Methods
The research is a quasi-experimental study conducted in February-March 2020. The sample of the research was comprised of 40 second year students attending the nursing process course at the department of nursing. The data of the research were collected with a questionnaire for socio-demographic characteristics, visual analog scale for assessing satisfaction, the

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problem-solving inventory and the nursing process planning table.

Results
There was no significant difference between the total and subscale scores of the Problem-Solving Inventory before and after the PICO game. The average satisfaction score of the students about the conduction of the course was found to be 9.38 ± 1.19 out of 10.

Conclusion
As a result of the research, the students were able to correctly identify the effective clinical questions and nursing diagnoses specific to PICO scenarios and the interventions and patient outcomes specific to these diagnoses.

Keywords: PICO, Game Based Learning, Nursing, Nursing Process, Problem Solving Skills

Introduction

Providing care forms the basis of nursing practices. Effective care delivery is made possible via the nursing process (NP), which is a systematic and planned process that integrates the problem solving approach into nursing care (1). Since it guides nurses in making planned and purposeful decisions, the use of NP in patient care allows the provision of a patient-centered, holistic and individualized care (1,2). The foundation of the knowledge and skills required for the use of the NP by nurses is laid in nursing education (3). The objectives of the undergraduate programs that provide nursing education include the training of graduates who would provide nursing care with a systematic approach.

The nursing process consists of steps such as identifying the problems of healthy/sick individuals, planning, implementing and evaluating the necessary nursing interventions. The diagnosis step helps the systematic collection of data on the patient's health problems. After diagnosis, the health problem of the patient is determined by using the collected data and the nursing diagnosis is formulated. The planning of nursing interventions specific to the problems and predicted patient outcomes constitutes another step (1,4). It is of importance that the nursing process is a tool that teaches students the steps of scientific problem solving, and it is essential that evidence-based practices are used while planning the care in accordance with national practice standards. The first step in the evidence-based nursing process is to develop clinical questions. Clinical questions are the questions that determine the best way to solve the nursing problems (diagnoses) identified during the diagnostic phase. The process of developing clinical questions actually constitutes the nursing diagnosis and planning steps of the NP (5). The reason for this is that clinical questions are crucial for students to be able to plan a purposeful intervention for the established nursing diagnoses.

Well-designed clinical questions increase the likelihood of practitioners establishing accurate diagnoses and finding the correct answers (6) Asking the question is the most challenging step in the evidence-based nursing process (7). In this research, the PICO method was used to develop effective clinical questions and the method was based on a game (8,9). Learning through games, which is commonly used in health education (10), is active and student-centered (11). Game-based teaching is a method that is conducted in a competitive environment with predetermined rules by the educator (12). Games are a teaching strategy used by educators to engage students in learning (10), increase self-confidence, develop group collaboration and enable interaction (13). The use of games in education draws the attention of students by making the learning environment interesting (11). In this way, the students are motivated and their self-esteem is increased (10,14). Games are also an effective tool for developing critical thinking skills (8,15,16). Increasing the retention of knowledge previously learned enhances the knowledge (11). The method of learning with games in nursing education, which dates back to the 1980s, improves critical thinking and problem solving skills that are effective in the clinical decision-making process (11,12). PICO stands for Problem, Intervention, Comparison and Outcome. PICO is one of the best tools that help formulate questions and directly contribute to finding solutions to the problems of individuals (8). The clinical questions to be determined by the students will contribute to their ability to establish nursing diagnoses specific to cases diagnoses and plan their interventions as well as predicted patient outcomes. In this way, students will be able to better understand the diagnosis and planning steps of the NP and perform more qualified and evidence-based nursing care after graduation. Furthermore, the effect of the PICO game to be used in the teaching of the NP on problem-solving skill will be examined.

It was determined that the PICO game was used to develop the ability of nursing students to create

evidence-based, consistent and systematic questions about practice problems (8,9,17), and in another study, it was used to provide web-based evidence-based practice experiential learning (18). In our study, unlike these studies, the PICO game was used to determine the nursing diagnosis and nursing interventions and the effect on students' problem solving skills.

This research was conducted to determine the effect of the PICO game on students' problem-solving skills as well as their ability to determine the diagnosis and planning in the nursing process.

Materials and Methods

Study Design and Sample

In this quasi-experimental research, a one-group pretest posttest design was used. The research was conducted at a faculty of health sciences between February-March 2020. The sample of the study consisted of 40 second year students out of those taking the NP course (N: 55) in the 2019-2020 academic year, who agreed to participate in the research. In the institution where the research was conducted, the NP course was given for 2 hours a week in one semester. In calculating the sample size of the research, power analysis was carried out post hoc by using the G * Power 3.1 software. The statistical power of the study was calculated as 0.86 with an alpha error probability of 0.05 and a large effect size of 0.5.

Intervention in the Classroom

Np course was designed to be instructed by using case discussion, lecture, question and answer method. The contents of NP were consisted of the history of nursing process, critical thinking, problem solving steps and steps of the nursing process. After teaching the nursing process and problem-solving steps, the students'problem-solving skills and sociodemographic characteristics were determined and the researchers explained how to play the PICO

Table 1 Sample PICO Tables

Case	P	I	C	O
The patient in the intensive care unit cannot use upper extremities. Oral care of the patient is provided by relatives. The patient has oral injuries. The use of 5% NaHCO3 is planned for oral care.	Impaired oral mucous membrane	Oral Health Restoration (NIC) Oral care with 5% $NaHCO_3$	Application by patient's relatives	Oral Health (NOC) There will be an improvement in patient's oral cavity.
The patient, who was hospitalized in the orthopedic clinic due to hip fracture, has pain marked as 6 in the visual analogue scale. Other nurses responsible for the patient's care are trying to cause distraction by asking different questions to the patient. However, there seems to be no decrease in the patient's pain. You are planning to teach the patient relaxation techniques.	Acute pain	Conscious Sedation (NIC) Relaxation techniques	Distraction	Pain Level (NOC) The patient will mark the pain level between 0-3 on the visual analogue scale.
You have a patient expressing an inability to defecate for five days. It seems that the patient has had fast food recently and hasn't paid attention to fluid intake.	Constipation	Constipation/ Impaction Management (NIC) Fluid intake Juicy foods	Fast food consumption, low fluid intake	Bowel Elimination (NOC) The patient will express ability to defecate.
You measured the fasting blood glucose level of your DM patient at the internal medicine clinic as 250 mg / dl. When you talk to the patient, you find out that s/he does not know how to comply with the recommended dietary regulations.	Deficient Knowledge	Teaching: Individual (NIC) Information on nutrition in diabetes	Previous level of knowledge	Knowledge of: Diet (NOC) The patient will state that s/he pays attention to his/her diet.

game to the students and play one sample. After that, PICO game was played with students in the classroom. The object of the PICO game is to be the first group player to complete 10 PICO table correctly. All the of students were assessed by the researcher with educator experience who had previously learned and practiced PICO game. In the PICO game, 10 cases and case-specific PICO tables and answer keys cards were created for the students to plan their nursing process by the researchers. There are 10 cases tables with different nursing process issues focusing on comparing an intervention to usual or standard of nursing care. Ten tables have a case and P, I, C, O word to match a case. At The PICO Game (P) is for identify problem and nursing diagnosis, (I) is for nursing intervention, (C) is for comparing attempts with existing evidence (O) is for expected patient outcomes from clinical cases that focus on interventions or treatments. Table 1 displays a sampling of cases and matching P, I, C, O. Group players are expected to correctly fill in each PICO tables distributed as soon as possible. Group players yell “PICO” when they think they have a completed question, and the researchers check it against the PICO answer key card. If it is correct, new PICO table is placed in front of that group player and the game continues. The PICO game was implemented in the following steps.

Steps 1: All students were divided into eight groups of five. Each researcher was responsible for four groups and checking the PICO tables.

Steps 2: The first of the PICO table was distributed to each group simultaneously in a sealed envelope. The game started with the warning "You can open the closed envelopes". Researchers observed groups of students. No clues were given.

Step 3: In accordance with the given case, students were asked to determine their nursing diagnoses, and plan their diagnostic interventions and patient outcomes on the PICO tables. Researchers observed groups of students. No clues were given.

Step 4: The researcher went to the first group that yelled PICO and checked the PICO table with the PICO Table answer key card. If it was correct, other PICO tables gave it. If there was an error, they were given feedback by the researcher to read the case carefully again.

Step 5: At last, the first group that finished all the PICO tables correctly won the game. The winning group was only applauded.

Instruments

The data of the research were collected with a questionnaire on sociodemographic characteristics, the visual analogue scale (VAS), the problem-solving inventory and the NP diagnosis and planning table.

Visual Analogue Scale (VAS): Students were asked to indicate their satisfaction level regarding how the course was given by choosing a value between 0-10 on the scale. Students marked on a scale from 0 to 10 (0 cm = very dissatisfied, 10 cm = very satisfied). The distance of the line from the zero point to the point marked by the individual indicates the condition of the person and is recorded in inches.

Problem Solving Inventory (PSI): The Turkish version of PSI developed by Heppner and Petersen (1982) was conducted by Şahin et al. (1993) (19,20). The scale consists of 35 items scored on a six-point Likert scale. The responses to the items correspond to the following points; “1: I always act like this; 2: I usually act like this; 3: I often act like this; 4: I sometimes act like this; 5: I rarely act like this; 6: I never act like this”. The total score that can be obtained from the PSI ranges between 32-192, and a high score indicates that the individual perceives himself/herself as inadequate in terms of problem solving while a low score indicates that the individual perceives himself/herself as adequate. The scale consists of three subscales which are as follows; Problem-Solving Confidence (PSC) (5, 10, 11, 12, 19, 23, 24, 27, 33, 34, 35. items) expresses the individual’s self-assurance while engaging in problem-solving activities, Approach/Avoidance (AA) (1, 2, 4, 6, 7, 8, 13, 15, 16, 17, 18, 20, 21, 28, 30, 31. items) refers to individuals’ reviewing their initial efforts in problem solving and actively researching alternative solutions, and Personal Control (PC) (3, 14, 25, 26, 32. items) which indicates individuals’ ability to maintain control in problematic situations (20). The total cronbach alpha value of the scale was determined to be 0.88 while the cronbach alpha value of the PSC subscale was 0.76, the cronbach alpha value of AA subscale was 0.78 and the cronbach alpha value of PC subscale was 0.69 (20). In this study, the total cronbach alpha value of the scale was found to be 0.89 and 0.92, the cronbach alpha value of the PSC subscale was 0.76 and 0.83, the cronbach alpha value of the AA subscale was 0.86 and 0.89, and the cronbach alpha value of the PC subscale was 0.46 and 0.69 respectively.

Nursing Process Diagnosis and Planning Table (PICO tables): is a table where students could plan their nursing processes in line with the given cases

as P (problem), I (intervention), C (comparison), and O (outcome).

Data collection

The data collection process took place in the classroom where the NP course was given and lasted for one class hour. The data collection phase was carried out by the researchers in the research (Figure 1).

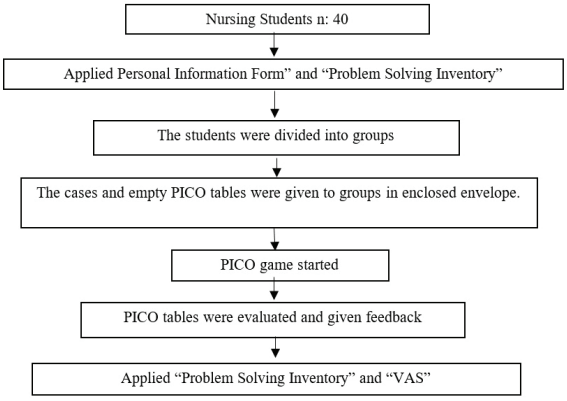

Figure 1
Flow of data collection

Stage 1: Nursing Process course was taught for 13 two hours with case discussion, lecture and question and answer method. The PICO game was played in the 8th week.

Stage 2: After teaching the nursing process and problem solving steps, the students who were voluntary were asked to fill out the "Personal Information Form" and "Problem Solving Inventory". The students were told how to play the PICO game and groups of 5 students were formed for the PICO game and PICO game was played.

Stage 3: One week after the PICO game, the students who were voluntary were asked to fill out "Problem Solving Inventory" and evaluate their satisfaction level regarding the course through "VAS".

Data Analysis

For the analysis of the study data, the statistical package for social sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows was used. In analyzing students' sociodemographic characteristics and satisfaction levels; number, percentage, arithmetic mean, and standard deviation were used. To evaluate the problem-solving skills of students before and after the PICO game, Paired Sample t test and Wilcoxon Signed Rank test were used.

Ethical Considerations

In order to conduct the research, written consent was obtained from the ethics committee of the institution (ethical committee number: 13/01 dated 26.12.2019) and the faculty where the research was conducted. The students who agreed to participate in the research were asked to fill in an informed consent form.

Results

A total of 40 students from the nursing department participated in the research. It was determined that the mean age of the students was 19.78 ± 0.76 and 75% (n = 30) were women. The mean VAS score used to measure students' satisfaction with the PICO game was determined as 9.38 ± 1.19.

The total mean scores and the mean subscale scores of the students obtained from the PSI are given in Table 2. It was found that the students PSI mean

Table 2 Comparison of the Students' Problem-Solving Inventory Total Scale and Subscale Mean Scores Before and After the PICO Game

PSI Total Scale and Subscale	Before PICO Game (n=40)	After PICO Game (n=40)	Statistical Analysis	
	M±SD	M±SD	t	p
PSC	25.13±6.84	24.50±7.79	.601	.552
PC	15.30±3.47	14.60±4.11	1.297	.202
AA	41.08±11.18	38.45±12.20	1.893	.066
Total Scale	95.25±18.55	90.68±20.47	1.912	.063

Note. M= mean; SD= standard deviation; t= paired sample t test, PSC=Problem-Solving Confidence, PC= Personal Control, AA= Approach/Avoidance,

Table 3 Comparison of the Male and Female Students' Problem-Solving Inventory Total Scale and Subscale Mean Scores Before and After the PICO Game

PSI Total Scale and Subscale	Female (n=30)			Male (n=10)		
	M±SD	MR	SR	M±SD	MR	SR
PSC	25.13±7.11	13.67	123.0	25.10±6.31	5.0	40.0
PSC*	23.60±8.02	14.17	255.0	27.20±6.68	7.50	15.0
	Z:-1,588 p= .112			Z:-1.283 p= .199		
PC	15.27±3.79	10.95	120.50	15.40±2.46	6.30	31.50
PC*	14.10±4.34	16.79	285.50	16.10±3.00	4.70	23.50
	Z:-1.885 p= .059			Z:-0.413 p= .679		
AA	40.23±12.10	13.44	121.00	43.60±7.81	5.83	17.50
AA*	37.03±13.01	15.70	314.00	42.70±8.54	4.58	27.50
	Z:-2.090 p= .037			Z:-0.595 p= .552		
Total Scale	94.43±19.70	12.11	109.00	97.70±15.23	5.25	21.00
Total Scale*	87.97±21.34	16.95	356.00	98.80±15.82	4.80	24.00
	Z:-2.541 p= .011			Z:-0.178 p= .859		

Note. M= mean; SD= standard deviation; MR= mean rank; SR= sum of ranks; Z= Wilcoxon signed rank test
* Post PICO game, PSC=Problem-Solving Confidence, AA= Approach/Avoidance, PC= Personal Control

score before the PICO game was 95.25, while it was found to be 90.68 after the game. Female students PSI mean score before the PICO game was 94.43, while it was found to be 87.97 after the game. Male students PSI mean score before the PICO game was 97.70, while it was found to be 98.80 after the game. There was no significant difference between the students' PSI total and subscale mean scores before and after the PICO game. In terms of gender, a significant difference was found between the total PSI mean scores of the female students before and after the PICO game (Z: -2.541 p: 0.011) as well as their scores from the Approach-Avoidance subscale (Z: -2.090 p: 0.037). As for the male students, no significant difference was found (Table 3).

Discussion

Since the basic principles of the nursing process are based on the scientific process of problem solving, it is necessary to make evidence-based decisions while forming the steps of the NP. In this research, PICO, one of the game-based learning strategies, was used to evaluate the evidence-based nursing process. The aim of the game is to be the first player/group of players to complete the PICO question correctly (9,21). In our study, 10 different clinical case were created by the researchers. Student groups were asked to determine their nursing diagnoses specific to clinical case and turn them into clinical questions. As a result of the research, it was seen that the average satisfaction level of students regarding the PICO game was high (9.38±1.19). In studies conducted with nursing students, it has been reported that students want the lessons to be supported by games (11,22). In a systematic review, it was stated that nursing students reported the benefits of games as providing an active learning environment, quick feedback; facilitating the understanding of complex situations, increasing experience, empathic skills, communication, interaction and motivation (23). In the research, PICO method was developed based on the game. Milner and Cosme (2017) reported that most students considered PICO to be an exciting and entertaining method (8).

In order to facilitate the evidence-based nursing process, student nurses are expected to have sufficient knowledge and skills for creating clinical questions (7). In our study, with the PICO game, each group of students was asked to determine the existing nursing diagnoses specific to the case, and the interventions and patient outcomes specific to these diagnoses. In this way, it was also possible

for the instructor to evaluate whether the students understand these stages correctly. The first group that won the PICO game completed the game in an average of 20 minutes. Except for only one group, the participating groups saw all the case and completed the PICO tables specific to these cases. One group did not have enough time to see the last two cases. Most of the student groups did not have any difficulty in identifying nursing diagnoses and interventions specific to the cases. However, there were groups that experienced difficulty in determining patient outcomes.

In this study, it was determined that the students perceived themselves at an intermediate level regarding problem solving skills. In other studies conducted on nursing students, the problem solving levels of the students were found to be similar to our study (24–28). Although there is no significant difference between the problem-solving skills of the students before and after the PICO game, a quantitative difference was found. Furthermore, the fact that female students perceived their problem-solving skills better after the PICO game is a result that indicates the contribution of PICO game to problem solving skills. The female students perceived themselves as more adequate in reviewing their problem-solving efforts and doing research for alternative solutions to solve a new problem. In another study, it was determined that female students perceived their perception of problem solving skills better (29) It can be said that gender has an effect on perception of problem solving skills.

One of the educational objectives that games will provide students with is the problem-solving element. The findings of a study demonstrate that it is essential to design a game-based learning environment to increase the motivation and participation of students and that this motivation is effective on problem solving results (30). The nursing process is a systematic method used for finding solutions to the problems of the healthy/sick individuals. The steps of the nursing process are similar to those of scientific problem solving. The problem-solving process enables one to notice problems. The basis of the problem-solving process in nursing is the diagnostic phase where the problems are noticed. In the diagnostic process, the problem is completely and accurately revealed. In this process, nurses reconsider the causes of the problems they notice. Furthermore, they also plan the interventions specific to the problem. In the research, the PICO game helped students identify case-specific patient problems, diagnostic-specific interventions, and patient outcomes, contributing to their problem-solving skills.

The limitations of the research are that the PICO game was played only once, the course is given with case discussions, lecture, question and answer method. The evaluation of students' problem-solving skills one week after PICO game is another limitation.

Conclusion

It was determined that students correctly identified the clinical questions, nursing diagnoses specific to the PICO cases as well as the interventions and patient outcomes specific to these diagnoses. It was found that students perceived themselves to be moderately adequate in problem solving skills. It was also determined that female students perceived their problem-solving skills more adequate after the PICO game. This finding shows that the PICO game contributes to students' problem-solving skills. Due to the students' high level of satisfaction regarding the lesson, it is recommended that game-based educational tools such as PICO are also used in addition to different educational methods in enabling students to gain the nursing process, which is the most important competency of nursing undergraduate education. The PICO game will be used repeatedly in teaching and evaluating the nursing process; thus, enabling students to perform more qualified and evidence-based nursing care after graduation. It is recommended to carry out studies in which the PICO game is played repeatedly during NP and others course teaching with large groups in the future. In addition, a long-term evaluation of students' problem-solving skills is recommended.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval

Ethical approval was obtained from the Ege University Ethics Committee (ethical committee approval number: 13/01, date: 26.12.2019)

Consent to Participate and Publish

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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MICROBIOTA AWARENESS SCALE VALIDITY AND RELIABILITY STUDY

MİKROBİYOTA FARKINDALIK ÖLÇEĞİ GEÇERLİLİK VE GÜVENİLİRLİK ÇALIŞMASI

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Öz

Amaç

Bu çalışmada kişilerin mikrobiyota farkındalık düzeylerini belirlemeye yönelik geçerli ve güvenilir bir ölçme aracı geliştirmek amaçlanmıştır.

Gereç ve Yöntem

Metadolojik türde yürütülen bu araştırma Eylül 2019-Eylül 2020 tarihleri arasında Isparta ili Eğirdir ilçesi aile sağlığı merkezine başvuran kişilerde yapılmıştır. Çalışmaya 301 kişi katılmış olup çoğunluğu (%61,5) kadındır. Literatür taranarak oluşturulan taslak ölçek formu daha sonra kapsam geçerliliği amacıyla konuyla ilgili uzman görüşüne sunulmuştur. Kapsam geçerliliği sonucunda katılımcılara uygulanan ölçeğe ait verilere açıklayıcı ve doğrulayıcı faktör analizi uygulanmıştır.

Bulgular

Yapılan açıklayıcı faktör analizi sonucu 4 faktörlü 20 maddeli bir yapı elde edilmiştir. Ölçeğe daha sonra doğrulayıcı faktör analizi yapılmış ve ölçeğin iyi uyum değerleri gösterdiği belirlenmiştir. Ölçeğin güvenirlik için hesaplanan Cronbach Alpha katsayısı 0,852 saptanmış olup iyi düzeydedir.

Sonuç

Çalışma sonucunda mikrobiyota farkındalık ölçeği'nin kapsamı ölçmeyle ilgili geçerli ve uygulanma metadolojisi açısından güvenilir bir ölçme aracı olduğu saptanmıştır. Ölçeğin faktörlere ayrılmadan toplanarak kullanılması tavsiye edilmektedir.

Anahtar Kelimeler: Mikrobiyota farkındalığı, probiyotik, prebiyotik, faktör analizi

Abstract

Objective

This study aimed to develop a valid and reliable measurement tool to determine the microbiota awareness levels of individuals.

Materials and Methods

This methodological study was conducted on people who applied to the family health center of Egirdir District of Isparta Province between September 2019 and September 2020. Three hundred one people participated in the research, and the majority (61.5%) were women. The draft scale form, created by scanning the literature, was then presented to the expert opinion on the subject for content validity. As a result of the content validity, explanatory and confirmatory factor analysis was applied to the data of the scale applied to the participants.

Results

As a result of the explanatory factor analysis, a structure with 4 factors and 20 items was obtained. Afterward, confirmatory factor analysis was

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performed on the scale, and it was determined that the scale showed good fit values. The Cronbach Alpha coefficient calculated for the scale's reliability was found to be 0.852 and is at a reasonable level.

Conclusion
As a result of the study, it has been determined that the microbiota awareness scale is a valid measurement tool for measuring the scope and a reliable measurement tool in terms of application methodology. It is recommended to use the scale without separating it into factors.

Keywords: Microbiota awareness, probiotic, prebiotic, factor analysis

Introduction

The human body is an ecosystem that supports trillions of living microorganisms (1). All of the microorganisms that can be found in different regions of the human are called the microbiota, and the genome of these microorganisms is called the microbiome (2). The gastrointestinal tract (GIS) is very suitable for colonization because it has a large surface area and contains rich nutrients (3). This ecosystem, which consists of these microorganisms colonized in the GIS and functions like an organ, is called the intestinal microbiota (4). The composition of the microbiota is region dependent and also highly dynamic. Changes in this composition can affect host physiology and health. Evidence shows that the etiology and persistence of both metabolic and behavioral disorders are related to the microbiota (5). Studies have shown that the intestinal microbiota is as unique as a fingerprint and creates a different pattern in each person (6). The genetic richness of the intestinal microbiota enables the microbiota to be considered an organ on its own. It can affect the intestines, brain, liver and other organs at the molecular level (7, 8).

When the national and international literature on this subject is examined, it has been observed that there is a lack of an up-to-date scale that has a holistic perspective, which has completed validity and reliability studies, therefore within the scope of the current study, it is aimed to develop a valid and reliable scale that measures the microbiota awareness levels of individuals.

Materials and Methods

This study was conducted methodologically in order to develop a measurement tool for assessing individual microbiota awareness levels and to evaluate the assessment tool's reliability and validity. The research sample consists of patients and their relatives aged 18 and above who have no communication problems and who applied to the Family Health Center in the Egirdir district of Isparta province at the time of the research. No sample selection method was used in the study. The data collection tool consists of two parts. In the first part, some questions investigate the participants' sociodemographic characteristics (age, gender, educational status, occupation, etc.). The other part consists of the draft form of the Microbiota Awareness Scale, in which the researchers by review the literature prepared. The draft form of the scale was developed in a five-point Likert type (1=strongly disagree, 2=disagree, 3=undecided, 4=agree, 5=strongly agree) and includes 27 positive and 2 negative statements. Two of the questions in the scale are information questions with five options, and marking each correct one in these questions was evaluated as 1 point, and not marking any incorrect one was assessed as 1 point. The last two questions of the scale were designed as open-ended questions, and evaluations were made in such a way that those who wrote no answer received 1 point, one answer 2 points, two answers 3 points, three answers 4 points, and those who answered four and above received 5 points. In order to enable people to understand the questions more easily, definitions of scientific words in the scale are given at the beginning of the scale form. The research was carried out with the approval of the Ethics Committee of the Faculty of Health Sciences of Süleyman Demirel University, dated 29.11.2019, and numbered 326. The data used in the research were collected between January 28 and February 11, 2020. In scale development studies, it is necessary to reach a sample size of 10 times the number of scale items (9). For this reason, a total of 301 people, 185 females and 116 males, who met the criteria and agreed to participate in the research, were reached.

Frequency, percentile, and mean tests were used to define the participants' sociodemographic characteristics. To perform validity and reliability analyses, the content validity of the draft scale was first checked, and then factor analysis was performed to evaluate the construct validity. For the validity and reliability studies of the scale, Keiser-Meyer-Olkin

Sample Adequacy Scale was used, Bartlett's Test of Sphericity was used for the suitability of the sample for analysis, Cronbach Alpha (α) was used for item analysis and item-whole correlations, followed by the Split-Half Test method and explanatory factor analysis method. The floor-to-ceiling effect and item distinctiveness index of the scale were also evaluated. The T-Test in independent groups and oneway ANOVA tests examined the relationship between the independent variables and the average scores obtained from the sub-factors and the whole scale. IBM SPSS 25 package program was used for the explanatory factor analysis to analyze the research data, and the AMOS 23 package program was used for the confirmatory factor analysis.

Results

The study determined that 61.5% of the participants were female, and 38.5% were male. The mean age of the individuals participating in the survey is 38.50±14.88, 22% are primary school graduates, and below, 10.6% are secondary school graduates, 38.5% are high school graduates, 10.3% are associate degree students, and 18.6% of them have undergraduate and postgraduate education. When we look at the distribution by occupational groups, it was determined that 36.9% of the participants do not work in any paid job, 14.6% are students, 3.3% are farmers, 4.3% are tradesmen, 20.3% are white-collar workers, 13% are blue-collar workers, 4.3% are health workers, and 3% were members of high-qualification occupational groups. In the study, 23.9% of the participants have at least one chronic disease, 62.1% have never smoked before, 13% have quit smoking, and 24.9% are still smoking. Looking at the family type, 87% of the participants had a nuclear family, 9.6% had an extended family, and 3.3% lived alone.

Content Validity

An expert primarily evaluated the Microbiota Awareness Scale consisting of 29 items in terms of grammar, and necessary revisions were made. Then, the Lawshe technique was used for content validity. Since the opinion of at least 5 and maximum 40 experts should be sought in this technique, the views of 11 experts were obtained (10).

Experts evaluated items in three categories as "Appropriate/ items can be used as such; partially appropriate/Item can be used with suggested corrections; "Not at all suitable/ Item should be removed." In addition, experts were asked to suggest additional item suggestions and indicate corrections for items that were thought to be changed. The qualitative data obtained from the expert opinion were converted into quantitative data by calculating the content validity ratio (CVR) and content validity index (CVI) (11). As a result of the evaluations, no item with a negative or zero content validity ratio (CVR) was found on our scale. Eleven experts evaluated the scale, and the equivalent of CVRs in the minimum value table was specified as 0.59 at the α=0.05 significance level (12). It was decided to exclude items with a CVR value less than 0.59 from the scale. As a result of the calculations, no item with CVR<0.59 was found. An item similar to the other questions in the scale was removed from the scale upon suggestions. In the calculation made with the remaining items, the content validity index (CGI) was 0.81. After the necessary arrangements were made, the draft version of the scale consisting of 26 positive and 2 negative propositions was determined.

Construct Validity and Reliability

For construct validity and reliability, item-whole correlations of the items, the change in the Cronbach's alpha coefficient when the item was removed, the common variance values in the items, and the item distinctiveness power indices were examined. If the item-whole correlation coefficient of an item is low, the contribution of that item to the scale is also low. The item-total correlation coefficient should be positive and greater than 0.25 (13). Five items with an item-whole correlation coefficient below +0.25 (m7, m11, m12, m22, m24) were identified in the scale.

These items were not included in the scale and were removed from the scale.

In determining the distinctiveness (item validity) of the items, the method of comparing the item averages of the lower and upper 27% groups was used, and the item distinctiveness power index was calculated. As a result of the analysis, it was determined that the t value for each item was positive and significant at the p<0.001 level (13).

In order to test the structural validity of the scale, the principal components method from explanatory factor analysis methods and direct oblimin method from oblique rotation methods were used. The load distributions formed according to the analysis were examined, and three items (6, 10, 15) with a load value difference of less than 0.1 in at least two factors were removed from the scale (14). Kaiser-Meyer Olkin (KMO), Bartlett Sphericity tests were performed, and anti-image correlation values were examined to examine the data's suitability for the

principal component analysis of the sample. The KMO coefficient of the Microbiota Awareness Scale was 0.834, and the chi-square value of the Bartlett test was found to be 1923.84 and was found to be significant ($p<0.001$). The anti-image correlation values of the questions in the scale were found above 0.50. Accordingly, due to the factor analysis with the remaining items, 20 items were grouped under four factors with an eigenvalue greater than 1.0 (Kaiser's Criterion). It is considered significant if the eigenvalue of the factors is greater than 1 (15). The resulting scree plot also supports the four-factor structure (Fig 1).

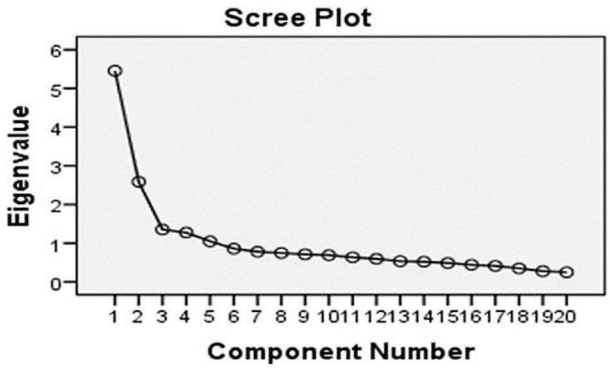

Figure 1
Factor number eigenvalue slope graph

According to the analysis results, the rate of total variance explained by the four-factor structure was 53,331%, and the eigenvalue was 1,273. The mean, standard deviation, item-total correlation, item distinctiveness index, factor analysis, and rotated factor analysis results of the items in each factor are shown in Table 1.

As a result of the factor analysis, it was seen that the Microbiota Awareness Scale, consisting of 20 positive statements, was distributed over four factors. Factors to reflect the content;

Factor 1: General Information (m1, m2, m4, m5, m6, m13),

Factor 2: Product Information (m17, m18, m19, m20),

Factor 3: Chronic Disease (m8, m10, m12, m14, m16),
Factor 4: It was named as Probiotic and Prebiotic (m3, m7, m9, m11, m15).

Reliability analysis of the scale consists of 20 items and 4 factors. According to the factors and as a whole, Cronbach's alpha reliability coefficient was calculated using the Spearman-Brown inter-half reliability formula and the Guttman inter-half reliability formula. The results regarding the reliability of the scale are shown in Table 2. The Spearman Brown reliability coefficient for the entire Microbiota Awareness Scale was 0.789; Guttman Split Half reliability value was found to be 0.782. The Cronbach Alpha reliability coefficient was found to be 0.852. If the scale is deleted in its final form, no item increases the alpha coefficient. In the study, Spearman-Brown, Guttman Split Half, Cronbach Alpha coefficient were also used to measure the reliability of the subgroups of the scale (Table 2).

Confirmatory factor analysis was applied on the sample in which explanatory factor analysis was performed, and fit indices related to the model were examined. Covariance in modification indices M.I. Covariance was created between 4 values e9-e10 and e16-e17 with a value above 50, and the fit values were improved. Confirmatory factor analysis compatibility values of the scale are shown in Table 3, and the path diagram for confirmatory factor analysis is shown in Fig 2.

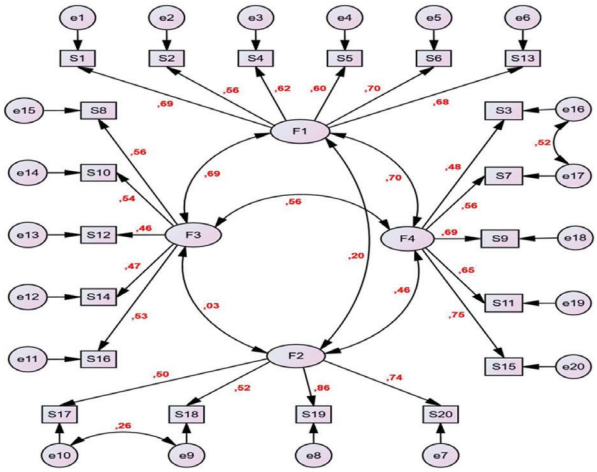

Figure 2
Confirmatory factor analysis diagram
of the Microbiota Awareness Scale.

Discussion

Since there are no physical tools for measuring individuals' attitudes, behaviors, and similar characteristics, different measurement tools (scales) are developed to obtain indirect measurements. There are two requirements for a newly developed scale to fulfill. These are validity and reliability (13). Validity means that a test can accurately measure the feature it wants to measure without confusing it with other features (16).

Table 1 Mean, Standard Deviation, Item Total Correlation, Factor Analysis, Rotated Factor Analysis, and Item Distinctiveness Index Results of Microbiota Awareness Scale Items

	Item Number	Average	Standard Deviation	Item Total Correlation	Factor Load	Rotated Factor Load	Item Distinctiveness Index
FACTOR 1	1	3,86	1,33	0,506	0,607	0,856	9101
	2	3,52	1,11	0,446	0,540	0,669	7526
	4	3,66	1,19	0,507	0,602	0,594	10331
	5	3,63	1,12	0,470	0,563	0,685	8334
	6	3,97	1,12	0,572	0,656	0,709	10454
	13	3,86	1,25	0,579	0,670	0,477	11348
FACTOR 2	17	3,03	1,21	0,295	0,566	0,629	8140
	18	1,98	1,27	0,345	0,517	0,770	7150
	19	1,67	0,96	0,376	0,679	0,764	7142
	20	1,48	0,96	0,295	0,596	0,849	5348
FACTOR 3	8	3,41	1,05	0,355	0,355	0,504	6246
	10	3,42	1,04	0,288	0,323	0,663	5337
	12	3,47	1,05	0,277	0,259	0,527	4727
	14	3,26	0,96	0,329	0,389	0,670	5864
	16	3,08	1,03	0,410	0,037	0,583	7514
FACTOR 4	3	3,06	1,29	0,454	0,186	0,717	9547
	7	3,05	1,29	0,467	0,234	0,821	10551
	9	3,58	1,12	0,594	0,192	0,473	11957
	11	3,40	1,04	0,522	0,225	0,543	9821
	15	3,47	1,05	0,603	0,145	0,556	12534

Table 2 Results Regarding the Reliability of the Scale

Factors	Item Number	Spearman Brown coefficient	Guttman Split Half	Cronbach Alfa
Factor 1	6	0.804	0.803	0.806
Factor 2	4	0.692	0.684	0.758
Factor 3	5	0.641	0.606	0.639
Factor 4	5	0.723	0.665	0.786
Microbiota Awareness Scale	20	0.789	0.782	0.852

Table 3 Confirmatory factor analysis compatibility values of the scale.

Model fit indices	Good Fit	Acceptable fit	Scale Values
NPAR			**48**
Chi-square(χ2)			**326,797**
p value	0,05<p£1	0,001<p£0,05	**0,000**
Degrees of Freedom(df)			**162**
Chi-square / Degrees of Freedom (χ2/df)	0£ χ2/sd £2	2< χ2/sd £3	**2,017**
The Root Mean Square Error of Approximation (RMESA)	0£ RMSEA£0,05	0,05< RMSEA£1	**0,058**
Standardized Root Mean Squared Residual (SRMR)	0£ SRMR£0,05	0,05< SRMR£1	**0,061**
Comparative Fit Index (CFI)	0,95£ CFI £1	0,90£ CFI <0,95	**0,908**
The Goodness of Fit Index (GFI)	0,95£ GFI £1	0,90£ GFI <0,95	**0,904**
Adjusted Goodness of Fit Index (AGFI)	0,90£ AGFI £1	0,80£ AGFI<0,90	**0,876**
Incremental Fit Index (IFI)	0,95£ IFI £1	0,90£ IFI <0,95	**0,909**
Tucker-Lewis Index (TLI)	0,95£ TLI £1	0,90£ TLI <0,95 (veya TLI>0,80)	**0,892**

Reliability, on the other hand, means that the expected results from the test are similar when a test is applied to the same individual more than once (13).

If the developed scale includes all the essential sub-headings of the subject to be examined, it is concluded that the scale has content/content validity (13). In this study, the opinions of eleven experts were consulted for content validity, and the CVR and CGI values of the scale were calculated accordingly. Questions with negative or zero CVR values are removed from the scale with priority. At α=0.05 significance level, the smallest CVR value required for eleven experts is 0.59. CGI is the average of the CVR values of the items. The CGI value found is required to be greater than 0.67 (13). There was no question for the microbiota awareness scale with a negative CVR value, zero or less than 0.59, and the total CGI value of the scale was found to be 0.81. Since this value is greater than 0.67, the scale was evaluated as statistically significant.

The structure can be defined as the whole or the pattern formed by the items related to each other. Factor analysis is often used to determine to construct validity. Factor analysis is basically of two types as explanatory factor analysis and confirmatory factor analysis (13). While the factor structure in the data is tried to be determined in explanatory factor analysis, confirmatory factor analysis aims to test the statistical significance of the structure with a certain number of items. In other words, we can check with confirmatory factor analysis that the sample data confirms the proposed structure (13, 17). KMO, Bartlett Sphericity test, and anti-image correlation values were calculated to evaluate the scale's suitability for factor analysis. It is used to determine the adequacy of the sample size for KMO factor analysis and the Bartlett sphericity test to assess the adequacy of the correlation ratio between the variables (18). The suitability of each question for factor analysis is determined by the anti-image correlation (19). KMO takes a value between 0-1, and it is required to be more than 0.80 for good factor analysis. A Bartlett Test p value less than 0.05 indicates a sufficient level of correlation for factor analysis (18). If the anti-image correlation value is less than 0.50, exclude the relevant item from the analysis (20). The KMO coefficient of the Microbiota Awareness Scale was 0.834, and the chi-square value of the Bartlett test was found to be 1923.84 and was found to be significant (p<0.001). The anti-image correlation values of the questions in the scale were found above 0.50. The results obtained showed that factor analysis could be performed on the scale.

After these stages, the confirmatory factor analysis stage is started to test the predetermined structure's accuracy. Accordingly, how well the model created explains the obtained data is determined through fit indices (22). The fit values of the scale were found as x^2/sd=2.017, RMSEA=0.058, SRMR=0.061, CFI=0.908, GFI=0.904, AGFI=0.876, IFI=0.909, and TLI=0.892. In line with the found fit indices, it was seen that the Microbiota Awareness Scale had good fit values, and the study was at an acceptable level.

The reliability of the scale includes internal consistency and stability. The Cronbach Alpha coefficient is frequently used to calculate the internal consistency of the Likert-type scale. The Cronbach Alpha coefficient for the whole scale was found to be 0.852. According to the literature, if the alpha coefficient is between 0.60-0.79, the scale is highly reliable, and if it is between 0.80-1, the scale is highly reliable (13). In this case, it can be said that the Microbiota Awareness Scale is highly reliable. Considering the sub-dimensions of the scale, it was found that general information sub-dimension (Cronbach Alpha value 0.806) was highly reliable, product knowledge (Cronbach Alpha value 0.758), chronic disease (Cronbach Alpha value 0.639), probiotic and prebiotic (Cronbach Alpha value 0.786) sub-dimensions were quite reliable. The scale's stability

Appendix Microbiota Awareness Scale TR-Form- Mikrobiyota Farkındalık Ölçeği

	Mikroorganizma: Gözle görülemeyen küçük canlı. **Mikrobiyota:** İnsanda farklı bölgelerde bulunabilen mikroorganizmaların tamamı. **Probiyotik:** Probiyotikler insanlarda çeşitli organların mikrobiyotasında yer alabilen mikroorganizmalardır. **Prebiyotik:** İnsan vücudunda bulunan probiyotiklerin gelişmesini teşvik eden bileşenlerdir.	**Kesinlikle katılmıyorum**	**Katılmıyorum**	**Kararsızım**	**Katılıyorum**	**Kesinlikle katılıyorum**
1.	İnsan vücudu çok sayıda mikroorganizma içermektedir.					
2.	Bağırsak mikrobiyotası bebek anne karnındayken oluşmaya başlamaktadır.					
3.	Prebiyotik ürünlerin neler olduğu hakkında bilgim var.					
4.	Antibiyotik kullanımı bağırsak mikrobiyotasını olumsuz yönde etkiler.					
5.	Bağırsak mikrobiyotasında meydana gelen bozulmalar obeziteye neden olur.					
6.	Beslenme şekli bağırsak mikrobiyotasını etkileyen önemli faktörlerden biridir.					
7.	Probiyotik ürünlerin neler olduğu hakkında bilgim var.					
8.	Mikrobiyotada meydana gelen değişiklikler bağırsak kanseri ile ilişkilidir.					
9.	Probiyotikler düzenli olarak tüketilmelidir.					
10.	Bağırsak mikrobiyotasında meydana gelen bozulmalar diyabete (şeker hastalığı) neden olur.					
11.	Probiyotik kullanımının ishal sorununu çözebileceğini düşünüyorum.					
12.	Bağırsaklarda zararlı bakteri sayısında meydana gelen artış alkole bağlı olmayan karaciğer yağlanmasına neden olabilir.					
13.	Anne sütü ile beslenme bebeğin bağırsak mikrobiyotasını olumlu yönde etkiler.					
14.	Bağırsak mikrobiyotasında meydana gelen değişiklikler çölyak hastalığıyla ilişkilidir.					
15.	Probiyotik kullanımının kabızlık sorununu çözebileceğini düşünüyorum.					
16.	Bağırsak mikrobiyotası ile depresyon ve alzheimer hastalıkları arasında ilişki vardır.					
17.	Aşağıdaki besinlerden probiyotik olanları kutucuk içine alınız. Kefir Çay Sirke Boza Yumurta	**				
18.	Aşağıdaki besinlerden prebiyotik olanları kutucuk içine alınız. Badem Muz Yulaf Soğan Kırmızı et	**				
19.	Probiyotik özelliğinden dolayı özellikle tükettiğiniz ürünleri yazınız.	***				
20.	Prebiyotik özelliğinden dolayı özellikle tükettiğiniz ürünleri yazınız.	***				

*1-16 arasındaki sorular kesinlikle katılmıyorum:1……kesinlikle katılıyorum: 5 olacak şekilde 1-5 arası puanlanmalıdır.

**17 ve 18 sorular:

$$\left(\frac{\text{İşaretlenen doğru sayısı}}{\text{Gerçek doğru sayısı}} - \frac{\text{İşaretlenen yanlış sayısı}}{\text{Gerçek yanlış sayısı}}\right) * 5$$ olarak hesaplanacak ve en yakın olduğu 1,2,3,4,5 rakamlarına yuvarlanacaktır.

(Doğru yanıt; 17: Kefir, sirke, boza- 18: Badem, muz, yulaf, soğan)

***19 ve 20 sorular: Her 1 doğru yanıta 1 eklenecektir, 4 ve üzeri doğru yapan 5 puan, hiç doğru yanıtı olmayan da 1 puan alacaktır.

was calculated by dividing the test into two halves. In this method, the test is divided into two halves. Spearman-Brown or Guttman approaches calculating the reliability coefficient between the two variables obtained from the sum of the items in each half. The Spearman-Brown coefficient of the scale was 0.789, and the Guttman coefficient was 0.782. According to the literature, if these coefficients are between 0.70-0.89, the scale is highly reliable, and if it is between 0.90-1, the scale is highly reliable (13). Accordingly, the scale is highly reliable in terms of stability.

Conclusion

As a result, the scale was constructed within the scope of this research to measure individual microbiota awareness. The Microbiota Awareness Scale was created due to the research and included 20 items and 4 sub. The scale's lowest score is 18, and highest score is 100. The high score obtained from the scale was evaluated as a high level of microbiota awareness. Explanatory and confirmatory factor analyzes obtained provided reliability and validity. Accordingly, it was determined that the Microbiota Awareness Scale could be used as a reliable and valid scale. It is thought that the developed scale will contribute to the literature within the scope of determining the microbiota awareness levels of individuals and taking the necessary precautions with the results obtained. The Microbiota Awareness Scale and TR-form are shown in Appendix.

Acknowledgment
This study, carried out within the framework of the Suleyman Demirel University Health Sciences Institute Public Health Department Master's Program, was approved by the Council of Higher Education as the thesis study numbered 641344.

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

Ethical Approval
Ethical approval was obtained from Suleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (Number: 326, Date: 29.11.2019).

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ANALYSIS OF FINE NEEDLE ASPIRATIONS OF THE THYROID: CYTOLOGICAL-HISTOPATHOLOGICAL CORRELATION AND OUTCOMES OF THE BETHESDA SYSTEM

TİROİD İNCE İĞNE ASPİRASYONLARININ ANALİZİ: SİTOLOJİK-HİSTOPATOLOJİK KORELASYON VE BETHESDA SİSTEMİNİN SONUÇLARI

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Öz

Amaç
Bethesda sistemi, tiroid nodüllerinin aspirasyonunu değerlendirmek için yaygın olarak kullanılmaktadır. Çalışmanın amacı sitoloji ve histopatoloji sonuçları arasındaki korelasyonun ışığında sistemin kullanılabilirliğini değerlendirmek ve literatür eşliğinde gözden geçirmektir.

Gereç ve Yöntem
Bethesda sistemi kullanılarak raporlanan tiroid nodüllerinin ince iğne aspirasyon sonuçları analiz edildi. Tiroidektomi sonuçlarına göre malignite oranları hesaplandı. Bethesda sisteminin gücünü analiz etmek için altı farklı alt grup tasarlandı. Duyarlılık, özgüllük, pozitif prediktif değer, negatif prediktif değer ve tanısal doğruluk bu alt gruplarda ayrı ayrı hesaplandı. Veriler, Windows için SPSS 20 kullanılarak analiz edildi.

Bulgular
Tiroid nodüllerin Bethesda'ya göre dağılımı sırasıyla 2212 (%33,5), 3163 (%47,9), 720 (%10,9), 67 (%1), 361 (%5,5) ve 75 (%1,1) idi. Tiroidektomi yapılan 873 nodülün 254'ü (%29.9) malignite tanısı aldı. Tiroidektomilere göre tanı kategorileri sırasıyla 233 (%26,7), 277 (%31,7) 137 (%15,7), 23 (%2,6), 163 (%18,7) ve 40 (%4,6) idi. Her Bethesda kategorisinin malignite oranları %14,5, %6,8, %32,8, %52,1, %66,8 ve %97,5 idi. İnce iğne aspirasyonunun sensitivitesi, spesifisitesi, pozitif prediktif değeri (PPV), negatif prediktif değeri (NPV), doğruluğu hesaplandı ve sırasıyla %61,8 ile %89,3, %79,6 ile %99,6, %70,4 ile %97,5, %84,5 ile %93,1 ve %79,5 ila %93,6 arasında değişmekteydi.

Sonuç
Bu çalışmanın sınırlılığı B1 kategorisinin çok yüksek olmasıdır. Ancak verilerin sadece bir patolog tarafından değerlendirilmesi ve en fazla vaka sayısına sahip ilk üç çalışmadan biri olması nedeniyle B1 dışındaki diğer kategoriler açısından literatüre önemli bir katkı sağlamaktadır. Bethesda sistemi, klinisyene uygun klinik takip ve doğru tedavi yaklaşımı sağlayan ve patologlar için gözlemciler arası uyumun yüksek olduğu bir sınıflandırmadır.

Anahtar Kelimeler: Tiroid, İnce iğne, Tiroidektomi, Bethesda

Abstract

Objective
The Bethesda system is widely used to evaluate aspiration of thyroid nodules. The aim of the study is to

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evaluate the usability of the system by the correlation between cytology and final histopathology results and to review the literature.

Materials and Methods
Fine needle aspiration of thyroid nodules reported using Bethesda system were analyzed. Malignancy rates were calculated by the results of thyroidectomies. To analyze the power of the Bethesda system six distinct subgroups were designed. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated separately in these subgroups. The data were analyzed using SPSS 20 for Windows.

Results
The distribution of thyroid nodules according to the Bethesda was 2212 (33.5%), 3163 (47.9%), 720 (10.9%), 67 (1%), 361 (5.5%) and 75 (1.1%), respectively. Of 873 nodules that underwent thyroidectomy, 254 (29.9%) were diagnosed as malignant. The diagnostic categories according to thyroidectomies were 233 (26.7 %), 277 (31.7%), 137 (15.7%), 23 (2.6%), 163 (18.7%) and 40 (4.6%), respectively. The malignancy rates of each Bethesda category were 14.5%, 6.8%, 32.8%, 52.1%, 66.8% and 97.5%. The sensitivity, spesifity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of fine needle aspiration was calculated and ranged from 61.8% to 89.3%, 79.6% to 99.6%, 70.4% to 97.5%, 84.5% to 93.1% and 79.5% to 93.6%, respectively.

Conclusion
The limitation of this study is that the B1 category is very high. However, since the data are evaluated by only one pathologist and it is one of the first three studies with the highest number of cases, it makes a significant contribution to the literature in terms of all categories except B1. The Bethesda system is a classification that provides the clinician with appropriate clinical follow-up and the accurate treatment approach, and a high interobserver agreement for pathologists.

Keywords: Thyroid, Fine-needle, Thyroidectomy, Bethesda

Introduction

Approximately 1 in 20 people have thyroid nodules and the risk of developing malignancy is 5% in these (1, 2). A reliable and feasible test is needed to identify this possibility (1). Fine needle aspiration of thyroid is primary choice and also most useful diagnostic tool. It has a critic role to distinguish benign and malignant nodules to avoid unnecessary surgery (3). The sensitivity and spesificity of the test are 57 to 99% and 45 to 99% in the literature, respectively (1).

The accepted classification for standardized diagnosis of thyroid nodules is The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) which was created in 2007, published in 2009 and revised in 2017. The system comprises six diagnostic categories which provide to predict the malignancy risk of each nodule and to make decision about clinical management (4, 5).

The aim of this study is to compare the results of the aspirations evaluated according to Bethesda system with the actual diagnoses after surgery and to determine the strength of the test. Also aimed to see the distribution of the data and compare the sensitivity, spesificity, positive predictive value, negative predictive value and accuracy of our data with the other publication's data in the literature.

Materials and Methods

This study was approved by the ethics committee of Manisa Celal Bayar University (18.9.2019, 20.478.486).

From January 2015 to June 2019 (54 months), the patients which have ultrasonography guided fine needle aspiration (FNA) cytology of thyroid were obtained. Conventional smears were prepared for all nodules. All of the slides were stained with May-Grunwald-Giemsa and evaluated by one expert pathologist using TBSRTC which included six diagnostic categories defined as Nondiagnostic (ND) or Unsatisfactory, Benign (BG), Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS), Follicular neoplasm (FN) or Suspicious for a Follicular neoplasm (SFN), Suspicious for Malignancy (SFM) and Malignant (MG), respectively. These categories were also abbreviated as B1, B2, B3, B4, B5 and B6, respectively. The patients who underwent thyroidectomy were also recorded and histopathologic diagnoses were noted. The cases diagnosed as FVPTC were reevaluated to determine whether they were noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) or not.

To analyze the power of the system six distinct subgroups were designed. The each subgroup was

categorized as negative and positive. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated according to each groups.

Results

A total of 6598 thyroid nodules in 4447 pathology reports from 3635 patients were included in this study. The mean age and standard deviation (SD) of aspirations was 52.19±13.44 with a range of 8-94 years. The mean of age was 51.58±13.67 for pathology reports (n=4447) and 51.31±13.88 for patients (n=3635). The female/male ratio was 3.44 (F/M=5114/1484) for all aspirations, 3.38 (F/M=3665/1082) for pathology reports and 3.53 (F/M=2834/801) for patients. 3240 (49.1%) of the nodules were located in the right lobe, 3050 (46.2%) of the nodules were located in the left lobe, 246 of (3.8%) nodules were in the isthmus and pyramidal lobe and 62 of them have unknown localization. The mean nodule size was 19.06 ± 10.86 mm and the range was 5-112 mm in 4972 nodules with known diameters.

The distribution of nodules according to the Bethesda category was 2212 (33.5%), 3163 (47.9%), 720 (10.9%), 67 (1%), 361 (5.5%) and 75 (1.1%), respectively. Overall, 594 (15.48%) patients underwent surgery for 873 (13.23%) nodules, and malignancies were identified in 254 nodules (29.09% of nodules

Table 1 The cytological diagnosis and cytological-histopathological correlation

CYTOLOGICAL DIAGNOSIS			BETHESDA CATEGORIES						
			ND	BG	AUS/FLUS	FN/SFN	SFM	MG	Total
			2212 (33.5%)	3163 (48%)	720 (10.9%)	67 (1%)	361 (5.5%)	75 (1.1%)	6598
HISTOPATHOLOGICAL DIAGNOSIS	BENIGN	FND/NG	182 (78.1%)	246 (88.8%)	69 (50.4%)	5 (21.7%)	28 (17.2%)	0	**530**
		HT	12 (5.2%)	10 (3.6%)	17 (12.4%)	0	13 (8%)	0	52
		FA/HCA	3 (1.3%)	1 (0.4%)	4 (2.9%)	6 (26.1%)	9 (5.6%)	0	23
		Others	2 (0.9%)	1 (0.4%)	2 (1.4%)	0	4 (2.4%)1	1 (2.5%)	10
	Total		**199 (85.5%)**	**258 (93.2%)**	**92 (67.2%)**	**11 (47.8%)**	**54 (33.2%)**	**1 (2.5%)**	**615**
	MALIGNANT	PTC	31 (13.3%)	17 (6.1%)	43 (31.4%)	10 (43.5%)	104 (63.8%)	38 (95%)	243
		FTC	1 (0.4%)	2 (0.7%)	1 (0.7%)	1 (4.3%)	1 (0.6%)	0	6
		MTC	1 (0.4%)	0	1 (0.7%)	0	2 (1.2%)	1 (2.5%)	5
	Total		**33 (14.1 %)**	**19 (6.9%)**	**45 (37.8%)**	**11 (%47.8)**	**107 (65.6%)**	**39 (97.5%)**	**254**
	NIFTP		1 (0.4%)	0	0	1 (4.4%)	2 (1.2%)	0	4
	Total		**233**	**277**	**137**	**23**	**163**	**40**	**873**

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, BG: benign, FA/HCA: follicular adenoma/hurthle cell adenoma, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm, FND/NG: follicular nodular disease/nodular guatr, FTC: follicular thyroid carcinoma, HT: hashimoto's thyroiditis, MG: malignant, MTC: medullary thyroid carcinoma, ND: nondiagnostic, NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, PTC: papillary thyroid carcinoma, SFM: suspicious for malignancy

with surgical resection). The diagnostic categories according to thyroidectomies were 233 (26.7 %), 277 (31.7%), 137 (15.7%), 23 (2.6%), 163 (18.7%) and 40 (4.6%), respectively.

The cytologic diagnosis of nodules which underwent thyroidectomy were described by individual categories and demonstrated in Table 1. The others category in Table 1 is included subacute thyroiditis and diffuse hyperplasia. Five cases which diagnosed as subacute thyroiditis in thyroidectomy were diagnosed as AUS (1 case), SFN (3 case) and MG (1 case). Five cases which diagnosed as diffuse hyperplasia in thyroidectomy were diagnosed as ND (2 case), BG (1 case), AUS/FLUS (1 case) and FN/SFN (1 case).

The malignancy rates of each Bethesda category were calculated. The rates were given in two different forms (without or with NIFTP) and were shown in Table 2.

Six subgroups were classified as FNA negative and FNA positive. In group I “BG (Bethesda 2)” was accepted as FNA-negative, and “MG (Bethesda 6)” was accepted as FNA-positive. The remaining four Bethesda categories (ND, AUS/FLUS, FN/SFN, SFM) were excluded from the evaluations of group I. The division of the other groups was shown in Table 3.

Table 2 The malignancy rates of each Bethesda category

Bethesda category	Prevalance	Tiroidectomies	Malignant diagnosis	NIFTP diagnosis	Malignancy rate without NIFTP	Malignancy rate with NIFTP
B1	2212	233	33	1	14.16%	14.59%
B2	3163	277	19	0	6.85%	
B3	720	137	45	0	32.84%	
B4	67	23	11	1	47.82%	52.17%
B5	361	163	107	2	65.64%	66.87%
B6	75	40	39	0	97.5%	
Total	**6598**	**873**	**254**	**4**		

NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features

Table 3 The created six new subgroups

	FNA positive	FNA negative
Group I	MG	BG
Group II	SFM + MG	BG
Group III	FN/SFN + SFM + MG	BG
Group IV	SFM + MG	BG + AUS/FLUS
Group V	FN/SFN + SFM + MG	BG + AUS/FLUS
Group VI	FN/SFN + SFM + MG	ND + BG + AUS/FLUS

AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance
BG: benign, FN/SFN: follicular neoplasm/suspicious for a follicular neoplasm,
MG: malignant, ND: nondiagnostic, SFM: suspicious for malignancy

According to the all prepared groups the diagnoses were noted as benign and malignant with or without NIFTP. The sensitivity, spesifity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of fine needle aspiration were calculated and showed in Table 4.

To detect the accuracy and availability of the test, we searched all publications including all metaanalyses. The number of aspirations of 27 publications with full text available was noted. [5-31] Monthly time of the study and number of aspirations per month were calculated for all studies. These data and the Bethesda

Table 4 The histopathological diagnosis, sensitivity, spesificity, PPV, NPV and accuracy of all subgroups

		Histopathologic diagnosis			Sensitivity		Specificity		PPV		NPV		Accuracy	
		Malignant If NIFTP ≠ CA	Malignant If NIFTP = CA	Benign	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA	NIFTP ≠ CA	NIFTP = CA
Group I	FNA positive	39	39	1	67.2	67.2	99.6		97.5	97.5	93.1	93.1	93.6	93.6
	FNA negative	19	19	258										
Group II	FNA positive	146	148	55	88.4	88.6	82.4		72.6	72.9	93.1	93.1	84.5	84.5
	FNA negative	19	19	258										
Group III	FNA positive	157	160	66	89.2	89.3	79.6		70.4	70.7	93.1	93.1	83.0	83.1
	FNA negative	19	19	258										
Group IV	FNA positive	146	148	55	69.5	69.8	86.4		72.6	72.9	84.5	84.5	80.6	80.7
	FNA negative	64	64	350										
Group V	FNA positive	157	160	66	71.0	71.4	84.1		70.4	70.7	84.5	84.5	79.5	79.6
	FNA negative	64	64	350										
Group VI	FNA positive	157	160	66	61.8	62.0	89.2		70.4	70.7	84.9	84.8	81.2	81.3
	FNA negative	97	98	549										

CA: carcinoma, NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, NPV: negative predictive value, PPV: positive predictive value

distribution for all series were shown in Table 5. The series with the highest and lowest percentage in the distribution of the series according to the Bethesda categories are marked in bold in Table 5. The numbers of the studies above the mean value in all categories were 10, 14, 12, 14, 10 and 7, respectively.

The malignancy rates of the 24 studies with both Bethesda (first and revised) were shown in Table 6 (1, 6-33). The malignancy rates of Bethesda was shown in the first two rows of Table 6 and the differences between the old and new Bethesda were showed as bold. Also the values above the Bethesda were marked in bold.

Table 5 The number of aspiration and the distribution of the Bethesda categories of each study

	Number of aspiration	Time period (month)	Aspiration per month	B1 %	B2 %	B3 %	B4 %	B5 %	B6 %
Yang et al 2007	4703	132	36	10.4	64.6	3.2	11.6	2.6	7.6
Yassa et al 2007	3589	120	30	7	66	4	9	9	5
Nayar et al 2009	5194	78	67	5	64	18	6	2	5
Theoharis et al 2009	3207	12	267	11.1	73.8	3	5.5	1.4	5.2
Jo et al 2010	3080	204	15	18.6	59	3.4	9.7	2.3	7
Renshaw 2010	7089	156	45	25	54	8	9	2	4
Kim et al 2011	865	36	24	1.8	58.5	16.3	1.2	6.2	16.2
Bohacek et al 2012	1000	130	8	5.6	67.1	0.8	17.2	2.4	6.9
Bongiovanni et al 2012	3724	36	103	3	55.4	6.7	**23.8**	6	5.1
Mufti et al 2012	250	72	3	11.6	77.6	**0.8**	4	2.4	3.6
Wu et al 2012	1382	36	38	20.1	39	**27.2**	8.4	2.6	2.7
Mondal et al 2013	1020	36	28	**1.2**	**87.5**	1	4.2	1.4	4.7
Williams et al 2013	1481	57	30	28.9	45.7	18.8	4.4	1.3	0.9
Naz et al 2014	528	unknown	unknown	4.7	76.3	12.7	2.1	3.4	**0.8**
Park et al 2014	1730	3	577	13.3	40.6	9.1	**0.4**	**19.3**	17.3
Arul et al 2015	603	30	20	2.7	65.2	10	10.6	5.3	6.3
Lee et al 2017	1925	6	321	9.4	57.1	10.7	1	3.5	18.3
Abdullah et al 2018	499	39	13	11.4	54.7	16.2	4	7.2	6.4
Nandedkar et al 2018	606	121	5	4.29	82.67	0.82	9.07	**1.15**	1.98
Paajenen et al 2018	363	12	30	26	49	9	9	5	2
Reuters et al 2018	980	24	41	11	59.8	7.1	8.5	5.1	8.2
Ke et al 2019	13351	68	196	13.5	**32.3**	13.2	2.8	9.5	**28.7**
Ronen et al 2019	287	49	6	21.6	55.1	13.2	4.2	3.8	2.1
Current study	6598	54	122	**33.5**	47.9	10.9	1	5.5	1.1
Total	64054		Mean value	12.52	59.70	9.33	6.94	4.59	6.96

Table 6 The malignancy rates of all the studies

	Number of resected nodules	Final diagnosis: malignant	MALIGNANCY RATES						
			B1 %	B2 %	B3 %	B4 %	B5 %	B6 %	Overall
Cibas 2009	-	-	**1-4**	0-3	**5-15**	**15-30**	**60-75**	97-99	-
Cibas 2017	-	-	**5-10**	0-3	**10-30**	**25-40**	**50-75**	97-99	-
Yang 2007	1052	478	11 (5/46)	1 (18/247)	19 (10/52)	32 (105/326)	65 (68/105)	98 (272/276)	46 (478/1052)
Yassa 2007	1242	433	10 (8/77)	0,3 (6/369)	24 (20/84)	28 (74/268)	60 (173/288)	97 (152/156)	35 (433/1242)
Nayar 2009	1413	334	9 (6/70)	2 (6/357)	6 (25/430)	14 (36/248)	53 (44/97)	97 (217/255)	24 (334/1413)
Theoharis 2009	378	202	32 (8/25)	**10** (8/82)	**48** (13/27)	34 (35/102)	**87** (26/30)	100 (112/112)	53 (202/378)
Jo 2010	892	276	9 (12/135)	3 (20/317)	17 (9/53)	25 (45/177)	70 (39/56)	98 (151/154)	31 (276/892)
Renshaw 2010	1331	425	2 (6/361)	**25** (50/204)	30 (53/179)	33 (27/108)	**99** (72/73)	50 (1/2)	32 (425/1331)
Kim 2011	204	182	NE	0 (0/8)	**76** (32/42)	**50** (4/8)	**100** (34/34)	100 (112/112)	89 (182/204)
Bohacek 2012	451	130	26 (5/19)	7 (12/173)	13 (1/8)	21 (33/160)	58 (14/24)	97 (65/67)	29 (130/451)
Bongiovanni 2012	1358	563	32 (8/25)	3 (4/158)	14 (19/132)	32 (224/698)	75 (137/183)	99 (161/162)	41 (563/1358)
Mufti 2012	84	20	20 (1/5)	**10** (6/60)	**50** (1/2)	20 (1/5)	**80** (4/5)	100 (7/7)	24 (20/84)
Wu 2012	221	64	14 (3/21)	**10** (6/63)	22 (11/51)	27 (13/49)	67 (12/18)	100 (19/19)	30 (64/221)
Mondal 2013	323	75	0 (0/3)	**5** (10/222)	20 (1/5)	31 (11/36)	75 (9/12)	98 (44/45)	23 (75/323)
Williams 2013	388	110	18 unknown	**16** unknown	25 unknown	32 unknown	**94** unknown	100 unknown	28 unknown
Naz 2014	61	16	0 (0/0)	**11** (5/45)	**33** (2/6)	25 (1/4)	**100** (4/4)	100 (2/2)	26 (16/61)
Park 2014	1547	761	35 (41/116)	**6** (39/702)	**69** (87/126)	**50** (2/4)	**99** (310/314)	99 (282/285)	49 (761/1547)
Arul 2015	392	59	0 (0/10)	1 (3/256)	24,4 (10/41)	28,9 (13/45)	70,8 (17/24)	100 (16/16)	15 (59/392)
Gunes 2015	1100	131	4 (4/103)	**5** (37/797)	21 (10/48)	16 (11/68)	68 (27/40)	95 (42/44)	12 (131/1100)
Lee 2017	381	307	27 (3/11)	**20** (9/46)	**56** (28/50)	33 (3/9)	**98** (42/43)	100 (222/222)	80 (307/381)
Abdullah 2018	101	52	100 (1/1)	11 (2/19)	25 (6/24)	27 (3/11)	**76** (16/21)	96 (24/25)	51 (52/101)
Nandedkar 2018	171	21	0 (0/0)	2 (3/142)	0 (0/2)	**50** (9/18)	**100** (3/3)	100 (6/6)	12 (21/171)
Pajanen 2018	78	27	33 (1/3)	0 (0/10)	8 (1/13)	13 (3/24)	71 (15/21)	100 (7/7)	35 (27/78)
Reuters 2018	418	140	26 (9/35)	**6** (10/166)	12 (3/25)	21 (16/77)	73 (29/40)	97 (73/75)	33 (140/418)
Ke 2019	3890	3396	67 (46/69)	**14** (33/233)	**54** (84/157)	30 (19/63)	**82** (586/715)	99 (2628/2653)	87 (3396/3890)
Ronen 2019	53	21	50 unknown	**25** unknown	27 unknown	**50** unknown	**83** unknown	100 unknown	40 (21/53)
Current study	873	258	14.5 (34/233)	**6.8** (19/277)	**32.8** (45/137)	**52.1** (12/23)	66.8 (109/163)	97.5 (39/40)	29 (258/873)
Total	18402	8481							

NE: not evaluated

Discussion

The classification systems provides to use the same terminology which predicts the correct malignancy rates. There were numerous study in the literature about the using TBSRTC (1, 3-14, 16-33).

According to this analyse, this study ranked third in the highest number of cases (Table 5). It was fifth in the number of aspirations evaluated monthly. The results of this series, which has a very high number of cases, will have a significant contribution to the literature.

For B1 category, the average of all series was 12.52%, and 3 of the 9 studies that were above this threshold were the highest series studies (Ke et al., Renshaw et al. and current study) (Table 5) (12, 24). Of the other six studies, only three had aspiration below 500 and B1 rates were 26%, 21.6% and 11.6% (18, 22, 26). The study with the lowest B1 rate belonged to Mondal et al with 1.2% and it's a great experience of aspiration (17). According to this analysis, this study, which is among the top three series with the highest case number, is the study with the highest ND rate. The reason for this is that the diagnostic criteria of Bethesda cannot be met and therefore the application of aspiration is insufficient. Our hospital does not have on-site and this rate can only decrease with routine on-site use.

Mondal et al was the first study in B2 category with 87.5%, B3 category was only 1% and B4 category was 4.2% (17). The B3 and B4 categories in this study were well below the average and the benign category was well above. In this study, when 323 (323/1020 = 31.6%) surgical follow-up was examined, the number of surgical cases in B2, B3 and B4 categories was 222, 5 and 36, respectively. The malignancy rates were 5, 20 and 31, respectively. Since the number of surgeries in the benign category is high, 87.5% was thought to reflect the actual rate. In this study, the B2 ratio is below the average of all studies, this may be because B1 category is well above average.

The average of all studies for the B3 category is 9.33%. In this study, our percentage of B3 is 10.9% and is close to the average. Wu et al. has the highest value with a rate of 27.9% and the benign category is quite low (29). When the number of cells in aspiration is low, the differential diagnosis between categories B2 and B3 can sometimes be difficult (4, 5). In this study, there may be a tendency to make B3 diagnosis in B2 cases. In the B4 category, the study of Bongiovanni et al., Yilmaz et al. and Bohacek et al. which had a significantly higher value than all other studies had a ratio of 23.8%, 17.5% and 17.2% respectively; where the mean was 7.7% (9, 10, 32). Among the other categories of these studies, B1 category was very low in all and B3 category was very low (0.8%) in one of them. Above the mean value there was ten studies in the B5 category but the first one (Yilmaz et al) was significantly higher than the others (21.3%) (32). In this study the authors studied only cases which have thyrodectomies. In the B6 category, Ke et al had a highest value with 28.7% where the B2 category was very low (12). This data shows that the nodules aspirated in these studies are made with more meaningful indications than other studies. In the current study the values of B4, B5 and B6 categories were 1%, 5.5% and 1.1 %, respectively. The B4 and B6 values of the study were below the mean but the malignancy rates were meaningful with 52.1%, 66.8% and 97.5%.

To review the B1 category is unnecessary for malignancy rates because usually its cause is insufficient aspiration not inadequate evaluation. The range of malignancy rates were 0-25% for B2, 0-76% for B3, 13-50% for B4, 45-100% for B5 and 50-100% for B6 in all studies. Today, the expected rates was 0-3% for B2 category and 15 (53.5%) of them above it. 35.7% of them had higher rates for B3, 21.4% of them for B4 and 50% of them for B5. Three of them had lower rates for B3 and seven of them for B4. The remaining of them were in normal rates (1, 4-14, 16-33). The current study's malignancy rates were 6.8% (high), 32.8% (high), 52.1% (high), 66.8% (normal) and 97.5% (normal). Most of the studies had higher rates for B2, this was because of the limited cellularity and difficulty in interpretation of the aspirations. The rate for B3 category is nearly high, it can be ignored. The rate of B4 category is high due to the low number of cases. When aspiration had adequate cellularity the correct diagnosis can be made.

According to the literature, the sensitivity and spesificity of the studies range from 50% to 96.5% and from 62.7% to 100%, respectively (12, 15). The B1 category should not be included for real evaluation. The sensitivity and spesificity of the current study is calculated for each created groups. The group IV is the ordinary evaluation and the results were 71% and 84% which were concordant with the literature. If B4 category was added the positive part, the ratios were changed minimally. If B3 category was extracted from the negative part the sensitivity was rising while the spesificity was falling. Because of the limited number of NIFTP cases in this study, the end results did not significantly different from each other. The PPV was 72% and NPV was 84% in the current study while the

accuracy was 80%. The accuracy ranged from 64.6% to 99% in the literature (12).

The limitation of this study is the high percentage of the B1 category. However, the data will make an important contribution to the literature as it is evaluated by only expert pathologist and is one of the first three studies with the largest number of cases.

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

Ethical Approval
Manisa Celal Bayar University Ethics Committee approval was obtained for the study (No: 20.478.486, Date: 18.9.2019). The study was conducted in line with the principles of the Helsinki Declaration.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
AT: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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KARACİĞER KİST HİDATİĞİNDE LAPAROSKOPİK PERİKİSTEKTOMİ DENEYİMİMİZ

OUR EXPERIENCE WITH LAPAROSCOPIC PERICYSTECTOMY IN LIVER HYDATID DISEASE

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Öz

Amaç
Çalışmanın amacı laparoskopik cerrahi tedavi uyguladığımız kist hidatik olgularını yaş, cinsiyet, kist yerleşimi, kist boyutu ve tipi, uygulanan tedavi, operasyon süresi, erken ve geç dönem komplikasyonları ve nüks açısından retrospektif olarak değerlendirmek ve bu bulguları literatürle karşılaştırmaktır.

Gereç ve Yöntem
Hastaların yaş, cinsiyet gibi demografik bilgileri, serolojik ve radyolojik tetkik sonuçları, kistlerin sayısı, Gharbi sınıflamasına göre tipi, boyutu, lokalizasyonu, operasyon şekli ve süresi, erken ve geç dönem komplikasyonları, hastanede kalış süreleri, mortalite ve morbidite verileri hastane kayıt sisteminden geriye dönük tarandı ve veri tabanı oluşturularak analiz edildi.

Bulgular
Hastaların yaş ortalaması 35.28 ±16.12 olup, %42.9'u kadın (6/14) ve %57.1'i erkek (8/14) hastalardan oluşmaktaydı. Hastaların en sık başvuru nedeni sırasıyla ağrı (%57.1) ve sarılık (%21.4) şikayetleriydi. Hastaların tamamına tanı aşamasında (Bilgisayarlı Tomografi) BT ve (Ultrasonografi) USG istendi. Medikal tedavi tüm hastalara uygulanmıştı. Tüm hastalara laparoskopik perikistektomi operasyonu yapıldı. Oral tedavi birinci gün başlandı. Hastaların üçünde (% 21.4) operasyon esnasında safra sızıntısı gelişti ve primer onarıldı. Postoperatif yedi hastada (%50.0, 7/14) safra sızıntısı gelişirken, bu hastalardan ikisinde (%14.3) ise Endoskopik Retrograd Kolanjiyo Pankreatografi (ERCP) gereksinimi oldu. Hastalar bir yıl süreyle takip edildi, bu sürede mortalite ve nüks gelişmedi.

Sonuç
Deneyimli merkezlerde ve tecrübeli cerrahlarca yapılan laparoskopik cerrahinin kist hidatik tedavisinde daha sık tercih edileceği düşünülmektedir.

Anahtar Kelimeler: Kist Hidatik, ERCP, Laparoskopi

Abstract

Objective
The aim of the study is to retrospectively evaluate hydatid cyst cases in which we underwent laparoscopic surgical treatment in terms of age, gender, cyst location, cyst size and type, treatment applied, duration of operation, early and late complications, and recurrence, and compare these findings with the literature.

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Materials and Methods
Demographic information of patients such as age, gender, serological and radiological examination results, number of cysts, type, size, localization, type and duration of operation, early and late complications, duration of hospital stay, mortality and morbidity data according to Gharbi classification. It was scanned retrospectively from the registry system and analyzed by creating a database.

Results
The mean age of the patients was 35.28 ±16.12 years, and 42.9% were female (6/14) and 57.1% were male (8/14).The most common complaints of patients were pain (57.1%) and jaundice (21.4%), respectively. CT (Computed Tomography) and USG (Ultrasound) were requested for all patients at the stage of diagnosis. Medical treatment was applied to all patients. All patients underwent laparoscopic pericystectomy operation. Oral treatment was started on the first day. Bile leakage developed during the operation in three (21.4%) patients and the primary was repaired. Bile leakage developed in seven patients (50.0%, 7/14) postoperatively, while two (14.3%) of these patients required Endoscopic Retrograde Cholangio-Pancreatography (ERCP). The patients were followed up for one year, during which time mortality and recurrence did not occur.

Conclusion
It is thought that laparoscopic surgery performed in experienced centers and by experienced surgeons will be preferred more frequently in the treatment of hydatid cyst.

Keywords: Hydatid Cyst, ERCP, Laparoscopy

Giriş

Kistik ekinokokkoz (KE) veya kist hidatik, Echinococcus granulosus'un neden olduğu, zoonotik enfeksiyon hastalığıdır (1). Hidatik kistler en sık karaciğerde (%70) görülmektedir. Ancak akciğer (%20), böbrek, dalak, pankreas, kalp, beyin, kemik gibi diğer birçok organ da (%10) rastlanabilmektedir (1-3). Vakaların çoğunun asemptomatik olmasına rağmen, tanı alan hastalarda baskın semptom karın ağrısıdır (4). Obstrüktif sarılık, iştahsızlık, kaşıntı, ve kitle basısına bağlı portal hipertansiyon diğer semptomlarıdır (5). Tanı indirekt hemaglütinasyon (İHAT), ultrasonografi (USG), bilgisayarlı tomografi (BT) ve manyetik rezonans (MR) görüntüleme yöntemleri ile konulmaktadır (6). Karaciğer kist hidatiğine yönelik yapılan USG'ye göre oluşturulan Gharbi sınıflaması ve DSÖ sınıflaması halen kullanılmaktadır (7).

Kist hidatik tedavisi medikal, cerrahi ve minimal invaziv yöntemlerle yapılmaktadır. Minimal invaziv teknikler girişimsel radyolojinin gelişmesiyle ön plana çıkmış yöntemlerdir. PAIR (ponksiyon, aspirasyon, injeksiyon ve reaspirasyon), PAIRD (ponksiyon, aspirasyon, injeksiyon, reaspirasyon ve drenaj), PEVAC (perkütan "evacuation"), MoCAT (modifiye kateterizasyon tekniği) yöntemleri kist hidatikte kullanılan minimal invaziv yötemlerdir. Kistektomi, parsiyel ya da total perikistektomi, hepatektomi, basit drenaj, pencere açma(unroofing) ve marsupializasyon ise cerrahi tekniklerdir. Cerrahi yöntemler açık ya da laparoskopik yöntemlerle yapılabilmektedir (8,9). Laparoskopik yöntemlerin genellikle komplike olmayan (Gharbi Tip 1-3), basit, anterior yerleşimli, beş cm'den küçük kistler için uygun olduğu düşünülmüştür. Segment I –VII –VIII' de yer alan ve derin yerleşimli kistler için uygun olmadığı söylenmesine rağmen endikasyonları halen net olarak ifade edilmemiştir (10). Laparoskopik olarak, basit drenajdan, seçilmiş vakalarda perikistektomi ve karaciğer segment rezeksiyonu gibi morbiditesi yüksek yöntemlere kadar birçok teknik uygulanabilmektedir (11).

Bu çalışmanın amacı laparoskopik cerrahi tedavi uyguladığımız kist hidatik olgularını yaş, cinsiyet, kist yerleşimi, kist boyutu ve tipi, uygulanan tedavi, operasyon süresi, erken ve geç dönem komplikasyonları ve nüks açısından retrospektif olarak değerlendirmek ve bu bulguları literatürle karşılaştırmaktır.

Gereç ve Yöntem

Çalışma için Balıkesir Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu onayı alındı (2021/274). Bu çalışmaya, 2018-2020 yılları arasında karaciğer kist hidatiği nedeniyle laparoskopik cerrahi uyguladığımız 14 hasta dahil edilmiştir.

Hastaların yaş, cinsiyet gibi demografik bilgileri, serolojik ve radyolojik tetkik sonuçları, kistlerin sayısı, Gharbi sınıflamasına göre tipi, boyutu, lokalizasyonu, operasyon şekli ve süresi, erken ve geç dönem komplikasyonları, hastanede kalış süreleri, mortalite ve morbidite verileri hastane kayıt sisteminden geriye dönük taranmış ve veri tabanı oluşturularak analiz edilmiştir.

Çalışmaya 18 yaş üstü Gharbi Tip1-3 hastalar dahil edilirken, 18 yaş altı hastalar ve Gharbi tip IV-V hastalar çalışma dışı bırakılmıştır.

Hastalara anestezi indüksiyonundan önce profilaktik antibiyotik (sefazolin 1 gr) verilmiştir. Ardından supraumbilikal bölgeye yapılan 1 cm'lik insizyondan katlar geçilerek fasyaya ulaşılmıştır. Weres iğnesi ile batına girilerek batın içi basıncı 12 mmHg olacak şekilde insüfle edilmiştir. Yeterli basınca ulaştıktan sonra bu bölgeye 10 mm trokar yerleştirildi ve 30° teleskop ile girilerek batın eksplore edilmiştir. Daha sonra kist yerleşimine göre 10 mm'lik bir trokar ve iki adet 5 mm'lik trokar epigastriuma yerleştirilmiştir. Rutin eksplorasyondan kist etrafına, morrison poşuna ve karaciğer etrafına hipertonik salin (%20 sodyum klorür) emdirilmiş gazlı bezler yerleştirilmiştir. Bu işlemin hastalarda konvülziyona neden olabilecek kadar ciddi hipernatremi oluşturabileceği bildirilmiştir (12). Bu nedenle operasyondan sonra serum sodyum düzeylerine bakılmıştır. Weress iğnesi kullanılarak kist içeriği boşaltıldı ve kist hipertonik salin ile yeniden doldurulmuştur. Hipertonik solüsyon 10 dakika kist içerisinde bırakılmış, ardından aspirasyon yapılmıştır. Kist duvarı perforatör öğütücü aspiratör ile delinmiş ve kistteki kız veziküller tamamen aspire edilmiştir. Perikist duvarı LigaSure™ (Valleylab, Boulder, CO, ABD) kullanılarak çıkarılmıştır. Eksize edilen perikist duvarı, germinal membran ve gazlar, bir endobag kullanılarak 10 mm'lik trokardan çıkarılmıştır. Daha sonra laparoskopi ile kist boşluğunda kist kalıntıları, kanama ve safra yolu rüptürü olup olmadığı incelenmiştir. Kist duvarı ile safra yolları arasında bir bağlantı gözlendiğinde, emilmeyen dikişlerle dikilmiş ve kistin konumuna göre dren yerleştirilmiştir. Omentum dolaşımı bozulmayacak şekilde hareket ettirilmiş ve kist boşluğuna yerleştirilmiştir. Rutin batın kapatma derlenme işleminden sonra hastalar servise alınmıştır. Tüm hastalara postoperatif birinci gün oral başlanmıştır. Günlük yara bakımları ve dren takipleri yapılmıştır. Spontan kapanmayan safra fistülleri için endoskopik retrograd pankreatikoduodenostomi (ERCP) ile müdahale edilmiştir. Takipleri tamamlanan hastalar kontrole çağırılmak üzere taburcu edilmiştir. Hastalar nüks, morbidite ve mortalite açısından ortalama bir yıl süre ile takip edilmiştir.

İstatistiksel Analiz

Çalışmada elde edilen veriler SPSS 22.0 (SPSS INC, Chicago, IL, USA) programına kaydedildi ve istatistiksel analizleri yapıldı. Kalitatif veriler yüzde olarak, kantitatif veriler ise yüzde ve ortalama±standart sapma olarak sunuldu.

Bulgular

Hastaların yaş ortalaması 35.28 ±16.12 olup, %42.9'u kadın (6/14) ve %57.1'i erkek (8/14) hastalardan oluşmaktaydı. Hastalardaki kistlerin özellikleri Tablo 1'de, preoperatif ve postoperatif dönem bulguları Tablo 2'de özetlenmiştir.

En sık tip-3 kist hidatik (%92.9) saptanmıştır. Hastaların %71.4'ünde tek kist (10/14) mevcuttu. Hastaların yarısında (7/14, %50.0) kistler sol lobda, %42.9'unda

Tablo 1 Kist Özellikleri

Kist Özellikleri		Sayı	%
Kist Tipi (Gharbi Sınıflaması)	Tip 2	1	7.1
	Tip 3	13	92.9
Kist Sayısı	Tek Kist	10	71.4
	İki Kist	3	21.4
	Üç Kist	1	7.1
Lokalizasyon	Sol Lob	7	50.0
	Sağ Lob	6	42.9
	Bilateral	1	7.1
Kist Çapı (Ortalama±SS)		66.70±34.20 (mm)	

SS: Standart sapma

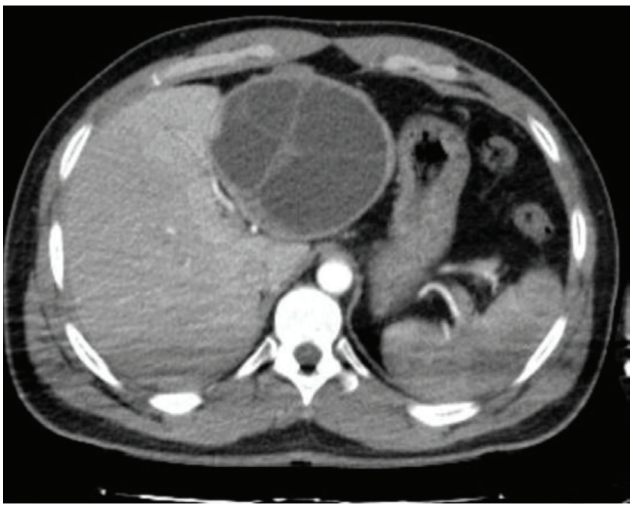
(6/14) ise sağ lobda yerleşikti. Yalnızca bir hastada (%7.1) bilateral tutulum vardı (Tablo-1).

Hastaların en sık başvuru nedeni sırasıyla ağrı (%57.1) ve sarılık (%21.4) şikayetlerinden oluşmaktaydı. Hastaların tamamına tanı aşamasında BT ve USG istenmiştir (Resim 1). Medikal tedavi tüm hastalara uygulanmıştır. Tüm hastalara laparoskopik perikistektomi operasyonu yapılmıştır. Oral tedavi birinci gün başlanmıştır. Hastaların üçünde (% 21.4) operasyon esnasında safra sızıntısı gelişmiş ve primer onarılmıştır. Postoperatif yedi hastada (%50.0, 7/14) safra sızıntısı gelişirken, bu hastalardan ikisinde (%14.3) ise ERCP gereksinimi olmuştur. Hastalarda laparoskopi sırasında iki hastada çok sınırlı miktarda kist içeriği batına dökülmüş olup kist etrafına yerleştirilmiş olan hipertonik salin emdirilmiş tamponlar sayesinde bulaşın önüne geçilmiştir. Hastalar bir yıl süreyle takip edilmiş, bu sürede mortalite ve nüks gelişmemiştir (Tablo-2).

Tablo 2 Preoperatif ve Postoperatif Dönem Özellikleri

Özellikler		**n(%), Ortalama±SS (min-max)**
Başvuru Semptomu	Ağrı	8 (57.1)
	Sarılık	3 (21.4)
	İnsidental	3 (21.4)
Radyoloji	BT	14 (100.0)
	USG	14 (100.0)
Medikal tedavi	Albendazol Tedavisi	14 (100.0)
Operasyon Şekli	Laparoskopik Perikistektomi	14 (100.0)
Operasyon Süresi	Ortalama±SS (min-max)	40.35±12.91 dakika (25-70)
Komplikasyonlar	Perioperatif komplikasyon Safra Sızıntısı (n:3)	3 (21.4) (Operasyon sırasında kapatıldı)
	Postoperatif komplikasyon Safra Sızıntısı (n:7)	3 (21.4) (3.gün spontan kapandı)
		2 (14.3) (7.gün spontan kapandı)
		1 (7.1) (15.gün ERCP sonrası kapandı)
		1(7.1) (20. gün ERCP sonrası kapandı)
Ortalama Yatış Süresi	Ortalama±SS (min-max)	6.64±4.34 gün (2-15)
Ortalama Dren Kalış Süresi	Ortalama±SS (min-max)	6.71±6.47 gün (1-20)
Mortalite	Yok	-
Nüks	Yok	-

BT: Bilgisayarlı Tomografi, USG: Ultrasonografi, ERCP: Endoskopik Retrograd Kolanjiyo Pankreatografi, SS: Standart sapma



Resim 1
Karaciğer Kist Hidatiği BT Görüntüsü

Tartışma

Kist hidatik hastalığının semptomları kistin tipine, boyutuna, lokalizasyonuna ve bulunduğu organa bağlı olarak değişmektedir. Karaciğer kist hidatiğinde en sık semptomun karın ağrısı olduğu bilinmektedir. Ahmed H.V ve ark. yaptıkları 37 vakalık seride karın ağrısı semptomu %51.5 oranıyla en sık görülen semptom olmuş ve bu da literatürle uyumlu bulunmuştur. Bizim çalışmamızda da %57.1 ile benzer sonuç saptanmıştır (4,13,14). Tanı aşamasında İHAT, USG ve BT yaygın olarak kullanılan tetkiklerdir. USG tanı aşamasında birincil görüntüleme yöntemi olmasına rağmen BT küçük kistleri tanımada ve anatomik ilişkileri ortaya koymada daha avantajlıdır. Bunların dışında karaciğer fonksiyon testleri de operasyonu planlama aşamasında gerekmektedir (15,16). Çalışmamızda tüm hastalara USG, BT, İHAT tetkikleri yapılmıştır.

Laparoskopik cerrahi yöntemlerin uygulanma oranları hem endemik hem de endemik olmayan bölgelerde hızla artmaktadır (11). Laparoskopinin kist içerisindeki safra kaçaklarını gösterme ve ulaşılması zor bölgelerde daha iyi görüntü sağlama konusunda avantajlı olduğu bilinmektedir. Bu sayede safra kaçaklarına operasyon sırasında müdahale etme olanağı sağlanmaktadır. Laparoskopik yöntemlerde kistektomi, parsiyel ya da total perikistektomi, hepatektomi, basit drenaj, pencere açma (unroofing) ve marsupializasyon gibi yöntemler yer almaktadır. Hastalarımıza total perikistektomi yöntemi uygulanmıştır (9,17). Laparoskopik cerrahi daha küçük bir insizyon, düşük morbidite, kısa hastanede kalış ve işe erken dönüş dahil olmak üzere birçok avantaj sunmaktadır. Bununla birlikte operasyon sırasında kist içeriğinin batına dökülmesi ve anaflaktik şok gibi korkulan komplikasyonların beklenenden az olduğu çalışmalarla gösterilmiştir (18-20). Shaikh ve ark.'larının (21) 35 vakayı içeren serilerinde üç (%8.5) hastada batına dökülme saptanmış ancak hiçbirisinde anaflaktik şok gibi korkulan komplikasyon olmamıştır. Bizim çalışmamızda da sadece iki (%14.28) hastada aspirasyon kanülünün kenarından minimal kist içeriği sızmış olup etrafa yerleştirilen hipertonik salin emdirilmiş tamponlar sayesinde bulaş engellenmiştir. Hastaların hiçbirinde anaflaktik şok meydana gelmemiştir. Safra sızıntısı açık kist hidatik operasyonlarında görülebildiği gibi laparoskopik yöntemlerde de görülebilir. Sıklıkla erişkinlerde kullanılan laparoskopik yöntemlerden, hepatik rezeksiyon ve total perikistektomide kanama ve safra kaçağının yüksek olduğu bilinmektedir. Al-Doghan ve ark.'larının (22) 54 hastayı içeren laparoskopik parsiyel kistektomi deneyiminde üç hastada (%5.6) safra kaçağı meydana gelmiş ve bir hastada ERCP gereksinimi olmuştur. Benzer şekilde, Kaya ve ark.'larının (23) laparoskopik serisinde iki hastada (11.11%100) safra kaçağı meydana gelmiştir. Çalışmamızda üç hastada (%21.4) operasyon sırasında safra kaçağı görülmüş ve onarılmıştır. Yedi hastada (%50.0) ise postoperatif dönemde drenden safra geldiği gözlenmiş olup, üç hastada (%21.4) postoperatif üçüncü günde, iki hastada (%14.3) postoperatif yedinci günde spontan kapanmıştır. İki hastada ERCP gereksinimi olmuş ve ERCP sonrasında bir hastada 15.günde diğer hastada ise 20.günde kaçak kapanmıştır. Safra kaçağı oranımızın literatüre göre yüksek olması cerrahi teknik olarak total perikistektomi kullanılmasından kaynaklı olduğu düşünülmektedir.

Laparoskopi cerrahiden sonra hastanede kalış süresinin daha kısa olduğu bilinmektedir. Çalışmamızda operasyon süresi 40.35±12.91 dakika (aralık 25-70 dakika), hastanede yatış süresi 6.64±4.34 gündür. Zaharie ve ark.'larının (10) açık ve laparoskopik tekniği karşılaştırdığı çalışmada ameliyat süreleri açık yapılan grupta 65 dakika (aralık 35-120 dakika) iken laparoskopik grupta 72 dakika (aralık 45-140 dakika) olarak bulunmuş ve istatistiksel olarak anlamlı olduğu bildirilmiştir. Hastanede kalış süreleri ise laparoskopik yöntem uygulanan grupta 6.42 gün (aralık 1-21 gün), açık cerrahi yapılan grupta ise 11.7 gün (aralık 4-80 gün) olarak bildirilmiştir. Kaya ve ark.'larının (23) çalışmasında ise laparoskopik yöntem uygulanmış olup operasyon süresi 75 dakika (aralık 50-135 dakika), hastanede kalış süresi 3.3 gün (aralık 2-7 gün) olarak sunulmuştur.

Dünya Sağlık Örgütü, opere edilen KE olgularının yaklaşık %6.5'inde nüks geliştiğini ve %2.2'sinin ölümle sonuçlandığını rapor etmektedir. Çalışmamızda bir yıllık takiplerde nüks ve mortalite saptanmamıştır.

Literatürde açık ve perkütan yöntemin laparoskopik cerrahi ile karşılaştırıldığı bir çalışmada nüksün daha az olduğu gösterilmiştir. Aynı çalışmada laparoskopik ve perkütan girişim sonrası mortalite saptanmazken, açık cerrahide %2.0 oranında mortalite saptanmıştır. Toplam 57 makale, 914 laparoskopik kist hidatik ameliyatının incelendiği derlemede iki hastanın (%0.22) öldüğü, 10 hastada da (%1.09) nüks geliştiği raporlanmıştır (11,24).

Sonuç

Çalışmamızdaki hasta sayısının az olması ve çalışmanın retrospektif olması kısıtlayıcı yanını oluşturmasına rağmen ülkemizde bu konuda yayınlanmış az sayıdaki çalışmalardan biridir. Laparoskopik kist hidatik cerrahisi uyguladığımız bu hasta grubunda operasyon süresi, hastanede kalış süresi, nüks ve mortalite oranları düşük olarak saptanmıştır. Deneyimli merkezlerde ve tecrübeli cerrahlarca yapılan laparoskopik cerrahinin kist hidatik tedavisinde daha sık tercih edileceği düşünülmektedir.

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The authors have no conflicts of interest to declare.

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Veriler, gizlilik veya diğer kısıtlamalar nedeniyle yalnızca yazarlardan talep edilebilir.

Yazar Katkıları
AFÇ: Çalışmanın planlanması; Verilerin İşlenmesi; Formal Analizler; Araştırma; Metodoloji; Validasyon; Görselleştirme; Makalenin Yazımı.
AD: Çalışmanın planlanması; Formal Analizler; Araştırma; Metodoloji; Makalenin Yazımı; Makalenin düzenlenmesi.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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BİR EĞİTİM VE ARAŞTIRMA HASTANESİNDE COVİD-19 ENFEKSİYONU NEDENİ İLE İMMÜN PLAZMA UYGULANAN HASTALARIN DEĞERLENDİRİLMESİ

EVALUATION OF PATIENTS WHO RECEIVED IMMUNE PLASMA DUE TO COVID-19 INFECTION IN AN EDUCATIONAL AND RESEARCH HOSPITAL

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Öz

Amaç
COVID-19 enfeksiyonu tedavisi için immün plazma uygulanan hastaların demografik ve klinik verilerinin ve immün plazma transfüzyonu ile ilişkili reaksiyonların değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem
Etik kurul onayı alınılan çalışma, retrospektif ve tanımlayıcı bir araştırmadır. 2020 yılında COVİD-19 enfeksiyonu nedeniyle immün plazma uygulanan 130 hasta çalışmaya dahil edildi. Hastaların dosyaları ve transfüzyon merkezi sisteminde kayıtlı olan bilgileri değerlendirilerek araştırmacılar tarafından SPSS paket programı kullanılarak analiz edildi.

Bulgular
İmmün plazma klinik uygulama kriterlerini sağlayan 130 hastaya 154 kez immün plazma transfüzyon uygulaması yapıldı. Hastaların bir ya da birden fazla kötü prognostik ölçüte sahip, orta ve ağır pnömoni hastaları olduğu, ortalama 17,9 gün hastanede yatarak tedavi gördüğü, %35,4'ünde sürecin ölümle sonuçlandığı belirlendi. İmmun plazma transfüzyon reaksiyonu sıklığı %1,95 olarak saptandı. Anti - A antikoruna sahip hastalarda %23,1'inde sürecin ölümle sonuçlandığı belirlendi.

Sonuç
İmmün plazma uygulanan bir veya daha fazla kötü prognostik kritere sahip orta ve şiddetli pnömonili hastalar hakkında veri sağlanmasının literatüre katkıda bulunabileceği düşünülmektedir.

Anahtar Kelimeler: İmmün plazma, Prognoz, Transfüzyon reaksiyonu, ABO grupları

Abstract

Objective
It is aimed to evaluate the demographic and clinical data of patients receiving immune plasma for the treatment of COVID-19 infection and reactions associated with

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immune plasma transfusion.

Materials and Methods
The study, which received the approval of the ethics committee, is a retrospective and descriptive study. In 2020, 130 patients who were administered immune plasma due to COVID-19 infection were included in the study. The patients' files and information stored in the transfusion center system were evaluated and analyzed by the researchers using the SPSS package program.

Results
Immune plasma transfusion was performed 154 times in 130 patients who met the criteria for clinical application of immune plasma. It was determined that the patients had moderate and severe pneumonia with one or more poor prognostic criteria, were hospitalized for an average of 17.9 days, and the process resulted in death in 35.4% of them. The frequency of immune plasma transfusion reaction was found to be 1.95%. It was determined that the process resulted in death in 23.1% of patients with anti - A antibody.

Conclusion
It is thought that the provision of data on patients with moderate and severe pneumonia with one or more poor prognostic criteria undergoing immune plasma may contribute to the literature.

Keywords: Immune plasma, Prognosis, Transfusion reaction, ABO groups

Giriş

Koronavirüs hastalığı 2019 (COVİD-19) pandemisine neden olan şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) virusu oldukça bulaşıcı ve patojenik bir koronavirüstür (1). İmmün plazma tedavisi, COVİD-19 için potansiyel yardımcı tedavilerden birisidir. Literatürde, immün plazma tedavisi sonrası klinik iyileşme olduğunu bildiren olgu serileri yer almaktadır (2, 3). Bunun yanısıra The United States Food and Drug Administration (FDA), COVİD-19 immün plazma kullanımının antikor aracılı enfeksiyon artışına, transfüzyonla ilişkili akut akciğer hasarına ve alerjik transfüzyon reaksiyonlarına neden olarak olumsuz etkilerinin de olabileceğini bildirmiştir (1). Pandemi döneminde Türkiye Cumhuriyeti Sağlık Bakanlığı (T.C. Sağlık Bakanlığı) immün plazma tedavisine yönelik hasta ve donör seçimine ait kriterlerlerin yer aldığı bir rehber yayımlamış ve süreç içinde güncellenmeler yapmıştır. Anti-SARS COV-2 antikoru içeren immün plazmanın hazırlanmasına ve klinik kullanımına ilişkin düzenleme ile belirlenen kurallara uygun olarak COVİD-19 enfeksiyonlu olgularda immün plazma tedavisi gerçekleştirilmiştir (4,5).

Çalışmamızda, immün plazma uygulanan hastaların demografik ve klinik verilerinin, laboratuvar sonuçlarının, immün plazma transfüzyonuna bağlı reaksiyonların ve hastaların klinik sonlanımlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem

Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulunun 12.06.2020 tarihli toplantısında 2395 karar numarası ile onaylanan çalışma retrospektif, tanımlayıcı bir araştırmadır. Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesine'ne COVİD-19 enfeksiyonu nedeni ile yatan hastaların tedavileri ulusal tedavi rehberleri doğrultusunda yürütülmekte olup 2020 yılında immün plazma uygulanan 130 hasta çalışmaya dahil edildi (4-6). COVİD-19 immün plazma ile hastanın ABO kan grubunun uyumlu olması, hastanın IgA eksikliği olmaması ve COVİD-19 İmmün Plazma Tedarik ve Klinik Kullanım Rehberinde yer alan klinik kullanım kriterlerinin sağlaması halinde hastalara COVİD-19 immün plazma, minimum doz 200 mililitre COVİD-19 immün plazma ünitesinden günde 1 adet, gerek görülürse 2 gün ara ile maksimum 3 doz (600 mililitre) şeklinde uygulandı.

Hemovijilans sorumlusu ve hemşiresi tarafınca, COVİD-19 immün plazma transfüzyonu ilişkili reaksiyonlar değerlendirilerek kayıt altına alındı.

COVİD-19 pandemisi sırasında immün plazma uygulanan hastaların dosyaları, transfüzyon merkezi sisteminde kayıtlı olan verileri değerlendirilerek araştırmacılar tarafından SPSS paket programıyla analiz edildi. Tanımlayıcı veriler olarak merkezi dağılım ve yayılım ölçütlerinin (sıklıklar, yüzdelikler, ortalama, ortanca, minumum-maksimum değerleri) tek değişkenli verilerin karşılaştırmasında sürekli değişkenlerde veri normal dağılıma uyuyorsa student-t testi, uymuyorsa Mann-Whitney U testi, kategorik değişkenler için ki-kare testi uygulandı.

Bulgular

Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesine'ne COVİD-19 enfeksiyonu nedeni ile yatan ve klinik kriterlere uyumlu olan 130 hastaya 154 kez immün plazma transfüzyon uygulama-

sı yapıldı. İmmün plazma hastaların %83,1'inde bir doz uygulanırken 22 hastaya birden daha fazla doz uygulandı. Hastaların tümü ulusal tedavi rehberlerine uygun olarak diğer standart tedavilerini aldı. İmmün plazma uygulanan hastaların özellikleri ve kötü prognostik göstergelerin dağılımı Tablo 1. ve Tablo 2.'de verilmiştir.

Transfüzyon öncesi yapılan kan grubu tetkikleri değerlendirildiğinde en sık saptanan kan grubu A Rh-pozitif oldu. ABO grubuna göre dağılımı; A grubu %50,8,

Tablo 1 İmmun plazma uygulanan hastaların demografik özellikleri ve kötü prognostik göstergelerin dağılımı

	Ortalama	Standart hata	Sayı	Yüzde
Yaş (yıl)	61,3	± 1,4 (min: 23 max:93)		
Cinsiyet Kadın Erkek			 40 90	 30,8 69,2
Kronik hastalık varlığı			91	70
Kan tetkiklerinde kötü prognostik ölçütler Lenfosit sayısı D-dimer Ferritin CRP	 932 3,02 692 82,7	 ± 587 (min:150 max:3400) ± 4,52 (min:0,04 max:27,3) ± 512 (min: 10,4 max:2000) ± 7,2 (min:0,09 max:315)		
IgA	2,7	± 1,2 (min:0,7 max:8,3)		
Almakta olduğu solunum destek tedavisi Maske veya nazal kanül ile O2 tedavisi Noninvaziv mekanik ventilasyon desteği İnvaziv mekanik ventilasyon desteği			 52 55 23	 40 42,3 17,7
SPO2	92,8	± 3,8 (min:80 max:99)		
Yoğun bakım yatışı olan hastalar (gün)	17,9	± 13,5 (min:0 max:65)	51	39,2
Hastanede yatış süresi (gün)	17,1	± 13,4 (min: 2 max:122)	130	100

Tablo 2 İmmun plazma uygulanan hastaların sonlanıma göre kötü prognostik faktörlerin dağılımı

	İmmun plazma uygulanan hastalarda		Ölen hastalarda		Sağ kalan hastalarda	
	Sayı	**Yüzde**	**Sayı**	**Yüzde**	**Sayı**	**Yüzde**
65 yaş üstü	60	46,2	20	43,5	40	47,6
Erkek	90	69,2	34	73,9	56	66,7
Diyabet Hipertansiyon Kronik akciğer hastalığı Kronik kalp hastalığı Malignite	39 56 26 30 14	30 43,1 20 23,1 10,8	18 25 13 16 7	39,1 54,3 28,3 34,8 15,2	21 31 13 14 7	25 36,9 15,5 16,7 8,3
Lenfosit sayısı <800/µl D-dimer > 1 mg/L Ferritin >500 ng/L CRP > NÜSX10	64 68 66 75	49,2 58,6 51,2 57,7	31 32 23 26	67,4 80 50 56,5	33 36 43 49	39,3 47,6 51,2 58,3
SPO2 < 93	59	45,4	27	58,7	32	38,1

O grubu %24,6, B grubu %15,4 ve AB grubu %9,2 olup, Rh'a göre dağılımın da ise %93,1'i Rh pozitif olarak saptandı. Hastaların %40'ı Anti-A antikoruna sahipti. İmmün plazma alan hastaların kan grubu dağılımı Tablo 3'te verilmiştir.

Uygulanan 154 İmmün plazma transfüzyonu sonucunda istenmeyen ciddi reaksiyonun doğrulandığı üç hasta (%1,95) oldu. Transfüzyon reaksiyonlarının dağılımı değerlendirildiğinde; %1,30'unda febril nonhemolitik, %0,65'inde hafif alerjik transfüzyon reaksiyonu saptandı.

Tablo 3 İmmun plazma uygulanan hastaların kan grubu dağılımı*

Hasta kan grubu	Hasta Sayısı	Hasta Yüzdesi
A Rh - pozitif	61	46,9
O Rh - pozitif	29	22,3
B Rh - pozitif	19	14,6
AB Rh - pozitif	12	9,2
A Rh - negatif	5	3,8
O Rh - negatif	3	2,3
B Rh - negatif	1	0,8
Toplam	130	100,0

*İstanbul ili 2012-2018 yılları arasında, 123,900 sağlıklı bireyin kan grupları analizinde; 47,496 (%38,3) kişi A Rh (+), 36,427 (%29,4) kişi O Rh (+), 16,294 (%13,2) kişi B Rh (+), 7,971 (%6,4) kişi AB Rh (+), 6,793 (%5,5) kişi A Rh (-), 5451 (%4,4) kişi O Rh (-), 2,560 (%2,1) kişi B Rh (-), 908 (%0,7) kişi AB Rh (-) olarak saptanmıştır (7).

Tablo 4 İmmun plazma uygulanan hastaların sonlanıma göre kötü prognostik faktörlerin dağılımı

Sonlanım	Ölü (Sayı:46 %35,4)				Sağ (Sayı:84 %64,6)			
	Ortalama	Standart hata	Sayı	Yüzde	Ortalama	Standart hata	Sayı	Yüzde
Yaş (yıl)	63,1	± 12,9			60,3	± 14,0		
Cinsiyet Kadın Erkek			 12 34	 26,1 73,9			 28 56	 33,3 66,7
Kronik hastalık varlığı			36	78,3			55	65,5
Kan tetkiklerinde kötü prognostik ölçütler Lenfosit sayısı D-dimer Ferritin CRP	 0,7 1,8 747,2 89	 ± 0,5 ± 0,4 ± 535,8 ± 82,6			 1,0 1,5 661,5 79,2	 ± 0,6 ± 0,5 ± 498,6 ± 66,4		
IgA	2,7	± 1,4			2,7	± 1,1		
Almakta olduğu solunum destek tedavisi Maske veya nazal kanül ile O_2 tedavisi Noninvaziv mekanik ventilasyon desteği İnvaziv mekanik ventilasyon desteği			 5 21 20	 10,9 45,7 43,5			 47 34 3	 56 40,5 3,6
Yoğun bakım yatışı olan hastalar (gün)	14,2	± 13,3			2,6	± 8,5		
Hastanede yatış süresi (gün)	19,2	± 13,2			17,3	± 13,8		

İmmün plazma uygulanan hastaların ortalama 17,9 gün hastanede yatarak tedavi gördüğü, %39,2'sinin ortalama 17,1 gün yoğun bakım yatışı olduğu belirlendi. Hastaların %35,4'ünde süreç ölümle sonuçlandı. Anti-A antikoruna sahip olan hastaların %23.1'i, Anti-A bulunmayan hastaların 43,6'sının ölümle sonuçlandığı belirlendi. İmmün plazma uygulanan hastaların sonlanıma göre kötü prognostik faktörlerin dağılımı Tablo 4'te yer almaktadır.

Tartışma

Pasif antikor tedavisi, belirli bir ajana karşı antikorların, o ajandan kaynaklanan bir bulaşıcı hastalığı önlemek veya tedavi etmek amacıyla duyarlı kişiye uygulanması şeklinde kullanılır (8). Pasif antikor tedavisi, solunum sistemini ilgilendiren bulaşıcı hastalıkların tedavisinde uzun süredir denenen bir tedavi stratejisidir. İmmün plazmanın, COVİD-19 enfeksiyonunun tedavisinde de kullanımı denenmiş ancak tedavideki etkinliği halen belirsizliğini korumaktadır (9,10). Solunum sistemini ilgilendiren bulaşıcı hastalıkların tedavisinde pasif antikor tedavisi deneyimleri; 2009 H1N1 influenza virüsü pandemisinde, yoğun bakım gerektiren şiddetli H1N1 2009 enfeksiyonunun immün plazma ile tedavisinin solunum yolu viral yükünü, serum sitokin yanıtlarını ve mortaliteyi azalttığını, Sierra Leone'de yapılan bir çalışmada, standart tedavi alanlara göre immün tam kanla tedavi edilenler için önemli ölçüde daha yüksek sağkalım olduğunu, H7N9 salgınında immün plazma kullanımının etkili olduğu hastaların hayatta kaldığını göstermişti (11-13). SARS - CoV - 1 gibi diğer koronavirüslerle gelişen önceki salgınlardan edinilen deneyimler ise bu tür immün serumların ilgili virüse karşı nötralize edici antikorlar içerdiğini göstermekteydi (14). Covid-19 pandemi sürecinde de immün plazma tedavisi sonrası klinik iyileşme olduğunu bildiren olgu serileri literatürde yer almış ve FDA COVİD-19 ile hastaneye yatırılan hastaların yönetimi için immün plazma kullanımına izin veren bir acil kullanım iznini yayınlayarak bilinen ve potansiyel faydalarının bilinen ve potansiyel risklerden daha ağır bastığını bildirmiştir (2,3,15). COVİD-19 hastalarında immün plazma tedavisinin etkinliğini değerlendiren 19 Nisan 2020 tarihine kadar yapılan çalışmaları kapsayan sistematik derlemede; COVİD-19 hastalarında immün plazma tedavisinin güvenli, klinik olarak etkili görünmesi yanında mortaliteyi azalttığı belirtilmiş ve Ye ve arkadaşlarının yaptığı çalışmada plazma tedavisi ümit verici olarak tanımlanmıştır (16, 17). İmmün plazma tedavisinin uygulama zamanlaması değerlendirildiğinde erken uygulama yapılan hastalarda daha iyi sonuçlar elde edildiği, tanıdan sonraki 3 gün içinde plazma transfüzyonu alan hastaların, tanıdan itibaren 3 günden uzun süre sonra transfüzyon alanlara kıyasla ya da daha yüksek antikor seviyelerine sahip plazma uygulamasıyla, hem 7 hem de 30 günde daha düşük ölüm oranlarına sahip oldukları bildirilmiştir (18, 19). Literatürde yer alan farklı çalışmalarda ise güçlü antiviral immün yanıtlar ve organ komplikasyonları geliştirmiş kritik hastalığı olan COVİD-19 hastalarının immün plazma tedavisinin etkinliğinin sınırlı olduğu belirtilmektedir (20, 21). İmmün plazmanın uygulanacağı hasta grubu net olarak tanımlayacak kontrollü bir çalışma mevcut olmadığı ancak pandemi sırasında medRxiv web portalında yayımlanan immün plazma tedavisinin iyi tolere edildiğini ve ciddi COVID-19 vakalarında viremiyi nötralize ederek klinik sonuçları potansiyel olarak iyileştirebileceğini gösteren çalışma ve FDA tarafından yayımlanan deklarasyonla, yaşamsal risk taşıyan hastalarda tercihen 7−14 gün aralığında ve sitokin fırtınası başlamadan önce kullanılması önerilmiştir (3,22). Literatürde yer bulan sürekli güncellenen bilimsel veriler doğrultusunda T.C. Sağlık Bakanlığı immün plazma tedavisine yönelik bir rehber yayınlanmış, klinik uygulamalarla ilişkili kriterler doğrultusunda COVİD-19 enfeksiyonunun tedavisinde immün plazma kullanılmıştır (4).

COVİD-19 pandemisinde hafif ve orta şiddette pnömoni varlığında, kötü prognostik faktör varlığı, ileri yaş ve komorbite hastalıkların bulunması halinde ve ağır pnömoni hastalarına hastane yatışı verilmesi, ek olarak immün plazmanın kesin (moleküler laboratuvar test sonucu pozitif) veya kuvvetle olası (klinik/radyolojik bulgular + PCR bekleniyor) COVID-19 tanısı olan, 18 yaşın üzerindeki hastalarda ve hastalığın ilk 14 gününde semptomların başlamasından 7-10 gün sonra kullanılması, Nisan-Ekim 2020 tarih aralığında yaşamsal risk taşıyan bu hastalardan belirli kriterleri sağlayanların tedaviyi alması, çalışmadaki hasta dağılımını etkilemiştir. Çalışmada, immun plazma uygulanan hastaların %69,2'si erkek cinsiyetteydi, %46,2'si 65 yaş üstündeydi ve %70'inin bir ve birden fazla kronik hastalığı vardı. Literatürde yer alan çalışmalarda erkek cinsiyet, ileri yaş ve komorbiditelerin, kötü prognoz ve ciddi hastalık ile ilişkilerine dair güçlü epidemiyolojik kanıtlara sahip olduğu vurgulanmaktadır (23, 24). COVİD-19'lu erkekler yaştan bağımsız olarak daha kötü sonuçlar ve ölüm için daha fazla risk altında olduğu bildirilmiştir (25). Şiddetli COVİD-19 hastalarının prognozunu SpO2, lenfosit, CRP, PCT ve LDH seviyelerinin öngörebileceği bildirilmektedir (6, 26). İmmün plazma uygulanan hastaların %2,3'ünün kan tetkiklerinde tanımlanan kötü prognostik ölçütlerden (SPO2, lenfosit sayısı, D dimer, ferritin, CRP) herhangi birine rastlanmadı.

İmmun plazma uygulamasında, hastaya verilecek olan COVID-19 immun plazma ile hastanın ABO kan

grubu uyumlu olmalıdır ancak Rh kan grubu göz ardı edilebilmektedir (4). İmmün plazma uygulaması öncesi yapılan ABO kan grubu değerlendirilmesinde en sık (%50,8) A kan grubuna rastlandı. Literatürde ABO grubu ile COVİD-19'un şiddeti veya mortalitesi arasında hiçbir korelasyon bulunmadığını, kan grubu A olan hastaların SARS - CoV - 2 enfeksiyonu için artmış risk taşıdığını, ABO kan gruplarının SARS - CoV - 2 duyarlılığı ile ilişkili olduğunu bildiren çalışmalar yer almaktadır. SARS - CoV - 2 enfeksiyonuna karşı değişken duyarlılığın, virüs-hücre yapışma sürecini etkileyebilecek ve hatta engelleyebilecek dolaşımdaki anti - A antikorlarına bağlanabileceği de farklı bir bakış açısı olarak literatürde yerini almıştır (27-30). Çalışmamızda immün plazma uygulanan hastaların %40'ı Anti - A antikoruna sahipti bunların %23,1'inde Covid-19 enfeksiyonu ölümle sonuçlandı.

Mekanik ventilasyon almayan COVİD-19 ile hastaneye yatırılan hastalar arasında, daha yüksek anti-SARS - CoV - 2 IgG antikor seviyelerine sahip plazma transfüzyonunun, daha düşük antikor seviyeli plazma transfüzyonuna göre daha düşük ölüm riski ile ilişkili olduğu bildirilmiştir (31). Anti-SARS COV-2 antikoru içeren immün plazmanın hazırlanması ile ilgili düzenlemede, plazmalardan anti-SARS - CoV - 2 titreleri nötralizan antikor değeri 1:80 ve üzerinde olanların seçilmesi planlanmış olup tüm immün plazmalar Türk Kızılay'ı tarafınca sağlanmıştır. İmmün plazma dozu 200 mililitrelik COVİD-19 immün plazma ünitesinden günde 1 adet, gerek görülürse 48 saat ara ile maksimum 3 doz (600 mililitre) şeklindedir (4). Çalışmamızda 154 immün plazma transfüzyonu gerçekleştiği ve 22 hastaya birden fazla doz verildiği belirlendi.

İmmün plazma uygulanmasından kaynaklanan riskler; bilinen ve teorik olmak üzere iki kategoriye ayrılır. Bilinen riskler, başka bir bulaşıcı hastalık ajanı ile yanlışlıkla enfeksiyonu ve serum hastalığı gibi immünolojik reaksiyonlar dahil olmak üzere serum bileşenlerine reaksiyonları içeren kan maddelerinin transferiyle ilişkili risklerdir. Kan yoluyla bulaşan patojenleri tarayan ve donör ve alıcıların kan grubuyla eşleşen modern kan bankası teknikleriyle, bilinen bulaşıcı ajanların yanlışlıkla transfer edilmesi veya transfüzyon reaksiyonlarının tetiklenmesi riski düşüktür (8). Tedavi amacı ile kullanılan immün plazma, transfüzyonla ilişkili akut akciğer hasarı (TRALI) için risk taşımaktadır (32). Rizk ve arkadaşlarının yaptığı çalışmada, immün plazmanın transfüzyonundan sonraki ilk 4 saat içinde hastaların %1'inden daha azında transfüzyonla ilişkili dolaşım yükü, transfüzyonla ilişkili akut akciğer hasarı, şiddetli alerjik transfüzyon reaksiyonu bildirilmiş bu olayların 146'sından sadece 13'ünün klinik olarak kesinlikle transfüzyonla ilişkili olarak değerlendirildiği bildirilmiştir (19). Çalışmamızda ise immün plazma transfüzyon uygulamalarının %1,30'unda febril nonhemolitik, %0,65'inde hafif alerjik transfüzyon reaksiyonu geliştiği saptandı.

Ağır COVİD-19 pnömonisi olan yetişkin hastaları kapsayan randomize kontrollü çalışmada toplam SARS - CoV - 2 antikor titrelerinin, müdahaleden sonraki ikinci günde immün plazma grubunda daha yüksek olduğu ancak olumsuz olayların ve ciddi yan etkilerin iki grupta da benzer olduğu bildirilmiştir. İmmün plazma ile tedavi edilen hastalar ile plasebo alan hastalar arasında klinik durumda veya genel mortalite açısından önemli bir farklılık gözlenmediği saptanmıştır (33). 1 Ocak 2020 ve 16 Ocak 2021 tarihleri arasındaki COVİD-19 enfeksiyonunda immün plazma tedavisinin mortalite üzerine etkilerinin değerlendirildiği çalışmalara ait bir meta analizde; immün plazma transfüzyonu yapılan COVİD-19 enfeksiyonu olan hastaların toplam mortalite oranının, immün plazma transfüzyonu yapılmayan hastalardan daha düşük olduğu, yüksek titreli plazmanın erken transfüzyonunun COVİD-19 hastalarında mortaliteyi azalttığı bildirilmiştir (34). Literatürde yer alan ciddi COVİD-19 enfeksiyonu olan hastaların dahil edildiği çalışmada ölüm oranı %61,5 olarak bildirilmişken, Grasselli ve arkadaşlarının yaptığı çalışmada %53,4'ünün hastanede yatış sırasında öldüğü bildirilmiştir (35, 36). Çalışmamızda immün plazma uygulanan hastalar ortalama 17,9 gün hastanede yatarak tedavi gördüğü, %39,2'sinin ortalama 17,1 gün yoğun bakım yatışı olduğu ve %35,4'ünde sürecin ölümle sonuçlandığı belirlendi.

Sonuç

COVID-19 pandemisi ortaya çıktığından beri, COVID-19 enfeksiyonu tedavisinde kullanılmak üzere immün plazma gibi alternatif tedavi yöntemlerinin kullanılması da dahil olmak üzere yapılan bilimsel çalışmaların sayısı her geçen gün artmaktadır. Pandemi dinamik bir süreç olup, pandemide hastane yatış kriterlerinin ve immün plazma klinik uygulama kriterlerini sağlayan hastalara immün plazma uygulaması yapılmasının çalışmadaki hasta dağılımını etkilediği görülmüştür. Bu nedenle çalışmada, çoğunlukla bir ya da birden fazla kötü prognostik ölçüte sahip orta ve ağır pnömoni hastaları yer almaktaydı. Çalışmamızın, immun plazma uygulanan bu hastalarda Covid- 19 enfeksiyonunun klinik seyrine, sonlanımına ek olarak immün plazmanın transfüzyonuyla ilişkilendirilen reaksiyonlara ait veri sağlamasının literatüre katkıda bulunabileceği düşünülmektedir.

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Herhangi bir çıkar çatışması yoktur.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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İNTRAPARENKİMAL KANAMALI HASTALARDA ASA SKORUNUN MORTALİTE ORANINA ETKİSİ

THE EFFECT OF ASA SCORE ON MORTALITY RATE IN PATIENTS WITH INTRAPARENCHYMAL HEMORRHAGE

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Öz

Amaç
İntraparenkimal hematom nedeniyle opere ettiğimiz hastaların hematom hacimleri ve preoperatif ASA skorlarının mortaliteye etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem
Çalışmamız hastanemiz Beyin ve Sinir Cerrahisi kliniğinde Şubat 2015 - Şubat 2020 tarihleri arasında intraparenkimal hematom nedeniyle opere edilen 34 hastanın dosyaları geriye dönük olarak taranması ile yürütüldü. Hastaların preoperatif glaskow koma skoru, hematom hacmi, antiagregan kullanımı, hipertansiyon varlığı, kanamanın lokalizasyonu ve ventriküle açılıp açılmadığı ve ASA skorları değerlendirilmek için toplandı.

Bulgular
Çalışmaya dahil edilen 34 hastanın 20'i erkek 14'ü kadın hastaydı. Hastaların geliş anındaki ortalama hematom hacimleri 120cm3 (min:41 – max: 278 cm3)'dü. Hastaların takiplerinde 28 tanesi ex olmuş olup mortalite oranımız %82'dir. Hematom hacimleri ile mortalite arasında anlamlı bir ilişki saptanmıştır (P<0.05). Hastaların 11'i ASA 2, 4' ü ASA 3, 17'si ASA 4 ve 2 hasta ASA 5 olarak değerlendirilmiştir. Hastaların ASA skoru ile mortalitesi değerlendirildiğinde anlamlı bir ilişki saptanmamıştır(P>0.05).

Sonuç
Glaskow koma skoru ve ASA skoru mortaliteyi belirleyen önemli faktörlerdir. Glaskow koma skoru ve ASA skoru birlikte değerlendirilmelidir. Glaskow koma skoru düşük bile olsa komorbid hastalıkları olmayan hastalarda mortalite azalmaktadır.

Anahtar Kelimeler: İntraparenkimal hematom, Hematom hacmi, Glaskow koma skoru, ASA, Mortalite

Abstract

Objective
We aimed to evaluate the effect of hematoma volumes and preoperative ASA scores on mortality of the patients we operated on due to intraparenchymal hematoma.

Materials and Methods
This study was conducted by retrospectively scanning the files of 34 patients operated on for intraparenchymal

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hematoma in our hospital's neurosurgery clinic between February 2015 and February 2020. The preoperative glasgow coma score, hematoma volume, antiaggregant use, presence of hypertension, localization of bleeding and whether it was opened to the ventricle and ASA scores of the patients were collected to evaluate.

Results
Of the 34 patients included in the study, 20 were male, and 14 were female. Preoperative mean hematoma volumes of the patients were 120 cm3 (min: 41 – max: 278 cm3). In the follow-up of the patients, 28 of them were dead, and our mortality rate was 82%. A significant correlation was found between hematoma volumes and mortality (P<0.05). 11 of the patients were evaluated as ASA 2, 4 as ASA 3, 17 as ASA 4, and 2 patients as ASA 5. No significant correlation was found between the patients' ASA score and mortality (P>0.05).

Conclusion
Glasgow coma score and ASA score are important factors determining mortality. The glasgow coma score and ASA score should be evaluated together. Even if the glasgow coma score score is low, mortality decreases in patients without comorbid diseases.

Keywords: Intraparenchymal hematoma, Hematoma volume, Glasgow coma score, ASA, Mortality

Giriş

İntraparenkimal hematomlar genellikle hipertansiyonun eşlik ettiği venöz veya arteriyal kanamalardır. İntraparenkimal hematomlar inme vakaların yaklaşık olarak %10-20 sini oluşturur (1). Antiagregan kullanımı, sistemik hastalığın varlığı, ileri yaş ve hipertansiyonu olan hastalar intraparenkimal hematomlar için riskli hastalardır. Gelişmiş toplumlarda kan basıncı kontrolunün daha düzenli yapılması sonucu hipertansiyona bağlı kanama oranı azalmıştır (2). Fakat gelişmekte olan toplumlarda intraparenkimal hematomların oranı azalmamıştır (3). İntraparenkimal hematom nedeniyle opere edilen hastaların morbidite ve mortalite oranları hematomun volümüne, lokalizasyonuna, ventriküle açılıp açılmamasına göre değişmektedir. Bu hastaların ilk 6 ayda sadece %20'si bağımsız olarak günlük hayatlarını sürdürebilirken, bir yıl içinde %50 den fazlasının kaybedildiği bilinmektedir (4, 5).

Cerrahi tedavi öncesi hastaların operasyon riskinin belirtildiği ASA (Amerikan Anesteziyoloji Derneği Sınıflaması) skorlaması anestezi uzmanlarınca kullanılmaktadır 14(Tablo 1) (6). ASA skorlaması komorbiditenin belirlenmesinin dışında pratikte kolay kullanılması bir avantajdır.

İntraparenkimal hematomlarda cerrahi tedavinin primer amacı beyin dokusu üzerindeki baskıyı azaltarak kafa içi basıncı düşürmek ve hematomun toksik bileşenleri ile beyin dokusu arasındaki teması azaltmaktır(6).

Yazımızda intraparenkimal hematom nedeniyle opere ettiğimiz hastaların preoperatif ASA skorları ve hematom hacimlerinin mortaliteye etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem

Çalışmamız için Eskişehir Osmangazi Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurul Başkanlığından etik kurul onayı alınmıştır (Tarih: 04.05.2021, Karar No:13). Çalışmamız Eskişehir Yunus Emre Devlet Hastanesi Beyin ve Sinir Cerrahisi kliniğinde Şubat 2015 - Şubat 2020 tarihleri arasında intraparenkimal hematom nedeniyle opere edilen 34 hastanın dosyaları geriye dönük olarak taranması ile yürütüldü. Tüm hastaların yakınlarından yapılacak cerrahi işlem ile ilgili yazılı ve sözlü olarak bilgilendirilme yapıldı ve daha sonra işlemi kabul ettiklerine dair yazılı onamlar alındı. Radyolojik veriler hastane arşivinden tarandı. Çalışmaya spontan intraserebral hematom sebebi ile hastaneye başvuran ve ilk 6 saat içinde opere edilen hastalar dahil edildi. Travma sonrası gelişen intraparenkimal hematomlar, vasküler patolojilerin eşlik ettiği hematomlar, enfarkt sonrası gelişen hematomlu hastalar ve 6 saat sonrası geç dönem hastaneye başvuran hastalar çalışma dışı tutuldu. Tüm hastalara ilk 6 saat içerisinde genel anestezi altında geniş kraniektomi ile hematom boşaltıldı ve dekompresyon amaçlı dura grefti ile dura genişletildi ve kemik yerleştirilmedi.

Değerlendirilen Parametreler

Hastaların preoperatif glaskow koma skoru(GKS), hematom hacmi, antiagregan kullanımı, hipertansiyon varlığı, kanamanın lokalizasyonu ve ventriküle açılıp açılmadığı ve ASA skorları değerlendirilmek için toplandı. Hastaların hematom hacmi preoperatif çekilen beyin tomografisinde OsiriX Dicom Viewer (Pixmeo SARL, CH-1233 Bernex. İsviçre) programı kullanılarak ölçümler yapıldı. Hacim A*B*C/2 formülü kullanılarak belirlendi.

İstatistiksel Analiz

İstatistiksel analiz için IBM SPSS 20.0 (IBM Corp.)

kullanıldı. Preoperatif ASA skoru ve hematom hacminin mortalite ile arasındaki ilişki için Mann-Whitney U testi kullanıldı. İstatistiksel anlamlılık P<0.05 olarak ayarlandı

Bulgular

Çalışmaya dahil edilen 34 hastanın 20'si erkek 14'ü kadın hastaydı. Tüm hastaların yaş ortalaması 69.76 (min:45-max:92) olup kadınların yaş ortalaması 68.28, erkeklerin yaş ortalaması 70.8'di. Hastaların 24'ünde hipertansiyon (HT), 5'inde diyabet (DM) ve 13'ünde antiagregan ilaç kullanımı vardı.

Hastaların geliş anındaki ortalama hematom hacimleri 120cm^3 (min:41 – max: 278 cm^3) olup erkek hastaların ortalama hacimleri 127,5 cm^3 iken kadın hastaların 109,2 cm^3 olarak hesaplandı. Hastaların cerrahi sonrası ve taburculuktan sonraki ilk ay içinde 28 tanesinin ex olduğu tespit edilmiş olup, mortalite oranımız %82 olarak hesaplanmıştır (Tablo 2). Hematom hacimleri ile mortalite arasında istatistiksel olarak anlamlı bir ilişki olduğu tespit edilmiştir (P<0.05).

Hastalarımızda bulunan hematomların 3 tanesi serebellar yerleşimli, 5 tanesi talamik yerleşimli ve 26 tanesi lober yerleşimliydi. Toplam 16 hastada (11 erkek, 5 kadın) hematomun ventriküle açılarak intraventriküler hematoma neden olduğu görüldü.

Hastaların preoperatif ASA değerlendirmeleri operasyon öncesi operasyona girecek anestezi uzmanı tarafından değerlendirildi. Değerlendirme sonucunda 11 hasta ASA 2, 4 hasta ASA 3, 17 hasta ASA 4 ve 2 hasta ASA 5 olarak operasyona alındı. Hastaların preoperatif ASA değerleri ile mortalite oranı karşılaştırıldığında istatiksel olarak anlamlı bir ilişki saptanmadı (P>0.05).

Hastalar ASA skorlaması yanı sıra GKS'lerine göre de değerlendirildi. 21 hastanın geliş GKS'si 3-7 arasında iken, 13 hastanın 8-13 puan arasında olduğu görüldü.

Tartışma

İntraserebral hematomlar dünya çapında yıllık 1 milyondan fazla insanı etkileyen ve en çok mortalite ve morbitideye neden olan inme türüdür (5). İntraserebral hemetomlar çeşitli lokalizasyonda görülebilmektedir ve %80'ni supratentoriyal yerleşimlidir (7). İntraserebral hematomlar için akut ve kronik hipertansiyon varlığı, ileri yaş, antiagregan kullanımı, erkek cinsiyet,

Tablo 1 ASA (Amerikan Anesteziyoloji Derneği Sınıflaması) Skoru

ASA 1	Elektif cerrahi yapılacak normal kişi
ASA 2	Hafif düzeyde sistemik hastalık varlığı
ASA 3	Ciddi düzeyde sistemik hastalığı olan fakat günlük aktiviteleri etkilenmeyen hasta
ASA 4	Günlük aktiviteleri etkileyen ve hayati tehlike yaratan ciddi sistemik hastalığın varlığı
ASA 5	Ölüm tehlikesi olan ve 24 saat fazla yaşam beklentisi olmayan hasta
ASA 6	Beyin ölümü olan ve organ nakli için bekletilen hasta

Tablo 2 Hematom hacimlerinin cinsiyete göre dağılımı ve mortalite oranları

Hacim	Kadın	Erkek	Mortalite (%)
0-50 cm^3	1	1	1 (%50)
50.1 – 100 cm^3	8	4	7 (%58)
100.1 cm^{3}ve üstü	5	15	20(%100)

alkol kullanımı ve diyabet risk faktörlerinden birkaçıdır (8). Hastalarımızın yaş ortalaması literatürle uyumlu olarak yüksektir (5) ve %70'inde hipertansiyon, %38'inde antiagregan kullanımı mevcuttu.

İntraserebral hematomların cerrahi tedavi endikasyonları ile tedavi sonuçları nöroşirürji pratiğinde en çok tartışılan ve üzerinde çalışma yapılan konulardan biridir (9). Hastanın yaşı, hematomun hacmi, hastanın nörolojik durumu ve hematomun lokalizasyonu cerrahi kararın verilmesinde önemli rol oynamaktadır. Cerrahi tedavinin primer amacı kafa içi basıncı azaltarak mortalite ve morbitideyi önlemektir (10). Bu yüzden hastalarımıza ilk 6 saate kraniektomi uygulanmıştır.

Yapılan çalışmalar incelendiğinde intraserebral hematomlarda mortalite oranı çok değişkenlik göstermektedir. Takip sürelerinin uzun olduğu çalışmalarda mortalite oranları da artmaktadır. Mortalite oranının artmasında birçok faktör rol oynamaktdır. Özellikle hematom hacminin 30 cm3'ün üzerindeki hastalarda mortalite oranı daha fazla olduğu bildirilmiştir (11). Ayrıca hematom hacminin her % 1 artığında mortalite oranında % 1 arttığı bildirilmiştir (12). Bizim çalışmamızda mortalite oranımız %82'dir. Literatürde intraserebral hematomlarda mortalite oranın %22-%91 arasında değişmektedir (13, 14). Mortalite oranımızın yüksekliği, hastalarımızın ortalama hematom hacminin 120 cm3 olmasına bağlı olduğunu düşünmekteyiz.

Hastaların preoperatif glaskow koma skoruda mortaliteyi etkilemektedir. Düşük glaskow koma skoru kötü prognoz göstergesidir(15). GKS 7 ve altında olan hastalarda mortalite % 100'e ulaşmaktadır (16).

İntraserebral hematomların mortalite oranını belirlemek bu multifaktöriyel etkenlerden dolayı oldukça zordur. Her bir parametre ayrı ayrı değerlendirildiğinde prognoz öngörülebilirken, birden fazla parametrenin birlikte olması zorlaştırmaktadır. Örneğin ileri yaş ve düşük GKS mortalite oranı yüksek iken, ileri yaş ve yüksek GKS olan hastalarda belirsizlik vardır. Hemphill ve arkadaşları yaş, hematomun hacmi, GKS, ventriküle içine açılıp açılmaması ve hematomun lokalizasyonunu içeren bir skorlama sistemi bildirmişlerdir (17). Bizim çalışmamızda mortalite oranı yüksek olmasına rağmen hastaların geliş GKS oranları değişiklik göstermektedir. Hematomun hacmi benzer hastalarda, GKS 7 ve altı olan hastaların mortalite oranları değişiklik göstermekteydi. Bu belirsizlik ASA skorunuda parametreler arasında değerlendirmemiz gerektiği hipotezini doğurmuştur.

İleri yaş intraserebral hematomlar için değiştirilemez risk faktörüdür. İleri yaşla birlikte hastalarda komorbidite oranı artmaktadır. Tayvan'da künt travma geçiren hastalarda yapılan bir çalışmada komorbiditenin yüksek mortaliteye neden olduğu rapor edilmiştir (18). Hastalar cerrahiye alınmadan önce anestezi hekimelerince komorbiditelerinin değerlendirildiği ASA skorlaması yapılmaktadır. İnme sonrası karotid endarterektomi yapılan hastalarda preoperatif ASA değeri 2'nin üzerinde olan hastalarda postoperatif nörolojik komplikasyon ve mortalite oranı ASA değeri 2 ve altında olan hastalara göre daha yüksektir (19).

Çalışmamızda GKS 7 ve altında olup ASA 2 olan hastalarda mortalite oranının %40 olduğunu gördük. Aynı şekilde GKS yüksek olan fakat ASA skoru 4 olan hastalara bakıldığında mortalite oranının %75 olduğu izlenmiştir. Çalışmamız sonucunda hastalarda GKS düşük olsa bile eşlik eden komorbid hastalıkların olmaması (ASA'nın düşük olması) mortaliteyi azaltmaktadır. Pateder ve ark. yaptığı çalışmada spinal cerrahi sonrasında morbitide ve mortalite riskinin ASA skoruyla doğru orantılı olduğu bildirilmiştir (20). GKS'nin yüksek olması komorbid hastalıklar eşlik ettiğinde (ASA'nın yüksek olması) mortaliteyi azaltmamaktadır.

Çalışmamızın limitasyonları; retrospektif olması, çalışmaya dahil edilen hastaların birçoğunun postoperatif kontrol tomografilerinin olmaması nedeniyle preoperatif görüntülerle karşılaştırılamaması ve cerrahi işlemlerin tek hekim tarafından yapılmamış olması sayılabilir.

Sonuç

İntraserebral hematomlu hastalarda mortaliteyi etkileyen birçok faktör vardır. Hastanın başvuru anındaki GKS ve ASA skoru mortaliteyi belirleyen önemli faktörlerdir. Komorbiditenin varlığı (kullanılan antiagregan ilaçlar ve kanama diatezi bozukluğu) hematomun hacmini de etkilemektedir. Bunun sonucunda oluşan nöral hasar mortaliteyi belirlemektedir. Hastanın mortalite riskini hesaplarken GKS, yaş ve hematom volümünün yanı sıra mutlaka ASA değerini de göz önünde bulundurmak gerekir. GKS 7 ve altı olsa bile her zaman mortal seyretmeyeceği, ASA değeri düşük olan hastalarda riskin de azaldığı akılda tutulmalıdır.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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THE ASSOCIATION BETWEEN GRADE OF PERIODONTITIS AND GCF LEVELS OF TNF-α AND MIP-1α: A PRELIMINARY STUDY

PERİODONTİTİS DERECESİ İLE DİŞETİ OLUĞU SIVISI TNF-α VE MIP-1α SEVİYELERİ ARASINDAKİ İLİŞKİNİN DEĞERLENDİRİLMESİ: ÖN ÇALIŞMA

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Öz

Amaç

Periodontitisin patogenezindeki sitokin ve kemokinlerin rolü,periodontitisin başlaması ve ilerlemesinde önemli fonksiyonlara sahip olan ile Tümör Nekroz Faktör alfa (TNF-α) ve Makrofaj İnflamatuar Protein 1α ile (MIP 1α) gösterilmiştir. Bununla birlikte, farklı periodontitis derecelerinin sitokin ve kemokin profilleri hala belirsizdir ve periodontitisin ilerleme hızı ile ilişkili biyobelirteçler hakkında henüz kesin bilgiler bildirilmemiştir. Bu nedenle, bu çalışmanın amacı Derece A, B ve C'deki dişeti oluğu sıvısındaki (DOS) MIP-1α ve TNF-α'nın düzeylerini tahmin etmek ve periodontitis derecesini belirlemede güvenilir biyobelirteçler olarak rollerini değerlendirmektir.

Gereç ve Yöntem

Bireyler periodontitis derecelerine göre Evre IV periodontitis tanısı alan ve Derece A (Derece A, n = 21), Evre IV periodontitis tanısı alan ve Derece B (Derece B, n =21) ve Evre IV periodontitis tanısı alan Derece C bireyler (Derece C, n = 21) olmak üzere üç gruba ayrıldı.

Bulgular

Ortalama TNF-α seviyeleri açısından gruplar arasında anlamlı bir fark olmamasına rağmen, Derece C'deki ortalama MIP-1α seviyesi Derece B ve Derece A'dan anlamlı derecede yüksekti. Derece B'deki ortalama MIP-1α seviyesi Derece A'dan önemli ölçüde daha yüksek ($p < 0.05$, Kruskal–Wallis testi) bulundu. Sonuç: MIP-1α, periodontitis derecesi için tanımlayıcı bir biyobelirteç olarak klinik kullanıma sahip olabilir.

Anahtar Kelimeler: Dişeti Oluğu Sıvısı, Kemokin, Periodontitis, Sitokin

Abstract

Objective

The role of cytokines and chemokines in the pathogenesis of periodontitis indicates that tumor necrosis factor alpha (TNF-α) and macrophage inflammatory protein 1α (MIP1α) have crucial functions in the initiation and progression of periodontitis. However, the cytokine and chemokine profiles of different grades of periodontitis are still unclear, and no conclusive information has yet been reported on biomarkers associated with the progression rate of periodontitis. Thus, the aim of the present study was to estimate the gingival crevicular fluid (GCF) levels of MIP-1α and TNF-α in Grades A, B, and C and to evaluate their role as reliable biomarkers in determining the grade of periodontitis.

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Materials and Methods
Individuals were divided into three groups according to their grade of periodontitis: individuals diagnosed as Stage IV periodontitis with Grade A (Grade A, n = 21), individuals diagnosed as Stage IV periodontitis with Grade B (Grade B, n = 21), and individuals diagnosed as Stage IV periodontitis with Grade C (Grade C, n = 21).

Results
Although there were no significant differences between groups in terms of mean TNF-α levels, the mean MIP-1α level of Grade C was significantly higher than that of Grade B and Grade A. The mean MIP-1α level of Grade B was significantly higher than that of Grade A ($p < 0.05$, Kruskal–Wallis test).

Conclusion
MIP-1α could have clinical utility as a screening biomarker for the grade of periodontitis.

Keywords: Chemokines, cytokines, gingival crevicular fluid, periodontitis

Introduction

Periodontitis is a consequence of the interaction between the host immune response and subgingival microbial communities. This interaction promotes the release of inflammatory mediators that results in the destruction of tooth-supporting structures.1 Cytokines and chemokines, which are among the inflammatory mediators present in the diseased periodontium, have been implicated in the pathogenesis of periodontitis.2

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that has a wide range of biological effects, from stimulation of inflammatory responses to protection. TNF-α induces alveolar bone resorption and plays a critical role in the pathogenesis of periodontitis. Higher gingival crevicular fluid (GCF) levels of TNF-α are found in diseased periodontal sites.3,4

Macrophage inflammatory protein 1α (MIP1α) is a biologically active chemokine secreted by a variety of cell types and plays various biological roles, such as recruiting inflammatory cells and maintaining the effector immune response. MIP-1α induces bone destruction, and higher levels have been reported in the GCF of patients with periodontitis.5,6

Periodontitis classification has been modified several times in the last 30 years in accordance with emerging scientific findings. The 2017 classification included the rate of periodontitis progression and disease susceptibility in addition to the severity of periodontitis, which had been used as a main identifier of periodontitis for a long time. Thus, periodontitis was reclassified into four stages (I, II, III, and IV) according to severity of the disease, and three grades (A, B, and C) were used to differentiate disease susceptibility and rate of periodontitis progression.7-9

Understanding the role of cytokines and chemokines in the pathogenesis of periodontitis revealed that TNF-α and MIP-1α have a crucial function in the initiation and progression of periodontitis. However, similarities and dissimilarities between cytokine and chemokine profiles of different grades of periodontitis are still unclear, and no conclusive information has yet been reported on biomarkers associated with the progression rate of periodontitis. Thus, the aim of the present study was to estimate the GCF levels of MIP-1α and TNF-α in Grades A, B, and C and to evaluate their role as reliable biomarkers in determining the grade of periodontitis.

Materials and Methods

This study was conducted between August 2019 and February 2020 in Uşak University, Faculty of Dentistry, Department of Periodontology. The individuals were informed about the study, and written consent was obtained. This study was designed according to Helsinki declaration principles and approved by the Uşak University Faculty of Medicine Ethics Committee (decision no: 38-38-14, date: 03.02.2021).

Participants

Individuals 18 years of age or older woman and man were included in the study. Exclusion criteria included periodontal treatment in the previous six months, use of antibiotics or anti-inflammatory drugs in the previous six months, smoking, diabetes, lactation, pregnancy, or any systemic condition.

Clinical Periodontal Measurements

All clinical examinations were performed by one examiner, who was calibrated as previously reported. 10 Plaque index (PI),11 gingival index (GI),12 probing depth (PD), and clinical attachment loss (AL) were assessed at six sites of all teeth except third molars using a manual periodontal probe (Williams, Hu-Friedy, Chicago, IL).

Classification of Individuals

Patients were classified using the 2017 classification of periodontal and peri-implant diseases and conditions. Individuals were divided into three groups according to their grade of periodontitis: individuals diagnosed as Stage IV periodontitis with Grade A (Grade A, n = 21), individuals diagnosed as Stage IV periodontitis with Grade B (Grade B, n = 21), and individuals diagnosed as Stage IV periodontitis with Grade C (Grade C, n = 21).

GCF Sampling

Clinical examination was performed one week before GCF samples were collected. Four nonadjacent and deep periodontal pockets were selected for GCF sampling. After supragingival biofilm removal, sites were isolated and gently dried to avoid saliva contamination. Standard paper strips were inserted approximately 2 mm into the pocket/sulcus for 30 seconds to collect GCF. Blood-contaminated strips were discarded, and the strips were immediately transferred into sterile Eppendorf Tubes and stored for further analysis.

Cytokine/Chemokine Quantification

Enzyme-linked immunosorbent assay was used to analyze the GCF levels of TNF-α and MIP-1α with commercially available kits. The tubes were vortexed for 30 seconds and centrifuged for 5 minutes at 1500 g to elute. Assays were carried out according to the manufacturer's recommendations. The results were described as the total amount (pg/30sn) of cytokine.

Sample Size

The effect size (0.84), type 1 error (α = 0.05), and test power (1-β = 0.80) were determined for sufficient sample size. According to these calculations, a minimum of 19 individuals per group (total sample size of 57 individuals) was necessary.

Statistical Analysis

Normality of data was checked by using Kolmogorov–Smirnov and Shapiro–Wilk tests. As the normality assumption was violated, nonparametric Kruskal–Wallis and chi-squared tests were used in the comparison of the groups. The data were considered as mean and the standard deviation and statistical significance level were set at 0.05.

Results

A total of 37 (58.7%) male and 26 (41.3%) female participants were included in the study. The mean age of the participants was 51.95±8.34. The mean age of the individuals in Grade C was significantly lower than that of the individuals in Grade B and Grade A ($p < 0.05$, Kruskal–Wallis test) (Table 1). There was no significant difference between the groups in terms of gender distribution ($p > 0.05$, chi-squared test) (Table 2).

Table 1 The mean age of groups

	Grade	n	Mean±sd	p	Difference
Age	A	21	58.43±6.25	0.001*	1-2 1-3 2-3
	B	21	54.71±4.70		
	C	21	42.71±3.59		

Table 2 Gender distribution of groups

Gender		**Grade**			**Total**	**p**
		A	**B**	**C**		
Male	**n**	13	11	13	37	0.771
	% Row	35.1%	29.7%	35.1%	100.0%	
	% Column	61.9%	52.4%	61.9%	58.7%	
Female	**n**	8	10	8	26	
	% Row	30.8%	38.5%	30.8%	100.0%	
	% Column	38.1%	47.6%	38.1%	41.3%	

Table 3 The mean periodontal clinical parameters of groups

Clinical parameters	Grade	n	Mean±sd	p	Difference
PI	A	21	2.11±0.34	0.651	-
	B	21	2.10±0.38		
	C	21	2.14±0.31		
GI	A	21	2.32±0.29	0.639	-
	B	21	2.33±0.24		
	C	21	2.37±0.20		
AL (mm)	A	21	5.57±0.87	0.801	-
	B	21	5.62±0.71		
	C	21	5.67±0.65		
PD (mm)	A	21	4.60±0.75	0.351	-
	B	21	4.65±0.63		
	C	21	4.89±0.65		

Table 4 The mean TNF-α and MIP-1α levels of groups

Inflammatory mediators	Grade	n	Mean±sd	p	Difference
TNF-α (pg/30sn)	A	21	25.21±25.46	0.255	-
	B	21	25.67±25.55		
	C	21	32.72±30.50		
MIP-1α (pg/30sn)	A	21	12.16±5.09	0.005*	1-3 2-3 1-2
	B	21	15.05±5.53		
	C	21	19.49±4.07		

*: p<0.05, Kruskal-Wallis test

There was no significant difference between the groups in terms of mean PI, GI, AL, and PD ($p > 0.05$, Kruskal–Wallis test) (Table 3). Although there was no significant difference between groups in terms of mean TNF-α level, the mean MIP-1α level of Grade C was significantly higher than that of Grade B and Grade A. The mean MIP-1α level of Grade B was significantly higher than that of Grade A ($p < 0.05$, Kruskal–Wallis test) (Table 4).

Discussion

In the 2017 classification, the grade of periodontitis includes a retrospective analysis of the rate of progression of periodontitis, which provides additional information about the biological characteristics of the disease. Grading also features an assessment of the risk of further progression and is based on an assessment of bone loss at the worst-affected tooth in the dentition as a function of age.9,13,14 To date, a comparison of inflammatory mediators in the GCF of individuals with different grades of periodontitis has not been performed. This is the first study investigating the GCF levels of TNF-α and MIP-1α in individuals with different grades of periodontitis.

The current study confirmed that gender was not significantly associated with periodontal disease

progression rate, which did not agree with previous studies reporting that periodontitis is more prevalent in men than in women.15,16 A possible explanation for this is that males and females have the same susceptibility to future disease progression, but the disease is more seen frequently among males.

According to this study, the grade of periodontitis increased as the mean age of the groups decreased, which was expected because formula used in the grade calculation is inversely proportional to age.7-9

The lack of difference in periodontal clinical parameters (PI, GI, AL, and PD) between the groups can be explained by the fact that the individuals had the same disease severity. In addition, this result suggests that conventional clinical diagnostic measures fail to recognize individuals who are at risk of further progression.

The results of this study showed an increased GCF level of MIP-1α with an increase in the progression rate of periodontitis. As the progression rate of periodontitis increases, that is, as the grade of periodontitis progresses from A to C, the GCF level of MIP-1α increases. Our result was confirmed by a study showing that GCF levels of MIP-1α are elevated prior to bone loss in patients with aggressive periodontitis, suggesting that this chemokine can identify sites susceptible to bone loss.17 Another study stated that there is a correlation between periodontitis severity and MIP-1α level, while yet another study, by Emingil et al., stated that there was no relationship between periodontal disease severity and GCF level of MIP-1α.18,19 Our study was the first to examine the relationship between grade of periodontitis and GCF level of MIP-1α; these other studies we considered were conducted according to the 1999 classification, and the severity of periodontitis destruction was generally evaluated, not the rate of progression.

This result indicates that MIP-1α can be a candidate as a diagnostic biomarker for the grade of periodontitis, and we highlight some possible related hypotheses. First, as the grade of periodontitis increases, the composition of pathogenic bacteria associated with periodontitis can change, and the level of Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis can also increase, which can induce polymorphonuclear leukocytes and epithelial cells to produce MIP-1 α.6,18 Second, monocytes from different grade levels of periodontitis can show dissimilarity in mediator release, and activated monocytes may indirectly amplify monocyte functions by recruiting additional cells to inflammatory sites.19,20 Therefore distinct macrophage phenotypes might indicate differences in the release of MIP-1α.

In the current study, no association was found between levels of TNF-α in GCF and different grades of periodontitis. The reason for the lack of difference between the groups may be that the individuals have the same periodontal destruction severity. This result demonstrates that TNF-α may be a biomarker of periodontitis severity rather than periodontitis progression rate and that this molecule could be used to compare different stages of periodontitis.

A strength of the present study is that it was the first to investigate the impact of different periodontitis grades on the GCF levels of MIP-1α and TNF-α. However, this study has some limitations. First, this is a cross-sectional study that cannot determine causal relationships. Second, this study is limited to one specific point in time, and longer follow-up of individuals by a prospective cohort study should be performed.

Conclusion

In conclusion, these findings suggest that MIP-1α could have clinical utility as a screening biomarker for the grade of periodontitis, whereas TNF-α might aid in identifying periodontitis severity. For a better understanding of cytokine and chemokine factors associated with the grade of periodontitis, further analysis is essential.

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

Ethical Approval
This study was designed according to Helsinki declaration principles and approved by the Uşak University Faculty of Medicine Ethics Committee (decision no: 38-38-14 , date: 03.02.2021)

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Author Contributions
U.Y: Conceptualization, Methodology, Data Curation, Writing–original draft, Writing, Review&Editing

F.K: Conceptualization, Methodology, Validation, Writing–original draft, Writing, Review&Editing, Visualization

A.D: Resources, Writing, Review&Editing

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ARE WOMEN AWARE OF THE VACCINE AGAINST HUMAN PAPILLOMAVIRUS? A HOSPITAL-FOCUSED CROSS-SECTIONAL STUDY

KADINLAR HUMAN PAPİLLOMA VİRÜS AŞISI OLDUĞUNU BİLİYOR MU? HASTANE ODAKLI KESİTSEL BİR ÇALIŞMA

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Öz

Amaç
Human Papilloma Virus (HPV) serviks kanserinin nedenidir. Aşılanma ile serviks kanserinin oluşması engellenebilir. Çalışmamızda ki amacımız Kars ilinde jinekoloji polikliniklerine başvuran kadınların HPV aşısı hakkında ki bilgi düzeylerini değerlendirmektir.

Gereç ve Yöntem
Bu çalışma Kars Harakani Devlet Hastanesi jinekoloji polikliniklerine 1-31 Aralık 2020 tarihleri arasında başvuran kadınları kapsayan kesitsel bir çalışmadır. Çalışmaya 380 kadın dahil edilmiştir. Kadınların HPV aşısını bilip bilmedikleri sorulmuştur.

Bulgular
Çalışmada kadınların HPV aşısını bilmeme riskini 34 yaş altında olmanın 4,013 kat, eve giren gelirin yetersiz olmasının 8,640 kat, 8 yıl ve altında eğitim almış olmanın 3,375 kat arttırdığı görüldü.

Sonuç
Serviks kanserine karşı HPV aşısı hakkında bilgi düzeyinin yetersiz olduğu görülmüştür.

Anahtar Kelimeler: HPV, Serviks kanseri, Aşı

Abstract

Objective
Human Papillomavirus (HPV) is the causative agent of cervical cancer. However, the disease can be prevented by vaccination. In this study, we aimed to evaluate the level of knowledge about HPV vaccination among women who applied to gynecology outpatient clinics in Kars, Turkey.

Materials and Methods
This cross-sectional study included women who were admitted to the gynecology outpatient clinics of Kars Harakani State Hospital in December 2020. Overall, 380 women were included in the study, and they were asked if they knew about the existence of the HPV vaccine.

Results
We observed that the risk of being uninformed about the HPV vaccine increased by 4.013 times in women aged <34 years, by 8.640 times in households with insufficient income, and by 3.375 times in women with education of ≤8 years.

Conclusion
Based on the findings, it could be concluded that

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the level of knowledge about the availability of HPV vaccine against cervical cancer is insufficient.

Keywords: Cervical cancer, Human papillomavirus, Vaccine

Introduction

Human Papillomavirus (HPV) belongs to the papillomavirus family and is a DNA virus that infects the basal epithelial layer cells on the skin and mucosal surfaces. The most important characteristic of the virus is that it can cause cancer in the regions of the cervix, penis, vulva, vagina, anus, mouth, oropharynx, and other mucosal areas [1].

There are many types of HPV, and most of them do not cause any problems. HPV infections disappear within a few months, and 90% of them are resolved within 2 years. However, a small percentage of infections that occur with some HPV types persist and can progress to cervical cancer. According to the data of the World Health Organization, cervical cancer is the 4th most common type of cancer in the world and is responsible for 7.5% of deaths due to all female cancers. Cervical cancer control consists of processes including vaccination against HPV (primary protection), screening and treatment of precancerous lesions (secondary protection), and diagnosis and treatment of invasive cervical cancer (tertiary protection). Among these processes, the most important factor in terms of cost and effectiveness is the vaccination of women [2].

Although vaccination is effective in preventing cervical cancers, it is not included in the routine vaccination program of most countries. In most of the developing countries such as Turkey, HPV vaccines are recommended but the vaccination is not included in the national immunization program [3].

One of the most important problems in vaccination programs is the lack of appropriate information, and the second is vaccine hesitancy. According to the literature, while vaccine hesitancy prevails even in the case of childhood vaccines, such as those against measles and whooping cough [4], lack of information is one of the main reasons for not getting the HPV vaccine [5,6].

The present study therefore aims to determine the level of knowledge amongst women in the age group of 15–49 years about the existence of HPV vaccine and to identify the sociocultural factors affecting this knowledge

Materials and Methods

Defining the region where the research was conducted

Turkey is divided into 30 health regions. The hospital where the study was conducted is located in the 30th health zone and is the largest and most important hospital in the region. Being the region in which the highest mountain of Turkey is located, this region is adjacent to Iran, Georgia, Nakhichevan, and Armenia. The main livelihood of the people in this region is agriculture and animal husbandry. The region is below the average socioeconomic development level in the country. Illiterate people account for 11.7% of the total population in the region, and those who never finished school account for 13.5% of the total population [7].

In terms of health personnel per thousand people, the region is below the national average. Infant deaths amount to 11.2 per 1.000 and maternal deaths to 24.5 per 100.000, which are above the national average (Turkey's average rates of infant deaths and maternal deaths are 6.8 per 1.000 and 14.6 per 100.000, respectively) [8].

Study Type

Hospital-focused cross-sectional study

Study Population

To determine the study population, women aged 15–49 years who applied to the Gynecology and Obstetrics Outpatient Clinic of Kars Harakani State Hospital in 2019 were considered. The total number of applicants was 36,230. The same number of patients was predicted to apply in 2020, during which the study was conducted.

Study Sample

Since the population of the study is known, the number of women to be included in the sample was calculated using the formula n = Nt2 p q/d2 (N-1) + t2 p q, where, N is the number of individuals in the universe, n is the number of individuals to be included in the sample, p is the frequency (probability) of occurrence of the investigated event, q is the frequency (probability) of the investigated event not occurring, t is the theoretical value found in the t table at the given degree of freedom and the detected level of error, and d is the ± deviation desired to be made according to the frequency of occurrence of the event [9]. Accordingly,

the sample size was calculated as 380 women, with p = 0.50, q = 0.50, t = 1.96, and d = 0.05.

Arriving at the Data Collection Form
The data collection form was prepared by the researchers, and it consisted of two parts. The first part included the sociodemographic, biodemographic, and socioeconomic information of the partiipants, and the second part included questions about HPV.

Research Variables
Dependent variable: The woman's state of being informed about the existence of HPV vaccine.

Independent variables: Sociodemographic, biodemographic, and socioeconomic characteristics

Ethics Committee and Written Approval
Ethics committee approval was obtained from Kafkas University Faculty of Health Sciences Non-Invasive Research Ethics Committee for the study (number/ issue: 81829502.903/100). The participants' written consents were also obtained. Our study was conducted in accordance with the Helsinki Declaration.

Data Collection
The data were collected in December 2020 by the researcher using face-to-face interview technique in the gynecology and obstetrics outpatient clinic.

Preliminary Trial of the Study
It was conducted with seven women aged 15–49 years who applied to the outpatient clinic. Necessary adjustments were made to complete the missing parts of the data collection form.

Statistical Analysis
Chi-square test was used for paired comparisons. The variables that were found to be significant in the hi-square test were included in the logistic regression (backward: LR) analysis. $p < 0.05$ was considered significant.

Results

In this study, 82.7% of women aged 15–49 years were not informed that HPV vaccine exists. While the paired analysis between marital status and the state of being informed or uninformed about the HPV vaccine did not reveal statistically significant difference ($p = 0.664$), there was a statistically significant difference in terms of residential place, age, family type, number of people in the household, health insurance, educational background, employment status, and income level ($p = 0.041$, $p = 0.001$, $p = 0.035$, $p = 0.046$, $p = 0.001$, $p = 0.001$, $p = 0.001$, $p = 0.001$, respectively) (Table 1).

As seen in Table 2, there was no statistically significant difference between the states of being informed and uninformed about HPV in terms of total number of pregnancies, knowing the name of the family physician, and knowing the name of the family health midwife ($p = 0.271$, $p = 0.661$, $p = 0.622$). However, there was a statistically significant difference between the state of being informed about the smear test and HPV vaccine ($p = 0.001$).

Table 3 presents the results of the logistic regression analysis. As seen in the table, the risk of being uninformed about the existence of HPV vaccine was 4.013 times (CI = 1.506–10.694) higher in women aged ≤34 years than in those aged ≥35 and over, 8.640 times (CI = 3.579–20.859) higher in women with insufficient household income than in those with sufficient household income, 3.375 times (CI = 1.385–10.074) higher in women with ≤8 years of education than in those with ≥9 years of education, and 29.119 times (CI = 11.477–73.880) higher in women who had not heard of the smear test than in those who had heard about it.

Discussion

Almost all cases of cervix cancer are due to HPV infection. However, it is a health problem that can be prevented with HPV vaccine and can be treated with early diagnosis [2]. The current study aims to determine whether women aged 15–49 years are informed about the existence of HPV vaccine.

According to the results of the present study, 82.7% of the women were uninformed about the existence of HPV vaccine. According to various studies conducted in different regions across Turkey, the rates of being uninformed about HPV vaccine range between 43.4% and 66.4% [3]. In a study conducted in Thailand, 60.0% of the women stated that they were uninformed about the existence of HPV vaccine [10]. The high difference among the studies with regard to knowledge on HPV vaccine is probably due to two reasons. The first of these reasons is that sociocultural and socioeconomic differences exist among the regions where the studies were conducted, and the second is that other studies were conducted in medical faculty hospitals [11].
The risk of being uninformed about the existence of HPV vaccine increased by 3.375 times in women with an education level of ≤8 years when compared to those with an education level of ≥9 years. In a similar study conducted in China where the junior schooler

Table 1 The effect of sociodemographic characteristics of women on their level of knowledge about the human papillomavirus vaccine (Kars, 2020)

Sociodemographic		Informed	Uninformed	Total	X^2	P
		n (%) *	n (%) *	n (%) **		
Place of residence	Village/town	8 (9.8)	74 (90.2)	82 (21.5)	4,177	**0.041**
	City/district center	58 (19.4)	241 (80.6)	299 (78.5)		
Age	≤34 years	43 (14.1)	262 (85.9)	305 (80.1)	11,100	**0.001**
	≥35 years	23 (30.3)	53 (69.7)	76 (19.9)		
Marital status	Married	60 (16.9)	294 (83.1)	354 (92.9)	0.487	0.664
	Not married	6 (22.2)	21 (77.8)	27 (7.1)		
Family type	Large	10 (10.3)	87 (89.7)	97 (25.5)	4,469	**0.035**
	Nuclear	56 (19.7)	228 (80.3)	284 (74.5)		
Number of persons in the household	≤4	50 (20.2)	198 (79.8)	248 (65.1)	3,997	**0.046**
	≥5	16 (12.0)	117 (88.0)	133 (34.9)		
Health insurance	No	13 (6.7)	180 (93.3)	193 (50.7)	30,611	**0.001**
	Yes	53 (28.2)	135 (71.8)	188 (49.3)		
Education	≤8 years	19 (9.7)	176 (90.3)	195 (51.2)	16,021	**0.001**
	≥9 years	47 (25.3)	139 (74.7)	186 (48.8)		
Employment	Housewife	34 (11.6)	258 (88.4)	292 (76.6)	28,149	**0.001**
	Income-generating	32 (36.0)	57 (64.0)	89 (23.4)		
Household income	Sufficient	46 (40.0)	69 (60.0)	115 (30.2)	59,144	**0.001**
	Insufficient	20 (7.5)	246 (92.5)	266 (69.8)		
Total*		**66 (17.3)**	**315 (82.7)**	**381 (100.0)**		

* row percentage, ** column percentage

is taken as the lower reference, awareness of HPV vaccination was increased by 2.175 times (CI: 1.966–2.406) in high school and by 5.026 times (CI: 4.527–5.580) in college [12]. Although multiple analyses were not conducted, it has been stated in studies involving paired analysis that awareness of HPV vaccine increases as the education level increases [13,14]. The probable reason for the increase in knowledge about the vaccine as the education level increases could be the higher health literacy of women with a high level of education. As a matter of fact, studies have reported that health literacy and vaccine awareness are directly proportional to each other [15,16,].

In the study, the decrease in the amount of household income increased the risk of being uninformed about the HPV vaccine in women by 8.640 times. In one study, it was reported that when compared to families with lower income levels, families with higher income levels were 3.752 (CI: 3.113–4.522) times more aware of the existence of HPV vaccine [11]. This situation is thought to stem from the social status of women. In Turkey, women with a high level of education are of higher social status; therefore, these women get a higher share of the national income. The received share paves the way to be benefitted from the services of the healthcare institutions to a greater extent. This may contribute to the increased awareness of many health-related issues among these women [17,18].

In this study, when women aged ≥35 years were taken as a reference, those aged ≤34 demonstrated 4.013 times higher risk of being uninformed about the existence of HPV vaccine. In a study [10], that did not fully match the present study, the younger group (aged <45 years) had a 2.33 (CI: 1.61–3.38) times greater desire for vaccination compared to the older

Table 2 The effect of healthcare use among women on their level of knowledge about the human papillomavirus vaccine (Kars, 2020)

Health service		Informed	Uninformed	Total	X^2	P
		n (%) *	n (%) *	n (%) **		
Total number of pregnancies	≤2	46 (18.9)	197 (81.1)	243 (63.8)	1,210	0,271
	≥3	20 (14.5)	118 (85.5)	138 (36.2)		
Name of family doctor	Informed	43 (16.7)	214 (83.3)	254 (67.5)	0,193	0,661
	Uninformed	23 (18.5)	101 (81.5)	127 (32.5)		
Name of family nurse	Informed	33 (18.3)	147 (81.7)	180 (47.2)	0,243	0,622
	Uninformed	33 (16.4)	168 (83.6)	201 (52.8)		
Knowledge about smear test	Informed	7 (2.9)	238 (97.1)	245 (64.3)	100,283	**0.001**
	Uninformed	59 (43.4)	77 (56.6)	136 (35.7)		
Total*		**66 (17.3)**	**315 (82.7)**	**381 (100.0)**		

* row percentage, ** column percentage

group (aged ≥45 years). This situation may arise from cultural differences between the countries. The most important control mechanism on women in Turkey is the "gender"-specific control mechanism. Among these control mechanisms, "honor rumor" comes first. Younger women are restricted by their family elders from using the public space without gaining social trust. As the age increases, the number of marriages and children increase, in other words, as the society cultivates a sense of trust toward women, the control mechanism on women decreases [20]. Therefore, interactions with public institutions at a younger age may reduce awareness of health-related issues.

In the study, when compared to women informed about the Pap smear test, those who were uninformed about the test had 29.119 times higher risk of not knowing about the existence of the HPV vaccine. In a study examining Thai women, it was shown that women's knowledge of the Pap smear test did not affect their knowledge about the HPV vaccine [10]. The probable reason for the state of being uninformed about the smear test increasing the risk of not knowing about the existence of the HPV vaccine is that physicians are advised to run the smear test only when there is a symptom. It is thought that the woman's awareness of the existence of the HPV vaccine is raised when the physician informs the patient about the existence of the HPV vaccine and recommends her to get the vaccination at the time of explaining the patient's result of the smear test.

The advantage of the study is that it is the first data about the region where the study was conducted, while the disadvantage is that it does not cover the entire eastern Anatolia region.

To conclude, being of young age, having ≤11 years of formal education, insufficient income of the household, and being uninformed about the smear test were found to be the risk factors for women not knowing that the HPV vaccine exists.

In this context, the government should include the HPV vaccine in the national vaccination program at the earliest. Visual and auditory advertisements should be initiated to raise awareness about this vaccination among the public. Especially, "family physicians"

and “family health midwives” who provide services in primary care should inform the young, less-educated, and poor women about the vaccination and monitor them closely.

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

Ethical Approval
Ethics committee approval was obtained from Kafkas University Faculty of Health Sciences Non-Invasive Research Ethics Committee for the study (Date: 30.10.2020, Number: 81829502.903/100). The study was conducted in accordance with the Helsinki Declaration.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ERKEK MEME KANSERİ CERRAHİ DENEYİMİMİZ

OUR MALE BREAST CANCER SURGERY EXPERIENCE

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Öz

Amaç
Erkek Meme Kanseri nadir görülen bir hastalıktır. İnsidansı son yıllarda artmakta, ancak sağkalım sonuçları iyileşmektedir. Prospektif randomize çalışmaların eksikliği nedeniyle, kadın meme kanseri kılavuzlarına göre tedavisi ve takibi yapılmaktadır. Ancak kendine özgü anatomi ve fizyolojisi nedeniyle hastalığın seyrinde farklılıklar olabileceği düşünülmektedir.

Gereç ve Yöntem
Süleyman Demirel Üniversitesi Tıp Fakültesi Cerrahi Onkoloji Kliniği' nde Ocak 2011 – Ocak 2020 tarihleri arasında meme kanseri nedeniyle opere edilen erkek hastaların verileri retrospektif olarak değerlendirildi. Adenokarsinom dışındaki meme patolojileri çalışmaya dahil edilmedi.

Bulgular
Çalışmaya 7 hasta dahil edildi. Aynı süre içerisinde 847 kadın hasta görülürken, erkek hasta oranı % 0,8 idi. Tüm hastalara total mastektomi ile birlikte level 1, 2, 3 aksiller diseksiyon yapıldı. Patoloji sonuçları değerlendirildiğinde; 1 (% 14,2) hastada evre 1, 2 (% 28,5) hastada evre 2, 3 (% 42,8) hastada evre 3, 1 (% 14,2) hastada evre 4 hastalık olduğu görüldü. Genel sağkalım ortanca değeri 48 ay (min: 35 - max: 53) olarak saptandı.

Sonuç
Erkek meme kanserinin aynı evredeki hastalarda prognozunun kadın meme kanserinden daha kötü olmadığı gösterilmiştir. Ancak geç tanı, tedaviye uyumsuzluk ve standardizasyon problemleri nedeniyle pratikte daha kötü prognoz söz konusudur. Erkek meme kanseri konusunda farkındalığın artırılması ve yapılacak geniş çaplı prospektif randomize çalışmalar neticesinde tedavinin erkek meme kanserine özgü, standardize edilmesi ile daha iyi sonuçlara ulaşılabileceğini düşünüyoruz.

Anahtar Kelimeler: Erkek meme kanseri, Mastektomi, Meme kanseri

Abstract

Objective
Male breast cancer is a rare disease. Its incidence has increased in recent years, but survival outcomes are improving. Due to the lack of prospective randomized trials, it is treated and followed up according to female breast cancer guidelines. However, it is thought that there may be differences in the course of the disease due to its unique anatomy and physiology.

Materials and Methods
The data of male patients who were operated for breast cancer in Süleyman Demirel University Medical Faculty Surgical Oncology Clinic between

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January 2011 and January 2020 were evaluated retrospectively. Breast pathologies other than adenocarcinoma were not included in the study.

Results
Seven patients were included in the study. During the same period, 847 female patients were seen, while the rate of male patients was % 0,8. Level 1, 2, 3 axillary dissection was performed in all patients along with total mastectomy. When the pathology results were evaluated, it was seen that 1 (14,2 %) patient had stage 1, 2 (28,5 %) patient stage 2, 3 (42,8 %) patient stage 3, 1 (14,2 %) patient stage 4 disease. The median overall survival was 48 months (min: 35 - max: 53).

Conclusion
It has been shown that the prognosis of male breast cancer in patients at the same stage is not worse than female breast cancer. However, in practice, the prognosis is worse due to late diagnosis, non-compliance with treatment and standardization problems. We believe that better results can be achieved by raising awareness about male breast cancer and standardizing treatment specific to male breast cancer as a result of large - scale prospective randomized trials.

Keywords: Male breast cancer, mastectomy, breast cancer

Giriş

Erkek meme kanseri (EMK) tüm meme kanserlerinin yaklaşık % 1' ini ve erkeklerde kanserle ilişkili ölümlerin % 0,1' inden azını oluşturmaktadır. Yaklaşık olarak 100.000 erkekten 1' inde görülmektedir[1]. Nadir görülmekle birlikte son yıllarda kadın meme kanseri (KMK) gibi insidansı artmakta, ancak sağkalım sonuçları iyileşmektedir[2]. Yüksek oranda hormon reseptör pozitifliği, düşük Her - 2 pozitifliği nedeniyle postmenopozal KMK ile benzer olarak değerlendirilmektedir[3]. EMK' nin nadir görülmesi nedeniyle geniş çaplı prospektif randomize kontrollü çalışmaların eksikliği görülmektedir. Bu nedenle EMK' ne yönelik takip ve tedavi yöntemleri spesifikleşmemiştir ve KMK kılavuzları kullanılmaktadır. Ancak erkek hastalarda meme anatomisi ve hormon üretim fizyolojisindeki farklılıklar nedeniyle, hastalığın seyri ve tedavi seçiminde KMK' ne özgü yaklaşımların yeterli olmayabileceği düşünülmektedir[4]. Bu çalışmada kliniğimizin erkek meme kanseri cerrahisi deneyimi paylaşılmıştır. Kısıtlı veriye sahip olduğumuz, nadir görülen bir hastalık olan EMK hakkında literatüre katkıda bulunmayı amaçlıyoruz.

Gereç ve Yöntem

Süleyman Demirel Üniversitesi Tıp Fakültesi Cerrahi Onkoloji Kliniği' nde Ocak 2011 – Ocak 2020 tarihleri arasında meme kanseri nedeniyle opere edilen erkek hastaların verileri retrospektif olarak değerlendirildi. Adenokarsinom dışındaki meme patolojileri çalışmaya dahil edilmedi.

Yaş, şikayet süresi, tümör lokalizasyonu, görüntüleme ve biyopsi yöntemleri, tanıdan operasyona kadar geçen süre, metastaz varlığı ve neoadjuvan tedavi " Preoperatif Veriler " olarak değerlendirildi. Hastalık evresi, tümör boyutu, aksiller lenf nodu tutulumu, hormon reseptörü ve Her - 2 varlığı, Ki - 67 oranı, lenfovasküler invazyon, nükleer grade, duktal karsinoma in situ varlığı, cilt ve pektoral kas tutulumu, yapılan ameliyat türü " Peroperatif Veriler " olarak değerlendirildi. Genel sağkalım süresi, hastalıksız sağkalım süresi, adjuvan tedaviler ve hastalığın mevcut durumu " Postoperatif İzlem Verileri " olarak değerlendirildi.

Tüm hastalara meme görüntüleme yöntemlerinin ardından patolojik tanı elde edilerek, metastaz taraması açısından 18 - FDG Pozitron Emisyon Tomografisi / Bilgisayarlı Tomografi uygulanmış. Hastalık evrelemesinin ardından operasyon uygulanmış. Klinik evreleme Tümör – Node - Metastaz (TNM) sınıflandırma sisteminin 8. baskısına göre yapıldı. Her - 2 pozitifliği 2 + ve 3 + olanları kapsadı. Ki - 67 oranı % 15' in altında " düşük " olarak değerlendirildi. Tüm hastalar taburculuk sonrası medikal onkoloji ve radyasyon onkolojisi bölümleri ile konsülte edilmiş. " Postoperatif İzlem Verileri " hastane veri tabanından temin edildi. Takipsiz hastaya telefonla ulaşılarak dış merkezde de kontrollerine gitmediği öğrenildi, takip amacıyla kliniğimize gelmesi gerektiği iletildi.

Sayısal veriler " ortanca " veya " ortalama " olarak değerlendirildi. Örneklem yetersizliği nedeniyle istatistiksel analiz yapılamadı.

Bulgular

Süleyman Demirel Üniversitesi Tıp Fakültesi Cerrahi Onkoloji Kliniği' nde 10 yıllık takipte meme kanseri nedeniyle 7 (% 0,8) erkek hasta, 847 kadın hastanın opere edildiği saptandı. Çalışmada erkek meme kanseri nedeniyle opere edilen hastalar değerlendirildi. Hastaların yaş ortalaması 63,7 (min: 50 - max:

80) olarak bulundu. Şikayetlerin başlamasından tanı anına kadar geçen sürenin ortanca değeri 3 ay (min: 2 hafta - max: 6 ay) olarak bulundu. Tanı anından operasyona kadar geçen süre ortalama 2 hafta idi. Kitle lokalizasyonu 6 hastada sağ meme, 1 hastada sol memede ve 6 hastada subareolar, 1 hastada alt dış kadran yerleşimliydi. Tüm hastalara preoperatif meme ultrasonografisi yapılmış, mamografi yalnızca 1 hastaya yapılmış. Altı hasta tru - cut biyopsi ile doku tanısı alırken, dış merkezden tarafımıza yönlendirilen hastanın eksizyonel biyopsi ile doku tanısını almış olduğu öğrenildi. Preoperatif PET - BT ile evreleme sonrası 1 hastada metastaz (multipl kemik metastazı) saptanmış. Hiçbir hastaya neoadjuvan tedavi verilmediği gözlendi.

Patoloji sonuçları değerlendirildiğinde 1 (% 14,2) hastada evre 1, 2 (% 28,5) hastada evre 2, 3 (% 42,8) hastada evre 3, 1 (% 14,2) hastada evre 4 hastalık olduğu görüldü. Tüm hastalara total mastektomi ile birlikte level 1, 2, 3 aksiller diseksiyon uygulanmış. 1 hasta dışında tüm hastalarda pektoral kasın rezeke edildiği saptandı. İki (% 28,5) hastada T1, 5 (% 71,4) hastada T2 tümör görülürken, T3 ve T4 görülmedi. Dört hastada deriye bitişik tümör, 1 hastada pektoral kas invazyonu görüldü. Aksiller diseksiyon sonucu yalnızca 1 (% 14,2) hastada aksiller lenf nodu tutulumu olmadığı görüldü. Rezeke edilen lenf nodu sayısı ortanca değeri 29 (min: 17 - max: 36) idi. Tüm hastalarda invaziv duktal karsinom olduğu saptandı. Yedi (% 100) hastada ER / PR pozitifliği saptandı. İki (% 28,5) hastada Her - 2 pozitifliği saptandı. Ki - 67 oranı ortanca değerinin % 15 (min: 2 - max: 25), 2 (% 28,5) hastada düşük oranda olduğu görüldü. İki (% 28,5) hastada luminal A, 5 (% 71,4) hastada luminal B tipi tümör saptandı. Altı (% 85,7) hastada nükleer grade 2, 1 (% 14,2) hastada nükleer grade 1 olarak görüldü. Beş (% 71,4) hastada lenfovasküler invazyon saptandı. 4 (% 57,1) hastada duktal karsinoma in situ birlikteliği saptandı.

Genel sağkalım verileri değerlendirildiğinde ortanca değer 48 ay (min: 35 ay - max: 53 ay) olarak saptanmıştır. 1 hastada mortalite izlendi. Semptomatik beyin metastazı olan hasta, postoperatif 39. ayda beyin ameliyatı sonrası postoperatif dönemde intrakranial hemoraji nedeniyle exitus olmuş. Hastalıksız sağkalım ortanca değeri 47 ay (min: 38 ay - max: 53 ay) olarak saptandı, takipsiz 1 hasta ve tanı anında metastatik olan 1 hasta değerlendirmeye dahil edilmedi. Bir hastanın postoperatif takibi bırakıp, adjuvan tedavi almadığı görüldü, kliniğe kontrole çağrıldı. Adjuvan tedavi olarak 4 (% 57,1) hastaya kemoterapi, 6 (% 85,7) hastaya hormonoterapi ve 4 (% 57,1) hastaya radyoterapi verildiği izlendi. Verilerin toplanması esnasında takipli 6 hasta arasından 3 (% 50) hastanın hastalıksız olarak takibi devam etmekteydi. Exitus olan hastada beyin ve akciğer metastazı, 1 hastada akciğer ve multipl kemik metastazı, tanı anında da multipl kemik metastazı olan hastada yeni kemik metastazlarının olduğu saptanmış.

Tartışma

Erkek meme kanseri tanı yaşı KMK' den daha ileri yaştadır. Sıklıkla 6. dekattan sonra tespit edilmektedir. Çalışmaların çoğunda ortalama tanı yaşı 60 ile 68 yaşları arasındadır[5]. Çalışmamızda literatür ile uyumlu olarak ortalama tanı yaşı 63,7 olarak tespit edilmiştir. Hormon düzeyindeki değişikliklerin EMK üzerinde etkin olduğu düşünülmektedir. Bununla birlikte EMK' de kalıtımsal faktörler KMK' ne oranla daha etkindir. EMK tanısı alan hastaların % 15 - 20' sinin ailede meme veya over kanseri öyküsü olduğu ve yaklaşık % 10' unda kalıtsal meme kanserine yatkınlık oluşturan gen mutasyonu saptanmıştır. Özellikle BRCA 2 kalıtsal EMK ile en sık ilişkilendirilen mutasyondur[2]. EMK hastalarında kontralateral meme kanseri riski 30 - 90 kat artarken, KMK hastalarında bu risk 2 - 4 kat artmıştır[6, 7]. Ayrıca EMK' de kontralateral meme kanserinin dışında ikinci primer kanser görülme riskinin de arttığı gösterilmiştir[8].

Erkek meme kanseri sıklıkla subareolar yerleşimli ağrısız kitle olarak ve sıklıkla sol memede görülmektedir[9]. Çalışmamızda literatürden farklı olarak hastalık % 85,7 oranda sağ memede görülmüştür. Erkeklerde meme volümünün azlığı nedeniyle, kitlelerde cilt veya göğüs duvarı invazyonu, lenfadenopati erken dönemde görülebilmektedir. Bu da EMK' nin ileri evrede tanısına neden olmaktadır. Yapılan birçok çalışmada erkeklerde hastalık tanısının yüksek evrede alındığı ve prognozun daha kötü olduğu gösterilmiştir[10, 11]. Ancak evre ve yaşa göre eşleştirildiklerinde erkeklerin kadınlardan daha iyi prognoza sahip olduğunu gösteren çalışmalar mevcuttur[12, 13].

Günümüzde görüntüleme yöntemlerinin yaygınlaşması ve farkındalığın artmasıyla, son 30 yıla göre EMK evre 1 ve 2' de tespit edilme oranları artmıştır. 1985' de evre 1 - 2 % 60 tespit edilirken 1995' de % 70' e, 2015 yılı çalışmasında % 82' ye yükselmiştir[14]. Batı ülkelerinde erken tanı oranında artış saptanırken Burkina Faso ve Fas' ta yapılan çalışmalarda % 80 - 88 oranlarında evre 3 - 4 hastalık saptanmıştır[15,16]. Çalışmamızda literatürden uyumsuz olarak evre 1 - 2 hastalık % 42,8 oranında bulundu. Kliniğimizde karşılaştığımız hasta grubu ve imkanları göz önüne alındığında, Afrika ülkelerindeki gibi sağlık hizmetine ulaşım problemi veya görüntüleme yöntemlerinde ye-

tersizlik söz konusu değildir. EMK erken tanısındaki yetersizliğin farkındalık eksikliğine bağlı olduğunu düşünmekteyiz.

Erkek meme kanseri erken tanı oranının artışı, adjuvan tedavi yöntemlerindeki gelişmelerle birlikte sağkalım sonuçlarında önceki yıllara oranla iyileşme saptanmaktadır. Bu gelişmelerle birlikte uygulanan cerrahi yöntemler de değişmektedir. KMK' nde olduğu gibi sentinel lenf nodu örneklemesi güvenle uygulanabilmektedir[4]. 1970' li yıllara kadar EMK' nde radikal mastektomi uygulanmaktaydı, sonrasında modifiye radikal mastektomi EMK cerrahisinde standart haline gelmiştir. Ancak son dönemde meme koruyucu cerrahi uygulama oranları artmıştır[17]. Yakın tarihli çalışmalarda erkek hastalarda olumlu benlik imajını korumak için meme koruyucu cerrahiye eğilim olduğu ve meme koruyucu cerrahinin olumlu psikososyal sonuçlarla ilişkili olduğu gösterilmiştir[18, 19]. Çalışmamızda 6 hastaya radikal mastektomi, 1 hastaya modifiye radikal mastektomi uygulandı. Radikal mastektomi uygulanan 1 hastada pektoral kas invazyonu saptandı.

Erkek meme kanserinde yüksek hormon reseptör pozitifliği nedeniyle adjuvan tedavinin önemli bölümünü hormonoterapi içermektedir. Çalışmamızda tüm hastalarda hormon reseptörü pozitifliği saptandı ve takipli tüm hastalara tamoksifen ile hormonoterapi verildi. Hormonoterapide tamoksifen standart tedavi olarak görülmektedir[2]. Aromataz inhibitörlerinin KMK' ndeki etkinliği göz önüne alınarak EMK' nde yapılan çalışmalarda aynı etkinlik izlenmemiştir[20, 21]. Bunda erkek ve kadın hormon fizyolojisinin farklılığı etkindir. Erkek hastalarda östrojenin yaklaşık % 20' sinin testisten direkt olarak salınımı nedeniyle aromataz inhibitörlerinin etkinliği sınırlanmaktadır ve bu nedenle standart tedavide önerilmemektedir. Ancak tamoksifen direnci olan hastalarda kullanımı söz konusudur ve medikal veya cerrahi orşektomi gerektirmektedir[4]. Tamoksifenin hormonoterapideki üstünlüğünün yanında, erkek hastaların tamoksifene kötü uyumu problem teşkil etmektedir[22]. Yapılan çalışmalarda erkek hastalarda azalmış libido, kilo alımı, sıcak basması ve değişen ruh hali saptanmıştır[23]. Buna bağlı olarak kadın hastalara oranla tedaviye devam oranının oldukça düşük olduğu saptanmış, daha kötü sağkalımla ilişkili olduğu gösterilmiştir[24, 25]. Çalışmamızda hasta grubunda tedavi başlanan tüm hastalar uyum ile devam etti.

Adjuvan tedavi yöntemlerinden özellikle radyoterapi konusunda, literatürdeki çalışmalara bakıldığında standardizasyon sağlanamadığı görülmektedir. Meme koruyucu cerrrahi uygulandığı halde radyoterapi uygulanmayan hastaların yanında, KMK kılavuzlarına göre radyoterapi endikasyonu olmayan hastalarda radyoterapi uygulandığı da görülmektedir [26-28]. Bunda EMK' nin daha agresif seyir gösterdiği fikrinin etkin olduğu düşünülmektedir. KMK' nde 5 cm' lik tümör sınırlamasının, EMK' nde meme anatomisi göz önüne alındığında ne kadar geçerli olduğu tartışılmaktadır [29]. Hasta grubumuzda takipli 6 hastanın 4' üne radyoterapi uygulandı. Takiplerde lokal nüks saptanmadı.

Erkek meme kanseri nadir olarak görülmektedir. Son dönem çalışmalarda aynı evredeki hastalarda prognozunun kadın meme kanserinden daha kötü olmadığı gösterilmiştir. Ancak geç tanı ve tedaviye uyum, standardizasyon problemleri nedeniyle pratikte daha kötü prognoz söz konusudur. Son yıllarda erken tanı, adjuvan tedaviler ve yeni cerrahi yöntemlerle daha iyi sağkalım sonuçları ve daha yüksek yaşam kalitesi mümkün olabilmektedir. Bu nedenle erkek meme kanseri konusunda farkındalığın artırılması ve yapılacak geniş çaplı prospektif randomize çalışmalar neticesinde tedavinin erkek meme kanserine özgü, standardize edilmesi gerektiğini düşünüyoruz.

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OLGU SUNUMU CASE REPORT

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PERICARDIAL EFFUSION AND CARDIAC TAMPONADE AFTER COVID-19 VACCINE: A RARE CASE REPORT

COVİD-19 AŞISI SONRASI GELİŞEN PERİKARDİYAL EFÜZYON VE KARDİYAK TAMPONAD: NADİR BİR OLGU SUNUMU

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Öz

Bilinen kronik hastalık öyküsü olmayan 44 yaşında kadın hasta, covid-19 aşısı (Pfizer-Biontech) sonrası taşikardi ve nefes darlığı şikayetiyle acil servise başvurdu. Kardiyolojiye konsülte edilen hastanın tansiyonu: 80/40 mmHg. Ekokardiyografi (EKO): Ejeksiyon Fraksiyonu %65, en geniş noktasında kalbi çepeçevre saran ve sağ kalp boşluklarını diyastolde kollabe ederek tamponad kliniğini oluşturan 5 cm perikardiyal efüzyon (PE) mevcuttu. Hastaya acil perikardiyosentez uygulandı. Hastanın perikardiyal sıvı içeriği seröz idi. Perikardiyosentez sonrası klinik durumu stabilize olan hasta koroner yoğun bakım ünitesinde takip edildi. Takiplerinde kontrol ekoda perikardiyal efüzyon izlenmedi. Hastanın Covid-19 a yönelik yapılan PCR sonuçları negatifti. Hasta kardiyoloji poliklinik kontrolü ile taburcu edildi.

Anahtar Kelimeler: Covid-19, Perikardiyal efüzyon, Aşı, Kardiyak tamponad

Abstract

A 44-year-old female patient with no known history of chronic disease was admitted to the emergency room with tachycardia and shortness of breath after covid-19 vaccine (Pfizer Biontech). The blood pressure of the patient who was consulted to cardiology: 80/40 mmHg. Echocardiography (ECHO): Ejection Fraction was 65%, pericardial effusion (PE) was present at its widest point, 5 cm encircling the heart, collapsing the right heart cavities in diastole, forming the clinic of tamponade. Emergency pericardiocentesis was applied to the patient. Pericardial fluid content of the patient was serous. The patient, whose clinical stability was stabilized after pericardiocentesis, was followed in the coronary intensive care unit. No pericardial effusion was observed in the control echo duringfollow-up. Thepatient's PCR results were negative. The patient was discharged with cardiology outpatient control.

Keywords: Covid-19, Pericardial effusion, Vaccine, Cardiac tamponade

Introduction

Since the outbreak of clusters of viral pneumonia due to the novel coronavirus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) in Wuhan, China in December 2019 (1).Coronavirus disease 2019 primarily infects the lungs, has demonstrated a wide spectrum of clinical manifestations and may even extend to other organs such as the cardiovascular system. Mounting evidence is now supporting that COVID-19 affects the cardiovascular system with acute cardiac injury, high risk of thrombosis including

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stroke, pulmonary embolism, and acute coronary syndrome. Conversely, very few attention has been paid to pericardial effusion (PE). Only very fewcase reports described PE, revealed by chest pain or a deterioration of general condition. (2-6).There is no case report of pericardial effusion and tamponade developing after covid-19 vaccine (pfizer-biontech) in the literature.

Case Report

A 44-year-old female patient with no known history of chronic disease was admitted to the emergency room with tachycardia and shortness of breath after covid-19 vaccine (Pfizer Biontech). The blood pressure of the patient who was consulted to cardiology: 80/40 mmHg. Electrocardiography (ECG) findings were consistent with sinus tachycardia, heart rate of 102 beats/min and low voltage (Figure 1). In the patient's laboratory parameters; ALT 65.5 U/L (reference: 0-33 U/L), AST 57 U/L (reference:0-32 U/L), CRP 28.44 mg/L (reference: 0-5 mg/L)) was detected. Troponin and other blood values of the patient were within normal reference ranges. Ejection Fraction was 65%, pericardial effusion (PE) was present at its widest point, 5 cm encircling the heart, collapsing the right heart cavities in diastole, forming the clinic of tamponade (Figure 2a, 2b, 2c). Emergency pericardiocentesis was applied to the patient. Pericardial fluid content of the patient was serous. The patient, whose clinical stability was stabilized after pericardiocentesis, was followed in the coronary intensive care unit. No pericardial effusion was observed in the control echo during follow-up. The patient's PCR result was negative. The patient was discharged with cardiology outpatient control.

Discussion

Although the pathophysiology is not completely understood, current literature attributes the development of pericardial effusion in COVID-19 patients to the systemic inflammatory response and subsequent cytotoxic and immune-mediated effects related to SARS-COV-2 (7). The pathogenesis of COVID-19 myopericarditis is yet unresolved.

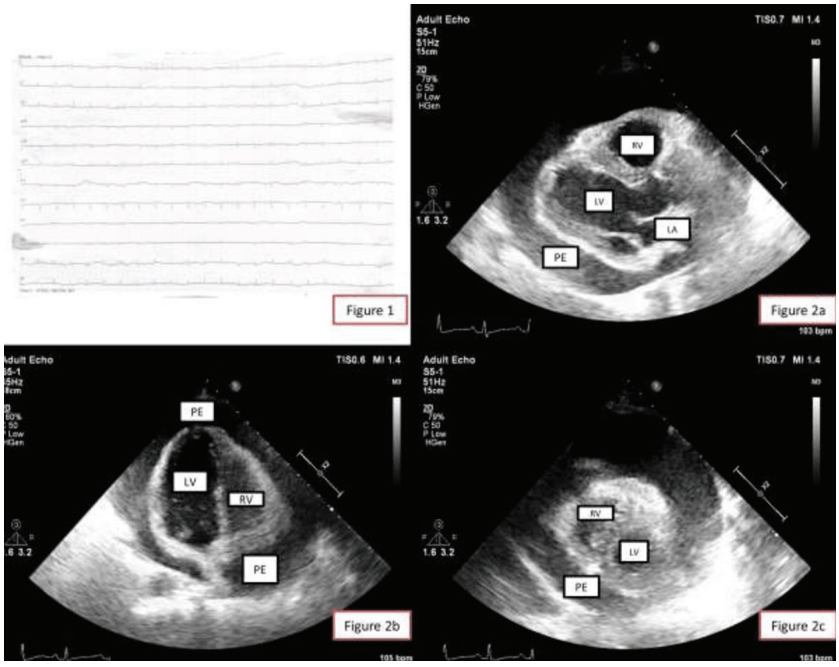

Figure 1
Electrocardiography (ECG) findings were consistent with sinus tachycardia, heart rate of 102 beats/min and low voltage.
Figure 2a
Echocardiography (ECHO): Parasternal long axis, pericardial effusion (PE)
Figure 2b
Apical four chambers, collapsing the right heart cavities in diastole, forming the clinic of tamponade.
Figure 2c
Short axis, Pericardial effusion surrounding the heart.

Abbreviations: *LV: Left ventricle RV: Right Ventricle LA: Left Atrium PE: Pericardial Effusion.*

Two predominant mechanisms could be relevant (8). This could lead to a cytokine storm syndrome and a direct myopericardial lesion by inflammatory cell infiltration, similarly to COVID-19 direct pulmonary lesions (10). First, the heart affinity of the virus could be explained by SARS-CoV-2 S protein direct binding to human angiotensin-converting enzyme 2 (9) present in the human heart, which allows for a cellular infection. Indirectly, myopericarditis could follow a viral replication and dissemination in the blood, from day 7 up to 1 month after symptoms beginning. There is no case report of pericardial effusion and tamponade developing after covid-19 vaccine (pfizer-biontech) in the literature. Whether these vaccines, which were approved for immediate use due to the pandemic, have such effects requires further research and similar case examples.

Conclusions

Presumably, there is a higher incidence of COVID-19-related cardiac diseases such as pericarditis that can manifest from minimal PE to cardiac tamponade. But there is no case report of pericardial effusion and tamponade developing after covid-19 vaccine (pfizer-biontech) in the literature. Cardiologists and emergency physicians should be aware and extensively look for PE at the time of the COVID-19 outbreak. Whether these vaccines, which were approved for immediate use due to the pandemic, have such effects requires further research and similar case examples. However, it should not be forgotten that the only and effective way to prevent the pandemic is stil vaccines, even though there are these and similar side effects.

Limitations

Serological and biochemical analysis of the pericardial fluid taken from the patient could not be performed due to technical problems.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Consent to Participate and Publish

Written informed consent to participate and publish was obtained from individual who included in the study.

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Author Contributions

All of the authors contributed planning, conduct, and reporting of the work. All contributors are responsible for the overall content as guarantors.

Data Availability

No additional data applicable

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DERLEME REVIEW

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OSTEOARTRİT YÖNETİMİ, YAŞAM KALİTESİ VE HEMŞİRENİN DESTEKLEYİCİ ROLÜ

OSTEOARTHRITIS MANAGEMENT, PATIENTS' QUALITY OF LIFE AND NURSE'S SUPPORTIVE ROLE

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Öz

Osteoartrit tüm dünyada en yaygın görülen kas-iskelet sistemi hastalıklarından biridir. Özellikle vücut ağırlığını taşımakla sorumlu olan kalça, diz, ayak gibi eklemlerde oluşan progresif enflamatuar deformatif süreç beraberinde ağrı, hareket kısıtlılığı, fonksiyonel kısıtlanma gibi yaşam kalitesini de olumsuz etkileyen pek çok semptomun ortaya çıkmasına neden olmaktadır. Osteoartrit hastalarında fiziksel sorunların yanı sıra depresyon, anksiyete, umutsuzluk, sosyal izolasyon gibi pek çok psikososyal sorunlar da görülebilmektedir. Osteoartritin yönetimi, bu sorunların kapsamlı bir şekilde değerlendirilmesini, akut alevlenmelerin azaltılmasını, komplikasyonların önlenmesini ve ilerlemesini geciktirmeyi sağlayarak yaşam kalitesini optimize etmeye odaklanır. Bu amaçla hastalara uygun farmakolojik ve farmakolojik olmayan girişimleri uygulama ve öz yönetimlerinin desteklenmesi gerekmektedir. Bu nedenle, sağlık profesyonellerinden hemşirelerin osteoartrit hastasına bütüncül yaklaşması, hastaların yaşam kalitesi başta olmak üzere yaşamın tüm boyutlarında optimal iyilik halini sürdürmeye yönelik girişimleri önem arz etmektedir.

Anahtar Kelimeler: Hemşirelik, Osteoartrit, Yaşam Kalitesi

Abstract

Osteoarthritis is one of the most common musculoskeletal diseases worldwide. The progressive inflammatory deformative process that occurs especially in joints that are responsible for carrying body weight, such as hips, knees, and feet, causes pain and functional limitation hat negatively affect the quality of life. In addition to physical problems, many psychosocial problems such as depression, anxiety, hopelessness and social isolation can be seen in osteoarthritis patients. The management of osteoarthritis focuses on optimizing quality of life by providing a comprehensive assessment of these issues, reducing acute exacerbations, preventing complications and delaying their progression. For this purpose, it is necessary to apply appropriate pharmacological and non-pharmacological interventions to patients and support their self-management. For this reason, it is important for nurses to approach patients with osteoarthritis holistically and to attempt to maintain optimal well-being in all aspects of life, especially in patients' quality of life.

Keywords: Nursing, Osteoarthritis, Quality of Life

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Giriş

Genetik, mekanik ya da biyokimyasal faktörlerin etkisiyle ortaya çıkan osteoartrit, özellikle ağırlık taşıyan eklemlerde sinoviyal inflamasyon, progresif kıkırdak yıkımı, kemik osteofit ve subkondral kemik sklerozunun oluşumu gibi sinoviyal membran ve eklem kapsülünün morfolojik değişikliğe uğradığı kronik enflamatuar dejeneratif bir eklem hastalığıdır (1-4). Klinisyenlere göre artrit, eklemlerin enflamasyonu anlamına gelirken, diğer taraftan eklemleri, eklemleri çevreleyen dokuları ve diğer bağ dokularını etkileyen 100'den fazla romatoid hastalık veya durumun tamamını içermektedir (2). Amerika Romatoloji Derneği'ne göre ise, osteoartrit, klinik, fizyolojik, anatomik ve moleküler düzeylerde heterojen özellikler gösteren bir hastalık olarak kabul edilir (5).

Ağırlık taşıyan eklemlerdeki dejenerasyonunun fazlalığından dolayı osteoartritin semptomatik olarak en sık tuttuğu eklem, diz eklemidir (2). Diz ekleminin yanı sıra kalça, omurga, el, ayak ve parmaklar en yaygın tutulumun olduğu diğer eklemlerdir (3). Özellikle dizdeki progresif kıkırdak yıkımı beraberinde hastaların eklem hareket açıklığında kısıtlılığı, şiddetli kronik ağrıyı ve ciddi kas atrofilerini getirmektedir. En yaygın görülen semptomlardan biri olan diz eklemi etrafındaki ağrı, keskin, künt, devamlı ya da aralıklı şekilde olabilmektedir. Fiziksel muayenesi esnasında duyulan eklemlerde sürtünme sesi, sertlik ve şişlik, hareket kısıtlılığı, sabah tutukluğu ve kas güçsüzlüğü yaygın görülen diğer problematik semptomlar arasında yer almaktadır (2, 6).

Osteoartrit Epidemiyolojisi

Eklemleri etkileyen pek çok artrit çeşidi olmasına rağmen en sık görülen türü osteoartrittir. Pek çok kronik hastalık gibi osteoartrit görülme oranı da yaşla birlikte artmakta ve toplumda en fazla 65 yaş üstü kadınları etkilemektedir (3, 7). Kadınlarda görülme oranının %42.1 iken, erkeklerde %31.2 olduğu bilinmektedir (8). Başka bir çalışmaya göre ise dünya genelinde 60 yaş üzerindeki erkeklerin %9.6'sı, kadınların ise %18'inin semptomatik osteoartrit deneyimlediği rapor edilmektedir (9). Radyografik ve semptomatik açıdan değerlendirme yapıldığında, kalça osteoartriti prevalansının sırasıyla %19.6 ve %4.2 (10); diz osteoartriti prevalansının %25.4 ve %15.4 (11, 12); radyografik ayak osteoartriti prevalansının %0.1-%61 (13) olduğu belirtilmiştir. Birleşik Devletlerde 14 milyon kişinin semptomatik diz osteoartritini deneyimlediği, semptomatik osteoartrit deneyimlenen 2 milyondan fazla kişinin 45 yaş altı bireylerden, 6 milyondan fazla kişinin ise 45-65 yaş arası kişilerden oluştuğu belirtilmektedir (14). Türkiye İstatistik Kurumu 2019 verilerine göre ise Türk toplumunda osteoartrit görülme oranının %11.2 olduğu belirlenmiştir (15).

Hastalık Patogenezi

Sinaviyal eklemi oluşturan kıkırdak, ligamentler, eklem kapsülü, subkondral kemik ve sinoviyal doku gibi eklemin tüm komponentlerini etkileyen osteoartrit, genetik, metabolik, mekanik ve biyokimyasal pek çok faktörün etkisiyle birlikte kemik yıkım ve onarımının arasındaki dengenin bozulduğu bir hastalıktır. Özellikle hastalığın ilk evrelerinde kıkırdak fibrilasyonu başlar ve fibrilasyon daha yüzeyel iken hastalığın ilerlemesiyle birlikte derin tabakalara doğru dejenerasyon ilerleyebilmektedir. Dolayısıyla da hastalığın primer değişiklikleri özellikle eklem kıkırdağındaki kaybı, subkondral kemik şekillenmesi ve osteofit oluşumu şeklinde karşımıza çıkmaktadır. Kıkırdak hasarına neden olan en önemli mediyatörler sinoviyal hücreler ve kondrositlerden sagılanan metalloproteinazlardır. Ayrıca interlökin, tümör nekrozis faktör alfa ve interlökin I7 salınımı da osteoartritte oluşan kıkırdak yıkımı sürecine katılan diğer mediyatörlerdir. Kemik kollajen üretiminin bozulması, osteoklastik aktivitenin artması, alkalen fosfataz ve non-kollajen protein üretiminin artmasıyla birlikte subkondral kemikte değişim oluşmaya başlamaktadır. Kıkırdaktaki dejenerasyonun artmasıyla birlikte kıkırdak uç kısımları yırtılarak eklem kısmından parçalar kopmaya başlar ve kıkırdağın kalınlığında azalma olur. Bu durum osteofit oluşumuna sebep olur (3, 6, 16-20).

Risk Faktörleri

Osteoartritin etiyolojisine bakıldığında multifaktöriyel bir hastalık olduğu görülmektedir. Yaş, obezite, cinsiyet, yaşam tarzı, beslenme alışkanlıklarındaki değişim, fiziksel inaktivite, eklem morfolojisi, mesleki zorlanma, propriosepsiyon bozukluğu, eklemde ciddi hasarlara neden olan geçirilmiş travmalar, metabolik disfonksiyon, sirkadiyen ritm, diğer komorbid hastalıkların varlığı ve genetik dispozisyon gibi pek çok etken osteoartrit açısından risk faktörü olarak görülmektedir (3, 21-24). Literatürde, osteoartrit risk faktörleri çeşitli şekillerde gruplandırılmaktadır. Buna göre primer ve sekonder osteoartrit açısından değerlendirme yapıldığında primer osteoartritte bilinen bir neden bulunamazken, sekonder osteoartritin etiyolojisinde travma, enfeksiyon, konjential deformite gibi eklem yıkımından kaynaklı risk faktörlerinin olduğu bilinmektedir. Eklem yıkımının ise yaş, cinsiyet, obezite, mesleki zorlanmalar, spor aktiviteleri gibi faktörlerin etkisiyle arttığı belirtilmektedir (25). Diğer taraftan risk faktörlerini, kişisel risk faktörleri (sosyodemografik özellikler ve aile öyküsü, obezite ve metabolik sendrom, beslenme ve vitamin faktörleri, sigara içme, kemik kitlesi ve kemik yoğunluğu, sosyoekonomik düzey) ve eklem

ile ilişkili risk faktörleri (kemik/eklem yapısı, yaralanma, kas kitlesi ve kas gücü, eklem yükü ve eklem dizilimi, meslek ve fiziksel aktivite durumu, olmak üzere 2 ana grupta ele alan yaklaşım söz konusudur (9, 26, 27). Risk faktörlerinin başka bir sınıflandırma çeşidi ise sistemik ve lokal faktörler olmak üzere iki ana başlıklandırma yapılmasıdır. Sistemik faktörler başlığı altında yaş, cinsiyet, genetik gibi değiştirilemez risk faktörleri, obezite, kemik mineral yoğunluğu ve beslenme kalitesi gibi değiştirilebilir risk faktörleri yer almaktadır. Lokal faktörler başlığı altında ise travma, fiziksel aktivite, mesleki aktiviteler gibi dışsal faktörler ve eklem dizilimi bozukluğu, ligament yetersizlikleri, kas gücü yetersizliği, propriosepsiyon kaybı gibi içsel faktörler yer almaktadır (28). Osteoartrit vakalarının %25'inden fazlasında obezite, diyabet, pulmoner ve kardiyovasküler hastalık, hipertansiyon, metabolik ve kas iskelet sistemi bozuklukları ve depresyon gibi komorbid hastalıklar bulunmaktadır (22).

Yaş: Osteoartritin en güçlü ve majör risk faktörlerinden birisi yaştır. Yaşın ilerlemesiyle birlikte osteoartrit görülme sıklığı, osteoartrit nedeniyle tutulan eklem sayısı artmaktadır. Özellikle 65 yaş üzerindeki bireylerde osteoartrit görülme sıklığı oldukça yüksektir. Yaşla birlikte osteoartrit görülme sıklığının artma nedeni, yaşlanma ile birlikte proteoglikanların yapısında bulunan kondroitin sülfat oranının azalması, keratin miktarının artması, mitokondriyal DNA hasarı ve inflamatuar sitokinlerin de sürece eklenerek kondrosit harabiyeti ile açıklanmaktadır. Kondrosit ve kıkırdak yıkımı ya da hasarı sonucunda reaktif oksijen ürünleri artarak kıkırdak yapısında incelme ve zayıflığa neden olmaktadır. Ayrıca yaşla birlikte doku harabiyeti, fiizksel aktivitenin bozulması, kas atrofilerinin oluşması da osteoartrit riskini artırmaktadır (29).

Cinsiyet: Östrojenin özellikle diz ve kalça kemikleri üzerindeki koruyucu etkisi bilindiğinden ve dolayısıyla da menapoz sonrası östrojen seviyesindeki azalma hastalığa yatkınlığı artırdığı için kadınlarda osteoartrit görülme olasılığı erkeklere kıyasla 2,6 kat daha fazladır. Menapozla birlikte görülen hormonal değişiklikler, kemikten kana kalsiyum emiliminin artmasına neden olur ve bu nedenle kemik kayıpları da artmaktadır (9, 29, 30).

Obezite: Osteoartrit için en önemli risk faktörlerinden diğeri obezitedir. Obezitesi olan kadınlarda osteoartrit riski 4-5 kat artmaktadır. Obezite nedeniyle özellikle diz eklemindeki hasar oldukça fazladır. Vücut ağırlığının artmasıyla birlikte eklem kıkırdağı üzerinde mekanik stresin de arttığı bilinmektedir. Diz eklemindeki mekanik yüklenmenin dışında obezite postürün bozulması, yürüyüş ve fiziksel aktivitenin azalması ve diz ekleminin biyomekanik yapısının bozulması ile de ilişkili olduğundan osteoartrit riskini artırmaktadır (9, 28-31).

Eklem bozuklukları ve travma: Özellikle diz osteoartritinin yaygın görülen diğer nedenlerinden birisi travmadır. Eklem içinde oluşan tekrarlayıcı nitelikteki majör ya da minör travmalar, ligament ve menisküste oluşan hasar/yırtık ya da geçirilmiş ameliyat öyküsü eklemlerin dejenerasyon sürecini hızlandırarak osteoartrit görülme oranını artırmaktadır (9, 32).

Beslenme faktörleri: Diyetle alınan C ve D vitaminleri ile süt ürünlerinin yetersiz olması, serum D vitamini düzeyinin düşük olması, K vitamini seviyesinin düşük olması gibi etkenler osteoartrit görülme sıklığını artırmaktadır. Özellikle E vitamininin kondrositleri olumlu etkileyen ağrıyı giderme özelliği nedeniyle analjezik ihtiyacının azalmasında etkili olduğu bilinmektedir (9, 11, 26, 31, 33).

Genetik faktörler: Diz osteoartritinin önemli belirleyicilerinden olup hastalık yatkınlığının %50'sinden sorumludur. Özellikle distal intelfalingial eklem tutulumu olan annenin kız çocuğunda heberden nodülü görülme olasılığı 2 kat daha yüksek olduğundan osteoartrit yatkınlığını artırmaktadır. Heberden nodülü, Bouchard nodülü, diz ve kalça tutulumunun görüldüğü primer osteoartritte özellikle Heberden nodülü belirgin şekilde görülmekte ve kadınlarda dominant genle taşınmaktadır (29).

Mesleki aktiviteler ve Spor aktiviteleri: Belirli mesleklerde tekrarlayan hareketler eklemlerin harabiyetine yol açarak osteoartrite neden olmaktadır. Kemik mineral yoğunluğunun artırılmasında etkili olan egzersiz yaşlılığın artmasıyla birlikte eklemlerde zedelenmenin artmasına neden olabilmekte, bu nedenle de osteoartrite zemin hazırlamaktadır. Sportif aktivitelerin yanı sıra çiftçi, halı dokuma fabrikalarında çalışan işçiler ve boksörlerde eklemler üzerindeki yükün artması ve eklemlerin zedelenmesi de fazla olduğundan osteoartrit riski artmaktadır (9).

Osteoartrit Tanı ve Tedavisi

Klinikte osteoartrit tanısı, öykü, fiziksel muayene ve radyolojik incelemeler aracılığıyla konulmaktadır. Öyküde özellikle şiddetli eklem ağrıları, sabah tutukluğu/sertliği, hareket kısıtlılığı, krepitasyon, eklem fonksiyonlarının bozulması ve eklemlerdeki şişlik varlığı tanı koymada yardımcı kriterlerden birisidir. Özellikle son ay içerisinde diz ağrısı deneyimlenen gün sayısının fazla olması, eklem hareketi ile krepitasyon varlığının olması, sabah tutukluğunun maksimum 30 dk olması, eklemlerde büyüme olması gibi klinik bulguları açısın-

dan hastanın değerlendirilmesi gereklidir. Aktivite sırasında ortaya çıkan ağrı hastalık ilerledikçe istirahat esnasında dahi ortaya çıkmakta ve hastaneye en çok başvuru şikayetini oluşturmaktadır. Yapılan fiziksel muayenede görülen krepitasyon, eklem hareketlerinin ağrılı olması, varus/valgusta görülen instabilite, özellikle quadriceps kasında görülen atrofi durumu ve kas güçsüzlüğü, eklem deformasyonları ve fonksiyon kaybının görülmesi tanı koymada yardımcı olan diğer seçenekten birisidir. Özellikle diz osteoartriti için çekilen radyografik tetkiklerde görülen subkondral kist ve sklerozun varlığı, tipik sinoviyal bulguları ve osteofit oluşumunun görülmesi ile de tanı konulabilmektedir. Ayrıca, kıkırdak yıkımıyla dolaylı ilişkili olan eritrosit sedimentasyon hızı, C-Reaktif protein, tam kan değerleri, romatoid faktör, antinükleer antikor gibi laboratuvar değerlerinin de takip edilmesi ve değerlendirilmesi gereklidir (25).

Osteoartrite yönelik direkt bir tedavi şekli olmamakla birlikte semptomların azaltılması, hastalık ilerleyiş hızının yavaşlatılması, hastalığın hastanın mobilitesi ve yaşam kalitesi üzerindeki olumsuz etkilerinin azaltılması ve hastanın sağlık bakım ihtiyaçlarının azaltılmasına yönelik tedavi seçenekleri uygulanmaktadır. Buna göre non-farmakolojik ve farmakolojik tedavi kombinasyonu Avrupa Osteoporoz, Osteoartrit ve Kas-İskelet Sistemi Hastalıklarının Klinik ve Ekonomik Yönleri Derneği (European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, ESCEO) tarafından yapılan güçlü önerilerden biridir ve özellikle diz osteoartritinin tedavisinde anahtar rol oynamaktadır (34).

ESCEO tarafından güçlü şekilde önerilen hasta eğitimi, aşırı kilolu olunması durumunda kilo verme ve aerobik ve güçlendirme egzersizlerinden oluşan egzersiz programının düzenlenmesi ve yaşam tarzı değişiklikleri osteoartritin tedavisinde önemli yer tutan non-farmakolojik yaklaşımlardır (34-37). Ayrıca tedavinin önemli parçasından diğeri istirahat etme ve travmatik durumlardan mümkün olduğunca uzak durmadır. Hastalığın akut döneminde hastanın istirahatinin sağlanması gereklidir. Hastanın aktivitesi esnasında ise yürüteç, baston, tabanlık, ortotik cihazlar gibi yardımcı araç-gereç kullanımı olası travmaların önlenmesinde önem taşımaktadır. Diz breysleri kullanılarak valgus deformiteleri önlenebilmektedir (25). Bunun dışında, EULAR grubununda (European League Against Rheumatism- Roamtizmaya Karşı Aprupa Birliği) önermiş olduğu tedavi modaliteleri düşünüldüğünde lazer ve spa uygulaması, pulse elektromanyetik alan tedavisi, akupunktur, bitkisel ilaçlar ve vitamin destekleri ve Transkutanöz Elektriksel Sinir Stimülasyonu (TENS) gibi non-farmakolojik yöntemler de kullanılmaktadır (25, 38).

EULAR tarafından önerilen farmakolojik tedavi yöntemleri ise parasetamol, non-steroid anti-inflamatuar ilaçlar, opioid analjezikler, hormon replasman tedavisi, kondritin ya da glukoamin gibi yavaş etkili semptomatik ilaçlar, psikotrop ilaçlar, non-steroid anti-inflamatuar içeren topikal ajanların kullanılmasıdır. Bunun dışında intra-artiküler ve artroskopi, osteotomi, diz replasmanı gibi cerrahi tedavi yöntemleri de kullanılmaktadır (38).

Osteoartiritte Yaşam Kalitesi ve Etkileyen Faktörler

Osteoartrit olan bireylerde sürekli hissedilen ağrı ve sertliğe bağlı gelişen fiziksel kısıtlılık bireyin günlük yaşam aktivitelerini yerine getirememeye, öz bakım yetersizliğine, fonksiyonel durumunda kötüleşmeye, sosyal ilişkilerde bozulmaya neden olarak yaşam kalitesinde azalmaya neden olabilmektedir (39). Bireylerin, yaşlandıkça vücut fonksiyonlarının yavaşlaması ve komorbidelerin görülmesi osteoartrit hastalarında uzun süreli sakatlık derecesini arttırır (40,41).Yaşlanan nüfustaki kas-iskelet sistemi rahatsızlıklarını önlemeye ve tedavi etmeye yönelik her türlü müdahalenin önceliklerinden biri yaşam kalitesinin iyileştirilmesi olmalıdır (40, 42).

Osteoartriti olan yaşlı hastalarda yaşam kalitesini etkileyen birçok faktör bulunmaktadır. Yapılan çalışmamalarda yaş, cinsiyet, medeni durum, eğitim durumu, klinik evre ve obezitenin yaşlı hastaların yaşam kalitesini etkilediği belirtilmektedir (41). Osteoartrit 40 yaşından önce nadir görülmekte olup ileri yaş hastalığıdır. Yaş, fiziksel durumu etkileyen bir faktördür ve ilerleyen yaş ile ortaya çıkan eklem kıkırdağındaki değişiklikler osteoartrit görülme sıklığını arttırır. Osteoartriti olan hastalarda yapılan bazı çalışmalarda kadınların yaşam kalitesi puanlarının erkeklere göre daha düşük olduğu belirmektedir (41). Kadınlarda menapoz sonrası östrojen hormonu eksikliği osteoartrit gelişiminin hızlanmasında önemli rol oynamaktadır (43).

Osteoartrit olan bireylerin eğitim düzeyi, öncelikle hastalığın erken tespiti ve yönetimi için düzenli sağlık muayenesi davranışını etkileyen faktörlerdendir. Eğitim düzeyinin özellikle osteoartrit gelişimini yavaşlatmak ve semptomların yaşam kalitesi üzerindeki olumsuz etkisini azaltmak için bireylerin öz yönetim konusunda farkındalığının daha yüksek olmasında etkili olduğu belirtilmektedir (39, 44). Hastalığın klinik evresi, hem fiziksel hem de ruhsal sağlıkla ilişkilidir ve hastalığın ciddiyetini yansıtan önemli bir risk faktörüdür. Klinik evre ilerledikçe hastalık semptomları ve semptomla-

rın şiddeti farklılık gösterir. Osteoartriti olan bireylerde evre ilerledikçe ağrı artar, eklem deformitesi ve fonksiyon kaybı gelişir (44). Yapılan bazı çalışmalarda klinik evre arttıkça ağrının arttığını belirtmiştir. Artan bu semptomların tümü, bireylerin sosyal aktivitelerini, fiziksel fonksiyonlarını ve yaşam kalitesini etkiler (40). Dünya genelinde giderek artan obezite prevelansı osteoartrit hastalığının gelişmesi ve tedaviye yanıt sürecindeki cevap için değiştirilebilir bir risk faktörüdür (45). Obezite ile eklem kıkırdağına yapılan baskı artar, semptomlar kötüleşir ve günlük yaşam aktivitelerinde kısıtlanmalar meydana gelir (46). Obezite, eklemlerdeki yükü arttırarak sadece mekanik sorunlara değil hormonal sistemi de etkileyerek metabolik nedenlerle de OA gelişimi riskini arttırdığı belirtilmektedir (47). Obezitesi olan bireylerin daha düşük yaşam kalitesine sahip olduğu belirtilmektedir (48, 49). Kanıta dayalı kılavuzlara ek olarak kilo kaybının OA semptomlarını azalttığını gösteren birçok çalışma mevcuttur (38, 45, 50). Toplumda yaşla birlikte artan kas-iskelet sistemi rahatsızlıkları, fonksiyonel durumu, yaşam kalitesini ve sağlık bakım maliyetlerinin artmasına neden olmaktadır. Yaşam kalitesinin arttırılmasında eğitim, kilo yönetimi, düzenli egzersiz etkili olmaktadır. Yaşlı bireylerin günlük yaşamlarındaki beslenme, ulaşım, boşaltım, sosyal ilişkideki birçok zorluk yaşam kalitesini olumsuz etkilemektedir. Bu nedenle osteoartritin öz yönetiminde yaşam kalitesinin iyileştirilmesi öncelik olmalıdır.

Osteoartritin Yönetimine Hemşirenin Rolü

Hemşirelerin, osteoartili hastaların yaşam kalitelerinin artırılmasında önemli destek rolleri bulunmaktadır. Hemşirelerin, eklem ağrısı ve sertliği olan hastaların eklem hareketliliğini korumalarına ve geliştirmelerine yardımcı olmaları ve eklem yaralanmasını en aza indirmeleri gereklidir. Hastaların kilolu olması durumunda, kilo verme, egzersiz yapma, sağlıklı yaşam tarzı davranışlarının kazanılması ve sürdürülmesi hususunda teşvikinin sağlanması ve kullanılan ilaçların etki ve yan etkileri konusunda eğitim ve danışmanlık hizmetini alması açısından destekleyecek olan sağlık profesyonellerinden birisi hemşiredir. Bunun yanı sıra hemşirelerin öz yönetim becerilerini geliştirmelerine yönelik yaptıkları hasta eğitimi aracılığıyla, hastaların semptomları yönetme ve yaşam tarzlarını değiştirme becerisini geliştirdiği gösterilmiştir (51).

Uluslararası Osteoartrit Araştırma Derneği, OA yönetiminin amaçlarının ağrı yönetimi ve optimal fonksiyonel yeteneği içerdiğini belirtmiştir. Bu amaçla, kalça ve diz OA'sının yönetimine ilişkin kılavuzlar geliştirilmiştir. Bu kılavuzlara dayalı hemşirelik müdahaleleri, ağrıyı reçete edildiği gibi yönetmek için uygun ilaçların verilmesini ve hastanın optimal hareketliliği sürdürme ve bağımsız kalma çabalarını kolaylaştırmayı içerir (52). Hastaların bakım ve teavisinden sorumlu olan hemşireler hastaları ile ilgili olarak kas iskelet sistemine odaklanarak hastayı kapsamlı değerlendirmeli ve hastanın kullandığı reçeteli ve reçetesiz olarak kulllandığı bitkisel ve besin takviyeleri ile ilgili olarak da bireyi sorgulamalıdır. Özellikle hastaların yaşadığı en temel semptom olan ağrının şiddeti, hareketlerini engelleme ve hareket aralığı, günlük yaşam aktivitelerini gerçekleştirme durumunu bilmelidir. Hastaya pozizyon verme, dizleri veya kalçaları desteklemek için yastık kullanarak eklemi ve çevresindeki kasları gevşetmeye yardımcı olma gibi uygulamalar ile hasta konforunu artırabilmektedir. Hastanın kilo vermesi ya da uygun diyet almasını sağlamaya yönelik diyetisyene ve hastaya uygun egzersiz rejiminin belirlenmesi, yardımcı araç ve gereçlerini kullanımında yardım için fizik tedavi uzmanına yönlendirme gibi konularda da hastaya destek olabilmektedir. Ayrıca hastanın yaşadığı çevrenin fiziksel ve sosyal faktörlerinin inceleyerek ergonomik yapının buna göre düzenlenmesine yardımcı olabilir. Örneğin; bireyin kullandığı klozet ve sandalye yüksekliklerinin arttırılması, merdiven ihtiyacını azaltma, kaymayan düzgün yer kaplamalarının uygulanması, uzun saplı ayakkabı çekeceği ve süpürge kullanımını sağlanması gibi girişimler yapılabilir. Hasta hareket ederken, günlük yaşam aktivitelerini yaparken hastanın güvenliğinin sağlanarak düşmelerden ve yaralanmalarından korunmasına yardımcı olurlar (52, 53).

Hemşireler hastaların bağımlılık durumlarını ve tanılarının etiyolojilerini göz önünde bulundurarak hastaya yönelik hemşirelik tanılarını ve girişimlerini belirlemeli ve uygulamalıdır. Başlıca bu hastalara yönelik belirlenebilecek en temel hemşirelik tanıları; Akut Ağrı/Kronik Ağrı; Fiziksel Harekette Bozulma ve Yaralanma Riskidir (53).

Sonuç

Sonuç olarak yaşlı bireylerde yaygın olarak görülen osteoartrit, ağrı, hareket kısıtlılığı, fiziksel kapasitede azalma, günlük yaşam ve sosyal aktivitelerin kısıtlanmasına ve çalışma kapasitesinde azalmaya neden olur. Bu hastalarda bilgi eksikliği, tedavilerinin uzun sürmesi, finansal kısıtlılıklar, etkisiz motivasyon ve egzersiz uygulamaları, motivasyon eksikliği gibi sorunlar ihmal ve memnuniyetsizliğe, yaşam kalitesinde azalmaya neden olmaktadır. Osteoartriti yönetmenin zorluklarından biri, insanlar arasında osteoartritin genel bir yaşlanma prosedürü olduğu ve hastalığın ilerlemesini yavaşlatmak için çok az şey yapılabileceği algısıdır. Bu nedenle hemşirelerin hastaları hastalık yönetimi konusunda eğitim, ağrının giderilmesi, yor-

gunluğun azaltılması, hareketin artırılması, beden bilincinin iyileştirilmesi ve bireysel bakımda yeterlilik kazandırılması gibi destek rolleri ile hastanın yaşam kalitesinin artırılmasının sağlamaları son derece önemlidir (53).

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DERLEME REVIEW

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WHAT IS EPIGENETIC CHANGE AND WHAT DO WE KNOW ABOUT ITS IMPACT ON MOLECULAR PATHOLOGIC MECHANISMS OF THE DISEASES?

EPİGENETİK DEĞİŞİKLİK NEDİR VE HASTALIKLARIN MOLEKÜLER PATOLOJİK MEKANİZMALARI ÜZERİNDEKİ ETKİSİ HAKKINDA NE BİLİYORUZ?

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Öz

Epigenetik değişiklik, kromatin modifikasyonu, DNA metilasyonu, histon modifikasyonu, kromatin düzenleyici proteinler ve kodlamayan RNA'lar yoluyla meydana gelmekte olup, kalıcı genotipik değişiklik olmaksızın gerçekleşen fenotipik bir değişikliği ifade eder. Transkripsiyon sonrası m6A RNA metilasyonu da yeni tanımlanmış bir epigenetik mekanizma olup, yeni bir tanısal biyobelirteç ve potansiyel terapötik hedef olduğuna inanılmaktadır. Epigenetik değişikliklerin birçok nonneoplastik ve neoplastik hastalığın gelişiminde ve ilerlemesinde önemli bir rol oynadığı iyi bilinen bir gerçektir. Bu nedenle epigenetik değişiklikler tanısal ve prognostik açıdan değerlidir. Öte yandan kişiselleştirilmiş tıp ve hedefe yönelik tedavi yaklaşımlarının gelişmesiyle birlikte epigenetik değişiklikleri hedefleyen tedavi stratejileri birçok hastalık için umut verici bir alan haline gelmektedir. Bu derlemenin amacı, epigenetik değişikliklerin mekanizmaları ve neoplastik / nonneoplastik hastalıkların gelişimindeki rolleri hakkında klinisyenlere ve laboratuvar tıbbı uzmanlarına daha sonraki araştırmalar için yardımcı olabilecek bilgiler sağlamaktır.

Anahtar Kelimeler: Epigenetik, Hastalık, Nonneoplastik, Neoplastik

Abstract

Epigenetic change refers to a phenotypic alteration without permanent genotypic change, which occurs through chromatin modification, DNA methylation, histone modification, chromatin-regulating proteins and non-coding RNAs. Post-transcriptional m6A RNA methylation is also a newly described epigenetic mechanism and believed to be a new diagnostic biomarker and potential therapeutic target. It is a well-

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known fact that epigenetic changes play a significant role in the development and progression of several nonneoplastic and neoplastic diseases. Therefore, epigenetic changes are of value in diagnostic and prognostic terms. On the other hand, with the development of personalized medicine and targeted treatment approaches, treatment strategies targeting the epigenetic changes are becoming a promising area for many diseases. The aim of this review is to provide information about the mechanisms of epigenetic changes and their role in the development of neoplastic and nonneoplastic diseases, which may be helpful for the clinicians and laboratory medicine experts for further researchs.

Keywords: Epigenetic, Disease, Nonneoplastic, Neoplastic

Epigenetic Change

Conrad Waddington proposed the concept of "epigenetics" in 1942 and this term expresses the phenotypic change without genotypic alteration [1]. Epigenetic changes consist of numerous chemical arrangements that can tell the genome what to do and what not to do. When the function of DNA changes epigenetically, the genome is marked and the DNA sequence does not change. These changes can be inherited through mitosis and meiosis [1, 2]. Expression of the gene appears to be more important rather than which genes are inherited [3]. Epigenetic modification mechanisms include; chromatin modification, DNA methylation, histone modification, chromatin regulating proteins and non-coding RNAs [2]. Recently, post-transcriptional modification of RNA is shown to play an important role in the development of several diseases as an epigenetic change mechanism. N6-methyladenine (m6A) RNA modification is the most investigated mechanism, and is involved in physiological conditions. Its dysfunction is thought to be involved in the development of various neoplastic and nonneoplastic diseases. More than 60% of all RNA modifications occur via methylation and m6A is the most abundant chemical modification in eukaryotic messenger RNA, which acts in regulation of cell fate, proliferation, metabolism and biogenesis of several tumor types [4, 5].

The Difference Between Epigenetic Change and Mutation

Epigenetic change is a mechanism that alters the expression of a gene without an alteration in the nucleotide sequence as opposed to mutations in which the nucleotide sequence is permanently altered [6]. Our genetic code is permanently determined, but acquired epigenetic traits are plastic and partially reversible. Epigenetic changes can occur due to the environmental exposure, but they do not occur equally in all periods of life. The most critical life periods are known as preconception, early development, pregnancy and early life periods [7]. Epigenetic changes play a key role in the control of cellular processes such as differentiation, embryogenesis, X chromosome inactivation and genomic suppression by regulating the expression of genes and changing protein levels. In many studies it has been shown that epigenetic regulations cause susceptibility to diseases. Errors in these mechanisms can cause cancer, neurological diseases, autoimmune diseases and various developmental disorders [8].

Mechanisms of the Epigenetic Change

Chromatin modification

Chromatin is a complex architectural chromosome unit consisting of DNA and proteins. It forms the physical basis of epigenetic changes. Chromatin modification is an important mechanism, which affects transcription factor binding as an important component of epigenetic modification, and differential gene expression between cell types [9]. The complex structure of chromatin is divided into two categories as heterochromatin and euchromatin. Heterochromatin has a condensed chromatin structure (30 nm chromatin fibril) and is inactive for transcription while euchromatin has a loose chromatin structure (11 nm chromatin fibril) and is active for transcription [10]. The location of the heterochromatin and euchromatin structure within the nucleus is also different. While the periphery of the nucleus is enriched for heterochromatin, euchromatin is located in the center of the nucleus, suggesting that the location of a gene within the nucleus is important for its epigenetic function [1].

The transcription initiating region called promoter and the regions that increase the speed of transcription, called enhancer, are the functional regions of our genome. Chromatin acts as a filter in terms of binding transcription factors to these functional regions. In order to activate a gene and copy it into mRNA, the chromatin in both the promoter and enhancer regions must be accessible. Therefore, in most

circumstances gene activation requires the transition from heterochromatin to euchromatin [11]. Chromatin remodeling factors play an important role in this transition by binding to transcription activators (Figure 1). Meanwhile, the opposite of these processes occur if these factors are linked to transcription suppressors to inhibit the transcription [2, 12]. While some of the epigenetic mechanisms enable genes to be silenced by converting chromatin into the form of heterochromatin, some of them enable genes to be activated by converting it into euchromatin form. Mechanisms of chromatin modification that can cause epigenetic changes include DNA methylation/unmethylation, nucleosome arrengement, histone methylation, dense/loose nucleosome packaging, and regulation of the nuclear organisation [1].

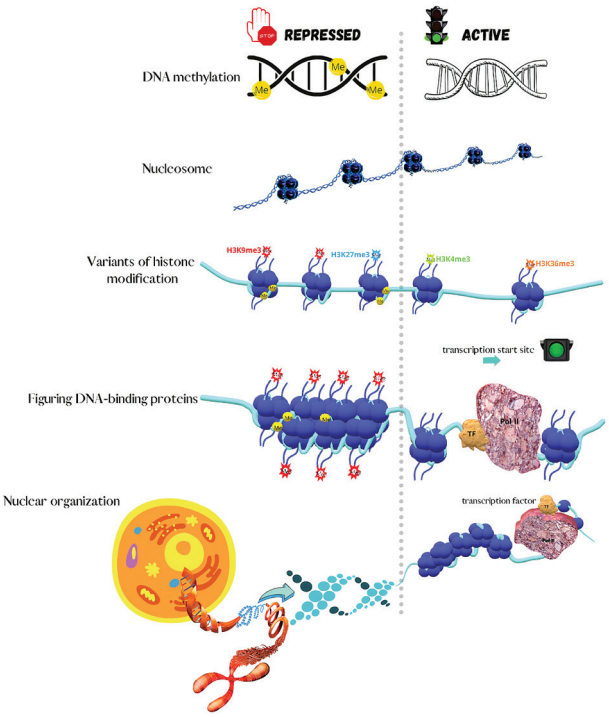

Figure 1
Mechanisms of the epigenetic remodeling of chromatine-associated with active or inactive gene expression.

DNA methylation

DNA methylation, an important epigenetic control mechanism involved in the protection of genome integrity, transcriptional regulation and developmental processes, is a covalent modification formed by the attachment of a methyl group to the carbon atom in the 5' position of the cytosine-guanine (CpG) dinucleotides [13]. DNA methyltransferase enzymes (DNMT) are responsible for this chemical reaction. This enzyme enables the methyl group transfer from S-adenosyl-methionine, which is the source of the methyl group, to the cytosine ring [14]. Although DNA methylation shows a conserved epigenetic inheritance in newly formed DNA strands after replication, it can be reversed through ten-eleven translocation (TET) enzymes [2].

Methylated cytosines constitute approximately 1% of the nucleotides in the whole genome and approximately 75% of the CpG dinucleotides. The regions including dense CpG dinucleotides throughout the genome are called CpG islands [15]. Approximately 60% of gene promoter regions in the human genome are associated with CpG islands. CpG islands in these regions are mostly unmethylated, except for some special tissues that show differentiation. CpG island methylation often leads to transcriptional suppression, which plays an important role in physiological processes such as determining which allele (maternal or paternal) to be expressed in a diploid cell (genomic imprinting or X chromosome inactivation) [13, 16]. DNA methylation-mediated gene silencing can occur directly by preventing binding of transcription factors or indirectly by binding methyl-CpG binding proteins to methylated DNA [17, 18].

In addition to the CpG islands, DNA methylation also occurs in CpG shores (regions containing less dense CpG dinucleotides), gene bodies and non-coding intragenic regions and act in transcriptional regulation. Methylation of the CpG shores leads to transcriptional suppression, and the methylation status in these regions in particular is thought to cause different DNA methylation patterns. In contrast, DNA methylation in gene body regions is usually observed in highly expressed genes and is associated with increased gene expression. DNA methylation in non-coded intragenic regions is predominantly seen in repetitive elements such as satellite DNA, SINE, LINE, and contributes to the protection of genome integrity [16, 19].

Histone modification

The DNA is organized around an octameric structure called nucleosome core particle, which consists of H2A, H2B, H3, H4 histone proteins. DNA fragments consisting of 145-147 bps are wrapped around this structure 1.65 times. H1 has a histone binding feature and contributes to chromosome structure outside the nucleosome (Figure 2). The histone structure is globular except for the N-terminal tail protruding from the nucleosome to communicate with other nucleosomes. This tail contains 130 amino acids.

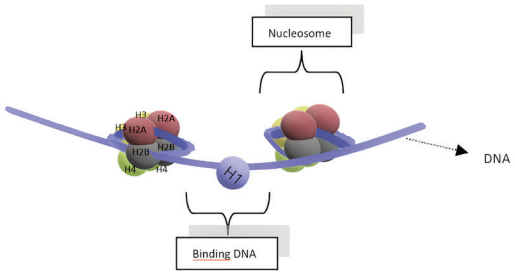

Figure 2
The structure of the Histone.

Histone modification processes neutralize acidic residues, weaken the connection between DNA and chromatin, and facilitate chromatin's accessibility [20]. The main post-translational modifications in the histone tail are acetylation, methylation, phosphorylation, ubiquitination, sumoylation and ADP-ribosylation [21].

Histone acetylation is a mechanism that provides transcriptional activity to the gene by neutralizing the positive charge of histone in the lysine tail and weakening the histone-DNA link. Histone acetylation is regulated by two antagonist enzymes, histone acetyl transferase (HAT) and histone deacetylase (HDAC). The HAT enzyme acetylates the lysine tail of the histone, weakening the histone – DNA connection. HDAC, on the other hand, reverses this mechanism and suppresses transcription by stabilizing the chromatin structure [20]. Histone methylation takes place in the lysine or arginine residue, causing condensation or relaxation of the chromatin relative to the modified residue site. Two antagonist enzymes, histone methyl transferase and histone demethylase, are available for histone methylation. The exact position of the methylated domain and the degree of methylation differ in transcriptional effect [22]. Histone phosphorylation results in a negative charge to the histone by adding a phosphate group to the serine, threonine and tyrosine residue [23]. ADP Ribosylation is a reversible process that takes place in the form of poly-/mono-ADP ribosylation in glutamate and arginine residues. Ubiquitination is a broad type of covalent modification unlike other identified modifications. Sumoylation is a type of modification related to ubiquitination and antagonizes the acetylation and ubiquitination mechanism that takes place in the same lysine region [21].

Chromatin-regulating proteins and non-coding RNAs

Chromatin-regulating protein complexes can cause epigenetic changes by changing the interaction between DNA and histones. They shift the nucleosomes into new positions by catalyzing the movement of histone octamers on DNA to enable transcription factors reach the specific regions in DNA. They also enable the interaction of specific DNA regions with proteins that regulate transcription and form non-nucleosome regions. These protein complexes can be brought into DNA via transcription activators and repressors. Thus, the initiation of transcription can be achieved or prevented by changing the sequences of nucleosomes [2].

The newest class of molecules that contribute to epigenetic changes are non-coding RNAs (ncRNA). Non-coding RNAs can be divided into two categories according to their functions as regulator RNAs and housekeeping RNAs, while regulator RNAs are also divided into two categories according to their size. Those larger than two hundred nucleotides are called as long non-coding RNAs (lncRNA), while those shorter than 200 nucleotides are called short-chain non-coding RNAs (siRNAs, miRNAs and piRNAs) [24]. Recent studies have revealed that ncRNAs play an important role in epigenetic changes and can regulate expression at the gene or chromosome level [25]. Short, 19-25 nucleotides long, miRNAs partially or completely match with the 3' regions (3'UTR) of target mRNAs to regulate gene expression through post-transcriptional silencing and/or degradation [26]. It has been shown that more than 30% of human genes, which act in cell growth, cell cycle regulation, apoptosis, differentiation, and cellular response to the stress, are targeted by the miRNAs [25]. Expression of miRNA is tissue-specific, and thanks to its ability to target post-transcription gene silencing, it can cause epigenetic changes by directly regulating gene transcription [27]. It has been shown that the siRNA, produced from long double-stranded RNA molecules that can be cut into 19-24 nucleotide-long RNA fragments by the Dicer enzyme is capable of transcriptional gene silencing in cells through DNA methylation and histone modification [28]. LncRNAs are known as key players for the gene regulation in a variety of human pathologies due to their impact on regulating the heterochromatin formation, histone modifications, DNA methylation and gene silencing. LncRNAs act by binding to transcription regulating proteins, including histone modification enzymes and chromatin remodeling factors. However, they are also known to act by binding to miRNAs or regulate mRNAs by binding directly [26].

Epigenetic Changes in Nonneoplastic Diseases

Genetic and neurodegenerative diseases

Epigenetic changes can lead to genetic diseases, particularly through increased or decreased DNA methylations in related genes [29]. One of the best example of these diseases is Silver-Russell syndrome, which is associated with epigenetic changes in the region that includes the IGF2/H19 domain of the telomeric section (11p15.5) on chromosome 11. Silver-Russell syndrome presents with intrauterine and postnatal growth retardation, facial dysmorphism, body asymmetry and nutritional problems in affected patients. Beckwith-Wiedemann, Prader-Willi and Angelman syndromes are also associated with epigenetic changes [29].

Neurodegenerative diseases, including Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, and Huntington's disease, are considered to be the second leading cause of death by replacing cancer around the world in 2050 [30]. It is not sufficient to explain the pathophysiology of neurodegenerative diseases with only genetic. In addition to genetic alterations, epigenetic changes appear to be involved in their pathogenesis. Although there are similarities among these diseases in terms of proteopathies formed by genetic and misfolded proteins, important epigenetic changes such as decreased DNA methylation in the temporal neocortex are also observed as in Alzheimer's [29-31]. Cytosine methylation and histone modification continue from early brain development to older age. Epigenetic changes in genes that initiate neurodegeneration in the substantial region include; hypomethylation, histone hypoacetylation and accompanying misfolded protein accumulation [29, 30].

Immunological diseases

The mechanisms of rearrangement of antigen receptors, allelic exclusion, and response to pathogens, which are characteristics of immune cells, are epigenetically controlled [32]. Internal and external environmental factors, such as smoking, nutrition, viral infection, and exposure to chemicals, contribute to the development of autoimmune diseases by regulating some genes through epigenetic mechanisms [33]. Various studies of systemic lupus erythematosus (SLE) have shown increased expression of integrin *ITGAL, CD40LG, Perforin 1, CD70, IFN gamma receptor 2, MMP14, Lipocalin 2*, and *rRNA* (18S and 28S) gene promoters by hypomethylation [34]. Hypomethylation and decrease in acetylation in synovial cells in rheumatoid arthritis (RA) cause excessive expression of inflammatory cytokines in synovial fluid. *IL-6* promoter gene hypomethylation in mononuclear cells in RA patients lead to the B cell response and increased inflammation [34]. In multiple sclerosis (MS), protein-arginine deaminase type 2 (*PAD2*) promoter region is hypomethylated. Overexpression of *PAD2* induces myelin imbalance and chronic inflammation [35].

Unlike SLE and RA in type 1 diabetes mellitus, hypermethylation activity is increased due to the changes in homocysteine metabolism. *CTLA4, TGF-ß, NF-κB, p38* mitogen-activated protein kinase, toll-like receptors and *IL-6* genes, which are associated with autoimmune mechanism and inflammation in lymphocytes, have been observed to increase H3K9me2. It is also known that the H3K4 and H3K9 modification is associated with hyperglycemia-associated gene expression [34]. Increased expression of miR-21, miR-34a and miR-146a in pancreatic islets increases the level of proinflammatory cytokines leading to beta cell failure [36].

Asthma and allergic diseases are characterized by an exaggerated immune reaction. Evidence about the efficacy of epigenetic mechanisms in this reaction is increasing. Various environmental factors such as air pollution, cigarette smoke, diet during pregnancy and vitamin D level also play a role in the development of these diseases by affecting epigenetic mechanisms. Atopy and asthma related genes (*IFN-γ, IL4, IL13, IL17*) and regulatory T cell related genes (*FOXP3, Arginase, iNOS*) are sensitive to epigenetic regulation. It has been observed that DNA demethylation in CpG regions of the *IFN-γ* gene induces IFN-γ. MiR-145 is also important for the proinflammatory process in patients with allergic respiratory tract [37].

Psychiatric diseases

In psychiatric disorders, DNA methylation and histone modifications have been shown to be important for neural and glial cell differentiation and gene regulation during brain development. They are also involved in the regulation of neuroplasticity, memory formation, emotional response, and neurogenesis in adulthood [38]. It is known that glucocorticoid hormone expression increases as a result of the stimulation of the hypothalamus-pituitary-adrenal gland (HPA) axis in response to stress in patients with depression. Overstimulation of the HPA axis is associated with glucocorticoid receptor down-regulation. DNA methylation in the glucocorticoid receptor gene was detected in postmortem studies. Increased brain-derived neurotrophic factor methylation

and increased H3K4me3 levels in synapsin genes in the prefrontal cortex have also been detected [38, 39]. GABAergic dysfunction, related to the basic cognitive symptoms, plays an important role in the pathogenesis of schizophrenia. The expression of *RELN* and *GAD1* genes (GABAergic genes) were shown to be decreased by hypermethylation and H3K4me3 modification [38, 40].

Epigenetic Changes in Neoplastic Diseases

Cancers of the gastrointestinal tract

In colorectal carcinogenesis, the silencing of tumor suppressor genes (TSG) such as *CDKN2A*, *MLH1* and *APC* by promoter methylation and activation of protooncogenes such as *HRAS* and *cMYC* by hypomethylation are the main epigenetic mechanisms [41]. Colorectal cancers are divided into three groups as chromosomal instable, microsatellite instable (MSI) and CpG islet methylator phenotype (CIMP). The most common mechanism in MSI tumors is the *MLH1* gene promoter methylation [42]. CIMP tumors develop as a result of inactivation by CpG islet methylation in the TSG promoter. LncRNA also affects cancer-related genes such as *WNT, TGF-B, EGFR* and *TP53* by different mechanisms. MiR-200, miR-143, mirRNA-145, miRNA-34a and let7 family have been reported as tumor suppressor miRNAs, while miR-21, miR-31, miR-34b and miR-34c have been reported as miRNAs with oncogenic effects [43].

DNA hypermethylation is also seen in EBV-associated gastric cancers, which are also defined as the CIMP phenotype in the stomach, and MSI tumors. DNA methylation affects the pathogenesis of gastric carcinoma through extrinsic (Helicobacter Pylori, inflammation, smoking, diet, age and physical activity) and intrinsic mechanisms. Helicobacter pylori inflammation has been associated with hypo- and hypermethylation of the gastric mucosa. EBV causes hypermethylation due to its pathogenic effect. Additionally, demethylating loss of TET1 is often present in MSI tumors exhibiting the gastric CIMP phenotype [44].

Many epigenetic mechanisms, including miRNA and DNA methylation, effect the esophageal carcinogenesis. Thirty-eight miRNAs were reported to be upregulated, while 74 were reported to be downregulated in esophageal adenocarcinomas [45]. Many studies have shown that miR21 has an effect on *PTEN* in esophageal squamous cell carcinomas and Barret adenocarcinomas. *CDX2* methylation has also been reported to effect the carcinogenesis [46].

Malignancies of the central nervous system

Among the central nervous system tumors, glioblastomas and ependymomas constitute the group of tumors whose epigenetic mechanisms are more elucidated. An epigenetic classification was made based on DNA methylation profiles in these two tumor groups. According to this classification, higher DNA methylation rates have been detected in tumors with the CIMP phenotype [47]. Global DNA hypomethylation and gene-specific hypermethylation, generally lead to genomic instability and silencing of TSGs in gioblastoma [48]. Global DNA hypomethylation occurs due to the decreased expression of DNMT3B in glioblastomas and is thought to contribute to tumorigenesis by silencing some genes. O6-methyl guanine-DNA methyl transferase (*MGMT*), is the most frequently suppressed gene in this way. Decreased MGMT levels, have been associated with 1p/19q codeletion, *IDH* and *TP53* mutations, and is blamed for shorter disease-free survival and resistance to treatment [47, 49].

Tumor suppressor genes such as *RB, CDKN2A, PTEN, TP53* and genes involved in apoptosis such as Ras association domain family 1A (*RASSF1A*) and *CASP8* are the other hypermethylated genes [48]. In addition, increased levels of miR-21 and miR-26a silence the TSGs, while decreased levels of miR-124, miR-128 and miR-451 contribute to tumorigenesis by stimulating proliferation and invasion ability [48].

Endocrine system malignancies

It is known that many genes related to regulation of cell proliferation and differentiation contain epigenetic changes in thyroid tumors, which are the most studied tumors in terms of epigenetic mechanisms among endocrine system tumors. Studies examining methylation profiles have found differences in gene methylation patterns in different thyroid carcinoma groups [50].

It has been reported that the *PTEN* gene, which inhibit the PI3K/Akt pathway, is frequently hypermethylated in papillary thyroid cancers (PTC) and follicular thyroid cancers (FTC). Coexistence of *BRAF* mutation in PTCs with hypermethylation of TSGs such as tissue suppressor of metalloproteinase enzyme (TIMP3) and death-associated protein kinase (DAPK) has been observed [50]. This association was found to be associated with aggressive clinicopathological parameters such as extrathyroidal spread, presence of lymph node metastasis and advanced stage [51]. Hypermethylation of the *RASSF1A* gene has mostly been reported in FTCs and anaplastic thyroid

carcinomas (ATC), leading to uncontrolled cell proliferation by stimulating the MAPK pathway, which is an important pathway in thyroid carcinogenesis. However, in studies examining the status of DNA methylation in the whole genome, it has been reported that global hypomethylation in gene promoters in ATCs is a more common epigenetic change than hypermethylation [52].

Non-coding RNAs also play a role in the tumorigenesis in thyroid carcinomas. MiR-21, miR-146b and miR-204 levels found to be associated with the degree of differentiation in thyroid tumors. There are studies reporting that increased miR-6 levels in PTCs are associated with advanced stage and aggressive course [51]. Decreased levels of miR-200 and miR-30 were found in ATCs in relation to epithelial mesenchymal transition and increased invasiveness [53].

Melanoma

It has been shown that a large group of genes are methylated in melanomas [54]. Among the TSGs that are reported to be hypermethylated most frequently in the process of melanoma development and progression are retinoic acid receptor-beta2 (*RAR-beta 2*), *RASSF1A, CDKN2A, PTEN* genes [55]. The transformation of 5 methyl cytosine to 5-hmc by TET enzymes (basic DNA demethylation mechanism) is an important epigenetic process affecting melanoma progression. Decreased levels of TET enzymes are also a more common finding in melanomas than in benign nevi [56]. Histone hypoacetylation is another epigenetic mechanism that leads to suppression of the TSGs in melanomas. Levels of EZH2 protein, a subunit of histone modifying enzymes, increase in the melanocytic nevus-melanoma spectrum [56]. In recent studies, it has been shown that increased levels of miR-221 and miR-137 are responsible for stimulation of cell proliferation, while miR-204 and let-7a are responsible for cell migration and invasion in melanomas [57].

Lung cancer

Epigenetic changes are responsible for silencing of TSGs and activation of oncogenes in lung cancer [58]. Smoking causes DNA methylation changes. Hypermethylation is observed in CpG islands, which constitute approximately 75-80% of the promoter regions of the genes in lung cancers. *MLH1* hypermethylation, most commonly defined in colorectal cancers, has also been identified in non-small cell lung cancer. *DAPK1* and *CDKN2A* promoter hypermethylation are common changes in lung carcinomas. Hypermethylation has been identified in more than 700 genes in lung cancers. Among these; *APC, PTEN, RASSF1A, MGMT, SHOX2, SEPT9, RARB2* and *E-cadherin* are the most frequently hypermethylated genes [19]. Histone modifications have been found more frequently in the *EGFR, KRAS, NRAS, MYC, ERBB2* and *MET* genes in lung cancer [59]. Studies have shown that a large number of miRNAs play a role in the development and progression of lung cancer. MiR-21, one of the most well-regulated miRNAs, inactivates oncogenes such as *RAS* and *MYC*. On the other hand, miR-34 plays a role in gene expression by creating tumor suppressing effect through p53. In addition, miR-21, miR-183, miR-126 and miR-155 were found to be associated with poorer prognosis in lung cancers [60]. Metastasis-associated lung carcinoma transcript 1 (MALAT1) lncRNA was found to be upregulated in lung cancers. It has been reported that TINCR lncRNA is down-regulated in lung adenocarcinoma and squamous cell carcinoma (SCC) when compared to normal tissues, while SNHG1 is upregulated in SCCs. The absence of SNHG1 has been found to inhibit tumor invasion and metastasis [61].

Head and neck cancers

The best defined epigenetic changes in head and neck SCCs is DNA methylation. Promoter hypermethylation has been detected in many genes in these tumors, and the most known ones are the genes that affect the *APC, MGMT, DAPK1, CDKN2A, RASSF1, EDNRB, Cadherin* family and the WNT signaling pathway. In these genes, methylation contributes to tumor development by causing loss of expression [19, 62]. Athough histone modifications are rare in head and neck cancers, H3K4, H3K9 and H3K27 methylation has been reported in oral SCCs [63]. Numerous miRNAs with increased or decreased expressions in tumors of different localization in the head and neck region have been reported [64].

Breast cancer and gynecological malignancies

A relatively small number of genes are frequently hypomethylated in breast tumors. In contrast, more than 100 genes have been shown to be hypermethylated in the CpG promoter region, and they play critical roles in apoptosis, cell cycle regulation, angiogenesis, invasion, metastasis, and hormonal signaling [65]. *CCND2* and *CDKN2A*, which act as cell cycle regulators, have been found to be widely methylated. *APC, TWIST* and *HOXA5*, which play a key role in the apoptosis, are silenced by DNA hypermethylation. *Estrogen receptor alpha* and progesterone receptor (*PgR*) are also frequently methylated. In addition to protein-encoding genes, it has been shown that tumor

suppressor miRNAs can also be silenced by DNA methylation in breast cancer cells [27]. It has also been shown that histone modification by demethylases play a role in the development of breast cancer through the Wnt1/Beta-catenin pathway [66]. The reduction of H3K9 trimethyl demethylase JMJD2B (component of the H3K4-specific methyltransferase) inhibits tumor growth by preventing estrogen-induced G1/S transmission [67].

MiRNAs are generally down-regulated in breast cancer. Depletion of the let-7 miRNA family in breast cancer leads to increased tumor development. MiRNAs, which are associated with high proliferative activity index (let-7c and let-7d), PgR status (let-7c), and positive lymph node status (let-7f-1, let-7a-3 and let-7a-2) have been defined [68]. In addition, miR-15/16 has been shown to be downregulated in breast cancer, leading to abnormal expression of *BCL2* [69]. However, amplification of some miRNAs, such as increased invasiveness and lung metastasis associated miR-21 overexpression, have also been identified in breast cancer [27].

Epigenetic changes such as hypermethylation of specific gene promoters have also been described in ovarian and endometrial cancers, which are the most common gynecological malignancies. Promoter hypermethylation of TSGs, such as *BRCA1* and *RASSF1A* is more frequent in ovarian cancers than they are in non-neoplastic tissues, causing genomic instability by inhibiting *BRCA1* function. In addition, chromatin regulating proteins also cause epigenetic changes in ovarian cancers [70]. Promoter hypermethylation is the most common epigenetic mechanism in endometrioid endometrial cancers. Epigenetic changes in TSGs cause microsatellite instability in 20-35% of endometrioid cancers, leading to alterations in the DNA repair, apoptosis, transcriptional regulation and signal transduction associated genes. The silencing of TSGs usually occur via *MLH1* promoter hypermethylation in endometrioid cancers. Epigenetic changes are less significant in non-endometrioid endometrial cancers [71].

Prostate cancer and malignancies of the urinary system

DNA hypomethylation, which can lead to structural and functional changes in the genome, has been observed in prostate cancer cells. Gene-specific hypomethylation has a role in invasion, metastasis and cell cycle control in prostate cancer. DNA hypermethylation is the most common and well-known epigenetic change in prostate cancer as well as in other cancers. Hypermethylated genes play critical roles in various biological processes, including DNA damage repair, signal transduction, adhesion, hormonal transmission, apoptosis, invasion, metastasis, and cell cycle control [27]. Changes in histone modifications have been shown to play an important role during prostate carcinogenesis by facilitating the activation of genes that enable cell growth and survival, and by silencing TSGs. Prostate cancer cells are enriched with H3K4me3, which is associated with the activation of genes such as BCL2 [72].

A large number of oncogenic miRNAs, such as miR-15a/16, miR-21, miR-125b, miR-32, miR-26a, miR-196a, miR-181a, miR-25, miR-92/-93, miR-221/-222, miR-488 and let-7i were found to be upregulated in prostate cancer. On the other hand, various tumor suppressor miRNAs, such as miR-101, miR-126, miR -205, miR-31, miR-146a, miR-330, miR-34 set, miR-218, miR-128, miR-203, and miR-200 family were found to be abnormally regulated and silenced [73, 74]. Additionally, miR-34 activation reduce the effect of proteins such as CDK4, CDK6, cyclin D1, cyclin E2, E2F3, BCL2 to increase cell cycle arrest and apoptosis [27].

Mechanisms of epigenetic changes have also been investigated in urinary tract malignancies such as kidney and bladder cancers. In clear cell renal cell carcinomas, it has been shown that abnormal DNA methylation can cause transcriptional defects in related genes, leading to some gene expression errors and cell differentiation errors. It has also been demonstrated that TSGs and DNA repair genes are silenced by hypermethylation [75]. In bladder cancers, the abnormal promoter methylation level was found to correlate with the clinicopathological profile, and hypermethylation in four genes (*RASSF1A, CDH1, CDH13* and *APC*) was found to be associated with more aggressive features [76].

Detection of the Epigenetic Changes

Epigenetic changes, caused by DNA methylation, can be detected by molecular pathologic methods such as polymerase chain reaction (PCR), next generation sequencing (NGS) and DNA microarray analysis. Selection of a specific method to detect the methylated CpG sequences depends on the objectives of the study. Bisulfite conversion - followed by sequencing or microarray analysis can be employed to uncover newly methylated sites. Bisulfite conversion - followed by qPCR / PCR and sequencing can be used to detect the extent of known methylated genes. Bisulfite conversion changes unmethylated cytosines

to uracil during library preparation process of NGS. Converted bases are identified (after PCR) as thymine in the sequencing data, and read counts are used to determine the % methylated cytosines [77, 78].

Conclusion

The mechanisms of epigenetic change, including recently identified m6A RNA methylation are believed to be diagnostic biomarkers and potential therapeutic targets for several nonneoplastic and neoplastic diseases. Therefore, they should be investigated in a wide variety of diseases to understand how they affect the development and progression of these diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Authors Contributions

KKB: Supervision; Writing-original draft

AT: Writing-review & editing

OE: Visualization; Validation; Writing-review & editing

RGÖ: Writing-review & editing

YÇ: Writing-review & editing

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ŞMÜ*:* Conceptualization; Supervision

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