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DergiPark tarafından yürürlüğe konulan kurallar çerçevesinde yazarların
"Etik İlkeler ve Yayın Politikası" ile "Yazım Kuralları" na uyulması konusunda ilgili başlıkları
dikkatlice incelemesi tavsiye edilmektedir.

Dergi 2022 yılından itibaren sadece İngilizce yazı kabul etmeye başlayacaktır.

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Değerli Bilim insanları,

Biyoteknolojik ve Stratejik Sağlık Araştırmaları Dergisi (JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH), Deneysel, Biyoteknolojik, Klinik ve Stratejik Sağlık Araştırmaları Derneği'nin uluslararası, bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan açık erişimli, bilimsel yayın organıdır. Dergi, Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanır. Dergi ağırlıklı olarak ingilizce yayın kabul etmektedir.

Derginin amacı; etik kurallara uyumlu hazırlanmış biyoteknolojik, kritik, stratejik sağlık araştırmaları ile ilgili bilimsel makaleleri, klinik ve deneysel çalışmaları, derleme, olgu sunumu, editöre mektup ve editöryel yorum türündeki yazıları yayınlayarak literatüre ve sağlık alanındaki tüm disiplinlerde katkı sağlamaktır.

Derginin hedef kitlesi; sağlık alanındaki tüm disiplinlerde çalışan araştırmacılardır.

Dergimizin 6. Yılı, Ağustos'2022 sayımızda da yine birbirinden ilginç derleme ve araştırma yazıları ile karşınızdayız. Makalelerini gönderen değerli yazar arkadaşlarımıza ve zaman ayıran hakemlerimize teşekkür eder, bilginin kullanılarak toplum sağlığına değerli katkılar sağlamasını temenni ederiz.

DergiPark tarafından yürürlüğe konulan kurallar çerçevesinde yazarların "Etik ilkeler ve Yayın Politikası" ile "Yazım Kuralları" na uyulması konusunda ilgili başlıkları dikkatlice incelemesi tavsiye edilmek-tedir.

Editör
Prof. Dr. Mustafa ALTINDİŞ
Editor in Chief

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YAZARLARA BİLGİLER

MAKALE YAZIM KURALLARI

Derginin Kapsamı

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH, yılda üç kez Deneysel, Biyoteknolojik, Klinik ve Stratejik Sağlık Araştırmaları Derneği tarafından yayımlanmakta olup tıp alanında ve sağlık bilimlerinin ilgili konularında yazılmış İngilizce veya Türkçe makaleler kabul edilmektedir. Dergiye kabul edilecek yazı türleri deneysel araştırmaları, klinik ve laboratuvar çalışmalarının sunulması amaçlı özgün makaleler, vaka sunumları, derleme makaleleri ve editöre mektuplardır.

A. Genel Bilgiler

➢ Etik Kurallar

Dergiye gönderilen makalelerin daha önce başka bir dergide değerlendirme sürecinde olmaması, yayım için kabul edilmemiş ve de yayınlanmamış, olması, bilimsel ve etik kurallara uygun şekilde hazırlanması gereklidir. Yazarlar, makalelerin bilimsel ve etik kurallara uygunluğundan sorumludur. (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms/).

Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "Yöntem" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH'ne gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin "Yöntem" bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Sonuç olarak, etik kurul kararı gerektiren klinik ve deneysel insan ve hayvanlar üzerindeki çalışmalar için etik kurul onayı alınmış olmalı, bu onay makalede "Etik Kurul Onay Numarası" ile belirtilmelidir ve belgelendirilmelidir.

Dergide çıkan yazıların tüm hakkı dergiye aittir. Yazılar için yazarlara telif hakkı ödenmez. Makaleye ek olarak yukarıdaki şartları kaşif taramalarına dayalı yazılarda Anabilim Dalı (Bilim Dalı) Başkanlığı, Başhekimlik veya Servis Şefliği tarafından arşivde çalışılmasına izin verdiğine dair bir belgenin çalışmaya eklenmesi zorunludur. Prospektif klinik çalışmalar için resmi gazetenin 29.01.1993 tarih ve 21480 sayılı nüshasında yayımlanan yönetmeliğe uygun bir şekilde Etik Kurulu onayı alınmalıdır. Dergide yer alan makalelerin etik sorumluluğu yazarlarına aittir.

Dergiye gönderilen makalelerden hakeme gönderilmesi uygun görülen makaleler konunun uzmanı hakemlere gönderilir. Makalenin yayımlanabilmesi için iki hakemin de olumlu görüş bildirmesi gerekmektedir. Değişikliğe gerek görüldüğü takdirde, istenilen değişiklikler yazarlarca 15 gün içerisinde yapıldıktan sonra yayın tekrar incelemeye alınır, yazım ve dil bilgisi hataları makalenin içeriğine dokunulmaksızın yayın kurulu tarafından düzeltilir.

Derleme yazılarında, tüm yazarların derleme konusu ile ilgili en az bir SCI/SCI-expanded indekse giren yayınının bulunması gerekmektedir.

Sonucu desteklemek için istatistiksel analiz genellikle gereklidir. İstatistiksel analiz, tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatistiksel analiz ile ilgili bilgi, Yöntemler bölümü içinde ayrı bir alt başlık olarak yazılmalı ve kullanılan yazılım kesinlikle tanımlanmalıdır.

Dergi İntihal İlkesi

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH'de makale göndermeden önce uygun intihal yazılım programlarıyla (iThenticate, Turnitin: Tezler için vb.) makalenizdeki benzerlik durumunu belirlemeniz beklenir. Benzerlik oranlarının dergimiz için kaynaklar hariç % 20'un altında olması istenmektedir.

Simgeler, Birimler ve Kısaltmalar

Dergimiz, İngilizce makalelerde Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.) uzlaşılarını; Türkçe makalelerde ise TDK Yazım Kılavuzu, Türkiye Bilim Terimleri ve TÜBA Türkçe Bilim Terimleri Sözlüğü'nü esas almaktadır. p, ×, μ, η, or v gibi karakterler, sözcük işlem uygulamasının simge menüsünden seçilerek kullanılmalıdır. Sayılarla birimler arasında bir boşluk bırakılmalı (örn. "3 kg"), sayılarla yüzde simgesi arasında boşluk bırakılmamalıdır (örn. "%45"). Tüm kısaltma ve kısa adlar, ilk kez kullanıldıklarında tanımlanmalıdır. Canlıların ve mikroorganizmaların jenerik isimleri, tür adını değiştirmeden, uygun şekilde kısaltılmalı ve yatık olarak yazılmalıdır.

Makale Hazırlama Şekli ve Biçimi & Gönderim

Makale gönderimi çevrimiçi olarak http://dergipark.gov.tr/bshr adresine Microsoft Word dosyası olarak eklenmelidir. "Öz", "Ana Metin ve Kaynaklar (Çizelgeler dahil)" Microsoft Word dosyası (.doc veya .docx uzantılı) olarak, 12 yazı tipi boyutunda, Times New Roman karakterleriyle, 1,5 satır aralığıyla ve paragraflar iki yana yaslanmış olarak yazılmalıdır. Makalelerin değerlendirilmeye alınabilmesi için, başvuru esnasında 'Telif Hakkı devir formu' doldurulmalıdır. Bu formu içermeyen yazılar değerlendirmeye alınmaz. Makaleler, Ana metnin sayfa numaraları, her sayfanın sağ alt köşesinde belirtilmelidir.

Makaleler, Türkçe veya İngilizce yazılabilir.

B. Yazım Kuralları

Metin içi ve metin sonu kaynak gösterimi için, AMA (Amerikan Tıp Birliği/American Medical Association) Stili kullanılmalıdır (http://library.nymc.edu/informatics/amastyle.cfm; https://drive.google.com/drive/folders/1hzvgxnau1lBPUBYfKN1vTBKbPE31LBXQ) .

Dergide kör hakemlik uygulaması söz konusu olduğundan makale ana metin üstünde yazarlara ilişkin herhangi bir bilgi bulunmamalıdır.

Tüm makale yazarlarının, ORCID iD (Open Researcher and Contributor ID) numaraları başlık sayfasına eklenmelidir.

B. 1. Başlık Sayfası

Yazılar başlık sayfasından başlanarak numaralandırılmalı, sayfa numaraları sağ alt köşeye yazılmalıdır.Başlık sayfasında; yazının başlığı (Türkçe ve İngilizce), başlık altında tüm yazarların ad ve soyadları, kurumları yer almalıdır. Sorumlu yazarın adı ve soyadı, telefon numarası, e-posta ve yazışma adresleri bulunmalıdır. Makale başlığı, 25 kelime ile sınırlı, Türkçe ve İngilizce dillerinde verilmelidir. Kısa başlık (running title, running head) 50 karakterle (boşluk dahil) sınırlı şekilde Türkçe ve İngilizce olmalıdır.

B. 2. Öz Sayfası

Öz (Abstract), Türkçe ve İngilizce olarak en fazla 250 sözcük olacak şekilde; 'Amaç (Objective)', 'Yöntem (Methods)', 'Bulgular (Results)' ve 'Sonuç (Conclusion)' bölümlerinden oluşmalıdır. Derleme ve olgu sunumunda öz sayfası bölümlere ayrılmadan yazılmalıdır.

Öz'ün altına "anahtar kelimeler" (en az 3, en fazla 6) verilmelidir. Anahtar kelimeler Türkçe ve İngilizce yazılmalıdır. İngilizce anahtar kelimeler Index Medicus'da "Medical Subjects Headings" listesine uygun olmalıdır (Bkz: www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler Türkiye Bilim Terimleri, uygun olarak verilmelidir (Bkz: www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

B. 3. Ana Metin

B. 3. 1. Özgün Araştırma

Sırasıyla ve kesin sınırlarla ayrılmış "Giriş", "Yöntem", "Sonuç" ve "Tartışma" bölümlerinden oluşmalıdır. Sonuç kısmı, ayrı bir bölüm olarak veya Tartışma'nın son paragrafı olarak yazılabilir. Tartışma kısmının son paragrafında çalışmanın sonuçları ifade edilebilir, ek bir başlık açılmasına gerek yoktur.

En çok 15 sayfa (öz, teşekkür ve kaynaklar hariç) olmalıdır.

Sistematik derleme ve meta-analiz özgün araştırma makalesi kapsamındadır. Yazarlar, taslaklarını gönderirken sistematik derleme ve meta-analiz için, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) beyanatı (http://www.prisma-statement.org/). yönergesine uyduklarını gösteren standart kontrol listelerini kullanmalı ve istendiğinde sunmalıdır.

Sözcük sayısı öz, teşekkür ve kaynaklar hariç en çok 5 000 olmalıdır. Kaynak sayısı, 50'yi geçmemelidir(derleme hariç). Metin boyunca bilimsel terimler yatık olarak yazılmalıdır.

B.3.2. Derleme

En çok 20 sayfa (öz ve kaynaklar hariç) olmalıdır. Derlemeler, standart yazı şeklinden farklıdırlar. Yazı yazmanın evrensel formatı IMRAD derleme yazılarında uygulanmamaktadır. Ana hatlarıyla "Giriş" bölümü daha geniş olmakta ve derlemenin amacını ve yazı gerekçesini açıklamaktadır.

"Yöntem" ve "Bulgular" kısmı bulunmamaktadır. Tartışma kısmı yine geniş tutulacak ve kişisel deneyimler doğrultusunda aynı konuda yapılmış çalışmalar ve onların sentezi yapılacaktır. Sonuç anlamında bir yorum ve değerlendirme paragrafı bulunmalıdır. Kaynaklar ise tüm yazılara göre daha fazla sayıda olacaktır. Ancak mutlaka yazarın kendi çalışmaları da bulunacaktır.

B.3.3. Olgu Sunumu

En çok 10 sayfa (öz, teşekkür ve kaynaklar hariç) olmalıdırr. Olgu sunumlarında ise sırasıyla giriş, olgu sunumu ve tartışma bölümlerini içermelidir.

B.3.4. Editöre Mektup

En çok 5 sayfa (öz ve kaynaklar hariç) olmalıdır. Çizim ve çizelge içermez. Bir makaleye ithaf olarak yazılmış ise sayı ve tarih verilerek belirtilmeli ve metnin sonunda yazarın ismi, kurumu ve adresi bulunmalıdır.

B.4. Çizim ve Çizelgeler

Metin içerisinde kullanılan fotoğraf, grafik, şekil, resim gibi görsel sunum araçları 'Çizim' olarak tanımlanır. 'Tablo' ise sınıflandırılmış verilerin yer aldığı görsel sunum araçlarıdır. Tablolar kaynaklardan sonra başlıklarıyla birlikte verilmelidir. Tablolar, başlığın alt ve üstünde, ayrıca alt satırın altında yatay kenarlık ve sol sütunun sağ dikey kenarlığı olacak şekilde düzenlenmelidir.

Figür ve Tablolar, numaraları ile metin içinde geçtiği yerlerde ilgili cümlenin sonunda ayıraç içinde belirtilmeli; sırayla numaralandırılmalıdır.

Örnek tablo:

Tablo 1. Araştırmaya katılanların ilk başvurularını birinci basamakta çalışan hekime yapmama nedenleri

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YAZARLARA BİLGİLER

Başvurmama Nedeni	*n	%
Sadece psikiyatri uzmanı ruh sağlığı hizmeti sunabilir		
Birinci basamakta çalışan hekimin bu hizmeti sunduğunu bilmemem		
Ebeveyn kararıydı		
Birinci basamakta çalışan hekime güveniyorum ancak tercih etmedim		
	47	53,4
	17	19,3
	12	13,6
	12	13,6

* Toplam hasta sayısı

Tablolar, metne dahil edilmemeli ve sistem üzerinden "Görseller" başlığı seçilerek yüklenmelidir. Görseller; JPG, GIFF, PNG veya TIFF formatında gönderilmelidir. Metine ek olarak sisteme yüklenen tüm çizim başlıkları, "Çizim Başlığı" altında, kaynaklardan sonra listelenmelidir. Kullanılan kısaltmalar çizim ve çizelgelerin altındaki açıklamada 10 yazı boyutunda belirtilmelidir. Ondalıklı sayıların belirtilmesinde Türkçe metinlerde virgül işareti, İngilizce metinlerde nokta işareti kullanılmalıdır. Yüzde ile belirtilen sayılarda Türkçe metinlerde sayı önünde, İngilizce metinlerde ise sayı arkasında % işareti kullanılmalıdır.

B. 5. Açıklamalar

Çalışmada teşekkür, daha önce sunulduğu kongre, çıkar çatışması olmadığı, maddi destek, bağış ya da teknik yardım gibi konular metnin sonunda kaynaklardan önce belirtilmelidir. Çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazı yazılmalıdır. Araştırma desteği (Üniversite Bilimsel Araştırma projeleri , TÜBİTAK projeleri ve benzeri kurumlardan) alınmışsa, proje numarası belirtilmelidir.

C. Kaynak Gösterimi

Dergimiz, kaynak gösteriminde AMA stilini kullanılmaktadır ve kaynak yazımında atıf düzenleme programlarının kullanımını tavsiye edilmektedir (EndNote, Mendeley, Zotero vb.).

C. 1. Metin İçinde;

Kaynaklar, metinde geçiş sırasına göre numaralandırılmalıdır ve kaynak numaraları üst simge olarak verilmelidir. Örneğin,"… belirtilmektedir8. , bildirilmiştir8,13,18. , şeklindedir8-10

C. 2. 'Kaynaklar' Başlığı Altında;

Kaynaklar ayrı bir liste olarak metin içindeki sıralamalarına göre numaralandırılarak verilmelidir. Kaynak sayısı özgün araştırmalarda en çok 50, olgu sunumlarında en çok 20, editöre mektuplarda ise en çok 5 olmalıdır.

Kaynaktaki yazar sayısı 3 veya daha az ise tüm yazarlar belirtilmeli; 3'den fazla ise, Türkçe kaynak gösteriminde sadece ilk 3 isim yazılmalı "ve ark." şeklinde, İngilizce kaynak gösteriminde ise ilk 3 isim yazılmalı ve "et al." şeklinde gösterilmelidir.

Dergi isimleri Index Medicus/Medline/PubMed'de yer alan dergi kısaltmaları ile uyumlu olarak kısaltılmalıdır. Index Medicus'ta indekslenmeyen bir dergi kısaltılmadan yazılmalıdır. Çevrimiçi yayınlar için DOİ (digital object identifier) numarası verilmelidir.

Örnek:

1. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. The American Journal of Medicine. 2000; 109(6): 481-488. doi:10.1016/S0002-9343(00)00545-3.

Örnekler:

1. Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia. 2003; 17: 427–436.
2. Ozcelik F, Oztosun M, Gülsün M, ve ark. İdiopatik trombositopenik purpura ön tanılı bir olguda EDTA'ya bağlı psödotrombositopeni. Turk J Biochem. 2012; 37(3): 336–339.

Örnek:

1. Yoldas O, Bulut A, Altindis M. Hepatit A Enfeksiyonlarının Güncel Yaklaşımı. Viral Hepatit J 2012; 18: 81-86.
2. Bir derginin ek sayısı (Supplement) kaynak gösterileceği zaman; İngilizce makalelerde (Suppl.) ve Türkçe makalelerde ise (ES) şeklinde gösterilmelidir.

Çevrimiçi makale ise tam yayın tarihi kullanılır. Genellikle cilt ve dergi sayıları, sayfa numaraları yoktur. Makaleye doğrudan ulaşım adresi ve erişildiği tarih verilmelidir.

Örnek:

5. Frederickson BL (2000, Mart 7). Cultivating positive emotions to optimize health and well-being. Prevention & Treatment 3, Makale 0001a. http://journals.apa.org./prevention/volume3/pre003000-1a.html adresinden 20 Kasım 2000'de erişildi.

Kitabın kaynak gösterimi ise yazarların adı, kitabın adı, birden çok basımı varsa kaçıncı basım olduğu, basımevi, basım yeri, basım tarihi belirtilmelidir

Örnek:

2. Strunk W Jr., White EB. The Elements of Style (4. baskı). Longman, New York, 2000.

Kaynak çok yazarlı bir kitabın bölümü ya da bir makalesi ise bölümün ya da makalenin yazarı, bölümün ya da makalenin adı, kitabın adı, kaçıncı baskı olduğu, cildi, kitabın yayın yönetmenleri, basım yeri, sayfaları, tarih yazılmalıdır.

Örnek:

3. Meltzer HY, Lowy MT. Neuroendocrin function in psychiatric disorders. American Handbook of Psychiatry, 2. Baskı, cilt 8, PA Berger, HKH Brodie (Ed), New York. Basic Books Inc, 1986; s. 110-117.

Çeviri kitaplar aşağıdaki şekilde kaynak olarak gösterilmelidir.

Örnek:

4. Liberman RP. Yetiyitiminden İyileşmeye: Psikiyatrik İyileştirim Elkitabı. American Psychiatric Publishing Inc. Washington DC. 2008. Çev. Mustafa Yıldız, Türkiye Sosyal Psikiyatri Derneği, Ankara, 2011.

Kaynak çevrimiçi (internette yer alıyor) ise erişim tarihi ile birlikte yazılmalıdır.

MAKALE SÜREÇ YÖNETİMİ

A. Çift-Kör Hakemlik

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH (J of BSHRS), yılda 3 kez yayınlanan ve çift-kör hakemlik sürecinden geçen bilimsel makalelerin yayınlandığı ulusal/uluslararası ve hakemli bir akademik dergidir. Yayınların incelenmesi için çalışmaların içeriğine ve hakemlerin uzmanlık alanlarına göre en az iki hakem, makale alan editörü/leri tarafından atanır. Bu süreçte hakem değerlendirme raporları elektronik ortamda isimsiz olarak gönderilir. Değerlendirmeyi yapan hakemlerin isimleri çift-kör yöntemi gereği raporlarda ve dergide belirtilmemektedir. Talep edilmesi halinde, hakem olarak dergiye katkı sağladığına ilişkin yazılı bir belge hakemlere verilebilir. Yazarlar, hakemlerle doğrudan iletişime geçemez, değerlendirme ve hakem raporları dergi yönetim sistemi aracılığıyla iletilir. Bu süreçte değerlendirme formları ve hakem raporları editör aracılığıyla sorumlu yazara iletilir.

B. Karar Alma Süreçleri

Yayınlanmak üzere gönderilen tüm çalışmalar, değerlendirme için alanlarında uzman en az iki hakeme gönderilir. İnceleme sürecinin tamamlanmasının ardından editör, söz konusu çalışmanın doğruluğu, araştırmacı ve okuyucular için önemi, hakem raporları, telif hakkı ihlali ve intihal gibi yasal düzenlemeleri de göz önünde bulundurarak hangi çalışmaların yayınlanacağına karar verir. Editör, bu kararı verirken diğer editörlerden veya hakemlerden de tavsiyeler alabilir.

C. İvedilik

Hakem değerlendirmesi yapmak üzere davet alan bir hakem, ilgili çalışma için hakemlik yapıp yapamayacağını yedi gün içinde editöre bildirmelidir. Kabul edilen hakemlik değerlendirme süreci onbeş, sorumlu yazara bildirilen değişikliklerin tamamlanması için, yazarlara verilen süre ortalama onbeş gündür. Sorumlu yazara son okuma için gönderilen metnin değerlendirme süresi ise üç gündür. Değerlendirme için hakemlere gönderilen çalışmalar gizli belge olarak tutulmalıdır. Çalışmalar başkalarına gösterilmemeli, içerikleri tartışılmamalıdır. Gerekli durumlarda editörün izni dahilinde hakemler başka meslektaşlarından tavsiye isteyebilirler. Editör, bu izni ancak istisnai bir koşul olması durumda verebilir. Gizlilik kuralı, hakemlik yapmayı reddeden kişileri de kapsamaktadır.

E. Tarafsızlık İlkesi

Değerlendirme sürecinde yazarlara yönelik kişisel eleştiri yapılmamalıdır. Değerlendirmeler, nesnel ve çalışmaların geliştirilmesine katkı sağlayacak şekilde olmalıdır.

F. Kaynak Belirtme

Hakemler, çalışmada atıf olarak belirtilmeyen alıntılar varsa bunları yazarlara bildirmekle yükümlüdür. Hakemler, alanda atıfta bulunulmayan eserlere ya da benzer eserlerle çakışan alıntılara özellikle dikkat etmelidir. Hakemler, daha önce yayınlanmış herhangi bir çalışma ya da bilgiyle benzerliği olan yayınların farkedilmesi durumunda editörleri bilgilendirmelidir.

G. Bilgilendirme ve Çıkar Çatışması

Hakemler, çalışmasını değerlendirmekle görevlendirildikleri herhangi bir yazar, şirket ya da kurumla işbirliğine dayalı herhangi bir bağlantıları olması durumunda değerlendirme yapmayı kabul etmemeli ve durumdan editörü haberdar etmelidir.

Hakemler, değerlendirme için gönderilmiş, yayınlanmamış eserleri ya da eserlerin bölümlerini yazar(lar)ının yazılı onayı olmadan kendi çalışmalarında kullanamaz. Değerlendirme sırasında elde edilen bilgi ve fikirler hakemler tarafından gizli tutulmalı ve kendi çıkarları için kullanılmamalıdır. Bu kurallar, hakemlik görevini kabul etmeyen kişileri de kapsamaktadır.

YAZI GERİ ÇEKME TÜM YAZARLARIN ONAYI İLE OLMALIDIR.

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Journal of Biotechnology and Strategic Health Research

HEALTH RESEARCH

INSTRUCTIONS FOR AUTHORS

Scope of the Journal

The JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH is published electronically 3 times a year by the Experimental, Biotechnological, Clinical and Strategic Health Research Association and accepts English or Turkish-language manuscripts in all fields of medicine(Experimental, Biotechnological, Clinical and Strategic Health Research) and other related health sciences. Contribution is open to researchers of all nationalities. The following types of papers are welcome: original articles (for the presentation of clinical and laboratory studies), case reports, review articles, and letters to the editor.

Submission Procedures

All manuscripts must be submitted electronically via the internet to the JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH through the online system for ULAKBIM dergipark http://dergipark.gov.tr/bshr You will be guided stepwise through the creation and uploading of the various files.

There are no page charges.

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All experimental or clinical researches done in humans or animals should follow the ethical rules. The ethical approval form must be sent and the number of approval must be given in the manuscript. The ethical problems belong only to the author(s).

All copyright of the published papers belong to Experimental, Biotechnological, Clinical and Strategic Health Research Association.

The copyright fee is not paid to all authors.

In manuscripts based on scanning of archieve records, a consent form is needed that shows the permission for retrospective work and signed by Head of the Department, hospital manager or clinic manager.

Preparation of Manuscript Style and format:

Manuscripts should be submitted to http://dergipark.gov.tr/bshr as Microsoft word file in Times New Roman font. All manuscripts including references should be typed in 12 font size,one and a half (1.5) line space and justified. Upon submission, the copyright release form should be filled and downloaded. The manuscript submissions without a copyright release form will not be evaluated.

Each page of main text of the manuscript should be numbered on the right hand side. Manuscripts should be written in Turkish or English. Contributors who are not native English speakers are strongly advised to ensure that a colleague fluent in the English language or a professional language editor has reviewed their manuscript. Repetitive use of long sentences and passive voice should be avoided. It is strongly recommended that the text be run through computer spelling and grammar programs.

Symbols, Units, And Abbreviations:

In general, the journal follows the conventions of Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.). Spaces must be inserted between numbers and units (e.g., 3 kg), but not between numbers and mathematical symbols (+, –, ±, ×, =, <, >) and between numbers and percent symbols (e.g., 45%). Please use International System (SI) units. All abbreviations and acronyms should be defined at first mention. Thereafter, generic names should be abbreviated as appropriate without altering the species name.

Typs of Manuscripts Original Article

It should consists of "Introduction", "Methods", "Results" and "Discussion". Conclusion may be written as a last paragraph of discussion, there is no need to add a separate section for conclusion. The whole length of text should be maximum 5 000 words (except abstract, acknowledgements and references). The numbers of references should be maximum 50. Also, scientific names should be spelled italics throughout the text.

Review

It should be maximum 6 000 words (except abstract and references). The author(s) should have at least one published paper in a journal indexed in SCI/SCI-expanded related to the topics of the review. The abstract should be as one paragraph and should be written without a section. The numbers of references should be maximum 100.

Case Report

It should be maximum 1 500 words (except abstract, acknowledgement and references). Case reports should consist of abstract, keywords, introduction, case report and discussion sections. The numbers of references should be maximum 10. Figures or Tables should follow the main text in a separate pages.

Letter to Editor

It should be maximum 1 000 words (except abstract and references). No Tables or Figures are included. If it was written refering to another article, the number and the date should also be added. The name, affiliation(s) and address of author(s) should be written at the end of the text. The numbers of references should be maximum 5.

Manuscript Arrangement

Manuscripts should be arranged as follows: "Title page", "Abstract", "Keywords", "Main text", "Acknowledgements", "References", "Tables",and "Figures".

Title page

All submissions must include a title page, which is to be uploaded as a separate document. The title page should contain the full title in sentence case (e.g., Urothelial cancers: clinical and imaging evaluation). The title should be limited to 25 words or less and should not containabbreviations.The title should be a brief phrase describing the contents of the paper.Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. It should be written in capital letters both in Turkish and in English. Title in English should be written using italic letters for Turkish manuscripts and vice versa. The first and the family names of the authors should be written in small letters as the first letter being the capital.

The full names and affiliations of all authors should be given clearly and briefly with theirinstitutions, address with zip code and name of country, and the contact details of corresponding author (E-mail address and telephone). In addition, ORCID (Open Researcher and Contributor ID) numbers of all authors should be included into the title page.

Abstract

The abstract should be brief, indicating the purpose/significance of the research, methodology, major findings and the most significant conclusion (s). The abstract shouldnot contain literature citations that refer to the main list of reference attached to the complete article. The abstract should be written as a single paragraph and should be in reported speech format (past tense); complete sentences, active verbs and the third person should be used.

The abstract should be structured to include the study's "Objective", "Methods", "Results", and "Conclusion" under 4 separate headings. Abstracts of review articles should be a brief overview of the main points from the review. In reviews and case reports, abstract should be written without any sections. The abstract (English and Turkish) should not be more than 300 words.

Keywords

The authors must provide 3-6 keywords for indexing purposes and to facilitate the retrieval of articles by search engines. Keywords should be different from the words that make up the title of the article. Keywords should be written below the abstracts both inTurkish andEnglish. Acronyms should be avoided. For English keywords, always try to use terms from the Medical Subjects Headings list from Index Medicus (www.nlm.nih.gov/mesh/MBrowser.html). For Turkish keywords, terms from Turkish Scientific Terms (www.bilimterimleri.com) should be used.

Main text

Introduction

The introduction should be clear and concise, with relevant references on the study subject and the proposed approach or solution. There should be no subheadings. Excessive citation of literature should be avoided. Only necessary and the latest citations of literature that are required to indicate the reason forthe research undertaken and the essential background should be given.

Methods

Explain clearly but concisely your clinical, technical, or experimental procedures. A precise description of the selection of your observational or experimental subjects (for example patients or laboratory animals including controls) must be presented. Experimental research involving human or animals should be approved by ethical committiee.All chemicals and drugs used must be identified correctly, including the generic names, the name of the manufacturer, city and country in parenthesis. The techniques or methodology adopted should be supported with standard references. Briefly describe methods that have been published but are not well known as well as new or substantially modified methods. Description of established procedures are unnecessary. Apparatus should be described only is it is non-standard; commercially available apparatus used should be stated (including manufacturers' name, address in parenthesis). Only SI units should be used for each measurements.

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Results

The result section should provide complete details of the experiment that are required to support the conclusion of the study. The results should be written in the past tense when describing findings in authors experiments. Previously published findings should be written in the present tense. Speculation and the detailed interpretation of the data should not be included in the results but should be put into the discussion section.

Discussion

Statements from the "Introduction" and "Results" sections should not be repeated here. The final paragraph shouldhighlight the main conclusions of the study.

Tables and Figures

The visual presentations like photographs, graphics, picturesetc. must be labelled "Figures". Whereas, the "Tables" shows the classifieddata.Tables should be added after the "References" section. Figure legends should be placed into the end of the main text. Figures should be uploaded as a separate file following the Dergipark System.

All tables and figures must have a caption and/or legend and be numbered (e.g., Table 1., Figure 2.), unless there is only one table or figure, in which case it should be labelled "Table" or "Figure" with no numbering. Captions mustbe written in sentence case (e.g., Figure 1. Macroscopic appearance of the samples.). The font used in the figures should beTimes New Roman. If symbols such as ×, μ, η, or ν are used, they should be added using the Symbols menu of Word.

All tables and figures must be numbered consecutively as they are referred in the text. Please refer to tablesand figures with capitalisation and unabbreviated (e.g., "As shown in Figure 2. …", and not "Fig. 2" or "figure 2").
The resolution of images should not be less than 118 pixels/cm when width is set to 16 cm. Images must bescanned at 300 dpi resolution and submitted in .jpeg, .png or .tif format.

Graphics and diagrams must be drawn with a line weight between 0.5 and 1 point. Scanned or photocopied graphs anddiagrams are not accepted.

Charts must be prepared in 2 dimensions unless required by the data used. Charts unnecessarily prepared in3 dimensions are not accepted.

Figures that are charts, diagrams, or drawings must be submitted in a modifiable format, i.e. our graphicspersonnel should be able to modify them. Therefore, if the program with which the figure is drawn has a "Save as"option, it must be saved as .pdf. If the "Save as" option does not include .pdf extension, the figure must becopied and pasted into a blank Microsoft Word document as an editable object. It must not be pasted as an imagefile (.tiff or.jpeg) unless it is a photograph.

Tables and figures, including caption, title, column heads, and footnotes, must not exceed 16 × 20 cm andshould be no smaller than 8 cm in width. For all tables, please use Word's "Create Table" feature, with no tabbedtext or tables created with spaces and drawn lines. Please do not duplicate information that is already presented inthe figures.
Tables must be clearly typed, each on a separate sheet, and single-spaced. Tables may be continued on anothersheet if necessary, but the dimensions stated above still apply.

Tables should be arranged as a horizontal borderline as well as below the last line. Moreover, there sould be vertical line on the right of first column on the left hand site. Abbreviations used in the tables such as (*) should be explained below the table in 10 font size.

In Tables written in Turkish, decimal numbers should be written with comma, however in English text, decimal numbers should be written with dots. Percentages (%) should be placed in front of the numbers without space and behind the numbers in Turkish and English text, respectively.

Example for a Table:

Table1. The reasons of not applying to general practioner for the first application.

The reasons	*n**	*%*
Only Psychiatrist can do it		
No information about general practioner Parents decision		
Not preferred	*47*	*53.4*
17	*19.3*	
12	*13.6*	
12	*13.6*	

**Total number of patients.*

Acknowledgement

All acknowledgements, poster/oral presentations, financial supports, grants, technical supports and the conflict of interest should be mentioned at the end of the text.

Funding

The type of Project or the financial support such as scientific projects of University, TUBITAK projects etc. should be added at the end of the text including the numbers and the year of the projects.

References

While talking about the source in the text, the first author's surname ın Er and his firends' study12"…… or ın Er et al.12. Both authors should be given the surnames of both authors (similar results were found in the study conducted by Öncü and Ilke13).

Citations in the text should be identified by numbers assuperscript, for example, "The results were as follows: 4
If there are more than one references, separate the numbers with comma, for example, "Several interventions have been successful at increasing compliance.11,14"

In following journals, first and the last numbers should be seperated by "-" , for example: Diabetes mellitus is associated with a high risk of foot ulcers1-3 or "As reported previously,1,3-6"

Do not include personal communications, unpublished data, or other unpublished materials as references, although such material may be inserted (in parentheses) in the text. In the case of publications in languages other than English, the published English title should be provided if one exists, with an annotation such as "(article inTurkish with an abstract in English)". If the publication was not published with an English title, provide the original title only; do not provide a self-translation. A short title for use as a running head (not to exceed 30 characters in length, including spaces between words) is needed. References should be formatted as follows (please note the punctuationand capitalisation):
The list of references at the end of the paper should be given in order of their first appearance in the text. All authors should be included in reference lists unless there are more than 6, in which case only the first 3 should be given, followed by "et al." in English and "ve ark." in Turkish references.

The number of references should not be more than 60 in original articles, not more than 100 in review articles, not more than 20 in case reports and not more than 5 in letter to editor. The journal requires DOI numbers, when available, to be included in all references. Personal experiences and researches without a DOI number should not be used.

In order to arrange the reference list easly, our journal suggest the use of reference arrangement programmes such as EndNote or Mendeley etc.).

For a reference in the reference list, the surname of author, the first letter of author's name, the title of the reference, the name of the journal, the year of the journal, the numbers of its volume, issue and pages should be written. The name of the journal should be abbreviated as in AMA (American Medical Association) ((http://library.nymc.edu/informatics/amastyle.cfm). If the abbreviation is not avalible, whole name of the journal should be written.

Published papers

Yoldas O, Bulut A, Altindis M. Current Approach to Hepatitis A Infections. Viral Hepatit J 2012; 18: 81-86..
Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia. 2003;17:427–436.
Ozcelik F, Oztosun M, Gülsün M, ve ark. Pseudothrombocytopenia due to EDTA in a case with idiopathic thrombocytopenic purpura. Turk J Biochem. 2012;37(3):336–339.

Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. Am J Med. 2000;109(6):481- 488. doi:10.1016/S0002-9343(00)00545-3.

If a supplement of a journal is referred, (suppl.) in English and (ES) in Turkish manuscripts should be used.

Electronic journal articles

If a journal from a website is used, the date of publishing is used. Usually, there is no numbers of volume, issue or pages. The web adress and date of download should be given.

Example:

Acetaminophen poisoning. In: DynaMed [database online]. EBSCO Information Services. http://0-search.ebscohost.com.topcat.switchinc.org/login.aspx?direct=true&site=DynaMed&id=113862.

Updated

March 09, 2010. Accessed March 23, 2010.

Book

Harmening D. Modern Blood Banking & Transfusion Practices. 6th ed. Philadelphia, PA: F.A. Davis Company; 2012.
Strunk W Jr., White EB. The Elements of Style. 4th ed. New York, NY: Longman; 2000.
Chapter in a book
Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. Allergens and Allergen Immunotherapy. 3rd ed. New York, NY: Marcel Dekker; 2004:585-606.
McCall RE, Tankersley CM. Phlebotomy and specimen considerations. In: Bishop ML, Fody EP, Schoeff LE, editors. Clinical Chemistry: Techniques, Principles, Correlations. Philadelphia, PA, USA: Lippincott Williams & Williams; 2010:33-73.

Conference proceedings

Weber KJ, Lee J, Decresce R, Subjasis M, Prinz R. Intraoperative PTH monitoring in parathyroid hyperplasia requires stricter criteria for success. Paper presented at: 25th Annual American Association of Endocrine Surgeons Meeting; April 6, 2004; Charlottesville, VA.

Chu H, Rosenthal M. Search engines for the World Wide Web: a comparative study and evaluation met-

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hodology. Paper presented at: American Society for Information Science Annual Conference; October 19-24, 1996; Baltimore, MD. http://www.asis.org/annual-96/electronicproceedings/chu.html. Accessed February 26, 2004.

Theses

Fenster SD. Cloning and Characterization of Piccolo, a Novel Component of the Presynaptic Cytoskeletal Matrix [master's thesis]. Birmingham: University of Alabama; 2000.

Publication Policy and Manuscript Evaluation Process

A. Double-blinded peer-reviewed method

Biotechnology and Strategic Health Research (J BSHRS) is published 3 times a year (April, August, December) and it is double-blinded peer-reviewed system national journal.

Editorial and publication processes of the BSHRS Derg. are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE). The journal is in conformity with Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). Processing and publication is free of charge with the Biyoteknolojik ve Stratejik Sağlık Araştırmaları Dergisi. Authors are not charged a fee at any point during the publication process. All manuscripts should be submitted through the journal's web page at http://dergipark.gov.tr/bshr.

For the evaluation of papers, at least two referees are determined considering the content of the manuscript or the professional scientific area of the referees. In this step, referee assessment form is sent via internet without names. The personal data of the referee is not shown since the double-blind peer-reviewed method is used. Upon request, a written document given to referee as the referee for that contribute to the journal. The authors cannot directly contact with the referees. The referee's evaluation report is sent by the journal management system. The evaluation forms and the referees' reports are sent to the corresponding author(s) by the editor.

B. Decision process

After the referees' evaluation process, the editor decides whether the manuscript will be accepted or not considering the accuracy and the importance of the work, referee's reports, copyright infringement and ethical problems such as plagiarism.

As the editor decides about the manuscript, he or she may require the suggestions of the other member of editorial board or referees.

C. Instancy

A referee invited to the journal for the evaluation of a manuscript should inform the editor about the acceptance in 7 days. The referee should complete the evaluation in 15 days and the corresponding author(s) should download the revised manuscript in 15 days. The requested reading time for the last version of the manuscript by the corresponding author is only 3 days.

D. Confidentiality (Privacy Statement)

Personal information such as names and electronic mail addresses are only used for the scientific purposes of the journal. Other than these purposes this information will not be used and will not be shared with the third parties. The manuscripts sent to referees for assessment are kept as confidential documents. The manuscripts are not shown to other people and the contents of them should not be discussed. If it is necessary, reviewers may need suggestions from their colleagues after editorial permission. The editor may give that permission only in the presence of exceptional condition. The confidentiality rules are also valid for the referees not accepting the assessment of the manuscript.

E. Objectivity principles

In the evaluation process, no personal criticism of the authors should be done. The evaluations should contribute to the development of works and be objective.

F. Citation to reference

The referees should inform the authors if there are any citations that are not referred in the manuscript. The referees should pay particular attention to the citations that do not refer to the subject or to the citations that coincide with similar works. The referees should inform the editors if any publications that have similarity to any previously published work or information are recognized.

G. Information and Conflict of Interest

The referees should not agree to make any evaluation if they have any relation with any author, company or institution in which they are tasked to evaluate their work and inform the editor. The referees may not use the unpublished works or sections of the works submitted for evaluation in their own work without the written consent of the author(s). The information and ideas obtained during the assessment should be kept secret by the referees and should not be used for their own interests. These rules include those who refuse the manuscript assessment.

H. Prevention of Plagiarism

J of Biotechnology and Strategic Health Research(J of BSHR) reports the similarity rates of the articles through the iThenticate and Turnitin programs and shows the care and sensitivity required to prevent plagiarism.

THE WITHDRAW OF THE ARTICLE MUST BE WITH THE APPROVAL OF ALL AUTHORS.

Corresponding Address

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DERLEME / *REVIEW*

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLES*

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HEALTH RESEARCH

DOI:10.34084/bshr.1160542 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Review / Derleme

http://dergipark.org.tr/tr/pub/bshr

Monkeypox virus; Epidemiology of the World and Turkey

Monkeypox virüsü; Dünya ve Türkiye Epidemiyolojisi

Hasan Bayrak

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Öz

Monkeypox virus has the potential to spread through zoonotic reservoirs. The virus reaches other geographical regions through displacements caused by war, migration, and other reasons. In previous years, human monkeypox was a rare zoonotic disease confined to West and Central Africa, however, this geographic range has expanded rapidly with the decline of smallpox vaccine-induced immunity in the world population. The multi-country monkeypox epidemic, which has been going on since the beginning of May 2022, was seen for the first time in many continents outside of Africa. Cases have been reported mostly from European countries and the Western Hemisphere of the World. Cases have been reported extensively from the European region and EU/EEA countries, most commonly Spain, Germany, France, and the UK. By 8 August 2022, over 28 000 confirmed cases and twelve deaths have been reported worldwide. Until 09 August 2022, 5 cases were reported from Turkey.

In this review, the epidemiology of Monkeypox and the general characteristics of the causative agent of Monkeypox is reviewed, with current information and data.

Anahtar Kelimeler Epidemiyology, Çiçek aşıları, Çiçek hastalığı, Maymun çiçek virüsü, Salgın.

Abstract

Maymun Çiçek Virüsü, zoonotik rezervuarlar yoluyla yayılma potansiyeline sahip bir virüstür. Virüs savaş, göç veya diğer nedenler kaynaklı yer değişiklikleri ile diğer coğrafik bölgelere ulaşmaktadır. Önceki yıllarda maymun çiçeği, Batı ve Orta Afrika ile sınırlı, nadir görülen bir zoonotik hastalık iken hastalığın bu coğrafik dağılımı, dünya nüfusunda çiçek aşısı kaynaklı bağışıklığın azalmasıyla birlikte hızla genişlemiştir. Mayıs 2022'nin başından beri devam eden ve birden çok ülkede izlenen maymun çiçeği salgını ilk defa Afrika dışında birçok kıtada görülmüştür. Bu vakaların çoğu Avrupa'dan ve Batı Yarımküreden bildirilmiştir. Vakalar, en sık İspanya, Almanya, Fransa ve İngiltere olmak üzere Avrupa Bölgesi ve EU/EEA ülkelerinden yoğun olarak bildirilmiştir. 8 Ağustos 2022'ye kadar dünya genelinde 28000'in üzerinde doğrulanmış vaka ve 12 ölüm bildirilmiştir. 09 Ağustos 2022 tarihine kadar Türkiye'den 5 vaka bildirilmiştir.

Bu derlemede, mevcut güncel bilgiler ve veriler ile maymun çiçeği hastalığının epidemiyolojisi ve maymun çiçek hastalığı etkeninin genel özellikleri gözden geçirilmiştir.

Keywords *Epidemiology, Monkeypox virus, Outbreak, Smallpox, Smallpox vaccines.*

INTRODUCTION

Monkeypox virus is a species of pox virus within the Orthopoxvirus genus of the Poxviridae family. This family of viruses can infect mammals, as well as reptiles, birds, and insects.[1] The Orthopox genus includes three other human pathogens, variola virus, cowpox virus, and vaccinia virus.[2] Numerous species of poxviruses are known to cause human infections, including Smallpox, Monkeypox, Cowpox, Vaccinia virus (VACV), and Molluscum contagiosum virus.[3] While the Monkeypox virus sporadically causes human disease, it also has a wide variety of potential host organisms to circulate for long periods in the wild.[3,4] Monkeypox virus was first isolated from monkeys. Also, squirrels, rats, and mice are natural hosts of the Monkeypox virus.[5]

Monkeypox can be transmitted through direct contact. Therefore, transmission is possible by direct contact with monkeypox rash, scabs, and bodily fluids of a person with monkeypox.[6] The virus can also be transmitted through contact with secretions such as saliva. Behaviors such as having sex with a person with monkeypox and using the same items can spread the virus.[6] Studies on the transmission route of the disease have shown that the monkeypox virus can be transmitted sexually. Epidemiological data up to June 2022 revealed that cases were particularly associated with men who had sex with men.[7,8]

In one study, various samples were taken from 12 patients and studied by PCR. Virus DNA was detected in all saliva samples of the patients and a high viral load was found in some of the saliva samples. In this study, rectal swab (11 of 12), nasopharyngeal swab (10 of 12), semen (7 of 9), urine (9 of 12), and stool (8 of 12) samples positivity were detected.[9]

In addition to the main modes of transmission of the infection, it is stated that the transmission via aerosol should not be ignored.[10] Respiratory transmission is possible by the release of large droplets by coughing or sneezing.[11] Although it is stated that it is possible to be transmitted through the placenta or by blood transfusion in addition to the mentioned modes of transmission, there is not enough data about this mode of transmission. In the current epidemic, the rashes on the genital areas of the patients support the transmission by sexual contact, but the transmission by sexual activity has not been clarified so far.[12]

Monkeypox virus has developed various mechanisms for entry into the host cell. In general, it is known that it enters the cell by micropinocytosis or fusion, releases its genome and proteins into the cytoplasm after entry into the host cell, and performs its replication here. As with other dsDNA viruses, it uses a DNA-dependent RNA polymerase enzyme to transcribe early viral mRNAs, followed by structural and non-structural viral proteins. After genome synthesis and protein synthesis, the virus is released from the cell after the assembly and envelope process and thus can pass to another cell.[13]

Transmission from animals to humans can occur through direct contact with one of the infected hosts (such as by eating the infected host's flesh) or their fluids.[1]

Studies have shown that the pathogen initially infects respiratory epithelial cells, spreads to lymph nodes, and then spreads systemically through monocytic cells.[14] The virus can infect most mammalian cells by attaching to structures abundant in cells such as chondroitin sulfate, heparin sulfate, and laminin.[15,16]

Epidemiology

Information on previous outbreaks and data on the latest outbreak

Monkeypox outbreak is an emerging infectious disease that is increasingly expanding geographically. The rapid spread of cases is a serious concern worldwide. Concern about the further spread of the outbreak is increasing as cases spread rapidly from Central Africa to other parts of the world.[17] This spread is thought to be due to the decline

in orthopox virus immunity worldwide following the cessation of the smallpox vaccine after smallpox was declared eradicated in 1980.[5,17]

Monkeypox was first isolated in 1958 in Denmark.[5] As with many other zoonoses, monkeypox is transmitted to humans by chance when they encounter infected animals. In 1970, the first human case was reported in Congo.[5] Before this new outbreak, human cases from outside Africa were rarely observed. In 2003, 71 cases of human monkeypox were reported in the USA. This outbreak started with the infection of prairie dogs housed in the same facility during the shipment of infected Gambia opossums, and human cases were seen after contact with these dogs.[18]

In sequencing studies with African and US isolates, two clades were determined by comparing the open reading frames of the genomes.[19] Monkeypox virus is currently classified into two clades (The West African clade and Kongo Basin clade), but a new classification has been proposed as clades 1, 2, and 3. Clade 3 is the cause of most human outbreaks in 2017, 2018, and 2022. It has been proposed that clade 3 can be divided into the lineages A, A.1, A.1.1, and B.1 (Figure 1).[19,20,21]

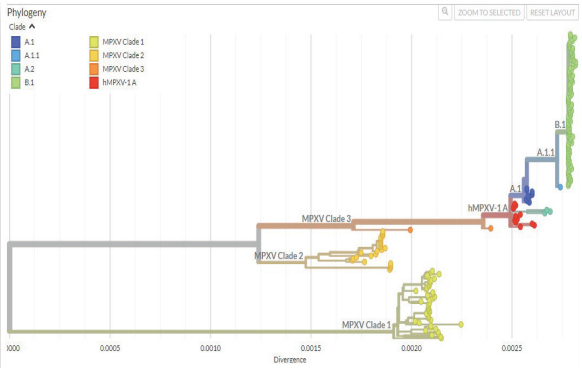

Figure 1. Genomic epidemiology of monkeypox virus.[21]

The West African clade is known to be detected from the western parts of Cameroon to Sierra Leone, whereas the Congo Basin clade (Central Africa) has been described from the central and southern regions of Cameroon to the Congo.[22]

Some differences in epidemiological and clinical features were identified between the two clades.[23] More significant morbidity, mortality, human-to-human transmission, and viremia have been detected in Congo Basin clade-related infections. Significant differences were also seen in morbidity factors such as disease severity and prominent rash. The West African clade is generally associated with milder symptoms than the Congo Basin clade.[1,23] Despite all these epidemiological and clinical differences, 0.55-0.56% nucleotide difference was found between the two strains.[23]

Case fatality rates of outbreaks in the Congo Basin have been reported as 1-10%. The clade circulating in this region appears to be associated with high virulence. The West African clade, responsible for outbreaks in Nigeria, is associated with a mortality rate of about 3%.[24]

Various ideas have been put forward as to the origin of the outbreak. Available data show that the sequences evaluated so far are nearly identical. Available data suggest that recent outbreaks outside of Africa may be associated with a single case. Studies have also shown that the sequences available in West Africa are similar to those from travel-related monkeypox cases that occurred outside of Africa in 2018 and 2019.[25]

Gene changes caused by mutations leading to loss of protein-coding genes or loss of regulatory regions detected in isolates from central Africa are thought to be associated with human-to-human transmission.[26]

The index case was confirmed in a person in the UK on 6 May 2022 and was associated with travel to Nigeria. Sequence analysis of the first isolate obtained in Portugal, collected on 4 May 2022, showed that these new isolates are genetically related to the Nigerian genome belonging to the West African clade.[27]

Other monkeypox genomes isolated in the USA and Belgium also show close genetic relatedness to West African

isolates.[28] Since the beginning of May 2022, thousands of cases have been detected, most of them without a history of travel to endemic countries. As of 28 July 2022, 21 067 cases have been confirmed worldwide, most of them in European countries and the USA (Figures 2 and 3).[29,30]

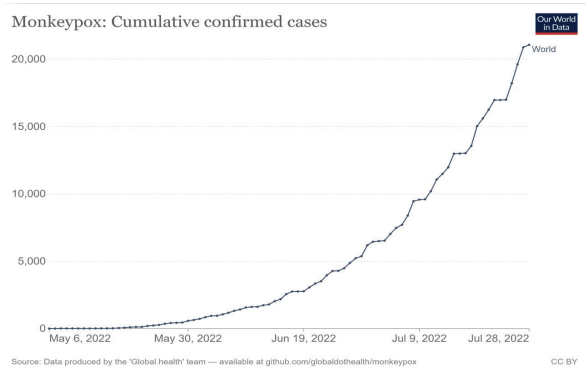

Figure 2. Confirmed cases.[29]

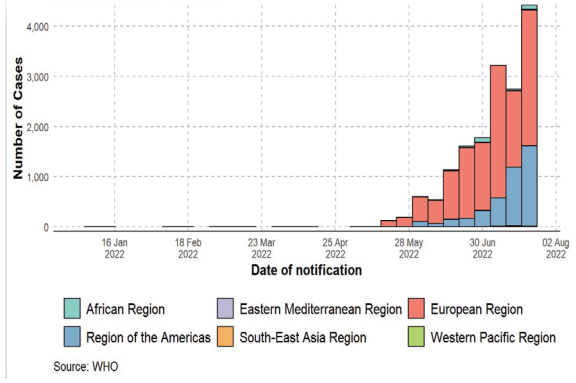

Figure 3. Cases reported up to 25 July 2022.[30]

As of 08 August 2022, 13 912 confirmed Monkeypox cases have been reported from 29 EU/EEA countries since the start of the outbreak with the leading cases from Spain (n=4 942 cases), Germany (n= 2 887) and France (n= 2 423 cases). Cases have been reported in almost all countries in this region. Until this date, five cases have been reported from Turkey.[31]

The first case in Turkey was detected at the end of June 2022. It has been reported that the patient is 37 years old and has an immune system deficiency.[32]

The geographical distribution of confirmed cases in the EU/EEA countries and Turkey until 2 August 2022 is shown in Figure 4.[33]

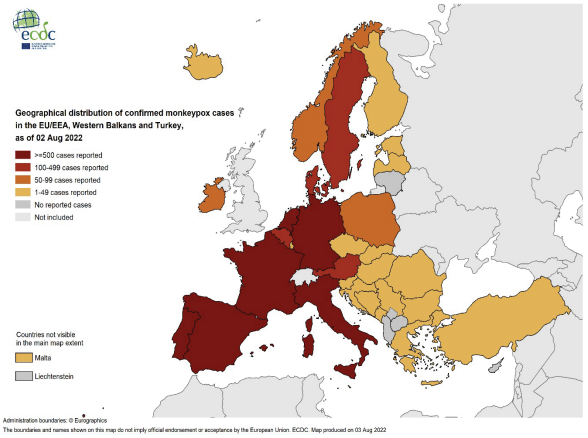

Figure 4. Geographical distribution of confirmed cases the in EU/EEA, Balkans, and Turkey.[33]

As of 06 August 2022, twelve deaths reported worldwide: Spain (n=2 deaths), İndia (n=1 death), Central African Republic (n=2 deaths), Nigeria (n=4 deaths), Ghana (n=1 death), Peru (n=1 death), and Brazil (n=1 death) (Figure 5).[34]

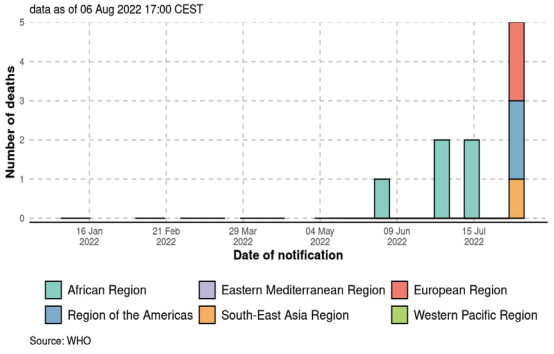

Figure 5. Reported deaths around the World.[34]

The outbreak was declared an International Public Health Emergency in late July 2022.[35]

Diagnosis, treatment options, and vaccines

Patients usually develop a rash on the genitals or anus or other contact areas such as hands, face, and mouth. The rash can be painful and sometimes manifested by itching. Although not all symptoms appear at the same time, other

symptoms are fever, headache, muscle pain, weakness, lymphadenopathy, and respiratory symptoms such as sore throat and cough.[36]

Although the disease is mostly self-limiting, the disease may be more severe in pregnant women, pediatric patients, and immunocompromised individuals.[37]

Swab samples taken from the lesion, mouth, and rectum or scab samples can often be used as examination specimens.[38]

Although other signs are useful in distinguishing vesiculopustular rashes of poxvirus infections from other infections, laboratory confirmation is required for definitive diagnosis. Various laboratory diagnostic tests such as virus isolation, electron microscopy, PCR, IgM and IgG ELISA, immunofluorescence tests, and histopathological examination can be used in the diagnosis of Monkeypox infections. Most of these methods cannot distinguish monkeypox infection from other poxvirus infections. Next-generation sequencing techniques continue to be used as the gold standard test for Monkeypox characterization.[1,39]

There are no licensed drugs for monkeypox so far. Brincidofovir and tecovirimat have been approved in the USA as treatment options for smallpox in case of a threat of bioterrorism.[40] Antivirals such as Tecovirimat have been recommended for those at risk of serious illness, such as those with compromised immunity.[41] Smallpox was reported to have been eradicated in 1977, due to the success of vaccination campaigns with the Vaccinia virus. As a result, it was recommended to stop the Vaccinia vaccine in 1980.[42] It is stated that the smallpox vaccine also has a protective effect against Monkeypox infections.[43] Vaccination is also thought to reduce the clinical manifestations of infection.[35] Currently, there are three smallpox vaccines available. Candidate vaccines are JYNNEOS and ACAM2000, licensed for smallpox, and Aventis Pasteur Smallpox Vaccine, an investigational vaccine for emergencies. JYNNEOS is indicated for adults at high risk.[43,44,45]

Vaccination is recommended for laboratory personnel working in the diagnosis of pox viruses and other healthcare workers at risk of exposure.[46] In case of exposure, it is recommended to start vaccination within 4 days after exposure. It is stated that vaccination 4-14 days after exposure can reduce symptoms but does not prevent the onset of the disease.[47]

Data show that the smallpox vaccine is at least 85% effective in preventing monkey disease. The risks from Monkeypox infections are greater than those from smallpox or monkeypox vaccines.[47]

Hyperimmune globulins are recommended for the treatment of serious complications of the vaccine (such as Eczema vaccinatum).[39] Immunoglobulins are also recommended in immunocompromised patients for whom the live vaccine is contraindicated.[39,48]

CONCLUSIONS

Monkeypox has been showing signs of becoming a global public health problem for many years, with minor outbreaks. The current epidemic is expected to spread gradually in the coming months. Therefore, it is necessary to work efficiently to control the epidemic. As we have learned from other outbreaks we have to share available resources early and efficiently.

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Clinical Characteristics of Monkeypox

Maymun Çiçeğinin Klinik Özellikleri

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Öz

Maymun çiçeği, Poxviridae ailesinden Orthopoxvirus cinsine ait Monkeypox virüsünün neden olduğu zoonotik bir hastalıktır. Ateş, yorgunluk, halsizlik, baş ağrısı, döküntü ve lenfanopati ile karakterize bir klinik sergilemektedir. Monkeypox, genellikle 2-4 hafta süren semptomlar ile kendi kendini sınırlayan bir hastalıktır. Bunun yanı sıra ağır vakalar da ortaya çıkabilmektedir. Bu çalışmanın amacı maymun çiçeğinin klinik özelliklerini gözden geçirmektir.

Anahtar Kelimeler: Maymun Çiçeği, Klinik, Komplikasyon

Abstract

Monkeypox is a zoonotic disease caused by the Monkeypox virus, which belongs to the Orthopoxvirus genus of the Poxviridae family. It exhibits a clinical condition characterized by fever, fatigue, malaise, headache, rash and lymphopathy. Monkeypox is a self-limited illness with symptoms usually lasting 2-4 weeks. In addition, severe cases may occur. The aim of this study is to review the clinical features of monkeypox.

Keywords: Monkeypox, Clinic, Compication

INTRODUCTION

Monkeypox is a viral zoonotic infection. It presents with a smallpox-like rash. However, its person-to-person spread and mortality rate is significantly lower than with smallpox. Monkeypox virus was first identified as a human disease agent in the Democratic Republic of Congo in the 1970s.[1] The prevalence of this disease, which is seen in 11 countries with tropical rainforests in Central and West Africa, especially in Nigeria and the Democratic Republic of Congo, is not known exactly. The disease is occasionally transmitted from the African continent to other parts of the world through infected animals or humans, where regional clusters of cases are observed in which a small number of people are affected. However, since the number of cases detected outside of Africa has so far increased to exceed the total number of cases seen outside of Africa, it has drawn the attention of the World Health Organization (WHO) and the scientific community. A new outbreak of monkeypox was first reported in Europe in May 2022.[2] On 23 July 2022, WHO declared this monkeypox epidemic a public health emergency of international importance.[3] In this review, I aimed to present the clinical features of Monkeypox.

Most patients with monkeypox were symptomatic during the global epidemic that emerged in 2022. Asymptomatic infections appear rare.[4,5] The clinical appearance of monkeypox is similar to smallpox, but less severe than smallpox in terms of complication rate, mortality rate and scar development.[6,7]

The incubation period of monkeypox virus infection is usually 5 to 13 days but can range from 4 to 21 days. In a study of 29 patients, it was reported that the estimated incubation period after exposure to the disease was 12 days. People with a history of animal bites or scratches were found to have a shorter incubation period than those with a history of contact (9 vs 13 days, respectively).[8-9] In addition, the duration of symptoms and signs is estimated at 2 to 5 weeks. The disease begins with non-specific symptoms and signs such as fever, chills, headache, lethargy, asthenia, lymph node swelling, back pain, and muscle pain, before rash appears. The prodromal period, which typically lasts up to five days, is characterized by fever, severe headache, lymphadenopathy, myalgia, and fatigue. Lymphadenopathy can be seen all over the body or localized to several areas. However, during the monkeypox epidemic that began in May 2022, some patients had genital, rectal, and/or oral lesions without an initial prodrome.[8] One to 5 days after the onset of fever, rashes of varying sizes appear first on the face, then on the body, hands, legs and feet. The rash tends to be more intense on the face, but usually develops on the palms and soles. The rash starts as a macule and then turns into papules, vesicles, and pustules. Finally, it crusts and over time, the crusts fall off with healing. Pharyngeal, conjunctival and genital mucositis may also be seen. Lesions typically begin to develop simultaneously and co-evolve elsewhere in the body.[10]

However, during the global monkeypox epidemic that began in May 2022, not all lesions were at the same stage of development.[11] The rash associated with monkeypox is often described as painful, but may become itchy during the healing phase.[10]

It is very difficult to distinguish the clinic of monkeypox from smallpox. Although clinical symptoms are milder than smallpox, it can be fatal. Complications such as secondary bacterial infections, bronchopneumonia, encephalitis, corneal infection causing vision loss, and diarrhea with dehydration have been reported. Mortality rates in epidemics vary between 1% and 10%. Deaths occur mostly among young adults and children. Especially those who are immunocompromised are at risk of serious illness. Lymphadenopathy occurs in up to 90% of patients and appears to be a clinical feature that distinguishes human monkeypox from smallpox.[12-16] In individuals vaccinated with smallpox vaccine, it provides some protection against monkeypox infection and the clinical course may be milder. Monkeypox is more common among those who have

not been vaccinated against smallpox. Compared to the vaccinated, the disease described for the unvaccinated is more severe, more mortal, and the rash is pleomorphic.[17-21] The first disease to be considered in the differential diagnosis is chickenpox with lesions on the palms and soles. The lesions in chickenpox are more superficial and occur in clusters of the same stage, more intensely on the body than on the face and extremities.[7,22]

Monkey pox can be confused with chickenpox, molluscum contagiosum, measles, rickettsial infections, bacterial skin infections, anthrax, scabies, syphilis, and drug reactions. Therefore, these should be considered in the differential diagnosis. The feature that distinguishes monkeypox from smallpox and chickenpox is lymphadenopathy.[23] In the study in which 7 patients followed up for Monkeypox virus infection in the UK between 15 August 2018 and 10 September 2021 were examined; 5 of the cases had LAP and 7 had rashes. All of the patients were young and had no previous comorbidities, and none of them had smallpox vaccination. However, most experienced a relatively mild course of illness and all recovered. Only two of the seven patients had sore throat.[24]

During the 2017-2018 outbreak in Nigeria, a report of 122 human monkeypox cases was identified. The rash was present in all patients and included all parts of the body, with the face most affected; fever, pruritus, headache, and lymphadenopathy were also common.[25]

During the 2003 United States outbreak, a detailed review of 34 patients found that the predominant signs and symptoms were rash (97%), fever (85%), chills (71%), lymphadenopathy (71%), headache (65%), and myalgia (56%) reported. The onset of fever was approximately two days before the rash, but the median duration of fever was shorter than the rash (8 and 12 days, respectively).[19] Atypical presentations have been described during the 2022 pandemic. Some cases started with a rash that appeared on the genitals, then spread to the face and body;[8] in other cases, the lesions did not involve the face or extremities at all. Patients also presented with visible perianal vesicular, pustular, or ulcerative skin lesions and anorectal pain, tenesmus, and rectal bleeding found to be associated with proctitis. Lesions have sometimes been at different stages of progression in a particular anatomical region. Prodromal symptoms such as fever, malaise, headache, and lymphadenopathy did not always precede the rash, and in some cases no prodrome was reported.[11]

Disease course and prognosis

For most people, monkeypox is a self-limiting illness with symptoms lasting two to four weeks. However, some patients may develop serious illness.

Risk factors for severe disease

Severe cases of monkeypox are more common among children and are related to the degree of exposure to the virus, the presence of underlying disease, and the severity of complications.[19,26]

Hospitalization rate

During the 2022 global pandemic, few hospitalizations were reported, most of them for the purpose of isolating the patient.[27] Other reasons for hospitalization include the need to provide adequate pain management and treat secondary infections.[4,28,29]

Mortality rate

The mortality rate associated with monkeypox has varied. In Central Africa, the mortality rate has been reported as about 10 percent, and deaths usually occur in the second week of illness.[30,31] In contrast, there were no deaths in the 2003 outbreak in the United States. In the case series of seven patients diagnosed with monkeypox between 2018 and 2021 in the UK, all patients made a full recovery.[24] As of mid-July 2022, no deaths were reported in non-endemic countries during the 2022 outbreak, but new cases continue to emerge.

Asymptomatic infection

Seroepidemiological studies in Africa suggest that some patients may have subclinical or asymptomatic monkeypox infection.[17] Asymptomatic infections were rare in the 2022 outbreak.[4,5] As an example, in a June 30, 2022 update from the European Center for Disease Prevention and Control, only one of 1435 patients reported with monkeypox was listed as "asymptomatic".[4] The potential for transmission from a person with an asymptomatic infection is uncertain. In an unpublished preprint study conducted at the beginning of the 2022 outbreak in Europe, preserved anogenital and oropharyngeal specimens from 224 men tested for gonorrhea and chlamydia were PCR tested for monkeypox; Three men had anorectal specimens that were positive for monkeypox DNA, although no symptoms or exposure to a person with monkeypox was reported.[5] While the finding raises concern that people with mild illness may contribute to continued transmission, none of the three men's contacts developed clinical monkeypox, and a follow-up monkeypox test was negative 21 to 37 days after the initial positive sample.

As a result, the incubation period is usually 5 to 13 days. Patients present with a systemic illness including fever, chills, and myalgia followed by a typic rash. The rash typically starts as macules and evolves into papules, vesicles, and then pustules. The lesions eventually crust over and these crusts dry up and then fall off. However, during the monkeypox epidemic in 2022, some patients had genital, rectal and/or oral lesions without an initial prodrome.

Conflict of Interest

There is only one author. The author declared no conflicts of interest with concerning to the authorship and/or publication of this article

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Maymun Çiçeği Virüsünün Yapısal Özellikleri ve Laboratuvar Tanısı

Structural Features and Laboratory Diagnosis of Monkeypox Virus

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Öz

Maymun çiçeği virüsü daha önce endemik olarak Afrika'da görülen ve çiçek hastalığı benzeri hastalığa neden olan bir zoonozdur. Son zamanlarda insandan insana bulaşların artması ve Afrika'nın ötesindeki salgınların ortaya çıkması ile dikkatleri üzerine çekmiştir. Hastalık genellikle kendini sınırlamaktadır ancak %10'a varan mortalite ve ciddi komplikasyonlar görülebilmektedir. Hastalığın spesifik bir klinik tablosu yoktur ve Maymun çiçeği virüsü diğer bazı virüs türleri ile yapısal benzerlik sergilemektedir. Henüz spesifik bir aşısı ve tedavisi olmayan bu etkenin hızlı ve erken tanınması salgın yönetimindeki en etkili basamak olacaktır. Bu derlemede Maymun çiçeği virüsünün yapısı ve laboratuvar tanısında kullanılan yöntemler gözden geçirilmiştir.

Anahtar Kelimeler: Maymun çiçeği virüsü, Orthopox virüs, tanı, salgın

Abstract

Monkeypox virus is a zoonosis that was previously endemic in Africa and causes a smallpox-like disease. The disease has recently gained attention due to increasing human-to-human transmission and the occurrence of outbreaks outside of Africa. The disease is usually self-limiting, but up to 10% mortality and severe complications can occur. The clinical manifestations of the disease are not specific, and Monkeypox Virus exhibits structural similarity to some other virus strains. Since there is no specific vaccine and treatment yet, rapid and early recognition of this agent will be the most effective step in epidemic management. This review discusses the structure of monkeypox virus and the methods used in laboratory diagnosis.

Keywords: Monkeypox virus, Orthopoxvirus, diagnosis, outbreak.

GİRİŞ

Maymun çiçeği virüsü (MPXV), Poxviridae ailesinde Orthopoxvirus genusunda yer almaktadır ve maymun çiçeği hastalığının etkenidir. MPXV'nin Orta Afrika (Kongo Havzası) ve Batı Afrika olmak üzere iki farklı evrimsel türü bulunur.[1] Orthopox virüsler Camelpox, Cowpox,Variola, hem aşı virüsü olan, hem de Güney Amerika'da sığır çiçeği (Bovine Vaccinia, BV) salgınlarına neden olan Vaccinia virüsü dahil olmak üzere insan ve veteriner tıbbı için büyük önem taşıyan virüsleri içerir.[2,3]

MPXV ilk kez 1958'de Singapur'dan Danimarka'ya araştırma tesisine gönderilen maymunların hastalanmasıyla izole edilmiştir. 1970 yılında da Demokratik Kongo Cumhuriyeti'nde çiçek hastalığı olduğundan şüphelenilen bir çocuktan tespit edilmiştir.[4] MPXV'in keşfinden bu yana, nadir görülen ve kendi kendini sınırlayan bir hastalık olduğu düşünüldüğü için pek ilgi görmemiş, ancak Mayıs ve Temmuz 2022 arasında 50'den fazla ülkede 10.000'den fazla vakayla devam etmekte olan salgın, MPXV'nin insanlar arasında önemli ölçüde yayılabileceği ve halk sağlığı için ciddi bir tehdit haline gelebileceği konusunda endişe yaratmıştır.[5]

MPXV'de rezervuar ve tesadüfi konaklar henüz tam olarak aydınlatılamamıştır. MPXV hayvandan insana, insandan insana veya kontamine ortamlardan insanlara bulaşabilmektedir.[6] En yüksek riskli bulaşma yolları doğrudan temas, damlacık veya fomitlerdir.[7]

Maymun çiçeği hastalığında insanlarda görülen en sık klinik bulgular; ateş, titreme, halsizlik, baş ve vücut ağrıları, lenfadenopati gibi spesifik olmayan semptomlar ve kabuklanarak iyileşen, papül ve veziküllere dönüşen karakteristik cilt döküntüleridir.[5] Ayırıcı tanıda su çiçeği, herpes simpleks virüsü, çiçek hastalığı diğer pox virüslerin neden olduğu hastalıklar (tanapox, orf) göz önünde bulundurulmalıdır.[2]

Maymun çiçeği hastalığının klinik belirtileri çiçek hastalığından genellikle daha hafif olmasına ve kendisini sınırlamasına rağmen, bir dizi önemli tıbbi komplikasyonun eşlik edebileceği ağır klinik tablolara yol açabilmektedir. MPXV'in vaka ölüm oranı, endemik bölgelerdeki salgınlarda %1 ila %11 arasında değişmektedir. Çocuklar ve genç yetişkinler arasında ölüm oranı daha yüksektir ve bağışıklık sistemi baskılanmış kişilerde seyir daha şiddetlidir. Sekonder bakteriyel enfeksiyonlar, solunum sıkıntısı, bronkopnömoni, ensefalit, görme kaybıyla sonuçlanan kornea enfeksiyonları, gastrointestinal sistem tutulumu gibi bir dizi komplikasyon bildirilmiştir.[8]

Günümüzde maymun çiçeği enfeksiyonu için klinik olarak kanıtlanmış spesifik bir tedavi yoktur. Çoğu viral hastalıkta olduğu gibi, semptomatik destekleyici tedavi uygulanmaktadır. Bu nedenle MPXV'nin hızlı ve doğru tanımlanması salgının yayılmasını ve meydana gelebilecek mortalite ve komplikasyonları önlemede çok önemlidir.[4,9]

Maymun Çiçeği Virüsü Yapı ve Organizasyonu

MPXV; Variola, Cowpox ve Vaccinia virüslerini içeren Poxviridae ailesindeki Orthopoxvirus genusu üyesidir. Maymun çiçeği hastalığına neden olan nadir bir zoonotik viral etkendir.[10] Poxviridae ailesi; böceklerde, sürüngenlerde, kuşlarda ve memelilerde bulunan, omurgalı-omurgasız ayrışmasından önce "çiçek hastalığı" oluşturduğu bilinen eski bir virüs ailesidir.[11]

Orthopoxvirus başta olmak üzere *Parapoxvirus, Avipoxvirus, Capripoxvirus, Leporipoxvirus, Suipoxvirus, Molluscipoxvirus, Yatapoxvirus, Cervidpoxvirus* ve *Crocodylidpoxvirus*'leri omurgalılarda görülen *Poxviridae* ailesi *Chordopoxvirinae* alt ailesinde yer alan genuslardır. Tümü çapraz reaktiviteye neden olan benzer antijenler ve benzer bir DNA dizisine sahiptir.[12,13]

Variola ve Vaccinia virüsleri MPXV'nin bilinen en yakın akrabaları olup, genom dizileri yüksek düzeyde benzerlik gösterir (%96); ancak filogenetik çalışmalarla birbirlerinden evrimleşmedikleri gösterilmiştir.[5,14] MPXV ve Variola

virüsünün gen dizi analizi ile karşılaştırıldığı bir çalışmada, temel enzimleri ve yapısal proteinleri kodlayan merkezi genomik bölgede %96.3 benzerlik gösterdikleri, farklılığın genomun virülans ve konak aralığını etkileyen genlerde, genomun bitimine yakın bölgelerde olduğu saptanmıştır.[14] MPXV'nin Batı Afrika ve Orta Afrika (Kongo Havzası) olmak üzere iki farklı soyu vardır. Bu farklılık Batı Afrika MPXV'den 10.000 bp'lik genom fragmanlarının kaybına yol açan bir rekombinasyon olayı ile ilişkilendirilmektedir.[5,7,15]

Pox virüsler bilinen en büyük ve en karmaşık yapılı virüslerden biridir. Lineer çift sarmallı DNA genomuna sahip, lipoprotein bir zarf ile çevrili tuğlaya benzer, pleomorfik şekilli virüslerdir. MPXV elektron mikroskobu ile bakıldığında yaklaşık 200-250 nanometre boyutundadır.[4,16] MPXV bikonkav dambıl şeklinde bir çekirdeğe sahiptir. Çekirdeğin içinde yer alan viral genom, DNA protein kompleksi ve viral enzimler ile birlikte bulunmaktadır. Bunlar birlikte nükleokapsit yapısını oluştururlar. Nükleokapsitin her iki tarafında yer alan oluklarda "Lateral Cisimcikler" bulunmaktadır. Kriyo-elektron mikroskobu ile görüntülenen bu cisimciklerin işlevleri bilinmemektedir; yapısal artefaktlar oldukları düşünülmektedir. Nükleokapsit, tübüler protein içeren lipit bir zarf ile çevrelenmiştir.[6,13,16-18]

Orthopox virüslerin enfeksiyonları esnasında yapı, fonksiyon ve konumuna göre 4 farklı formları vardır; hücre içi olgun virüs (Intracellüler Matur Virion, IMV), hücre içi zarflı virüs (Intracelluler Envelope Virion, IEV), hücre ilişkili zarflı virüs (Cell-associated Enveloped Viruses, CEV) ve hücre dışı zarflı virüs (Extracelluler Envelope Viruses, EEV).

Virion, hücreye girdiğinde IMV formundadır. Bu form 12'den fazla farklı glikozile edilmemiş viral proteinin gömülü olduğu çift tabaka lipit bir zarfa sahiptir. Hücre lizisi ile salınırlar ve enfeksiyonu hem organizmaya hem de bir konakçıdan diğerine yayarlar. IEV ise IMV'nin iki ek zarfla çevrilmiş formudur; dış zarflarında en az 9 viral protein içerir. IEV'ler hücresel mikrotübüllere bağlanarak hücre yüzeyine doğru hareket ederler ve bu arada kendi dış membranları ile sitoplazmik membranın füzyonu gerçekleşir. Bu süreç sonunda CEV'ler ortaya çıkar. CEV iki çift katmanlı lipit zarfla çevrilidir ve aktin filamentleri tarafından hücre dışına taşınır. Hücre dışına taşınan bu serbest virionlara EEV denir. EEV, CEV'lerle aynıdır; ancak CEV enfeksiyonun hücreden hücreye yayılmasında etkinken, EEV'ler bir konakçıdan başka bir konakçıya yayılımı sağlarlar.[13,16]

Pox virüs ailesi üyeleri genomu 200-500 kb büyüklüğündedir ve her iki DNA zincirinde 150-200 gen bulunmaktadır. Sahip oldukları genlerin büyük bir kısmı aslında virüs replikasyonu için gerekli değildir; fakat konakçının antiviral yanıtında önemli roller oynarlar. Bu genlerin 49'u tüm Pox virüslerde korunmuş ortak genlerdir. *Chordopoxvirinae* alt ailesinde ise korunmuş ortak gen sayısı 90'dır.[13,18,19] Korunan genler genomun merkezinde yer alan, yapısal proteinler, transkripsiyon faktörleri ve enzimleri kodlayan, genom replikasyonu ve viral çoğalma için esansiyel olan genlerdir. Korunmamış genler ise DNA'nın her iki ucundaki ters çevrilmiş terminal tekrar (ITR) bölgelerinde yer alırlar ve virülans ile ilişkilidirler. Bu genler apoptoz inhibisyonu, antijen sunumu ve tanınmasının engellenmesi, immün uyarıcı sitokinlerin tetiklediği interferon ve sinyal yolaklarını bozma gibi virüsün konakçı savunma mekanizmalarından kaçmasını sağlayan gen ürünlerini kodlarlar.[5,13,18]

MPXV ile çok benzer olan Vaccinia virüs için replikasyon döngüsü iyi karakterize edilmiştir ve bu replikasyon döngüsünün temel özellikleri tüm Pox virüs ailesi üyeleri için benzerdir. Pox virüsler için henüz spesifik hücre reseptörleri tanımlanmamıştır; ancak memeli hücre yüzeyinde bulunan glikozaminoglikanların virionun hücre zarına bağlanmasında çok önemli olduğu düşünülmektedir. Enfeksiyon döngüsü "hücre içi olgun virion" ve yüzey glikoproteinlerinin ekspresyonunda farklılık gösteren "hücre dışı zarflı virion" olmak üzere iki farklı form ile başlatıla-

bilmektedir.[18,19]

Pox virüslerin hücreye invazyonu adsorbsiyon, membran füzyonu ve çekirdek invazyonu olmak üzere üç basamakta gerçekleşmektedir. Hücre duvarına adsorbsiyonda yardımcı 4 viral protein tanımlanmış olup, bunlar D8, A27, A26 ve H3'tür. D8 kondroitine, A27 ve H3 heparana, A26 ise laminine bağlanır. Bu proteinler ayrı fonksiyonlara sahiptirler ve MPXV'de karşılık gelen ortolog genler sırayla E8, A29, A28 ve H3'tür.[18]

Vaccinia virüsleri için membrana füzyon ve çekirdek invazyonu IMV tarafından 11 viral protein aracılığıyla düzenlenmektedir: A16, A21, A28, F9, G3, G9, H2, J5, L1, L5 ve O3. Bu proteinler bir araya gelerek viral adsorpsiyondan sonra giriş füzyon kompleksini oluştururlar. O3 dışında kalan 10 protein Pox virüs replikasyonu için gereklidir.[18]
Diğer memeli DNA virüsleri çoğalmak için çekirdeğe ulaşmak zorundayken, Pox virüsler "viral fabrikalar" adı verilen bölmelerde tamamen sitoplazma içerisinde çoğalırlar. Genomları içerisinde kendi RNA ve DNA polimerazları, transkripsiyon faktörleri, RNA modifikasyonu ve nükleik asit metabolizmasında yer alan birçok enzim için gerekli genetik bilgiye sahiptirler. Çekirdekte bulunan hücresel replikasyon mekanizmasını kullanmalarına gerek yoktur; ancak mRNA'larının translasyonu için tamamen konakçı ribozomlarına bağımlıdırlar.[13,20]

MPXV diğer DNA virüsleri gibi çift sarmallı DNA'nın daha yüksek stabilitesi ve DNA polimerazının 3'-5' düzeltme ekzonükleaz aktivitesi nedeniyle RNA virüslerine göre (influenza ya da SARS-CoV-2 gibi) çok daha nadir mutasyona uğrar. Bu virüsler ayrıca virülansları, bağışıklık sistemiyle etkileşim ve ondan kaçınma yeteneklerinden sorumlu olan büyük bir genetik donanıma sahiptirler.[5,12]
MPXV kuruluğa ve düşük sıcaklığa dayanıklıdır; 4°C'de uzun süre canlılığını koruyabilir. Ancak ısıya dayanıklı değildir; 56°C'de 30 dakikalık işlemden sonra inaktive olmaktadır. Virüs formaldehit, metanol, sodyum dodesil sülfonat (SDS), fenol ve kloroform gibi organik çözücüler tarafından kolaylıkla etkisiz hale gelmektedir.[18]

Maymun Çiçeği Virüsü Laboratuvar Tanısı

MPXV Kongo Havzası ve Batı Afrika soyları olmak üzere 2 farklı suşu bulunmaktadır. Batı Afrika soyunun mortalitesi daha düşüktür ve daha az bulaşıcıdır; bu nedenle bu iki suşu ayırt etmek önemlidir.[14] Ayrıca klinik ayırıcı tanıda su çiçeği, kızamık, uyuz, sifiliz, tanapox (yatapox) gibi Pox virüs ailesi ile ilişkili hastalıklar, bakteriyel cilt enfeksiyonları ve ilaca bağlı allerjiler gibi döküntülü hastalıklar göz önünde bulundurulmalıdır.[2,18,21]

Pox virüs türlerinin ayrımı ve tanımlanması klinik öykü ve çeşitli analitik laboratuvar yaklaşımlarını kapsar. Bunlar virüsün üretilmesi, histolojik inceleme, elektron mikroskobik inceleme, serolojik ve moleküler testlerdir.[21]

Günümüzde şüpheli lezyon materyalinden MPXV DNA'sının PCR ile analizi en hızlı ve hassas birincil laboratuvar tanı tekniğidir. Mukozal örneklerde lezyon mevcut ise solunum yolu, vajinal veya rektal mukozal örnekler tanıda kullanılabilir. MPXV cinsel temas ile de bulaşabildiğinden proktit vakalarında rektal örneklerin de gönderilmesi tavsiye edilir.[12] Sınırlı viremi süresi nedeniyle kan örnekleri yerine kuru kabuklar, sürüntüler ve lezyondan aspire edilen sıvılar tercih edilmektedir. Bu numunelerden çalışıldığında alınan sonuçlar hem enfektivite hem de enfeksiyonun klinik seyri açısından en iyi korelasyonu göstermektedirler.[2] Mümkün olduğunda biyopsi de bir seçenektir. Lezyon örnekleri kuru, steril bir tüpte (viral taşıma ortamı yok) saklanmalı ve soğukta tutulmalıdır.[7]

Numune Saklama Koşulları

MPXV çalışılmak için toplanan numuneler, toplandıktan sonra bir saat içinde ya buzdolabında (2-8 °C) muhafaza edilmelidir ya da dondurulmalıdır (-20 °C veya daha düşük). Test edilecek numune için transfer süresi 7 günü aşarsa, numuneler -20 °C veya daha düşük sıcaklıklarda saklanmalıdır. Numeneler toplandıktan sonra 60 gün ve üzerinde saklanması gerekiyorsa -70°C'de saklanması öne-

rilmektedir. Numunelerin kalitesini etkileyebileceği için tekrarlayan dondurma-çözdürme işlemlerinden kaçınılmalıdır.[22]

Histolojik Tanı

Pox virüsler epidermal hücrelerde çoğalmaktadır. Virüslerin çoğalması sırasında hücre yapısında birtakım değişikler meydana gelir ve bunlar Hematoksilen&Eosin gibi histokimyasal boyalarla farklı boyanma şekilleri gösterirler. A tipi inklüzyon asidofilik boyanır; Marchal ve Downie cisimciklerini oluşturur. B tipi veya Guarnieri inklüzyon cisimcikleri bazofilik boyanır ve DNA sentezinin göstergesidir.

Klinik ayırıcı tanıcıda yer alan Herpesviridae ailesinden Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), *Poxviridae*'nın diğer üyeleri ve *Orthopoxvirus* genusu üyelerinin, MPXV' den histolojik olarak ayırt edici özellikleri vardır.

Hücre içinde görülen inklüzyonlara bakıldığında Cowpox virüs sitoplazmik Tip A ve B inklüzyon; MPXV, Variola virüs, Vaccinia virüs, Yatapoxvirüsler/Parapoxvirüsler sitoplazmik Tip B inklüzyon gösterirken ayırıcı tanıda benzer lezyonlara sahip HSV ve VZV'de nükleer inklüzyonlar görülmektedir. *Molluscum contagiosum*'da diğer Poxvirüslerde görülmeyen karakteristik asidofilik boyanan *Molluscum* cisimcikleri gözlenir. Pratikte histolojik tanı yanlızca *Molluscum contagiosum*'un doğrulanmasında kullanılmaktadır.[21]

Hemaglütinasyon aktivitelerine göre *Orthopox* genusu içerisinde MPXV yüksek aktiviteye sahipken, *Vaccinia* ve *Cowpox* virüslerinde bu aktivite zayıf veya yoktur, diğer Pox virüslerden *Molluscum contagiosum* virüsü, P*arapox/ Yatapox* virüslerinde yoktur. Ayırıcı tanıda yer alan *Herpesviridae*'de üyesi HSV ve VZV'de hemaglütinasyon aktivitesi bulunmaz.[21]

Viral Kültür

Pox virüsler ve bazı epiteliotrop karakterdeki virüslerin hücre kültürü için embriyonlu tavuk yumurtasındaki Korio-Allantoik Membran (CAM)'a ekim yapılmaktadır.[23] Farklı türlerin CAM'da ekim sonrası oluşturdukları lezyonların görünümleri tanıda ipucu verebilir. CAM'a ekim sonrası Cowpox virüslerin lezyonları düz, zayıf tanımlanabilen, hemorajik, izole beyaz poklardır. MPXV ise CAM'a ekildiğinde merkezi hemorajik, izole büyük beyaz poklar şeklinde görülür. Variola virüsler monomorfik, beyaz keskin yapıda, kubbe benzeri poklar şeklinde, Vaccinia virüsler ise büyük beyaz veya gri düz poklar şeklinde görülürler. *Yatapox/Parapox* virüs ve *Molluscum contagiosum* virüslerde korio allantoik membranlarda lezyon oluşmaz. VZV'de de CAM'a ekimde lezyon oluşmaz. HSV'de ise küçük beyazımsı lezyonlar oluşur.[21]

Hücre kültürü daha fazla karakterizasyon için virüs suşları sağlar, ancak uygulaması biyogüvenlik seviyesi 3 laboratuvarlarıyla sınırlıdır ve deneyimli personel gerektirir.[19]

Elektron Mikroskobik Tanı

Elektron mikroskopisi ile enfekte epidermal hücrelerin sitoplazmasında bol miktarda *Orthopox* virüs partikülü görülebilir.[12] Ancak elektron mikroskopisi MPXV ve diğer Pox virüslerini morfolojik olarak ayırt edemediği için tanıyı doğrulayamaz; sadece virüsün Pox virüs ailesinden olduğuna dair bir ipucu sağlayabilir. Bunun dışında bu yöntemin duyarlılığı yüksek değildir; numune hazırlama süresi oldukça karmaşık ve uzundur.[18]

Serolojik Testler

Serolojik testler, virüse özgül IgG ve IgM antikorlarının tespitinde enzim immün assay (EIA) ve viral antijen tespiti için immünohistokimyasal yöntemleri içerir.[11]

Maymun çiçeği teşhisi için plazma veya serumdan antikor tespiti tek başına kullanılmamalıdır. Ancak yapılan testlerde kesin sonuç alınamadığında, akut hastalıkta IgM sonucu ve birincisi hastalığın ilk haftasında olmak üzere 21 gün

arayla alınan çift serum örneğinde elde edilen IgG sonucu tanıya yardımcı olabilir.[22] *Orthopox* virüsler serolojik olarak çapraz reaktif olduğundan, antijen ve antikor saptama yöntemleri, maymun çiçeğine özgü doğrulama sağlamaz. Bu nedenle, kaynakların sınırlı olduğu durumlarda tanı veya vaka incelemesi için seroloji ve antijen saptama yöntemleri önerilmez. Ayrıca çiçek hastalığı eradikasyonu öncesinde aşılanmış kişilerde aşı yanıtı nedeniyle serolojik çalışmaların yapılması önerilmez.[2]

İmmünohistokimyasal incelemeler, biyopsi numunelerindeki antijenleri belirlemek ve diğer şüpheli ajanları dışlamak veya tanımlamak için kullanılabilir.[1]

Moleküler Testler

Yeni nesil dizileme (NGS) teknolojilerini kullanan tam genom dizilimi, MPXV tanısında altın standarttır ancak maliyeti yüksektir, yüksek personel deneyimi ve bilgi gerektirir.[6] Bu nedenle şüpheli lezyon materyalinden MPXV DNA'sının PCR ile analizi en hızlı ve hassas olan birincil laboratuvar tanı tekniğidir.

Orthopox virüsler ve özellikle MPXV için literatürde yayınlanmış, PCR testlerinde kullanılmak üzere tasarlanmış olan bir dizi primer ve prob setleri mevcuttur. *Orthopox* virüsleri diğer Pox virüslerden ayrımda kullanılan spesifik gen bölgelerinden E9L geni *Orthopox* virüsleri cins düzeyinde tanımlarken, hemaglutinin (HA) proteinini kodlayan gen bölgesi ile tür düzeyinde ayrım yapılabilmektedir. MPXV için F3L ve TNF reseptör gen bölgesinde yer alan G2R ayırt edici gen bölgeleridir. MPXV içinde Kongo Havzası ve Batı Afrika kümelerinin ayırt edilmesinde Batı Afrika için TNF reseptör geni içinde yer alan G2R_WA ve G2R_G gen bölgeleri, Kongo Havzası için ise kompleman bağlayıcı protein (C3L) gen bölgesi kullanılmaktadır. Ayrıca Variola virüs için spesifik B12R gen bölgesine yönelik problar mevcuttur.[14,22,24-26]

Laboratuvar Sonuçlarının Yorumlanması

MPXV enfeksiyonunun doğrulanmasında klinik ve epidemiyolojik veriler dikkate alınmalıdır. Pozitif bir Orthopox virüs PCR testinin ardından MPXV PCR ve/veya sekanslama yapılması veya şüpheli vakalarda direk MPXV PCR testinden elde edilen pozitif bir sonuç MPXV enfeksiyonunu doğrular.

Negatif PCR sonuçlarına rağmen klinik bulgular ve epidemiyolojik verilere dayanarak MPXV'den şüphelenildiğinde, ek olarak serolojik testler faydalı olabilir. Numunenin kalitesi, hatalı transfer süreci veya DNA ekstraksiyonundaki teknik sorunlar yanlış negatif sonuçlara sebep olabilir. Genetik dizileme MPXV tanısına ek olarak, virüsün kökenlerini, epidemiyolojisini ve özelliklerini anlamaya yardımcı olacak değerli bilgiler sağlayabilir. Bu yüzden farklı hastalardan mümkün olduğunca çok sayıda pozitif numuneden genetik dizileme (Sanger veya Yeni Nesil Dizileme) yapılması önerilmektedir.[22]

2022 yılında meydana gelen Maymun çiçeği hastalığı salgını hem endemik hem de endemik olmayan bölgelerde uluslararası ilgi odağı olmuştur.[19] Bütün enfeksiyon hastalıklarında olduğu gibi erken tanı; izolasyon, tedavi ve hastalığın yayılmasının önlenmesi açısından çok önemlidir. Bunun yanı sıra klinisyenler Maymun çiçeği enfeksiyonu açısından dikkatli olmalı ve enfeksiyonun bazen atipik şekillerde ortaya çıkabileceğini unutmamalıdırlar.[19]

SONUÇ

Variola virüsü yaygın aşılama yoluyla eradike edilmiş olmasına rağmen, doğada insanlar için patojenik olan diğer Orthopox virüsler dolaşımına devam etmektedir. Endemik olmayan bölgelerde Maymun çiçeği hastalığı vakalarındaki hızlı artış, bu zoonotik virüsün insanlar arasında hızlı bir şekilde yayılabileceğini ve dolayısıyla küresel halk sağlığı için bir risk oluşturabileceğini düşündürmektedir. Bütün enfeksiyon hastalıklarında olduğu gibi "erken tanı"; izolasyon, tedavi ve hastalığın yayılmasının önlenmesi açısından çok önemlidir. Bunun yanı sıra klinisyenler Maymun çiçeği hastalığı konusunda dikkatli olmalı ve enfeksiyonun atipik klinik tablolarla da ortaya çıkabileceği

unutulmamalıdır.

Yazarlık Katkıları

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Maymun Çiçeği Virüsüne Karşı Antiviral Yaklaşım ve Bağışıklık

Immunity and The Antiviral Approach Against The Monkeypox Virus

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Öz

İnsan maymun çiçeği, çift sarmallı DNA (dsDNA) virüslerinin Poxviridae ailesindeki Orthopoxvirus cinsinin bir üyesi olan maymun çiçeği virüsünün neden olduğu zoonotik bir enfeksiyondur.

Maymun çiçeği virüsü hastalığı (MÇVH) hastaların çoğunda medikal tedavi ile birlikte iyileşmektedir. Semptomları hafifletmek, komplikasyonları azaltmak için klinik bakım ve destekleyici tedavi verilmelidir. Kusma, ishal gibi sıvı kayıplarının olduğu gastrointestinal semptomları olan hastalara oral ya da intravenöz sıvı tedavisi gerekmektedir. Sekonder bakteriyel enfeksiyon izlendiği durumlarda, bakteriyel etkene özgü ve uygun antibiyotik tedavisi verilmelidir. Atipik bölgelerdeki (örneğin ağız, gözler, genital bölge) maymun çiçeği enfeksiyonu için tedavi düşünülebilir.

Birtakım ilaçlar denenmiştir, fakat etkinliği net değildir. Etkinliği olabileceği düşünülen antiviraller; Tecovirimat (TCV), brincidofovir (BCV) ve cidofovir (CDV)'dir. Bazı uzmanlar şiddetli hastalığı olan hastalarda TCV ve CDV ile ikili tedavi önerebilse de, şu anda TCV tercih edilen tedavidir.

MÇVH riskini azaltabilecek iki mevcut aşı vardır. Yüksek risk maruziyeti olan bireylere temas sonrası 14 gün içinde aşılama önerilir. Maruziyet sonrası aşılama, düşük risk maruziyeti olanlar için endike değildir. CDC, hastalığın başlamasını önlemek için aşının maruziyet tarihinden itibaren 4 gün içinde verilmesini önermektedir. Aşının maruziyetten 4-14 gün sonra verilmesi durumunda, hastalığın semptomlarını azaltabildiği ancak hastalığı önlemediği belirtilmiştir.

Anahtar Kelimeler: Maymun çiçeği, tedavi, bağışıklama

Abstract

Human monkeypox is a zoonotic infection caused by the monkeypox virus (MPV), a member of the Orthopox genus in the family Poxviridae among the double-stranded DNA (dsDNA) viruses.

MPV disease resolves with medical treatment in the majority of cases. Clinical care and support therapy must be provided in order to ameliorate symptoms and reduce complications. Patients with gastrointestinal symptoms involving fluid loss, such as vomiting and diarrhea, require oral or intravenous fluid therapy. Appropriate agent-specific antibiotic therapy must be given in case of secondary bacterial infection. Treatment can also be considered for monkeypox infection in atypical regions (such as the mouth, eyes, and genital region).

Various medications have been investigated, but their effectiveness remains uncertain. Antivirals thought to be potentially efficacious include tecovirimat (TCV), brincidofovir (BCV), and cidofovir (CDV). Although some experts may recommend dual TCV and CDV therapy in patients with severe disease, TCV is currently the preferred treatment.

There are currently two vaccines capable of reducing the risk of MPV disease. Vaccination within 14 days of contact is recommended for individuals with high-risk exposure. Post-expose vaccination is not indicated for individuals with low-risk exposure. The CDC recommends that the vaccine be given within 4 days of exposure to prevent disease onset. It has been stated that if the vaccine is given 4-14 days after exposure, it can reduce the symptoms of the disease but does not prevent the disease.

Keywords: Monkeypox, treatment, immunization

GİRİŞ

ANTİVİRALLER

1.TECOVİRİMAT

Tecovirimat (TPOXX®) çiçek virüsü ve maymun çiçeği virüsü gibi orthopox virüsler için geliştirilen Avrupa ve ABD'de onaylanan tek antiviral ilaçtır[1,2]. Tecovirimat, orthopox virüslerine karşı aktiviteye sahiptir, ancak diğer dsDNA virüslerine karşı kayda değer bir aktiviteye sahip değildir. Tecovirimat, inek çiçeği hastalığında, aşı virüsü F13L genine homolog olan V061 genini hedefler. Bu, ortopoksvirüslerde iyi korunmuş bir protein olan ve hücre dışı zarflı virüsün oluşumundan sorumlu olan membran proteini p37'yi kodlar. Tecovirimat, orthopoxvirüs'ün VP37 zarf proteininin aktivitesini inhibe ederek, Rab9 GTPaz ve TIP47 (bir Rab9'a özel efektör protein) ile etkileşimini bloke eder. Bu inhibisyon virüsün konakçıda yayılması için gerekli olan viryonların oluşumunu engeller. Tecovirimat, DNA, protein sentezini inhibe etmez ve hücre lizisine kadar konakçı hücrede kalan matür virüsün oluşumunu inhibe etmez. Tek bir amino asit mutasyonu ile TCV direnci oluşabilir. Tecovirimat, CDV'ye dirençli aşı virüsü suşlarına karşı aktiviteye sahiptir ve tecovirimat ile CDV veya BCV arasında belgelenmiş bir çapraz direnç yoktur. 2018 yılında yetişkinlerde ve >13 kg ağırlığındaki pediyatrik hastalarda variola virüsünün neden olduğu insan çiçek hastalığının tedavisi için FDA tarafından onaylanmıştır[2-4]. Çiçek hastalığı olan insanlarda yapılan klinik çalışmalar etik veya uygulanabilir olmadığından, tecovirimat FDA tarafından desteklemek için yeterli ve iyi kontrollü hayvan çalışmalarından elde edilen etkililik verileri kapsamında onaylanmıştır. Bu nedenle tecovirimatın etkinliği, variola olmayan orthopox virüsleri ile enfekte olmuş primatlarda ve tavşanlarda belirlenmiştir. Bağışıklığı baskılanmış hayvan modellerinde etkinliğin azaldığını gösteren çalışmalara dayanarak, bağışıklığı baskılanmış hastalarda tecovirimatın etkinliği azalabilmektedir[2,5].

Tecovirimatın intravenöz ve oral formulasyonları mevcuttur. Tok halde uygulandığında, TCV aç kalmaya göre 1,6 kata kadar daha fazla maksimum konsantrasyon (Cmax) ile daha iyi bir emilim sağlayabilir. TCV'ın, makak maymunlarında maymun çiçeği virüsüne karşı da dahil olmak üzere, orthopox virüslerin çoklu hayvan modellerinde etkili olduğu gösterilmiştir. Hayvan modellerinde TCV, uygulaması geciktiğinde bile lezyon şiddetini azaltmaktadır. Poxvirüse maruz kaldıktan sonraki 4-72 saat içinde TCV uygulaması, çeşitli hayvan modellerinde ölümün önlenmesinde ve lezyonların şiddetinde azalmada etkinlik göstermiştir. Tecovirimat'ın vaccinia virüsünün uzak dokulara viral yayılımını azalttığı gösterilmiştir[2]. Tecovirimat, BCV ile birlikte uygulandığında sinerjik aktiviteye sahip görünmektedir. İnek çiçeği ile enfekte olmuş farelerde yapılan bir çalışmada, BCV ve TCV, özellikle tedavi önemli ölçüde ertelendiğinde kombinasyonun, tek başına her iki ilaca kıyasla mortaliteyi azalttığı gösterilmiştir. En etkin tedavi süresi 14 gün olarak belirlenmiştir. 5-7 günden kısa süreli tedaviler enfeksiyonun yeniden ortaya çıkmasına neden olabilmektedir, çünkü T hücre bağışıklığı 10 günden önce gelişmemektedir. Bağışıklığı baskılanmış hastalarda, uzun süreli tedaviler veya kombinasyon tedavisinin düşünülmesi gerekebilmektedir[5-7].

Tecovirimat'ın 200 mg'lık kapsülleri ve 200 mg/20 mL intravenöz (IV) formulasyonları mevcuttur. On dört gün boyunca önerilen dozu ≥40 kg olan hastalarda günde iki kez 600 mg, ≥25 ila <40 kg olan hastalarda günde iki kez 400 mg ve ≥13 ila <25 kg olan hastalarda günde iki kez 200 mg'dır. Tecovirimat, orta veya yüksek yağlı bir yemekten sonra 30 dakika içinde oral yoldan uygulanmalıdır. Kapsülleri yutamayan hastalarda, her bir kapsül dikkatlice açılmalı ve içeriğin tamamı 30 mL sıvı (örn. süt) veya yumuşak gıdalar (örn. elma püresi, yoğurt) ile karıştırılmalıdır. Karışımın tamamı, bir yemekle birlikte hazırlandıktan sonra 30 dakika içinde uygulanmalıdır[1,2].

Tecovirimat'ın Faz I ve II çalışmaları, güvenli ve iyi tolere edildiğini göstermiştir. Suda zayıf çözünürlüğü nedeniyle IV tecovirimat beta-siklodekstrin ile çözülür. Böbrek yetmezliği olan hastalarda dikkatli olunması önerilmektedir. Ayrıca, hayvan modellerinde hızlı infüzyonu takiben yük-

sek Cmax ataksi, titreme ve uyuşukluk dahil olmak üzere geri dönüşümlü kraniyal sinir toksisiteleriyle sonuçlandığından, IV ürünü ile hızlı infüzyondan kaçınılmalıdır. IV dozlama: 3 kg – 34 kg: 6 mg/kg 12 saatte bir, 35 kg – 119 kg: 300 mg 12 saatte bir, 120 kg ve üzeri: 300 mg 12 saatte bir şeklindedir[2].

Kapsül formunda renal doz ayarlama yoktur. IV formu GFR <30 ise kontrendikedir. Hepatik doz ayarı yoktur. Hayvan çalışmalarında embriyo toksisitesi gösterilmemiş, insanlarda veriler kısıtlıdır. Baş ağrısı, karın ağrısı, bulantı, kusma, ağız kuruluğu, aşırı duyarlılık görülebilecek yan etkilerdir[2,5].

2. BRİNCİDOFOVİR

Brincidofovir (BCV; heksadesiloksipropil-sidofovir [HDP-CDV] veya CMX001 olarak da adlandırılır), nükleotid analog cidofovir'in (CDV) bir lipid konjugatıdır. CDV ile karşılaştırıldığında, BCV'nin hücresel alımı ve hücre içi enzimler tarafından aktif forma geçişi daha iyi olmaktadır[8,9].

CDV'den farklı olarak, BCV oral olarak biyoyararlanımı iyidir. İlacın tablet ve süspansiyon formülasyonları mevcuttur. Ek olarak, BCV, CDV gibi renal organik anyon taşıyıcı 1 (OAT1) tarafından aktif olarak alınmaz, bu da BCV'nin renal güvenlik profilinde önemli gelişmeler sağlar[10,11].

BCV'nin antiviral etkisi, viral DNA'ya dahil edildikten sonra viral DNA polimerazın inhibisyonuna neden olması bakımından TPOXX'unkinden farklıdır. CDV ve BCV, daha önce adenovirüsler ve çiçek virüsleri dahil olmak üzere birkaç çift sarmallı DNA virüsüne karşı antiviral etkiler göstermiştir[12].

BCV, farklı Orthopoxvirus (OPXV) hayvan modellerinde de umut verici sonuçlar göstermiştir. MPXV fare deneyinde ve birkaç Vaccinia virüsü fare deneyinde MPXV'ye karşı değerlendirme için, STAT1 eksikliği olan fareler 5.000 PFU ile enfekte edilmiş ve enfeksiyon gününde BCV tedavisine başlanılmış (ilk doz için 10 mg/kg ve toplam 14 gün boyunca 48 saatte bir 2.5 mg/kg) ve tüm farelerin enfeksiyondan kurtulduğu görülmüştür. Ancak, maruziyet sonrası tedavi bu deneyle değerlendirilmemiştir[12-14].

BCV hücre içerisine alındıktan sonra hücresel fosfolipazlar tarafından CDV'ye hidrolize edilir ve CDV-pp'ye fosforile edilir. CDV-pp, hücresel membranları daha verimli bir şekilde geçme kabiliyeti nedeniyle BCV uygulamasından sonra daha yüksek hücre içi konsantrasyonlara ulaşır. CDV gibi, BCV'nin hücre içi yarılanma ömrü uzar ve poxvirüslerin DNA replikasyonunu inhibe eder. BCV, CDV'ye dönüştürüldüğünden, BCV ve CDV arasında çapraz direnç beklenir[8,9,12].

İnsanlarda yapılan çalışmalarda, oral BCV'nin açlık durumunda emildiğini ve plazmada daha düşük doruk CDV konsantrasyonlarına sahip olduğunu göstermiştir. Bu, BCV'ye oral kullanım kolaylığı sağlamaktadır. Ek olarak, BCV, böbreklerde daha düşük konsantrasyonlarda olmasına rağmen, akciğer, dalak ve karaciğer dokularına önemli ölçüde daha yüksek bir penetrasyon göstermiştir. Organic anion transporter 1 (OAT1)'in böbreklerde birikmesi ve böbrek hasarına neden olması OAT1 tarafından proksimal kıvrımlı tübüllere taşınan CDV'den farklı olarak BCV'yi CDV'den böbrekler için daha güvenli kılmaktadır. BCV, OAT1 için bir substrat değildir. Böylece, BCV böbreklerde birikmez ve nefrotoksik riski daha düşüktür[12-14].

BCV çoklu poxvirüs hayvan modellerinde denenmiştir. Ectromelia virüsü ile enfekte olmuş farelerde, CDV ve BCV ile tedavide plaseboya kıyasla mortalitenin önemli ölçüde azaldığı gösterilmiştir. Ayrıca BCV'nin, maymun çiçeği hastalığı ile ilk lezyonun ortaya çıkma zamanı benzer olduğu düşünülen intranazal ectromelia virüsü enfeksiyonundan sonraki beş gün içinde verildiğinde mortaliteyi önlediği görülmüştür. Tedavinin lezyon görünümünün ilk gününde başlatıldığı bir tavşan çiçeği modelinde, enfeksiyondan sonraki üçüncü günde tedavi edilen tavşanlar,

dördüncü günde tedavi edilenlere kıyasla sağkalımı iyileştirdiği, lezyonların ne zaman oluştuğuna bakılmaksızın dördüncü günden sonra verilirse plaseboda istatistiksel bir iyileşme olmadığı gözlenmiştir[12,14].

Benzer şekilde, bir intradermal tavşan çiçeği modeli, ateş anında (enfeksiyondan sonraki iki gün civarında) hemen başlatıldığında BCV'nin sağkalımı arttırdığını göstermiştir[12].

Faz I/II/III çalışmalarından elde edilen havuzlanmış veriler, BCV ile yaygın yan etkilerin gastrointestinal ve hepatoselüler toksisiteyi içerdiğini göstermektedir. Bu yan etkiler doz ve sıklıkla ilişkili görünmektedir. CDV ile karşılaştırıldığında, BCV daha düşük nefrotoksisite oranlarına ve oral uygulama avantajına sahiptir[8,10,11].

Allojenik hematopoietik hücre nakli (HCT) alıcılarında birincil CMV profilaksisi için BCV'yi inceleyen bir Faz II çalışması, plaseboya kıyasla haftada iki kez 100 mg BCV verilen grupta CMV olaylarında önemli bir azalma göstermiştir. Bu çalışmada, diyare haftada iki kez 200 mg'da doz sınırlayıcı olmuştur. Bununla birlikte, aynı endikasyonu değerlendiren sonraki bir Faz III çalışması, haftada iki kez 100 mg BCV verilen grup ile plasebo arasında CMV enfeksiyonu için klinik olarak anlamlı bir fark gösterememiş ve BCV kolunda daha yüksek oranda ciddi advers olay göstermiştir. Artan yan etki oranı çoğunlukla akut graft-versus-host hastalığı ve diyare tarafından yönlendirilmiştir. Ek olarak, BCV grubunda 24. haftada tüm nedenlere bağlı mortalite biraz daha yüksek izlenmiştir. Allojenik HCT alıcılarında adenovirüs viremisinin önleyici tedavisi için BCV'yi değerlendiren diğer bir Faz II çalışmasında ve BCV'nin haftada iki kez 100 mg uygulayan kolda sayısal olarak daha düşük bir tedavi başarısızlığı ve tüm nedenlere bağlı daha düşük ölüm oranı gösterilmiştir. Bununla birlikte, BCV grubunda daha yüksek oranda akut graft-versus-host hastalığı gözlenmiştir. BCV'nin ek retrospektif çalışmaları, dirençli CMV ve Herpes simpleks tedavisinde ve Varicella zoster profilaksisi için kullanıldığında etkinliği olduğunu göstermiştir[8,15].

BCV'nin 100 mg tablet ve 10 mg/mL süspansiyon şeklinde formülasyonları bulunmaktadır. Yetişkin, pediyatrik ve yenidoğanda kullanımı mevcuttur. Dozlaması; <10 kg: 6 mg/kg (süspansiyon) haftada bir kez x 2 doz (1. ve 8. Gün), 10 kg ila <48 kg: 4 mg/kg (süspansiyon) haftada bir x 2 doz (1. ve 8. Gün), 48 kg ve üzeri: 200 mg (20 mL veya 1 tablet) haftada bir x 2 doz (1. ve 8. Gün) şeklindedir. IV formu yoktur. ALT> 10x normalin üst sınırı/ UL ise veya karaciğer iltihabının belirti ve semptomları varsa 2. Doz yapılmamalıdır. Tablet formunun aç karnına veya az yağlı yemeklerle kullanımı önerilir. Süspansiyonun aç alınması önerilir. Gebelerde kullanılmamalıdır. Doğurganlık çağındaki bireylere ilaç kullanımı sonrasında 2 ay kontrasepsiyon önerilir. İshal, bulantı, kusma, karın ağrısı, bilirubinde ve transaminazlarda yükselme görülebilecek yan etkilerdir[8,16].

3. CİDOFOVİR

Cidofovir (Vistide®), ortopoksvirüsler dahil birçok DNA virüsüne karşı etkili olmasına rağmen, yalnızca sitomegalovirüs retiniti tedavisi için FDA tarafından onaylı bir ilaçtır. Cidofovir (CDV), önce konakçı hücrelere girmesi gereken, daha sonra hücresel enzimler tarafından aktif form olan CDV difosfata (CDV-pp) fosforile edilmesi gereken bir ön ilaçtır. Fosforillendikten sonra CDV-pp'nin hücre içi yarılanma ömrü uzar. DNA replikasyonu sırasında, CDV-pp büyüyen DNA zincirine dahil edilir ve DNA sentezini yavaşlatır. CDV-pp ayrıca DNA polimeraz 3'-5' eksonükleaz aktivitesini de inhibe edebilir[16,17].

CDV'nin oral yoldan emilimi çok zayıftır. Sadece intravenöz kullanımı etkindir. Plazma CDV hızla renal olarak filtrelenir ve salgılanır, buna karşın hücre içi fosforile metabolitlerin yarılanma ömrü uzundur, bu da haftalık veya iki haftada bir doz kullanım olanağı sağlar[8,17].

CDV, proteinüriyi takiben glukozüri, azalmış bikarbonat, ürik asit ve fosfat ile karakterize nefrotoksisite göstere-

bilmektedir. Nefrotoksisite görüldükten sonra CDV'ye devam edilirse, renal yetmezlik şiddetlenebilir. CDV'ye bağlı nefrotoksisite doza bağlıdır ve organik anyon taşıyıcı 1 (OAT1) yoluyla böbrek proksimal tübül hücrelerinde CDV birikmesinden kaynaklanır. Nefrotoksisite, OAT1 taşınmasının bir inhibitörü olan ve proksimal tübüler hücrelerde CDV birikimini azaltan probenesid ile kısmen iyileştirilebilir[17,18]. Edinilmiş immün yetmezlik sendromu (AIDS) olan hastalarda yapılan Faz I/II çalışmalarında, özellikle > 3 mg/kg CDV dozlarında ön hidrasyon ve probenesid nefrotoksisite oranlarını azaltmıştır. Bu nefrotoksisite nedeniyle CDV, serum kreatinin > 1.5 mg/dL, kreatinin klerensi < 55 mL/dk veya > 2+ proteinürisi olan hastalarda kontrendikedir ve eş zamanlı nefrotoksik ilaçlardan kaçınılması önerilir. 5 mg/kg IV haftada bir x 2 hafta (bundan sonra her hafta 5 mg/kg tekrarlanabilir). CDV için Poxvirüslerde kesin doz önerisi bulunmamaktadır. Sınırlı veride maymun çiçeğinde 5 mg/kg tek doz olarak kullanım mevcuttur. Karaciğer yetmezliğinde doz ayarlaması yoktur.100 mL serum fizyolojik içesirinde 1 saatlik infüzyon ile verilir. Probenesid 2 g CDV'den 3 saat önce verilir. Gebelerde kullanımı önerilmez. Nötropeni, azalmış oküler basınç, nefrotoksisite ve Probeneside karşı aşırı duyarlılık reaksiyonları, döküntü, bulantı, kusma görülebilecek yan etkilerdir[8,19].

TEMAS SONRASI PROFİLAKSİ

Maymun çiçeği virüsü bulaşma riskini belirlemek için hem toplumdaki hem de sağlık bakım ortamlarındaki maruziyetler değerlendirilmelidir. Teyit edilmiş maruziyeti olan tüm bireylerde semptom izlenmelidir. Aşı ile maruziyet sonrası profilaksi önerileri maruziyet riskine bağlıdır. Yüksek riskli maruziyet aşağıdakilerden biri olarak kabul edilir:

- Bir kişinin cildi veya mukoza zarları ile maymun çiçeği olan bir kişinin cildi, lezyonları veya vücut sıvıları arasında korunmasız temas (örn. cinsel temas, hastanın tükürüğünün bir kişinin gözlerine veya ağız boşluğuna yanlışlıkla sıçraması, hastayla eldivensiz temas) veya
- Kontamine malzemeler (örn. çarşaflar, giysiler) ile temas.
- N95 veya eşdeğer bir maske takmadan enfekte aerosollere maruziyet.

CDC, orta düzeyde riske maruz kalmayı aşağıdakilerden biri olarak değerlendirir:

- Cerrahi maske takmadan maskesiz bir maymun çiçeği hastasının üç saat veya daha fazla süre ile bir buçuk metre yakınında bulunmak.
- Bir kişinin giysisinin kolları ve diğer parçaları ile hastanın cilt lezyonları, vücut sıvıları, kirli çarşafları veya pansumanları arasında temasa neden olan bir faaliyette bulunmak.

Düşük riskli maruziyetler aşağıdakilerden herhangi birini içerir:

- Maruz kalma süresine bakılmaksızın, bir veya daha fazla kez, gözlük veya yüz koruyucu takmadan maymun çiçeği olan bir kişinin odasına girmek.
- Hasta bakım alanına veya odasına tüm girişlerde önlük, eldiven, gözlük veya yüz koruyucu ve cerrahi maske kullanılması.
- Maymun çiçeği olan maskesiz bir kişinin en az bir buçuk metre yakınında, cerrahi maske takmadan üç saatten az bulunmak.

Maruz kalma risk düzeyine bakılmaksızın tüm bireylerin, son maruziyetlerinden sonra 21 gün boyunca semptomları izlenmelidir. Maymun çiçeği olan bir hastaya bakarken uygun kişisel koruyucu ekipman (KKE) kullananlar da buna dahildir. Semptom izleme aktif (örneğin, iş sağlığı veya halk sağlığı uzmanı, günlük olarak doğrudan maruz kalan kişiyi takip eder) veya pasif (örneğin, maruz kalan birey kendini izler) olarak yapılabilir. Korunmasız maruziyetleri olan sağlık personeli, semptomlar için aktif izlemeden geçmelidir. Uygun KKE kullanırken ve tanımlanmış herhangi bir ihlal olmadan maruz kalan sağlık çalışanları aktif veya pasif izlemeye tabi tutulabilir. Asemptomatik kalan kişiler rutin günlük aktivitelerine devam edebilir. Bununla birlik-

te, semptomlar gelişirse, derhal kendilerini izole etmeli ve sağlık kuruluşuna başvurmalıdır[20,21].

Orthopoxvirus Aşıları

Maymun çiçeği geliştirme riskini azaltabilecek iki mevcut aşı vardır. Modifiye Ankara Aşısı (MVA) (Amerika Birleşik Devletleri'nde JYNNEOS, Avrupa Birliği'nde IMVANEX ve Kanada'da IMVAMUNE)ve ACAM2000 aşısı 21. MVA aşısı, yüksek oranda zayıflatılmış, replike olmayan bir aşı virüsünden yapılır ve bağışıklığı baskılanmış kişilerde ve cilt bozuklukları olanlarda bile mükemmel bir güvenlik profiline sahiptir. MVA aşısı, dört hafta arayla deri altından iki doz halinde uygulanır.

Amerika Birleşik Devletleri'nde JYNNEOS, çiçek hastalığı ve maymun çiçeğinin önlenmesi için onaylanmıştır.

ACAM2000, yalnızca seçilmiş hastalarda kullanılabilen ve MVA aşısından daha fazla yan etkiyle ilişkilendirilen çiçek aşısıdır. Amerika Birleşik Devletleri'nde, ACAM2000 çiçek hastalığının önlenmesi için onaylanmıştır. CDC aracılığıyla genişletilmiş erişim araştırma amaçlı yeni ilaç (IND) uygulaması kapsamında maymun çiçeği için kullanılabilir.

MVA aşısı mevcut değilse ve aşılama endikeyse, ACAM2000 belirli klinik ortamlarda kullanılabilir (örneğin, sağlıklı, hamile olmayan, yüksek riske maruz kalan bağışıklığı yeterli kişi). Bu aşı, kolun deltoid bölgesinin epidermisine skarifikasyon adı verilen bir işlemle uygulanır.

Maymun çiçeğine yüksek risk maruziyeti olan bireyler için, MVA aşısı ile temas sonrası aşılama önerilir. Maruziyet sonrası aşılama, düşük risk maruziyeti olanlar için endike değildir. Temas sonrası profilaksi için uygun olan kişiler, maruziyetten sonraki dört gün içinde aşılanmalıdır. Aşı maruziyetin 14 gününe kadar önerilse de, 4. ve 14. günler arasında verilirse, aşının hastalığın semptomlarını azalttığı, ancak hastalığı önlemediği düşünülmektedir[21,22].

SONUÇ

MÇVH'ın kesin tedavisi yoktur. Semptomları hafifletmek ve komplikasyonları azaltmak için destek tedavisi verilebilir. Virüs yayılmasını önleyerek salgınlar önlenebilir. Çiçek aşısının MÇVH'dan korunmada oldukça etkili olduğu kabul edilmektedir. Yüksek riskli maruziyette aşı önerilmektedir.

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Perceptions of Students on Distance Education and E-Learning in Dentistry Education: Challenges and Opportunities

Diş Hekimliği Eğitiminde Öğrencilerin Uzaktan Eğitim ve E-Öğrenme Algıları: Zorluklar ve Fırsatlar

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Abstract

Aim Developing information and communication technology have led to advent of distance education term and new learning materials in training institutions; unforeseen situations like a pandemic can turn distance education into a necessity rather than an option. This study aimed to evaluate the undergraduate dentistry students' perceptions of distance education implemented to adhere to compulsory social isolation measures.

Material and Method In the current study, a structured e-questionnaire comprising 27 items, including a 5-point Likert scale with 10 items (Google Forms®) was administered to undergraduate dental students in Turkey. A total of 1208 complete responses were received and examined in the final statistical analyses to assess students' perception of distance education.

Results Most students were not familiar with the term evidence-based. Many respondents (n = 723, 59.9%) noted that they were better motivated in their lessons with face-to-face education in the classroom. Cronbach's alpha value of the distance-education perceptions scale was 0.629. Factor analysis identified five sub-dimensions. The distance-education scores of the students at the foundation university were significantly higher than those of students at the state university.

Conclusion The results of this study show that students need more training on seeking and evaluating evidence-based information online. The study found that the training institution is a factor affecting students' perceptions of distance education for dental instruction. Institutions need to re-evaluate their available educational programs as to the effectiveness of training modalities of distance education and e-learning for professional training in dentistry.

Keywords distance education, e-learning, dental education, pandemia

Özet

Amaç *Gelişen bilgi ve iletişim teknolojisi, eğitim kurumlarında uzaktan eğitim döneminin ve yeni öğrenme materyallerinin ortaya çıkmasına neden olmuştur; Pandemi gibi öngörülemeyen durumlar, uzaktan eğitimi bir seçenekten ziyade bir zorunluluk haline getirebilir. Bu çalışma, diş hekimliği lisans öğrencilerinin zorunlu sosyal izolasyon önlemlerine uymak için uygulanan uzaktan eğitime ilişkin algılarını değerlendirmeyi amaçlamıştır.*

Gereç ve Yöntem *Bu çalışmada, Türkiye'deki diş hekimliği lisans öğrencilerine 10 maddelik 5'li Likert ölçeği (Google Forms®) dahil 27 maddeden oluşan yapılandırılmış bir e-anket uygulanmıştır. Öğrencilerin uzaktan eğitim algısını değerlendirmek için toplam 1208 tam yanıt alındı ve nihai istatistiksel analizlerde incelendi.*

Bulgular *Çoğu öğrenci kanıta dayalı terimine aşina değildi. Katılımcıların çoğu (n = 723, %59.9) sınıfta yüz yüze eğitimle derslerinde daha iyi motive olduklarını belirtti. Uzaktan eğitim algıları ölçeğinin Cronbach alfa değeri 0.629'dur. Faktör analizinde beş alt boyut belirlenmiştir. Vakıf üniversitesindeki öğrencilerin uzaktan eğitim puanları devlet üniversitesindeki öğrencilere göre anlamlı derecede yüksekti.*

Sonuç *Bu çalışmanın sonuçları, öğrencilerin çevrimiçi kanıta dayalı bilgileri arama ve değerlendirme konusunda daha fazla eğitime ihtiyaç duyduklarını göstermektedir. Çalışma, eğitim kurumunun öğrencilerin dişhekimliği eğitimi için uzaktan eğitim algılarını etkileyen bir faktör olduğunu bulmuştur. Kurumların, diş hekimliğinde mesleki eğitim için uzaktan eğitim ve e-öğrenme eğitim yöntemlerinin etkinliği açısından mevcut eğitim programlarını yeniden değerlendirmeleri gerekmektedir.*

Anahtar Kelimeler *uzaktan eğitim, e-öğrenme, diş hekimliği eğitimi, pandemi*

INTRODUCTION

In the 21st century, developments in information and communication technology had an important influence on societies and the function of educational institutions[1,2]. Digital learning (d-learning) has become a significant tool in education and training systems due to its potential to provide lower-cost education, its accessibility at any time from anywhere, and because it's lack of dependency on classrooms and faculty[3-5]. D-learning is the combination of electronic learning (e-learning) and mobile learning (m-learning)[6]. During the COVID-19 pandemic, social distancing has forced distance education to play a crucial role in our daily lives. Distance education can disseminate online learning and all forms of instructional delivery and formats to off-campus students, based on any training approach that replaces face-to-face in terms of specific time and place. Physical encounters between students and their teachers are required only rarely[7].

Dental education requires that content be evidence-based and up-to-date and that training methods be extremely experiential and pragmatic[7]. Evidence-based dentistry is the judicious integration of systematic reviews of clinically relevant scientific evidence regarding the patient's oral and medical condition and history with the dentist's clinical expertise and the patient's treatment needs and preferences. Many changes have been made in curricula to directly engage students in learning by improving problem-solving skills, providing continuous and learner-centered learning[8]. Advances in information and communication technology have contributed to these changes. D-learning and online learning are being used increasingly to improve traditional teaching methodology[6,9,10]. It has been reported in the literature that various e-learning or online learning tools and methods may be effective tools and methods for expanding teaching and learning opportunities in healthcare professions, including dental education[3-5,11-13]. However, online learning methods have a greater impact on student satisfaction, motivation, and self-assessment when integrated with traditional instructional formats[3,14,15]. Students in the health professions need to acquire and apply theoretical and clinical knowledge in appropriate teaching environments in order to become safe and competent health professionals. Teaching and learning of clinical skills are key areas for medical education[16,17]. One-to-one supervision and practical training in such areas are requirements that e-learning curriculum and distance education cannot fully meet. Therefore, face-to-face education maintains its importance in education[14,17].

The purpose of this study was to evaluate students' perceptions of distance education and their views on the use of e-/m-learning tools in dental education. In addition, the study evaluated how dental students use online learning to obtain information on vocational topics.

MATERIALS and METHODS

Ethics Statement

The study was approved by the ethics committee of Health Sciences University, Hamidiye Clinical Research Ethics Committee (IRB approval no. 20/53). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Data Collection

The online questionnaire (see Appendix) was administered using Google® Forms. Internet links to the questionnaire were sent to dental students at various Turkish universities by email or WhatsApp messages. Returning the questionnaire was interpreted as indicating willingness to participate in the study. Respondents who agreed to participate in the research with their own consent were included.

Sample Size

The sample size required for instrument development meets the suggested 200 participants[18]. The sample size was calculated to detect the mean distance-learning perception scores with a confidence interval of 99%. It was calculated that 1041 participants were required to detect mean levels with sigma = 0.5 and a margin of error of 0.04[19]. A total of

1208 completed web-based questionnaires were returned, giving a response rate of 40%.

Questionnaire design

A comprehensive literature review[1,9,14,15,20] was carried out regarding the assessment and success factors of distance education, availability of technology as a learning tool, and the use of e-learning platforms in dental education. An expert panel of four specialists-one in restorative dentistry, a periodontist, an oral-maxillofacial surgeon, and a biostatistician-contributed to item development. The content validity index was calculated using the Davis technique. In the Davis technique, the number of experts who stated "appropriate" or "item should be reviewed" was divided by 4 and the "content validity index" for the item was determined. Questions with an index value above 0.80 were included in the questionnaire. The initial item pool for the distance-education perceptions scale consisted of 10 items. These were examined by specialists to evaluate the clarity of the wording and relevance of the items. Two items were removed and minor item disposition corrections were made based on suggestions from the panel of specialists. The questions in this section were developed by the researchers to measure distance-education perception. All the questions were designed using a five-point Likert scale ranging from1 (strongly disagree) to 5 (strongly agree). Higher scored indicate a more positive perception of distance education. Seventeen demographic and comparison questions were also asked, which included a combination of selected answer questions (Likert-type scale) and closed-ended questions (yes / no or select one or all that apply options). The final questionnaire consisted of 27 items.

The final online questionnaire included questions regarding the following:

1. Individual characteristics (demographic information, digital skills, e-learning experience) (6 items)
2. Digital learning tools' acceptability, knowledge, and skill (11 items)
3. Distance-education perception scale (10 items)

Face validity of the scale was checked on a sample of 20 participants.

Statistical analyses

Data from the questionnaire were analyzed using SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA). The significance level was set at $p < 0.05$. Descriptive statistics were generated with percentages for data reporting. One-way ANOVA, Kruskal-Wallis and independent-samples t-test were used to analyze differences in responses between the groups. The normality assumption was tested using skewness values, and Levene's test was performed to check for homogeneity of variances.

RESULTS

Questionnaire reliability

For reliability and factor analysis, 1208 students were given the final version of the questionnaire. The internal reliability of the distance-education perception scale (10 items) was established using Cronbach's alpha, and reliability of the scale was 0.629.

Individual characteristics

These results were indicated in the Table 1. The mean age of the students was[21]. 3 years (range 18-36), and 66.6% were female. About their institutions, 80.7% were from state, 10.3% were from private, and 8.9% were from the foundation university. The sample consisted of 167 (13.8%) first-year, 367 (30.4%) second-year, 495 (41%) third-year, 140 (11.6%) fourth-year, and 39 (3.2) fifth-year students. Half (50.2%) reported that digital skill proficiency depends on the task, and 36% reported that they are either very skillful or skillful. Most of the participants (81.9%) reported having previous e-learning/distance education experience.

Table 1: Individual characteristics (N=1208)

Variables				
Age, years	Mean	21.3		
	Range	18-36		
Gender (frequence/ percentage)	F	804 (66.6%)		
	M	404 (33.4%)		
Institution (frequence/ percentage)	State university	975 (80.7%)		
	Private university	125(10.3)		
	Foundation university	108 (8.9)		
Year of University (frequence/ percentage)	1	167 (13.8%)		
	2	367 (30.4%)		
	3	495 (41%)		
	4	140 (11.6%)		
	5	39 (3.2)		
		Frequence (percentage)	Mean	SD
Digital skill proficiency	Not sure	26 (2.2%)		
	Inadequate	140 (11.6%)		
	Depends on the task	607 (50.2%)		
	Skillful	336 (27.8%)		
	Very skillful	99 (8.2%)		
			3.28	0.85
		Responses N (Percent)	Percent of Cases	
E-learning/distance education experience#	Online course	189 (11.0%)	15.6%	
	Online lesson (class)	806 (47.0%)	66.7%	
	Online seminar (Webinar)	238 (13.9%)	19.7%	
	Online congress	171 (10.0%)	14.2%	
	No experience	311 (18.1%)	25.7%	

#On these questions, students were asked to check all that apply, so percentages total greater than 100%.

Digital learning tools' acceptability, knowledge, and skill

These results are indicated in the Table 2. Most (91.8%) of the responding students stated that they use smartphones and PCs to research subjects in an electronic environment. Responses identifying the online sites they use to search for information on lecture topics were 92.3% Google, 82.4% academic information websites, and 61.9% Wikipedia. The students reported verifying the reliability of the information they found using the official validity of the site (74.3%), academic references (79.5%), advice (21.9%), and number of followers (8.4%). The results showed that most of the students (66.3%) did not know what the term evidence-based dentistry means. Most reported that technology should be either an important part (51.7%) or an indispensable essential part (33.1%) of dentistry education. The results showed that 30.1% of students generally use and 38.2% of students occasionally used video channels, such as YouTube and Instagram, for further information and guidance after lectures. Most students (74.9%) reported that social media made it easier to access information. A substantial number (40.9%) strongly agreed or agreed that there is social pressure to use technology in education. More than half (59.9%) noted that they are better motivated by lessons with face-to-face instruction in the classroom, 41.6% expressed that they ask questions more easily in the classroom, and 63% reported that in online teaching-distance education, they are generally or occasionally distracted.

Table 2: Digital learning tools' availability, acceptability, and knowledge (N=1208)

		Responses		Percent of Cases
		N	Percent	
Which device do you use to research on a subject in electronic environment?#	Smartphone	829	42.3%	68.6%
	PC	970	49.5%	80.3%
	Tablet	147	7.5%	12.2%
	Other (Kindle etc.)	12	0.6%	1.0%
Which online sites do you use when searching for information on lecture topics?#	Google	1115	30.2%	92.3%
	YouTube	629	17.0%	52.1%
	Instagram	110	3.0%	9.1%
	Twitter	49	1.3%	4.1%
	Akademik bilgi sites	995	27.0%	82.4%
	Facebook	20	0.5%	1.7%
	Wikipedia	748	20.3%	61.9%
	Diğer	24	0.7%	2.0%
How do you check reliability on the internet?#	By the number of followers	101	4.5%	8.4%
	By the official validity of the site	897	40.1%	74.3%
	By the academic reference	960	42.9%	79.5%
	By advice	265	11.9%	21.9%
	Other	13	0.6%	1.1%
Do you have any ideas about evidence-based dentistry?	Yes	407	33.7%	
	No	801	66.3%	
How do you think the place of technology in dentistry education should be?	Should not be used in education	17	1.4%	
	Partially helpful tool	166	13.7%	
	Important part	625	51.7%	
	Indispensable essential part	400	33.1%	
Social media easies access to information.	Strongly disagree	23	1.9	
	Disagree	114	9.4	
	Neutral	167	13.8	
	Agree	648	53.6	
	Strongly agree	256	21.2	
Do you use video channels on social media (YouTube, Instagram etc.) for further information and guidance after the lectures?	Never	68	5.6%	
	Rarely	210	17.4%	
	Occasionally	462	38.2%	
	Generally	364	30.1%	
	Every time	104	8.6%	
Do you think there is social pressure to use technology in education?	Strongly disagree	35	2.9%	
	Disagree	282	23.3%	
	Neutral	397	32.9%	
	Agree	394	32.6%	
	Strongly agree	100	8.3%	

Do you ask questions more easily in the lesson, with distance education or in classroom education?	Distance education	168	13.9%	
	Classroom education	503	41.6%	
	I can ask for both	285	23.6%	
	I cannot ask for both	178	14.7%	
	Neutral	74	6.1%	
Are you better motivated by lessons with distance learning or classroom education?	Distance education	167	13.8%	
	Classroom education	723	59.9%	
	I can motive for both	152	12.6%	
	I cannot motive for both	123	10.2%	
	Neutral	43	3.6%	
Do you find electronic instruction-distance education distracting?	Never	65	5.4%	
	Rarely	177	14.7%	
	Occasionally	352	29.1%	
	Generally	409	33.9%	
	Every time	205	17.0%	
#On these questions, students were asked to check all that apply, so percentages total greater than 100%.				

Distance-education perception scale

Factor analysis

Principal-component analysis with varimax rotation was used for factor analysis, which summarized the 10 questionnaire items into five underlying factors. The minimum coefficient was 0.602 (Table 3). 75% of the total variance can be explained by five dimensions. (Table 3). The five factors with mean scores in Table 4 are defined as follows:

- Factor 1. The importance of distance education: This includes items relating to students' opinions of the integration of distance learning into classroom education and its usefulness.
- Factor 2. Learning online training techniques: This consists of questions about the need for training on searching for information online relating to the course.
- Factor 3. Internet and digital competence: This comprises questions focusing on areas such as students' knowledge and skills in using the internet and digital media as learning tools.
- Factor 4. Human and equipment infrastructure: This comprises items relating to the infrastructure competence of the educational institution to provide distance education and the competence of trainers in using distance education tools.
- Factor 5. Internet as a learning tool: This includes questions relating to students' use of the internet as a learning tool and verifying the accuracy of information from the internet.

The five factors above were used to assess students' perception of distance education in dental education.

Independent sample t-test statistics indicated a significant difference between genders in only Factor 3: internet and digital competence ($p = 0.011$) (Table 5). Significant differences were observed among types of institutions in ANOVA and Tukey statistics (Table 6) in the mean scores for distance-education perception. Distance education scores of students at the foundation university (mean = 3.76; SD = 0.47) were significantly higher than those of students at the state university (mean = 3.55, SD = 0.47; $p < 0.001$). The Kruskal-Wallis and Dunnett T3 statistics (Table 6) showed that Factor 3 mean scores of students at the foundation university (mean = 4.07; SD = 0.53) were significantly higher than those of students at the state university

Table 3: Component factors from the distance education perception scale

Rotated Component Matrixa Component					
	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
I find distance education useful	0.910				
Education in the classroom should be supported by distance education	0.792				
An expert training should be given to search for information, to find evidence-based and academically adequate information and about applications, in the online environment.		0.778			
Education should be given about how to access information about the course.		0.789			
I know how to use the internet as a learning tool			0.804		
I know how to digitally research a topic related to the course			0.881		
The infrastructure of my university is sufficient to provide distance education				0.888	
Instructors have competence to use technology in education				0.725	
I search for accuracy when searching for course information on the internet.					0.846
I find it right to use the internet as a learning tool.					0.602
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. a. Rotation converged in 6 iterations.					

Table 4: Factor Means

	Mean	**Std. Deviation**
Distance education perception score	3.58	0.47
Factor 1: The importance of distance education	3.03	1.09
Factor 2: Learning online training techniques	3.97	0.67
Factor 3: Internet and digital competence	3.90	0.61
Factor 4: Human and equipment infrastructure	3.07	0.98
Factor 5: Internet as a learning tool	3.90	0.68

Table 5: Comparative test of mean values between gender

	Gender	**Mean SD**	**t**	**p value**
Factor 1: The importance of distance education	F	2.991 (1.065)	-1.878	0.061
	M	3.119 (1.137)		
Factor 2: Learning online training techniques	F	3.984 (0.664)	0.793	0.428
	M	3.952 (0.701)		
Factor 3: Internet and digital competence	F	3.866 (0.610)	-2.550	0.011*
	M	3.962 (0.630)		
Factor 4: Human and equipment infrastructure	F	3.098 (0.967)	1.503	0.133
	M	3.007 (1.016)		
Factor 5: Internet as a learning tool	F	3.891 (0.675)	-0.788	0.431
		3.925 (0.703)		
Significant values at p <0.05				

Appendix					
Individual characteristics					
1. Age					
2. Gender					
O Male	O Female				
3. Institution					
O State university	O Private university	O Foundation university			
4. Year of University					
O 1	O 2	O 3	O 4	O 5	
5. Digital skill proficiency					
O Not sure	O Inadequate	O Depends on the task	O Skillful	O Very skillful	
6. E-learning/distance education experience (You can check multiple options)					
O Online course	O Online lesson (class)	O Online seminar (Webinar)		O Online congress	O No experience
Digital learning tools availability, acceptability, knowledge					
7. Which device do you use to research on a subject in electronic environment? (You can check multiple options)					
O Smartphone	O PC	O Tablet	O Other (Kindle etc.)		
8. Which online sites do you use when searching for information on lecture topics? (You can check multiple options)					
O Google	O YouTube	O Instagram	O Twitter	O Akademik bilgi sites	O Facebook
O Wikipedia	O Other				
9. How do you check reliability on the internet? (You can check multiple options)					
O By the number of followers		O By the official validity of the site		O By the academic reference	
O By advice	O Other				
10. Do you have any ideas about evidence-based dentistry?					
O Yes	O No				
11. How do you think the place of technology in dentistry education should be?					
O Should not be used in education (Kindle etc.)			O Partially helpful tool		
O Important part		O Indispensable essential part			
12. Social media easies access to information.					
O Strongly disagree	O Disagree	O Neutral	O Agree	O Strongly agree	
13. Do you use video channels on social media (YouTube, Instagram etc.) for further information and guidance after the lectures?					
O Never	O Rarely	O Occasionally	O Generally	O Every time	
14. Do you think there is social pressure to use technology in education?					
O Strongly disagree	O Disagree	O Neutral	O Agree	O Strongly agree	
15. Do you ask questions more easily in the lesson, with distance education or in classroom education?					
O Distance education		O Classroom education		O I can ask for both	
O I cannot ask for both		O Neutral			
16. Are you better motivated by lessons with distance learning or classroom education?					
O Distance education		O Classroom education		O I can motive for both	
O I cannot motive for both		O Neutral			
17. Do you find electronic instruction-distance education distracting?					
O Never	O Rarely	O Occasionally		O Generally	O Every time

Distance education perception scale					
	Strongly disagree	Disagree	Neutral	Agree Agree	Strongly agree
18. I find distance education useful	O 1	O 2	O 3	O 4	O 5
19. Education in the classroom should be supported by distance education	O 1	O 2	O 3	O 4	O 5
20. An expert training should be given to search for information, to find evidence-based and academically adequate information and about applications, in the online environment.	O 1	O 2	O 3	O 4	O 5
21. Education should be given about how to access information about the course.	O 1	O 2	O 3	O 4	O 5
22. I know how to use the internet as a learning tool.	O 1	O 2	O 3	O 4	O 5
23. I know how to digitally research a topic related to the course.	O 1	O 2	O 3	O 4	O 5
24. The infrastructure of my university is sufficient to provide distance education.	O 1	O 2	O 3	O 4	O 5
25. Instructors have competence to use technology in education.	O 1	O 2	O 3	O 4	O 5
26. I search for accuracy when searching for course information on the internet.	O 1	O 2	O 3	O 4	O 5
27. I find it right to use the internet as a learning tool.	O 1	O 2	O 3	O 4	O 5

(mean = 3.86, SD = 0.61; p = 0.001).

DISCUSSION

The current study provides contemporary insight into students' perception of e-learning and distance education, their adaptation, and their use of online tools in dental education. The primary outcome of our study is that students have a positive perception of the use of distance education as a supporting tool. The results of this study conducted with undergraduate dentistry students who are globally encountering social isolation due to the COVID-19 infection that has been recently experienced by the whole world may provide important informations.

Previous researches[7,14,21] have reported the relative weaknesses and threats associated with distance education from a professional perspective. Similar to those studies, we noted a problem with students losing their motivation to learn. Another problem is distraction. In line with other studies, our results indicated that distance education causes distraction and a lack of motivation for students. Previous studies have reported that issues with student distraction can be attributed to phones, web browsing, noise in the room where the lesson is being followed, and people coming in and out[22,23]. It has been suggested that for effective learning, students need individual learning motivation to focus their attention to the e-lesson and to be able to ask questions during it[21,24]. Therefore, student participation and motivation were seen as important factors for successful e-learning; intrinsically motivated students can control their own learning processes.

Social pressure refers to a student's perception of normatively appropriate behavior with regard to the use of technology—the internet and the web-in dental education[25]. It has been reported that the level of peer pressure exerted by one student on another fostered greater internet use in distance learning[25-27]. In this study, a significant number of students (40.9%) thought that there was social pressure to use technology in education. Not all students may be capable or willing enough to keep up with new devices and tools. In our results, male students were more efficient in their use of the internet and digital platforms than female students ($p < 0.05$). According to the results of a study 14, students did not want electronic/mobile learning to be the core or essential part of dental education. It has been expressed that not all students may be adequately skilled in using new devices and tools straight away. In the current study, 65.4% of students stated that they preferred to use technology as a complement to their education. Loss of motivation, distraction, and perception of social pressure may have affected this result. These factors that may

cause some students to feel excluded or left behind should be considered when integrating distance education and e-learning into the dental curriculum.

A major concern is whether the information transferred using distance education and e-learning in dentistry education can adequately achieve educational learning outcomes to ultimately graduate competent professionals. It has been reported that the learning benefits for students are not inherent in the technology but depend upon interactions between them and their teachers[4,15]. The fact that many students (41.6%) in the current study stated that they asked questions more easily in the classroom affirms the importance of this interaction.

Literature has shown that the capability of the university and the training of faculty members are also very important in the effective implementation of e-learning and distance education in dental education. In addition, it has been noted that dental schools need an infrastructure framing the expectations of future professionals and students providing comfortable use of new technology[7,9,28]. Students participating in this study were not completely negative about the human and equipment infrastructure competence of their educational institutions. However, it was seen that they did not find the current conditions sufficient. Furthermore, foundation university students had a more positive perception ($p < 0.05$) of the use of distance education in dental education. Our results showed that students' educational institutions were a factor affecting their perceptions of the usefulness of distance education in dental education. Foundation university students' perception of internet and digital competence was significantly higher than that of students at state universities. The scores from private universities were high but statistically insignificant. It can be concluded that socioeconomic status affects the results obtained.

In a study with a flipped classroom model, students expressed that the video lectures were better than face-to-face lectures for understanding the content. The opportunity to listen to the lecture again was an advantage they noted[20]. The fact that students have positive perceptions (mean = 3.575) of the use of distance education and e-learning in dental education in this study supports studies[7,9,20,29] in which students report that e-learning is advantageous. Our findings revealed that students attach importance to distance education in their dentistry education. Online knowledge, lectures, educational films help only at the early stage of education or expand already acquired knowledge and clinical practice. However, they cannot replace practical exercises on phantoms and treating patients.

Healthcare students may lack adequate skills and knowledge to search for, evaluate, and synthesize evidence-based information on the internet. Studies have reported that students rely on well-known websites such as Google and YouTube instead of using evidence-based research tools to search for information[12,14,30]. Previous studies suggest that dental students need specific training and detailed instructions to differentiate misleading and non-evidence-based information from reliable sources[14,31]. Our study results showed that the majority of students (66.3%) are not familiar with the term "evidence-based"; the number of those in the first three years of education who did not know this term was very high. Based on this result, it was concluded that information literacy and awareness increase in the later years of university. This study illustrated that students tend to use familiar websites, such as Google, YouTube, and Wikipedia, to search for dental lecture topics. Some students in the present study said they check the reliability of the information on the internet by the number of followers, comments, advice, and likes. Previous studies[12,32] have determined that YouTube is being used increasingly for dental- and medical-related videos, especially by professionals. Findings from the current study showed that video channels on social media (YouTube, Instagram, etc.) are used by most students for supplemental information and guidance after the lectures. On the other hand, there is a perception among students that they need training in

using online tools. Today, when technology is used very actively, students should be educated in earlier years of university to make the distinction of evidence-based knowledge. There are concerns regarding professionalism and ethical guidelines related to the use of social media tools in dental education[33,34]. This issue should be taken into account by educators.

There were some limitations in our study. First, this questionnaire did not include a question to determine the year of university in which clinical education begins. Therefore, the perceptions of students with clinical experience could not be evaluated separately. Second, the fact that the first-year students included in the study were not familiar with a dentistry education other than distance education before may be insufficient for comparison. Third, it may not accurately reflect the population from which the sample was taken due to the use of voluntary participants. Students who do not use the internet and online tools frequently may not have responded to the online survey. These research limitations should be considered for future studies. So that research can be developed and the knowledge obtained can be further increased.

CONCLUSION

Digital technology will play an important role in the future of dental education. The recent pandemic the world has experienced has made distance education a mandatory alternative. However, it is necessary to emphasize the aspect of the form of online education as insufficient, regardless of the reconstruction of educational programs during the pandemic. Because the knowledge transferred in online exercises will not replace the practical aspect during the education of students from dental faculties. Besides all these, the integration of e-learning models with conventional education models may have the potential to overcome the shortages of face-to-face education. Dental schools need to re-evaluate their available educational programs and implement online learning methods in their curricula. Universities should focus on improving information literacy among their students to graduate students who have the ability to search and evaluate evidence-based information online and through apps/videos. Further research is needed to uncover the concerns and needs of students, educators, and institutions in order to prepare dentistry students to learn and practice through online learning technologies and enhance the quality of the training.

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The authors of this study have no conflict of interest.

Conflict and Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Author Contributions

Idea/Concept: Ayşe Toraman, Ebru Sağlam; Design: Ayşe Toraman, Ebru Sağlam, Serhat Köseoğlu; Supervision/Consulting: Ayşe Toraman, Ebru Sağlam, Serhat Köseoğlu; Data Collection and/or Processing: Ayşe Toraman, Ebru Sağlam, Serhat Köseoğlu; Analysis and/or Interpretation: Ayşe Toraman, Ebru Sağlam; Literature Review: Ayşe Toraman; Writing the Article: Ayşe Toraman, Ebru Sağlam, Serhat Köseoğlu; Critical Analysis: Serhat Köseoğlu;

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Network Analysis on Graves' Ophthalmopathy

Graves Oftalmopatisi İle İlgili Yayınların İşbirliğine Dayalı Ağ Analizi

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Abstract

Aim Graves' ophthalmopathy (GO), sometimes known as Graves' orbitopathy, is an eye illness that can lead to vision loss. Despite significant developments in ophthalmology over the previous few decades, there is no comprehensive bibliometric description of the quality and quantity of GO research in the peer-reviewed literature. The purpose of this study was to examine the trends in GO publications.

Material and Method The bibliometric search was conducted using the Web of Science (WoS) Core Collection advanced search engine. Keywords related to "Graves" and "ophtalmopathy" or "orbitopathy" were used. The time span was set from 1970 to 2021. The researchers looked at data on publishing growth, the most active countries and institutions, the most cited journals, and publishing and keyword mapping. The articles were investigated thoroughly. The maps were visualized using the VOSviewer technique.

Results The Wos database yielded 958 articles about GO. These 958 articles had an average of 29.59 citations each. These items have a H index of 81. The majority of the papers found were in the fields of endocrinology and metabolism (38.83 percent), followed by ophthalmology (25.99 percent), with the United States as the leading country. The articles garnered a total of 28348 citations, averaging 29.59 per article. Annual citation growth of GO was sluggish until the 1990s, then skyrocketed in the subsequent decade.

Conclusion The USA was the leading country but the rest of the world made a significant contribution. The quantity of citations is great, yet global collaboration is required to address this increasing and worrisome issue.

Keywords graves ophthalmopathy; eye; bibliometric analysis; research publications.

Özet

Amaç *Graves' orbitopatisi olarak da bilinen Gravesoftalmopatisi (GO), görme kaybına yol açabilen bir göz hastalığıdır. Oftalmolojide son yıllarda önemli gelişmelere olmasına rağmen, literatürlerde GO araştırmasının kalitesi ve miktarına ilişkin kapsamlı bir bibliyometrik tanım bulunmamaktadır. Bu çalışmanın amacı, GO yayınlarındaki eğilimleri incelemektir.*

Gereç ve Yöntem *Bibliyometrik arama, Web of Science (WoS) Core Collection gelişmiş arama motoru kullanılarak yapıldı. "Graves" ve "oftalmopati" veya "orbitopati" ile ilgili anahtar kelimeler kullanıldı. Zaman aralığı 1970' den 2021' e kadar belirlendi. Araştırmacılar, yayın büyümesi, en aktif ülkeler ve kurumlar, en çok alıntı yapılan dergiler ve yayıncılık ve anahtar kelime eşleme ile ilgili verilere baktılar. Makaleler kapsamlı bir şekilde incelenmiştir. Haritalar VOSviewer tekniği kullanılarak görselleştirildi.*

Bulgular *Wosveritabanı, GO hakkında 958 makale verdi. Bu 958 makalenin her biri ortalama 29.59 atıf aldı. Bu makalelerin H indeksi 81' di. Bulunan makalelerin çoğu endokrinoloji ve metabolizma (%38,83) alanlarındaydı, bunu oftalmoloji (%25,99) izledi ve Amerika Birleşik Devletleri lider bu konuda lider ülkeydi. Makaleler, makale başına ortalama 29,59 olmak üzere toplam 28348 atıf aldı. GO' nun yıllık atıf büyümesi 1990' lara kadar yavaştı, ardından sonraki on yılda hızla arttı.*

Sonuç *GO ile ilgili çalışmalarda ilk sırada ABD yer almaktadır. Yapılan yayınların alıntılanma sayısı oldukça fazla olmasına rağmen konu ile ilgili bilimsel verilerin elde edilmesi için küresel iş birliğine ihtiyaç vardır.*

Anahtar Kelimeler *graves oftalmopatisi; göz; bibliyometrik analiz; araştırma yayınları.*

INTRODUCTION

Graves' ophthalmopathy (GO), commonly known as Graves' orbitopathy, is a potentially blinding ocular disease that has confused doctors and scientists for nearly 200 years. Thyroid-associated ophthalmopathy, also known as thyroid eye illness, organ-specific autoimmune disease, or thyroid eye illness, is a condition that affects individuals who have hyperthyroidism or have had hyperthyroidism in the past due to Graves' disease.[1] GO is the most common extrathyroidal symptom of Graves' disease and its whole clinical presentation can significantly reduce patients' quality of life.[2]

Patients with persistent autoimmune thyroiditis, whether euthyroid or hypothyroid, may also be affected. The disease has a yearly adjusted incidence rate of 16 women and 3 men per 100,000 individuals.[1] Intravenous steroids/immunosuppression can effectively cure active inflammation, although this does not always result in complete remission, as inflammation quickly leads to persistent fibrosis and an increase in orbital fat. It's vital to keep risk variables under control in order to avoid progressing to more severe phases (smoking cessation, adequate thyroid function, selenium supplementation). A detailed assessment of GO activity and severity should be used to guide treatment. To restore function and beauty, many people require rehabilitative surgery (orbital decompression, squint surgery, and eyelid surgery). These patients have antibodies against the thyroid-stimulating hormone (TSH) receptor, which have been associated to the advancement of thyroid and ocular disease. At various phases of the disease, antibody levels can be used to guide therapy decisions.[2]

Despite significant developments in ophthalmology over the previous few decades, there is limited comprehensive bibliometric description of the quality and quantity of GO research in the peer-reviewed literature. As a result, the purpose of this research was to examine the development of GO articles in global contributions since 1970.

MATERIALS and METHODS

Study setting & design

The bibliometric search was conducted using the Web of Science (WoS) Core Collection advanced search engine, which provides a standard dataset for analyzing and tracking bibliographical factors such as author names, country, journal title, affiliation, keywords, number of citations, and subject areas. The data for this bibliometric analysis was gathered from the WoS core collection between 1970 and 2021. In January 2022, data recruiting was completed. There was no need for ethical approval because the data was taken from publicly available research.

Search strategy

Keywords related to "graves" and "ophtalmopathy" or "orbitopathy" were used in a search query in the WOS search engine. The time span was set from 1970 to 2021. Data on publishing growth, the most active countries and institutions, the most cited journals, and publishing and keyword mapping were examined. The articles were analysed in detailed.

The VOSviewer technique was used to visualize the maps, which were evaluated to present several bibliometric indications. VOSviewer (Leiden University, Leiden, Netherlands) is a software application for visualizing bibliographic linking, co-citation, co-authorship, keyword and co-occurrence analysis in publications.[3]

The Hirsch (H) index was utilized as marker of publication impact.[4]

Data analysis

For analysis, the data was exported into Microsoft Excel (Microsoft® Corp., Redmond, WA). Quantitative data included the total number of publications, articles, citations, journal titles, and organization-enhanced publications. By manually examining the retrieved parameters, the validity of the search method was determined.

RESULTS

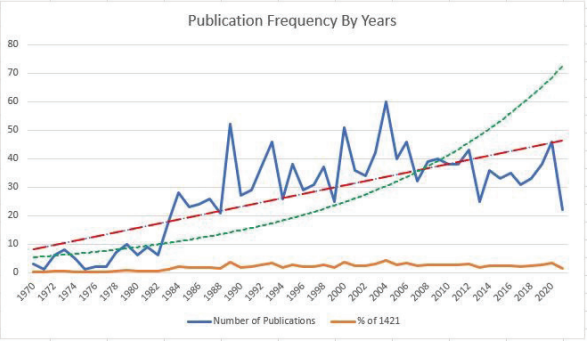
1. Publications

A total of 1421 journal publications were retrieved with an average of 24.26 citations per article. H index was found to be 85. Even if study search the publications in the period between 1970 and 2021 first article was in 1971. Distribution of publications showed in Table 1.

Table 1. Publications types.

Document Types	Number of Publications	% of 1421
Article	958	67.417
Meeting abstract	150	10.556
Letter	126	8.867
Proceedings paper	90	6.334
Review	72	5.067
Editorial material	65	4.574
Note	11	0.774
Correction	6	0.422
Book chapter	4	0.281
Early access	4	0.281
Discussion	3	0.211
Correction addition	1	0.07
Retraction	1	0.07

During the study period, the annual growth of GO articles showed a rising pattern. The majority of the publications (n=1357; 95.49 percent) were written in English, followed by German (n=37; 2.60 percent) and French (n=15; 1.056 percent). The remaining languages were Portuguese, Serbian, Korean, Russian, and Spanish (Graphic 1).



Graphic 1. The number of publications by the years.

2. Articles

Of the total publications, 958 (67,417) were research articles. The average number of citations of these 958 articles was 29.59. (High H index) The h index of these articles, which were cited 28348 times in total, was 81. And the detailed analysis of the articles was shown as follows. Endocrinology and Metabolism (n=372; 38.83%), Ophthalmology (n=249; 25.99%), General Internal Medicine (n=120; 12.52%), Radiology/ Nuclear Medicine/ Medical Imaging (n=64; 6.68%), Immunology (n=41; 4.28%), and the rest were from diverse fields (Table 2).

Table 2. Top List of Research Areas of the Articles.

Research Areas	Number of Articles	% of 958
Endocrinology Metabolism	372	38.831
Ophthalmology	249	25.992
General Internal Medicine	120	12.526
Nuclear Medicine/ Medical Imaging /Radiology	64	6.681
Immunology	41	4.28
Surgery	33	3.445
Research Experimental Medicine	32	3.34
Oncology	24	2.505
Cell Biology	15	1.566
Otorhinolaryngology	15	1.566
Pharmacology Pharmacy	15	1.566
Biochemistry Molecular Biology	13	1.357
Neurosciences Neurology	12	1.253
Pediatrics	12	1.253
Science Technology Other Topics	12	1.253
Genetics Heredity	9	0.939
•Only main research areas were shown.		

2 a. Active countries, institutions, and journals

The leading country on journal number is USA with (n=210; 21.92%), followed by Italy (n=88; 9.18%), China (n=76; 7.93%). Other 50 countries which around the globe were (n=584; 60.96%). Turkey ranked 9th (Table 3).

Table 3. The list of top 15 ranked countries in publishing GO articles.

Countries/Regions	Number of Articles	% of 958
USA	210	21.921
Italy	88	9.186
Peoples Rebuplic of China	76	7.933
Germany	75	7.829
Netherlands	75	7.829
Taiwan	50	5.219
Japan	49	5.115
England	47	4.906
Turkey	43	4.489
Poland	29	3.027
Brazil	27	2.818
Sweden	25	2.61
Canada	24	2.505
Australia	20	2.088
South Korea	20	2.088

2.b. Affiliations.

Amsterdam University and Mayo Clinic were the leader affiliations on GO research (Table 4).

Table 4. The list of top affiliations.

Organizations	Number of Articles	% of 958
Amsterdam University	52	5.428
Mayo Clinic	78	8.142
The University of Pisa	40	4.175
National Taiwan University Hospital	42	4.104
The Netherlands Ophthalmic Research Institute	15	1.566
University of Southern California	15	1.566
Stanford University	13	1.357
National Yang-Ming University	12	1.253
University of Munich	12	1.253
China Medical University	10	1.044
China Medical University Hospital	10	1.044
University of Insubria	10	1.044
Gazi University	9	0.939
Kurume University	9	0.939
Lund University	9	0.939

2.c. International and author collaboration

Papers co-authored by authors from multiple countries were designated as "international collaborations."

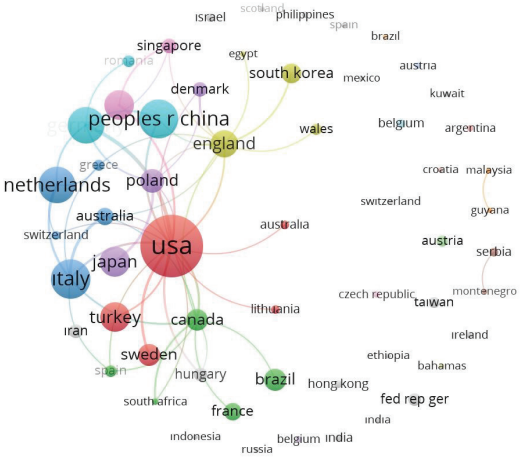


Figure 1. Co-authorship network visualization map among nations with at least one GO publication. Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with higher circle sizes or font sizes had more articles per capita.

Figure 1 depicts a network map of international collaboration. Using the VOSviewer approach, an investigation of international cooperation for active nations with at least one document revealed that there were clusters of international collaboration (Figure 2 and Figure 3).

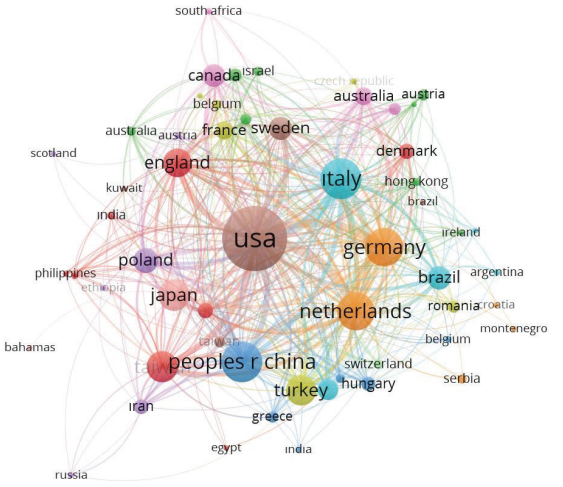


Figure 2. Countries with at least one GO publication are represented in a network visualization map of citations. Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration.

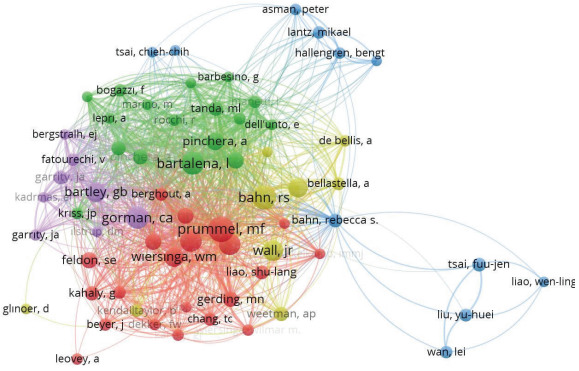


Figure 3. Citation visualization map of the top 66 authors with at least five publications on Google Scholar. Citations are shown by lines connecting nations. Authors with a greater circle size or font size had a higher number of citations.

Keyword analysis

Graves' ophthalmopathy, Graves' disease, and ophthalmopathy were mostly preferred keywords. The keywords other than the name of the disease were mostly about treatment protocols and pathogenesis (Table 5). The keyword mapping was also given in the Figure 4.

Table 5. The list of the keywords used more than 5 in the documents

keyword	occurrences
graves' ophthalmopathy	199
graves' disease	105
ophthalmopathy	58
graves ophthalmopathy	50
hyperthyroidism	15
exophthalmos	14
thyroid eye disease	14
radiotherapy	13
methylprednisolone	12
orbital decompression	12
thyroid-associated ophthalmopathy	12
clinical activity score	11
graves dısease	11
corticosteroids	10
quality of life	10
magnetic resonance imaging	9
smoking	9
adipogenesis	8
glucocorticoids	8
graves disease	8
graves' orbitopathy	8
autoimmunity	7
cytokine	7
graves&#8217	7
graves'	7
polymorphism	7
autoimmune thyroid disease	6
cytokines	6
diagnosis	6
extraocular muscles	6
orbit	6
orbitopathy	6
oxidative stress	6
radioiodine	6
thyroid	6
endocrine ophthalmopathy	5
pathogenesis	5
proptosis	5
rituximab	5
strabismus	5
thyroid disease	5

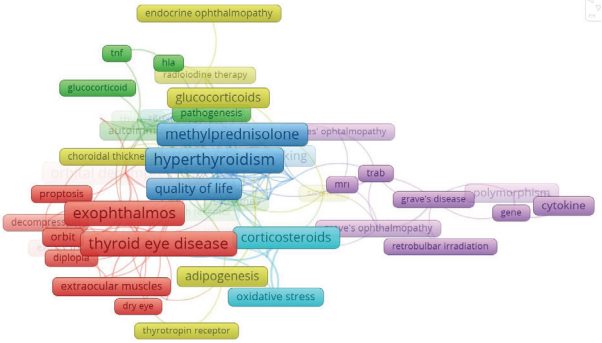
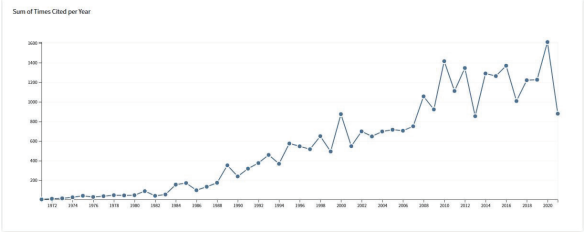


*Figure 4. Keyword mapping. *Keyword visualization map of articles on GO with at least one occurrence. In articles, linked lines indicate occurrence relationships. Keywords denoted by a higher circle size or text size appeared in the articles more frequently.*

2.d. Citing analysis

The total number of citations for the articles that were found was 28348, with an average of 29.59 citations per article. The H index of the articles that was 81. A total of 885 articles (92.37%) were cited at least once, while 73 articles (7.62%) were not cited at all. The number of citations has risen steadily over time. The annual citation growth of GO was sluggish until the 1990s, but exploded in the subsequent decade. The annual growth of citations on GO was depicted in Graphic 2. The year with the most citations was 2020, with a total of 2080 citations (Graphic 2).



Graphic 2. Graphics of citation by years between 1973 -2021. Line express the citing numbers.

The most cited article was published in the Journal of Clinical Endocrinology and it was cited for 555 times. The summary of the most cited 10 articles were given in Table 6.

Table 6. Top cited journals and number of citations.

Article Title	Journal	Times Cited, All
Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy	Clinical Endocrinology	555
Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy	New England Journal Of Medicine	471
Clinical-criteria for the assessment of disease-activity in graves ophthalmopathy - a novel-approach	British Journal of Ophthalmology	442
Occurrence of ophthalmopathy after treatment for graves hyperthyroidism	New England Journal Of Medicine	401
Thyrotropin receptor autoantibodies are independent risk factors for graves' ophthalmopathy and help to predict severity and outcome of the disease	Journal of Clinical Endocrinology & Metabolism	275
Epidemiology and prevention of Graves' ophthalmopathy	Thyroid	264
Randomized double-blind trial of prednisone versus radiotherapy in graves ophthalmopathy	Lancet	261
Supervoltage orbital radiotherapy for graves ophthalmopathy	Journal of Clinical Endocrinology & Metabolism	259
Prednisone and cyclosporine in the treatment of severe graves ophthalmopathy	New England Journal of Medicine	255
Orbital cobalt irradiation combined with systemic corticosteroids for graves ophthalmopathy - comparison with systemic corticosteroids alone	Journal of Clinical Endocrinology & Metabolism	246

DISCUSSION

The most common cause of hyperthyroidism is Graves' disease. Despite the effectiveness of antithyroid medications and radioactive iodine, surgery is still the preferable treatment for many patients.[5] GO is an autoimmune orbital disease most commonly associated with Graves' disease that necessitates close interdisciplinary collaboration.[2] It's a difficult phenomenon that necessitates collaboration among several specialists (endocrinologists, ophthalmolo-

gists, radiologists, radiotherapeutic, and orbital surgeons) for the better clinical outcome. In order to plan an effective treatment for GO, a precise diagnostic assessment is essential. To control the disease, medical therapy, radiation, or surgery may be required. There are numerous therapy techniques, as well as more modern medicines based on pharmacologic immunomodulation.[6] In summary, GO is a hot topic in multidiciplinary aproheces needed.

Systematic reviews, meta-analyses, and bibliometric analyses can be used to describe trends in a field. Systematic reviews and meta-analyses are primarily used to compare the efficacy or side effects of various treatment procedures or pharmaceuticals, and they can provide definitive or suggestive data. They do not, however, provide descriptive statistical analysis of research in a given field.[7,8] Bibliometric analysis is a statistical tool for defining the features of large-scale data and finding the key development trends based on database searches on a certain topic.[8,9]

Bibliometric analysis extracts data on the number of publications, countries, institutions, authors, and research areas, resulting in visual findings representing research status.[9]

Despite the fact that many bibliometric analyses have been undertaken in the field of medicine on a variety of issues from Turkey[9-21], there are only two studies that are equivalent to our research in the literature[21,22]. Cao et al.[21] looked at the GO literature from 1999 to 2019, while Elubous et al.[20] looked at the last two decades. The current analysis looked at the literature from 1970 to 2021. Similar to our study, Cao et al.[21] and Elubous et al.[22] employed the same database for analysis.

In this work, we aimed to give a bibliometric review of the literature on GO from 1970 to 2021. To do so, we used the well-known WOS database, which has already been used in published bibliometric research.[13,16,17] According to our findings, the number of GO articles has been gradually increasing over the last decade. The higher H-index demonstrates the importance of this topic to a wide range of doctors and academics, despite the modest number of publications. The United States and Italy came in first and second place, respectively. The increased number of GO investigations in these countries is noteworthy and deserves more research. The gap in co-authorship and citation data shows that this is a global problem that need far more international cooperative research (co-authorship).

The USA also had the most GO research outputs similar to Cao et al.'s study.[21] In our study, however, the second-leading country was Italy (n = 88; 9.18%). But Cao et al.[21] reported that China was in second place. In Cao et al.'s[21] study, all kinds of publications were analyzed, but we also only analyzed research articles. Elubous et al.[22] also the analyzed research articles too.

In the last two decades, the number of scientific studies on GO has risen. The visualization map shows a strong collaboration between European countries, which forms a cluster; most of any European country's linkages are with other European countries. The United States, on the other hand, collaborates with countries from other clusters, implying that it engages in more worldwide GO research collaboration. The study's two most mentioned articles were authored by a consortium of authors from different European countries (European Group of Graves Orbitopathy [EUGOGO]). Several studies have demonstrated that international co-authorship has a positive impact on citation count. Our findings were similar to Elubous et al.[22] reports. In bibliometric analysis, co-citation analysis is a useful approach for identifying publications that are often cited by multiple authors. Articles with a high number of co-citations imply a close link. Co-citation analysis can also help us figure out what the authors have to say about a given issue.[22] We examined at the topics of highly referenced articles in this study. The most cited article was published in the Journal of Clinical Endocrinology and it was cited 555 times and its topic was about the treatment.

Also in keyword mapping analysis, it was determined that, the keywords other than the name of the disease were mostly about treatment protocols and pathogenesis

CONCLUSIONS

Over the last two decades, the number of publications on GO has risen. According to the findings, the majority of the publications on GO are supplied by the United States, which has a growing number of publications, particularly in North American countries. The rest of the world made a significant contribution. This bibliometric investigation revealed the world's expanding population. The quantity of citations is great, yet global collaboration is required to address this increasing and worrisome issue. As a result of keyword mapping analysis treatment protocols and pathogenesis were hot topics on GO.

Limitatitons

There are some limitations in the current study. It wasn't possible to include papers from journals that weren't indexed in the WOS database. Furthermore, because the keywords were all in English, publications in other languages may have gone unnoticed. Another problem was the lack of other databases such as Scopus and Pubmed. The analyses were carried out using the VOSviewer; however, alternative tools (such as CiteSpace II and Bibexcel) could be used in future studies.

Ethical Approval

For bibliometric investigations, no approval is required.

Conflict of Interest

As there is only one author, there is no need to declare a conflict of interest.

Acknowledgements

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A Quantitative Study of The Most Influential Articles on Cytomegalovirus in Solid Organ Transplantation

Solid Organ Transplantasyonunda Sitomegalovirüs Üzerine En Etkili Makalelerin Nicel Bir Çalışması

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Abstract

Aim In this quantitative study, the previous literature on the topic of Cytomegalovirus (CMV) in solid organ transplant (SOT) recipients was analysed. Our overarching goal was to explore the publications in this field and to identify research hotspots.

Material and Method The Web of Science (WoS) database was utilized to research publications. The following terms were included in the search strategy syntax: "CMV" or "CMV infection" or "Cytomegalovirus" and "solid organ" or "hepatic" or "liver" or "pancreatic" or "lung" or "heart" or "transplantation" or "organ donation". Articles were selected as the document type. The complete text data of the included publications was retrieved from the WoS database. The VOSviewer (version 1.6.10, Leiden University, Netherlands) was used to do the bibliometric study in order to display the collaboration network, emphases, and future trends in the relevant topic.

Results 2432 results were reached from the Wos Core Collection. 1390 of them were articles. The USA was the top-ranked country (29.928%). Germany, Japan, England, and France (6.043%) were ranked in the first 5 countries. Turkey ranked 16th. 1351 (97.194%) of the publications were published in SCI-EXPANDED journals. The first article was published in the year 1971. 990 (71.87%) of the articles were published after 2000. The highest number of publications was in the year 2020 (4.892%). The H index of the articles was 100. There were a total of 45063 citations and an average of 32.42 per item. The number of citations and publications has increased over the last 30 years. The University of London was the top-ranked affiliation. Most of the articles (11.871%) were published in the journal "Transplantation Proceedings".

Conclusion The number of publications in this field is very low, especially for developing countries. The USA, Japan, and European countries are the countries with the highest number of publications.

Keywords Bibliometric, citation analysis, scientific publications, Cytomegalovirus, solid organ transplantation.

Özet

Amaç *Bu nicel çalışmada, solid organ nakli (SOT) alıcılarında Sitomegalovirüs (CMV) konusunda önceki literatür analiz edildi. Kapsamlı hedefimiz, bu alandaki yayınları keşfetmek ve araştırma noktaları belirlemekti.*

Gereç ve Yöntem *Yayınları araştırmak için Web of Science (WoS) veritabanı kullanıldı. Arama stratejisi anahtar kelimeleri olarak şu terimler kullanıldı: "CMV" veya "CMV enfeksiyonu" veya "Sitomegalovirüs" ve "solid organ" veya "karaciğer" veya "hepatik" veya "pankreatik" veya "akciğer" veya "kalp" veya " nakil" veya "organ nakli". Belge türü olarak makaleler seçildi. Dahil edilen yayınların tam metin verileri WoS veri tabanından alındı. VOSviewer (versiyon 1.6.10, Leiden University, Hollanda), ilgili konudaki işbirliği ağını, vurguları ve gelecekteki eğilimleri görüntülemek için bibliyometrik çalışmayı yapmak için kullanıldı.*

Bulgular *Wos Core Collection'dan 2432 sonuca ulaşıldı. Bunların 1390'ı makaleydi. ABD (%29.928) en üst sıralamadaki ülke idi. Almanya, Japonya, İngiltere ve Fransa (%6.043) ilk 5 ülkede yer aldı. Türkiye 16. sırada yer aldı. Yayınların 1351'i (%97.194) SCI-EXPANDED dergilerinde yayınlanmıştı. İlk makale 1971 yılında yayınlanmıştı. Makalelerin 990'ı (%71.87) 2000 yılından sonra yayınlanmıştı. En fazla yayın (%4.892) 2020 yılında yayınlanmıştı. Makalelerin H indeksi 100 idi. Toplam 45063 atıf ve makale başına ortalama 32.42 atıf yapılmıştı. Son 30 yılda atıf ve yayın sayısı artmıştı. Londra Üniversitesi en üst sıralamada yer alan kurum idi. Makalelerin çoğu (%11,871) "Transplantation Proceedings" dergisinde yayınlanmıştı.*

Sonuç *Bu alandaki yayın sayısı özellikle gelişmekte olan ülkeler için oldukça düşüktür. ABD, Japonya ve Avrupa ülkeleri en fazla yayına sahip ülkelerdi.*

Anahtar Kelimeler *Bibliyometrik, atıf analizi, araştırma yayınları, Sitomegalovirüs, solid organ nakli.*

INTRODUCTION

Human Herpes virus 5, often known as cytomegalovirus (CMV), has the biggest genome of any known human virus (230 kb), with 200 genes encoding proteins. After solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT), CMV is one of the most common infections, especially in seronegative receivers of seropositive donors (D+/R–) and seropositive recipients (R+). CMV infection is considered "high risk" in these people. CMV-seropositive SOT recipients have prior CMV-specific cell-mediated immunity and are thus at an intermediate risk for CMV infection, with D+/R+ recipients being at a higher risk than D–/R+ recipients due to the possibility of donor-derived virus superinfection.[1,2]

CMV infection develops in the majority of high-risk SOT patients without antiviral prophylaxis, resulting in viremia, CMV disease, and end-organ damage. Its immunomodulatory properties may hasten graft rejection and make patients more susceptible to opportunistic infections. While ganciclovir or valganciclovir have been the standard of therapy for high-risk SOT recipients for decades, these medicines are associated with higher costs, neutropenia, and a high incidence of postprophylaxis illness.[2,3] Prophylaxis and preemptive therapy are the two main approaches for CMV prevention. After SOT, prophylaxis effectively avoids CMV infection, although it is linked with high rates of neutropenia and delayed-onset postprophylaxis illness. Preventive treatment, on the other hand, has the advantage of lowering CMV illness rates and promoting robust humoral and T-cell responses. It's commonly used in hematopoietic cell transplant recipients, but it's less common following SOT due to logistical issues, which could be addressed by new approaches to monitor CMV viremia using self-testing platforms.[3]

Screening tests have advanced significantly in recent years, both in terms of type and quality, allowing for more precise and savvy treatment. Advances in diagnostics include the development of an international standard, which should allow for comparison of results across different methodologies, as well as as assays for cellular immune function against CMV. Ganciclovir is the mainstay of treatment, but new evidence suggests that oral valganciclovir medication isn't inferior to intravenous ganciclovir therapy. Treatment of resistant viruses is still difficult, although the availability of a variety of new treatment medicines has made it easier.[2]

In this study, we conducted a bibliometric overview of the previous literature on the topic of CMV in SOT recipients. Our overarching goal was to explore the importance of publications in this field all over the globe and to identify research hotspots.

METHODS

As this was a literature survey, there was no need for ethics committee approval. In most bibliometric investigations, no ethical approval is necessary because neither humans nor animals are involved.

The Web of Science (WoS) database (Clarivate Analytics, Philadelphia, PA, USA) was utilized to find CMV and SOT research publications. On March 25,2022, data for this study was retrieved from WoS. The following infection-related terms were included in the search strategy syntax: "CMV" or "CMV infection" or "Cytomegalovirus" and "solid organ" or "hepatic" or "liver" or "pancreatic" or "lung" or "heart" or "transplantation" or "organ donation". The search language was chosen as English, which is the most dominant scientific language worldwide. For our search, articles were selected as the document type. To manage the downloaded findings and erase duplicate information, Microsoft Office Excel was used.

We accessed the information through the online library and digital resources of the Çanakkale Onsekiz Mart University.

Overview of the output from the WoS database

The publication year, location or nation, study category,

authorship, and citation counts of the retrieved publications were all identified using the WOS database. Only articles published between 1970 and 2022 were included in the timeframe. Since the most significant advancements in medicine have occurred in recent years, this study focused on publications published after the 1970s. In addition, the publications from Turkey were analysed for comparison with the global literature.

Network analysis

The complete text data of the included publications was retrieved from the WoS database. The VOSviewer (version 1.6.10, Leiden University, Netherlands) was used to do the bibliometric study in order to display the collaboration network, emphases, and future trends in the relevant topic. The VOSviewer software was used to import the obtained data. The following information was extracted and analyzed: authorship, affiliation, citation, keywords, and theme words. Finally, bubble maps were created to display the results of the bibliometric analysis. Colors indicate item clusters in the bubble maps, while the distance and breadth of lines between two bubbles reflect co-occurrence frequency. The diameters of the bubbles under co-authorship, citations, keywords/theme words, and co-occurrence analysis, respectively, show the number of documents, citations, and occurrences.

RESULTS

2432 results were reached from the Wos Core Collection. 1390 of them were articles. The USA was the top-ranked country with 416 (29.928%) published articles. Germany (10.216%), Japan (9.281%), England (7.122%), France (6.043%), Spain (5.468%), Italy (5.180%), Netherlans (4.964%), China (4.748%), South Korea (3.381%), Australia (3.022%), Switzerland (2.590%), Sweden (2.158%), Brazil (2.014%), Austria (1.727%), and Belgium (1.583%) ranked among the top 15.Turkey ranked 16th with 17 (1.223%) published articles. 484 of them were published as open access. 1330 (95.683%) of them were written in English. Furthermore, French (1.439%) and German (1.295%) were the most preferred languages.

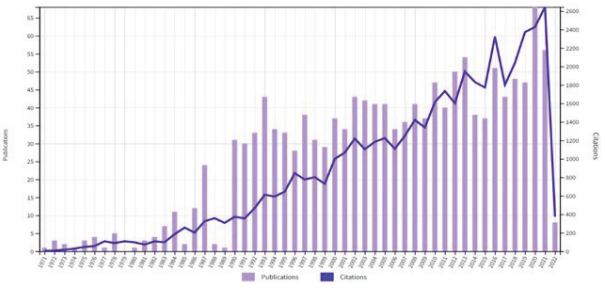
1351 (97.194%) of the publications were published in SCI-EXPANDED journals. The remains were published in the other indexes [CPCI-S: 177 (12.734%), ESCI: 34 (2.446%), BKCI-S: 5 (0.360%), and 4 (0.156%), SSSI: 2 (0.360%) indexed journals].

The first article was published in the year 1971. 990 (71.87%) of the articles were published after 2000. The highest number of publications was in the year 2020 (n = 68, 4.892%).

The H index of the articles was 100. There were a total of 45063 citations and an average of 32.42 per item. The number of citations and publications has increased over 30 years (Graphic 1). The articles were mostly (46.906%) from the Transplantation area (Table 1).

Table 1. Research areas.

Web of Science Categories	Record Count	% of 1.390
Transplantation	652	46.906
Immunology	646	46.475
Surgery	413	29.712
Hematology	313	22.518
Infectious Diseases	225	16.187
Microbiology	120	8.633
Oncology	108	7.770
Medicine General Internal	95	6.835
Biophysics	78	5.612
Virology	61	4.388
Respiratory System	47	3.381
Urology Nephrology	47	3.381
Gastroenterology Hepatology	39	2.806
Cardiac Cardiovascular Systems	37	2.662
Pediatrics	34	2.446
*Showing 15 out of 53 entries		



Graphic 1. Growing number of citations and publications since 1970.

Michael Boeckh from the USA was the top-ranked author (Table 2). 2.086% of the articles were published by group authors. Infectious Diseases Working Party Europe (n = 2, 0.144) was the most published group.

Table 2. Top ranked authors list.

Authors	Record Count	% of 1.390
Boeckh, Michael (USA)	33	2.374
Kanda, Yoshinobu (Japan)	27	1.942
Einsele, Hermann (Germany)	23	1.655
Razonable, Raymund R. (USA)	20	1.439
Griffiths, Paul D. (England)	17	1.223
Showing 5 out of 8.035 entries		

The University of London was the top ranked affiliation with 108 articles (Table 3).

Table 3. Top ranked affiliations.

Affiliations	Record Count	% of 1.390
University of London	108	7.77
University of Washington	98	6.15
Fred Hutchinson Cancer Center	56	4.029
Mayo Clinic	43	3.094
Assistance Publique Hopitaux Paris	34	2.446
Pennsylvania Commonwealth System of Higher Education	33	2.374
Unıversity of Pittsburgh	31	2.230
Harvard University	28	2.014
Showing 8 out of 1.346 entries, 8 record(s) (0.576%) do not contain data in the field being analyzed		

Most of the articles (n = 165, 11.871%) were published in the journal "Transplantation Proceedings" (Table 4).

Table 4. Journals mostly published the articles on CMV&SOT.

Journals	Record Count	% of 1.390
Transplantation Proceedings	165	11.871
Transplantation	105	7.554
Transplant Infectious Disease	88	6.331
Bone Marrow Transplantation	77	5.540
Biology of Blood And Marrow Transplantatıon	59	4.245
Blood	41	2.950
Journal of Infectious Diseases	38	2.734
Clınıcal Infectious Diseases	30	2.158
Clinical Transplantation	28	2.014
American Journal of Transplantatıon	27	1.942
Journal of Heart and Lung Transplantation	25	1.799
Journal of Medical Virology	23	1.655
International Journal of Hematology	19	1.367
Britıih Journal of Haematology	18	1.295
Transplant International	18	1.295
Journal of Clinical Microbiology	17	1.223
Annals of Hematology	16	1.151
Liver Transplantation	13	0.935
Pediatric Transplantation	11	0.791
Transplantation and Cellular Therapy	11	0.791
Showing 20out of 332 entries		

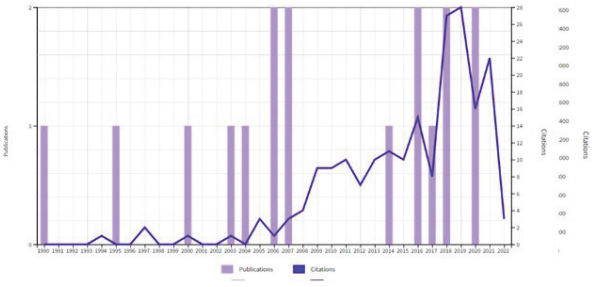
The United States Department of Health and Human Services funded most of the articles (11.799%) on this topic (Table 5).

Table 5. The funding agencies.

Funding Agencies	Record Count	% of 1.390
United States Department of Health Human Services	164	11.799
National Institutes of Health Nih USA	161	11.583
Nih National Cancer Institute	89	6.403
Nih National Institute of Allergy Infectious Diseases Niaid	41	2.950
Nih National Heart Lung Blood Institute	39	2.806
European Commission	35	2.518
Nih National Institute Of Diabetes Digestive Kidney Diseases	29	2.086
National Natural Science Foundation of China	27	1.942
Instituto De Salud Carlos Iii	21	1.511
Merck Company	15	1.079
Showing 10 out of 529 entries, 943 record(s) (67.842%) do not contain data in the field being analyzed		

Contribution of Turkey

There were 17 articles from Turkey. The articles had 201 citations (11.82 per article) and the H index was 6. The number of publications and citations had an irregular distribution over the years (Graphic 2).



Graphic 2. Times cited and publications from Turkey since 1970.

Baskent University and Ankara University were the leading affiliations, with four articles each (Table 6).

Table 6. Top three affiliations from Turkey.

Ranked	Affiliations	Record Count	% of 17
1	Baskent University	4	23.529
1	Ankara University	4	23.529
2	Ege University	3	17.647
2	Hacettepe University	3	17.647
3	Adana Numune Traınıng Research Hospital	2	11.765
3	Akdenız University	2	11.765
3	Antalya Traınıng Research Hospital	2	11.765
3	Childrens Hospital	2	11.765
Showing 8 out of 35 entries			

DISCUSSION

Organ transplantation (OT) is one of contemporary medicine's most effective innovations. Patients with end-stage disease often have no other option except to undergo transplantation. Even before the first transplant, it was evident that OT could only be successful if it was approached in a multidisciplinary manner.[5] In 1933, Ukrainian physician Voronoy, U.U. performed the first human-to-human transplant in the Soviet Union.[5,6]

The United Network of Organ Sharing (UNOS), which was founded in 1984, was the next significant step in the evolution of OT. This organization oversees all transplant activities in the United States, including the upkeep of a national transplant list for all forms of transplantation, data gathering, and educational activity coordination. A number of organizations with identical functions exist throughout Europe and Asia.[5] The Middle East Dialysis and Organ Foundation was founded in 1984, and has now evolved into the Middle East Society for Organ Transplantation (MESOT), a significant step forward for organ transplantation in the region and a member of the Transplant Society.[7] MESOT has managed to operate and hold international congresses despite worldwide turmoil in the

Middle East. Many issues linked to transplantation have been addressed by MESOT member countries in countries with similar sociocultural features.[8]

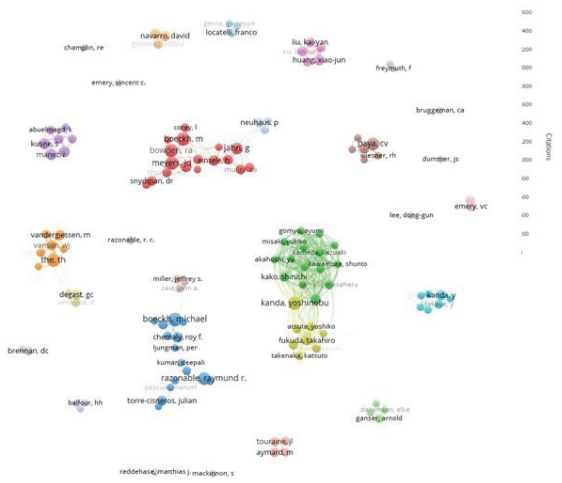


Figure 1. Citation visualization map among authors with a minimum of 5 publication and 1 citation.
***Lines connecting countries are indicative of citation. Authors represented with larger circle size or font size had relatively more citation.*

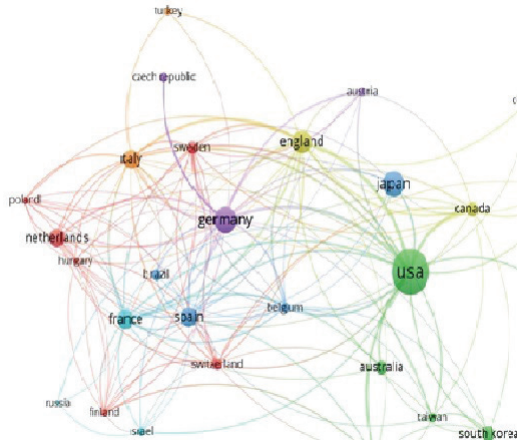


Figure 2. Network visualization map of co-authourship among countries.
***Lines connecting countries are indicative of collaboration. Thicker lines indicate stronger collaborations. Countries represented with larger circle size or font size had relatively more international collaboration.*

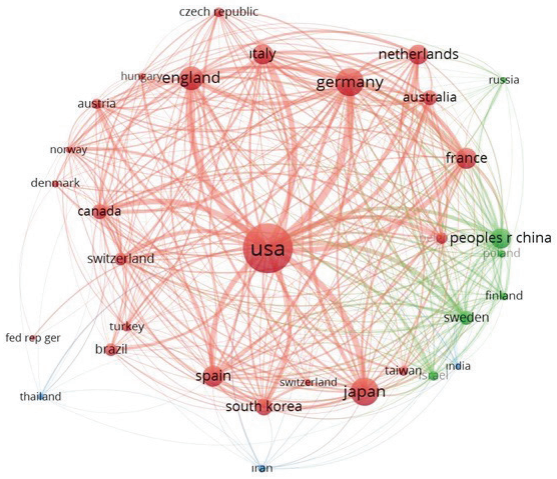


Figure 3. Network visualization map of citation map among countries.
***Lines connecting countries are indicative of collaboration. Thicker lines indicate stronger collaborations. Countries represented with larger circle size or font size had relatively more international collaboration.*

Along with the successful transplantation of an organ, the management of infections that may develop in the patient is one of the most important issues in organ transplantation, and infections are one of the main causes of death in these patients. CMV is one of the most important infectious agents in both SOT and HCT recipients.[1-3] Despite advances in molecular technologies for CMV detection and the introduction of extremely efficient preventative therapies, CMV continues to be a primary cause of morbidity and mortality in HCT recipients. Pneumonia, hepatitis, colitis, retinitis, and encephalitis are among the tissue-invasive diseases caused by CMV. HCT recipients with CMV illness have a mortality rate of up to 60%. CMV infection has been linked to an increased risk of secondary bacterial and fungal infections, graft-versus-host disease, and high non-relapse mortality rates after HCT.[9] The topic of CMV in transplantation seems to be becoming even more popular as the number of both HCT and SOT recipients is increasing globally.[5-8]

The scientometric or bibliometric analysis is used to map the scientific knowledge field objectively, while the critical evaluation is used to suggest research themes and difficulties based on the scientometric results[10,11]. Despite the fact that bibliometric analyses on transplantation have been found in the medical literature[10-16], no similar study could be found in the available literature on CMV infection in SOT, which is one of the most important problems for posttransplant patients. Only Chen et al.[17] conducted a bibliometric study to research the status of CMV infection after hematopoietic stem cell transplantation.

Our research is the first to conduct a global bibliometric examination of current scholarly output on CMV and SOT. In addition, the publications from Turkey were analysed for comparison with the global literature. This bibliometric study will help researchers better understand the state of CMV research in SOT recipients and predict future trends. In the next few years, understanding risk factors for peritransplantation CMV infections and developing efficient therapies for infectious complications should be prioritized.

In this study, we evaluated 1390 articles in the WOS core collection based on the research topic of CMV and transplantation, using various statistical items like references and keywords in Vosviewer, and came to strong conclusions from the visualization analysis. Furthermore, by assessing the findings of our study, readers will be able to identify the biggest scientific communities in the field, as well as the most referenced academics and journals, which will aid them in their search for potential research collaborators.

According to a bibliometric analysis of the most cited articles in this field, the plurality of the top 100 most cited publications on transplantation were published mostly in the USA between 2000 and 2009. Most of the top 100 papers on transplantation were published in the New England Journal of Medicine, followed by Transplantation and Nature journals.[10]

Chen et al.[17] conducted their study on the same database (WOS) on June 15, 2021, and they used CiteSpace V visualization software. They reported that a total of 1,476 documents were found to be relevant. The United States, Germany, Japan, China, and Italy ranked first through fifth in terms of the number of publications. The Fred Hutchinson Cancer Research Center, the University of Washington, the University of Minnesota, the Karolinska Institute, and Peking University were the top five institutions by number of publications. The Fred Hutchinson Cancer Research Center, Henri-Mondor Hospital, the National Cancer Center, Karolinska University Hospital, and the University of Pavia were the top four institutions for centrality scores. With a centrality score of 0.01, there were just 4 writers. The research was mostly published in prestigious hematological journals as well as immunization and transplantation journals. In our study, we found that since 2000, the number of articles on CMV and transplantation has steadily increased, with no noticeable spikes, indicating the field's constant development. 990 (71.87%) of the articles were published after 2000. The highest number of publications was in the year 2020 (n = 68, 4.892%). When looking at the literary sources, the USA, which is at the forefront of this research, has published over 400 pieces of literature (n = 416, 29.928%) in the past, and the USA is home to a plethora of vital agencies and reputable researchers. Furthermore, Germany (10.216%), Japan (9.281%), England (7.122%), France (6.043%), and Spain (5.468%) all play important roles in research. The most cited article was published in the journal The Journal of Infectious Diseases. Despite the fact that the University of London was the most mentioned and prolific country in the field of CMV and transplantation research, the USA was the most cited and productive country. This could be owing to the abundance of institutions and financial assistance in the USA.

In 1989, the Turkish Ministry of Health launched a national organ sharing program, and in 2001, National Co-

ordination Centers for dead donor organ distribution were established.[18] The World Transplantation Society (TTS) promoted the establishment of kidney and liver transplant programs in low- and middle-income nations. By accepting large numbers of fellows from each country, Baskent University has played a major role in the teaching and research of local health professionals.[19] There were a limited number of articles (17 articles) from Turkey on CMV and transplantation. Baskent University and Ankara University were the leading affiliations, with four articles each. The first article was published in 1990, and for some years, no documents were published.

This bibliometric study can help researchers better understand the state of CMV research in SOT recipients and predict future research trends. In the coming years, identifying risk factors for peritransplantation infections and developing effective therapies for infectious complications should be prioritized. The number of publications in this field is very low, especially for developing countries. The USA, Japan, and European countries are the countries with the highest number of publications. Although there has been an increase in the number of articles published in recent years, our scientific output results have shown that the numbers are not at the desired level. The number of publications should be increased, especially from the countries where SOT is performed, and these countries should be scientifically supported by governments and institutions.

Limitations of the study

The study's findings are based on literature screened from the WOS core collection, and efforts are being made to improve scientific and effective analytical results from the private document library. However, the quality and amount of articles will fluctuate depending on the source of literature and subjective criteria. Furthermore, changing Vosviewer parameter settings will alter the visualization analysis outcome. As a result, there are certain limitations to this research. In addition, the most cited articles were not examined.

Conflicts of Interest

All authors have filled out the ICMJE uniform disclosure form. There are no potential conflicts of interest for the authors to disclose.

Ethical Statement

The authors are responsible for all aspects of the work, including ensuring that any questions about the work's accuracy or integrity are thoroughly examined and resolved.

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The Clinical Management Of 59 Tubo-Ovarıan Abscess Cases

59 Tubaovaryan Abse Olgusunun Klinik Yönetimi

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Abstract

Aim This study aims to retrospectively evaluate the incidence, risk factors, clinical and laboratory outcomes, complications and management strategies of the tubo-ovarian abscess (TOA).

Material and Method The records of 59 patients who had been hospitalised with the diagnosis of tubo-ovarian abscess between January 2016 and January 2021 were studied retrospectively. The patients' clinical and laboratory results, operational methods applied, and the complications raised were recorded. Demographic data and sonographic findings of the patients were reported.

Results The mean age of the patients was 36.53 ± 9.26 years. The most common complaints were pelvic pain (100%), vaginal discharge (42.4%), fever (35.6%) and menstrual irregularity (30.5%). The mean abscess size was 6.31 ± 2.08 [3-12] cm. The patients were divided into two groups as those who underwent surgery and received only medical treatment. While only medical treatment was sufficient in 28 (47.5) patients, surgical treatment was applied to 31 (52.5%) patients. There was no statistical difference in terms of gravida, parity, BMI, duration of the marriage, PIH (pelvic inflammatory disease) history, previous operation history and additional systemic disease. The presence of an intrauterine device (IUD), duration of IUD use, and TOA size were significantly higher in the surgical group. Abscess sizes in patients who used only medical treatment were statistically significantly lower than in those who required surgery (4.22 × 1.94 cm, 8.15 × 2.28 cm; p<0.001). The hospital stay was also shorter in the medical treatment group (p: 0.629). The most common surgical complications were bladder damage (12.9%), bowel perforation (9.6%), and ureteral damage (9.6%), respectively. The pathology report of only one patient was detected as malignant (3.2%).

Conclusion Early diagnosis and treatment of TOA are essential as it has severe life-threatening consequences such as morbidity and mortality. The appropriate treatment method should be selected according to the operator's experience, the patient's age, fertility desire, abscess size and spread, the patient's risk factors, and clinical and laboratory results.

Keywords Medical Treatment, Surgical Treatment, Tubo-ovarian abscess, Pelvic Inflammatory Disease

Özet

Amaç *Retrospektif olarak, tubo-ovaryan abse (TOA) olgularının insidansını, risk faktörlerini, klinik ve laboratuvar sonuçlarını, komplikasyonlarını ve yönetim stratejilerini değerlendirmek.*

Gereç ve Yöntem *Ocak 2016- Ocak 2021 yılları arasında, klinik ve sonografik olarak TOA tanısı ile kliniğimize yatışı yapılan 59 hastanın dosyası retrospektif olarak incelendi. Hastaların demografik verileri ve sonografik bulguları raporlandı. Hastaların klinik ve laboratuar sonuçları, uygulanan operasyon yöntemleri ve gelişen komplikasyonlar kaydedildi.*

Bulgular *Hastaların ortalama yaşı 36.53 ± 9.26 idi. En sık pelvik ağrı (100%), vajinal akıntı (42,4%), ateş yüksekliği (35,6%) ve adet düzensizliği (30,5%) şikayetiyle başvuruldu. Ortalama abse boyutu 6.81 ± 2.08 [3-12] cm idi. Hastalar operasyon olanlar ve olmayanlar olarak iki gruba ayrıldı. Yirmi sekiz (47,5%) hastada sadece medikal tedavi yeterli olurken, 31 (52,5%) hastaya cerrahi tedavi uygulandı. Hastaların gravide, parite, BMI, evlilik süresi, PIH (pelvik inflamuar hastalık) öyküsü, geçirilmiş operasyon öyküsü ve ek sistemik hastalık açısından istatistiksel fark görülmedi. Rahim içi araç (RİA) varlığı ve kullanım süresi, TOA boyutu cerrahi yapılan grupta anlamlı olarak daha fazla bulundu. Sadece medikal tedavi uygulanan hastaların abse boyutları, operasyon gereken hastalara göre istatistiksel anlamlı olarak daha düşük saptandı (4.22 ± 1.94cm, 8.15 ± 2.28cm; p<0.001). Hastanede kalma süresi de medikal tedavi edilen grupta daha kısa idi (p:0.629). En sık cerrahi komplikasyon sırasıyla; mesane hasarı (12,9%), barsak perforasyonu (9,6%) ve üreter hasarı (9,6%) olarak gözlendi. Sadece bir hastanın patoloji sonucu malign olarak tespit edildi (3,2%).*

Sonuç *TOA'nın erken tanı ve tedavisi, morbidite ve mortalite gibi hayatı tehdit eden ciddi sonuçları olmasından dolayı önemlidir. Operatör deneyimi, hastanın yaşı, fertilite arzusu, abse boyutu ve yayılımı, hastanın risk faktörleri, klinik ve laboratuvar sonuçlarına göre uygun tedavi yöntemi seçilmelidir.*

Anahtar Kelimeler *Cerrahi tedavi, Medikal tedavi, Pelvik inflamatuar hastalık, Tubo-ovaryen abse.*

INTRODUCTION

Pelvic inflammatory disease (PID) is an inflammatory disease of the upper female genital tract covering different spectrums such as endometritis, salpingitis, oophoritis and pelvic peritonitis[1]. A tubo-ovarian abscess (TOA) usually occurs as a complication after acute and chronic PIH[2]. TOA is reported to occur in 33% of hospitalised patients with acute PID[3]. It often occurs because of recurrent infections of the adnexal organs. As a result of the progression of the infection, involvement of the intestines, uterus, omentum, and bladder may occur[4].

The clinical presentation of TOA varies. It usually presents with symptoms such as pelvic pain (90%), vaginal discharge, irregular bleeding, nausea, and vomiting. Fever higher than 37.8 ºC is present in 60-80% of cases, and leucocytosis is present in 60%.[5]. Detection of pelvic mass by gynaecological examination and radiological interventions supports the diagnosis[6]. Ultrasonography (USG), Computed Tomography (CT) and Magnetic Resonance (MR) are imaging modalities used to monitor the response of patients to treatment and monitor complications[7]. First-line therapy in unruptured cases is broad-spectrum antibiotics. In unsuccessful antibiotic therapy, the required surgical treatment is either laparoscopy, laparotomy, or imaging-guided drainage[8,9]. It is crucial to determine the risk factors of TOA, which has high complication, morbidity, and mortality rates. In this respect, patients' early diagnosis and treatment strategies should be determined, and more effective preventive methods should be developed.

This study aims to evaluate the incidence, demographic characteristics, risk factors, complications, and management strategies of patients hospitalised with TOA diagnosis in our clinic in the last five years and thus contribute to the literature.

METHOD

The records of a total of 59 patients aged between 15-and 50 years who were hospitalised with the diagnosis of TOA in the gynaecology and obstetrics clinic of the Health Sciences University (SBU) Bursa Yüksek İhtisas Training and Research Hospital between January 2016 and January 2021 were analysed retrospectively. Only 1 patient was excluded from the study due to insufficient recorded information. This study was approved by the ethics committee of SBU Bursa Yüksek İhtisas Training and Research Hospital.

Demographic characteristics of the patients, complaints at the time of admission, risk factors, recent operation or intrauterine surgical intervention history were investigated. Clinical and physical examination findings, laboratory values, USG and/or CT results were determined. TOA was diagnosed according to clinical and laboratory findings and results of USG and CT images or during operations performed with indications such as the acute abdomen and pelvic mass. Clinical findings and laboratory values were taken as ≥38 ºC for fever, >9,000 /μL for blood leukocyte count, and >1.5 mg/dL for CRP at the first admission. TOA was defined as a dense, complex cystic mass on USG and a complex mass with regular or irregular thick margins and an air-fluid level on CT. The diameter and characteristics of the mass were examined by imaging methods.

Triple antibiotic therapy [ceftriaxone (2x1g/day) + clindamycin (3x600mg/day) + gentamicin (2x80mg/day)] was started as primary treatment for the cases. Surgical approach was considered in cases that did not respond to antibiotic therapy within 24-48 hours. Considering the patient's age, fertility request, and the extent of the abscess, surgery was planned based on the severity of the case.

Data were evaluated in SPSS (Statistical Package for Social Sciences) for Windows 12, Epi Info, and Microsoft Office Excel programs for statistical analysis. Since the data did not have a normal distribution, descriptive statistics, chi-square frequency distributions and Mann Witney U test were used. Variables were expressed as mean and standard deviation. The results were considered statistically signifi-

cant if they were within the 95% confidence interval and p<0.05.

Findings

The mean age of 59 tubo-ovarian abscess cases included in the study was calculated as 36.53 ± 9.26 years. Gravida's number was 2 [0-7]. Considering the risk factors, 29 (49.2) of the cases had intrauterine device (IUD) use. The most common symptom was pelvic pain with 59 (100%). Ultrasound examination was performed in all of the cases, and the most common imaging method after the ultrasound was computed tomography with 38 (64.4%). The number of abscesses was 1.25 ± 0.44, and the size of the abscess was 6.81 ± 2.08 cm. Surgical treatment was performed in 31 (52.5%) of the cases, and the most common surgery was unilateral salpingo-oophorectomy (18 (58.1%). During surgery, the most common complication was bladder damage with 4 (12.9%). Demographic information and clinical and laboratory parameters of the cases are given in Table 1.

When the patients who underwent surgical treatment and those who received medical treatment were compared, the parameters of age, gravida, parity, BMI, abscess size, WBC, CRP, duration of antibiotic use and length of hospital stay were found to be similar in both groups (p>0.05). The rate of IUD use (18 (%58) vs 11 (%39.2), p=0.013), and duration of IUD use (4 [0-9] vs 1 [0-6], p=0.002) were found to be higher in the surgical group than in the medical treatment group. The size of the abscess (8.15 ± 2.28 vs 4.22 ± 1.94, p<0.001) was found to be larger in the surgical group than in the medical treatment group. Surgical treatment was applied to 31 patients out of 59, and medical treatment was applied to 28 patients. The comparison of the demographic and clinical data of the medical treatment group and the surgical treatment group according to the operation status is given in Table 2.

Table 1. Demographic information, clinical and laboratory parameters of the cases

	Mean±SD Median (min-max) n(%)
Age (years)	36.53 ± 9.26
	39 [21-65]
Gravida	2.17 ± 1.53
	2 [0-7]
Parity	1.88 ± 1.47
	2 [0-7]
BMI (kg/m2)	0.81 ± 3.92
	31.2 [17.3-39.5]
Duration of marriage	6.07 ± 4.90
	[1-10]
Risk factors IUD use n (%) Duration of IUD use PID history n (%) Operation history n (%) Additional Systematic disease n (%)	29 (49.2) 2.98 ± 3.41 0 [0-12] 29 (49.2) 26 (44.1) 22 (37.3)
Symptoms n(%) Fever Pelvic Pain Irregular menstruation Vaginal discharge	 21 (35.6) 59 (100) 18 (30.5) 25 (42,4)
Scan n(%) USG BT MR	 59 (100) 38 (64.4) 23(38,9)
Laboratory findings WBC (μL) CRP (mg/dL)	 15.30 ± 7.98 72.0 [18.4-297.0]
Number of abscesses	1.25 ± 0.44 1.0 [1-2]
Abcess size (cm)	6.81 ± 2.08 6.0 [3-12]
Operation Type n(%) Medical Surgical	 28 (47.5) 31 (52.5)
Applied operation n(%) TAH+BSO USO Percutaneous drainage	 11 (35.4) 18 (58.1) 2 (6.5)
Complications n(%) Bowel perforation Bladder damage Ureteral damage Peritonitis	 3 (9.6) 4 (12.9) 3 (9.6) 1 (3,2)

Table 2. Comparison of demographic and clinical data according to the operation status

	Surgical Treatment (n=31)	Medical treatment (n=28)	p
Age (years)	37.31 ± 8.58	34.64 ± 9.89	0.065
Gravida	2 [0-6]	2 [0-7]	0.754
Parity	2 [0-7]	2 [0-7]	0.888
BMI (kg/m2)	31.32 ± 3.27	30.40 ± 4.37	0.377
Risk factors IUD use n (%) Duration of IUD use PID history n (%) Operation history n (%) Additional Systematic disease n (%)	 18 (58) 4 [0-9] 15 (48.3) 14 (45.1) 12 (38.7)	 11 (39.2) 1 [0-6] 14 (50) 12 (42.8) 10 (35.8)	**0.013** **0.002** 0.193 0.412 0.184
Number of abscesses	1.23 ± 0.43	1.27 ± 0.45	0.719
Abcess size (cm)	8.15 ± 2.28	4.22 ± 1.94	< **0.001**
Laboratory findings Wbc (μL) CRP (mg/dL)	 15.30 ± 7.98 72.0(18.4-297.0)	 13.69 ± 4.96 70.0(6.7-279.0)	0.347 0.300
Antibiotic use period	10 [2-23]	7 [2-20]	0.825
Length of stay in hospital	10,11 ± 1,9 [2-23]	8,02 ± 1,1 [2-22]	0.629

DISCUSSION

This study aimed to determine the management of TOA cases and the risk factors in operated patients retrospectively. TOA is an inflammatory, infectious disease of the tuba uterine, ovaries and surrounding adnexal tissues[10]. It is thought that infectious agents come ascending from the lower genital tract and occur after PID. The incidence of TOA increases in parallel with the increase in sexually transmitted diseases[11]. It is commonly seen in the reproductive age. It is observed to a lesser extent in the menopausal period[12]. In this study, all patients were women of reproductive age with regular menses, with a mean age range of 36.53 ± 9.26 years.

Generally, TOA is manifested by an adnexal mass, fever, abdominopelvic pain and/or vaginal discharge, high leukocyte count and/or elevated CRP (C reactive protein); however, the picture of this disease can be quite variable. In untreated conditions, abscess rupture and subsequent life-threatening sepsis and mortality can occur, so any clinical concern for this diagnosis requires rapid evaluation and treatment[13]. In our study, patients were admitted with the most frequent complaints of pelvic pain (100%), vaginal discharge (42.4%) and fever (35.6%), respectively. When the complaints of patients with TOA were examined in similar studies, abdominopelvic pain (90%) was the most common, followed by fever (50%), vaginal discharge (28%), and abnormal uterine bleeding (21%) (5,13). When we analysed the laboratory results of our patients, leucocytosis (mean 12.700/μL) and CRP elevation were detected in all patients. While CRP was above 5.5 in 88% of the patients, CRP was below 5.5 in 12%. Medical treatment [(ceftriaxone(2x1g/day) + clindamycin (3x600mg/day) + gentamicin(2x80mg/day)] was sufficient in patients with CRP below 5.5. Similarly, Reljic et al. found a 94% increase in CRP in TOA patients[14]. Studies on this subject have emphasised that high serum CRP is due to the prevalence of tissue damage and that high concentration reflects the severity of the clinic[14,15].

TOA is reported to occur in 33% of hospitalised patients with acute PID[3]. The most common risk factors associated with PID are young age, age at first intercourse, multiple sexual partners, socioeconomic status, low education level, presence of bacterial vaginosis and sexually transmitted diseases. It is also known that the use of an intrauterine device (IUD) is a significant risk factor in the development of PID[11,16]. In this study, the presence of IUD was detected in 49.3% of the patients, and the IUD was withdrawn after 48 hours of antibiotic pressure. In the study of Turan et al., the presence of IUD was observed in 41% of cases[17]. Karakulak et al. reported this rate as 48.7% (18). Similar to other studies, in our study, the presence of IUD was relatively high in patients with TOA, with a mean duration of use of 2.98 3.41(0-12) years. In addition, the presence and duration of IUD use were found to be statistically significantly higher in patients requiring surgery in our study.

Although the traditional approach in TOA is surgical drainage, with the introduction of new generation antibiotics with broad-spectrum and penetrating the abscess wall, there may be cases where only medical treatment is sufficient. In this study, the mean abscess size was 6.31 cm. De-witt et al. correlated abscess size with treatment success and reported 43% treatment failure in abscesses >8 cm[19]. Reed et al., on the other hand, predicted that there is an inversely proportional relationship between the success of medical treatment and TOA size and that TOAs larger than 10 cm have a more than 60% probability of requiring surgery[20]. Only medical treatment (triple antibiotic therapy) was sufficient in 47.5% of the patients in our study. The abscess size of these patients was (4.22cm), and it was found to be statistically significantly lower than the patients who required surgery (8.15cm) ($p<0.001$). In addition, the duration of hospitalisation and antibiotic use of these patients was shorter. This is an essential advantage in terms of patient cost. Improvement of clinical symptoms, decrease in fever, decrease in leucocytosis and CRP, and decrease in abscess mass were accepted as indicators of response to medical treatment. When there was no response to the treatment within 48-72 hours, we performed laparoscopy, laparotomy, USG or CT guided abscess drainage in addition to medical treatment. In the literature, there are also studies suggesting direct interventional drainage with medical treatment at the beginning and advocating that treatment success is high[21,22]. According to current data, laparoscopy is accepted as the gold standard surgical method, especially in cases with suspected abscess rupture[23]. However, laparotomy is preferred as the primary approach in TOA treatment by most gynaecologists. In our study, laparoscopy was preferred as the surgical method in cases where it was thought that there was no response to medical treatment (56%). In addition, TAH+BSO applied cases were less frequent (25.4%). This may be due to the fact that the mean age in the patient group included in the study was compatible with the reproductive period. In addition, 2 cases (6.5%) were hospitalised with the diagnosis of abscess rupture and surgical laparotomy was performed under emergency conditions. Abscess rupture has been described in the literature at a rate of 15% in TOA cases[24]. We applied wig drainage under antibiotic pressure for 48-72 hours in two patients who had previously been operated on for TOA and developed recurrence. All patients who were given triple antibiotic therapy during the postoperative period were discharged after an average of 7 days. The most common surgical complications were bladder injury (12.9%), bowel perforation (9.6%) and ureteral injury (9.6%), respectively. Our results were higher than the literature[24,25]. We attributed this to the fact that our patients had high adhesions due to the high rate of previous operation history (45.1%).

CONCLUSION

When our study is evaluated in the light of the literature, early diagnosis and treatment of TOA are essential because it has serious life-threatening consequences such as morbidity and mortality. The surgical approach may vary depending on the operator's experience, the patient's age, desire for fertility, and the extent of the abscess. In addition, we believe that among the risk factors, especially the

presence of IUD, duration of IUD use, and abscess size increase the need for surgery.

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Conflict of ınterest

The authors have no conflict of interest.

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Examination of Underlying Lower Extremity Vascular Pathologies In Patients With Diabetic Foot Infection and Clinical Outcomes

Diyabetik Ayak Enfeksiyonu Olan Hastalarda Alt Ekstremite Damar Patolojilerinin Incelenmesi ve Klinik Sonuçları

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Abstract

Aim Diabetes and vascular disorders raise the risk of diabetic foot infection and lower extremity amputation. Although DFI risk factors and microbiological analyses have been thoroughly researched, data for this specific group is limited. This study aimed to examine the underlying vascular risk factors of patients who were followed up and treated with the diagnosis of DFIs and clinical outcomes.

Material and Method Clinical, demographic, laboratory, microbiological, and foot examination data for 153 patients referred to our center for DFI between 2016 and 2021 were collected retrospectively from the hospital information system.

Results A total of 153 DFI patients with a mean age of 67.71±15 years were included in the study. There were 104 patients in the non-vascular induced DFI group and 49 vascular induced DFI group. The top two comorbidities of DFI patients were cardiovascular disease and hypertension respectively. The rate of male patients was statistically higher in the vascular-induced DFI group (p=0.003). History of extremity amputation/debridement, having Wagner grade 5 DFI and Gram-negative microorganism growth in tissue cultures were more common in the vascular-induced DFI group (p=0.01, p=0.01, and p=0.0006). Extremity amputation/debridement rates were higher in the vascular-induced DFI group (p=0.01).

Conclusion DFIs cause an increased risk of amputation, prolonged antibiotic therapy, increased hospitalization, and increased healthcare costs as a result of investigations. Awareness of the vascular pathologies underlying DFIs can help clinicians manage the disease. The aim of this study is to emphasize the importance of vascular factors.

Keywords diabetic foot infection, vascular risk factors, clinical outcomes.

Özet

Amaç *Diyabet ve damar hastalıkları, diyabetik ayak enfeksiyonu (DAE) ve alt ekstremite amputasyonu riskini artırır. DAE risk faktörleri ve mikrobiyolojik analizler kapsamlı bir şekilde araştırılmış olmasına rağmen, bu özel grup için veriler sınırlıdır. Bu çalışma DAE tanısı ile takip ve tedavi edilen hastaların altta yatan vasküler risk faktörlerinin ve klinik sonuçlarını incelenmeyi amaçladı.*

Gereç ve Yöntem *2016-2021 yılları arasında DAE için merkezimize başvuran 153 hastanın klinik, demografik, laboratuvar, mikrobiyolojik ve ayak muayene verileri hastane bilgi sisteminden geriye dönük olarak toplandı.*

Bulgular *Çalışmaya yaş ortalaması 67.71±15 yıl olan toplam 153 DAE hastası dahil edildi. Vasküler kaynaklı olmayan DAE grubunda 104, vasküler kaynaklı DAE grubunda 49 hasta vardı. DAE hastalarının ilk iki komorbiditesi sırasıyla kardiyovasküler hastalık ve hipertansiyondu. Vasküler kaynaklı DAE grubunda erkek hasta oranı istatistiksel olarak daha yüksekti (p=0,003). Ekstremite amputasyonu/debridman öyküsü, Wagner grade 5 DAE ve doku kültürlerinde Gram negatif mikroorganizma üremesi vasküler kaynaklı DAE grubunda daha sıktı (p=0.01, p=0.01 ve p=0.0006). Vasküler kaynaklı DAE grubunda ekstremite amputasyon/debridman oranları daha yüksekti (p=0.01)*

Sonuç *DAE'ları, yüksek ampütasyon riski, uzun süreli antibiyotik tedavisi, artan hastane yatışı ve tetkikler sonucu artan sağlık maliyetlerine neden olur. DAE'larının altında yatan vasküler patolojilerin farkındalığı, klinisyenlerin hastalığı yönetmesine yardımcı olabilir. Bu çalışmada amaç vasküler faktörlerin önemini vurgulamaktadır.*

Anahtar Kelimeler *diyabetik ayak enfeksiyonu, vasküler risk faktörleri, klinik sonuçlar.*

INTRODUCTION

Diabetic foot infections (DFI) are caused by many reasons such as trauma, diabetic neuropathy, and peripheral vascular pathologies (arterial or venous). Neuropathy leads to foot deformities, and this causes higher pressure on the foot and may result in a foot ulcer. When ulcer formation occurs the limb is at high risk of invasive infection.[1] Although the etiology of DFI is complex, three major components are neuropathy, ischemia, and infection, all contribute to tissue necrosis and ulcer formation.[2]

DFIs are known to be a major diabetes mellitus (DM) complication, and they cause significant morbidities and fatalities. The fatality rate associated is predicted to be 5% in the first 12 months, with a 5-year fatality rate of 42%. Surgical debridement if needed, vascular evaluation, dressings to promote a moist wound environment and exudate control, off-loading, infection and glycemic controls are all routine practices in DFI therapy.[3]

DFI treatment can be challenging, and underlying patient comorbidities, as well as a lack of patient compliance, might impede recovery. Diabetes impairs healing by interfering with cell responses to cytokines and chemokines, macrophage function, angiogenesis, epidermal barrier function, and the creation of collagen and granulation tissue.[4] Medical and surgical management, and percutaneous transluminal angioplasty of stenosed or blocked lower extremities arteries are all options for diabetic ischaemic foot treatment. In diabetics, foot ulceration is the most common cause of amputation.5 Irresolvable rest pain and claudication, as well as nonhealing ulcers despite appropriate medical care, are indications for arterial reconstruction surgery.[4]

Critical leg ischemia in diabetic patients can be prevented with rapid vascular interventions. Diabetes and vascular disorders raise the risk of diabetic foot infection and lower extremity amputation. Although DFI risk factors and microbiological analyses have been thoroughly researched, data for this specific group is limited. In this study, it was aimed to examine the underlying vascular risk factors of DFIs patients and the outcomes.

MATERIAL and METHODS

This is a retrospective study that was performed on collected data from DFI patients, who were hospitalized in the Çanakkale Onsekiz Mart University Hospital, between 2016-2021. This study included adult patients who presented as DFI and were admitted to the in-patient clinic. A list of all patients diagnosed with DFI was retrieved from the hospital database. The list included 198 patients of which 45 patients were excluded from the study due to missing data. The patient's confidentiality was guaranteed by issuing each patient a number code for reference and the codes were only accessible to the authors. Demographic data, clinical symptoms, vital signs, underlying diseases, underlying vascular pathologies, recurrent DAI, duration of DM, a treatment used for DM (not receiving treatment, oral antidiabetic, insulin), DAI location, tissue or wound cultures, history of extremity amputation, lack of access to health care, patient compliance, uncontrolled diabetes, vascular insufficiency, peripheral motor neuropathy, neuro-osteo-arthropathic deformities, serum hemogram parameters, inflammatory parameters [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], glycated hemoglobin (Hb A1C) levels, imaging procedures and results, the length of hospitalization, the outcome of the treatment were examined in detail.

The Wagner classification was used to classify each patient's wound. The Wagner classification system uses the following grades to determine ulcer depth and the occurrence of osteomyelitis or gangrene: Grade 0 (no skin lesions, hyperkeratosis below or above bony prominences); degree 1 (partial/ full-thickness ulcer); grade 2 (probing to tendon or capsule); grade 3 (deep tissues always implicated, osteomyelitis may be present); grade 4 (partial foot gangrene); and grade 5 (whole foot gangrene) (whole foot gangrene).[6]

The mentioned department used magnetic resonance imaging (MRI), X-ray if available nuclear medicine imaging, or histopathologic examinations to identify osteomyelitis. At referral, peripheral arterial/venous disease was defined as a documented history of lower extremity revascularization and/or the presence of angiographically or Doppler ultrasonographically characterized peripheral vascular disease.

The patients were divided into two groups based on their clinical presentation: "vascular induced DFI group" and "non-vascular induced DFI group."

Inclusion criteria

- Being over the age of 18,
- Having a diagnosis of DAI,
- Inpatients,
- Cases who had at least one microbiological positive culture result,
- Cases who underwent doppler or computerized tomography angiography (CTA) scan

Exclusion criteria

- Being under the age of 18,
- Pregnancy,
- Outpatients,
- Missing data

Statistical analysis

The Statistical Package for Social Sciences (SPSS) statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA), was used for descriptive statistics. All nominal variables' frequencies and percentages, as well as the mean and range of all measurable variables, were determined. For all measurable variables, the t-test was employed for comparisons between the groups, whereas the chi-square test was utilized for all nominal variables. A p-value of under 0.05 was deemed significant.

RESULTS

The present center collected a total of 153 DFI patients over 5 years this period. There were 86 males and 67 women with a mean age of 67.71±15 years. There were 104 patients in the non-vascular induced DFI group and 49 vascular induced DFI group. The vascular-induced DFI group consisted of cases diagnosed as a peripheral arterial disease (documented history of lower extremity revascularization and/or the presence of angiographically or Doppler ultrasonographically characterized peripheral arterial disease). The top two comorbidities of DFI patients were cardiovascular disease and hypertension respectively. The summary of characteristics of 153 DFI patients were given in Table 1.

The rate of male patients was statistically higher in the vascular-induced DFI group (p=0.003). Also, hypertension and cardiovascular disease were more common in the vascular-induced DFI group (p=0.0006, p=0.01). History of extremity amputation/debridement, having Wagner grade 5 DFI, and Gram-negative microorganism growth in tissue cultures were more common in the vascular-induced DFI group (p=0.01, p=0.01, and p=0.0006). Extremity amputation/debridement rates were higher in the vascular-induced DFI group (p=0.01) (Table 2).

Table 1. Summary of clinical characteristics of 153 DFI patients	
Age, mean (years)	67.71±15 years
Sex, male (%)	86(56.2)
Body mass index (kg/m2), mean ± SD	25.8 ± 5.78
Diabetes duration (years), mean ± SD	12±0.2
Diabetes medication, n (%)	
-only insulin	65(42.5)
-only oral antidiabetics	72(47)
- Insulin plus oral antidiabetics	16(10.4)
Uncontrolled diabetes	18(11.8)
Comorbidities	
- Hypertension	72(47)
- Cardiovascular disease	42(27.5)
- Chronic lung disease	13(8.5)
-Malignancy	3(2)
History of mechanical trauma/injuries	13(8.5)
Foot deformities	18(11.8)
Previously diagnosed as diabetic neuropathy	42(27.5)
Wound location, n (%)	
-Forefoot	72(47)
-Midfoot	42(27.5)
-Hindfoot	30(19.6)
-Entire foot	9(5.9)
History of extremity amputation/debridement (6 months)	42(27.5)
Orally antibiotics treatment before admission (15 days (%))	46(30.1)
Sepsis at admission	18(11.8)
Fever at admission	36(23.5)
Localization of DFI	
Left	70(45.8)
Right	80(52.2)
Bilateral	3(2)
Type of vascular disease (total:49)	
arterial	30(19.6)
venous	12(7.8)
both arterial and venous	7(4.6)
Wagner classification	
-grade 2	12(7.8)
-grade 3	53(34.6)
-grade 4	46(30.1)
-grade 5	42(27.5)
tissue cultures,	
Gram negative microorganism, n (%)	72(47)
Gram positive microorganism, n (%)	80(52.2)
Fungal microorganism, n (%)	1(0.7)
Interval between onset of DFI symptoms and referral, days, mean ± SD)	25.24± 15.1
Extremity amputation/debridement	70(45.8)
Hospitalization days	18.6±12.3
Mortality	4(2.8)
Abbreviations: DFI, diabetic foot infection; SD: standard deviation.	

Table 2. Characteristics of patients with DFI

Patient characteristics	Group 1 (non-vascular induced DFI group) (n=104)	Group 2 (vascular induced DFI group) (n=49)	P-value
Male (%)	50 (48)	36 (73)	0.003
Age (years) (SD)	66 ±15	62±15	0.019
Weight, kg	70±22	73±26	0.46
Hypertension	39 (38)	33 (67)	0.0006
Cardiovascular disease	22 (21)	20 (41)	0.01
Chronic renal failure	11 (11)	7 (14)	0.51
Chronic lung disease	9 (9)	4 (8)	0.99
History of mechanical trauma/injuries	9 (9)	4 (8)	0.99
Foot deformities	11 (11)	7 (14)	0.51
Duration of diabetes (years)	12 ± 4	12 ± 5	0.94
Insulin treatment for diabetes	44 (42)	21 (43)	0.95
Uncontrolled diabetes	11 (11)	7 (14)	0.51
Previously diagnosed as diabetic neuropathy	22 (21)	20 (41)	0.01
History of extremity amputation/debridement (6 months)	22 (21)	20 (41)	0.01
Orally antibiotics treatment before admission (15 days (%))	26 (25)	10 (20)	0.53
Sepsis at admission	11 (11)	7 (14)	0.51
Fever at admission	26 (25)	10 (20)	0.53
Wagner grade 5	22 (21	20 (41)	0.01
Gram negative microorganism growth in tissue cultures, n (%)	39 (38)	33 (67)	0.0006
DFI symptoms before admission, days, mean ± SD)	15 ±33	47 ±46	<0.0001
Extremity amputation/debridement	40 (39)	30 (60)	0.01
Hospitalization days	17± 20	22 ±16	0.09
Mortality	4 (4)	0 (0)	0.31
C- reaktive protein (mg/dl)	3.3 ±4.2	4.9± 4.3	0.03
Erythrocyte sedimentation rate (mean ± SD)	89± 24	87± 25	0.64
White blood cell (K/µL) (mean ± SD)	12±4	12 ± 5	0.94
Hemoglobin(103/µL) (mean ± SD)	12 ± 5	12 ± 5	0.71
HbA1c, % (mean ± SD)	9.5 ±5.3	9.4 ±4.2	0.93

DISCUSSION

Diabetic patients are more prone to foot ulcers caused by neuropathy, ischemia, and weakened immunity. Ischemia lowers local defenses against infections by reducing the flow of oxygen, vital nutrients, and growth factors to tissues. Because of the nature of the foot's compartments, tendon sheaths, and neurovascular systems, DFIs spread quickly.[7] Diabetes and vascular disorders raise the risk of DFIs and lower extremity amputation. Although DFI risk factors and microbiological analyses have been thoroughly researched, data for this specific group is limited.[5,7,8] In this study, it was aimed to examine the underlying vascular risk factors of patients who were followed up and treated with the diagnosis of DFIs and outcomes.

Our findings support the findings of Patil and Mane9, who observed that diabetes individuals between the ages of 51 and 60 developed foot ulcers. In the present study, there mean age of the patients was 67.71±15 years.

A similar study performed in the Kingdom of Saudi Arabia[8] found that the majority of DFIs were caused by non-vascular etiology. The factors that were substantially related to DFIs due to arterial disease were senility, a history of coronary artery disease, or peripheral artery disease in the unaffected limb. In our study, group 1 (non-vascular induced DFI group) patients were older than group 2 (vascular-induced DFI group) patients. Hypertension and cardiovascular disease were more common in the vascular-induced DFI group.

Modern data on the microbiologic characteristics of DFIs have produced conflicting results. Geographic distribution, meteorological circumstances, and socioeconomic level were all connected with the results. Whereas gram-positive isolates with high Staphylococcus aureus isolation rates predominated in the Western literature, more recent research from the Middle East and the Far East, as well as African countries, demonstrated gram-negative predominance with high Pseudomonas aeruginosa isolation rates.[7,9-15] The high prevalence of P. aeruginosa as a causal pathogen was also noted in our country's the National Consensus Report for the Diagnosis, Treatment, and Prevention of Diabetic Foot Wounds and Infections, and these findings were recommended to be taken into account in the empirical treatment of DFI patients.[16]

It has also been reported that polymicrobial infections are to blame for persistent wounds and more complex infections.[11,15] Körpınar[17] reported that the most common pathogens identified in deep wound cultures from DFIs in end-stage renal disease patients were S. aureus and P. aeruginosa, accounting for 27 (21.2%) and 16 (12.5%) of all 127 isolates, respectively. In our study, the most common pathogens were gram-positive isolates (52.2%). But gram-negative microorganism growth in tissue cultures was more common in the vascular-induced DFI group.

It has been found that limbs with chronic wounds (>6 weeks) attain full healing in only 57% of cases after a year.[18] Furthermore, chronic wounds usually have an underlying etiology that contributes to their nonhealing, which is either infectious or ischemic in etiology.[19] In our study, underlying vascular pathology was found in 49 (32%) of 153 patients with DFI. Of all cases, 19.6% had arterial, 7.8% had venous, and 4.6% had both arterial and venous vascular disorders. However, this number represented cases with radiological evidence. Since the involvement at the microvascular level will not show any radiological findings, this situation may have caused bias.

In the comparison between these two groups, a history of extremity amputation/debridement and Wagner grade 5 DFI were more common in the vascular-induced DFI group. Limb amputation/debridement rates were higher in the vascular-induced DFI group. Mortality rates were higher in the non-vascular-induced DFI group. This data on mortality can be attributed to the many different etiologies of mortality. However, mortality-related risk factors were not examined in detail in our study.

CONCLUSIONS

A dedicated facility offering vascular assessment, a multidisciplinary pre-coordinated strategy, and vascular management will be more effective in managing a diabetic patient with a foot wound. To reduce the number of major amputations in the diabetic community, better arterial evaluation and treatment are required (vascular functional testing and revascularization when possible). Peripheral vascular disease is highly curable if intervention is initiated promptly and collaboratively.

Ethical consideration

The Institutional Review Board Committee of Çanakkale Onsekiz Mart University approved this study (Decision Date: 19.01.2022; Decision No: 2022-02)

Conflict of interest

The authors declare no personal or financial conflict of interest.

Disclosure

No financial support was received.

Author Contributions

Main idea/Planning- SŞ, SA, Analysis/Comment- SŞ
Data provision- All authors, Spelling- SŞ, SA, AŞ, Review and Correction- AŞ, Literature Search- SŞ, SA, Writing - SŞ, SA, Confirmation-All authors

Limitatitons

This is a retrospective, single center study. The vascular pathology informations depends on radiological findings.

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Global Trends On Rotavirus Vaccine's Studies

Rotavirüs Aşısı Çalışmalarında Küresel Trendler

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Abstract

Aim The aim of the current study was to investigate global research trends and collaborations on the Rotavirus vaccines.

Material and Method We conducted bibliometric research in this study on the Web of Science database with the keywords related to the rotavirus vaccine. And also visualization techniques were used for mapping the collaborations. We only included the research articles and review articles.

Results We reached 5093 publications according to our search, and 52.916% were published as open access. The most preferred publication languages were English (96.682%). Most of the articles (13.627%) on the rotavirus vaccine were published in the Vaccine journal. The publications were from 164 countries globally. Most of the publications were from the United States of America (USA) (42.981%), England (9.641%), India (6.892%), Australia (6.146%), and Belgium (5.910%). The Centers For Disease Control Prevention, League of European Research Universities Leru, and World Health Organization (WHO) were the leading affiliations on rotavirus vaccine studies. The Hirsch (H) indexes of the publications from the USA were higher (H index: 127), but the Belgian publications' average number of citations per publication was the highest.

Conclusion The quantity of papers on the rotavirus vaccine has increased over time. The Centers for Disease Control and Prevention, the League of European Research Universities Leru, and the WHO were the most active institutions, and the USA was the most productive country. The number of publications from countries where the disease is common was below the desired level.

Keywords Rotavirus vaccine, bibliometric analysis, research trends.

Özet

Amaç *Mevcut çalışmanın amacı, Rotavirüs aşıları üzerindeki küresel araştırma eğilimlerini ve iş birliklerini araştırmaktı.*

Gereç ve Yöntem *Bu çalışmada, Rotavirüs aşısı ile ilgili anahtar kelimeler ile Web of Science veri tabanında bibliyometrik araştırma yapıldı. Ayrıca iş birliklerinin haritalandırılması için görselleştirme teknikleri kullanıldı. Sadece araştırma makaleleri ve derleme makaleleri dahil edildi.*

Bulgular *Araştırmamıza göre 5093 yayına ulaşıldı ve %52,916'sı açık erişim olarak yayınlanmıştı. En çok tercih edilen yayın dili İngilizce (%96,682) idi. Rotavirüs aşısı ile ilgili makalelerin çoğu (%13,627) Vaccine dergisinde yayınlanmıştı. Yayınlar dünya çapında 164 ülkeden idi. Yayınların çoğu Amerika Birleşik Devletleri (ABD) (%42,981), İngiltere (%9,641), Hindistan (%6,892), Avustralya (%6,146) ve Belçika'dan (%5,91) idi. Hastalık Kontrol Önleme Merkezleri, Avrupa Araştırma Üniversiteleri Birliği Leru ve Dünya Sağlık Örgütü (DSÖ) rotavirüs aşı çalışmalarında önde gelen kuruluşlardı. ABD kaynaklı yayınların Hirsch (H) indeksleri daha yüksekti (H indeksi: 127), ancak Belçika yayınlarının yayın başına ortalama atıf sayısı en yüksekti.*

Sonuç *Rotavirüs aşısı ile ilgili yayınların sayısı zamanla artmıştı. Hastalık Kontrol ve Önleme Merkezleri, Avrupa Araştırma Üniversiteleri Birliği Leru ve DSÖ en aktif kurumlardı ve Amerika Birleşik Devletleri en üretken ülkeydi. Hastalığın sık görüldüğü ülkelerden yayın sayıları istenen seviyenin altındaydı.*

Anahtar Kelimeler *Rotavirüs aşısı, bibliyometrik analiz, araştırma eğilimleri.*

INTRODUCTION

Rotavirus vaccination protects against rotavirus infections, which are the major cause of severe diarrhea in children under the age of five[1]. It was estimated that Rotavirus infection caused 440,000 fatalities, two million hospitalizations, and 25 million outpatient visits each year in children aged five years old over the world[2]. The transmission route is the fecal-oral route. It can cause severe diarrhea and even death. Even the nosocomial epidemics. Severe rotavirus gastroenteritis is seen in children who are usually immunosuppressed, unvaccinated, and aged between six months and two years of age[3].

Rotavirus vaccines have been introduced or will be introduced into national or subnational immunization programs in over 70% of nations and 90% of countries in the Global Alliance for Vaccines and Immunization[4]. It has been reported that rotavirus vaccines prevent 15-34% of severe diarrhea in developing countries and 37-96% of severe diarrhea in industrialized developed countries[5]. Animal rotavirus strains, human-animal rotavirus reassortants, attenuated human rotaviruses, subunits of rotavirus virions, and virus-like particles have all been used to develop rotavirus vaccines[6,7]. As most human rotaviruses grow too weak in cell culture to produce normal vaccine batches for large-scale immunization campaigns, reassortants are required for live virus-based vaccines. In humans, monovalent vaccinations made from animal rotaviruses have not proven effective. Human trials for rotavirus subunit vaccine candidates have begun[6-8].

In this study, bibliometric methods and advanced visualizing techniques were used for investigating the global Rotavirus vaccine research outputs.

MATERIAL and METHODS

The data was retrieved from the Thomson Reuters' Web of Science (WoS) Core Collection database. We selected in the topic (abstract, title, keywords) the search term "(rotavirus vaccine* OR "rotavirus vaccine* " OR " Rotarix *" OR RotaTeq*" OR, Rotavac*" OR, Rotavin-M1*" OR, Lanzhou lamb*" OR, Rotasiil*)" was used. The document type filter "article and review article" was used to limit the search to only research related "Rotavirus vaccine," while other document categories such as letters and conference abstracts were excluded. The search was limited to 1970 to December 31st, 2021, ensuring that only years completed by the time of the search were considered in the study. In this study, human rotavirus vaccines were selected within the sample pool.

The information was transferred to Microsoft Excel 2013 for Windows (Microsoft Corp., Redmond, WA, United States of America, USA). The WoS database was used to analyze the citations. The number of publications was considered as a metric of research quantity, and the Hirsch-Index (H-index) was used as an indicator of research output quality. For each publication, the total number of citations as well as the average number of citations per item were calculated (citation rate). The bibliometric data from the findings was saved in a separate database and shown in visualizations using tables.

Mapping

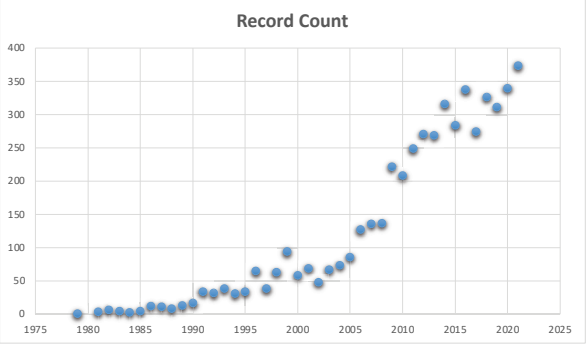
The VOSviewer software version 1.6.16 was utilized for visualization mapping (http://www.vosviewer.com).

Co-authorships, co-occurrences, countries, author keywords, and co-citations of the cited sources were analyzed with visualization mapping techniques. Which collaborations were used were defined under the map figures explanations. To show the collaborations between countries or institutions, we used linking lines to illustrate our findings.

RESULTS

We reached 5093 publications according to our search, and 52.916% were published as open access. The most preferred publication languages were English (96.682%), French (0.864%), Spanish (0.844%), German (0.471%) and Portuguese (0.353%).

The first report was published in the year 19799. 2021 (n=381) was the year with the highest number of publications (Graphic 1).



Graphic 1. The number of publications by the years.

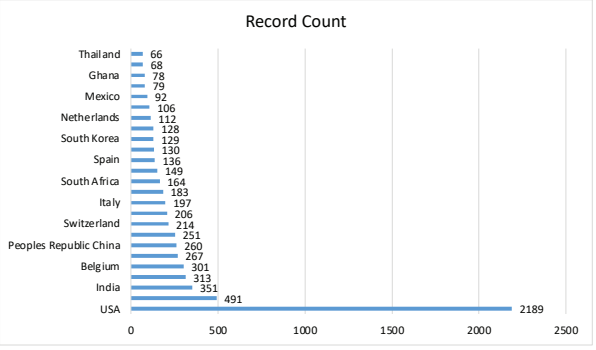
Most of the publications were published in Science Citation Index Expanded (SCI-Expanded) journals (n = 4737, 93.01%) indexed journals (Graphic 2).

Most of the articles (13.627%) on the rotavirus vaccine were published in the Vaccine journal (Table 1).

Table 1: The list of mostly published journals on rotavirus vaccine

Journals	Record Count	% of 5.093
Vaccine	694	13.627
Pediatric Infectious Disease Journal	250	4.909
Journal of Infectious Diseases	212	4.163
Human Vaccines Immunotherapeutics	180	3.534
Journal of Medical Virology	140	2.749
Plos One	113	2.219
Infection Genetics and Evolution	94	1.846
Clinical Infectious Diseases	91	1.787
Pediatrics	87	1.708
Journal of Virology	84	1.649
Journal of Clinical Microbiology	71	1.394
Archives of Virology	65	1.276
Expert Review of Vaccines	56	1.100
BMC Infectious Diseases	47	0.923
Journal of Clinical Virology	47	0.923
Communicable Diseases Intelligence	40	0.785
Vırology	38	0.746
Viruses Basel	36	0.707
Lancet	33	0.648
Epidemiology and Infection	32	0.628
Scıentıfic Reports	31	0.609
Emergıng Infectious Diseases	30	0.589
Journal of Virological Methods	29	0.569
BMC Public Health	28	0.550
Journal of General Virology	28	0.550
*Showing 25 out of 959 entries		

The publications were from 164 countries globally. Most of the publications were from the United States of America (USA) (42.981%), England (9.641%), India (6.892%), Australia (6.146%), and Belgium (5.910%). Figure 1 depicts trends in the number of papers with authors from each of the two major regions (the USA and the European Union) (Graphic 2).



Graphic 2. The most publishing countries on rotavirus vaccine.

The Rotanet-Italy Study Group (n=14, 0.274%), Australian Rotavirus Surveillance (n=10, 0.196%) and Vacsurv Consortium (n=10, 0.196%) were the main study groups on rotavirus vaccine studies. Umesh D.Parashar from the Centers for Disease Control & Prevention (CDC) – USA was the most published author on rotavirus vaccine studies.

The USA Department of Health and Human Services funded most of the publications (14.137%) (Table 2).

Table 2: The list of the leading funding agencies		
Funding Agencies	Record Count	% of 5.093
The USA Department of Health Human Services	720	14.137
National Institutes of Health USA	574	11.270
National Institute of Allergy Infectious Diseases	374	7.343
Glaxosmithkline	307	6.028
Bill Melinda Gates Foundation	258	5.066
Centers For Disease Control Prevention USA	150	2.945
European Commission	147	2.886
Merck Company	143	2.808
World Health Organization	106	2.081
Wellcome Trust	91	1.787

Showing 10 out of 2.556 entries;2.172 record(s) (42.647%) do not contain data in the field being analyzed.

The CDC, League of European Research Universities Leru, and World Health Organization were the leading affiliations on rotavirus vaccine studies (Table 3).

Table 3: The leading affiliations on rotavirus vaccine		
Affiliations	Record Count	% of 5.094
Centers For Disease Control Prevention USA	695	13.644
League of European Research Universities Leru	262	5.143
World Health Organization	217	4.260
Glaxosmithkline	212	4.162
National Institutes of Health USA	202	3.965
Universiy of London	176	3.455
Johns Hopkins Universiy	171	3.357
Cincinnatı Children S Hospital Medıcal Center	144	2.827
Merck Company	139	2.729
PATH	139	2.729

Showing 10 out of 4.748 entries; 34 record(s) (0.667%) do not contain data in the field being analyzed.

The H indexes of the publications from the USA were higher (H index: 127), but the Belgian publications' average number of citations per publication was the highest (Table 4).

Table 4: The number of publications, citations and H indexes of top listed five countries				
Country	Number of publications	Number of citations	H indexes	Number of citations avarage per publication
USA	2,189	98618	127	45.05
England	491	22655	68	46.14
India	351	17767	49	50.62
Australia	313	14388	49	45.97
Belgium	301	22195	60	73.74*
Total	5,093	155050	143	30.44
*Showing the highest number				

Mapping

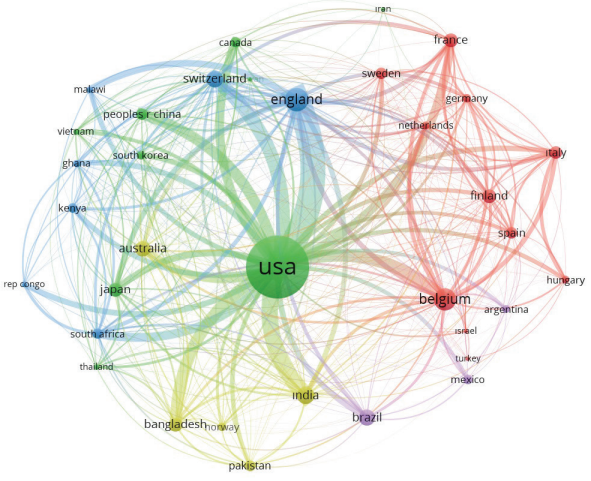


Figure 1. Mapping of countries in international collaboration with at least 50 publication and 50 citations.

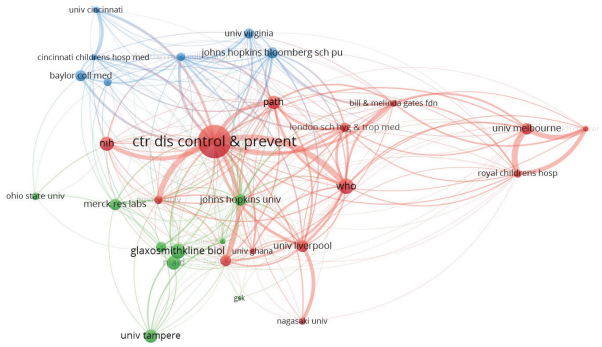


Figure 2. Mapping of organizations in international collaboration with at least 50 publication and 50 citations.

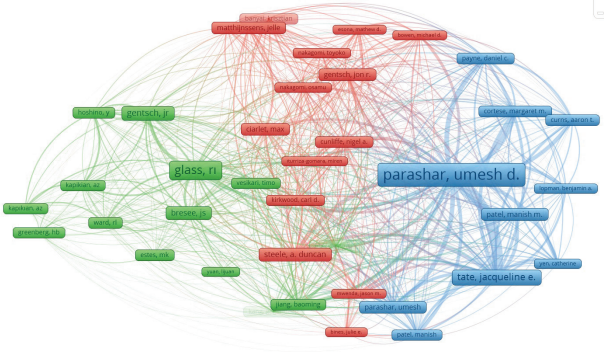


Figure 3. Citation visualization map among authors with at least 30 publication and 30 citations.

*The lines connecting the authors are indicative of citations. Relatively more cited authors represented by larger circle size or font size.

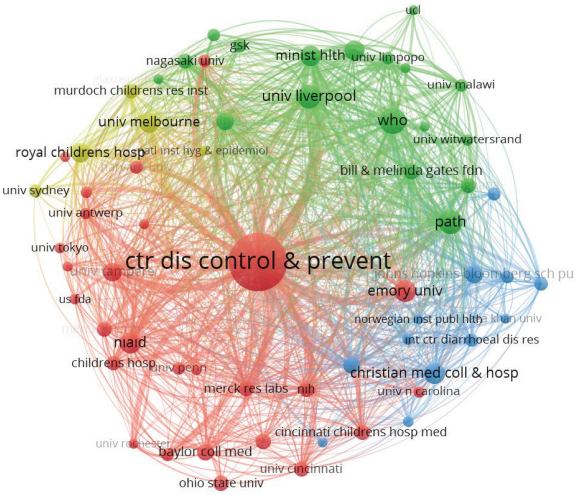


Figure 4. Citation visualization map among organization with at least 30 publication and 30 citations.

*The lines connecting the authors are indicative of citations. Relatively more cited authors represented by larger circle size or font size.

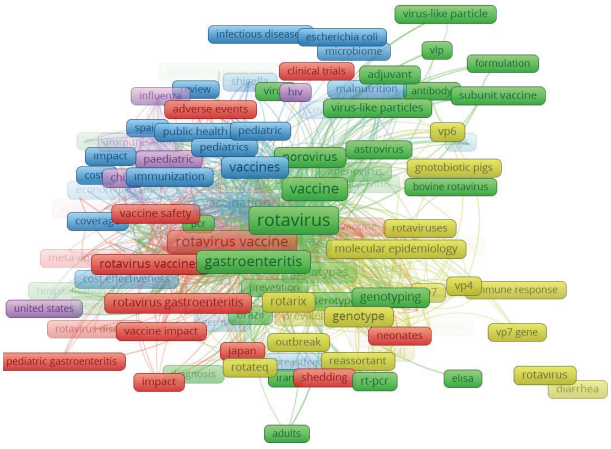


Figure 5. Keyword visualization map of publications that are mentioned at least 10 times.

*Converging lines are indicative of occurrence relationships in articles. Keywords represented by larger circle size or font size appeared relatively more in article.

DISCUSSION

Bibliometric analysis is an important technique for assessing and analyzing the output and trends of scientific research. Sharing extremely early information with the public, researchers, government organizations, institutes, and at national and international levels is of considerable interest. Safety measures and guidelines are implemented based on this type of information[11-20]. A few bibliometric studies have been performed on research relating to rotavirus[19,20], but no similar studies on rotavirus vaccine have been published yet.

Bibliometric analyses aid in revealing the state of a certain field of science as well as influencing next studies[11-20]. The rotavirus vaccine has been the subject of several excellent scientific investigations. It will be advantageous for scientists who wish to pursue this topic further to look at the studies of the specified researchers and to collaborate[11-20]. This bibliometric analysis of global research output in the field of the rotavirus vaccine reveals an increase in the number of publications during the last two decades. We conducted a preliminary search in the Wos database using keywords related to the rotavirus vaccine. We chose the WOS database for the extraction since it is a scientific database in the biomedical field with a precise and particular search engine. Also, we chose research articles and review articles. With this study, the bibliometric analysis of the rotavirus vaccine was conducted for the first time in the available literature.

Rotavirus infection has become extremely important all over the world1[4,5]. Vaccination studies on this disease, which affects the whole world, have also gained importance. Therefore, we wanted to address this topic in our study. As a result, the current study attempted to assess the overall global research output and visualize the rotavirus vaccination research area. The fact that the number of articles increased over the years (Graphic1) in our study reveals that this issue is a hot topic.

Rotarix (GlaxoSmithKline Biologicals SA, Rixensart, Belgium) and RotaTeq (Merck & Co., Inc., West Point, PA, USA) were both licensed and rapidly integrated into national immunization programs in many countries in 2006. WHO recommends primarily rotavirus vaccines. Inclusion in national immunization programs around the world in 2009 live attenuated oral vaccines has been found to be effective in developing countries in Africa and Asia[21]. By the end of 2018, 92 countries had integrated the rotavirus vaccine into their national immunization programs, with another 6 countries implementing the vaccine in stages or regions[4]. Only four countries account for roughly half of all rotavirus-related deaths (India, Nigeria, Pakistan, and the Democratic Republic of the Congo)[22]. But our results showed that there are limited studies from underdeveloped countries such as Nigeria, Pakistan, and the Democratic Republic of the Congo where the diseases is endemic. In our study, it was determined that, in addition to global organizations such as CDC and WHO, industrial organizations such as GlaxoSmithKline both provide funds for these scientific outputs and produce scientific articles. Also, the countries (Belgium and the USA) where the two important vaccines were produced had the biggest number of publication numbers (Graphic 2).

Bibliometric analyses can be carried out using pre-existing databases of publications on a subject or, depending on the preferences of the researchers, using datasets that they have produced themselves. Mapping techniques can be used23-25. In this study we analysed the keywords, international collabrations, coauthorship analyses by using Vos Viewer programme (Figure 1-5).

In our study, a total of 5093 publications on the rotavirus vaccine were analyzed. We found that the number of publications published has increased significantly in the last 20 years. In this study, the most frequent keyword and author co-occurrence keywords were given in Figure 5. The H indexes of the publications from the USA were higher (H index: 127), but the Belgian publications' average num-

ber of citations per publication was the highest. The most productive country was the USA. According to the previous bibliometric analysis in the rotavirus search[15,19], the leading country was the USA. This once again showed the importance given to scientific studies and the fact that the USA has many scientific institutions[17-19].

CONCLUSION

This is the first bibliometric study to provide comprehensive data on the rotavirus vaccine's published literature. The quantity of papers on the rotavirus vaccine has increased over time. The CDC, the League of European Research Universities Leru, and the WHO were the most active institutions, and the USA was the most productive country. The number of publications from countries where the disease is common was below the desired level. Rotavirus was the most common co-occurrence author keyword. This study's conclusions may be useful to researchers, policymakers, and educational goals. Funding agencies can use it to assess current research and potential research trends in rotavirus vaccines. Future research paths are still focused on developing effective vaccines and treatment therapies.
Limitations: This study only covers one database's results with the preferred keywords. Additionally, since the keywords were exclusively in English, it's possible that publications written in other languages were left out. This research did not use content analysis. Future comparison studies may be planned to be more thorough.

Ethics Approval

As there is no human or animal involvement in most bibliometric investigations, no ethical approval was necessary.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Institutional and Financial Support

The authors declared that they had received no financial support for this study

Author Contributions

SOM, CU: Contributed to the conception of the work, conducted the study, revised the data, approved the final version of the manuscript, and agreed to all aspects of the work. SOM, CU: Contributed to the collecting data of the work. SOM, CU: Contributed to the conception of the work, revising the data, approved the final version of the manuscript, and agreed to all aspects of the work.

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Investigation of Factors Associated with Countries' Covid-19 Disease Fatality Rates

Ülkelerin Covid-19 Hastalığı Fatalite Hızlarıyla İlişkili Faktörlerin Araştırılması

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Abstract

Aim In this study, it was aimed to investigate the factors associated with the Covid-19 disease fatality rate of countries.

Material and Method The research is of ecological type. In the study, the relationship between Covid-19 disease fatality rates and variables like socioeconomic state, healthy life expectancy at birth, population ages 65 and above, cardiovascular disease frequency, tobacco use frequency, vaccination rates, Human Development Index, Gender Inequality Index and Global Gender Gap Index were investigated. Mean, standard deviation, median, minimum and maximum values were used to summarize data. Pearson/Spearman correlation coefficient was used to investigate the relationships and a linear regression model was established. P<0.05 was considered statistically significant.

Results One hundred and thirty countries with no missing data were included in the study. Twelve point three percent of these countries were in low socioeconomic state. The mean fatality rate of 130 countries was 0.016±0.018. A statistically significant relationship was determined between fatality rate and all variables except tobacco use frequency (p<0.05). All the variables were included in the multiple linear regression model established for the prediction of the fatality rate. Among these variables, Global Gender Gap Index was the only variable that made a statistically significant contribution to the model.

Conclusion Considering these variables in similar epidemic disease states that may occur in the future and improving the conditions related to these variables on a global scale may be important to ensure epidemic control.

Keywords Covid-19 pandemic, fatality rate, related factors, ecological study

Özet

Amaç *Bu araştırmada ülkelerin Covid-19 hastalığı fatalite hızıyla ilişkili faktörlerin araştırılması amaçlanmıştır.*

Gereç ve Yöntem *Araştırma ekolojik tiptedir. Araştırmada Covid-19 hastalığı fatalite hızlarıyla sosyoekonomik durum, doğumda beklenen sağlıklı yaşam umudu, 65 yaş ve üzeri nüfus yüzdesi, kardiyovasküler hastalık sıklığı, tütün kullanım sıklığı, İnsani Gelişmişlik İndeksi, Toplumsal Cinsiyet Eşitsizliği İndeksi ve Küresel Cinsiyet Uçurumu İndeksi gibi değişkenlerin ilişkisi araştırılmıştır. Verilerin özetlenmesinde ortalama, standart sapma, ortanca, minimum ve maksimum değerleri kullanılmıştır. Veriler arası ilişkilerin araştırılmasında Pearson/Spearman korelasyon katsayısı kullanılmış ve lineer regresyon modeli kurulmuştur. P<0,05 istatistiksel olarak anlamlı kabul edilmiştir.*

Bulgular *Verilerinde eksiklik bulunmayan 130 ülke çalışmaya dahil edildi. Ülkelerin %12,3'ü düşük sosyoekonomik sınıftaydı. Yüz otuz ülkenin ortalama fatalite hızı 0.016±0.018 idi. Fatalite hızıyla tütün kullanım sıklığı hariç tüm değişkenler arasında istatistiksel olarak anlamlı ilişki belirlendi (p<0.05). Tüm değişkenler, fatalite hızının tahmini için oluşturulan çoklu doğrusal regresyon modeline dahil edildi. Modele istatistiksel olarak anlamlı katkı sağlayan tek değişken Küresel Cinsiyet Uçurumu İndeksi oldu.*

Sonuç *Gelecekte ortaya çıkabilecek benzer salgın durumlarında bu değişkenlerin dikkate alınması ve bu değişkenlerle ilişkili koşulların küresel ölçekte iyileştirilmesi salgın kontrolünün sağlanması açısından önemli olabilir.*

Anahtar Kelimeler *Covid-19 pandemisi, fatalite hızı, ilişkili faktörler, ekolojik çalışma.*

INTRODUCTION

Covid-19, which seriously threatens public health and progresses as a pandemic, is a viral disease identified in late 2019. The disease, the first case of which was observed in Turkey on March 11, 2020, can be asymptomatic or mild, or it can have a severe course that requires hospitalization and intensive care unit admission and leads to death[1]. There are various vaccines that are thought to be effective in protecting against Covid-19[2]. In addition, personal protective behaviors such as frequent hand washing/disinfectant use, not touching the face with hands, wearing masks appropriately, complying with social distance, not leaving the house unless necessary, keeping surfaces/items clean also seem to be important for breaking the way of transmission of Covid-19[3]. These personal protective behaviors are also called non-drug public health measures and are thought to play a key role in preventing the spread of Covid-19 disease in the community[4].

Social determinants of health are shown as factors that may affect the transmission of the Covid-19 disease and/or the severity of the disease. These factors include socioeconomic status, race/ethnicity, working status, housing conditions, education level, nutritional status, immigration, gender inequality, cultural factors, social policies, and the state of the health system[5]. In a systematic review that investigated the factors affecting the incidence rate of Covid-19 disease and included 42 studies, socioeconomic status, housing conditions, nutritional status, education level, race, and working status were determined as effective factors[6]. It is thought many factors can affect that fatality rate of Covid-19 disease, such as demographic factors, health infrastructure, access to public health services, ethnicity, economic conditions, environmental factors, and chronic disease frequency[7-9].

In this study, it was aimed to investigate the factors associated with the Covid-19 disease fatality rate of countries.

MATERIALS and METHODS

The research is of ecological type. Ethics committee approval was got from Ankara University's Rectorate Ethics Committee and approval from the Ministry of Health Scientific Research Platform in order to conduct the research. The research was conducted between 15.11.2021 and 15.04.2022. In the study, the relationship between Covid-19 disease fatality rates and socioeconomic state, physicians per ten thousand people, healthy life expectancy at birth, deaths among 30-70 years because of non-communicable diseases, population ages 65 and above (% of total population), diabetes mellitus (DM) frequency, cancer frequency, cardiovascular disease (CVD) frequency, chronic lung disease (CLD) frequency, tobacco use frequency, health expenditure as a percentage of gross domestic product (GDP), vaccination rates, Human Development Index (HDI), Gender Inequality Index (GII) and Global Gender Gap Index (GGGI) variables were investigated.

From the data of the study, the variables of the number of cases and deaths of Covid-19 disease and the number of physicians per ten thousand people were got online from WHO[10,11], countries' socioeconomic state and population ages 65 and above (% of total population) from the World Bank[12,13], healthy life expectancy at birth, and death among 30-70 years because of non-communicable diseases from WHO Health Statistics 2021[14], DM, CVD, cancer and CLD frequencies from Global Burden of Disease Study 2019[15], tobacco use frequency from WHO Report on Tobacco Use Prevalence Trends[16], health expenditure as a percentage of GDP from Global Burden of Disease Study Health Financing working group[17], countries' vaccination rates from Our World in Data[18], HDI and GII from United Nations[19,20], GGGI from the World Economic Forum[21]. In data selections, the most recent ones were selected and used.

Statistical Analysis

Data entry, analysis, and report writing were carried out in the computer environment. Countries with no missing data were included in the analysis. The mean, standard

deviation, minimum and maximum values were used to summarize the data. Pearson/Spearman correlation coefficient (r) was used to investigate the relationships between variables. In the evaluation of the calculated coefficients, 0.90-1.00 very strong relationship, 0.70-0.89 strong relationship, 0.40-0.69 moderate relationship, 0.20-0.39 weak relationship and 0.00-0.19 was interpreted as a negligible relationship. Negative correlation coefficients show that the variable decreases while the other increases or, on the contrary, positive correlation coefficients show that the variables decrease and increase together[22]. Linear regression analysis was performed and scatter plots were drawn to determine the variables associated with Covid-19 disease fatality rates. P<0.05 was considered statistically significant.

RESULTS

One hundred and thirty countries with no missing data were included in the study. Twelve point three percent of these countries were in low (n=16), 25.4% in lower middle (n=33), 26.2% in upper middle (n=34) and 36.2% in high (n=47) socioeconomic state (Figure 1).

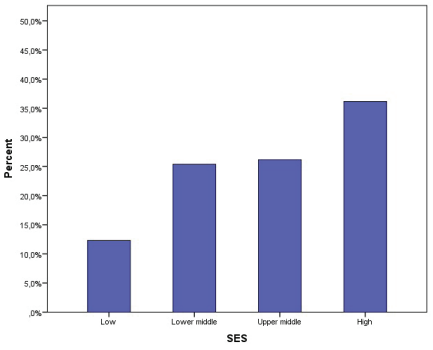

Figure 1. Countries' Socioeconomic States

The mean fatality rate of 130 countries was 0.016±0.018. The mean number of physicians per ten thousand people was 22,071±18,225. The characteristics of the variables of the countries included in the study are presented in Table 1.

A statistically significant relationship was determined between fatality rate and all variables except tobacco use frequency (p<0.05). The correlation coefficients and p values calculated between the fatality rate and the research variables are presented in Table 2.

Table 1. Characteristics of Country-Related Research Variables

Variables	Mean	Standard Deviation	Median	Minimum	Maximum
Fatality rate	0,016	0,018	0,012	0,000	0,182
Physicians per ten thousand people	22,071	18,225	22,100	0,350	84,200
Healthy life expectancy at birth (year)	64,192	6,254	65,800	44,200	74,100
Death among 30-70 years because of non-communicable diseases (%)	18,555	7,403	18,500	7,300	42,700
Population ages 65 and above (%)	10,253	6,984	7,825	1,264	28,397
DM frequency (%)	0,067	0,036	0,067	0,011	0,164
CVD frequency (%)	0,076	0,037	0,064	0,029	0,165
Cancer frequency (%)	0,015	0,014	0,008	0,001	0,066
CLD frequency (%)	0,068	0,032	0,056	0,029	0,161
Tobacco use frequency (%)	0,337	0,210	0,326	0,025	0,880
Health expenditure as a percentage of GDP ($)	1358,869	2091,691	423,000	22,000	11345,000
Vaccination rate (%)	129,789	77,857	138,372	0,105	312,384
HDI	0,745	0,154	0,779	0,394	0,957
GII	0,337	0,210	0,326	0,025	0,880
GGGI	0,708	0,066	0,712	0,492	0,892

Table 2. Fatality Rates According to Socioeconomic State and WHO Region

		Fatality Rates					P
		Mean	Standard Deviation	Median	Minimum	Maximum	
WHO regions	Europe	0,010	0,008	0,008	0,001	0,042	<0.001
	Americas	0,020	0,015	0,016	0,006	0,060	
	Africa	0,019	0,009	0,019	0,000	0,040	
	South East Asia	0,017	0,010	0,014	0,006	0,032	
	Western Pasific	0,006	0,007	0,003	0,001	0,022	
	Eastern Mediterranean	0,026	0,046	0,011	0,002	0,182	
Socioeconomic state	Low	0,031	0,041	0,022	0,000	0,182	<0.001
	Lower middle	0,018	0,010	0,017	0,001	0,048	
	Upper middle	0,018	0,013	0,013	0,005	0,060	
	High	0,007	0,006	0,006	0,001	0,024	

The relationships of the variables with the fatality rate were analyzed with scatter plots and presented in Figure 2.

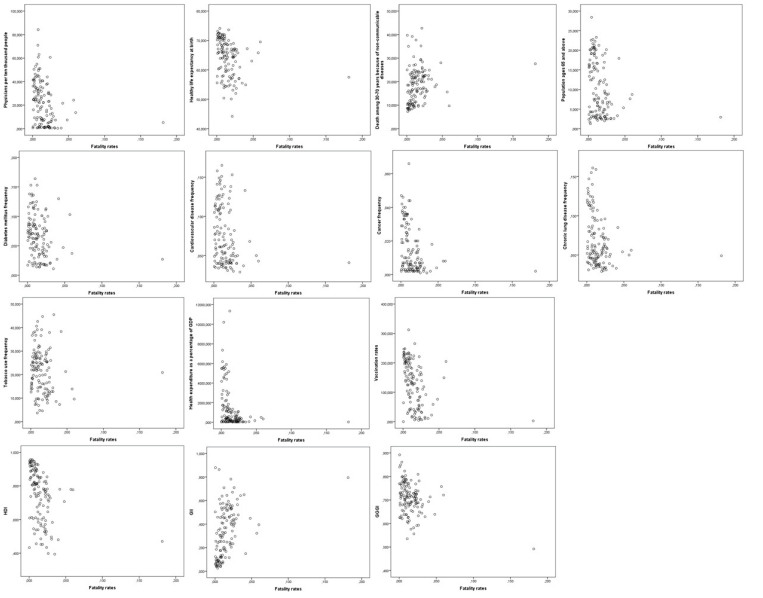

Figure 2. Scatterplots of the Relationships of Research Variables with Fatality Rate

All the variables were included in the multiple linear regression model established for the prediction of the fatality rate. Among these variables, GGGI was the only variable that made a statistically significant contribution to the model. The model is presented in Table 3.

All the variables were included in the multiple linear regression model established for the prediction of the fatality rate. The WHO region variable, which is not an ordinal or numerical variable, was included in the analysis as a dummy variable, considering the Western Pacific region with

the lowest fatality rate. Among these variables, GGGI was the only variable that made a statistically significant contribution to the model. The model is presented in Table 4.

Table 3. Investigation of Correlation Between Fatality Rate and Research Variables

Variables	Correlation Coeffients	P
Socioeconomic state	-0,546	0,001*
Physicians per ten thousand people	-0,439	0,001*
Healthy life expectancy at birth (year)	-0,437	0,001*
Death among 30-70 years because of non-communicable diseases (%)	0,337	0,001*
Population ages 65 and above (%)	-0,317	0,001*
DM frequency (%)	-0,316	0,001*
CVD frequency (%)	-0,298	0,001*
Cancer frequency (%)	-0,444	0,001*
CLD frequency (%)	-0,343	0,001*
Tobacco use frequency (%)	-0,162	0,065
Health expenditure as a percentage of GDP ($)	-0,499	0,001*
Vaccination rate (%)	-0,544	0,001*
HDI	-0,568	0,001*
GII	0,523	0,001*
GGGI	-0,296	0,001*

*It shows values with P<0.05.

Table 4. Linear Regression Model for Prediction of Fatality Rate

Variables	Standardized Coefficients	t	P
Socioeconomic state	-0,277	-1,162	0,248
WHO region (Western Pasific/Others)	-0,101	-1,013	0,313
Physicians per ten thousand people	0,023	0,138	0,890
Healthy life expectancy at birth (year)	0,104	0,481	0,632
Death among 30-70 years because of non-communicable diseases (%)	0,046	0,265	0,791
Population ages 65 and above (%)	0,312	0,989	0,325
DM frequency (%)	0,030	0,229	0,819
CVD frequency (%)	-0,148	-0,471	0,639
Cancer frequency (%)	-0,065	-0,231	0,818
CLD frequency (%)	0,133	0,702	0,484
Tobacco use frequency (%)	-0.015	-0.153	0.879
Health expenditure as a percentage of GDP ($)	-0.059	-0.360	0.720
Vaccination rate (%)	-0.201	-1.117	0.266
HDI	0.125	0.374	0.709
GII	0.186	0.821	0.413
GGGI	-0.270	-2.461	0.015
B=0.044 **R**=0.501 **R^2**=0.251 **F**=2.367 **p**=0,004			

DISCUSSION

In our study, socioeconomic state, physicians per ten thousand people, healthy life expectancy at birth, death among 30-70 years because of non-communicable diseases, population ages 65 and above (% of total population), DM frequency, CVD frequency, cancer frequency, CLD frequency, tobacco use frequency, health expenditure as a percentage of GDP, vaccination rates, HDI, GII and GGGI were determined as variables related to the Covid-19 fatality rate. In the established regression model, GGGI variable is the only variable with a significant p value among the variables that contribute to the model. In the study conducted by Coccia in which 160 countries were evaluated, gross domestic product (GDP) per capita, high health expenditures and air pollution were associated with fatality[8]. Jain et al. investigated the factors affecting Covid-19 mortality in India and western countries. In the study, variables such as the elderly population, diseases affecting the immune system, including genetics, mutant types of the virus, temperature and humidity, long-term quarantine practices, BCG vaccine, recurrent respiratory system infections, obesity, race and ethnicity were discussed as possible factors[23]. In the study of Upadhyay and Shukla, the factors affecting the Covid-19 fatality rate in the states of India were investigated and a positive correlation was determined with life expectancy, prevalence of overweight, Covid-19 test positivity rates and death rates from H1N1[24]. In a systematic review of 114 studies by Mehraeen et al., advanced age, hypertension, and DM were found to be associated variables[25]. In a meta-analysis by Sepandi et al., in which 13 studies were evaluated, advanced age, male gender, DM, hypertension, kidney diseases, respiratory system diseases and heart diseases were found to be associated with Covid-19 mortality[26]. de Oliveira et al., in their study at the beginning of the pandemic, associated the variables of GDP per capita, health expenditure as a percentage of GDP, infant mortality rate, physicians per thousand people, urban population ratio, number of people per km2 with mortality and fatality rates[9]. Upadhyaya et al. found obesity, population ages 65 and above (% of total population), urbanization, and GDP per capita to be associated with Covid-19 mortality[27]. In the literature, the variables associated with Covid-19 mortality and fatality in studies related to the subject are Goh et al. population over 65 years of age and DM[28], Pan et al., number of tomography per million population and prevalence of tobacco use[29], number of tests by Velasco et al., advanced age, rural population, air temperature, population density[30], Sorci et al. population over 70 years of age, GDP per capita, level of democracy, the number of hospital beds per thousand people, DALY due to CVS, cancer and chronic respiratory diseases, smoking-related death rate and lower respiratory tract infection in people over 70 years old[31], population density of Sornette et al., elderly population ratio and frequency of quarantine measures[32], Hasan et al. population over 65, population density, number of Covid-19 tests, GDP per capita, Yesterday either-wide management indicators (an index) and obesity prevalence[33], Banik et al. access to public health services, age structure of the population, poverty level and BCG vaccination[7], Silva and Tsigaris population over 65 years of age, international travel restrictions, public health nationality able to travel with no delays, number of tests and visas for information campaigns and testing policies[34].

Socioeconomic status of countries and some comorbidities were found to be factors associated with fatality rates in all the studies reviewed, including ours. This situation makes us think that many social, cultural, economic and individual factors play a role not only for non-communicable diseases but also for communicable diseases at all stages starting from transmission, and in fact, just like non-communicable diseases, there is a multifactorial aspect in communicable diseases as well. The part that should be considered and interpreted carefully is that the factors found in our study and in similar studies in the literature can be factors individually as the determinant of the fatality rate, they can be factors when they are together or their effects can be more when they are together. For this reason, it may be more appropriate to examine and evaluate these factors

together instead of examining them individually.

Highlights and Limitations of the Research

The study is important to research and trying to reveal the factors associated with an infectious disease that is as a pandemic. Because it is necessary to know the related factors in order to manage the situations related to other viral factors that may occur soon. In addition, fatality rates and all Covid-19 variants were included in the study since the beginning of the pandemic. These are the highlights of the research.

Countries with missing data were not included in the study. Since the research is of ecological type, it is necessary to be careful in the evaluation of the determined relationships in terms of causality. The relationships identified are prone to ecological fallacy, because of the type of research. These are the limitations of the research.

CONCLUSION

As a result of the research, socioeconomic state, physicians per ten thousand people, healthy life expectancy at birth, deaths among 30-70 years because of non-communicable diseases, population ages 65 and above, DM frequency, cancer frequency, CVD frequency, CLD frequency, health expenditure as a percentage of GDP, vaccination rates, HDI, GII and GGGI were determined as variables associated with the Covid-19 disease fatality rate. The only variable found statistically significant in the regression model was GGGI.

Considering these variables in similar epidemic disease states that may occur in the future and improving the conditions related to these variables on a global scale may be important to ensure epidemic control.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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Author Contributions

Concept – ENYÖ, MÖ, MU; Design – ENYÖ, MÖ, MU.; Supervision – MU; Funding – None; Materials – ENYÖ, MÖ, MU; Data collection and/or processing – ENYÖ, MÖ; Data analysis and/or interpretation – ENYÖ, MÖ, MU.; Literature search – ENYÖ, MÖ, MU; Writing – ENYÖ, MÖ, MU; Critical review – MU.

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Survey of COVID-19 Vaccine Hesitancy and Investigating Reasons for Vaccine Refusal Among Healthcare Professionals

Sağlık Çalışanları Arasında COVID-19 Aşı Tereddütlüğü ve Aşı Reddi Nedenlerinin Araştırılması

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Abstract

Aim Although there are many vaccine development and vaccine side-effect studies around the world, the literature on COVID-19 vaccine hesitancy and rejection is limited. We aimed to investigate the reasons for refusal of the COVID-19 vaccine and vaccine hesitancy among healthcare professionals.

Material and Method In the study, an online questionnaire was applied to healthcare workers who were not vaccinated with the full dose of COVID-19 vaccine in two pandemic hospitals.

Results A total of 74 healthcare professionals who were not fully vaccinated with the COVID-19 vaccine participated in the survey. The majority of the respondents are women (n = 49, 66.2%) and nurses (n = 35, 47.3%), and the mean age of health professionals is 32.2± 7.8 year. 55.4 % of healthcare professionals were not vaccinated against COVID-19; 44.6% had received a single dose of the COVID-19 vaccine. It was determined that 50% of healthcare workers had hesitations about the COVID-19 vaccine. 63.5% of healthcare professionals reported that they were vaccinated because they expected a different form of the current vaccine. 58.1% of healthcare professionals reported that they thought the vaccine was not necessary after infected with COVID-19.

Conclusion Measures should be taken to increase the COVID-19 immunization rates of healthcare professionals. The level of knowledge of healthcare professionals about COVID-19 vaccines should be increased. If possible, be given the opportunity to be vaccinated with different forms of COVID-19 vaccines.

Keywords COVID-19, vaccine, anti-vaccination, vaccine hesitancy, vaccine refusal.

Özet

Amaç *Dünya çapında birçok aşı geliştirme, aşı yan etki çalışmaları olmasına rağmen, COVID-19 aşı tereddüt/reddi ile ilgili literatür bilgisi sınırlıdır. Çalışmamızda sağlık çalışanlarının COVID-19 aşısını reddetme ve aşı tereddütü nedenlerini araştırmayı amaçladık.*

Gereç ve Yöntem *Çalışmada, iki pandemi hastanesinde COVID-19 aşısı ile tam doz aşılanmayan sağlık çalışanlarına yönelik çevrimiçi bir anket uygulandı.*

Bulgular *Ankete COVID-19 aşısı ile tam doz aşılanmamış toplam 74 kişi sağlık profesyoneli katıldı. Ankete katılanların büyük çoğunluğu kadın (n=49, %66,2) ve hemşirelerden (n=35, %47,3) oluşmakta olup, sağlık profesyonellerin yaş ortalaması 32,2±±7,8 yıl idi. Sağlık profesyonellerin %55,4'ü COVID-19'a karşı aşılanmamıştı, %44,6'sı tek doz COVID-19 aşısı olmuştu. Sağlık çalışanlarının %50'sinin COVID-19 aşısı konusunda tereddütü olduğu saptandı. Sağlık profesyonellerinin %63,5'i mevcut aşının farklı bir formunu bekledikleri için aşılandığını bildirdi. Sağlık çalışanlarının %58,1'i aşılı kişilerin COVID-19 ile enfekte olduktan sonra aşının gerekli olmadığı düşündüklerini bildirdi.*

Sonuç *Sağlık profesyonellerin COVID-19 bağışıklama oranlarını artıracak önlemler alınmalıdır. Sağlık profesyonellerinin COVID-19 aşıları hakkındaki bilgi düzeyi artırılmalıdır. Mümkünse COVID-19 aşılarının farklı formları ile aşılanma fırsatı verilmelidir.*

Anahtar Kelimeler *COVID-19, aşı, aşı karşıtlığı, aşı tereddütü, aşı reddi.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declined as a pandemic by the World Health Organization (WHO) in March 2020. To prevent its spread, vaccination studies have been started rapidly.[1] Since January 24, 2020, the University of Queensland in Australia started the COVID-19 vaccine development study, many vaccine studies continue globally.[1,2] In February 2020, the World Health Organization (WHO) announced that it does not expect a vaccine against SARS-CoV-2 to be available in less than 18 months and increasing mortality and morbidity rates led to the global application of rapid vaccination.[1,3,4] The United States Food and Drug Administration (FDA) approved the emergency use of the vaccine on December 11, while the European Medicines Agency (EMA) approved its use in member countries on December 21. The Pfizer / BioNTech vaccine was first administered in England on December 8, New York on December 14, and in European countries on December 27. At least 13 different vaccines have been administered in many countries. The Pfizer/ BioNtech Comirnaty, the SII/Covishield and AstraZeneca/AZD1222, The Janssen/Ad26.COV 2.S, The Moderna COVID-19 vaccine (mRNA 1273), the Sinopharm COVID-19 and The Sinovac-CoronaVac vaccines are listed in WHO listed for Emergency Use Listing (EUL) vaccines.[5]

In Turkey healthcare professionals (HCPs) who are at the forefront of the fight against COVID-19 are the priority group for the COVID-19 vaccine, and inactivated Sinovac vaccination started with this group first. The logistics management of cold chain materials such as vaccines, antiserum, syringes, and transport containers used in preventive health services in Turkey is carried out by the Vaccine/Antiserum Logistics Unit of the Ministry of Health, General Directorate of Public Health, Department of Vaccine-Preventable Diseases. All purchased vaccines are analyzed by the Turkish Medicines and Medical Devices Agency of the Ministry of Health and offered for use after being evaluated in terms of safety. And additionally; COVID-19 vaccines are administered by trained personnel, and vaccines are administered completely free of charge.6 But there are still HCPs who are not, yet COVID-19 vaccinated.

Despite there being many vaccines development and vaccine side-effect studies, globally, limited literature information on COVID-19 vaccine hesitancy/rejection on HCPs. In our study, we aimed to investigate the underlying reasons for this behavior of HCPs who did not fully vaccinated against COVID-19.

METHODS

Study design and Setting

This study was a cross-sectional survey study, conducted during April 15st to April 30st 2021 at xxx Hospital and xxxx.

Participants

An online questionnaire was administered to HCPs employed whom were not vaccinated with COVID-19 vaccine during the study period at two hospitals. The study included all HCPs. In order to attain an adequate number of HCP, this study was conducted at two pandemic hospital. Unvaccinated HCPs were identified as potential participants. The number of people who did not receive the COVID-19 vaccine was estimated to be around 400.

Study instrument

The questionnaire is comprised of four parts. Part (1) the socio-demographic characteristics (age, sex, marital status, occupation, education level, years of working experience), Part (2) COVID-19 vaccine hesitation related questions, and Part (3) COVID-19/ COVID-19 vaccine-related questions. Part (4) the reason why they had not been vaccinated.

Due to the outbreak of COVID-19, a web-based self-reported questionnaire was designed by researchers. The survey was delivered to the HCPs working in 2 participating pandemic hospitals via in-hospital social media links. This questionnaire was prepared by authors XXX and

XXX.

Statistical analysis

All analyses of the data were performed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). Data are expressed as number and percentage or median (min-max), as appropriate. The conformity of the data to the normal distribution was examined with the Kolmogorov Smirnov test. Significance was defined as a two-tailed P-value of less than 0.05.

Ethical considerations

The Ethics Committee at XXX (date:24.05.2021 decision no:21/4-XIV) provided ethical approval for this study. All the participants provided online informed consent form in accordance with the revised Declaration of Helsinki, prior to participation. The participants were asked to complete the online questionnaire anonymously. To ensure confidentiality, data was stored in the principal investigator's encrypted computer.

Results

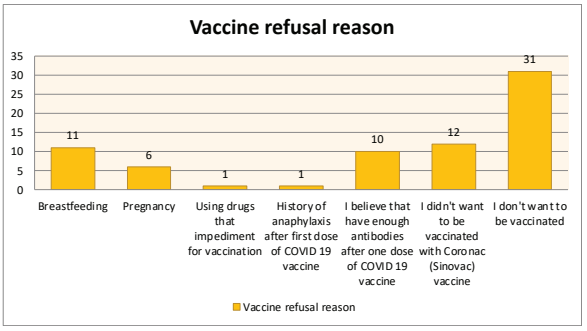
A total of 58 HCPs were excluded from the study because they did not answer all of the survey questions. Only 74 participants who were not fully vaccinated could be included in the study.

A large majority of respondents were female (n=49,66.2%) and nurses (n=35,47.3%), the average age of HCPs was 32.2 ± 7.8 year. Most (86.4%) of unvaccinated HCPs were between the years of 21-40 age (Table 1).

68.9 % of HCPs was never been infected with COVID-19, 55.4 % of HCPs was not vaccinated against COVID-19, 44.6 % of HCPs was one dose COVID-19 vaccinated (Table 2).

50% of HCPs were confused about the COVID-19 vaccine, 51.4 % of HCPs stated that they did not trust the statements of the Ministry of Health and the World Health Organization regarding COVID-19 vaccines. 36.5 % of HCPs gave 2 points as COVID-19 vaccine confidence score answer (interval was min 0- max 5 points). 63.5% of HCPs were not vaccinated as they were waiting for a different form of the current vaccine. 58.1% of HCPs believe that the vaccine doesn't effective as vaccinated people became infected (Table 3).

Most (n=31,41.9%) of HCPs did not vaccinate as they only not to be vaccinated and not to be vaccinated with inactive Coronac (Sinovac) vaccine (Graphic 1).



Graphic 1. Reasons of the vaccine refusal among HCPs (n).

DISCUSSION

Vaccination programs prevent vaccine-preventable infectious diseases, therefore aims to prevent deaths or permanent sequelae. Individual immunity is provided by vaccination and the person is free from the disease and at the same time provides social immunity. As the number of vaccinated individuals in society increases, the number of people susceptible to an infection in society decreases.[7,8] Twenty years ago, the concepts of "vaccine hesitancy/vaccine rejection" were introduced in the world, and the increasing cases of vaccine rejection have caused decreases in vaccination rates and have led to an increase in the incidence of preventable diseases. In Turkey, the opposition to vaccination has been present for about 10 years.[9] Vaccine hesitancy/rejection can be caused by many reasons, such as religious/traditional beliefs, individual/philosophical beliefs, and concerns about the safety of vaccines in general.[10]

Table 1. The summary table of characteristics of HCPs.		
Characteristic	n (%)	
Age		
18-20 years	2 (10.8)	<0.001 (21-30 years and 31-40 years)
21-30 years	32 (43.2)	
31-40 years	32 (43.2)	
>41 years	8 (10.8)	
Gender (female)	49 (66.2)	<0.001
Department		
Ward	32 (43.2)	<0.001 (ward)
Intensive care unit	8 (10.8)	
Policlinic	17 (23)	
Laboratory	5 (6.8)	
Other	12 (16.2)	
Marital status (Married)	55 (74.3)	<0.001
Education level		
Primary	8 (10.8)	<0.001 (university)
High school	17 (23)	
University	45 (60.8)	
Post graduate	4 (5.4)	
Occupation		
Doctor	21 (28.4)	<0.006 (Nurse)
Nurse	35 (47.3)	
Patient care staff	5 (6.8)	
Technician (laboratory or radiology)	5 (6.8)	
Other	2 (2.7)	
Experience years		
<1 years	3 (4.1)	0.087
1-4 years	11 (14.9)	
5-10 years	28 (37.8)	
>11 years	32 (43.2)	
H**aving chronic disease**	12 (16.2)	0.752
Chronic drug usage	13 (17.6)	0.989
*Total participians: 74		

Table 2. COVID-19/ COVID-19 vaccine related questions.		
Answers	**n (%)**	**p**
Have you ever had COVID-19 infection?		
none	51 (68.9)	<0.001 (not infected)
mild infection	18 (24.3)	
hospitalized	1 (1.4)	
no idea	4 (5.4)	
Have you heard of the COVID- 19 vaccine?(Yes)	73 (98.6)	<0.001
Where did you heard about the COVID-19 vaccine?		
TV	32 (43.2)	0.036 (TV)
Internet	19 (25.7)	
Social media	4 (5.4)	
Scientific publications	19 (25.7)	
What is your level of knowledge about COVID-19 vaccines?		
I have very detailed information	32 (43.2)	0.989
I don't have the exact information.	42 (56.8)	
Does anyone in your family or friends unvaccinated against COVID-19?		
Yes	61 (82.4)	<0.001
No	13 (17.6)	
Have you been vaccinated against COVID-19?		
No		0.899
Yes		
If you did not vaccinated for recommended dose, how many doses of vaccine did you not receive?		
Two	41 (55.4)	0.788
One	33 (44.6)	
*Total participians: 74		

Table 3. COVID-19 vaccine hesitation related questions.		
Answers	**n (%)**	**p**
Do you trust the COVID-19 vaccine?		
Yes	27 (36.5)	0.588
No	9 (12.2)	
Confused	37 (50)	
No idea	1 (1.4)	
Do you trust the statements of the Ministry of Health and the World Health Organization about COVID-19 vaccines?		
Yes	20 (27)	<0.05 (no)
No	38 (51.4)	
Confused	14 (18.9)	
No idea	2 (2.7)	
What is your confidence score for the COVID-19 vaccine? (Score from 1 to 5 points)		
1 points	3 (4.1)	<0.05 (2 points)
2 points	27 (36.5)	
3 points	11 (14.9)	
4 points	18 (24.3)	
5 points	15 (20.3)	
I want to wait for the side effects to become clearer		
Yes	21 (28.4)	>0.05
No	29 (39.2)	
Confused	21 (28.4)	
No idea	3 (4.1)	
I believe that my antibodies are sufficient since I had COVID-19 infection before.		
Yes	8 (10.8)	<0.001 (no)
No	45 (60.8)	
Confused	14 (18.9	
No idea	7 (9.5)	
I was not vaccinated as I was waiting for a different form of the current vaccine.		
Yes	47 (63.5)	<0.001 (yes)
No	15 (20.3)	
Confused	11 (14.9)	
No idea	1 (1.4)	
I was afraid of being vaccinated.		
Yes	38 (51.4)	<0.001 (yes)
No	20 (27)	
Confused	14 (18.9)	
No idea	2 (2.7)	
I'm allergic to many vaccines.		
Yes	10 (13.5)	<0.001 (no)
No	50 (67.6)	
Confused	9 (12.2)	
No idea	5 (6.8)	

I had a previous history of anaphylaxis against vaccines.		
Yes	3 (4.1)	<0.001 (no)
No	60 (81.1)	
Confused	3 (4.1)	
No idea	8 (10.8)	
I don't believe the vaccine is protective.		
Yes	12 (16.2)	<0.05 (no)
No	35 (47.3)	
Confused	25 (33.8)	
No idea	2 (2.7)	
COVID-19 vaccine can cause paralysis		
Yes	5 (6.8)	<0.05 (no)
No	36 (48.6)	
Confused	24 (32.4)	
No idea	9 (12.2)	
I may be disabled after the COVID-19 vaccine.		
Yes	4 (5.4)	<0.05 (no)
No	37 (50)	
Confused	22 (27.9)	
No idea	11 (14.9)	
I may be infertile after COVID- 19 vaccine.		
Yes	20 (27)	<0.05 (no)
No	38 (51.4)	
Confused	14 (18.9)	
No idea	2 (2.7)	
I can die after COVID-19 vaccination.		
Yes	8 (10.8)	<0.05 (no)
No	35 (47.3)	
Confused	19 (25.2)	
No idea	12 (16.2)	
There were people who became infected with COVID-19 after the COVID-19 vaccination, which proves the vaccine doesn't effective.		
Yes	43 (58.1)	<0.05 (yes)
No	15 (20.3)	
Confused	15 (20.3)	
No idea	1 (1.4)	
Do you think that not being vaccinated is a bad example for other individuals?		
Yes	29 (39.2)	>0.05
No	26 (35.1)	
Confused	18 (24.3)	
No idea	1 (1.4)	
*Total participians: 74		

The most important part of society and management in epidemics are HCPs, certainly. In addition, HCPs have a higher risk for COVID-19 infection. This group has to comply fully with infection control measures and should be fully vaccinated.[1,11] However, as seen in our study, it was determined that some of the HCPs still did not receive the COVID-19 vaccine. In our study, we aimed to investigate the reasons for this situation.

In Turkey, CoronaVac (Sinovac) vaccines which were brought from China, and "Emergency Use Approval" were given after the analyzes were completed by the Turkish Medicines and Medical Devices Agency. After that vaccines were started to be applied to HCPs on 14 January 2021 all over our country. The first CoronaVac vaccine was given to the Minister of Health of Turkey.[12] At the time of our study, the time elapsed from the start of Coronovac vaccination was approximately three months, and there were approximately 400 HCPs estimated to be unvaccinated in two hospitals. On the other hand, 132 people agreed to participate in the online survey based on volunteerism. 58 of the participants were not included in the study because they did not answer all of the survey questions.

In the USA the KFF COVID-19 Vaccine Monitor project, which is an ongoing research project, tracks the public's attitudes and experiences with COVID-19 vaccinations. It uses a combination of surveys and qualitative research. And it aims to track the dynamic nature of public opinion as vaccine development and distribution unfold, including vaccine confidence and acceptance, information needs, trusted messengers, and messages. As of May 2021, 37% of adults have not yet received the COVID-19 vaccine. The unvaccinated group has a younger age, lower education levels, and lower income than the vaccinated group. c In our study; a large majority of respondents were female (n=49,66.2%) and mostly (86.4%) of not vaccinated HCPs were between the years of 21-40 age. Although the KFF COVID-19 Vaccine Monitor project contains a lot of detailed information about unvaccinated people, including political views, no gender information was found. This project highlights, unvaccinated adults reported having different concerns, a number of people taking a "wait and see" approach, and some of these people reported that some encouragement might persuade them. Examples of these were different incentive requests, from the U.S. Food and Drug Administration (FDA) approval of vaccines to the organization of sports competitions and even free concert tickets.[13] It was determined that 51.4% of the participants in our study were not trusted the information provided by WHO and the Ministry of Health, 28.4% of HCPs were only the ''wait and see" group.

As well as COVID-19 studies, studies are continuing to prevent anti-vaccination and to encourage people to be vaccinated. French et al.[14] had published practice guidelines for the COVID-19 vaccination strategy. This guide aims to set out in short form-critical guidelines to enhance the impact of a COVID-19 vaccination strategy[14]. However, these studies are limited and COVID-19 vaccine hesitation continues to globalize.

A similar study from Canada with 2,761 respondents included the study. The most important reasons for vaccine rejection were that the vaccine was new and wanting to see other people's vaccination results. 74% of healthcare professionals who refused to vaccinate reported that they would agree to vaccinate in the future.[15] Our study included a small number of participants as only 2 pandemic hospitals were included in this study. And 63.5% of HCPs were not vaccinated as they want to wait for a different form of the current vaccine.

To date, serious side effects have not been encountered in the clinical studies and current vaccine applications for COVID-19 vaccines. Side effects after vaccination are often mild. These are mild side effects such as fatigue, headache, fever, chills, muscle/joint pain, vomiting, diarrhea, pain in the injection area, redness, and swelling. However, although rare, allergic reactions may occur.[16] As the COV-

ID-19 pandemic continues to spread, HCPs have a duty to not only be involved in the treatment of COVID-19 patients but also to inform the public about developments in COVID-19.[16,17] In a study from Italy, factors associated with COVID-19 vaccine hesitancy were using Facebook as the main source of information and being a non-physician HCPs.[18] In our study, it was determined that most of the HCPs who refused the vaccine obtained information about COVID-19 from TV (43.2%). To avoid vaccine hesitancy, the level of knowledge on the HCPs COVID-19 vaccine needs to be increased. Therefore, especially HCPs should keep their knowledge up to date from reliable scientific sources.

When vaccine rejection and vaccine instability are examined, various reasons emerge. Among these, lack information, negative perspective caused by the perception of defamation against vaccination, distrust of the vaccine, fictional approaches, belief, worry that the vaccine will not work, the idea that the vaccine is an economic market, not at risk, health problems that the vaccine will bring, the difficulty of geographical conditions, ineffectiveness government policies, the way the vaccine is produced, the idea that vaccination is used as a tool of globalization (infertility, playing with people's gene structures, etc.), negative attitudes and behaviors of healthcare workers towards the vaccine.[19-21] In our study, most of the responders don't have negative perspectives on the COVID-19 vaccine.

The movement of vaccine rejection and vaccine hesitancy not only frightened people but also caused the re-emergence of eradicated diseases in various parts of the world. Increasing vaccine rejection continues to increase infectious diseases and is a serious public health epidemic. This situation has brought up vaccine-preventable diseases, vaccine efficacy, and clinical features of vaccines again.[19-25] Vaccines developed in various countries have been made available for the COVID-19 pandemic, which is the last experienced in the world and still affects the world effectively. However, here too, vaccine rejection, vaccine hesitancy, and vaccine hesitancy are at a visible level in both the public and healthcare professionals. Anti-vaccination demonstrations were held in many countries, and opinions and emphasis that compulsory vaccination is against medical freedom drew attention.[26] In the months when the epidemic was intense, the rate of waiting for the vaccine is quite high all over the world, people are willing to vaccinate and the vaccine is the hope of humanity, but after the vaccination applications started, this rate started to decrease. Yadigaroğlu et al.[25] conducted a study in 15 countries from January 28-31, 2021. They reported that the intention to be vaccinated for COVID-19 is high worldwide (88% in Brazil, 85% in China, 71% in the USA, and Germany). 68% and 57% in France). When the reasons for COVID-19 vaccine rejection are investigated, in addition to the general reasons for vaccination rejection, there are conspiracy theories about current COVID-19 vaccines as the production technique of the vaccines is fast despite the developing technology. Different causes of vaccine reflux have also been reported in the literature, such as the thought that current vaccines will be ineffective due to the constant mutation of SARS COV 2, the side effects of the vaccine, and the opinions that the vaccine is mandatory in some countries.[27,28]

In a similar study from France, 1,965 HCPs were included[29]. 60% of auxiliary nurses and technicians expected to be vaccinated, compared to 60-79% of nurses and support workers, and>80% of medical professionals. Age, occupation, vaccine experience, and the AstraZeneca vaccine tolerability dispute were all found to be independently linked with COVID-19 vaccine intention in a multivariate analysis.[29] In a similar study from Cape Town, South Africa, it was found that % of HCWs, including physicians, nurses, biomedical scientists, allied HCPs, hospital administrators, and others, were afraid of the COVID-19 vaccination. HCPs have a prevalence of 41%, which is fairly significant.[30] In a systematic review, only studies published by July 2021 were included. And it was found that there was a 40.8% prevalence of vaccine hesitancy among HCPs

in the United States.[31]

Most HCP accept vaccines, according to a recent study from the United States, but many expressed reservations about COVID-19 vaccines due to the psychological antecedents of vaccination: confidence (vaccines are effective), complacency (vaccines are unnecessary), constraints (difficult to access), calculation (risks/benefits), and collective responsibility (need for vaccination when others vaccinate). HCP who were only hesitant about COVID-19 vaccines differed from those who were hesitant about all vaccines: those with lower confidence were more likely to be younger and female, those with higher constraints were more likely to have clinical positions, those with higher complacency were more likely to have recently cared for COVID-19 patients, and those with lower collective responsibility were more likely to be non-white. These findings can be used to develop interventions to persuade HCPs to use COVID-19 vaccinations.[33]

A similar study from Turkey, observed that healthcare professionals' willingness to be vaccinated against COVID-19 differed according to their roles in the hospital, and doctors were the widest group to accept vaccination.[34]

Concerns about safety, efficacy, and side effects were shown to be the top three significant reasons for COVID-19 immunization hesitation among HCWs in the vast majority (> 75 %) of studies[30-34]. Insufficient knowledge about the vaccines, belief that COVID-19 does not exist or is not a serious disease, vaccine development speed, politics surrounding vaccine development, misinformation from social media, previous COVID-19 infection or health conditions, and mistrust in authorities, health experts, and pharmaceutical companies were among the other reasons for COVID-19 vaccination hesitancy[30-34]. In our sudy, 50% of HCPs were confused about the COVID-19 vaccine, 51.4 % of HCPs stated that they did not trust the statements of the Ministry of Health and the World Health Organization regarding COVID-19 vaccines.

COVID-19 vaccine hesitancy was reported by 22.51 % of 76,471 HCWs worldwide, according to the findings of a review. Given the nature of HCWs' work, the public would expect that they would have no reservations about taking the COVID-19 vaccine.[35] The male gender was shown to be an enabling factor in the majority of research when it came to characteristics related with decreased COVID-19 vaccination reluctance and increased willingness for COVID-19 immunizations.[35] Female gender was found to be a statistically significant predictor of vaccine hesitancy in our study. But our study results were limited to the lack of participants.

CONCLUSION

The COVID-19 pandemic has once again left humanity in a dilemma about vaccination. On the one hand, the fear of the epidemic is stuck between the unproven and vague discourses about vaccine rejection, which has been expected for months as the only remedy. Opposition to vaccination, the risk and fear of death created by the epidemic, and the desire to return to normal life have driven human beings to a dead end, and human beings in the middle have exhibited various health behaviors. The solution to the problem is seen as possible by believing in science, trusting science, and enlightening society by providing accurate information from governments. Due to the fact that the HCPs group is considered to be highly risky for exposure to COVID-19 infection, it is crucial to ensure that the entire group of HCPs is vaccinated against COVID-19. To ensure an adequate workforce to treat patients, health systems must attain high COVID-19 immunization coverage rates among frontline HCPs as soon as a vaccine is available. It is their obligation to educate HCPs so that they can make solid vaccine recommendations and successfully respond to vaccine-skeptical patients. Future study in this area should concentrate on practicing physicians, nurses, and dentists, as well as students in these fields, because all of these professionals are involved in direct patient care and may be tasked with giving vaccine recommendations to patients.

Limitations of study

Our research has some limitations. First, because subjects are recruited on a voluntary basis, representability cannot be guaranteed. During the study period, we were able to gather COVID-19 vaccine intention from almost a third of the unvaccinated population. Furthermore, in terms of occupation and age, the features of our sample were comparable to the entire structure of our hospital workforce (data not shown). Second, our research was conducted in two centers over the course of two weeks, and the results may not apply to other situations. This constraint is especially important considering the wide range of vaccination reluctance across time and across countries. Finally, we only collected declarative data and were unable to control answer accuracy.

Conflict of interest

The authors declare no conflicts of interest.

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Liver Biopsy in Chronic Hepatitis Patients: Our Single Center Experience

Kronik Hepatit Hastalarında Karaciğer Biyopsisi: Tek Merkez Deneyimimiz

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Abstract

Aim Liver biopsy, which is used to determine fibrosis in patients with chronic hepatitis B, is an invasive procedure and may have complications. In this study, we planned to evaluate blinded and ultrasonography (USG)-guided liver biopsies and compare complications.

Material and Method This is a retrospective study containing the data of a total of 436 chronic hepatitis B patients who underwent liver biopsy in our hospital.

Results 150 (34.4%) of the patients included in the study were female, and the mean age was 33.3±13.1/year. Complications developed in 174 (39.9%) of the patients. Of these, 110 (51.9%) developed in patients who underwent blind biopsy, 64 (28.6%) developed in patients who underwent USG guided biopsy, and the difference was statistically significant ($p<0.001$). Among the major complications, bleeding developed only in 2 (0.5%) patients who underwent blind biopsy, and bile leakage in 2 (0.5%) patients who underwent blind biopsy. No major complications were observed in any of the patients who underwent USG guidance. Minor complications were also detected predominantly in patients who underwent blind biopsy.

Conclusion Liver biopsy is still a reliable method in terms of complications in the evaluation of fibrosis in patients followed up with chronic hepatitis B. Minor complications are less common in USG-guided biopsies.

Keywords Chronic hepatitis B, liver biopsy, complication

Özet

Amaç *Kronik hepatit B hastalarında fibrozisin belirlenmesinde kullanılan karaciğer biyopsisi invaziv bir işlem olması nedeniyle beraberinde komplikasyonları da olabilmektedir. Biz bu çalışmada kör ve ultrasonografi (USG) eşliğinde yapılan karaciğer biyopsilerini değerlendirmeyi, komplikasyonları karşılaştırmayı planladık.*

Gereç ve Yöntem *Bu çalışma hastanemizde karaciğer biyopsisi yapılan toplam 436 kronik hepatit B hastasının verisini içeren bir çalışmadır.*

Bulgular *Çalışmaya alınan hastaların 150 (%34,4)si kadın, yaş ortalaması 33,3±13,1 /yıl idi. Hastaların 174 (%39,9)ünde komplikasyon gelişmişti. Bunların 110 (%51,9)u kör biyopsi yapılan hastalarda, 64 (%28,6)ü ise USG eşliğinde biyopsi yapılan hastalarda gelişmişti ve aradaki fark istatistiksel olarak anlamlıydı ($p<0.001$). Major komplikasyonlardan kanama sadece kör biyopsi yapılan 2 (%0,5) hastada yine safra kaçağı kör biyopsi yapılan 2 (%0,5) hastada gelişmişti. Ultrasonografi eşliğinde yapılan hiçbir hastada major komplikasyon görülmemişti. Minör komplikasyonlar da ağırlıklı olarak kör biyopsi yapılan hastalarda tespit edilmişti.*

Sonuç *Kronik hepatit B ile takip edilen hastaların fibrozisinin değerlendirilmesinde karaciğer biyopsisi komplikasyonlar açısından hala güvenilir bir yöntemdir. Minör komplikasyonlar USG eşliğinde yapılan biyopsilerde daha az görülmektedir.*

Anahtar Kelimeler *Kronik hepatit B, karaciğer biyopsi, komplikasyon*

INTRODUCTION

Chronic hepatitis B (CHB) is an important problem that concerns the world population. The World Health Organization reported that there were approximately 257 million people infected with hepatitis B virus (HBV) in the world in 2015, and an estimated 887,000 people died from HBV-related complications in the same year[1-3]. The effective vaccination programs in many countries have resulted in a significant reduction in the incidence of HBVinfection. Despite this, it is still an important cause of morbidity and mortality[4].

The age, comorbidity, and family history should be taken into account when making a treatment decision in a patient followed up for CHB. The level of HBV DNA and alanine aminotransferase (ALT) and the degree of liver disease are the most important criteria in making this decision. Although the use of non-invasive tests has increased recently in defining the degree of liver disease and determining fibrosis, liver biopsy is still used[5]. Liver biopsy can be performed percutaneously, transjugularly, laparoscopically and intraoperatively. Percutaneous biopsy can also be performed with palpation/percussion, accompanied by blind biopsy and ultrasonography (USG)[6,7]. However, biopsy is an invasive procedure and it should be kept in mind that minor/major complications may develop. In this study, we aimed to evaluate blinded and USG-guided liver biopsies and to compare complications.

METHODS

This study includes the data of a total of 436 patients who were hospitalized in the Infectious Diseases Clinic of our hospital between 2011-2019 and underwent liver biopsy. The ethics committee approval for the study was obtained from the Medical Ethics Committee of our hospital (Date/Number: 02.07.2021/821). The consent was obtained from all patients before biopsy was performed. Anticoagulant drugs were discontinued 7 days before. Platelet count, prothrombin and partial thromboplastin times were studied before biopsy. Blind biopsy was performed in 212 (48.6%) patients, and ultrasound guided biopsy was performed in 224 (51.4%) patients. Epidemiological data such as age, gender, underlying diseases and complications of the patients were obtained from the hospital database and files. The data of patients who underwent blind biopsy and those who underwent USG guided biopsy were compared.

Biopsy procedures

Blind biopsy was performed by an infectious diseases specialist in the infectious diseases service, using a single-use (Hepafix®, B.Braun Melsungen AG, Germany) set containing Menghini type needle. The patients were fasted for at least 8 hours before the procedure. The patient was placed in the supine position and the right hand was placed under the head. Starting from under the right clavicle with percussion, the liver dullness was determined and the area to be entered was marked. The biopsy site was wiped with 1% povidone iodine and then cleaned with alcohol. The area was covered with a sterile drape. In the marked interval, local anesthesia was performed with 2-4 ml of lidocaine over the lower rib. An incision was made above the lower rib. Progress was made by entering through the incision with a biopsy needle. The needle was entered towards the xiphoid and parallel to the ground. After passing the skin and subcutaneous tissues, the plunger was held back while the needle was advanced. Then, a small amount of saline was poured to clear the occlusive tissues in the needle without entering the liver capsule. At the same time, the patient was asked to fully exhale and remain in expiration. The plunger of the injector was retracted. The needle was pushed into the liver and then quickly removed. The biopsy material taken was placed in formol solution.

Ultrasonography-guided liver biopsy was performed by an expert radiologist in the interventional radiology unit. All patients were processed in the supine position. Before the biopsy procedure, the biopsy area was prepared under standard sterile conditions and the patient was covered with a sterile drape, except for the biopsy area. A sterile sheath was placed on the USG probe. Local anesthesia was

applied to the skin first, then to the subcutaneous tissues and liver capsule in the planned transition line. After local anesthesia, a small incision was made on the skin and under the guidance of USG, vascular structures were avoided and a 17G coaxial needle was inserted into the liver parenchyma. The co-axial system consists of an outer cannula and an inner needle (Stile) system. It provides the opportunity to take more than one tissue sample with a single parenchymal passage and to apply embolizing material through the system in case of possible bleeding. The inner needle (stylet) was removed and the 18G needle automatic biopsy gun (Tru-Core™ II) was inserted into the cannula. And biopsy samples were taken. If there was arterial or disturbing amount of venous bleeding before the cannula was removed, a bioabsorbable sponge plug was applied through the cannula and hemostasis was achieved throughout the trace. After the biopsy, the patients were placed on the right side and pressure was applied to the biopsy area. Blood pressure and heart rate were monitored every 15 minutes for the first two hours, and every 30 minutes for the next four hours, by administering intravenous fluids.

Statistical analysis

Data analysis was done in SPSS's Windows 22.0 package program. Whether the distribution of continuous variables was close to normal was investigated using the Shapiro Wilk test. Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables, and frequency analysis and percentage (%) for categorical variables. The significance of the difference between the groups in terms of means was investigated using the Mann-Whitney U test. Categorical variables were analyzed with Pearson's Chi-Square test. For $p<0.05$, the results were considered statistically significant.

RESULTS

Of the 436 patients included in the study, 150 (34.4%) were female, and the mean age was 33.3±13.1/year (min-max: 15-78). Forty-nine (11.2%) patients had comorbidities [diabetes mellitus: 16 (3.7%), hypertension: 15 (3.4%), coronary artery disease: 10 (2.3%), rheumatic disease: 3 (0.7%), chronic lung disease: 5 (1.1%)]. Blind biopsy was performed in 212 (48.6%) patients (group 1), and USG guided biopsy was performed in 224 (51.4%) patients (group 2). Evaluation could not be made because insufficient material was taken in 12 (2.8%) of the patients. Complications developed in 174 (39.9%) patients (Table 1).

Table 1. Characteristics of patients with CHB who underwent liver biopsy

Variable	n (%)
Age±SD	33.3±13.1
Gender	
Female	150 (34.4)
Male	286 (65.6)
Biopsy size, mm ± SD	11.8±5.8
Comorbidity	
Diabetes mellitus	16 (3.7)
Hypertension	15 (3.4)
Coronary artery disease	10 (2.3)
Rheumatic disease	3 (0.7)
Chronic lung disease	5 (1.1)
Complication	174
Pain	135 (31)
Nausea	58 (13.3)
Vomiting	28 (6.4)
Bleeding	2 (0.5)
Bile leakage	2 (0.5)
Insufficient sample	12 (2.8)

Of these, 110 (51.9%) developed in group 1 patients, 64 (28.6%) developed in group 2 patients, and the difference was statistically significant ($p<0.001$). Pain was present in 135 (31%) patients, nausea in 58 (13.3%), vomiting in 28 (6.4%), intra-abdominal bleeding in 2 (0.5%), and bile leakage in 2 (0.5%). Of the patients in group 1, 86 (40.6%) had pain, 35 (16.5%) nausea, 16 (7.5%) vomiting, 2 (0.9%) bleeding, 2 (0.9%) bile leakage was available. In Group 2 patients, 49 (21.9%) had pain, 23 (10.3%) had nausea, 12 (5.4%) had vomiting, and no bleeding or bile leakage was observed. There was a significant difference in pain be-

tween the two groups (p<0.001). (Table 2).

Table 2. Comparison of complications in patients who underwent blind liver biopsy (group 1) and USG guided biopsy (group 2).

Variable	Group 1 (N=212)	Group 2 (N=224)	P value
Pain	86 (40.6 %)	49 (21.9 %)	<0.001
Vomiting	16 (7.5 %)	12 (5.4 %)	0.351
Nausea	35 (16.5 %)	23 (10.3 %)	0.055
Bile leakage	2 (0.9 %)	0 (0 %)	<0.001
Bleeding	2 (0.9 %)	0 (0 %)	<0.001
Insufficient material	12 (5.7 %)	0 (0 %)	<0.001

DISCUSSION

Liver biopsy is considered the gold standard for evaluating fibrosis due to CHB. Liver biopsy is a method that still maintains its importance in the diagnosis of liver diseases, although imaging methods have been developed and used frequently[8]. Since it is an invasive procedure, complications observed during and after the procedure can sometimes be serious. Factors such as biopsy technique and the experience of the physician who performed the biopsy affect the development of complications. Liver biopsy can be performed in three ways: percutaneous, transvenous, and laparoscopic[9,10]. Percutaneous liver biopsies can be performed in two different ways as fine needle aspiration biopsy (FNAB) or cutting needle biopsy (tru-cut). In our study, biopsies performed with blinded FNAB and ultrasonography-guided cutting needle biopsy were taken. The complication rate due to percutaneous liver biopsy is 1-5% and the mortality rate is 0.01-0.009%. Percutaneous biopsies using imaging modalities have largely prevented the complications of blind biopsy[11]. Pain may develop at the biopsy site or in the right shoulder. The most common complication is pain and is seen in 25-30% of patients[12]. It is thought that the negative pressure created in blind biopsies performed with the menghini method causes more pain after biopsy[13]. In the study of Weigand et al., in which 715 patients were evaluated, pain complications developed in 40 (5.6%) patients that did not require analgesics and in 13 (1.8%) patients that required analgesics[14]. Pain developed in a total of 31% of our patients. Most of these developed after blind biopsy and the difference between the two methods was significant. In the study of Vivas et al., 18% of patients developed pain, and the majority were women (30% vs. 15%)[15]. It was determined by Onay et al. that severe pain developed in 2.9% of patients with CHB who underwent USG-guided biopsy[16]. Pain developed in 21.9% of our patients who underwent biopsy with USG. Medication was required in only 9.3% (n=21) of these patients. In the our study, other minor complications such as nausea and vomiting were also at a lower rate after USG-guided biopsy. Bleeding is the most common cause of mortality in patients undergoing biopsy. Therefore, bleeding parameters should be closely monitored before and after biopsy. While intra or perihepatic bleeding can be seen in 20% of cases after percutaneous biopsy, blood transfusion may be required in approximately 1 in 500 biopsies[17-18]. Bleeding developed in only 0.5% of our patients, and these patients were patients who underwent blind biopsy. The incidence of biliary peritonitis is less than 2%. In our patients, bile leakage developed only in 2 patients who underwent blind biopsy.No major complications were observed after the USG-guided biopsy. None of the patients developed exitus. The size of the material obtained in the biopsy is important for the diagnosis. It is widely believed that if the biopsy material is 15 mm long, it will contain at least 6-8 portal areas and this will be sufficient[19]. The average size of the biopsy material we obtained from our patients was 11.8 mm. Twelve patients with insufficient material were those who underwent blind biopsy. In the study of Flemming et al., which included 100 chronic hepatitis C patients, it was reported that higher quality samples were obtained than blind biopsy in liver biopsies performed under USG guidance[20].

CONCLUSION

Liver biopsy is still a reliable method in terms of complications in the evaluation of fibrosis in patients followed up with CHB. In our study, it was found that minor com-

plications were seen less frequently when performed with USG. Although major complications in blind biopsy are very rare, they were not seen in patients who underwent USG-guided biopsy.

Conflict of interest

There is no person/organization that financially supports the work and the authors have no conflict of interest.

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Sağlık Çalışanlarının COVID-19 Aşısı Yaptırma Konusundaki Tutumlarını Etkileyen Faktörler

Factors Affecting the Attitudes of Healthcare Workers to Get COVID-19 Vaccination

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Öz

Amaç Sağlık çalışanlarında SARS-CoV-2 maruziyeti riski genel toplumdan daha yüksektir. Tıbbi konularda toplumda rol model olan sağlık çalışanlarının aşılara karşı tutumu toplumun da yaklaşımını etkilemektedir. Bu çalışma ile Erzurum ilinde görev yapan sağlık çalışanlarının COVID-19 aşısına karşı tutumlarının ve aşı kararsızlığı yaşayanlarda etkili faktörlerin değerlendirilmesi amaçlanmıştır.

Yöntem Kesitsel tipte planlanan bu çalışma, 2021 yılı Ocak-Mayıs arasında Erzurum ilinde görev yapan sağlık çalışanlarına online anket formu ile uygulandı. Verilerin analizi SPSS v25 programı ile yapıldı.

Bulgular Araştırmaya katılan 235 sağlık çalışanının yaş ortalaması 36.3±9.2 yıl ve %56.2'si kadındı. Katılımcıların %69.4'ü hekim, %20'si hemşire, %10.6'sı destek personeli olup, meslekte çalışma süresi ortalaması 12.1±9.2 yıldı. Katılımcıların %27.6'sı aşı yaptırmak istemiyor veya kararsızdı. Sağlık çalışanlarının %75.3'ü COVID-19 aşısını yakınlarına veya kendilerine danışanlara önerebileceğini belirtti. COVID-19 aşısı konusunda kararsız olan veya yaptırmak istemeyen katılımcıların %32.3'ü yan etkiler konusunda endişe duyduklarını, %26.1'i aşı hakkında yeterli bilgiye sahip olmadıklarını belirtmişti. Erkek cinsiyet ve meslekte çalışma süresindeki artış aşıya karşı tutumu olumlu yönde etkileyen faktörler olarak öne çıkmıştır. Katılımcılardan mevsimsel influenza aşısını düzenli yaptıranlar arasında COVID-19 aşısına olumlu yaklaşanların sıklığı %88.6 iken, yaptırmayanlarda %68.6 idi (p<0.001). Katılımcı hekimlerde COVID-19 aşısını yakınlarına/kendilerine danışanlara önerme oranı diğer sağlık çalışanlarına göre anlamlı düzeyde daha yüksekti (p=0.025).

Sonuç Toplumda gün geçtikçe daha da önemli bir problem haline gelen aşı kararsızlığı, sağlık çalışanları arasında da yüksek oranlarda görülmekte ve genel olarak bu durumun nedeni bilgi eksikliği gibi görünmektedir. Daha etkin bir meslek içi eğitim ile bu konudaki endişe ve bilgi eksikliklerinin giderilmesi gerekmektedir.

Anahtar Kelimeler Aşı kararsızlığı, aşı reddi, bağışıklama, COVID-19, sağlık çalışanı

Abstract

Objective *Healthcare workers are at high risk of exposure to SARS-CoV-2. Attitudes of healthcare workers towards vaccines also affect the approach of society to vaccines. In this study, it was aimed to evaluate the attitudes of healthcare workers in Erzurum towards the COVID-19 vaccine and the factors affecting vaccine hesitations.*

Methods *This cross-sectional study was applied to healthcare workers in Erzurum between January and May 2021 with an online questionnaire. SPSS v25 program was used in data analysis.*

Results *The mean age of 235 healthcare workers participating in the study was 36.3±9.2 years and 56.2% were women. 69.4% of the participants were physicians, 20% were nurses and 10.6% were support personnel. The rate of vaccine hesitancy/rejection among the participants was 27.6%. 32.3% of the participants who have COVID-19 vaccine hesitancy/rejection, stated that they were worried about side effects and 26.1% stated that they did not have enough information about the vaccine. Male gender and increase in working time were factors that positively affected attitudes towards vaccination. The approach to the COVID-19 vaccine was more positive in the participants who had the seasonal influenza vaccine regularly (p<0.001). The rate of recommending the COVID-19 vaccine by physicians participating in the study was higher than other healthcare workers (p=0.025).*

Conclusion *Vaccine hesitancy is an increasing problem in society and it's also high among healthcare workers. In general, the reason for this situation is the lack of information. It is necessary to eliminate the concerns and lack of knowledge on this subject with regular vocational training.*

Keywords *Vaccination hesitancy, vaccine refusal, immunization, COVID-19, healthcare workers*

GİRİŞ

Bağışıklama temel sağlık hizmetlerinin önemli bir parçasıdır. Bulaşıcı hastalıklardan korunmada en etkili yöntemlerden biri olduğu bilinen aşılar sayesinde dünya genelinde her yıl yaklaşık 2-3 milyon ölümün önüne geçildiği bilinmektedir[1]. Dünya Sağlık Örgütü (DSÖ), bağışıklamayı aşı ile önlenebilen hastalıkların ve bu hastalıklar sonucunda meydana gelen ölümlerin engellenmesinde en maliyet etkili müdahalelerden biri olarak kabul etmektedir[2]. Aşılar, tedarik zinciri ve hizmet sunumu dahil on yıl boyunca maliyetlerinden yaklaşık 16 kat daha fazla net getiri sağlamaktadır[3].

Aşılar koruyucu etkilerini direkt ve indirekt olarak gösterir. Direkt etkiler aşılı bireylerde hastalık insidansının azalması şeklindedir. İndirekt etkileri ise toplumda aşılanmamış bireylerin de o hastalıktan korunmasıdır[4]. Bu "toplumsal bağışıklık" olarak adlandırılır. Dünya Sağlık Örgütü, toplumsal bağışıklığı; "bulaşıcı bir hastalığa karşı aşılama veya enfeksiyonun geçirilmesi yoluyla bağışıklık kazanılması" olarak tanımlamaktadır[5]. Yani bir bulaşıcı hastalığa karşı toplumsal bağışıklık sağlanması ile söz konusu hastalığa bağışık olmayan bireyler de korunabilmektedir. Aşıların toplum sağlığı açısından kanıtlanmış yararlarına rağmen, özellikle son iki dekadda dünyada "aşı kararsızlığı" ve "aşı reddi" kavramları ile ifade edilen aşılara karşı olumsuz bir tutum ortaya çıkmıştır. Aşı kararsızlığı, DSÖ tarafından "hizmetlerin mevcut olmasına rağmen aşıların kabulünde gecikme veya bazı aşıları reddetme" olarak tanımlanmaktadır. Aşı kararsızlığı kayıtsızlık, erişim güçlüğü, güven gibi pek çok faktörden etkilenen, söz konusu aşıya ve zamana göre değişebilen kompleks bir olgudur[6]. DSÖ, 2019'da açıkladığı küresel sağlığı tehdit eden on problem arasında aşı kararsızlığına da yer vermiştir[7].

Çin'in Wu-han kentinden 29 Aralık 2019'da bildirilen COVID-19, 11 Mart 2020'de pandemi olarak ilan edilmiştir. Şu ana kadar dünya genelinde COVID-19 kaynaklı 350 milyondan fazla vaka ve 5,5 milyondan fazla ölüm görülmüştür[8]. COVID-19 ile karşılaşma riski en yüksek olan meslek grubu sağlık çalışanlarıdır[9]. Türk Tabipler Birliği'ne göre Türkiye'de 31 Mayıs 2021 tarihine kadar 403 sağlık çalışanı COVID-19 nedeniyle hayatını kaybetmiştir, 220 binden fazla sağlık çalışanında da PCR pozitifliği saptandığı tahmin edilmektedir[10]. Dünya genelinde de Ocak 2020-Mayıs 2021 tarihleri arasında ortalama 115.500 sağlık çalışanının COVID-19 nedeniyle hayatını kaybettiği DSÖ tarafından tahmin edilmektedir. Dünya Sağlık Örgütü, önde gelen risk grubu olan sağlık çalışanlarının hızla aşılanması gerektiğini bildirmektedir[11]. Sağlık çalışanlarının topluma rol model olmaları nedeniyle de aşılanması önemlidir. Şüphesiz ki, topluma aşı konusunda en güvenilir bilgiyi sağlık çalışanları sunmaktadır[12]. Sağlık çalışanının kendisine veya çocuğuna söz konusu aşıyı yaptırmış olması da güven verici olup toplumda aşı kararsızlığını gidermede etkilidir[13,14]. Salgının kontrol altına alınabilmesi için kişisel koruyucu önlemlerin yanında toplumsal bağışıklığı sağlamak üzere aşılama programlarının kararlı şekilde uygulanması oldukça önemlidir.

Bu çalışma ile Erzurum ilinde görev yapan sağlık çalışanlarının COVID-19 aşısına karşı tutumlarının ve aşı kararsızlığı yaşayanlarda etkili faktörlerin değerlendirilmesi amaçlanmıştır.

YÖNTEM

Kesitsel tipte planlanan çalışma, 2021 yılı Ocak-Mayıs arasında Erzurum ilinde yürütüldü. Çalışma evrenini Erzurum il merkezinde görev yapmakta olan 7210 sağlık çalışanı oluşturmaktaydı. Pandemi şartları nedeniyle internet ortamında ulaşılabilen 278 sağlık çalışanı ankete cevap verdi. Uygun şekilde doldurulduğu değerlendirilen 235 katılımcının verileri araştırmaya dahil edildi. Çalışma için T.C. Sağlık Bakanlığı ve Atatürk Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan gerekli izinler alındı.

Çalışma verileri, Google Formlar üzerinden oluşturulan online anket formu kullanılarak toplandı. Toplam 26 sorudan oluşan anket formunda; sosyo-demografik, görev,

meslek, kurum, kronik hastalık durumu, varsa çocuklarının rutin aşılarını ve mevsimsel influenza aşısı yaptırma durumu, evde risk grubu birey bulunma durumu, kendisi ve yakınlarının COVID-19 hastalığı geçirme durumu ve hastalığa yakalanma endişesi, COVID-19 aşısı yaptırma durumu, varsa aşı yaptırmama veya kararsızlık durumunun sebebi, aşıyı kendilerine danışanlara önerme durumu ve toplumda aşı kararsızlığı nedenleri konusundaki düşünceleri sorgulandı.

Verilerin analizi SPSS v25 programı aracılığı ile yapıldı. Ölçümle belirlenen veriler ortalama±standart sapma, sayımla belirlenen veriler sayı ve yüzde olarak sunuldu. Kategorik değişkenler arasındaki ilişkilerin değerlendirilmesinde ki-kare testi kullanıldı. Regresyon modelinde yer alacak (sağlık çalışanlarının toplumda rol model olduğuna inanma, aşı yaptırma kararının kişilerin özerklik hakkı kapsamında değerlendirilmesi gerektiğine inanma) bağımsız değişkenleri alt kategorileri birleştirilerek (evet-hayır) analize dahil edildi. Aşı yaptırma kararı üzerinde etkili risk faktörlerini değerlendirmek üzere tek değişkenli regresyon analizinde anlamlı çıkan değişkenler kullanılarak backward LR yöntemi ile binary lojistik regresyon analizi uygulandı. Tüm analizlerde $p<0.05$ olduğunda sonuçlar anlamlı kabul edildi.

BULGULAR

Çalışmaya dahil edilen 235 katılımcının yaş ortalaması 36.3±9.2 yıl, %56.2'si kadın ve çoğunluğunu doktorlar (%69.4) oluşturuyordu. Katılımcıların meslekte çalışma süreleri ortalama 12.1±9.2 yıl olup, %13.2'sinin tanı almış bir kronik hastalığı mevcutken, %33.2'sinin evinde risk grubu en az bir birey (kronik hastalıklı, 65 yaş üzeri, gebe vb.) bulunuyordu. Tablo 1'de katılımcıların sosyo-demografi özellikleri sunuldu.

Tablo 1. Katılımcıların Sosyodemografik Özellikleri

Sosyodemografik Özellik	Sayı	Yüzde
Cinsiyet		
Kadın	132	56.2
Erkek	103	43.8
Medeni durum		
Evli	168	71.5
Bekar/Dul/Boşanmış	67	28.5
Görev		
Doktor	163	69.4
Hemşire	47	20.0
Personel	25	10.6
Görev yapılan kurum		
Sağlık Bakanlığı	147	62.6
Üniversite	88	37.4
Kronik hastalık		
Var	31	13.2
Yok	204	86.8
Çocuk sahibi olma durumu		
Evet	143	60.9
Hayır	92	39.1
Evde risk grubu birey		
Var	78	33.2
Yok	157	66.8

Çocuk sahibi olan katılımcıların tamamı çocuklarının rutin aşılarını eksiksiz yaptırmıştı. Mevsimsel grip aşısını ise katılımcıların sadece %18.7'si her yıl düzenli olarak yaptırıyordu ve meslek grupları arasında mevsimsel grip aşısı yaptırma durumuna göre anlamlı düzeyde bir ilişki yoktu ($p>0.05$).

Katılımcıların %68.1'i COVID-19 geçirmemiş ve %73.2'si hastalığa yakalanma konusunda endişeli olduğunu belirtmişti. Ev halkı ya da birinci derece yakınlarından COVID-19 geçirmiş katılımcıların sıklığı ise %54.5 ve %91.5'i yakınlarının hastalığa yakalanması konusunda endişe içindeydi. Bununla beraber katılımcıların %27.6'sı COVID-19 aşısı yaptırmak istemiyor ya da kararsızdı. Aşı konusunda kararsızlık yaşayan ya da yaptırmak istemeyenlerin

%32.3'ü yan etkiler konusunda duyduğu endişeyi, %26.1'i aşı hakkında yeterli bilgisinin bulunmamasını ve %15.4'ü ise aşının koruyuculuğu konusunda şüpheler bulunmasını neden olarak belirtmişti (Tablo 2).

Tablo 2. Katılımcıların aşı reddi ya da kararsızlığı nedenleri

Nedenler	**Sayı**	**Yüzde**
Yan etkiler konusunda endişe duyma	21	32.3
Aşı hakkında yeterli bilgi olmaması	17	26.1
Aşının koruyuculuğu konusunda şüpheler olması	10	15.4
Diğer	9	13.9
Aşının üreticisine güvenmeme	5	7.7
Aşının gereksiz olduğuna inanma	3	4.6
Toplam	**65**	**100.0**

Cinsiyet, medeni durum, görev, evde risk grubu birey (65 yaş üzeri/kronik hastalığı olan/gebe) bulunması, çocuk sahibi olma ve COVID-19 hastalığı geçirme durumu ile aşı yaptırma kararı arasında anlamlı düzeyde ilişki yoktu ($p>0.05$). Katılımcılardan mevsimsel influenza aşısını düzenli yaptıranlar arasında COVID-19 aşısına olumlu yaklaşanların sıklığı %88.6 iken, yaptırmayanlarda %68.6 idi ($p<0.001$, OR= 3.6, CI: 1.3-9.5). Katılımcı hekimler ile hemşire ve diğer sağlık personeli arasında COVID-19 aşısını yakınlarına veya kendilerine danışan kişilere önerme konusunda (sırasıyla %80.4, %63.9) anlamlı düzeyde fark bulunuyordu ($p=0.025$).

Katılımcılar, toplumda aşı kararsızlığının başlıca nedenlerini yan etkiler (%19.3), içerikteki maddelere güvenmeme (%16.6) ve bilgisizlik (%13.3) olarak belirtmişti. Tablo 3'te katılımcıların toplumdaki aşı kararsızlığı ve reddinin nedenleri konusundaki görüşlerinin dağılımı sunuldu.

Tablo 3. Katılımcıların toplumda aşı kararsızlığı ve reddinin nedenleri konusundaki görüşlerinin dağılımı

Nedenler	**Sayı**	**Yüzde**
Yan etkiler	166	19.3
İçeriğindeki maddeler	143	16.6
Bilgisizlik	115	13.3
Etkinliğine güvensizlik	111	12.9
Korunma dışında amaçlarla yapıldığına inanılması	87	10.1
Düşük eğitim düzeyi	87	10.1
Aşıların ticari amaçlarla çıkarıldığına inanılması	78	9.0
Sağlık sistemine güvensizlik	55	6.4
Dini nedenler	20	2.3
Toplam*	**862**	**100.0**

*: Sonuçlar çoklu yanıt olarak verildiğinden toplam, katılımcı sayısını aşmaktadır.

Katılımcıların %79.0'u rutin programa dahil edilen aşıları tereddüt etmeden kendisine ve çocuğuna yaptırabileceğini, %89.8'i aşı konusunda sağlık çalışanlarının toplumsal sorumluluklarının bulunduğunu belirtmişti. Sağlık çalışanlarının %55.3'ü bireylerin aşı yaptırma konusundaki kararlarının özerklik hakkı kapsamında değerlendirilmesi gerektiğini düşünüyordu.

Yapılan lojistik regresyon analizinde cinsiyet, meslekte çalışma süresi, sağlık çalışanlarının toplumda rol model olduğuna inanma ve aşı yaptırma kararının özerklik hakkı kapsamında değerlendirilmesi gerektiğine inanma risk faktörleri olarak ön plana çıktı. Lojistik regresyon analizi sonuçları Tablo 4'te sunuldu.

Tablo 4. Lojistik regresyon analizi sonuçları

Değişkenler	B (SE)	Wald	p	Exp(B)	%95 CI
Cinsiyet (erkek)	0.971 (0.354)	7.535	0.006	2.640	1.320-5.281
Meslekte çalışma süresi	0.069 (0.022)	9.621	0.002	1.071	1.026-1.119
Evde 65 yaş üzeri birey (evet)	1.162 (0.617)	3.550	0.060	3.197	0.954-10.711
Rol model inancı (evet)	1.600 (0.390)	16.844	< 0.001	4.955	2.307-10.642
Özerklik hakkı düşüncesi (evet)	-1.085 (0.361)	9.041	0.003	0.338	0.167-0.685
R^2= 0.219 (Cox&Snell), 0.317 (Nagelkerke), $X^2(8)$= 4.885 (Hosmer&Lemeshow)					

TARTIŞMA

Bulaşıcı hastalıklardan korunmanın bilinen en etkili yolu aşılardır. Aşıların kabulünde aşının türü, aşılara erişim, üreticilere güvensizlik gibi pek çok faktör rol oynamaktadır[6]. Bununla birlikte, tıbbi konularda bilgi ve birikimiyle topluma yol gösterici pozisyonda olan sağlık çalışanlarının aşılara karşı tutumu da toplumun yaklaşımını etkileyebilir. Uygun iletişim teknikleri ve uygun bilgilendirici içerik, aşı kararsızlığını önlemede etkili olabilir[15]. Kendisi aşı kararsızlığı yaşayan sağlık çalışanı topluma aşıyı önermekten de kaçınmaktadır[16]. Dolayısıyla sağlık çalışanlarının aşı kararsızlığı yaşamaları, başta kendi sağlıkları olmak üzere toplum sağlığını da olumsuz etkileyebilmektedir.

Bu çalışmayla, Erzurum il merkezinde görev yapmakta olan sağlık çalışanlarının COVID-19 aşısına karşı tutumları ile etkili faktörler değerlendirilmiş ve sağlık çalışanlarının %10.6'sının aşı yaptırmayı düşünmediği, %17'sinin ise kararsız olduğu belirlenmiştir. Aşı geliştirme çalışmaları devam ederken İzmir'deki sağlık çalışanlarının %68.6'sı etkili ve güvenli bir aşı bulunduğunda yaptıracağını, %19.9'u kararsız olduğunu ve %11.4'ü yaptırmayacağını belirtmiştir[17]. Ülkemizde 1015 tıp fakültesi öğrencisinin katıldığı bir başka çalışmada ise COVID-19 aşısı kullanıma sunulduğunda sadece %29.2'sinin yaptırmak istediği bildirilmektedir[18]. Aşı kararsızlığı konusunda diğer ülkelerden bildirilen sonuçlar da benzerdir. İngiltere ve Fransa'da yapılan çalışmalarda COVID-19 aşısı yaptırma konusunda sırasıyla katılımcıların %17 ve %22.4'ünün tereddüt yaşadığı ya da yaptırmak istemediği bildirilmektedir. Fransa'da sağlık çalışanları arasında ise bu sıklık %18.5'tir[19,20]. Çalışma sonuçları dünyada COVID-19 aşı kararsızlığının %20-50 arasında değiştiğini göstermektedir[21–23]. Çalışmamızdaki aşı kararsızlığı oranları literatürdeki diğer çalışmalarla benzer bulunmuştur. Bununla birlikte literatürdeki diğer çalışmaların henüz aşı geliştirme çalışmaları devam ederken yapılmış olmasına karşın çalışmamızın COVID-19 bağışıklama programı yürütülmeye başlandıktan sonra gerçekleştirilmesi ile aşı kararsızlığı oranları görece daha düşük bulunmuş olabilir.

Çalışmamızda medeni durum, görev, evde risk grubu birey (65 yaş üzeri/kronik hastalığı olan/gebe) bulunması, çocuk sahibi olma durumu, COVID-19 hastalığı geçirme durumu ile aşı yaptırma kararı arasında anlamlı düzeyde bir ilişki gözlenmemiştir. Bununla birlikte literatürle benzer şekilde erkek cinsiyet ve meslekte çalışma süresi aşıya karşı tutumu olumlu yönde etkileyen faktörler olarak öne çıkmıştır (Tablo 4). Yurt içinde yürütülen çalışmalarda COVID-19 aşısı olma isteği erkeklerde, genç yaş gruplarında ve sağlık çalışanlarında yüksek olarak bildirilmektedir[17,24]. Fransa ve İsrail'de yürütülen çalışmalarda ileri yaş, erkek cinsiyet, COVID-19 korkusu, sağlık çalışanı olma ve bireysel COVID-19 risk algısı, çocuk sahibi olma COVID-19 aşısının kabulü ile ilişkili bulunmuştur[20,25]. ABD'de yürütülen çalışmaya göre ise genç yaş, siyah ırk ve düşük eğitim seviyesi aşı kararsızlığının ana belirleyicileri olarak bildirilmektedir[23]. İlgili literatürde COVID-19 aşısına karşı tutumu etkileyen sosyodemografik özelliklerin, muhtemelen sosyokültürel nedenlerle bölgeler arasında farklılık

gösterdiği göze çarpmaktadır. Erkeklerde COVID-19 nedenli mortalitenin kadınlara göre daha yüksek olması[26], aşıya karşı sergilenen olumlu tutumla ilişkili olabilir. Bunun yanında kadınların aşı konusunda kararsızlık yaşamalarının sebebi gebelik, emzirme ya da gebelik planları olabilir.

Bu çalışmada mevsimsel influenza aşısını düzenli yaptıran sağlık çalışanlarında COVID-19 aşısı yaptırma isteği, literatürle benzer şekilde düzenli mevsimsel influenza aşısı yaptırmayanlara göre (yaklaşık 3.5 kat) yüksek bulunmuştur[17,23,24]. Her iki enfeksiyonun benzer klinik özellikler sergilemesi bireylerde benzer risk algısı oluşturuyor gibi görünmektedir.

Aşıların kabulünü etkileyen bağlamsal, bireysel ve aşıya/aşılamaya bağlı faktörler bulunmaktadır[27]. Bu çalışmada aşı kararsızlığı yaşayan sağlık çalışanlarında ve toplumda en sık nedenin yan etkiler konusunda duyulan endişe (sırasıyla %32.3 ve %19.3) olduğu görülmektedir. Konuyla ilgili çalışmalarda da aşı kararsızlığı nedenleri arasında başta aşı yan etkilerinden çekinme olmak üzere aşıların içeriğine, etkinliğine ve aşı geliştiricilere güvenmeme ana nedenler olarak bildirilmektedir[17,21,23–25]. Yeni bir ürün olan COVID-19 aşısına yönelik aşı kararsızlığıyla ilgili olarak daha çok içerik ve özellikle uzun vadedeki yan etki endişelerinin ön plana çıktığı görülmektedir. Hem aşı çalışmaları hem de COVID-19 pandemisi konusunda yaşanan bilgi kirliliği, doğru bilgiye ulaşılmasını zorlaştırmakta ve toplumda tereddüte yol açmaktadır.

Bu çalışmada sağlık çalışanlarının %75.3'ünün COVID-19 aşısını yakınlarına ya da kendilerine danışan kişilere önerebileceği görülmüştür. Sağlık çalışanları, dünya genelinde aşılar hakkındaki en güvenilir bilgi kaynağı olarak görülmektedir[12,28–31]. Çalışmamızda hekim ve hekim dışı sağlık çalışanları arasında aşıyı yakınlarına önerme konusunda anlamlı fark gözlenmiştir. Şüphesiz ki, toplumdaki aşı kararsızlığını gidermede yalnızca hekimlerin değil diğer sağlık çalışanlarının da aşıya karşı tutumları önemlidir.

Çalışma verileri, pandemi şartları nedeniyle çevrimiçi bir anket yardımıyla toplanmış ve yoğun çalışma ortamı nedeniyle sınırlı sayıda katılımcıya ulaşılabilmiştir. Bununla birlikte; bu çalışma bölgemizde daha önce konuyla ilgili yapılmış bir çalışma bulunmaması ve ilgili literatürdeki çalışmaların çoğunlukla aşılar kullanıma sunulmadan önce yapılmış olması nedeniyle önemlidir.

SONUÇ

Toplumda gün geçtikçe daha da önemli bir problem haline gelen aşı kararsızlığı, sağlık çalışanları arasında da yüksek oranlarda görülmekte ve genel olarak bu durumun nedeni bilgi eksikliği gibi görünmektedir. Mevcut COVID-19 aşıları için etkinlik, güvenlik ve yan etkilere ilişkin pek çok bilimsel araştırmaya rağmen sağlık çalışanlarında görülen bilgi eksikliği, aslında pandemi gibi olağanüstü koşullarda önde gelen belirleyicilerin toplumdan farklı olmadığını göstermektedir. Sağlık çalışanlarının hem SARS-CoV-2 etkeni ile karşılaşma riskinin diğer kesimlere göre çok daha yüksek olması hem de toplumda rol model olmaları nedeniyle eğitim çalışmaları için öncelikli hedef grup olarak düşünülmesi gerekmektedir. Sağlık çalışanlarının mezuniyet öncesi eğitimlerinde de toplumda giderek artan aşı kararsızlığına yönelik olarak verilecek eğitimler etkili bir müdahale yöntemi olabilir. Aynı zamanda tüm sağlık çalışanlarına doğru, güncel ve bilimsel bilgi kaynaklarına ulaşım imkanları sağlanmalıdır.

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The Predictive Power of Biological Markers for Malignant Thyroid Nodules. Single-Center Experience

Malign Tiroid Nodülleri için Biyolojik Belirteçlerin Prediktif Değeri. Tek Merkez Deneyimi

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Abstract

Aim Thyroid nodules are mostly benign. Although it varies by region, 5.4% of nodules in men and 6.5% of nodules in women may be malignant. In rural regions where a radiologist, an endocrine surgeon, a cytologist, and an endocrinologist are not present, difficulties may be experienced in the management of thyroid nodules.

Material and Method This present study aims to determine if it is possible to comment on whether the nodule is malignant by evaluating the biological markers in patients with thyroid nodules.

Results We reviewed retrospectively the data of patients between January 2019 and September 2020 who underwent total thyroidectomy in terms of thyroid ultrasonography results, thyroid fine-needle aspiration biopsy results, neutrophil, platelet, lymphocyte, red blood cell, and mean erythrocyte volume (MCV) values, histopathological examination results of thyroid specimens. Subsequently, we calculated Mentzer index, Systemic immune-inflammatory index, and neutrophil-lymphocyte ratio for each patient.

Conclusion 140 patients were included in the study. 110 (78.6%) of the patients were female and 30 (21.4%) were male. The mean age of the patients was 48 ± 12.5 (20-76). There was no statistically significant difference in Mentzer index, Systemic inflammatory index, and neutrophil-lymphocyte ratios between patients with malignant and benign thyroid nodules.

Keywords Biological markers have limited predictive power in the management of thyroid nodules. Therefore, the use of biomarkers that we have studied in the treatment of thyroid nodules does not seem possible at present.

Özet

Amaç *Tiroid nodülleri çoğunlukla benign özelliktedir. Yerleşim bölgelerine göre değişmekle birlikte erkeklerde nodüllerin % 5,4'ü, kadınlarda ise % 6,5'i malign olabilir. Radyoloji, endokrin cerrahisi, patoloji ve endokrinoloji uzmanlarının bulunmadığı kırsal bölgelerde tiroid nodüllerinin yönetiminde zorluklar yaşanabilir. Çalışmamızda, tiroid nodülü olan hastalarda bazı biyolojik belirteçlerin analizi ve nodülün benign malign ayırımı açısından öneminin belirlemesi amaçlanmaktadır.*

Gereç ve Yöntem *Ocak 2019-Eylül 2020 tarihleri arasında total tiroidektomi yapılan hastaların tiroid ultrasonografi sonuçları, tiroid ince iğne aspirasyon biyopsi sonuçları, tiroidektomi örneklerinin histopatolojik inceleme sonuçları, nötrofil, trombosit, lenfosit, eritrosit sayıları ve ortalama eritrosit hacmi (MCV) değerleri retrospektif olarak gözden geçirildi. Daha sonra her hasta için Mentzer indeksi, Sistemik immün-inflamatuar indeks ve nötrofil-lenfosit oranları hesaplandı*

Bulgular *Çalışmaya 140 hasta dahil edildi. Hastaların 110'u (% 78,6) kadın, 30'u (% 21,4) erkekti. Hastaların yaş ortalaması 48 ± 12.5 (20-76) idi. Mentzer indeksi, Sistemik inflamatuar indeks ve nötrofil-lenfosit oranlarında malign ve benign tiroid nodülleri olan hastalar arasında istatistiksel olarak anlamlı fark yoktu.*

Sonuç *Biyolojik belirteçlerin tiroid nodüllerinin tedavisinde sınırlı prediktif gücü vardır. Bu nedenle tiroid nodüllerinin tedavisinde halihazırda çalıştığımız biyobelirteçlerin kullanımı mümkün görünmemektedir.*

Anahtar Kelimeler *Mentzer Index, Systemic Inflamatuar Index, Neutrophil to Lymphocyte Ratio, Thyroid Nodule, Thyroid Cancer*

INTRODUCTION

Thyroid nodules are present in 19% - 68% of the population and are more common in women and older[1,2]. Additionally, the thyroid nodules are mostly benign. Although it varies by region, 5.4% of nodules in men and 6.5% of nodules in women may be malignant[3]. The incidence rate of malignant thyroid nodules is increasing day by day. It has been reported in various publications that the reason for this situation may be the detection of previously undetected small malignant nodules due to the developments in imaging techniques rather than the increase in the frequency of the disease[4]. Detection of malignant thyroid nodules when they are much smaller in size, determination of new cytological and pathological criteria, performing molecular tests, and current developments in treatment methods enable the management of these nodules in a personalized way, with algorithmic and evidence-based care[5]. For this purpose, national and international guidelines for the follow-up and treatment of thyroid nodules have been determined[6,7]. In centers where a radiologist, an endocrine surgeon, a cytologist, and an endocrinologist are present, the follow-up and treatment of thyroid nodules can be performed accurately according to these guidelines. However, in rural regions where these facilities are not available, difficulties may be experienced in the management of the treatment of thyroid nodules. Patients in these regions can be consulted to central hospitals by specialists. Still, failures may occur in the diagnosis from time to time due to a lack of basic information that should be given about the patient, which may cause physician and patient dissatisfaction due to overtreatment or undertreatment[8].

There are various studies in the literature on the use of biological markers in kidney failure, in inflammatory conditions such as appendicitis, cholecystitis, and cancer diseases to predict the course of the current disease[9-12]. Biological markers may assist specialists working in rural hospitals in the management of thyroid nodules[9,13].

This present study aims to determine if it is possible to comment on whether the nodule is malignant by evaluating the biological markers in patients with thyroid nodules.

MATERIAL and METHODS

The Ethics Committee of the Sakarya University School of Medicine approved the study and data collection on 1st of October 2021 (71522473/050.01.04/64743/437).

We reviewed retrospectively the data of patients who underwent total thyroidectomy in our clinic between January 2019 and September 2020. We included patients over 18 years of age who have not had previous thyroidectomy surgery and patients without a history of hematological disease.

In our clinic, we examine every patient thought to have a thyroid nodule by ultrasonography (US), and we report these USs according to the Thyroid Imaging Reporting & Data System (TIRADS). When we detect a thyroid nodule on the US, we perform a fine needle biopsy (FNB) for nodules extending out of the thyroid tissue, for subcapsular nodules located adjacent to the recurrent laryngeal nerve or trachea, for nodules showing rim calcification, for over 1 cm, solid and hypoechoic nodules, for nodules with suspected malignancy lymph node accompanied, for nodules with suspected malignancy such as irregular borders on ultrasound. These biopsies are reported by pathologists using the BETHESDA classification.

We evaluated the patients' most recent preoperative thyroid ultrasonography (US) and thyroid fine-needle aspiration biopsy (FNAB) results, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), neutrophil, platelet, lymphocyte, red blood cell, mean erythrocyte volume (MCV) values, histopathological examination results of thyroid specimens. We calculated Mentzer index (MI) (MCV/RBC), Systemic immune-inflammatory index (SII) (Plt x neutrophil / lymphocyte), neutrophil-lymphocyte ratios (NLR) for each patient.

Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. Accordingly, the independent sample t-test and the Kruskal Wallis test were used to compare the numeric variables between groups. The numeric variables were presented as mean ± standard deviation or median [Q1 – Q3]. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A p-value <0.05 was considered significant. Receiver operator characteristic (ROC) curve analysis was used to identify the best cut-off value and assess the performance of the test score for appendicitis. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.)

RESULTS

140 patients were included in the study. 110 (78.6%) of the patients were female and 30 (21.4%) were male. The mean age of the patients was 48 ± 12.5 (20-76). Histopathological examination of total thyroidectomy specimens of 140 patients included in the study revealed that while 53 patients had malignant nodules (37.9%), 87 patients (62.1%) did not. When the blood parameters were examined, the mean TSH value was 2.14 mU/ml ± 7.32 mU/ml (0.0-76.7), the mean fT3 value was 4.8 pg/ml ± 1.2 pg/ml (2.5-3.6), the mean fT4 value was 12.5 ng/dl ± 3.49 ng /dl (2.4-41.1), mean neutrophil value was 4.2 (10^3/uL) ± 1.5 (10^3/uL) (1.8-14.3), mean lymphocyte value was 2.2 (10^3/uL) ± 0.5 (10^ 3/uL) (0.8-4.1), mean platelet value was 277.1 ± 198.8 (128-2500), mean MCV value was 85.6 fL ± 10.2 fL (29-99.4), mean Rbc value was 4.6 (10^6/uL) ± 0.4 (10^6/uL) (3.6-7.1). Ultrasonographic examination of the patients revealed TIRADS 2 findings in 25 (18%) patients, TIRADS 3 findings in 54 (39%) patients, TIRADS 4 findings in 52 (37%) patients, and TIRADS 5 findings in 9 (6%) patients. Fine needle aspiration biopsy revealed Bethesda 2 findings in 61 (43.5%) patients, Bethesda 3-4 in 13 (9%) patients, Bethesda 5 in 54 (38.5%) patients, and Bethesda 6 in 13 (9%) patients (Table 1,2).

The mean MI was 18.7 ± 3.04 (6.04-25.7), the mean NLR was 2.08 ± 1.2 (0.6-11.5), and the mean SII was 584.2 ± 580.3 (140.8-5643.9) (Table 1,2).

Table 1: Classification of preoperative ultrasonographic examination and fine-needle aspiration biopsies according to postoperative histopathological examination results.

		Malignant	Benign	p Value
Ultrasonography	TI-RADS 1	0 0 (0%)	0 0 (0%)	0.00
	TI-RADS 2	5 (20%)	20 (80%)	
	TI-RADS 3	8 (14.8%)	46 (85.2%)	
	TI-RADS 4	32 (61.5%)	20 (38.5%)	
	TI-RADS 5	9 (100%)	0 (0%)	
Fine Needle Aspiration Cytology				
	Bethesda 1	0 (0%)	0 0 (0%)	0.00
	Bethesda 2	12 (19.7%)	49 (80.3%)	
	Bethesda 3-4	5 (42%)	7 (58%)	
	Bethesda 5	25 (46.3%)	29 (53.7%)	
	Bethesda 6	12 (92.3%)	1 (7.7%)	
TI-RADS: Thyroid Imaging Reporting & Data System				

Table 2: Distribution of patients in terms of gender, age, blood parameters, Metzer index, neutrophil-lymphocyte ratio, and systemic inflammatory indices.

		Malign	Benign	p-Value
Gender	Female	40 (36.4%)	70 (63.6%)	
	Male	13 (43.3%)	17 (56.7%)	
Age		47.1 ± 13.6 (20-76)	49.9 ± 11.7 (21-76)	0.19
Thyroid Stimulating Hormone		1.8 mU/ml ± 2.6 mU/ml (0.0-17)	2.3 mU/ml ± 9.05 mU/ml (0-76.7)	0.05
Free Triiodotironin (fT3)		4.8 pg/ml± 1.4 pg/ml (2.5-13.6)	4.8 pg/ml± 1.1 pg/ml (2.7-12.5)	0.43
Free Tiroksin (fT4)		12.5 ng/dl ± 2.5 ng/dl (5.3-20.3)	12.5 ng/dl ± 3.9 ng/dl (2.4-41.1)	0.66
Neutrophil		4.5 (10^3/uL) ± 1.8 (10^3/uL) (2.28-14.1)	4.07 (10^3/uL) ± 1.3 (10^3/uL) (1.86-8.7)	0.10
Lymphocyte		2.1 (10^3/uL) ± 0.5 (10^3/uL) (0.8-3.3)	2.2 (10^3/uL) ± 0.6 (10^3/uL) (1.2-4.1)	0.98
Red Blood Cell (Rbc)		4.7 (10^6/uL) ± 0.4 (10^6/uL) (3.9-5.7)	4.5 (10^6/uL) ± 0.5 (10^6/uL) (3.6-7.1)	0.07
Platelet (Plt)		305.8 ± 313.9 (128-2500)	259.6 ± 59.3 (147-399)	0.56
Mean Corpuscular Volume (MCV)		85.6 fL ± 10 (29-96)	85.6 fL ± 10.4 (29-99.4)	0.83
Mentzer index		18.3 ± 2.9 (6-23.5)	18.9 ± 3.1 (6.9-25.7)	0.42
Neutrophil Lymphocyte Ratio (NLR)		2.3 ± 1.7 (1-11.5)	1.9 ± 0.8 (0.6-6.9)	0.10
Systemic Immune Inflammatory Index (SII)		715.2 ± 871.4 (224.2-5643.9)	504.5 ± 261.2 (140.8-1732.1)	0.11

According to the results of the histopathological examination, when the patients are categorized according to the presence of benign and malignant disease:

Patients With Malignant Thyroid Nodules

Malignant thyroid nodules were determined in 54 (38%) patients in histopathological examination. Forty (75%) of the patients were female, and 13 (25%) were male. The mean age of the patients was 47.1 ± 13.6 (20-76), mean TSH value was 1.8 mU/ml ± 2.6 mU/ml (0.0-17), mean fT3 value was 4.8 pg/ml ± 1.4 pg/ml (2.5-13.6), mean fT4 value was 12.5 ng/dl ± 2.5 ng/dl (5.3-20.3), mean neutrophil value was 4.5 (10^3/uL) ± 1.8 (10^3/uL) (2.28-14.1), mean lymphocyte value was 2.1 (10^3 /uL) ± 0.5 (10^3/uL) (0.8-3.3), mean Rbc value was 4.7 (10^6/uL) ± 0.4 (10^6/uL) (3.9-5.7), mean plt value was 305.8 ± 313.9 (128-2500), mean MCV value was determined as 85.6 fL ± 10 fL (29-96). US revealed TIRADS 2 findings in 5 (9%) patients, TIRADS 3 findings in 8 (15%) patients, TIRADS 4 findings in 32 (59%) patients, and TIRADS 5 findings in 9 (17%) patients. FNB revealed Bethesda 2.5 in 12 (22.2%) patients, Betheta 3-4 in 5 (9.4%) patients, Bethesda 5 in 25 (46.2%) patients, and Bethesda 6 in 12 (22.2%) patients (Table 1,2).

Mean MI was 18.3 ± 2.9 (6-23.5), mean NLR rate was 2.3 ± 1.7 (1-11.5), mean SII was 715.2 ± 871.4 (224.2-5643.9) (Table 1,2).

Patients With Benign Thyroid Nodules

Benign thyroid nodules were found in 86 (62%) patients in histopathological examination. Seventy (80%) of the patients were female and 17 (20%) were male. The mean age of the patients was 49.9 ± 11.7 (21-76). The mean TSH value of the patients was 2.3 mU/ml± 9.05 mU/ml (0-76.7), the mean fT3 value was 4.8 pg/ml ± 1.1 pg/ml (2.7-12.5), the mean fT4 value was 12.5 ng/dl ± 3.9 ng/dl (2.4-41.1), the mean neutrophil value was 4.07 (10^3/uL) ± 1.3 (10^3/uL) (1.86-8.7), the mean lymphocyte value was 2.2 (10^3/uL) ± 0.6 (10^3/uL)) (1.2-4.1), the mean Rbc value was 4.5 (10^6/uL) ± 0.5 (10^6/uL) (3.6-7.1), the mean Plt value was 259.6 ± 59.3 (147-399), the mean MCV value was 85.6 fL ± 10.4 fL (29-99.4). Ultrasonographic examination of the patients revealed TIRADS 2 findings in 20

(23.2%) patients, TIRADS 3 findings in 46 (54%) patients, and TIRADS 4 findings in 20 (23.2%) patients. Fine needle aspiration biopsy revealed Bethesda 2 in 49 (57%) patients, Betheta 3-4 in 7 (8.1%) patients, Bethesda 5 in 29 (33.7%) patients, and Bethesda 6 in 1 (1.2%) patients (Table 1,2). The mean MI was 18.9 ± 3.1 (6.9-25.7), the mean NLR was 1.9 ± 0.8 (0.6-6.9), the mean SII was 504.5 ± 261.2 (140.8-1732.1) (Table 1.2).

There was no significant difference in terms of age and gender between patients with malignant and benign diseases as a result of histopathological examination (p values 0.19, 0.48, respectively).

Although the rate of TIRADS 2 and 3 diseases in the US examination was higher in patients with benign thyroid nodules than in patients with malignant nodules, the rate of TIRADS 4 and 5 diseases in the US was statistically significantly higher in patients with malignant thyroid nodules (p= 0.00).

Bethesda 2,3,4 disease rate in fine-needle aspiration biopsy was found to be statistically significantly higher in patients with benign thyroid nodules in histopathological examination. Bethesda 5,6 disease rate in fine-needle aspiration biopsy was found to be statistically significantly higher in patients with malign thyroid nodules in histopathological examination. (p=0.00).

We evaluated the preoperative blood parameters of the patients, and no significant difference was found between the groups in terms of TSH, fT3, fT4, neutrophil, lymphocyte, RBC, PLT, MCV, MI, NLR, and SII in patients with malignant disease (respectively p. values: 0.05, 0.43, 0.66, 0.10, 0.98, 0.07, 0.56, 0.83, 0.42, 0.10, 0.11).

In the ROC analysis, it was observed that the MI (AUC: 0.46), NLR (AUC: 0.58), and SII (AUC: 0.57) failed to predict malignancy in thyroid nodules (Figure 1).

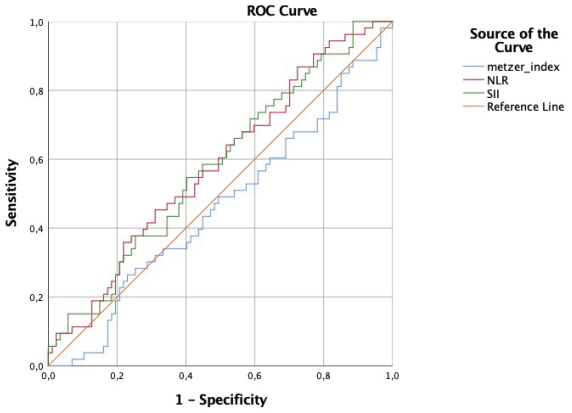

Figure 1: ROC analysis of the power of Mentzer index, Neutrophil Lymphocyte ratio, and Systemic immune-inflammatory index to predict Thyroid malignancy.

DISCUSSION

Since inflammation has a critical role in malignancy, there are studies proposing that NLR may also increase in malignancies in the literature[14–18]. Kocer D. et al. In their study with 232 patients who were operated on for multinodular goiter in 2015, stated that NLR might be used to differentiate malignant and benign thyroid diseases[19]. Song CY et al., in their study with 220 patients in 2021, stated that NLR might be used to predict lymph node metastases in the central neck region in Papillary Thyroid Cancer patients[9]. On the other hand, Ito Y et al. stated that the prognosis would be worse in the presence of distant metastases in PTC and in cases where NLR is >3[20]. In our study, we did not find a statistically significant difference in terms of NLR between patients with benign or malignant thyroid nodules. The reason why the difference between the two groups was not statistically significant may be the fact that NLR is not specific for malignancy; there may be other accompanying inflammatory diseases that may affect the rate of NLR together with the thyroid disease present in the patients. Furthermore, the inflammatory response may be different in each patient.

SII is calculated by multiplying platelet and NLR and also increases in cases of increased inflammation[21]. Various

studies in the literature propose that SII may be used to determine prognosis in patients with malignant disease[22–24]. Zhang et al. stated that SII could be used to predict central lymph node metastasis in PTC patients in their study conducted in 2021 with 406 PTC patients with no clinically detected central neck lymph node metastasis (cN0)[21]. In our study, we did not find a significant difference between patients with benign and malignant disease in terms of SII. Many factors can affect the platelet count, such as spleen diseases, thrombopoietin level, and hematological diseases[25]. Moreover, in addition to these factors that can affect the platelet count, we think that the fact that many factors may affect the neutrophil and lymphocyte counts, as we mentioned above, explains the lack of statistical difference in terms of SII between groups.

The Mentzer index is calculated by dividing the mean erythrocyte volume by the red blood cell, primarily used for the differential diagnosis of iron deficiency anemia and thalassemia[26,27]. Anemia occurs in half of the cancer patients due to many etiological factors[28]. We compared the patients with malignant thyroid nodules and benign thyroid nodules in terms of MI, due to our hypothesis that there may be an increase in the Mentzer index in patients with malignant thyroid nodules. No statistically significant difference was found between the groups. Anemia in cancer patients is mainly due to tumor-related blood loss, increased red blood cell (RBC) destruction, and decreased RBC production. The reason why there was no statistically significant difference between the groups may be the absence of these three etiological factors in thyroid malignancies.

In our study, we found that the rate of detection of malignancy in nodules reported as TIRADS 4 and 5 on the US was much higher than in TIRADS 2 and 3 nodules, consistent with the literature[29]. We observed that nodules reported as high stage according to the Bethesda classification on FNA, in accordance with the literature, were more malignant than the nodules reported as lower Bethesda stage on FNA.

Management of thyroid nodules is specified in current guidelines developed based on recent developments and evidence-based medicine[5]. Diagnosis and treatments performed regardless of these guidelines for various reasons may result in overtreatment or undertreatment (30,31).

Limitations of the study

The study was conducted in a single center and with a small number of patients.

CONCLUSION

Although there are studies proposing that biological markers may be used in the differential diagnosis of thyroid diseases, there are studies in the literature suggesting that these markers have limited predictive power in the management of thyroid nodules, as in our present study. For this reason, it may be recommendable to not manage thyroid nodules in centers where there is no radiologist, surgeon, pathologist experienced in the thyroid, and patients may need to be consulted to centers where these facilities are available. Besides, it should be kept in mind that TIRADS and BETHESDA classifications are still superior to all other methods.

Conflict of Interest

None declared by the authors.

Financial Disclosure

None declared by the authors.

Ethics Comittee Approval

This is study was approved by Sakarya University Ethics Committee (01/10/ 2021: 71522473/050.01.04/64743/437).

Informed Consent

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Authors contributions:

All authors have read and approved the final manuscript. Concept: R.C, Z.B and E.G, Design: R.C, Z. B, E.G, Data Collection or Processing: E.G, T.H, F.K, M.C, H.D Analysis or Interpretation: R.C, E.G, T.H Literature Search: Z.B, M.C, F.K, H.D, Writing: R.C, Z.B, E.G

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Primary Immunodeficiency and Malignant Disease Coexistency: Two Case Reports

Primer İmmün Yetmezlik ve Malign Hastalık Birlikteliği: İki Olgu Sunumu

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Abstract

Primary immunodeficiency diseases are that predispose to malignancies other than recurrent infections. Genomic instability due to some unknown mechanisms and defective DNA repair processes in patients with primary immunodeficiency causes an increase in cancer risk, and it is thought that the risk of developing cancer in these patients varies between 4.7-5.7%. After infections, the most common cause of death in patients with primary immunodeficiency is malignancies. In this article, our first case was admitted to the hospital with a cough and was diagnosed with Burkitt lymphoma in the follow-up. A low level of immunoglobulins was detected in the tests performed, and it was diagnosed as common variable immunodeficiency at the same time. In our second case, acute lymphoblastic leukemia developed while she was being followed up due to transient hypogammaglobinemia of infancy. Here, we draw attention to the fact that the unusual first presentation of patients with a primary immunodeficiency may be associated with malignancy. In addition, we aimed to increase the awareness of clinicians following primary immunodeficiency patients about the development of malignancy.

Keywords Acute Lymphoblastic Leukemia, Burkitt's lymphoma, Common Variable Immunodeficiency

Özet

Primer immun yetmezlikler tekrarlayan enfeksiyon dışında malignitelere yatkınlık oluşturan hastalıklardır. Primer immun yetmezlikli hastalarda bazı bilinmeyen mekanizmalar ve kusurlu DNA onarım süreçleri nedeniyle oluşan genomik instabilite, kanser riskinde artışa neden olur ve bu hastalarda genel olarak kanser gelişme riskinin % 4,7- 5,7 arasında değiştiği düşünülmektedir. Primer immun yetmezlikli hastaların enfeksiyonlardan sonra en sık ölüm nedeni malignitelerdir. Bu makalede sunmuş olduğumuz ilk olgumuz öksürük şikâyetiyle hastaneye başvuran ve takibinde Burkitt Lenfoma tanısı alan, bu aşamada tetkiklerinde immünglobülinlerinde düşüklük saptanarak lenfoma tanısına eş zamanlı olarak yaygın değişken immün yetmezlik tanısı eklenen hastamızdır. İkinci olgumuz primer immun yetmezlik nedeniyle takipliyken akut lenfoblastik lösemi gelişen hastamızdır. Burada primer immun yetmezlikli hastaların olağanın dışında ilk başvurusunun maligniteyle beraber de olabileceğine dikkat çekmeyi ve primer immun yetmezlikli hasta takip eden klinisyenlerin malignite gelişimine karşı farkındalıklarını arttırmayı amaçladık.

Anahtar Kelimeler *Akut Lenfoblastik Lösemi, Burkitt Lenfoma, Yaygın Değişken İmmun Yetmezlik*

GİRİŞ

Primary immunodeficiency disease (PID) or Inborn errors of immunity (IEI) is a heterogeneous group of diseases characterized by a disorder of the immune system. Patients with IEI may present with variable symptoms, the most common clinical manifestations being recurrent infections, autoimmunity, and malignancies. In 2019, the International Union of Immunological Societies (IUIS) published an updated phenotypic classification of IEI. There are 430 single gene IEI diseases underlying various phenotypes such as infection, malignancy, allergy, autoimmunity, and autoinflammation. In addition, the European Society for Immunodeficiencies (ESID) working definitions for clinical diagnosis of PID are available. Common variable immunodeficiency (CVID) and transient hypogammaglobinemia of infancy (THI) are included in these classifications.[1,2]

The susceptibility to tumor formation seen in these patients is associated with various reasons such as defects in DNA damage repair, irregularities in the immune response that plays a role in the clearance of oncogene viruses such as EBV and HPV, and chronic antigenic stimulation, and deterioration in apoptosis. In some PIDs, malignancies are more common. The most common malignancy is lymphoma, and it is known to be associated with EBV infection in some patients.[3,4] In this case report, we wanted to draw attention to the coexistence of PID and malignancy by presenting our patients who were diagnosed with CVID simultaneously with Burkitt lymphoma and developed pre-B acute lymphoblastic leukemia (ALL) during follow-up with the diagnosis of THI.

CASE-1

A 6-year-old female patient applied to the pediatric emergency department with complaints of fever and cough that started 3 days ago. The patient had a history of obesity, asthma, and dust mite allergy. There was no feature in the family history of the patient. On physical examination, respiratory sounds were found to be decreased in the right baseline. Other system examinations were unremarkable. In laboratory examinations, white blood cell count: 10.980/mm3, absolute neutrophil count: 7.590/mm3, absolute lymphocyte count 2.560/mm3, Hemoglobin: 12.4 gr/dl, platelet: 537.000/µL, and CRP: 83.5 mg/dl. Thoracic ultrasonography (USG) was performed because of the increase in opacity in the right hemithorax in the chest X-ray of the patient. Thoracic USG revealed pleural effusion. A thorax tube was inserted by the pediatric surgeon and thoracentesis was performed. The patient's thoracentesis fluid was compatible with the exudate and he was admitted to the ward with antibiotherapy. On the 9th day of hospitalization of the patient, who responded to the treatment in the control chest X-ray, respiratory sounds could not be obtained from bilateral baselines. One day later, the patient's respiratory effort increased and her general condition deteriorated, and hepatomegaly, intra-abdominal mass, and free fluid were detected in the abdominal USG of the patient who developed abdominal distension. The patient with uric acid: 10.57 mg/dl and LDH: 2.439 U/L was transferred to the Department of Pediatric Hematology and Oncology for further examination and treatment with a preliminary diagnosis of malignancy. The cytological examination was sent from the thoracentesis fluid and PET/CT was taken to the patient, and EBV-VCA immunoglobulin G (IgG) was positive. The patient was consulted by the Department of Pediatric Immunology and Allergy, when the tests taken during this period showed IgG: 196 mg/dL, IgM 21.7 mg/dL, and IgA: 35.7. Anti-B titer was ¼ positive in the patient's antibody responses, but vaccine antibody responses (Rubella, hepatitis B, etc.) were low (table-1). The patient was diagnosed with CVID. Intravenous immune globulin (IVIG) treatment was started once every 4 weeks. The patient, who was diagnosed with Burkitt's lymphoma, continues to receive IVIG treatment together with chemotherapy. (Informed consent was taken from the parents of the patient for this presentation.)

Table 1. Immunological data of patients at the time of diagnosis

	Ig A (g/L)	Ig G (g/L)	Ig M (g/L)	Anti-A/ Anti-B	Anti-HbS (0-10)	Anti-Rubella IgG
Case 1	37.6	194	184	1/4	14.6	negative
Case 2	34	523	75	1/2	negative	82.9

CASE-2

She was 3.5 years old and had transient hypogammaglobinemia of infancy for the last 1.5 years (table-1). The patient applied to the outpatient clinic to receive monthly IVIG treatment. From her anamnesis, it was learned that she last received IVIG treatment 4 months ago. The patient had bone pain for 1 month. She was examined by an adult rheumatologist due to bone pain in the last month, and pediatric hematology outpatient control was recommended to the patient without any further examination. She didn't want to step on his feet anymore. She had a fever and weakness for the last 4 days. The patient looked sluggish. Other than that, the systemic examination was normal. There was no organomegaly and focus of fever. Her examinations were requested and she was admitted to the service for IVIG. In the examinations of the patient, white blood cell: was 63.890/mm3, absolute neutrophil: was 4.290/mm3, and absolute lymphocyte count could not be calculated. Hgb: 11.6 g/dl, platelet: 17.000/μL, uric acid: 7.1 mg/dl, and LDH: 668 U/L. She was consulted by the Department of Hematology and Oncology. The patient, who had atypical cells in her peripheral smear, was diagnosed with pre-B acute lymphoblastic leukemia as a result of further investigations. The patient is still receiving chemotherapy and concomitant IVIG. (Informed consent was taken from the parents of this patient for this presentation.)

DİSCUSSİON

Primary immunodeficiencies are rare diseases with a wide variety of genetic inheritances. The clinical phenotype varies according to the affected immune system cells, impaired immune functions, and associated infectious or neoplastic processes. As seen in our two different cases, the first clinical picture may be infection, sometimes malignancy, sometimes autoimmune diseases, and lymphoproliferative disease may develop in patients diagnosed with PID over time.

The World Health Organization (WHO) evaluated lymphoproliferative lesions seen in immunocompromised patients as a separate section in the 2017 lymphoma classification. In this section, the clinical pictures of lymphoproliferative lesions are collected under 4 main headings and their distribution among PID cases according to the data of different studies. According to this classification; incidence rates in combined T and B cell deficiencies: 9-18%, in immunodeficiency cases including CVID and other antibody deficiencies, especially in immunoglobulin deficiency: 53-72%, and incidence rates in defined immunodeficiency syndromes such as Ataxia Telangiectasia, Nijmegen Syndrome, Bloom Syndrome: 5-22%, incidence rates in diseases such as immune regulation disorder, an autoimmune lymphoproliferative syndrome characterized by X-linked lymphoproliferative disease: 1-3%.[5,6]

Common variable immunodeficiency is one of the most common congenital immunodeficiency encountered in clinical practice.[7] Diagnosis is made by demonstrating decreased serum concentrations of IgG, IgA, and IgM with loss of protective antibodies.[2] The genetics of this syndrome are complex and still under investigation. The term "variable" in its name describes the heterogeneity of the clinical picture in this disease (infections, chronic lung disease, autoimmune diseases, gastrointestinal disorders, malignancy, etc.). Non-infectious autoimmune or inflammatory conditions may be the first and only sign that a patient has a significant immune defect. These manifestations include splenomegaly, generalized or alarmingly large lymphadenopathy and malignancy, particularly lymphoma, episodes of immune thrombocytopenia, autoimmune

hemolytic anemia, or neutropenia.[8,9] Supporting this situation, the finding of our first patient at the time of diagnosis was malignancy and she was diagnosed with CVID. There were no complaints of frequent infections.

Non-Hodgkin lymphoma (NHL) is the most common type of B-cell lymphoma with a rate of 32%. B-cell lymphomas identified in approximately 31% of the patients were found to be associated with EBV.[3] Our case was positive for EBV serology, and our patient was diagnosed with Burkitt's lymphoma, one of the subtypes of NHL. In addition, although lymphoma is the most common malignancy in patients with PID, leukemia may also develop, as in our other case.

CONCLUSİON

It should be kept in mind that the first presentation of patients with PID may also be with unusual findings and malignancy every malignancy is the result of an immune disorder. We suggest that clinicians following patients with PID should pay attention to the precursor examination findings of lymphoproliferative diseases such as organomegaly and lymphadenopathy in their patients at each visit and be aware of this issue.

Declaration

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