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AĞRI TIP FAKÜLTESİ DERGİSİ

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AĞRI TIP FAKÜLTESİ DERGİSİ YAZIM KURALLARI

Genel Bilgiler

Ağrı Tıp Fakültesi Dergisi (Ağrı Medical Journal; Ağrı Med J) Ağrı İbrahim Çeçen Üniversitesi Tıp Fakültesi'nin resmi yayın organı olan bilimsel bir dergidir. Ağrı Tıp Fakültesi Dergisi yılda 3 defa (Şubat, Haziran ve Ekim), Türkçe veya İngilizce olarak sadece DergiPark üzerinden yapılan çevrimiçi (onli ne) başvuruları kabul etmektedir ve herhangi bir başvuru veya işlem ücreti talep etmemektedir.

Amaç

Ağrı Tıp Fakültesi Dergisi olarak öncelikli amacımız ülkemizde bilimsel standartlara uygun, bilimsel değeri yüksek, kaliteli ve güncel yayınlar içeren ve kolay erişilebilir bir yayın organı oluşturmaktır. Ülkemiz için öncelikli olarak belirlediğimiz hedeflere ulaşıldıktan sonra, öncelikli amacımızdan taviz vermeden, Ağrı Tıp Fakültesi Dergisi'nin tüm dünyada görünürlüğünü ve kullanılırlığını arttırmayı amaçlamaktayız.

Kapsam

Ağrı Tıp Fakültesi Dergisi tıp bilimlerindeki (temel tıp bilimleri, dahili tıp bilimleri ve cerrahi tıp bilimleri) tüm etik yönergelere uygun olarak hazırlanmış klinik ve deneysel araştırma makalelerini, olgu sunumlarını, derleme makaleleri, teknik notlar ve editöre mektupları yayınlamaktadır.

Değerlendirme İlkeleri

Ağrı Tıp Fakültesi Dergisi bağımsız çift kör hakem ilkesine dayanan, açık erişimli ve çevrimiçi bir yayın organıdır. Ağrı Tıp Fakültesi Dergisi daha önce yayınlanmamış veya başka bir yerde yayınlanmak üzere gönderilmemiş orijinal yayınları yayımlayarak tıp literatürüne katkı sağlamayı amaçlamaktadır. Ağrı Tıp Fakültesi Dergisi'ne, kabul edilme sürecindeki değerlendirilmelerde aranan temel özellik 'bilim literatürüne katkı ve özgünlüktür'.

Ağrı Tıp Fakültesi Dergisi 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) uygun olarak yayınlanmaktadır. Ağrı Tıp Fakültesi Dergisi'nin editoryal ve yayın süreçleri, Uluslararası Medikal Dergisi Editörleri Komitesi (International Committee of Medical Journal Editors) (ICMJE), Dünya Tıbbi Editörler Birliği (World Association of Medical Editors) (WAME), Bilim Editörleri Konseyi (Council of Science Editors) (CSE), Yayın Etiği Komitesi (Committee on Publication Ethics) (COPE), Avrupa Bilim Editörleri Derneği (European Association of Science Editors) (EASE) ve Ulusal Bilgi Standartları Örgütü (National Information Standards Organization) (NISO) yönergelerine uygun olarak şekillendirilmiştir.

Ağrı Tıp Fakültesi Dergisi'ne gönderilen yazılarda tüm yazarların bilimsel katkıları bulunmalıdır. Yazar olarak belirlenen isimler çalışmayı planlamalı veya yapmalı veya yazıyı yazmalı veya revize etmelidir. Ayrıca tüm yazarlar makalenin son halini kabul etmelidir.

Makalelerin tıbbi ve etik sorumluluğu yazarlara; telif hakları Ağrı Tıp Fakültesi Dergisi'ne aittir. Makalenin içeriğinde bulunan tüm metin, şekil ve kaynaklardan yazarlar sorumlu olup; kullanılan şekil, tablo veya başka resimlerin telif izinlerinin temini yazarların görevidir. Bahsedilen konular nedeniyle dergiye yapılacak hak taleplerinden yazarlar sorumludur. Çalışmada herhangi bir finansal destek ya da materyal desteği alındıysa, yazarlar tarafından ilişkinin türü de açıkça belirtilerek (danışman, başka anlaşmalar) beyan edilmelidir. Ayrıca herhangi bir ticari ürün, ilaç, ilaç şirketiyle bir ilişki varsa bu durum açıkça belirtilmelidir. Herhangi bir destek veya ilişki mevcut değilse bu durum da başvuru sırasında ve başlık sayfasında açıkça belirtilmelidir.

Yayınlanan makalelerdeki veriler, fikirler ve ifadelerden yazarlar sorumludur ve editörler, editör kurulu, yayıncı ve Ağrı Tıp Fakültesi Dergisi bu konularda herhangi bir sorumluluk kabul etmemektedir.

Tüm makaleler Telif Hakkı Devir Formu eşliğinde gönderilmelidir. Bu form tüm yazarlar tarafından başlık sayfasındaki isim sırasına göre imzalanmalıdır. Bu formu imzalayarak yazarlar, makalenin ve verilerin daha önce başka bir yere gönderilmediği veya başka bir yerde yayınlanmadığını, yazarların makaleye bilimsel katkısının olduğunu ve sorumlulukları kabul ettiklerini beyan etmiş olacaklardır. Telif Hakkı Devir Formu ile yüklenilmeyen yazılar değerlendirmeye alınmayacaktır.

Makalelerin Formatı

Makaleler "MS Word" programı formatında, "Times New Roman 12 punto" yazı stiliyle, 1,5 kat satır boşluklu ve her iki yana yaslı olarak yazılmalıdır. Sayfa düzeni A4 sayfa boyutunda, üst, alt, sağ ve soldan 2,5 cm girintili olmalıdır. Makaleler açık, kısa ve akıcı bir Türkçe veya İngilizce ile yazılmalı, imla kurallarına uyulmalıdır.

Türkçe dilinde gönderilen makalelerin gönderildiği metin dosyasının içinde sırasıyla: Türkçe başlık, Türkçe anahtar kelimeler, İngilizce başlık, İngilizce anahtar kelimeler, makalenin metinleri, kaynaklar, her sayfada bir tablo olmak üzere tablolar ve son sayfada şekillerin (varsa) alt yazıları şeklinde olmalıdır.

İngilizce dilinde gönderilen makalelerin gönderildiği metin dosyasının içinde sırasıyla: İngilizce başlık, İngilizce anahtar kelimeler, Türkçe başlık, Türkçe anahtar kelimeler, makalenin metinleri, kaynaklar, her sayfada bir tablo olmak üzere tablolar ve son sayfada şekillerin (varsa) alt yazıları şeklinde olmalıdır.

Metin dosyanızın içinde, yazar isimleri ve kurumlara ait bilgi, makalede kullanılan şekil ve resimler olmamalıdır.

MAKALE YÜKLENMESİ SIRASINDA İSTENİLEN BELGELER

1. Başlık sayfası (Title Page)

- Makale Başlığı (Full Title) (Türkçe ve İngilizce olarak, herhangi bir kısaltma olamadan ve ele alınan konuyu açıklayıcı olarak)
- Makalenin kısa başlığı (Short Title)
- Tüm yazarların tam isimleri ve kurumları
- Tüm yazarların ORCID numaraları

- Sorumlu yazarın adı, adresi, e-posta adresi, telefon ve faks numarası
- Varsa, çalışmanın sunulduğu bilimsel toplantının yer ve tarihi.
- Çalışma için herhangi bir mali destek alınmışsa veya yazarlar arasında çıkar çatışması mevcut ise onun belirtilmesi.

2. Makale sayfası (Manuscript)

- Öz (Araştırma makaleleri için en fazla 250 kelime içeren yapılandırılmış ve anahtar kelimeleri içeren, vaka sunumları için en fazla 150 kelime içeren yapılandırılmış ve anahtar kelimeleri içeren)
- Ana Metin (Araştırma makaleleri için giriş, gereç ve yöntem, bulgular, tartışma ve kaynaklar alt başlıklarını içeren, vaka sunumları için giriş, olgu sunumu, tartışma ve kaynaklar bölümünü içeren)

3. Araştırma makaleleri için Etik Kurul Onam Formu (Karar numarası ve tarihi içeren)
- (Ethical Approval Form)

4. Vaka sunumları için hasta (lar) dan alınmış Bilgilendirilmiş Onam Formu
- (Informed Consent)

5. Mevcut ise ayrı sayfada hazırlanmış Tablolar sayfası (ayrı bir MS Word sayfasında)
- (Tables)

6. Mevcut ise konu ile alakalı Resimler
- (Figures)

7. Telif Hakkı Devir Formu
- (Copyright Transfer Form)

8. Yazar Katkı Formu
- (Author Contribution Form)

9. Başlık Sayfası (Title Page)

Başlık sayfası makale yükleme süreci sırasında tüm makale türlerinde ayrı bir belge olarak "MS Word" programı formatında yüklenmelidir.

Başlık sayfası makalenin ana başlığını, kısa başlığını, makaleye katkısı olan yazarların isimlerini ve kurumlarını içermeli ve aşağıdaki sıra ile bilgiler verilmelidir:

• Makale Başlığı (Türkçe ve İngilizce olarak, herhangi bir kısaltma olmadan ve açıklayıcı olarak)
• Makalenin kısa başlığı
• Tüm yazarların tam isimleri ve kurumları
• Tüm yazarların ORCID ID numaraları
• Sorumlu yazarın adı, adresi, e-posta adresi, telefon ve faks numarası
• Varsa, çalışmanın sunulduğu bilimsel toplantının yer ve tarihi.
• Çalışma için herhangi bir mali destek alınmışsa veya yazarlar arasında çıkar çatışması mevcut ise onun belirtilmesi.

Makalelerin Yapılanması

Bilimsel Araştırma Makaleleri İçin

Bilimsel araştırma makaleleri klinik gözlemleri, yeni teknikleri veya laboratuvar çalışmalarını içeren klinik araştırmaları içerir.

Bilimsel araştırma makaleleri başlıklar, özetler, anahtar kelimeler, giriş, gereç ve yöntem, bulgular, tartışma, çalışmanın kısıtlılıkları ve önerileri, sonuçlar, kaynaklar, tablo/şekil/resimler ve teşekkür bölümlerinden oluşmalıdır.

Başlık, öz ve anahtar kelimeler bölümleri hem Türkçe hem de İngilizce olarak hazırlanmalıdır.

Öz (Abstract)

Özet bölümü Türkçe ve İngilizce dillerinde 250 kelime ile sınırlı olarak yazılmalıdır. Bu bölümde kaynaklara yer verilmemelidir. Kısaltmalar mümkün olduğunca az kullanılmalıdır.

Bilimsel araştırma makaleleri için özet şu başlıkları içermelidir.

• Amaç (Aim): Çalışmanın amacı açıkça belirtilmelidir.
• Gereç ve Yöntem (Material and Method): Çalışma tarif edilmelidir, çalışmanın randomize olup olmadığı, prospektif veya retrospektif olduğu ve kullanılan istatistik yöntemler belirtilmelidir.
• Bulgular (Results): Çalışmanın detaylı sonuçları verilmelidir ve istatistiksel anlamlılık düzeyleri belirtilmelidir.
• Sonuç (Conclusion): Çalışmanın kısa özü ve sonuçların anlamını içermelidir.
• Anahtar Kelimeler (Key Words): Özetten sonra en az 3 en çok 6 anahtar kelime verilmelidir.

• İngilizce anahtar kelimler "Tıbbi Konu Başlıkları (Medical Subject Headings [MESH])" ile uyumlu olmalıdır (https://meshb.nlm.nih.gov/search).

• Türkçe anahtar kelimler MESH terimlerinin direk çevirisi ve Türkiye bilim Terimleri'nden (https://www.bilimterimleri.com/) seçilmelidir.

Ana Metin

• Giriş (Introduction): Kısaca konuyu açıklamalıdır ve literatür desteği ile çalışmanın amacı belirtilmelidir.
• Gereç ve Yöntem (Material and Method): Çalışma planı açıkça tarif edilmelidir. Çalışmanın randomize olup olmadığı, retrospektif veya prospektif oluşu, deney/deneklerin sayısı ve özellikleri ve kullanılan istatistik metodu içermelidir. Çalışmaya dahil etme ve çalışmadan çıkarma kriterleri belirtilmelidir.
• Bulgular (Results): Çalışmada elde edilen bulgular tablo ve şekillerle verilmelidir, istatistik değerlendirme yöntemleri ile

sonuçlar sunulmalıdır.

• Tartışma (Discussion): Sonuçlar tartışılmalı ve literatür ile karşılaştırılmalıdır. Çalışmanın sonucu belirtilmelidir.

• Sonuç (Conclusion): Çalışma ile elde edilen veriler tekrarlardan kaçınılarak ve tıp literatürüne hangi katkıları yaptığı vurgulanarak sergilenmelidir.

• Çalışmanın kısıtlılıkları ve Öneriler (Limitations and Suggestions): Çalışma tasarımı ve çalışmanın olgunlaştırılması sırasında karşılaşılan güçlükler açıkça belirtilmelidir. Ayrıca çalışmanın farklı araştırmacılar tarafından yapılabilmesi veya geliştirilmesi için öneriler sunulmalıdır.

• Kaynakçalar (References): Kaynakların kullanım ve düzeni ile ilgili ayrıntılı bilgiyi "Kaynakça" başlığından inceleyiniz.

• Teşekkürler (Acknowledgments): Çalışmaya yönelik herhangi bir teknik, finansal desteği ya da düzenleme katkısını (istatistik analiz, Türkçe/İngilizce değerlendirme) içermelidir.

• Çıkar Beyannamesi (Conflict of Interest): Yazarlar çalışma üzerinde direk ya da potansiyel etkisi olabilecek veya yanlılığa neden olabilecek herhangi bir ilişki ve durumu belirtmek zorundadırlar. Eğer yoksa, "herhangi bir çıkar çatışmasının olmadığını yazarlar beyan etmektedirler" yazarak belirtmelidir.

• Yazar(lar) katkı Formu (Author[s] Contribution Form): Çalışmada ismi geçen yazarların yazıya hangi aşamada katkı oldukları belirtilmelidir.

Vaka Sunumları İçin

Vaka sunumları nadir görülen, teşhis ve tedavisi zor veya mevcut tıbbi bilgiye katkı yapan vakaları içermelidir.

İlk sayfa Türkçe başlığı, 200 kelimeyi geçmeyen Türkçe özeti, Türkçe anahtar kelimeleri ve İngilizce başlığı, İngilizce özeti (Abstract) ve İngilizce anahtar kelimeleri (Key Words) içermelidir.

Ana metin giriş, vaka sunumu, tartışma, sonuç ve kaynaklar bölümlerinden oluşmalıdır. Olgu sunumlarının kaynakça bölümü, derginin makale yazım kurallarına göre yazılmalıdır.

Derleme Makaleleri İçin

Derleme makaleleri klinik veya laboratuvar tıbbi bilimlerin herhangi bir konusu hakkında olabilir ve literatürü derinlemesine inceler. Bu tür makaleler genellikle editörlerin daveti üzerine hazırlanır fakat diğer yazarlarca da derleme yazıları dergiye gönderilebilir.

Derleme yazılarının ilk sayfası Türkçe ve İngilizce başlık, özet ve anahtar kelimeleri içermelidir. Ayrıca tüm kaynaklar belirtilmeli ve kaynak sayısı en fazla 50 olmalıdır.

Editöre Mektuplar İçin

Editöre mektuplar, tıp alanındaki güncel gelişmeler ve bunların bilimsel ve sosyal ilişkileri üzerine kısa yazıları içerebilir veya daha önce dergide yayınlanmış bir makale hakkında soru sorabilir veya o makaleye katkı yapabilir. Editöre mektuplar başlık ve özet bölümleri olmadan, 1000 kelimeyi aşmadan ve en fazla 10 kaynak içerecek biçimde düzenlenmelidir.

İstatistik Bölümü

Çalışmada kullanılan istatistiksel analizler, 'Gereç ve Yöntem' bölümünde belirtilmelidir. Çalışmada kullanılan paket programına veya programlama diline atıf yapılmalı ve sürümü yazılmalıdır.

P<0,05 veya p>0,05 notasyonları yerine karşılaştırma sonuçlarına ait gerçek p değerleri rapor edilmelidir (p=0,002; p=0,695 gibi).

Çalışmalarda varsayımların hangi testler ile test edildikleri belirtilmelidir (normallik dağılımı için Kolmogorov-Smirnov; varyans homojenliğinin testi için Levene Testi gibi). Tablolarda grup karşılaştırmaları için farklı testler kullanılmışsa hangi p değerinin hangi test sonucunda elde edildiği tablo altında dipnot ile belirtilmelidir (*: Student's t test, **: Mann-Whitney U Testi gibi).

Kaynakça Gösterimi

Kaynaklar, yazı içinde geçiş sırasına göre numaralandırılmalıdır. Kaynakça bölümü yazılırken gerek metin içi gösterimde gerekse ana kaynakça bölümünde kullanılacak olan Vancouver stilidir. Endnote programı kullanılarak kaynakça bölümü oluşturulması sırasında mevcut olan Vancouver stilinde dergi adları uzun bir şekilde yazılı olup; dergi adları National Library of Medicine https://www.ncbi.nlm.nih.gov/nlmcatalog/ uygun olarak kısaltılmalıdır.

Metin içi gösterimde kaynakça, cümle sonunda noktadan hemen önce normal parantez içerisinde numerik rakamla veya cümle içerisindeki ilgili bölümde normal parantez içerisinde numerik rakamla belirtilmelidir. Birden fazla kaynak var ise kaynaklar aralarına virgül konularak ayrılmalıdır. Birbirlerini izleyen makalelerde, ilk ve son numara '-' işareti ile ayrılarak gösterilmelidir.

Örneğin: …… bildirilmektedir (1).

Örneğin: The faculty of the USC School of Pharmacy is active in many types of research, including Alzheimer's disease mechanisms (1), therapeutics (2), and risk factors (3).

Örneğin: Kalaycı ve ark. (8) yaptığı çalışmada……..

Örneğin: ……..…. bildirilmektedir (8,13,18).

Örneğin: …… bildirilmektedir (3,13-16).

Kaynak gösterilen makalede altı veya daha az yazar varsa tüm yazarların isimleri yazılmalı; yedi veya daha fazla yazar olduğunda ilk üç yazarın ismi yazılmalı, sonrasında Türkçe kaynaklarda "ve ark.", İngilizce kaynaklarda "et al." kullanılmalıdır.

Kaynakça internet adresinden alınmış ise erişim tarihi ve erişilen internet sitesi belirtilmelidir.

Kitaptan yapılan atıflarda belirtilen format kullanılmalıdır [Yazar AA veya Editör AA, ed. Kitabın adı. Baskı numarası (yalnızca ilk baskı dışında bir baskı ise dahil edin). Yayıncı adı; yayın yılı.]

Kitaptan yapılan atıflarda editör sayısı 6ve daha az ise tüm editörler belirtilmeli ve sonuna (eds) eklenmelidir. 7'den fazla editör bulunan kitaplarda sadece ilk 3 editör yazılmalı ve sonuna (eds) eklenmelidir.

Kitap içerisinde bir bölümden atıf yapıldığı zaman ise belirtilen format kullanılmalıdır [Bölümün yazar(lar)ı. Bölüm Başlığı. Bölüm editör(ler)i, ed(s). Kitabın adı. Baskı numarası (yalnızca ilk baskı dışında bir baskı ise dahil edin). Yayıncı adı; yayın yılı.]

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Tablo, Şekiller, Ölçüm Birimleri, Kısaltmalar ve Semboller

Yazı içindeki grafik, şekil ve tablolar Arap sayıları ile numaralandırılmalıdır. Şekillerin metin içindeki yerleri belirtilmelidir.

Tablolar

Tablolar bilgileri etkin bir şekilde gösterir ve ayrıca bilginin istenen tüm ayrıntı seviyelerinde verilmesini sağlar. Bilgileri metin yerine tablolarda vermek genelde metnin uzunluğunu kısaltır. Her tablo ayrı bir sayfada tek sütun veya çift sütün olacak şekilde sunulmalıdır. Tabloları metindeki sıralarına göre numaralayıp, her birine kısa bir başlık verilmelidir. Her sütuna bir başlık verilmelidir.

Yazarlar açıklamaları başlıkta değil, dipnotlarda yapmalıdır. Dipnotlarda standart olmayan tüm kısaltmalar açıklanmalıdır. Dipnotlar için sırasıyla aşağıdaki semboller kullanılmalıdır: (*, †, ‡, §, ||, ¶, **, ††, ‡‡). Varyasyonun, standart sapma ya da standart hata gibi istatistiksel ölçümleri belirtilmelidir. Metin içinde her tabloya atıfta bulunulduğuna emin olunmalıdır. Eğer yayınlanmış ya da yayınlanmamış herhangi başka bir kaynaktan veri kullanılıyorsa izin alınmalı ve onlar tam olarak bilgilendirilmelidir.

Şekiller

Şekiller ya profesyonel olarak çizilmeli ve fotoğraflanmalı ya da fotoğraf kalitesinde dijital olarak gönderilmelidir. Şekillerin basıma uygun versiyonlarının yanı sıra JPEG ya da GIF gibi elektronik versiyonlarda yüksek çözünürlükte görüntü oluşturacak biçimlerde elektronik dosyaları gönderilmeli ve yazarlar göndermeden önce bu dosyaların görüntü kalitelerini bilgisayar ekranında kontrol etmelidir. Şekiller ve resimler JPEG en az 300 dpi olmalıdır.

Röntgen, bilgisayarlı tomografi, manyetik rezonans ve diğer tanısal görüntülemeler ve patolojik fotomikrografik preparatlar ve örnekler genelde tek veya çift sütun boyutlarında yüksek kalitede basılmış olarak gönderilmelidir. Bu nedenle şekillerin üzerindeki harfler, sayılar ve semboller açık ve tüm makalede eşit ve yayın için küçültüldüklerinde bile okunabilecek boyutlarda olmalıdır.

Şekiller mümkün olduğunca tek başlarına anlaşılabilir olmalıdır. Fotomikrografik patoloji preparatları iç ölçekler içermelidir. Semboller, oklar ya da harfler fonla kontrast oluşturmalıdır. Eğer insan fotoğrafı kullanılacaksa ya bu kişiler fotoğraftan tanınmamalıdır ya da yazılı izin alınmalıdır. Şekiller metinde geçiş sıralarına göre numaralandırılmalıdır. Eğer önceden yayınlanmış bir şekil kullanılacaksa, yayın hakkını elinde bulunduran bireyden izin alınmalıdır.

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

Ölçüm Birimleri

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

Kısaltmalar ve Semboller

Sadece standart kısaltmaları kullanın, standart olmayan kısaltmalar okuyucu için çok kafa karıştırıcı olabilir. Çalışma başlıklarında kısaltma kullanılmasından kaçınılmalıdır. Standart bir ölçüm birimi olmadıkça kısaltmaların uzun hali ilk kullanılışlarında açık, kısaltılmış hali parantez içinde verilmelidir.

Contents/ *İçindekiler*

Research Article/ Araştırma Makalesi DOI: 10.61845/agrimedical.1382060

Can Mean Platelet Volume Potentially Serve as A Novel Indicator of Activity in Ankylosing Spondylitis? Can Vitamin D Level Affect Disease Activity?

Ortalama Platelet Hacmi Ankilozan Spondilitte Yeni Bir Aktivite Belirteci Olabilir mi? Vitamin D Seviyesi Hastalik Aktivitesini Etkileyebilir mi?

Volkan Ecesoy[1], Rahim Kocabas[2], Serkan Kuccukturk[3], Hilal Ecesoy[4]*

ABSTRACT

Aim: In AS patients' disease activity isn't correlated with acute phase reactants. The Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) serve as valuable indicators for assessing inflammation. Vitamin-D deficiency could result in heightened disease activity. The aim of this study was to investigate the relationship between mean platelet volume (MPV), vitamin D and NLO, PLO, and disease activity.

Material and methods: The study comprised 112 patients and 116 controls, with retrospective data collection.

Results: Statistically significant differences were identified in the values of Vitamin-D, MPV, erythrocyte sedimentation rate (ESR), NLR, PLR, and C-reactive protein (CRP) between the patient and control groups. Except for MPV, there were no discernible differences in these values between inactive and active patients. Significantly lower MPV values were observed in patients with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores of ≥4. CRP and ESR exhibited a negative correlation with MPV and a positive correlation with NLR and PLR. There was a negative correlation between BASDAI and MPV. However, no correlation was found between Vitamin-D and acute phase reactants, as well as NLR and PLR.

Conclusions: In existing studies, a definitive consensus on the connection between inflammation and Vitamin-D remains elusive, and the values of MPV also exhibit considerable variability. In our study, the Vitamin-D levels of patients were significantly higher than those of the control group, while MPV was significantly higher in the control group. No significant difference was observed between the control group and the BASDAI<4 group. However, a statistically significant difference was identified between the control group and the BASDAI≥4 group, with significantly higher MPV values observed in the control group. These findings suggest that MPV may help us as a valuable indicator for detecting inflammation. In the study, MPV demonstrated a negative correlation with BASDAI, ESR, and CRP. The results imply that MPV could be a cost-effective method aiding in the assessment of disease activity. Wider prospective studies are essential to validate the utility of this cost-effective and readily accessible parameter in disease monitoring.

Key Words: Mean Platelet Volume, Ankylosing spondylitis, Vitamin-D

ÖZ

Amaç: AS hastalarında hastalık aktivitesi, akut faz reaktanları ile ilişkili değildir. İnflamasyonu değerlendirmek için Nötrofil/Lenfosit Oranı (NLO) ve Platelet/Lenfosit Oranı (PLO) kullanılabilir. Vitamin-D eksikliği hastalık aktivitesinin artmasına neden olabilir. Biz çalışmamızda Ortalama platelet hacmi (OPH), Vitamin-D ve NLO, PLO ve hastalık aktivitesi arasındaki ilişkiyi belirlemeyi amaçladık.

Gereç ve yöntemler: 112 hasta ve 116 kontrolün dataları retrospektif olarak kaydedildi.

Bulgular: Vitamin-D, NLO, PLO, OPH, Eritrosit Sedimentasyon Hızı (ESH), C Reaktif Protein (CRP) değerlerinde hastalar ile kontrol grubu arasında istatistiksel olarak anlamlı fark tespit edildi. OPH dışında bu değerlerde aktif ve inaktif hastalar arasında fark yoktu. OPH; BASHAİ≥4 (Bath Ankilozan Spondilit Hastalık Aktivite İndeksi) hastalarda anlamlı olarak düşüktü. OPH; CRP, ESH ile negatif, NLO, PLO ile pozitif korelasyon gösterdi. BASHAİ ile OPH arasında negatif korelasyon bulunurken, Vitamin-D ile akut faz reaktanları, NLO ve PLO arasında korelasyon bulunmadı.

Sonuç: Çalışmalarda Vitamin-D ile inflamasyon arasındaki ilişki konusunda kesin bir görüş birliği yoktur ve OPH değerleri de oldukça değişkendir. Çalışmamızda hastaların Vitamin-D düzeyi kontrollere göre anlamlı olarak yüksekti; OPH ise kontrol grubunda anlamlı olarak daha yüksekti. Kontrol grubu ile BASHAİ<4 grubu arasında fark bulunmazken BASHAİ≥4 grubu ile arasında istatistik açısından anlamlı fark vardı ve kontrol grubunun OPH değerleri anlamlı olarak yüksekti. Bu bize OPH'nin inflamasyonu tespit etmemize yardımcı olabileceğini düşündürmektedir. Çalışmada OPH; BASHAİ, ESH ve CRP ile negatif korelasyon göstermektedir. OPH, hastalık aktivitesine yardımcı olabilecek ucuz bir yöntem gibi görünmektedir. Bu ucuz ve kolay elde edilen parametrenin hastalık takibinde kullanımının kabul edilebilmesi için daha geniş prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ortalama Platelet Hacmi, Ankilozan Spondilit, Vitamin-D

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, inflammatory autoimmune disease primarily damages the spine and sacroiliac joint (1). It especially affects young men, and when diagnosed late, ankylosing spondylitis (AS) can disrupt the professional lives of patients, leading to workforce loss and imposing an economic burden on the country.

Ankylosing spondylitis is diagnosed through a combination of clinical and radiological assessments, as there is no specific diagnostic test available. Disease activity in AS is frequently not correlated with traditional acute phase markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Furthermore, these markers are not specific indicators of inflammation. They can elevate in various conditions, including pregnancy, obesity, and infectious diseases, making them less specific for pinpointing inflammation. This has prompted the exploration of alternative markers to assess activity, particularly in these patients.

In studies of various diseases, systemic inflammation has found to be associated with both the composition and volume of circulating blood cells. The active participation of neutrophils, lymphocytes and platelets is important in the development of inflammation, and qualitative and quantitative changes in these cells have been recorded as a response to inflammatory processes. Platelet/lymphocyte rate (PLR) and neutrophil/lymphocyte rate (NLR) calculations have diagnostic value in evaluating the inflammatory response in patients with local or systemic inflammation, such as coronary artery disease, diabetes, inflammatory arthritis, and ulcerative colitis (2).

Mean platelet volume (MPV) is considered an indicator of platelet function and activation. High MPV values have been shown to be an independent risk factor for acute myocardial infarction, renal artery stenosis, diabetes mellitus, hypertension, and hyperlipidaemia. Additionally, MPV values are elevated in some systemic inflammatory diseases and are positively correlated with CRP (3). On the other hand, increased pro-inflammatory cytokines and acute phase reactants can suppress platelet size and decrease mean platelet volume (MPV) by affecting megakaryopoiesis and platelet release from the bone marrow (4).

Vitamin D, a fat-soluble vitamin, is synthesized from cholesterol and exhibits hormone-like functions in the body. Serum levels of 25-OH D3 are widely acknowledged as the key indicator for determining vitamin D levels in the body. Assessing individual vitamin D levels necessitates measuring 25(OH)D levels, which have a half-life of two to three weeks. This duration reflects both the endogenous production of vitamin D and the intake of exogenous vitamin D (5). Research has shown that vitamin D plays a significant role in the functions of organs beyond bone metabolism (6). In healthy people, normal serum 25(OH) D3 concentrations must be 30 ng/mL and above. Vitamin D levels below 20 mg/dl are considered vitamin D deficiency. If serum 25(OH) D3 levels are between 21-29 ng/mL, it is described as vitamin D insufficiency (5).

The identification of vitamin D receptors in active inflammatory cells in peripheral blood has brought attention to the function of vitamin D in the immune system. Vitamin D deficiency causes a decreased T-cell response (7). This shows that vitamin D is effective in T-cell development (8). T-helper 1 (Th1) cells, which create a strong immune response by increasing proinflammatory cytokine production, and T-helper 2 (Th2) cells, which are responsible for the release of anti-inflammatory cytokines, are two different types of T cells (9). Vitamin D exhibits dual effects on the immune system. On one hand, it suppresses the proliferation of Th1 cells and hinders the production of proinflammatory cytokines like interleukin-2 and interferon γ (10). On the other hand, it enhances the anti-inflammatory response by activating Th2 and Treg cell responses (11). In vitamin D deficiency, the activation of proinflammatory cytokines associated with the Th1 response contributes to the etiopathogenesis of autoimmune-based chronic diseases, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (IBD) (12). In this study, our objective was to investigate the correlation between vitamin D levels and NLR, PLR, and MPV, as well as to assess the association of these parameters with disease activity in patients with ankylosing spondylitis.

MATERIALS AND METHODS

Patients aged 18 years and older old and classified as AxSpA (AS and nr-AxSpA) according to ASAS classification criteria (13) who applied to the rheumatology outpatient clinic of Karamanoglu Mehmetbey University, Faculty of Medicine, Karaman Training Research Hospital were incorporated in this retrospective study. Ethics committee approval was assured before commencing the investigation (Date: 11/10/2021/15).

After ethics committee approval was obtained, since the study design was retrospective, the files between May 2021 and September 2021 were scanned to evaluate the vitamin D level in the summer months, and ankylosing spondylitis patients whose vitamin D level was measured during this period were included in the study. The process extended until March 2022, as consent was obtained as the patients came to the outpatient clinic for follow-up.

Individuals diagnosed with another rheumatological disease were excluded from the study. As the control group, individuals who sought care at the same polyclinic and were matched for age and sex, with no history of chronic diseases, medication use, inflammatory conditions, or findings indicative of inflammatory diseases, were included in the study. Patients' data were obtained from the hospital database. Demographic data, vitamin D, CRP, ESR levels, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) values, and hemogram data of the patients were retrospectively recorded. The NLR was calculated by dividing the neutrophil value by the lymphocyte value, and the PLR was determined by dividing the platelet value by the lymphocyte value. Mean platelet volume (MPV) normal reference values are 6.5-12 fL due to our laboratory systems. Cut-off values for elevated C-reactive protein (CRP) were set at >5 mg/L, for erythrocyte sedimentation rate (ESR) >15 mm/hour for males and >20 mm/hour for females, and high leukocyte levels were defined as >10 x 103/μL. Vit-D ranges >30 ng/mL were considered normal, <20 ng/mL deficiency, and 30>vit D> 20 ng/mL insufficiency. Patients with a BASDAI value ≥ 4 were categorized as active.

Serum 25-hydroxyvitamin D (25(OH)D) levels were assessed using an Advia-Centaur XP device (Siemens AG, Munich, Germany) and Vit-D kits from Siemens. Hemogram parameters were measured using the Mindray BC 6800 (Mindray, Shenzhen, P.R. China) automatic hematology analyzer.

Statistical analysis

Statistical analysis was conducted using Jamovi (version 1.2.27). The distribution of data was assessed with the one-sample Kolmogorov–Smirnov test. For nonparametric quantitative data, group differences were examined using the Mann–Whitney U test. The chi-square test was employed to analyze significant differences in qualitative variables. Correlations were assessed using the Spearman correlation coefficient. Data were presented as the median (Q1-Q3) unless otherwise specified. All p values were two-sided, and statistical significance was considered at

p<0.05.

RESULTS

The study encompassed a total of 228 participants, consisting of 112 patients (75 male, 37 female) and 116 controls (77 male, 39 female). Table I provides details on demographic, clinical, and laboratory data.

Table I. Demographic, biochemical data and comparisons

	Patients	Controls	p Values
(n)	112	116	
Gender (Female/ Male)	37/75	39/77	>0.05
Age (Years)	45 (36-51.75)	41.5 (35-49)	>0.05
25(OH)D (ng/mL)	18.42 (12.52-25.33)	14.64 (9.44-20.99)	0.003
NLR (Ratio)	2.18 (1.73-3.07)	1.94 (1.46-2.49)	0.002
PLR (Ratio)	123.94 (98.48-155.12)	106.03 (88.92-127.87)	0.002
MPV (fL)	9 (8.4-9.78)	9.5 (8.8-10.20)	0.003
CRP (mg/L)	7 (2.55-17.70)	1.8 (0.8-3.25)	<0.001
ESR (mm/hour)	14 (5-31)	9 (4-16.5)	0.001
BASDAI	5.66 (3.94-7.49)		

Values are expressed as Median (Q1-Q3). Mann-W U test. *Fisher's Exact Test

NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

A notable difference was observed between the control and patient groups regarding Vit-D, NLR, PLR, MPV, CRP, and ESR. Except for the MPV value, the measured levels were lower in the control group compared to the patient group.

In accordance with the BASDAI cut-off of 4, Vit-D showed marginal significance among patients, but no significant differences were detected in terms of NLR, PLR, CRP, and ESR values. However, MPV values were found to be significantly lower in individuals with BASDAI≥4 (refer to Table II).

Table II. Comparisons between active and inactive patients

	BASDAI<4	BASDAI≥4	p Values
(n)	30	82	
Age (year)	47 (38-53.5)	45 (36-51.25)	>0.05
25(OH)D (ng/mL)	20.17 (15.94-27.43)	16.77 (12.08-24.17)	>0.05
NLR (Ratio)	2.15 (1.96-2.78)	2.21 (1.66-3.15)	>0.05
PLR (Ratio)	125.23 (79.51-148.54)	123.94 (101.10-155.79)	>0.05
MPV (fL)	9.4 (8.68-10.43)	8.9 (8.28-9.53)	0.025
CRP (mg/L)	5.7 (2.65-13.78)	7.35 (2.48-17.73)	>0.05
ESR (mm/hour)	7.5 (5-22.845)	17 (5-40.25)	>0.05
BASDAI	3 (1.99-3.52)	6.7 (5.5-7.83)	0.000

Values are expressed as Median (Q1-Q3). Mann-W U test.

NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

In the comparison of patients based on gender, it was observed that CRP and Vit-D levels were significantly lower in females compared to males. Conversely, MPV, ESR, and BASDAI levels were significantly higher in males. However, no significant difference was found in terms of NLR and PLR (refer to Table III; P1).

The levels of CRP showed a notable increase specifically in female patients compared to both the patient and control groups among females (Table III; P3). In male patients, on the other hand, Vit-D, NLR, PLR, CRP, and ESR values were significantly elevated, while MPV values were significantly lower compared to the control group (Table III; P4).

In comparison to the control group, active patients exhibited significantly higher levels of Vit-D, NLR, PLR, CRP, and ESR, while the MPV level was significantly lower (Table IV).

Table III. Comparisons between sexes

	P-Patients		C-Controls		P-F/M	C-F/M	F-P/C	M-P/C
	F (n:37)	M (n:75)	F (n:39)	M (n:77)	P1	P2	P3	P4
25(OH)D (ng/mL)	15.78 (10.07-19.65)	19.53 (14-26.16)	13.86 (8.39-21.75)	14.74 (10.47-20.31)	0.014	>0.05	>0.05	0.001
NLR (Ratio)	2.06 (1.63-2.81)	2.21 (1.89-3.32)	2.09 (1.48-2.61)	1.82(1.43-2.44)	>0.05	>0.05	>0.05	0.001
PLR (Ratio)	124.26 (102.79-166.46)	127.27 (96.93-155.73)	122.51 (105.17-150)	101.65 (84.47-115.09)	>0.05	<0.001	>0.05	<0.001
MPV (fL)	9.5 (8.55-10.55)	8.8 (8.2-9.4)	9.5 (8.74-10.2)	9.5 (8.8-10.25)	0.008	>0.05	>0.05	<0.001
CRP (mg/L)	4.5 (1.55-10.65)	8.3 (2.8-19.8)	2.2 (1-3.1)	1.4 (0.75-3.4)	0.018	>0.05	0.005	<0.001
ESR (mm/hour)	18 (11-37)	11 (4-31)	20 (12-31)	6 (4-12.75)	0.045	<0.001	>0.05	<0.001
BASDAI	6.53 (5.29-7.75)	5.4 (3.5-7.44)	-	-	>0.05	-	-	-

P1: In Patient- Comparisons between Female and Male, P2: In Control- Comparisons between Female and Male, P3: In Female- Comparisons between Patient and Control, P4: In Male- Comparisons between Patient and Control: Patient. C: Control. F: Female. M: Male. Values are expressed as Median (Q1-Q3). Mann-W U test.

NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

Table IV. Comparisons between controls and patients with BASDAI ≥4

	Controls	BASDAI≥4	p Values
(n)	116	82	
Age (year)	41.5 (35-49)	45 (36-51.25)	>0.05
25(OH)D (ng/mL)	14.64 (9.44-20.99)	16.77 (12.08-24.17)	0.046
NLR (Ratio)	1.94 (1.46-2.49)	2.21 (1.66-3.15)	0.004
PLR(Ratio)	106.03 (88.92-127.87)	123.94 (101.10-155.78)	0.001
MPV(fL)	9.5 (8.8-10.2)	8.9 (8.275-9.53)	0.000
CRP (mg/L)	1.8 (0.8-3.25)	7.35 (2.475-17.73)	0.000
ESR (mm/hour)	9 (4-16.5)	17 (5-40.25)	0.000

Values are expressed as Median (Q1-Q3). Mann-W U test.

NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

In all patients, there was a negative correlation between CRP and ESR with MPV (r: -0.305, p < 0.001; r: -0.192, p: 0.013) and a positive correlation with NLR (r: 0.411, p < 0.001; r: 0.245, p = 0.009) and PLR (r: 0.377, p < 0.001; r: 0.397, p < 0.001), respectively. Additionally, there was a negative correlation between BASDAI and MPV (r: -0.219, p = 0.020), and no relationship was observed between Vit-D and either acute phase reactants or NLR or PLR.

DISCUSSION

Vitamin D, primarily synthesized endogenously in the skin through the influence of sunlight's ultraviolet B rays, plays a crucial role in promoting bone homeostasis, especially during the summer months. In recent years, there has been a growing recognition of the association between vitamin D insufficiency and deficiency and various chronic diseases including cardiovascular diseases, metabolic syndrome, common cancers, as well as infectious and autoimmune diseases. (14). This deficiency, which is considered a natural phenomenon in countries where the sun's rays are not sufficiently taken, is now recognized as a global epidemic due to the fact that many people avoid the sun, use extensive sunscreens, and work in offices that are not exposed to the sun throughout the day. Although the relationship between vitamin D deficiency and inflammation has been scrutinized in many studies, no consensus has yet been reached on this condition (15). It has been shown that "active vitamin D receptors" are found in immune cells, and these cells can also activate vitamin D locally. Therefore, investigation on vitamin D deficiency and its relationship with infections and autoimmune diseases is of high interest at present (16).

The effect of high vitamin D (1,25OHD) production suppresses T-cell growth by switching from Th1 to Th2 phenotype, resulting in increased production of anti-inflammatory immune markers such as IL-10 and inflammatory cytokines (TNF-α, IFN-γ, IL-17, IL-21) . Current evidence suggests that the level of circulating 25(OH)D may be critical for the optimal anti-inflammatory response of human monocytes. Low levels of vitamin D in the body can reduce the expression of anti-inflammatory cytokines that inhibit pro-inflammatory cytokines such as IL-10. This can lead to an increase in unwanted inflammation, tissue damage, and autoimmune disease (17).

Diagnosing ankylosing spondylitis does not rely on specific laboratory tests. Although ESR, CRP, and other acute phase reactants help in diagnosis and follow-up, they often do not correlate with disease activity (18). Novel methods are needed to ensure the correlation. During systemic inflammation, it is clear that there are changes in the composition and amount of circulating blood cells. Normochromic microcytic anemia, neutrophilia, lymphopenia, and thrombocytosis are associated with many inflammatory conditions. Hence, the components of the blood cells in the circulation could be used to evaluate inflammatory activity (19).

Previous studies have explored the correlation between ankylosing spondylitis (AS) activity and vitamin D levels. (20). Some studies have indicated that vitamin D levels are lower in the ankylosing spondylitis (AS) group compared to the control group (21), while other studies have reported no significant difference in vitamin D levels between the AS and control groups (22). In our study, we found 25(OH)D levels in AS patients to be significantly higher than those in the control group, as in the studies of Deng et al. and Klingberg et al. (22,23). The inconsistency may be attributed to the small number of patients, seasonal and regional variations, and vitamin D supplementation. In our study, we did not find a correlation between vitamin D data and BASDAI, CRP, and ESR, which indicate disease activity, or between NLR, PLR, and MPV, which can be an indicator of inflammation. The literature shows significant variability in the relationship between vitamin D levels and disease activity indicators. Like our findings, certain studies have not identified a correlation between vitamin D levels and BASDAI (24). However, some studies have found a strong correlation in which an increase in vitamin D levels corresponds to a reduction in markers of disease activity (25).

In some of the studies, the control group exhibited lower MPV values compared to the patient group, and there was a negative correlation between MPV and acute phase reactants in these investigations (26,27). In some cases, MPV values were observed to be lower in the patient group than in the control group. They observed reduced MPV values in patients with active inflammatory bowel disease (28). Kisacik et al. discovered that MPV values were lower in patients with active rheumatoid arthritis (RA) and ankylosing spondylitis (AS) compared to controls, and these values increased significantly after treatment (19). In our study, like to these investigations, we observed a significantly higher MPV level in the control group. No difference was observed between the control group and the group with a BASDAI of <4 (data not shown). However, a significant difference was noted between the patients with a BASDAI of ≥4, with the MPV values of the control group being significantly higher. This suggests that MPV can help us detect inflammation. In our study, we also observed a negative correlation between MPV and BASDAI, an indicator of disease activity. In situations where acute phase reactants, such as in ankylosing spondylitis (AS), may not be indicative of disease activity, examining the MPV level appears to be a cost-effective method that can aid in detecting disease activity.

Variations in the literature may be attributed to the stage of inflammation in the patient and the duration of the sample collection. It has been shown clinically that inflammatory diseases influence hematopoiesis, causing the most thrombocytosis and anemia (29). It has been suggested that elevated cytokines, particularly IL-6 levels, could influence platelet stimulation, leading to the release of a significant number of platelets from the bone marrow (30). This could elucidate the higher MPV values observed in some studies among AS patients compared to the control group, potentially due to an increase in circulating young platelets. In some studies, reduced MPV values might be attributed to the substantial consumption of platelets in the inflamed area (31). Moreover, it has been proposed that the excessive production of proinflammatory cytokines and acute phase reactants may impact the megakaryopoiesis process,

leading to the future release of small-volume platelets from the bone marrow and consequently a decrease in platelet size (32,33). Additional studies are necessary to elucidate and clarify this situation.

In our study, the NLR and PLR did not show statistically significant differences in the patient group when analyzed according to sex. Although MPV and CRP were higher in males, BASDAI was higher in females. It can be thought that this is because females feel pain due to lower vitamin D levels and that conditions such as fibromyalgia are more common in females (34). Furthermore, in the comparison between the male patient and control groups, MPV was lower, while Vit-D, NLR, and PLR levels were significantly higher in the patient group. These values were not different between the female patient and control groups. This may be due to the small number of females.

The study had several limitations. Firstly, it is important to note that this study is limited by its single-center design and a relatively small sample size. Another constraint is that the control group was chosen from individuals experiencing nonspecific joint or muscle pain rather than from a pool of healthy volunteers. Additionally, the retrospective nature of the evaluation is another notable limitation. Prospective randomized studies with well-defined control groups are likely to yield more accurate results. Moreover, the retrospective analysis limited our access to clinical data, preventing us from tracking changes in NLR, PLR, and MPV values with treatment during follow-up. It is clear that vitamin D levels are affected by seasonal changes. Although the tests were analyzed between May and September, this parameter also affected the results of our study. In conclusion, while our study identified higher serum 25(OH)D3 levels in ankylosing spondylitis patients compared to healthy controls, no significant correlation was observed between these serum levels and the severity of the disease. However, we found a significant negative correlation between serum MPV level and BASDAI, CRP, and ESR, which are indicators of disease activity. Larger prospective investigations are needed to accept the use of inexpensive and easily available MPV in disease follow-up.

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Knowledge And Opinions Of Individuals With Chronic Obstructive Pulmonary Disease About Long-Term Oxygen Therapy

Uzun Süreli Oksijen Tedavisi Uygulanan Kronik Obstrüktif Akciğer Hastalığı Olan Bireylerin Oksijen Tedavisi Hakkındaki Düşünceleri ve Bilgi Düzeyleri

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ABSTRACT

Aim: The aim of the study was to determine the feelings and thoughts of patients who have received long-term oxygen, the problems they experience, and their level of knowledge about oxygen use.

Material and methods: In the study, in-depth interviews were conducted with 12 patients who were treated in a training and research hospital and underwent long-term oxygen therapy. It was a qualitative study and the data were recorded on a voice recorder using a patient information form and a semi-structured interview form. After the data were analyzed, content analysis was conducted and reported.

Results: Three main themes and seven sub-themes were found through the analysis of the data. The main themes are reactions to long-term oxygen use, what is known about the issues to be considered in long-term oxygen use, and the effects of long-term oxygen use on patients. Conclusion. As a result of our study, it was found that patients with COPD who were on long-term oxygen therapy had limited knowledge about long-term oxygen use, oxygen use had positive effects on dyspnea and home activity management, made them feel good, but they had difficulties due to reasons related to the transportation of oxygen outside the home.

Keywords. COPD, knowledge level, long-term oxygen use, nursing, qualitative research.

ÖZ

Amaç: Araştırmanın amacı, uzun süreli oksijen kullanan hastaların oksijen kullanımı hakkında duygu ve düşünceleri, yaşadıkları sorunlar ve bilgi düzeylerinin belirlenmesidir.

Yöntem: Araştırmada bir eğitim ve araştırma hastanesinde tedavi gören ve uzun süreli oksijen tedavisi uygulanan 12 hasta ile derinlemesine görüşme yapıldı. Nitel bir araştırma olup, veriler hasta bilgi formu ve yarı yapılandırılmış görüşme formu kullanılarak, ses kayıt cihazına kayıt edildi. Veriler incelendikten sonra içerik analizi yapıldı ve raporlandırıldı.

Bulgular: Verilerin analizi ile üç ana tema ve yedi alt tema bulundu. Ana temalar; uzun süreli oksijen kullanımına verilen tepkiler, uzun süreli oksijen kullanımında dikkat edilmesi gereken hususlar hakkında bilinenler, uzun süreli oksijen kullanımının hastalar üzerindeki etkileri şeklindedir.

Sonuç: Yaptığımız çalışma sonucunda KOAH olan ve uzun süreli oksijen tedavisi uygulanan hastaların uzun süreli oksijen kullanımı konusunda kısıtlı düzeyde bilgilerinin olduğu, oksijen kullanımının dispne ve ev içi aktivite yönetiminde olumlu etkilerinin olduğu, kendilerini iyi hissetmelerini sağladığı, ancak ev dışında oksijenin taşınması ile ilişkili nedenlerden dolayı sıkıntı yaşadıkları saptandı.

Anahtar kelimeler: KOAH, bilgi düzeyi, uzun süreli oksijen kullanımı, hemşirelik, nitel araştırma.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, treatable, and preventable condition characterized by chronic airflow limitations and progressive respiratory symptoms (1). In COPD, long-term oxygen therapy (LTOT) is the most commonly used treatment method for acute and chronic respiratory failure (2). LTOT is recommended to be used for more than 15 hours a day (3,4). Oxygen therapy prevents pulmonary vasoconstriction, stabilizes or reduces pulmonary arterial pressure, improves pulmonary hemodynamics, increases exercise tolerance, improves sleep quality and profile, reduces dyspnea, polycythemia, and nocturnal arrhythmias (5,6), and decreases morbidity and hospitalizations (4,7).

Patients undergoing LTOT should be informed about issues such as concentrator cleaning and maintenance, use of a humidifier, and length of the connection hose (8). Especially when used in high concentration and for a long time, oxygen; It should not be forgotten that it may cause toxic effects such as hypoventilation, atelectasis, pulmonary oxygen toxicity, irritation, oxidative stress, and peripheral vasoconstriction (6,9). In oxygen therapy, accidents and fires associated with transportation, filling, and use of oxygen devices present the greatest risk (10). A distance of at least 1.5 m must be maintained between oxygen cylinders and heat sources and electrical appliances. Patients should be advised not to use oxygen therapy while smoking due to the risk of fire and explosion (11). To prevent facial and upper respiratory tract burns, it should be recommended not to have a beard and not to use hair care products containing alcohol and oil (12).

LTOT is a distressing treatment that restricts daily activities, and treatment compliance has been shown to be around 17%–70% (13). In a study by Anar et al. (2012), anxiety, and depression levels were found to be high in patients receiving LTOT and the reason for this was defined as the almost complete loss of functionality of patients receiving LTOT, dependence on people around them and oxygen concentrator, and inadequate family and community support (14).

In a study by Godoy et al. (8), it was found that patients who underwent LTOT did not comply with the recommended daily amount of oxygen use and flow meter setting, continued to smoke, and were exposed to cigarette smoke despite not smoking (8). Moreover, in a study by Gediktaş et al. (15), it was found that patients did not have sufficient knowledge about oxygen use and therefore received irregular and ineffective oxygen therapy (15).

By determining the thoughts and knowledge levels of individuals with COPD who undergo LTOT regarding oxygen use, training and approaches tailored to the needs of individuals can be provided. The aim of this study was to determine the feelings and thoughts, problems experienced and knowledge levels of individuals, who underwent LTOT, about oxygen use.

Material and Methods

The research was carried out in a phenomenological design with a qualitative research method. In line with this aim, the following questions were sought to be answered: (1) What are the perspectives of individuals diagnosed with COPD on home-based LTOT? (2) Do individuals diagnosed with COPD have sufficient knowledge about the process of applying LTOT at home? (3) What are the problems experienced by individuals diagnosed with COPD during the LTOT application process?

Population and Sample of the Study

The study was conducted with individuals diagnosed with COPD and who received LTOT in a hospital between October and November 2022. Patients to be interviewed in the study were selected by a non-probability-based, purposive, and homogeneous sampling method. Twelve patients who had been receiving oxygen therapy for at least 6 months, had no hearing and speech problems, were over 35 years of age, were inpatients in the chest diseases department, and agreed to participate in the study were interviewed. Patients who did not want to participate in the study, who had hearing-speech disabilities, who could not communicate due to speaking different languages, and who were diagnosed with major psychiatric illnesses (dementia, schizophrenia, etc.) were excluded from the study.

In qualitative research, there is no definite rule for the number of people to be included in the research. The sample size is determined mostly in line with the research question and its purpose. It is stated that it will be sufficient to continue the interviews until no new information emerges (16). For this reason, data collection was continued until the point where concepts and processes that could answer the research question started to repeat (saturation point). In this study, with 12 patients, the data collection process was completed with the feeling that the data was now repeating itself.

Data Collection Tools

The "patient information form" and "semi-structured interview form" created by the researchers were used as data collection tools. The patient information form includes questions about the patient's age, gender, how many hours a day they use oxygen, and information about oxygen use. There are three questions in the semi-structured interview form: (1) What were your feelings and thoughts when you learned that you needed to apply oxygen therapy at home? (2) How should be the use of oxygen at home, what should be considered? (3) How did your long-term use of home oxygen therapy affect your daily life? What kind of problems did you have? How has oxygen therapy made your life more comfortable?

Data Collection

The interview was conducted by an experienced female nurse who completed her master's degree. The researchers had no affiliation with the participants before the study began. During the interview, there was no one in the room except the participants and the researcher. The interviews were conducted in quiet, well-lit, single-person patient rooms where individuals could express themselves uninterruptedly. Patients were informed that their identity would remain confidential and that the information they provided would not be used for purposes other than scientific research. The patient was informed about the purpose of the interview and that a voice recorder would be used during the interview. Written and verbal consent was obtained before the interview. The researcher asked the patients the questions in the interview form and the interview was recorded on a voice recorder. The interviews lasted about 20 min. A second interview was not conducted with the patients.

Analysis of Data

Thematic analysis was used in data analysis. The interviews recorded with the tape recorder by the researcher were turned into written documents. The data turned into written documents were coded. The documented data were examined repeatedly and codes suitable for the purpose were obtained. Each code was a descriptive tag with a specific meaning in accordance with the research purpose. These codes and themes were then evaluated by the other researcher. After all the documents were coded, the codes obtained were evaluated together according to their similarities and sub-themes and themes were created. Documents were not provided to patients

for comment or correction. No feedback was requested from the patients about the codes obtained. A consensus was reached by the researchers about the codes and themes. Afterwards, all data were analysed and made into a report.

Measures Taken for Validity and Reliability

The validity of qualitative research is the observation of the subject as objectively as possible. For this, methods such as participant confirmation, peer confirmation, and expert review should be used. The collected data should be presented directly with a descriptive approach. To ensure the internal reliability (consistency) of the research, the collected data should be presented directly with a descriptive approach (17). Interviews were conducted without any guiding behaviour or subjective judgments. To ensure the internal validity of the study, the patient information form and semi-structured interview questions were created and the literature on LTOT and patients using this treatment was reviewed. To ensure the internal reliability of the research, all the findings were given directly without comment. After the interview, patients were asked if there were any issues they would like to add or remove.

Ethical Aspect of Research

Ethics committee approval was received from Istanbul University-Cerrahpaşa Social and Humanities Research Ethics Committee (approval dated 27/05/2022 and numbered 2022/150). All participants gave their informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki.

Results

The data obtained from 12 patients with COPD who underwent LTOT in the study are shown in Table 1.

Three main themes and seven sub-themes were identified from the reported data. The distribution of main themes and sub-themes is shown in Table 2.

Main Theme 1. Responses to long-term oxygen use

In line with the information provided by the patients, two sub-themes were created under the main theme of "responses to long-term oxygen use".

Sub-theme 1.1. Positive responses to long-term oxygen use

It was determined that the patients expected to use oxygen for a long time, felt that oxygen use would be good for them, and were satisfied with this situation.Patients stated that they were happy and delighted when they learned that they would be using oxygen for a long time.

"I did it willingly. I felt nothing. I was not surprised. Because I knew it would happen. I had COPD for 8-9 years before, so I knew it was coming." (Patient 2)

"Well, it was very nice" (Patient 7)

"I wanted to feel fine at that moment. I felt that I would be fine" (Patient 8)

Sub-theme 1.2. Negative responses to long-term oxygen use

It was determined that patients' learning that they would continue their lives with a device they did not know caused them to develop negative feelings towards oxygen use. Patients stated that they were worried and upset when they learned that they would be using oxygen for a long time. It was found that they developed a positive perspective after they were informed about the use of oxygen and felt that oxygen therapy was good for them.

"When I found out, I was hesitant at first. I will continue my life dependent on oxygen. This is the case. So I was afraid. I am now informed. We need oxygen care every week because I know." (Patient 1)

"At first I felt very bad. I felt like I could live connected to the machine. But when I saw its benefits, of course, I learned it on my own and I'm trying it right now. Inevitably, it throws you off balance because something that you are not used to comes across and you do not know what to do. But we must get used to it in time." (Patient 5)

"They already gave it to me in the hospital. I said, I guess I will have a machine next to me from now on. That's all. I mean, I was upset about something else." (Patient 3)

"I hesitated. How to use it. I learned how to use the machine after being hospitalized here after learning it. Then I thought it would be to my benefit." (Patient 4)

"At first I was afraid of the machine. It is not easy to live with them. It's hard to get used to. I couldn't get used to it at first. But then, you get used to it. So it's not possible without them anymore. Because it is superb when you get used to it." (Patient 11)

"I just felt bad. You feel that you are falling behind in healthy living. That's the first thing. You get used to it. You're going where life isn't that bad. A new life enters the life that oxygen enters. It becomes your life companion. Without it, you have a hard time." (Patient 12)

Main Theme 2. What is known about the points to be considered in long-term oxygen use?

In line with the information provided by the patients, three sub-themes were created under the main theme of "What is known about the issues to be considered in long-term oxygen use".

Sub-theme 2.1. Moisturizing

It was determined that the patients paid attention to the issues of filling the water tank to the maximum and washing and drying the water tank during long-term oxygen use.

"Now I must change the water, wash the jar and add water again." (Patient 1)

"We check if there is water in the bottle." (Patient 2)

"There is water in this big machine. I'll take that one, it's the same one. So this is a bit over the level. Over the level." (Patient 4)

"We were told to change the water daily, that it should be at the bottom of the maximum, so we leave it there." (Patient 6)

"We check the water level. It must not run out of water. Water must be" (Patient 8)

"You must change the water in five days." (Patient 9)

"Yes, I was putting some (water) at home. It was good for me." (Patient 11)

"We always use with water. It has indicators. As soon as it goes below the mark, you must put the water in." (Patient 12)

Sub Theme 2.2. Flowmeter adjustment.

It was found that the patients knew the need for flowmeter adjustment in oxygen use. The patients' have explained that they made adjustment of flowmeter by their as taught.

"The doctor already determines it, adjusts it according to the doctor's thing, we use it." (Patient 1)

"When we looked at its ball, there was this bead. If that bead

Table 1. Patient information form data

Patients	Gender	Age	Oxygen use time at home	Daily oxygen usage time (hours)	Oxygen flowmeter setting (lt/min)	Status of traininig about the use of oxygen
Patient 1	Male	62	1 year	1	2	No
Patient 2	Male	75	6 mount	24	4	No
Patient 3	Male	46	6 mount	24	3	Yes
Patient 4	Male	67	3year	16	3	Yes
Patient 5	Female	39	6 mount	10	5	Yes
Patient 6	Female	75	1 year	24	2.5	Yes
Patient 7	Male	76	8 mount	24	5	No
Patient 8	Female	64	6 year	20	1.5	Yes
Patient 9	Male	70	1 year	20	3	Yes
Patient 10	Male	68	3 year	15	3	Yes
Patient 11	Female	42	1 year	20	5	Yes
Patient 12	Male	63	13 year	10	2.5	Yes

Tablo 2. Main themes and sub-themes

Main Theme	Sub-theme	n (declaration)
Responses to long-term oxygen use	Positive responses to long-term oxygen use	3
	Negative responses to long-term oxygen use	6
What is known about the points to be considered in long-term oxygen use?	Moisturizing	7
	Flowmeter adjustment	8
	Maintenance of the device	5
Effects of long-term oxygen use on patients	Making feel fine	7
		7

goes up, you adjust accordingly. So you can do it there. The one at home will be at 3 at the most. Maybe at 4." (Patient 4)

"I must use the flowmeter between 5 and 6. I use an average of 5.5." (Patient 5)

"We were told that the standard should be used at 2.5." (Patient 6)

"It will be in the same setting, as I just said (flowmeter) it will not be too much. 1.5." (Patient 8)

"I know there is a setting. It needs to go from 3." (Patient 9)

"They adjusted it from where we got it (flowmeter). We use it accordingly. It goes from 5-6." (Patient 11)

"Well, as I said, from the highest to the lowest, of course. At 2.5" (Patient 12).

Sub Theme 2.3. Maintenance of the device

It was determined that patients were knowledgeable about device maintenance. The patients stated that device maintenance and filter changes were made at certain intervals.

"There is a certain time to change the filters." (Patient 1)

"It takes 2 years to change the filter and I changed it in one year." (Patient 6)

"When the 5 months are up, I will take it to the service. Well will do maintenance." (Patient 9)

"Device is serviced. We have it serviced every two years." (Patient 11)

"Even mechanics say that. When it goes to the maintenance." (Patient 12)

Main theme 3. Effects of long-term oxygen use on patients

In line with the patients' explanations, two sub-themes were created under the main theme of "The effects of long-term oxygen use on patients".

Sub Theme 3.1. Making feel fine

It was determined that long-term oxygen use had positive contributions to the patients' treatments, improved their current health levels and made them feel good because it enabled them to do indoor activities more comfortably. Patients stated that LTOT was good for them, that it eased their breathing, and that they felt bad if they did not use oxygen.

"If you don't use it, you can't sustain your life. When you put it on, the oxygen gives a comfort. In short, it saves lives and gives breath." (Patient 1)

"Oxygen has its benefits. It made my breathing easier." (Patient 2)

"But when you use it regularly, I see the benefits very well. I got better." (Patient 5)

"No, it didn't cause any problems. No, it's comforting. It did me good to be well." (Patient 7)

"Well, it felt very good for us to get this oxygen. I feel bad when I don't use it. I couldn't walk properly. You can't go down the stairs, you can't breathe, so this relaxes your body." (Patient 4)

"So far so good. It's a good day for us. It relaxes me." (Patient 9)

"I could never walk, I couldn't do any work. There was some

strength when there was oxygen." (Patient 11)

Sub-theme 3.2. Restrictions on daily activities

It was determined that the patients' experienced restrictions in daily activities due to their dependence on the device both inside and outside the home. Patients stated that they experienced restrictions in daily activities due to dependence on the device, restriction of movement within the home, transportation of the device, and difficulty in accessing electricity outside the home.

"When you want to go somewhere, you can't go because it is plugged into the electricity. It is not clear when it (shortness of breath) will come, whether you are stuck in the evening or during the day, I wear it when I am stuck." (Patient 1)

"If we want to go out and look for something, we can't. Because you will constantly transfer the tube to the chair, you will put the tube on and then you will go." (Patient 2)

"You can't cook, you can't do your work, it affects everything. You are connected to a machine." (Patient 5)

"I can't say anything. I can't go to the restroom. I can't take a bath comfortably, so..." (Patient 3)

"There are many ways in which it makes life difficult. You can't go anywhere. When you go to your hometown, you'll carry it back and forth. That's the way it is. You are having difficulties." (Patient 10)

"I cannot take my son to school as he wants. His grandmother brings him. I can't do the hustle and bustle. I was very active in the house, I was not like that." (Patient 11)

"When you start using oxygen, you can no longer move on your own. You've got a man with you. On the way to and from the hospital. You wear oxygen all the time. Yes, you start to depend on someone." (Patient 12)

Discussion

Psychosocial responses to the disease are all cognitive, emotional, and behavioral responses that occur to protect the psychological integrity of the patient (18). The most common emotional reactions that generally occur in patients are anxiety, fear, anger, powerlessness, sadness, inadequacy, failure, shame, guilt, hope-despair, and relief. Ellis and Nowlis (19) defined the disease process in patients with physical illness in five stages after the onset of the disease: disbelief and denial, irritability and anger, attempt to gain control, depression, acceptance, and cooperation (19). In the sub-theme of "Positive responses to long-term oxygen use" in this study, patients stated that they were happy and delighted when they learned that they would use long-term oxygen. In the sub-theme "Negative responses to long-term oxygen use", it was determined that patients were worried and upset when they learned that they would use long-term oxygen, but developed a positive perspective after they were informed about oxygen use and felt that oxygen therapy was good for them. The patients' statements are similar to the psychosocial reactions to the disease encountered in the literature.

The application of LTOT is decided by arterial blood gas values (20,21) and should be applied at a certain flow rate (22). Oxygen therapy given at high concentrations for a long time and without humidification causes drying and irritation in mucous membranes (23,24). To prevent drying and irritation of the mucous membranes, if the oxygen flow is above 4lt/min, oxygen should be used by humidifying it (8,22,25,26). In a study, it was found that 97% of patients used oxygen by humidifying (8). In this study, under the main theme of "What is known about the issues to be considered in long-term oxygen use", in the sub-theme of "Humidification", it was determined that patients had knowledge about humidification in long-term oxygen use. In the sub-theme "Flowmeter adjustment", it was found that patients were informed about the need for flowmeter adjustment. The data obtained are similar to those reported in the literature.

Device maintenance and adjustments are important for optimal benefit from the devices (27). The filters of the devices should be cleaned regularly and replaced according to the manufacturer's instructions (28). In a study, it was reported that 34.2% of patients had regular device maintenance and 65.8% did not have regular maintenance (27). In this study, in the sub-theme of "Device Maintenance", patients stated that they had device maintenance and filter replacement at certain intervals. It was determined that the patients had knowledge about device maintenance in the use of oxygen.

Dyspnea is a common and uncomfortable symptom for patients with COPD. Dyspnea management includes optimized COPD treatment with bronchodilators, pulmonary rehabilitation, regular use of low-dose opioids, and home oxygen therapy (29). Although it has been reported that LTOT may help to improve respiratory and general health-related quality of life (5), there are also studies reporting that long-term supplemental oxygen does not reduce dyspnea in daily activities, does not affect health-related quality of life (30,31,32) and does not have a consistent benefit in relation to depression, anxiety or functional status measures (33). In a study, 85.5% of patients receiving LTOT stated that they benefited from oxygen use, whereas 11.8% stated that they did not benefit (27). In this study, there is a sub-theme of "feeling good" under the main theme of "The effects of long-term oxygen use on patients". When the literature is reviewed, it is reported that there is no consistent benefit of long-term oxygen therapy in terms of decreased dyspnea level, quality of life, depression, anxiety, or functional status measurements in patients using oxygen. Yet, in this study, patients stated that LTOT was good for them, that it relieved their breathing, and that they felt bad if they did not use oxygen.

Caregivers of oxygen-using patients play an important role in the management of oxygen equipment outside the home (28). n a study conducted with patients using portable oxygen, it was reported that patients were afraid that the oxygen would run out of the cylinder when they were away from home and that the cylinder was heavy to carry (33). Tanrıverdi and Hasanoğlu (34) reported that patients experienced problems related to the restriction of movement (34). Moreover, in another study, it was reported that oxygen use restricted patients' travel (30%) and socialization (22%) (35). In this study, regarding the sub-theme of "restriction in daily activities", patients reported dependence on the device because they needed to use oxygen continuously, restriction in daily activities due to limitations of movement within the house, the transportation of the device, difficulty in accessing electricity outside the house, and problems when going out of the house. Patients' statements about the restriction of movement are similar to the findings in the literature.

Conclusion

LTOT is among the preferred methods in the management of COPD. Based on the results of the study, it was found that LTOT application had positive effects on dyspnea and in-home activity management in patients with COPD, and made the patients feel better, but they experienced difficulties due to reasons related to the transportation of oxygen outside the home. It is crucial for the patients who have undergone LTOT to have knowledge about the use of oxygen to maintain the treatment effectively and reliably. Based on the results of the study, it has been determined that patients have a partial understanding of the uses of oxygen. It is recommended that patients should be

trained to maintain LTOT effectively and reliably and that the training should be repeated according to patient needs.

It is recommended that the study be conducted with larger sample groups.

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Conflicts of interest

The author(s) declare no competing interests.

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Use of platelets and their properties in predicting fibrosis and activity in HBV infection

Platelet ve özelliklerinin HBV enfeksiyonunda aktivite ve fibrozis tahmininde kullanımı

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ABSTRACT

Aim: Although liver biopsy is the gold standard diagnostic method for showing histological activity and fibrosis today, there are some non-invasive methods using biochemical calculations as an alternative since it is an invasive procedure. In our study, we aimed to examine the relationship between platelets and some related parameters and histopathology in patients who underwent liver biopsy due to chronic hepatitis B virus (HBV).

Material and Method: 70 patients diagnosed with chronic HBV and followed up between 2009 and 2013 were included. Demographic data, liver histopathological results and laboratory parameters of all patients were documented. The relationship between histopathology and platelets and some related laboratory parameters was examined.

Results: A total of 70 patients, 28 (40%) of whom were women, were included in the study. A statistically significant relationship was detected between hepatic activity index (HAI) and AST (p=0.001), ALT (p=0.001), Sedimentation (p=0.026, r=0.5) and aspartate aminotransferase and alanine aminotransferase ratio (AAR), aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on the 4 factor (FIB-4) (p<0.05). A statistically significant relationship was found between fibrosis and International Normalized Ratio (INR), between PDW/Platelet count, and between Platelet count/PDW (p<0.05). Additionally, the relationship between fibrosis and APRI, FIB4 and red cell distribution (RDW) width to platelet ratio (RPR) was statistically found significant. (p<0.05). No correlation was found between HAI and Platelet, RDW, PDW (p>0.05).

Conclusions: Platelet, RPR and RDW have been shown to be associated with the degree of fibrosis. It is thought that RPR, which is an inexpensive and easily calculable index, can predict significant fibrosis and cirrhosis with relatively high accuracy in chronic hepatitis patients, potentially reducing unnecessary liver biopsies.

Key Words: Fibrosis, Chronic hepatitis B, Inflammation, Platelet, RPR.

ÖZ

Amaç: Günümüzde histolojik aktiviteyi ve fibrozisi göstermede altın standart karaciğer biyopsisi olmasına karşın invaziv bir işlem olması nedeniyle alternatif olarak biyokimyasal hesaplanan bazı noninvaziv yöntemler bulunmaktadır. Biz de çalışmamızda kronik hepatit B virüsü (HBV) nedeniyle karaciğer biyopsisi yapılan hastalarda platelet ve ilişkili bazı parametrelerin histopatoloji ile olan ilişkisini incelemeyi amaçladık.

Gereç ve yöntem: Kronik HBV tanısı ile 2009 ile 2013 yılları arasında takipli, 70 hasta dahil edildi. Tüm hastaların demografik verileri, karaciğer histopatolojik sonuçları ile laboratuvar parametreleri dökümante edildi. Histopatoloji ile platelet ve ilişkili olduğu bazı laboratuar parametreleri arasındaki ilişki incelendi.

Bulgular: Çalışmaya 28 (%40) kadın olmak üzere toplamda 70 hasta alındı. Hepatik aktivite indeksi (HAİ) ile AST (p=0.001), ALT (p=0.001), Sedimantasyon (p=0.026, r=0.5) ve aspartat aminotransferaz ve alanin aminotransferaz oranı (AAR), aspartat aminotransferaz/trombosit oranı indeksi (APRI), 4 faktöre dayalı fibrozis indeksi (FIB-4) arasında istatistiksel olarak anlamlı ilişki saptandı (p<0.05). Fibrozis ile İNR arasında, PDW/Platelet arasında, Platelet/PDW arasında (p<0.05) istatistiksel olarak anlamlı ilişki bulundu. Ayrıca Fibrozis ile APRI, FIB4 ve kırmızı hücre dağılımı ile RPR arasındaki ilişki istatistiksel olarak anlamlı bulundu (p<0.05). HAİ ile Platelet, RDW, PDW korelasyonu bulunamadı (p>0.05).

Sonuç: Trombosit, RPR ve RDW'nin fibrozisin derecesi ile ilişkili olduğu gösterildi. Pahalı olmayıp kolay hesaplanabilir bir index olan RPR, potansiyel olarak gereksiz karaciğer biyopsilerini azaltarak kronik hepatit hastalarında nispeten yüksek doğruluk oranıyla belirgin fibrozis ve sirozu tahmin etmeyi sağlayabileceği düşünülmüştür.

Anahtar kelimeler: Fibrozis, Kronik hepatit B, İnflamasyon, Platelet, RPR.

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Introduction

Hepatit B virus (HBV) is a member of the hepa-DNA virus family, and HBV infection is one of the most important causes of cirrhosis and hepatocellular carcinoma. HBV, for which there is an effective vaccine, continues to be a serious public health problem all over the world (1, 2). Liver fibrosis is a chronic process that is seen in the course of all chronic liver diseases, regardless of their etiology, and ends with the development of cirrhosis if it is not treated. Liver fibrosis and cirrhosis are the most important causes of morbidity and mortality in chronic hepatitis B patients. Although antiviral treatment significantly reduces the risk of fibrosis and cirrhosis, advanced fibrosis and cirrhosis may develop in some patients (1, 2).

Laboratory (serum transaminases), serological diagnosis, molecular diagnosis and pathological diagnosis methods are used in the diagnosis of chronic viral hepatitis. Histopathological examination of the liver, especially hepatic activity index (degree/grade) and fibrosis (stage/stage), has an important place in the diagnosis and staging of liver disease, estimating the prognosis, and making treatment decisions for patients (3).Treatment decisions are often made based on the results of liver biopsy, which is an invasive procedure. Liver biopsy is the gold standard in determining the histo-pathological results of liver disease (3, 4). However, biopsy is an invasive procedure and involves some complications (4). Therefore, non-invasive, economical and simple methods should be developed to determine the severity of hepatic fibrosis.

In studies conducted on non-invasive tests, it has been thought that some calculated values such as Fibrosis-4 (FIB4), Aspartate Amino Transferase-Platelet Ratio Index (APRI), Aspartate Amino Transferase-Alanine Amino Transferase Ratio (AAR) may be related to fibrosis and histological stage (5, 6). Following the studies carried out, the use of non-invasive methods in places with limited examination was added to the diagnosis and treatment guide by the World Health Organization (WHO) in 2015 (7). Therefore, we aimed to determine whether platelets and their properties could be effective in determining histological activity index and fibrosis in HBV infection.

Materials and Methods

70 chronic hepatitis B patients who were diagnosed, treated and followed up by our hospital's Hepatology outpatient clinic between 2009 and 2013 were included in this clinical study. Our study was designed retrospectively. Patients with HBsAg positivity and/or high liver function test levels and HBV-DNA positive results for six months were evaluated as chronic HBV and liver biopsy was performed. Demographic data (age, gender) of all patients were recorded. Histopathological data of the patients were documented. A comparison was made in terms of biochemical parameters in chronic HBV patient groups.

Biochemical and hematological measurements:

Biochemical parameters were measured from antecubital venous blood samples taken after 8 hours of fasting. Among the biochemical parameters, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl trans peptidase (GGT), total bilirubin, direct bilirubin, albumin, prothrombin time (PT), INR level were measured. Some formulas as were calculated from the biochemical parameter sex amin.

1. AAR=Obtained by dividing AST by ALT (8).

2.APRI=APRI: Calculated using the formula [(AST/Upper Limit of Normal/PLT (10^9/L)] × 100 (9).

3. FIB4=FIB-4 score was calculated using the formula = Age ([year] x AST [U/L]) / ((PLT [109/L]) x (ALT [U/L])(1/2)) (10).

4. RPR= RDW(%) / Platelet (10^9/L) (11).

Liver biopsy and histopathological evaluation

Liver biopsy was performed using a 16 G biopsy needle under ultrasonography guidance. Samples with liver biopsy material length less than 1.5 cm and insufficient number of portal areas for evaluation were excluded from the study. The received materials were evaluated by three different experienced pathologists without providing clinical information. Knodell histological hepatic activity score was used to make grade and staging (12). The presence of fibrosis in liver biopsies was determined according to the Scheuer score (13).

Ethical Approval

Approval was received for this study from İnönü University Ethics Committee.

Statistical Analysis

The results of our study were analyzed with the program "The Statistical Pack age for the Social Sciences 22.0 (SPSS Armonk, NY: IBM Corp.)". Continuous data were given as mean (± standard deviation), and categorical data were given as frequency and percentage (n,%). Data were tested for normal distribution using the Kolmogorov-Simirnov test, histogram and ± SD. Parametric data of the groups were compared between paired groups were made using post-hoc test. Chi-square test was used to test categorical data. $P<0.05$ were considered statistically significant.

Results

Seventy patients with chronic hepatitis B who underwent liver biopsy were included in the study. 60% (42) of the patients included in the study were male and 40% (28) were female. The average age was found to be 42.1±12.8 years (age range 20-67 years).When the laboratory values of the patients are analyzed; AST=44.8±34.9 (14-209) IU/mL, ALT=68.6±59.5 (5-318) IU/mL, ALP=73.1±26.6 (23-153) IU/mL, GGT=36.9±24.1 (9-125) IU/mL, LDH=195.8±72.1 (105-611) IU/mL, INR=1.06±0.9 (0.8-1.3) was detected as. HAI score in our patients; it ranges from 1 to 14, and the average was found to be 5.88 ± 2.4.

The fibrosis score ranged from 0 to 6, with an average of 2.3 ± 1.2 (Figure 1). A significant correlation was detected between fibrosis and HAI (p=0.000 correlation r=0.57). The correlation between HAI and AST (p=0.001) and ALT (p=0.001) was found to be statistically significant. Statistically significant differences were found between HAI and AAR, APRI, FIB4. A correlation was observed between HAI and erythrocyte sedimentation rate (p=0.026, r=0.5). No correlation was found between HAI and Platelet, RDW, PDW. A correlation was observed between fibrosis and INR (p=0.02, r=0.2). A statistically significant difference was found between fibrosis and PDW/PLT. The relationship between fibrosis and APRI, FIB4 and RPR was found to be statistically significant (Table 1). The relationship between HAI, fibrosis scores and PLT and PDW is presented in detail in Figure 2.

Discussion

HBV infection continues to be an important health problem in the world. Although liver biopsy is the gold standard for demonstrating hepatic tissue damage in diagnosis and follow-up, it is an invasive procedure that may have complications. Studies have shown that some laboratory parameters are close to biopsy in showing hepatic fibrosis (14, 15). The examinations are less costly than liver biopsy and provide more advantages in terms of accessibility (2, 15).

In a study conducted by Baode Chen et al. in 2012, they

Table 1. Relationship between HAI and Fibrosis values and laboratory parameters

		HAI	Fibrozis	Wbc	Hgb	Hct
HAI	r value	1	0,572	0,027	-0,103	-0,101
	p value		0	0,822	0,397	0,403
Fibrozis	r value	0,572	1	-0,053	-0,085	-0,093
	p value	0		0,661	0,482	0,446
		MCV	PLT	RDW	PDW	AST
HAI	r value	-0,085	-0,06	0,127	0,058	0,383
	p value	0,486	0,62	0,294	0,635	0,001
Fibrozis	r value	0,024	-0,226	0,032	0,169	0,225
	pvalue	0,843	0,06	0,794	0,162	0,061
		ALT	ALP	GGT	LDH	INR
HAI	r value	0,420	0,007	0,233	0,251	0,093
	pvalue	0	0,954	0,052	0,036	0,445
Fibrozis	r value	0,196	-0,048	0,275	0,177	0,268
	pvalue	0,104	0,69	0,021	0,142	0,025
		T.billirubin	D.billurubin	Albumin	Sedimentation	CRP
HAI	r value	0,048	0,063	0,157	0,510	0,126
	pvalue	0,692	0,606	0,193	0,026	0,682
Fibrozis	r value	0,076	0,069	-0,011	0,267	0,321
	pvalue	0,532	0,572	0,93	0,27	0,285
		PDR/ PDW	AAR	APRI	FIB4	RPR
HAI	r value	0,048	0,063	0,157	0,510	0,126
	pvalue	0,692	0,606	0,193	0,026	0,682
Fibrozis	r value	0,076	0,069	-0,011	0,267	0,321

investigated whether platelets and their properties were related to the development of fibrosis and cirrhosis in HBV infection;

RDW has been shown to be positively correlated with significant fibrosis and cirrhosis, while platelets and hemoglobin are negatively correlated with significant fibrosis and cirrhosis. It has been observed that the severity of liver fibrosis is significantly associated with the gradual increase in RDW and the decrease in hemoglobin and platelets. Compared to hemoglobin, platelet count was found to be more closely related to the degree of fibrosis. For this reason, it has been reported that RDW and platelets are the strongest determining risk factors in liver fibrosis (16). Similarly, in their study by Yuyun et al., where 1282 patients were evaluated; it was reported that RPR showed the best accuracy in predicting hepatic fibrosis, regardless of etiology. It has also been reported that combining RPR with white blood cell (WBC) count further increases the accuracy of grading hepatic fibrosis. This study arguest hattheuse of RPR, both alone and in combination with inflammatory parameters, would be beneficial to increase the accuracy of scoring hepatic fibrosis (11).

APRI score; It is a ratio calculated to estimate fibrosis with AST and platelet count parameters measured in the routine follow-up of patients with chronic hepatitis. The scoring system was first used by Wai et al. in patients with hepatitis C (17). In the study in question, the AUROC value of APRI was found to be 0.80 and 0.89, respectively, in the calculations made to predict fibrosis and cirrhosis. In a meta-analysis for the APRI score, the negative predictive value and the probability of excluding cirrhosis increased when the APRI score fell below 0.5; It was determined that when the scores increased above 1.5, the positive predictive value and the probability of cirrhosis increased (18).

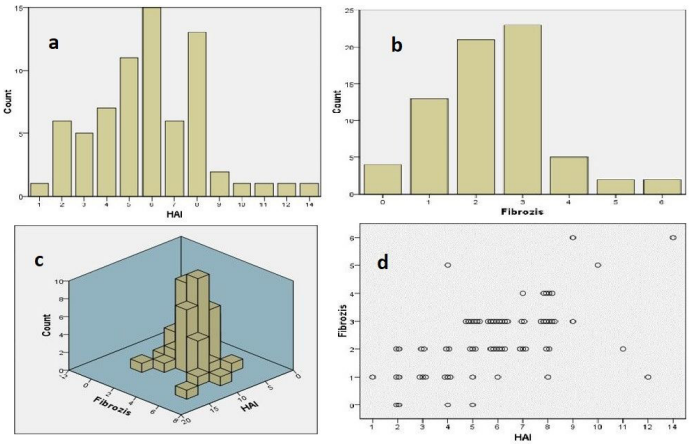

Figure 1. a. HAI (Histological Activity Index) rates of the patients included in the study, b. Fibrosis rates, c. Cross-relationship between HAI and Fibrosis, d. Cross-relationship between HAI and Fibrosis

There are studies in the literature showing that the AAR value is superior to the APRI value in determining fibrosis. In the studies in question, the positive predictive value for showing significant fibrosis was close to 90% when the AAR value was ≥1; It has been shown that in cases where the AAR value is <1, the negative predictive value indicating the absence of significant fibrosis is around 80% (19).

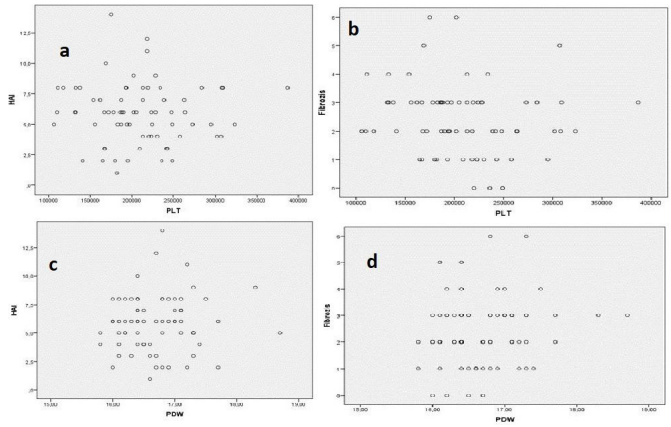

Figure 2. a. Relationship between HAI values and PLT of the patients included in the study, b. Relationship between fibrosis values and PLT, c. Relationship between HAI values and PDW, d. Relationship between fibrosis values and PDW

Fibrosis index (FIB-4), which is based on four parameters; AST is a formulation calculated using the ALT level, platelet count and age of the patient (20). The basic foundations of this approach are; These can be listed as increasing the duration of the disease and therefore fibrosis with age, increasing the AST value more than the ALT value due to the decrease in mitochondrial damage and clearance, and decreasing thrombopoietin and platelet values with periportal fibrosis (21). In the study conducted by Lee et al. in 2021; APRI and FIB-4 scores have been shown to have comparable performance to biopsy in risk stratification of liver-related mortality and morbidity in patients with non-alcoholic fatty liver disease (22).

Although our study is an important study examining the relationship between biochemical parameters and inflammation and fibrosis, it has some limitations. First of all, our study was designed retrospectively and the number of samples was small.

In addition, failure to detect certain conditions such as drugs and infections that may affect the level of biochemical parameters may lead to different results. On the other hand, the presence of all fibrosis stages in our patient group and the ability to make comparisons between fibrosis stage sare the strengths of our study.

Conclusion

Platelet and related parameters were shown to have a significant relationship with fibrosis. It has been shown that platelet and related parameters RDW and RPR are related to the degree of fibrosis. It is thought that RPR, which is an inexpensive and easily calculable index, can predict significant fibrosis and cirrhosis with relatively high accuracy in chronic hepatitis patients, potentially reducing unnecessary liver biopsies. However, more comprehensive studies are needed for non-invasive tests to replace liver biopsy.

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The Impact of the COVID-19 Pandemic on Maternal Mortality: An Example From A Province

COVID-19 Pandemisinin Anne Ölümü Üzerine Etkisi: Bir İl Örneği

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ABSTRACT

Aim: The aim of this study is to investigate the impact of the COVID-19 pandemic on maternal mortality in Kayseri.

Material and Method: In this descriptive study examined maternal deaths that occurred in Kayseri between 2017-2021. The maternal mortality ratio was calculated for Kayseri as the maternal deaths per 100,000 live births based on the total number of live births and maternal deaths for each year. The ratios for Kayseri and Türkiye were visualized using a histogram and a box-plot graph. The statistical analyses were performed using the SPSS, and a P-value of <0.05 was considered statistically significant. The Student's t-test was used to evaluate the mean differences between groups.

Results: The maternal mortality ratio for Kayseri was 18.6 per 100,000 live births in 2017, and it increased to 80 per 100,000 live births in 2021. At least one pregnancy-related risk factor was present in 84.6% of the cases, with obesity being the most common risk factor (34.4%). COVID-19-related deaths (30.6%) were the leading cause of maternal death. According to provincial health department reports, 73.1% of deaths were classified as indirect and 38.5% as preventable.

Conclusion: In Kayseri, there was a significant and unusual increase in maternal mortality in 2021, especially during the year when the delta variant of COVID-19 was active. Indirect maternal deaths predominated, and most of these were reported to be unpreventable.

Key Words: Maternal mortality, COVID-19, Coronavirus

ÖZ

Amaç: Bu çalışmanın amacı, COVID-19 pandemisinin Kayseri'deki anne ölümleri üzerine olan etkisini araştırmaktır.

Gereç ve Yöntem: Bu tanımlayıcı çalışmada, 2017-2021 yılları arasında Kayseri'de meydana gelen anne ölümleri incelenmiştir. Anne ölüm oranı, her yıl için toplam canlı doğum ve anne ölümü sayıları temel alınarak 100.000 canlı doğum başına düşen anne ölümü olarak Kayseri için hesaplanmıştır. Kayseri ve Türkiye'ye ait oranlar histogram ve box-plot grafiği kullanılarak görselleştirilmiştir. İstatistiksel analizler SPSS kullanılarak gerçekleştirilmiş ve P<0.05 olması istatistiksel olarak anlamlı kabul edilmiştir. Gruplar arasındaki ortalama farklılıkları değerlendirmek için Student's t-testi kullanılmıştır.

Bulgular: Kayseri için anne ölüm oranı 2017 yılında 100.000 canlı doğumda 18,6 iken 2021 yılında 100.000 canlı doğumda 80'e yükselmiştir. Vakaların %84,6'sında gebelikle ilişkili en az bir risk faktörü mevcut olup, obezite en yaygın risk faktörüdür (%34,4). COVID-19'a bağlı ölümler (%30,6) anne ölümlerinin önde gelen nedenidir. İl sağlık müdürlüğü raporlarına göre, ölümlerin %73,1'i dolaylı ve %38,5'i önlenebilir olarak sınıflandırılmıştır.

Sonuç: Kayseri'de 2021 yılında, özellikle COVID-19'un delta varyantının aktif olduğu yıl boyunca, anne ölümlerinde önemli ve olağandışı bir artış olmuştur. Dolaylı anne ölümleri ön planda olup, bunların çoğunun önlenemez olduğu bildirilmiştir.

Anahtar Kelimeler: Anne ölümü, COVID-19, Koronavirüs

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Introduction

The immunological and physiological changes that occur during pregnancy make pregnant women more susceptible to respiratory infections and complications (1). In particular, the involvement of the cardiopulmonary system increases the susceptibility of pregnant individuals to infections and poses a risk in terms of respiratory failure. As a consequence of maternal respiratory failure, adverse pregnancy outcomes such as hypoxemia, fetal distress, miscarriage, and preterm birth can occur (2). When examining the impact of COVID-19 on pregnancy, it has been observed that COVID-19 positive pregnant women have a higher likelihood of preterm birth, admission to the intensive care unit, and admission of their babies to the neonatal intensive care unit compared to others. Additionally, an increased risk of maternal mortality has been observed (3). In pregnant women diagnosed with COVID-19, it has been found that there is an increased risk of maternal and perinatal mortality compared to those without the diagnosis. In pregnant women experiencing severe COVID-19 symptoms, the risk of serious maternal complications is 2.5 times higher, the risk of perinatal complications is 1.8 times higher, and the likelihood of referral to an intensive care unit, hospitalization, or death is increased by 11.8 times compared to non-pregnant individuals (4). Centers for Disease Control and Prevention (CDC) advises pregnant women to be aware of the potential risks associated with severe COVID-19 disease and to take all necessary precautions to avoid exposure to COVID-19 (5).

Direct maternal deaths are deaths caused by obstetric complications, medical interventions, negligence and improper treatment during pregnancy, birth and postpartum period. Indirect maternal deaths are deaths caused by a non-obstetric disease that existed before pregnancy or developed during pregnancy, exacerbated by the physiological changes of pregnancy (6). COVID-19 not only directly affects pregnant and postpartum women, leading to more severe illness and various complications but also indirectly impacts maternal health, increasing maternal mortality due to its secondary effects (7) . Indirect effects are caused by factors such as travel restrictions during the pandemic, limited availability of resources, inadequate infection control measures, individuals' reluctance to seek healthcare due to fear of contracting the infection, and disruptions in the routine functioning of healthcare systems, leading to challenges in healthcare service delivery. These factors contribute to the indirect impact of COVID-19 on maternal health (7, 8). World Health Organization (WHO), in a report related to the provision of essential healthcare services during the COVID-19 pandemic, has warned that all healthcare services, including essential healthcare services for maternal health, have been disrupted, and this situation could lead to an increase in maternal mortality (9). Due to the measures taken to protect individuals from COVID-19 and to treat those who are infected, pregnant women may face difficulties in accessing both essential and other healthcare services. This can increase the risk of mortality, especially for high-risk pregnancies and obstetric emergencies (7). In a study conducted in 118 countries, it has been estimated that a reduction in the coverage of maternal health services by 9.8% to 18.5% over six months during the COVID-19 pandemic would result in an additional 12,200 maternal deaths. Similarly, a more significant reduction in coverage by 39.3% to 51.9% would lead to an additional 56,700 maternal deaths. These additional deaths correspond to a monthly increase in maternal mortality ranging from 8.3% to 38.6% (10).

On the other hand, while research in many countries has concluded that maternal mortality ratios during the pandemic exceeded expectations, there are also publications suggesting that COVID-19 infection is associated with an increased risk of admission to intensive care and mechanical ventilation during pregnancy but may not be directly linked to an increased risk of mortality (11, 12) . To our knowledge, there have been only a few hospital-based studies on this topic in Türkiye, and these studies have not covered the entire province or region (13).

The aim of this study is to investigate the impact of the COVID-19 pandemic on maternal mortality in the province of Kayseri, Türkiye.

Material And Method

This descriptive study retrospectively examined maternal deaths in all healthcare institutions under the Kayseri Provincial Health Directorate between January 2017 and December 2021. This study utilized data from the 'Maternal Death Registration Forms' provided by the Kayseri Provincial Health Directorate. The research collected and analyzed data on particular sociodemographic factors, gravidity, parity, miscarriages, living children, prenatal care visits, and the duration between the last pregnancy and the current pregnancy. To present the findings, descriptive frequency tables were generated.

The maternal mortality ratio, defined as the number of maternal deaths per 100,000 live births, was calculated for Kayseri based on the total number of live births and maternal deaths for each year. The number of live births for each year is based on data from the Turkish Statistical Institute (14). Maternal mortality ratios for the entire country of Türkiye were obtained from the Health Statistics Yearbook for each year (15). Data for Kayseri and Türkiye were visualized using box-plot and histogram.

Descriptive and frequency tables were created for data related to maternal risk factors, timing of maternal deaths, and methods of pregnancy termination. Information regarding the locations of births and maternal deaths was collected. The number of prenatal care visits before and during the pandemic was obtained, the normal distribution of the data was tested using the Shapiro-Wilk test, and the mean differences between groups were evaluated using the Student's t-test. P-value of <0.05 was considered statistically significant.

The causes, types, and preventability status of maternal deaths were examined. While the types of deaths reported by the Ministry of Health (Central) and Provincial Health Directorate were categorized into three groups as direct, indirect, and unspecified, the causes of deaths were divided into three groups as preventable, non-preventable, and unknown. Deaths caused by the three delay models, consisting of reasons related to the expectant mother, problems related to transport to the health facility, and delays after transport to the health facility, were considered preventable, while the others were considered non-preventable (6). Those categorized as 'unknown' are cases where the reports have not yet been completed.

Written permission was obtained from Kayseri Provincial Health Directorate and ethical approval dated 02.08.23 and numbered 2023/99 was obtained from Erciyes University Clinical Research Ethics Committee. SPSS 20.0 statistical programme was used to evaluate the data.

Results

Between January 2017 and December 2021, 28 maternal deaths occurred in Kayseri, two of which were excluded from the evaluation as they were considered accidental. In the assessed maternal deaths, the average age of the mothers at the time of death was found to be 32.1± 6.6 years (min: 19, max: 44). Some sociodemographic characteristics, chronic medical conditions, obstetric histories and risk factors of the cases are presented in

Table 1. COVID-19 was the most common cause of death (33.3%, n:5) among mothers without chronic disease (n:15). Among mothers who died from COVID-19 (n:9), 55.5% (n:5) had no chronic disease. When investigating the risk factors associated with maternal mortality related to COVID-19, it is evident that the most significant factors are obesity (44.4%, n:4) and being above 35 years of age (44.4%, n:4).

Table 1. Some Sociodemographic Characteristics, Chronic Diseases, Obstetric Histories, Risk Factors of The Mothers.

Nationality	**Value**	**%**
Türkiye	23	88.5
Foreign	3	11.5
Educational Status		
Primary school	11	42.3
High school	9	34.6
University	3	11.5
Unknown (Refugee)	3	11.5
Chronic diseases		
Cardiovascular disease	4	15.4
Diabetes mellitus	1	3.8
Epilepsy	1	3.8
Asthma	1	3.8
None	15	57.7
Unknown	4	15.4
Total	26	100.0
Obstetric Histories	**Mean**	**SD**
Gravidaa	3.0	2.1
Parity	2.1	1.3
Number of miscarriage[a]	0.6	1.6
Number of living childrena	2.0	1.4
Number of prenatal visits	9.8	5.1
Interpregnancy interval (in months)	62.2	45.0
Risk Condition	**Value**	**%**
Present	22	84.6
Unknown	4	15.4
Total	26	100.0
Risk Factors[b]		
Obesity	9	34.4
Pregnancy after age 35	8	30.6
Rh incompatibility	5	19.1
History of previous C-section	5	19.1
Smoking	4	15.3
Cardiovascular disease	4	15.3
IVF pregnancy	2	7.6
Short inter-pregnancy interval (<2 years)	1	3.8
Others (asthma,DM,epilepsy)	3	11.5

[a]Data for three refugees were unavailable, leading to their exclusion from the analysis.
[b]Multiple risk factors may be present.

When examining the number of live births and maternal deaths in the Kayseri province by year; in 2017, there were 21,519 live births and 4 maternal deaths, in 2018, there were 20,770 live births and 2 maternal deaths, in 2019, there were 19,542 live births and 4 maternal deaths, in 2020, there were 18,070 live births and 2 maternal deaths, in 2021, there were 17,480 live births and 14 maternal deaths. Maternal mortality ratios were calculated using data obtained from recorded maternal deaths by year (Figure 1 and Figure 2).

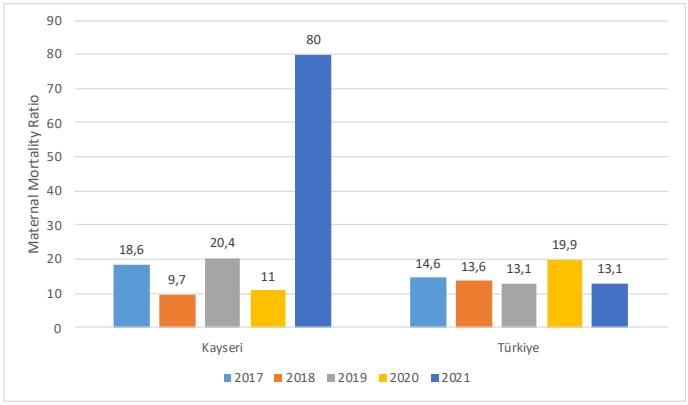

Figure 1. Distribution of Maternal Mortality Ratios in Kayseri and Türkiye Between 2017-2021

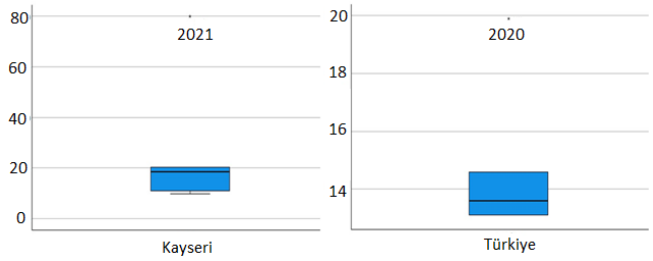

Figure 2. Box-Plot Representation of Maternal Mortality Ratios in Kayseri and Türkiye Between 2017-2021

Deaths occurred during the antepartum period in 7.7% (n:2) of cases and during the intrapartum period in 7.7% (n:2) of cases. The mean gestational age at death in the antepartum period was 28.0 ± 15.5 weeks. 73.1% (n:19) of maternal deaths occurred in the postpartum period, within 42 days, with a mean time to death in the postpartum period of 9.2 ± 11.4 days. Among those who died in the intrapartum-postpartum period, the most common type of abortion was C/S (65.3%, n:17) and the second most common type was vaginal delivery (7.7%, n:2). The most common pregnancy termination methods of mothers who died due to COVID-19 were C/S (55.5%, n:5) and vaginal delivery (22.2%, n:2), respectively.

Among the mothers who gave birth, third level health facilities were the most common place of delivery (85.7%, n:18), followed by second level health facilities (14.3%, n:3). Among mothers with a completed pregnancy, the mean gestational age at which the pregnancy ended was 31.2 ± 8.8 weeks. 71.4% (n:15) of newborns are alive at the end of pregnancy.

The places where maternal deaths occur most frequently are, respectively, third level health facilities (84.6%, n:22) and second level health facilities (3.8%, n:1). 11.5% (n:3) of the deaths occurred in unknown locations.

In terms of prenatal care (PNC), the average number of first level PNC visits is 2.8 ± 1.4, the average number of second level PNC visits is 3.0 ± 3.1, and the average number of third level PNC visits is 3.8 ± 3.7. When the number of prenatal care (PNC) visits was evaluated with reference to the year 2020, the year in

which the first case was seen in Türkiye, the average number of PNC visits before the pandemic (2017-2019) was 9.7 ± 6.3, while the average number of PNC visits during the pandemic (2020-2021) was 9.9 ± 4.2, and no statistically significant difference was observed between them. (P=0.94).

Table 2. Causes, Types and Preventability of Maternal Deaths

Causes of death[a]	Value	%
COVID-19	9	30.6
DIC	4	13.6
Hypertensive disorder	3	10.2
Amniotic fluid embolism	2	6.8
Cardiac disorder	2	6.8
HELLP syndrome	1	3.4
Viral pneumonia (COVID-19 Compatible Chest CT)	1	3.4
Pulmonary embolism	1	3.4
Obstetric haemorrhage	1	3.4
Unknown	5	17.0
According to the decision of the Central Committee on Maternal Death, the type of death		
İndirect	7	26.9
Direct	7	26.9
Unspecified	12	46.2
According to the decision of the Central Committee on Maternal Death, preventability status		
Unpreventable	10	38.5
Preventable	4	15.4
Unknown	12	46.2
According to the decision of the Provincial Committee on Maternal Death, the type of death		
İndirect	19	73.1
Direct	4	15.4
Unspecified	3	11.5
According to the decision of the Provincial Committee on Maternal Death, preventability status		
Unpreventable	13	50.0
Preventable	10	38.5
Unknown	3	11.5
Total	26	100.0

[a] Multiple causes of death may exist.

The causes, types and preventability of maternal deaths are examined in Table 2. The leading cause of death is COVID-19-related deaths (30.6%). In Kayseri, 64.3% (n:9) of deaths in 2021, at the peak of maternal mortality, were due to COVID-19. All of the COVID-19-related deaths occurred in the year 2021. According to the Ministry of Health's report, both direct and indirect maternal deaths were found to have a ratio of 26.9%, and it was determined that 15.4% of the deaths were preventable. According to the Provincial Directorate of Health, 73.1% of deaths are indirect. 38.5% of these are preventable.

Discussion

According to the results of our study, maternal mortality ratios in the Kayseri province followed a normal trend up until the year 2020, which is considered the beginning of the pandemic in Türkiye. However, in 2021, there was a sudden increase, reaching 80 per 100,000 live births. When looking at the overall trend in Türkiye, there was an unusual increase in 2020 (19.9 per 100,000 live births), but in 2021, it appeared to be similar to the pre-pandemic period (13.1 per 100,000 live births).

The difference in trends between Kayseri and Türkiye as a whole may be influenced by the variation in the distribution of COVID-19 cases across provinces and over time in Türkiye. According to the Health Statistics Yearbook, the maternal mortality ratio in the Central Anatolia region, which includes Kayseri, is higher compared to the Turkish average (16). Additionally, Türkiye implemented comprehensive restriction measures even when the number of COVID-19 cases was relatively low due to the declaration of the pandemic, effectively preventing rapid spread of the virus. Consequently, the impact of the pandemic became evident in our country towards the end of 2020 and the beginning of 2021(17). On the other hand, the identification of the delta variant as a genetic variant of SARS-CoV-2 in May 2021, and its documented effect in increasing maternal mortality ratios in the literature, also support this situation (13, 18) .

In a study conducted, it was observed that maternal deaths in Colombia in 2020 were 12.6% higher than expected (12) . When looking at U.S. data, there was an 18.4% increase in maternal deaths in 2020 compared to the previous two years (19). A similar increase in Türkiye can also be attributed to the impact of the COVID-19 pandemic on maternal mortality ratios. In Brazil, it was reported that there was a 223% increase in maternal deaths related to COVID-19 in 2021 compared to 2020 (20). Similarly, in Kayseri province, there was a peak in maternal mortality ratios in 2021. This finding may also support the effect of the pandemic in increasing maternal mortality ratios. In Türkiye, despite the increase observed in 2020, the return of maternal mortality ratios to their normal levels in 2021 may have been influenced by the positive effects of vaccination. COVID-19 vaccination in Türkiye began on January 14, 2021, and vaccination ratios steadily increased. As of May 24, 2021, the proportion of the population who received the first dose of the vaccine was 19.1%, and as of August 14, 2021, this ratio was calculated to be 70.6% (21, 22) . Indeed, it is known that women who have been vaccinated have a reduced risk of severe symptoms, complications, and death (4). On the other hand, in one study, the fact that the median vaccine coverage rate in Kayseri in July 2021 was lower than that of Türkiye as a whole can be reconciled with the dramatic increase in maternal mortality in Kayseri in 2021, unlike Türkiye as a whole (23).

When examining the causes of maternal mortality, it is observed that in recent years, indirect causes have become one of the leading causes of maternal deaths in various parts of the world (24). In Türkiye, over the years, while the role of direct causes among the causes of maternal mortality has decreased, the influence of indirect causes has proportionally increased (6). According to the results of our study, when looking at commission reports in Kayseri province, it is similarly evident that indirect causes of maternal mortality are prominent. According to the Central Review Commission data, both indirect and direct causes of maternal mortality are equally represented (Table 2). The difference may be due to maternal deaths reported as unknown or unspecified causes.

According to WHO data, most maternal deaths that occurred in 2020 were due to preventable causes (25). However, according

to our study, both pre-pandemic and pandemic-related maternal deaths, as reported in both the Central Review Commission and Kayseri province commission reports, are largely not preventable (Table 2). Despite the relatively high maternal mortality ratios in our country compared to the average maternal mortality ratio in developed countries, the fact that the majority of maternal deaths are attributed to non-preventable causes raises questions about the need to reevaluate measures against maternal mortality in Türkiye (26).

According to the The Turkey National Maternal Mortality Study Report for the year 2019, the most common causes of maternal mortality in Türkiye were cardiovascular diseases (29%), embolism (16.1%), hypertension (14.2%), and hemorrhage (10.3%) (6). However, in our study, it is observed that COVID-19-related deaths were the most common cause. Despite our study's time frame (2017-2021) encompassing the pre-pandemic period, the fact that COVID-19 ranks first among the causes of death may indicate its direct impact on maternal mortality.

It is known that the COVID-19 pandemic has created challenges for the clinical management of pregnant women, not only due to its direct effects but also because of its impact on the provision of regular antenatal care (27). Indeed, at the beginning of the pandemic, such concerns were evaluated in the literature, and it was reported that even pregnant women who reached healthcare facilities could not receive timely care (28) . It is also known that the quality of antenatal care, including access to antenatal care and health services, affects maternal mortality ratios. Therefore, studies have been conducted in this regard, and the pandemic has been shown to further affect the utilization of healthcare services for women, especially in regions with high maternal mortality ratios, such as sub-Saharan Africa (10, 29). It should be noted that not only developing countries but also developed countries have faced challenges in dealing with the COVID-19 pandemic. Among the reasons cited for these challenges are the inability of primary healthcare services to meet the demands of patients and insufficient intensive care unit (ICU) and bed capacities relative to the population (30). However, our study shows that the average number of antenatal visits, which is an indicator of the quality of antenatal care, was not affected by the pandemic, indicating that efforts were made to maintain basic healthcare services in our country. Türkiye is known to have one of the best ICU capacities among OECD countries (31). The dedicated work of healthcare professionals and sufficient bed capacity likely contributed to the continuation of basic healthcare services under challenging conditions such as the pandemic. Furthermore, this situation raises the possibility that the increased maternal mortality ratio observed in our country and specifically in Kayseri province during the pandemic may have stemmed from the direct impact of the COVID-19 pandemic.

Conclusion

In Kayseri province, there has been a significant increase in maternal mortality ratios, especially during the year 2021, when the delta variant of COVID-19 was active. Indirect maternal deaths have been predominant, and most of them have been reported as non-preventable. The increased deaths are thought to be related to the direct impact of COVID-19. The vaccination status of the cases is unknown, and in future studies, when evaluated in conjunction with immunity status and other potential confounding factors, a more detailed assessment of the impact of COVID-19 on maternal mortality can be conducted.

Limitations And Suggestions

The fact that our study was conducted in only one city may be a limitation in generalizing to the whole community. In future studies, it would be useful to make evaluations based on a larger population.

CONFLICT OF INTEREST

No conflict of interest.

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Ethics Committee Approval

Written permission was obtained from Kayseri Provincial Health Directorate and ethical approval dated 02.08.23 and numbered 2023/99 was obtained from Erciyes University Clinical Research Ethics Committee.

ORCID and Author's contributions

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Case Report/ Olgu Sunumu

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Non-Traumatic Full-Thickness Duodenal Perforation: A Case Report

Non-Travmatik Tam Kat Duodenum Perforasyonu: Vaka Sunumu

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ABSTRACT

Duodenal perforation is a life-threatening condition with high mortality and morbidity. In this study, we aim to present a case of spontaneous duodenal perforation that was detected and treated. The 66-year-old male patient, who applied to the emergency clinic with complaints of malaise, fever, weakness and shortness of breath, had no additional disease other than Chronic obstructive pulmonary disease and dementia. Pneumonia was diagnosed based on physical examination and imaging findings, and he was admitted to the pulmonology clinic and treated. During follow-ups, the patient developed sepsis and an acute abdominal pain. An emergency laparotomy revealed a non-traumatic spontaneous duodenal perforation, which caused near ruptured duodenum. The perforated duodenum part was resected and gastrojejunostomy was performed. The rupture of the duodenum and large duodenal perforation can occur in association with iatrogenic or trauma-related causes. In the patient who had no history of trauma, the most likely cause of perforation was thought to be peptic ulcer. It was thought that possible peptic ulcer perforation expanded with necrosis over time. In cases without a history of trauma, the possibility of large duodenal perforation or rupture should not be ruled out, and if there is suspicion of spontaneous duodenal perforation, laparotomy should not be avoided.

Key Words: Intestinal perforation, Pneumonia, Acute Abdomen

ÖZ

Duodenal perforasyon hayatı tehdit edebilen yüksek mortalite morbiditeye sahip bir durumdur. Bu çalışmada spontan duodenal perforasyon saptanan ve tedavi edilen olguyu sunmayı amaçladık. Genel durum bozukluğu, ateş, halsizlik ve nefes darlığı şikayetleri ile acil polikliniğine başvuran 66 yaşında erkek hastanın Kronik obstruktive akciğer hastalığı ve demans dışında ek hastalığı yoktu. Fizik muayene ve görüntüleme bulguları ile pnömoni tanısı koyularak, göğüs hastalıkları servisine interne edilerek tedavisi yapılmıştır. Takiplerinde sepsis ve akut batın tablosu gelişen hastanın yapılan acil laparotomisinde rüptüre olmak üzere olan nontravmatik spontan duodenum perforasyonu saptanmıştır. Perfore duodenum bölümü rezeke edildi ve gastrojejunostomi yapıldı. Duodenum rüptürü ve geniş duodenum perforasyonu iyatrojenik veya travmaya bağlı sebeplerle beraber görülebilir. Travma öyküsü olmayan hastada perforasyonun en olası nedeninin peptik ülser olduğu düşünüldü. Olası peptik ülser perforasyonunun zamana bağlı olarak zamanla gelişen nekroz ile genişlediği düşünülmüştür. Travma öyküsü olmayan durumlarda da geniş duodenum perforasyonu veya rüptürü olabileceğinden spontan duodenum perforasyonundan şüpheniyorsa laparotomi yapmaktan çekinilmemelidir.

Anahtar Kelimeler: Bağırsak perforasyonu, Pnömoni, Akut batın

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Introduction

Duodenal perforation is a surgical emergency presenting with acute abdominal pain. Although it is usually 0.5 cm in size, it can also reach several cm in size (1). Perforations larger than 3 cm are very rare and they have higher leakage, mortality and morbidity rates. In such perforations, treatment options such as partial gastrectomy and creating an omental plug by suturing the omentum to the nasogastric tube are indicated (2).

The most common presenting symptoms are severe epigastric pain, vomiting, and abdominal distension (3). In patients who cannot express their symptoms, signs of perforation may go unnoticed and may be confused with conditions such as pneumonia (4).

The medical history and physical examination play a crucial role in the diagnosis of patients presenting to the emergency outpatient clinic with non-traumatic abdominal pain. Since some patients require urgent surgical treatment while others may benefit from symptomatic therapy, achieving an accurate diagnosis rapidly is essential. While some of the causes of non-traumatic abdominal pain such as obstruction or perforation of the intra-abdominal organ, require urgent surgical intervention, metabolic and hormonal-related diseases do not require urgent surgical intervention.

We present a patient who was admitted to the ward due to pneumonia, and in subsequent examinations, a subphrenic abscess was detected, and for this reason, he was operated on and a full-thickness duodenal injury was observed.

CASE REPORT

A 66-year-old male patient presented to the emergency department with a 3-day history of general deterioration and weakness. The patient has no additional diseases other than chronic obstructive pulmonary disease and dementia. The patient had no history of trauma and did not use any medications other than inhalers. Due to dementia, the patient was unable to express his complaints and the physical examination was suboptimal and general abdominal tenderness was observed. Coarse lung sounds were heard on chest auscultation. In laboratory findings, white blood cell count was 14000 10^6/L, kreatinin was 1,16 mg/dL and CRP was 80 mg/L. There was no other laboratory anomaly. The thorax tomography scan showed an image consistent with pneumonia. The patient was admitted to pulmonology clinic. Moxifloxacin treatment was initiated for pneumonia. On the 4th day of admission, the patient had abdominal distension, tenderness in the abdomen. An increase in infectious parameters was observed; White blood cell count was 16000 10^6/L, CRP was 144 mg/L and procalcitonin was 17,15 ng/mL. A contrast-enhanced abdominal computerized tomography was performed. The tomography revealed a right subphrenic abscess and subhepatic free air (Figure 1). An emergency decision for laparotomy was made for the patient.

During exploration, omental adhesions were observed in the right upper quadrant. Upon opening the adhesions, a perihepatic abscess of nearly 1.5 liters was drained. The small bowel and colonic loops were explored, and no pathology was observed. A full-thickness perforation site was identified at the junction of the first and second parts of the duodenum. The lumen was observed to be opened up to 270 degrees (Figure 2). The duodenum was mobilized with kocher maneuver and the distal end was closed with a linear stapler. The proximal end was resected with partial gastrectomy. A Roux-en-Y reconstruction was performed, creating a gastrojejunostomy. A drain was placed in the surgical site, and the procedure was concluded.

The patient was followed up in the intensive care unit and the pneumonia treatment was continued. Apart from moxifloxacin, second generation cephalosporin and metronidazole treatment was started. The patient was not given an oral regimen for 2 days. On the 3rd day, the patient was given water containing methylene blue orally. No blue dyed fluid was seen coming from the drain. Thereupon, water intake started. As he tolerated the regimen and gas and stool were observed, soft liquid food was started on the 4th day. The patient was taken to the ward for follow-up on the 6th day. No active discharge was observed from the drain, the wound was found to be clean, the drain was removed and the patient was discharged on the 9th day. Pathological examination of the resection material revealed partial stomach-duodenum with congestion and hemorrhage.

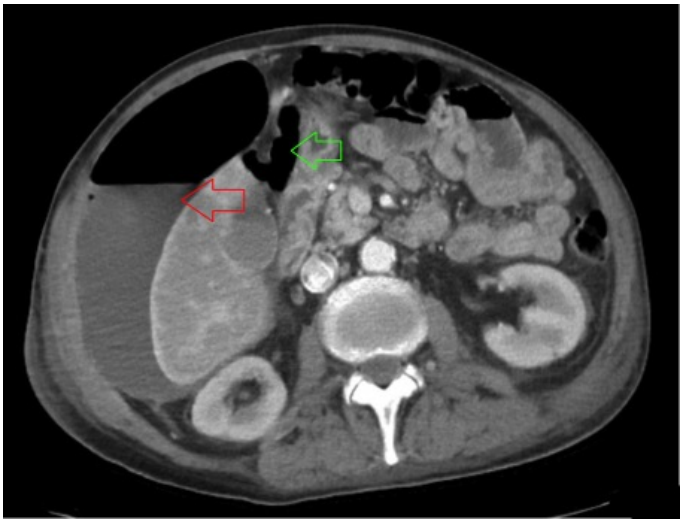

Figure 1. Abdominal tomography image; Perihepatic abscess (red arrow) and subhepatic free air image (green arrow)

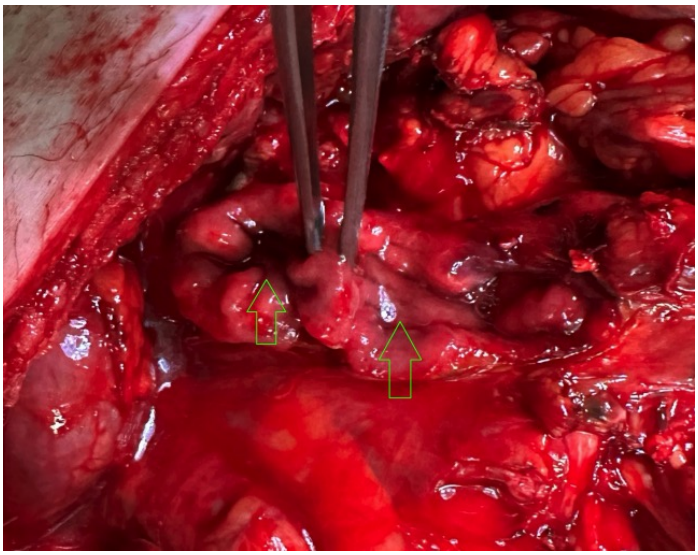

Figure 2. Double lumen appearance (green arrows) in the nearly ruptured duodenum

Discussion

Spontaneous duodenal perforation is an important reason for admission to the emergency department with acute abdominal pain. Chronic diseases such as peptic ulcer and inflammatory bowel diseases, which are not diagnosed and treated, may present to the emergency department with perforation as a form of complication (5). Approximately one-third of patients presenting to the emergency department with non-traumatic abdominal

pain require urgent surgical intervention. Spontaneous duodenal perforations, due to their deep location (retroperitoneal), pose a significant challenge for surgeons. Delays in the diagnosis and treatment of this condition are common, leading to an increase in mortality and morbidity.

Duodenal perforation is a life-threatening condition with a mortality rate ranging from 8% to 25%. The incidence has gradually decreased over time with the use of proton pump inhibitors. While peptic ulcers are the most common cause, duodenal diverticula, duodenal ischemia, infectious diseases, and autoimmune conditions may also be associated. Additionally, it can be linked to endoscopic or perioperative interventions and abdominal traumas (6).

Duodenal ulcers are often associated with Helicobacter pylori infection. Certain medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin, can also cause duodenal ulcers. Smoking, alcohol consumption, and stress contribute to susceptibility to duodenal ulcers as well.

Peritoneal irritation occurs when bile and stomach contents escape from the lumen. Depending on this, a physical examination such as sensitivity and defense occurs. Laboratory findings show an increase in infectious parameters. In imaging, free air under the right diaphragm can be seen in plain radiographs, while free air and free fluid under the right diaphragm and subhepatic can be seen in abdominal tomography. Once the diagnosis is made, surgical intervention is considered. Nonoperative follow-up was also thought to be successful in patients whose general condition was good and who did not have severe abdominal physical examination findings (7). Surgical abdominal exploration is performed in patients requiring surgical intervention. The perforation area is found and surgical repair is performed.

The patient's age, comorbidities, and delays in diagnosis and treatment are factors that can reduce the success of treatment. Closure of defect and omentopexy may be sufficient for perforations smaller than 0.5 cm and can be managed with lapararoscopic intervention, but in larger defects, such approaches are associated with a higher leakage rate. Various methods such as gastric diversion, duodenal resection and tube duodenumostomy have been described in the literature for large perforations (2,8,9). Full-thickness duodenal injuries or duodenal ruptures are typically attributed to iatrogenic or trauma-related causes. The surgical planning depends on the location of the rupture. Most injuries can be repaired with primary sutures without the need for diversion (9). After the repair, the abdomen is abundantly irrigated and washed to prevent postoperative intra-abdominal infection. A nasogastric tube is placed to reduce flow in posteperative period.

During postoperative follow-up, abdominal physical examination findings and vital signs are monitored. During follow-up, anaerobic strain effective antibiotics are started to prevent intra-abdominal infection and wound infection. Proton pump inhibitors are given for the treatment of peptic ulcers. The patient's oral intake is restricted until the 3rd day, and the regimen is started gradually. Gastroscopy is recommended to the patient 4-6 weeks after discharge.

Conclusion

The gastrointestinal perforation is considered in a patient who presents with an acute abdominal clinic, shows signs of increased infection, and has free air and fluid in the abdomen on imaging. Most of the time, the perforation location cannot be clearly identified by imaging. The perforation area is found with abdominal exploration. In cases of colonic or small bowel perforations, resection and anastomosis is considered and diverting ostomy is considered depending on the status of intra-abdominal infection. Primary repair is considered in gastroduodenal perforations such as peptic ulcer perforation. In cases where there is a larger defect, resection is considered.

The presented patient was initially diagnosed with pneumonia, and four days after admission, a diagnosis of perforation was established. During laparotomy, it was observed that the duodenal lumen was almost completely separated.

In the literature, duodenal rupture due to non-traumatic causes has not been reported. In our patient, the delayed diagnosis of perforation, along with general malaise, was considered as the reason for the occurrence, leading to tissue necrosis and expansion of the perforation site. Considering the poor general condition of the patient and the perceived low success rate of primary repairs, gastric diversion was performed. Additionally, a drain was placed for the purpose of monitoring potential duodenal stump leakage.

Due to high morbidiy and mortality in patients presenting to the emergency department with non-traumatic abdominal pain, the possibility of spontaneous duodenal perforation, although rare, should be considered.

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A Rare Case That Can Be Confused with Cerebral Palsy: Incontinentia Pigmenti

Serebral Palsi İle Karışabilen Nadir Bir Olgu: Incontinentia Pigmenti

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ABSTRACT

Incontinentia pigmenti (IP), which is inherited predominantly on the X chromosome, is organ involvement arising from ectoderm and mesoderm; It is a rare disease that primarily affects the central nervous system, skin, eyes, and teeth. The neurological findings seen in this disease resemble the clinical features of Cerebral Palsy (CP) in later stages. CP is a childhood syndrome characterized by non-progressive, permanent motor impairment due to damage to the mature brain. Especially in centers focused on physical therapy and rehabilitation, some neurological diseases of different etiologies whose diagnosis is not clear are considered as CP, and perhaps for this reason patients are exposed to incorrect treatment. In this regard, we aimed to present the characteristics of the rare genetically inherited IP, which brings CP to mind in the first evaluation, different from CP and similar features to CP.

Our case, a 48-month-old baby girl, was taken to the hospital immediately after birth due to extensive wounds on her body. IP was diagnosed through detailed examination and genetic screening. The patient had motor retardation and musculoskeletal problems. The family applied to our department due to the patient's neurological findings and developmental problems. We wanted to present this case, which is rare in the literature and was confused with CP until diagnosed.

Keywords: Incontinentia Pigmenti, Cerebral Palsy, Genetic disease, Bloch-Sulzberger syndrome.

ÖZ

Incontinentia pigmenti (IP), X-kromozomuna bağlı dominant geçişli, ektoderm ve mezoderm kaynaklı organ tutulumu görülen; başta merkezi sinir sistemi olmak üzere cilt, göz ve dişleri etkileyen nadir bir hastalıktır. Bu hastalıkta görülen nörolojik bulgular ilerleyen dönemlerde Serebral Palsi'nin (SP) klinik özelliklerine benzemektedir. SP ise matür beynin hasarına bağlı, ilerleyici olmayan, kalıcı, motor bozukluk ile karakterize bir çocukluk çağı sendromudur. Özellikle fizik tedavi ve rehabilitasyon odaklı merkezlerde farklı etiyolojide tanısı netleşmeyen bazı nörolojik hastalıklar SP olarak değerlendirilmekte ve belki bu sebeple hastalar yanlış tedaviye maruz kalmaktadırlar. Bu doğrultuda ilk değerlendirmede SP'yi akla getiren, nadir görülen genetik geçişli IP'nin SP'den farklı özelliklerini ve SP'ye benzer özelliklerini sunmayı amaçladık.

Olgumuz 48 aylık kız bebek doğumdan hemen sonra vücudunda oluşmuş ciddi yaralar sebebiyle hastaneye götürülmüştür. Hastanede yapılan genetik taramayla IP tanısı konmuştu. Olgumuzda motor gerilik, kas iskelet sistemi problemleri bulunmaktaydı. Aile hastadaki nörolojik bulgular ve gelişim problemleri sebebiyle bölümümüze başvurdu. Literatürde az rastlanan ve tanı konuluncaya kadar SP ile karıştırılan bu vakayı sunmak istedik.

Anahtar kelimeler: Incontinentia Pigmenti, Serebral Palsy, Genetik hastalık, Bloch-Sulzberger sendromu.

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Introduction:

Incontinentia pigmenti (IP), was first described in 1906. It is an X-chromosome-dominant disease with organ involvement of ectodermal and mesodermal origin, affecting the skin, eyes, teeth, and central nervous system (1).Mutations in NEMO (nuclear factor-kappa-B essential modülatör) gene is located in Xq28 have been shown to cause IP. Due to X inactivation, this disease is more common in female infants and lethal in males and phenotype MIM (Online Mendelian Inheritance in Man) number is 308300, Inheritance X linked dominant, gene locus IKBKG (Inhibitor Of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma), gene MIM number 300248 (2).

The skin lesions first seen in this disease have four basic stages. In some cases these steps are not followed (3). Lesions such as erythema, vesicles and typical linear pattern appearing blisters are encountered in the first stage, papules, verrucous lesions and hyperkeratoses in the second stage, hyperpigmentation in the third stage, and hypopigmentation and skin atrophy in the last stage (4). In addition, central nervous system (CNS), musculoskeletal, cardiovascular, dental, ocular and auricular anomalies may accompany the disease. Therefore, a multidisciplinary treatment approach is required in the continuous follow-up of the patient (5). Existing neurological findings of the disease show very similar features with CP in the later stages. CP is a childhood disease characterized by non-progressive, permanent movement and posture disorder due to damage to the developing brain (6). Especially in rehabilitation oriented approaches, many diseases of different etiology are considered as CP and therefore the right treatment option cannot be applied. In this direction, we aimed to emphasize the characteristics of IP, which is a rare disease that first brought CP to mind, and distinguishes it from CP.

Case Report

Our case is a 48-months-old baby girl. The weight of her was 16.7 kg and her height was 98 cm. After she was born, she applied to the hospital due to intense wounds on her body; a diagnosis of IP was made with a detailed examination and genetic screening. The patient's arms and legs were linearly located, hyperkerotatic papules and plaques on the erythematous background, and erythematous papules on the face were found. On subsequent examination of the patient, hyperpigmented macular lesions following Blaschko's lines on the trunk; hypopigmented macular lesions in the middle surrounded by a hyperpigmented ring were seen on the extremities (Figure 1). As a result of the skin analysis, incontinentia pigment was found to be compatible with stage 1. IKBKG gene mutation analysis and DNA isolation was made in the peripheral blood sample of the patient. IKBKG gene encoded 1-10. Exon and exon-intron boundary regions were analyzed by PCR-DNA sequencing method. As a result, c.1056-6t>c homozygous was found. In the gene screening performed on the parents, it was determined that the mother carried this gene as heterozygous. There was no consanguinity between the mother and father. She had a history of 2 miscarriages before.The family applied to us because of the neurological findings in the patient. At first, the patient was thought to be a typical CP case. However, as a result of detailed evaluations, it was understood that it was IP.

The patient had stiffness in the left lower and upper extremities and the right lower extremities. Head control was poor; supported sitting had just begun. Her turning skill was incomplete, her grasping skills were quite weak. In our case, skin findings compatible with the disease were noticeable. Her hair was quite sparse and there was a lot of shedding in places. Her teeth were misshaped and dysfunctional, although they had erupted very late.

On intraoral examination, there were one tooth in the upper jaw and two teeth in the lower jaw. The teeth were pointed and misshapen. The hair had alopecia, dullness, coarse and brush-like appearance. Strabismus in the eyes was among the findings.

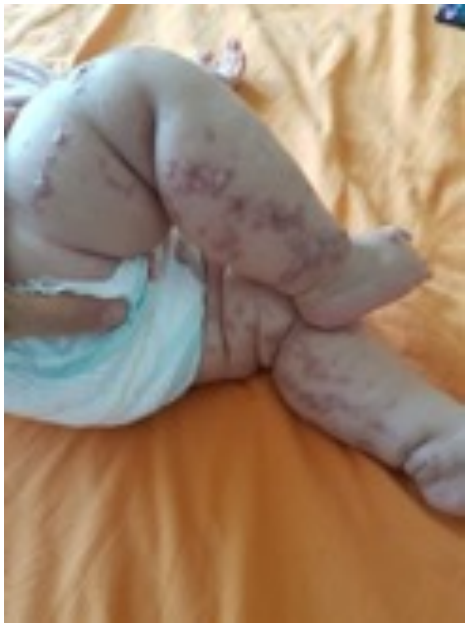

Figure 1: Wound condition on the patient's body when she was 1 month old

Discussion

In our study, the clinical findings and symptomatic treatment methods of a 48-month-old female baby diagnosed with IP were evaluated. Our case had clinical features consistent with the literature. However, we aimed to introduce this case to the literature, as it can be evaluated as CP at first glance due to some physical, mental and cognitive skill problems.

IP, a rare disease that affects ectoderm-derived organs and tissues such as skin, teeth, hair, eyes and central nervous system, which was first described in 1903 and seen in infancy, takes its name from the morphological changes seen in the skin when examined under a microscope (7,8). Its incidence is 1/40 000 and more than 95% of patients are girls, since it is fatal in boys (8).

Our case was also a 48-month-old baby girl. In a study, a 40-year-old patient was also reported and the patient's daughter also had the same problems (9).

The first noticed findings in the disease are usually skin findings. Skin manifestations are present at birth in most patients or occur within the first 2 weeks of life (4). In our patient, intense wounds on her body were remarkable.

Symptoms such as mental retardation, eye findings, shed or weak hair, and misshapen teeth or no teeth at all can also be seen in this disease (7). In a study, it was seen that the patient had 4 wedge-shaped teeth, 2 in the upper and 2 in the lower jaw (8). In our case, although the hair was weak, the number of teeth was three and abnormally shaped.

Although clinical findings are very important in the diagnosis, skin biopsy, family history and genetic examination of first-degree relatives may be required for diagnosis. In addition, detailed neurological examination, eye examination and general examinations should be performed. Although microbiological

examinations, radiological examinations and EEG evaluations are important in the diagnosis, the definitive diagnosis is confirmed by genetic screening (10).

Skin lesions in IP usually progress in stages. The first stage is the vesiculobullous stage, which is usually seen at birth and is observed in the first weeks of life. Our patient also had these lesions at birth. Verrucous stage in the form of hyperkeratotic papules and verrucous plaques after a few weeks or months; so the second phase follows. First and second stage lesions regress at 4 and 7 months on average. Some cases may continue into adulthood (11). The third stage usually occurs between the 12th and 26th weeks and is characterized by brown or gray patches that follow the blaschko lines. Stage 4 of IP is characterized by linear or reticulated hyperpigmented atrophic lesions. However, it may not always follow the order, it can start directly in the 3rd phase. In our patient, the skin lesions present at birth started with stage 1 and passed to stage 4 by the 10th month (7).

In a previous study, no findings were found in the physical and neurological examination of the patient (4). In our case, there were signs of epilepsy and mental retardation accompanied by neurological involvement.

A multidisciplinary approach is very important in the diagnosis and treatment of IP patients. Some treatment programs can be applied in order to prevent conditions that may occur later in the treatment of organs such as skin, teeth, hair and eyes for early diagnosis (12). The late emergence of neurologic findings should not make one forget the possibility that IP may be confused with other diseases, especially CP.

Conclusion

With this case report, we first wanted to emphasize that the IP case suggestive of CP had skin, teeth and hair findings unlike CP, and that the disease should be investigated and treated with a multidisciplinary approach since it affects many different systems.

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Case Report/ Olgu Sunumu

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Unilateral Painless Vision Loss Detected Incidentally During the Driver's Health Examination at the Family Medicine Polyclinic: Case Report

Aile Hekimliği Polikliniğinde Sürücü Sağlık Muayenesinde Tesadüfen Saptanan Tek Taraflı Ağrısız Görme Kaybı: Olgu Sunumu

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ABSTRACT

Introduction: Family medicine encompasses a unique set of competencies and characteristics aimed at providing primary care with a patient-centered focus. In this paper, we aimed to present a case study demonstrating how family practice competencies were utilized in the management of central retinal vein occlusion (CRVO).

Case: A 48-year-old diabetic man, seeking a driving license health report, presented without complaints. Even though he self-reported normal vision, a comprehensive examination revealed a visual loss in his left eye, leading to a diagnosis of CRVO. Despite the absence of typical risk factors such as hypertension or hyperlipidemia, detailed examination and comprehensive evaluation of the patient offered the patient a chance for diagnosis and treatment.

Discussion: CRVO often manifests as painless unilateral vision loss. Family physicians play a crucial role in early detection through comprehensive assessments, even in asymptomatic patients. Rapidly diagnosis and prompt referral to ophthalmologists allow for timely intervention, as seen in this case where intravitreal bevacizumab injections led to improved visual acuity.

Conclusion: This case highlights the importance of family physicians detecting signs of disease, in patients without obvious symptoms. Family physicians contribute to the early diagnosis and effective management of many diseases with their comprehensive approach and patient-oriented care.

Keywords: Family practice, comprehensive health care, vision loss, central retinal vein occlusion

ÖZ

Giriş: Aile hekimliği, hasta merkezli, birinci basamak sağlık hizmeti sunan, benzersiz bir dizi yeterlilik ve özelliği sahip bir tıp disiplinidir. Bu vaka takdiminde, aile hekimliği çekirdek yeterliliklerinin kullanılarak santral retinal ven tıkanıklığının (CRVO) tanısı ve yönetiminin tartışıldığı bir vaka sunmayı amaçladık.

Vaka: Ehliyet sağlık raporu almak isteyen 48 yaşındaki diyabet tanılı erkek hasta şikayetsiz olarak başvurdu. Görüşünün normal olduğunu bildirmesine rağmen, kapsamlı muayene sonucunda sol gözde görme kaybı olduğu tespit edildi. Hastaya ileri değerlendirme ile CRVO tanısı konuldu. Hipertansiyon veya hiperlipidemi gibi tipik risk faktörlerinin bulunmamasına rağmen hastanın ayrıntılı muayenesi ve kapsamlı değerlendirilmesi hastaya tanı ve tedavi şansı sunmuştur.

Tartışma: CRVO sıklıkla ağrısız tek taraflı görme kaybı olarak kendini gösterir. Aile hekimleri, asemptomatik hastalarda bile kapsamlı değerlendirmeler yaparak erken teşhisin sağlanmasında önemli bir rol oynamaktadır. Hızlı tanı ve oftalmologlara hızlı sevk; intravitreal bevacizumab enjeksiyonlarının görme keskinliğinde iyileşme sağladığı bu vakada görüldüğü gibi zamanında müdahaleye olanak tanır.

Sonuç: Bu vaka, aile hekimlerinin, belirgin semptomları olmayan hastalarda bile, hastalıkların bulgularını tespit etmelerinin önemini vurgulamaktadır. Aile hekimleri kapsamlı yaklaşımları ve hasta odaklı bakımlarıyla birçok hastalığın erken tanısına ve etkili yönetimine katkıda bulunur.

Anahtar Kelimeler: Aile hekimliği, kapsamlı sağlık yaklaşımı, görme kaybı, santral retinal ven oklüzyonu

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Introduction

Family medicine is defined by WONCA (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) Europe as an academic and scientific discipline, with its own educational content, research, evidence base and clinical activity, and a clinical specialty orientated to primary care. It is also considered as a primary care-focused clinical specialty (1). Family Medicine has six accepted core competencies and twelve fundamental characteristics. The core competencies of Family Medicine include primary care management, person-centered care, specific problem-solving skills, comprehensive approach, community orientation, and holistic modeling (1,2). Twelve characteristics that family physicians must have are within the scope of these core competencies. Family physicians are the first point of contact in the healthcare system, a requirement of primary care management, and they care for all patients regardless of age, gender, or disease. They ensure coordination with other health professionals, institutions, and organizations. They have an advocacy role for the patient when needed. Family physicians provide person-centered care for the individual, family, and society, contribute to improving health, and provide continuous care services. They also effectively communicate with patients to establish a unique patient-physician relationship.

In family medicine, diseases occur at a frequency close to societal prevalence, which requires a special decision-making process. Both acute and chronic diseases are managed simultaneously, and this is made possible by the core competency of family medicine, which is specific problem-solving skills. Thanks to the comprehensive approach, undifferentiated disorders in the early stages of development and requiring urgent intervention are managed, treating each encounter as an opportunity for general assessment. These approaches assist in diagnosing diseases, even if the individual does not present with any complaints yet. Family doctors develop both the patient and the environment in which they live.

Family medicine's society-oriented nature indicates its responsibilities regarding the health of society and the environment. A holistic perspective requires addressing health problems in terms of their physical, spiritual, social, cultural, environmental, and existential dimensions (3). The family physician utilizes these core competencies and associated fundamental characteristics in patient examination and follow-up.

Retinal vein occlusion describes a group of diseases where the venous return of the retina is compromised. Depending on the location of the occlusion, it is classified as branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO), or central retinal vein occlusion (CRVO) (4). CRVO is often associated with systemic atherosclerotic diseases and risk factors (5). CRVO is a leading cause of vision loss, particularly in elderly individuals, with an estimated global prevalence of 0.08% (6). CRVO can be of ischemic and non-ischemic type. While ischemic CRVO is more common in people over the age of 65, non-ischemic CRVO can also be seen in young adults. Ischemic CRVO has more than 10 nonperfused disc spaces. The large number of nonperfused disc areas increases the risk of neovascularization and subsequent development of neovascular glaucoma. In ischemic CRVO, visual acuity is usually less than 6/60. Nonperfused disc areas are rarely seen in non-ischemic CRVO. Vision is usually above 6/60, with post-treatment vision generally satisfactory. Macular edema can be seen in both types. About 23-30% of non-ischemic CRVO can turn into ischemic CRVO. Visual acuity, relative afferent pupil defect, Electroretinography, Goldmann perimetry, and fundus fluorescein angiography can be used to differentiate ischemic from non-ischemic CRVO (7,8). Cases of retinal vein occlusion present with a wide spectrum of symptoms, ranging from asymptomatic to loss of light perception (4).

This article aims to present a case study showing how the core competencies and fundamental characteristics of Family Medicine, especially the use of comprehensive care and a patient-centered approach, contribute to the diagnosis of CRVO.

Case

A 48-year-old diabetic man applied for a driving license health report. He did not have any complaints about his health. He even mentioned his vision as normal on his individual health information form. In his medical history, he had diabetes mellitus type II for 6 months. He did not have hypertension or cardiovascular or cerebrovascular diseases. He is a non-smoker.

He is overweight, with a body mass index of 30 kg per m2. He is taking empagliflozine and metformin. His blood pressure was 128/85 mm Hg, and his pulse was 90 beats per minute.

During his eye examination, Snellen's chart visual acuity showed 6/20 in his left eye and 6/6 in his right eye. All other system examinations were normal. He did not describe any trauma, headache, palpitations, eye pain, eye discharge, itching of the eye, or other neurological symptoms. No afferent pupillary defect was noted. Blood tests were normal, including complete blood cell count, coagulation tests, kidney and liver functions, blood glucose, and lipid profile. HbA1c was 6.6%.

On fundoscopic examination, macular edema was seen in the left eye, and the right eye was normal. The patient was referred to an ophthalmologist for further investigation and later diagnosed with central retinal vein occlusion (CRVO). His intraocular pressures were normal in both eyes. The patient was treated with intravitreal Bevacizumab injections at one-month intervals for three months. The visual acuity following injections was 6/6 in both eyes.

Discussion

Health report examination is quite common in family medicine practices in Turkey. Many reports are requested from family physicians, such as a driver's health report during the process of obtaining and renewing a driver's license, a marriage health report before marriage, an employment health report when applying for a job and recruitment, an athlete health report when obtaining an athlete's license, military recruitment health report during military recruitment, mental health report in case of old age or illness, and a smoothbore shotgun report. These applications provide an opportunity for comprehensive evaluation for family physicians. As a requirement of the comprehensive approach, one of the core competencies of Family Medicine, examination for reports needs to be performed comprehensively, even if the patient does not report any complaints. Some findings can be revealed through detailed medical examination, even if the patient has no complaints.

In family medicine practice, complaints-free applications and undifferentiated disorders are frequently observed. Undifferentiated disorders refer to disorders that are seen in the early stages of the disease, where the picture is not well established and do not give a clear clue for diagnosis. In complaints-free applications, patients apply for periodic health examinations, screenings, and to get health reports. In both cases, family physicians must carefully examine the application and follow the patient with decision-making methods specific to the family medicine discipline.

The patient can miss unilateral vision loss because one-sided vision loss can be compensated by the healthy side. Central retinal

vein occlusion is one of the most common diseases causing unilateral vision loss. It is characterized by the occlusion of the retinal vein due to thrombosis. This leads to retinal hemorrhages and macular edema.

There are several risk factors that are thought to have an impact on the occurrence of CRVO. Advanced age, hypertension, hyperlipidemia, diabetes mellitus, oral contraceptive pill usage, raised intraocular pressure, smoking, and other rare causes are some of the risk factors for CRVO (9). However, in our case, there were no other risk factors other than diabetes, where blood sugar was not very high. This shows us the importance of comprehensive examination even if patients have no risk factors and/or symptoms.

CRVO usually presents as a painless unilateral loss of vision in of patients who often have other health issues such as high blood pressure, diabetes, glaucoma, and blood diseases. Macular edema (ME) is a complication of CRVO and is the primary reason for loss of vision in this condition (10). As a family physician, when we detect moderate/high-grade vision loss, we need to refer the patient to a specialist ophthalmologist in order to detect the underlying disease, prevent complications, and provide early treatment.

The available treatments for CRVO include Panretinal photocoagulation, anti-VEGF therapy, intravitreal injection of steroids, intravitreal injection of tissue plasminogen activator (tPA), and pars plana vitrectomy. Bevacizumab, ranibizumab, aflibercept, and triamcinolone appear to be effective in treating macular edema secondary to CRVO (11). Bevacizumab can effectively improve best-corrected visual acuity and reduce central macular thickness in patients with macular edema secondary to central retinal vein occlusion without systemic side effects (12).

Conclusion

Unilateral vision loss may be compensated by the healthy eye, and this may cause the patient to be unaware of this important sign. One of the most common reasons for unilateral vision loss is CRVO, which can be easily recognized by fundoscopic examination and treated successfully by intravitreal injections, resulting in improved visual acuity. Applications without complaints, such as requests for a health report, are frequently encountered in family medicine practice. Family physicians contribute to the early diagnosis and effective management of many diseases with their comprehensive approach and patient-oriented care in these applications without complaints. Therefore, family physicians have an important role in the early diagnosis of the disease and in guiding the patient.

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Experimental Models in Parkinson's Disease: Advantages and Disadvantages

Parkinson Hastalığında Deneysel Modeller: Avantajlar ve Dezavantajlar

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ABSTRACT

Parkinson's disease is a complex neurodegenerative disease that affects millions of people worldwide. The incidence and prevalence of Parkinson's disease, the second most common neurodegenerative disease after Alzheimer's disease, is gradually increasing. Although it is an important public health concern, the mechanisms related to Parkinson's disease have not been fully elucidated. One of the main approaches to research on mechanisms and treatment related to Parkinson's disease is the use of experimental models. In vitro and in vivo models enable the investigation of disease-related molecular and cellular processes and the testing of potential treatments. A variety of experimental models are used in Parkinson's disease research, including toxin-induced models, genetic models, and transgenic models, each with their strengths and limitations. Experimental models come to the fore in research on Parkinson's disease, which does not yet have a radical treatment. However, it is important to recognize that no experimental model truly represents all aspects of human Parkinson's disease. For this reason, the findings obtained from the studies need to be supported by different test systems and interpreted carefully. Experimental models are invaluable in the quest to elucidate the mechanism of Parkinson's disease and develop effective treatments.

Keywords: 6-OHDA, Haloperidol, MPTP, Paraquat, Reserpine, Rotenone

ÖZ

Parkinson hastalığı dünya çapında milyonlarca insanı etkileyen kompleks nörodejeneratif bir hastalıktır. Alzheimer hastalığından sonra en sık görülen ikinci nörodejeneratif hastalık olan Parkinson hastalığının insidansı ve prevalansı giderek artmaktadır. Önemli bir halk sağlığı problemi olmasına rağmen, Parkinson hastalığına ilişkin mekanizmalar tam olarak aydınlatılamamıştır. Parkinson hastalığıyla ilişkili mekanizmaların ve tedaviye yönelik araştırmaların temel yaklaşımlarından biri deneysel modellerin kullanılmasıdır. İn vitro ve in vivo modeller, hastalıkla ilişkili moleküler ve hücresel süreçlerin araştırılmasına ve potansiyel tedavilerin test edilmesine olanak sağlamaktadır. Toksin kaynaklı modeller, genetik modeller ve transgenik modeller de dahil olmak üzere, Parkinson hastalığı araştırmalarında her birinin güçlü ve sınırlayıcı yönleri bulunan çeşitli deneysel modeller kullanılmaktadır. Henüz radikal bir tedavisi bulunmayan Parkinson hastalığı araştırmalarında deneysel modeller ön plana çıkmaktadır. Ancak hiçbir deneysel modelin insandaki Parkinson hastalığının tüm yönlerini, tam anlamıyla temsil etmediğini kabul etmek önemlidir. Bu nedenle çalışmalardan elde edilen bulguların farklı test sistemleriyle desteklenmesi ve dikkatle yorumlanması gerekmektedir. Deneysel modeller, Parkinson hastalığının mekanizmasının aydınlatılması ve etkili tedaviler geliştirme arayışında paha biçilmez yöntemlerdir.

Anahtar Kelimeler: 6-OHDA, Haloperidol, MPTP, Parakuat, Rezerpin, Rotenon

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1.Introduction

Parkinson's disease (PD) is a progressive and chronic illness that was first described as "shaking palsy" by Dr. James Parkinson in 1817 (1). According to data from the World Health Organization (WHO), the incidence of PD has increased by 81% in the last 25 years, resulting in 329,000 deaths since the year 2000 (2). It is a neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of cytoplasmic protein inclusions called Lewy bodies (3). Symptoms of PD include motor impairments such as bradykinesia, rigidity, resting tremor and postural instability, as well as non-motor impairments such as constipation, orthostatic hypotension, sleep disturbances, anxiety, depression and dementia (4).

Although PD is rare in individuals under the age of 40, its incidence increases with the aging of populations. It is reported to affect around 3% of individuals aged 80 and above (5). With advances in medical care leading to longer lifespans and increased exposure to environmental pollutants, it is expected that the incidence of PD will surpass 12 million by the year 2040. This is likely to result in a significant rise in healthcare and caregiving expenses (6, 7).

The most significant risk factor for PD is age. However, there is also notable attention given to the association between the disease and exposure to environmental pollutants such as industrial chemicals, pesticides, solvents and metals. Although evidence has been reported suggesting that smoking may lead to a decreased risk of developing PD, whether this causal relationship remains controversial (8). Furthermore, it has been observed that death rates attributed to PD in men are significantly higher than in women, across all age groups and in various countries (9).

Although the exact mechanisms underlying the pathogenesis of the disease are not fully understood, factors such as oxidative stress, mitochondrial dysfunction, neuronal excitotoxicity, and neuroinflammation have been reported to play a role in the development of PD (10). Additionally, similar to other neurodegenerative diseases, age-related biological dysfunctions, including telomere dysfunction, genomic instability, epigenetic changes, ubiquitin-proteasome and autophagy-lysosomal system impairments, have been proposed to accelerate neuronal death in PD (11). One distinctive cytological feature of PD is the Lewy body, which involves the misfolding of α-synuclein protein. Lewy bodies are believed to be influenced by various factors in their formation, and the accumulation of the same protein is observed in related disorders such as multiple system atrophy and Lewy body dementia, which are collectively referred to as "synucleinopathies" (12).

Understanding the pathogenesis of PD also involves a key strategy of exploring the underlying genetic basis. Approximately 5-10% of PD cases can be attributed to monogenic forms. For monogenic forms, genes such as synuclein alpha (SNCA), leucine-rich repeat kinase 2 (LRRK2), vacuolar protein sorting ortholog 35 (VPS35), parkin RBR E3 ubiquitin protein ligase (PRKN), PTEN-induced kinase 1 (PINK1), park-7 (DJ1), as well as a recently reported multitude of genes including coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), LDL receptor related protein 10 (LRP10), transmembrane protein 230 (TMEM230), ubiquinol-cytochrome C reductase core protein 1 (UQCRC1) and vacuolar protein sorting 13 homolog C (VPS13C) are believed to play a role in the development of PD (13).

Currently, the treatment of PD is primarily symptomatic, focusing on slowing down the progression of degeneration, providing neuroprotection, and improving the patient's quality of life. Therefore, an integrative treatment strategy for PD is described, encompassing pharmacotherapy, rehabilitation, supportive care, and surgical options (14). Pharmacological treatment includes agents such as levodopa, carbidopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine and glial cell-derived neurotrophic factor (GDNF). Surgical treatment involves deep brain stimulation (DBS), while speech therapy, physical therapy, and cognitive-behavioral therapy (15). However, the medications used are not capable of reducing the damage caused by PD. Additionally, high doses of levodopa may lead to uncontrollable movements. Dopamine agonists are not as effective as levodopa in treating the symptoms of PD (16).

One of the primary barriers in the development of neuroprotective drugs is the incomplete understanding of specific molecular mechanisms that trigger neurodegeneration in PD. Although recent discoveries have provided information about molecular pathways likely to be crucial in the pathogenesis of PD, these advancements have not significantly contributed to comprehending other important aspects of the disease (17). For this purpose, experimental animal models are used to understand biological processes in diseases, conduct drug research for specific conditions, prevent drug toxicity, and comprehend drug effects (18). PD can be modeled using both in vitro and in vivo methods. Each experimental model has its advantages and limitations, which determine its suitability for a specific experiment. The harmful effect of chronic exposure to agricultural chemicals on neurons is well-known. Studies have reported that prolonged exposure to agricultural agents can lead to neurotoxicity and an increased risk of PD. These findings have allowed researchers to create various PD models using different neurotoxins (19, 20).

Among the commonly used neurotoxins to induce dopaminergic neurodegeneration, 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, and rotenone are included. It is believed that all these toxins trigger the formation of reactive oxygen species (ROS). Despite exhibiting significant differences, including ease of use in animals, rotenone and MPTP are similar in their strong ability to inhibit complex I. Only MPTP is clearly associated with a type of human Parkinsonism and therefore, it is the most extensively studied model (17).

6-OHDA is used to induce monoaminergic neuronal toxicity. Injection of 6-OHDA into the striatum causes degeneration of axon terminals in the striatum and subsequently dopaminergic neurons in the substantia nigra (SN). Since 6-OHDA cannot cross the blood-brain barrier, it requires direct application to the SN using stereotaxic procedures. Due to the ease of toxin transmission in a relatively wide brain area, this application is generally preferred in rats rather than mice (21, 22). While 6-OHDA cannot mimic all aspects of the disease, it appears to be a replica of PD in humans. This animal model created with the neurotoxin has been reported to be useful in evaluating the effects of candidate drugs on motor skills (23).

MPTP is one of the neurotoxins that destroys dopaminergic neurons and has been commonly used to create animal models for PD research. Its high lipophilic property allows it to easily cross the blood-brain barrier and it is oxidized in glial cells through the use of MAO-B to form 1-methyl-4-phenylpyridinium ion (MPP+) (Figure 1). MPP+ enters dopaminergic neurons via the dopamine transporter (DAT) and induces apoptotic factors in the SN such as cytochrome C and caspases (24). While rodents are less sensitive to MPTP toxicity compared to primates, mice are frequently used as a model due to their ease of use, cost-effectiveness, and high repeatability. The rapid and transient neurodegeneration observed in animal models using MPTP poses a significant challenge in PD research. Considering the gradual emergence of MPTP-induced symptoms, alternative solutions can be considered (22). MPTP is commonly used in experimental animals

to create PD models due to its ability to induce tremor, rigidity, akinesia, and postural instability in non-human primates. Its cost-effectiveness, ease of use, and lower ethical concerns compared to other toxin-induced animal models make it a preferred choice. However, MPTP-induced Parkinsonism does not lead to the formation of typical Lewy bodies. Moreover, MPTP may not fully replicate the behavioral symptoms of PD in humans (25).

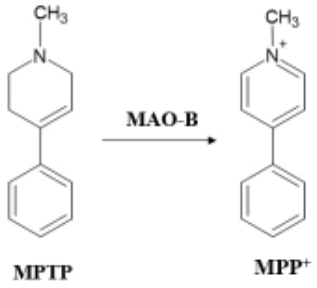

Figure 1. Oxidation of MPTP

Rotenone is a natural neurotoxin found in the roots of certain plants and is currently used as an insecticide, piscicide, and pesticide. It acts as a complex I inhibitor of mitochondrial NADH-dehydrogenase, blocking the use of oxygen during oxidative phosphorylation and driving the cell towards glycolysis and energy reserve depletion. Studies have shown that rotenone induces α-synuclein aggregation (26, 27). Due to its high mortality rate at high doses, the use of rotenone to create PD animal models poses a risk factor (26). However, because of its effects on various pathogenic pathways involved in dopaminergic cell death, such as oxidative stress, α-synuclein phosphorylation and aggregation, and Lewy pathology, as well as its lipophilic nature, rotenone is still used in PD animal models (28).

Paraquat is a pesticide with a chemical structure similar to MPP+ and causes dopaminergic neuron loss in animals. Despite its structural similarity to MPP+, it does not affect mitochondrial respiratory chain complexes like other neurotoxins that induce PD symptoms. As the PD phenotype develops chronically, using paraquat-induced models can be beneficial for examining early stages of the disease compared to other models (19). It enters dopaminergic neurons through DAT and exerts its toxic effects through high ROS levels, such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. Rodent models induced with paraquat are used to investigate Lewy body pathology in dopaminergic neurons. The use of paraquat-induced models has been reported to be advantageous for studying early stages of the disease due to the chronic development of the PD phenotype, compared to other models (21).

Reserpine is an alkaloid extracted from Rauwolfia serpentina and is used as an antihypertensive drug. By inhibiting the vesicular monoamine transporter 2 (VMAT2), it leads to a decrease in the levels of brain and peripheral monoamines, including noradrenaline and dopamine. Behaviorally, reserpine induces akinesia and hind limb rigidity in rats, rabbits, guinea pigs, cats, and monkeys (29). Although it mimics PD behaviors, it has been reported that reserpine is not a useful model compared to other neurotoxin and genetic models due to its inability to induce neurodegeneration and protein aggregation, lack of specificity for dopaminergic neurotransmission, and rapid decline in its levels in the organism after maintenance (30).

Haloperidol is an antipsychotic that acts primarily as a D2 receptor antagonist and is mainly used to control agitation and aggression in the acute phase of schizophrenia. Extrapyramidal side effects such as dystonia, rigidity, tremor, and akathisia can be observed with haloperidol administration (31). Catalepsy induced by systemic haloperidol administration in rodents is attributed to the blockade of D2 dopaminergic receptors in the nigrostriatal pathway, making it a useful animal model for studying motor disturbances observed in PD and screening potential antiParkinsonian compounds (32). However, it fails to trigger any other specific feature of PD and therefore its use is limited (29).

Genetic models of PD are created through transgenic expression of α-synuclein and LRRK2 or through knockout/knockdown of genes such as PARKIN, DJ-1, and PINK1, which play a role in PD pathology, to investigate the molecular mechanisms of genes involved in PD (19). These models generally do not encompass significant specific features of PD, including degeneration of dopaminergic neurons and motor symptoms (29). However, only a few of these models exhibit all the characteristics of the disease and are often quite different from the human condition. In support of this, most genetic models have been reported to fail in inducing the main pathological feature of PD, which is the loss of dopaminergic neurons (19). While PD is not considered a strongly genetic disease due to genetic variations accounting for only about 5% of all cases, these genetic models are thought to be useful for studying idiopathic PD (22).

In addition to the mentioned models, as a new approach for PD, in vitro studies using organoids derived from induced pluripotent stem cells (iPSCs) of PD patients can potentially reflect the progression of the disease in humans (19).

In this review, in vitro and in vivo PD models have been examined with their advantages and disadvantages, aiming to shed light on the mechanisms underlying dopaminergic neuron death and potential drug treatments, as well as exploring new therapeutic approaches.

2. Experimental PD Models

2.1. PD Model Using 6-Hydroxydopamine (6-OHDA)

6-OHDA is a compound that an analog of dopamine (Figure 2). The neurotoxic effects of 6-OHDA have been substantiated in studies (33, 34). It is taken up by presynaptic catecholaminergic neurons primarily through transporters such as DAT and noradrenaline membrane transporter (NAT). Once inside these neurons, it induces toxic effects by generating free radicals like superoxide, hydrogen peroxide, hydroxyl radicals, and initiating mitochondrial damage. As a consequence, it leads to cell death in catecholaminergic neurons (21).

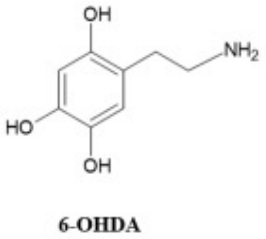

Figure 2. Chemical Structure of 6-OHDA

Although the intracellular toxicity mechanism in both peripheral and central catecholaminergic neurons is the same, the toxic effects of 6-OHDA show significant differences depending on the administration method, allowing its utilization in various studies. Unable to cross the blood-brain barrier, systemic administration of 6-OHDA damages neurons in the sympathetic nervous system, leading to a chemical sympathectomy effect and affecting the function of many autonomic organs. Due to this effect, it is frequently used to create a sympathectomy model in several investigations (35-37). Moreover, intracerebral applications of 6-OHDA, such as hippocampal infusion, result in spatial and memory impairments, while infusion to the medial preoptic area or cortex leads to disruptions in the sleep-wake cycle and attention abilities. Infusions into the striatum, SN,

and medial forebrain bundle (MFB) induce physiological and motor disorders resembling human PD (38, 39). For this reason, 6-OHDA was initially used in the first animal model of PD (22, 40). In in vivo models, Caenorhabditis elegans, non-human primates, and rodents can be used, but rodents are preferred more due to their mammalian nature and cost-effectiveness (23). Rats are often favored over mice because the small size of mice poses challenges in localizing stereotactic applications. Stereotactic applications are usually performed unilaterally to ensure each animal has a lesion-free hemisphere as its own control (41). Although bilateral applications induce bilateral motor deficits, severe bradykinesia, aphasia, and adipsia, these symptoms may not be well tolerated by the subjects. To create bilateral motor deficits, a study using repeated intraventricular administrations was conducted to increase the animals' tolerance by gradually transitioning symptoms from unilateral to bilateral (42).

6-OHDA is used to model both early and late stages of PD, depending on the injection site and concentration (43). The application of this toxin induces not only motor deficits but also non-motor PD symptoms such as cognitive impairments, depression/anxiety, pain, and sleep disturbances in a dose-dependent manner (44). For instance, low doses may lead to motor deficits, while high doses may cause depression (45). This helps researchers to focus on the specific aspect they want to study. Additionally, in vitro studies using various cell lines such as mouse dopaminergic neuronal cell line (MN9D), rat pheochromocytoma cell line (PC12), rat dopaminergic neural cell line (N27), human neuroblastoma cell line (SH-SY5Y), and lund human mesencephalic (LUHMES) are widely employed to investigate the potential intracellular pathways involved in 6-OHDA-induced PD, including oxygen radicals and mitochondrial damage, as well as to test potential therapeutic agents (46-49). However, the model created by 6-OHDA does not fully replicate the pathology of PD as seen in MPTP, as it does not affect the locus coeruleus, does not lead to the reported norepinephrine depletion in PD, and does not form Lewy bodies (21). On the other hand, the fact that 6-OHDA cannot cross the blood-brain barrier in the Parkinson's model necessitates intracerebral administration, leading to serious ethical concerns. However, these local applications are widely used because they allow precise targeting of the desired region with much lower doses, avoiding systemic side effects caused by the toxin (50).

2.2. PD Model Using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

MPTP is a synthetic analogue of the narcotic agent meperidine (51). Due to its ability to induce symptoms similar to PD and the positive response of PD patients with MPTP usage to levodopa treatment, it has been defined as a ''Parkinson-related substance'' (52). MPTP possesses a lipophilic structure that allows it to easily cross the blood-brain barrier and exhibit specific toxicity to dopaminergic neurons (40). Following systemic administration, MPTP is oxidized by MAO-B in glial cells to form a toxic metabolite called MPP+, which cannot cross the blood-brain barrier but can be easily taken up by dopaminergic neurons via norepinephrine and dopamine transporters due to its structural similarity to dopamine. This metabolite accumulates in the synaptic vesicles and mitochondria of dopaminergic and noradrenergic neurons through DAT and NAT. It enters the vesicles via VMAT2 and reduces the entry of dopamine into the vesicles, leading to its degradation in the cytoplasm and an increase in dopamine-associated oxidative stress. MPP+ further inhibits the uptake of dopamine into synaptic vesicles and its release, resulting in a decrease in dopamine levels. In mitochondria, it binds to NADH dehydrogenase and inhibits complex 1, causing a decrease in ATP production and accumulation of reactive oxygen species. Consequently, pathways such as the mitochondrial apoptotic pathway, inflammatory pathway, and induction of oxidative stress in the locus coeruleus, striatum, and SNpc regions lead to cell damage in dopaminergic and noradrenergic neurons (41, 53). Moreover, MPTP can mimic other known biochemical features of PD, such as decreased levels of striatal dopamine and tyrosine hydroxylase, increased levels of both striatal precursor proteins preproenkephalin and acetylcholine (ACh), elevated extracellular glutamate levels, and decreased glutathione (GSH) in the basal ganglia (54). In vitro studies using various cell lines, including MN9D, PC12, N27, SH-SY5Y, and LUHMES, utilize MPTP to induce PD models and shed light on potential intracellular pathways associated with PD pathology and test therapeutic agents (55-58).

In vivo models induced by MPTP allow the development of both bilateral motor and non-motor symptoms of PD, but there are conflicting results regarding whether it induces memory impairment (59-61). In MPTP modeling, repeated intraperitoneal injections are commonly used. Some studies argue that systemic injections fail to induce the formation of Lewy body-like cytoplasmic inclusions, while others suggest that high doses of MPTP do lead to the formation of α-synuclein, the main component of Lewy bodies (41, 62).

While zebrafish, Caenorhabditis elegans, and non-human primates can be used in MPTP-induced PD models, rodents are more commonly used due to their mammalian nature and cost-effectiveness. However, despite MPTP fails to induce significant dopaminergic neurodegeneration in rats, rats are preferred over mice for modeling (41, 63). Although MPTP can be easily administered intraperitoneally, mice are less sensitive to MPTP compared to primates, and high doses are required to induce α-synuclein formation, which increases the risk of mortality and toxicity (54).

The most significant disadvantage of this model is the rarity of Lewy body formation and the difficulty in replicating the behavioral features observed in PD (19, 25). However, due to its cost-effectiveness, ease of use, and fewer ethical concerns, it is still widely employed in the generation of PD models (52).

2.3. PD Model Using Reserpine

Reserpine is one of the first anti-hypertensive agents developed for human use. It irreversibly binds to VMAT1 and VMAT2 in adrenergic vesicles in neurons, inhibiting the storage of monoamines within the vesicles. This leads to the breakdown of monoamines in the cytoplasm, increasing oxidative stress and causing cell damage (64-66). Chronic clinical use of reserpine has been observed to cause drowsiness, depression, and motor disturbances in patients, leading to its use in modeling motor and non-motor disorders in rodents (30). In in vivo studies, reserpine administration has been shown to rapidly reduce extracellular dopamine concentration in the SNpc and striatum to undetectable levels. Animal studies have reported that reserpine induces motor disorders such as akinesia, hypokinesia, catalepsy, limb rigidity, and oral tremor, as well as anxiety and depressive disorders (30, 67). Although some studies suggest that reserpine could be used in a PD dementia model, others claim that it does not lead to memory impairment (68, 69). In vivo models are conducted in rodents, cats, monkeys, Caenorhabditis elegans, and even Drosophila through repeated subcutaneous injections or oral administration (70, 71). Many studies have shown that reserpine induces □-synuclein formation in in vivo and in vitro models (64, 72, 73). Despite studies linking the induced pathology to movement disorders, the molecular etiology remains uncertain (67). Therefore, numerous in vitro studies are being conducted to elucidate the intracellular pathways responsible for these pathologies and to test potential therapeutic agents (64, 74).

Indeed, while reserpine can successfully induce motor and sensory disorders similar to the main biochemical components

of PD, it is no longer considered a popular choice as a PD model due to its temporary effects and lack of sufficient selectivity for dopamine (29).

2.4. PD Model Using Haloperidol

Haloperidol is an antipsychotic that acts as a dopamine type 2 receptor antagonist and is commonly used in the treatment of acute and chronic psychoses, as well as various neuropsychiatric disorders (75). Antipsychotics, including haloperidol, are the most common cause of drug-induced Parkinsonism, leading to motor function disorders such as tardive dyskinesia, tardive dystonia, akathisia, myoclonus, and tremor, especially after their use by patients. Therefore, many patients using antipsychotics have been misdiagnosed with PD and treated with antiParkinsonian drugs (76). Haloperidol usage can also lead to extrapyramidal side effects such as akinesia and rigidity. These observed motor disturbances have led to the use of haloperidol to create animal models for studying and screening potential antiParkinsonian compounds. In in vivo studies, haloperidol is commonly administered intraperitoneally, but subcutaneous and intramuscular routes are also used to create the model. Systemic administration of haloperidol in rodents blocks D2 dopaminergic receptors in the nigrostriatal pathway, inducing catalepsy characterized by bradykinesia and rigidity, which are important symptoms of PD (32, 77, 78). However, the use of haloperidol to create in vivo models is limited as it fails to trigger any other specific features of PD apart from catalepsy and rigidity (29). Additionally, our literature search did not find any studies related to in vitro investigations involving haloperidol.

2.5. PD Model Using Rotenon

In PD pathophysiology, chemicals, particularly pesticides, are believed to play a significant role. However, the examination of toxicological and epidemiological studies related to pesticides is inconclusive in establishing a causal relationship with any specific pesticide (79). A meta-analysis of studies on PD and environmental factors by Priyadarshi et al. noted that due to the presence of uncertain data and heterogeneity among the reported studies, a significant dose-response relationship could not be established (80).

Rotenone is a natural insecticide and pesticide extracted from the roots of plants belonging to the Lonchocarpus and Derris genera. Due to its lipophilic nature, it easily crosses all biological barriers, including the blood-brain barrier. The lipophilic property of rotenone allows for its systematic administration, making it technically less challenging compared to models that require stereotactic injection into the brain (81). Rotenone is classified as a ''moderately hazardous'' pesticide by the WHO. It is widely used to model PD in animals through its inhibition of mitochondrial complex I (82). Rotenone was first used in 1985 by Heikkila et al. for modeling PD. Another attempt to model PD using rotenone was made in 1997 by Ferrante et al. who administered 18 mg/kg/day intravenously to rats (28). Since 2000, various species such as rats, mice, fish, and Drosophila have been used in in vivo PD models using rotenone (83).

Studies have shown that chronic oral administration of rotenone induces dopaminergic neurodegeneration and motor impairments, leading to behavioral symptoms of PD in C57BL/6 mice. At high concentrations, rotenone affects peroxisome morphology and distribution in COS-7 cells, which can influence the peroxisome-mitochondria redox relationship and contribute to PD pathogenesis. Similarly, rotenone has been demonstrated to cause degeneration in human dopaminergic SH-SY5Y cells through the PI3K/Akt/GSK-3β/CREB signaling pathway by reducing phospho-CREB levels. Other studies have shown that rotenone application in SH-SY5Y cells reduces PARKIN expression, increases PINK1 expression, and leads to mitochondrial dysfunction, oxidative stress, and cell death. Rotenone-induced neurotoxicity can also result from microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived superoxide release. Additionally, rotenone activates calcium/calmodulin-dependent protein kinase II, increasing intracellular free Ca2+ ions and inducing neuronal apoptosis. In another study, rotenone exposure was shown to cause dysbiosis of the gut microbiota, which may play a significant role in the development of PD. Advantages of using rotenone in PD modeling include its ability to produce complex systemic inhibition, unlike MPTP, which only inhibits catecholaminergic neurons' complex I. Even at low doses, rotenone induces dopaminergic neurodegeneration, and compared to other animal models, it more prominently produces and accumulates α-synuclein. However, some drawbacks of using rotenone in PD modeling include the lack of well-documented cases of rotenone-induced PD in humans. Rotenone is less specific to dopaminergic neurons compared to the MPTP-induced model, and the motor impairment induced by rotenone is not highly specific to nigrostriatal neurodegeneration (86).

2.6. PD Model Using Paraquat

Paraquat is widely used as an herbicide in many parts of the world. Human exposure to paraquat occurs through inhalation and dermal absorption (87). In experimental models, paraquat, which induces oxidative stress, and rotenone, which inhibits mitochondrial complex I, lead to the loss of nigral dopaminergic neurons and behavior disorders associated with human PD. Since the 1980s, an association between PD and various pesticides, including paraquat, has been recorded (88). However, although there is a possibility of a link between PD and pesticides, many studies have not definitively linked any specific pesticide to PD in humans (89, 90). The results of previous studies associating paraquat with PD are also controversial (91). Compared to other studies on paraquat use in PD, a study by Mandel et al. supports the findings of Tanner et al. it highlights the importance of focusing on pesticides in studies with a well-defined population exposed to pesticides, considering complex 1 inhibition or oxidative stress (79).

Paraquat is a pesticide belonging to the family of 1,1'-dimethyl-4,4'-bipyridil (Figure 3). It is structurally similar to MPTP, and this resemblance is the reason for why it is associated with PD. In in vivo rodent models of PD, paraquat has been shown to cause dopaminergic neuron loss. Prolonged exposure to paraquat reduces dopamine levels and/or increases the accumulation of α-synuclein in the brain. However, the mechanisms by which paraquat crosses the blood-brain barrier and its detrimental effects on dopaminergic neurons and astrocytes are not yet fully understood (92).

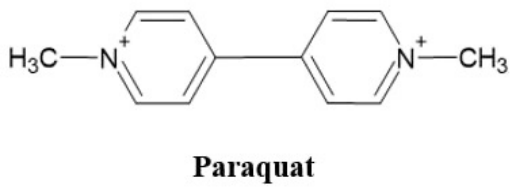

Figure 3. Chemical Structure of Paraquat

The meta-analysis study, which includes twelve reviews based on paraquat, does not conclude that paraquat causes PD (92-94). However, many authors in recent publications have proposed an association between paraquat exposure and PD. Nevertheless, updating these systematic reviews and meta-analyses relies on new studies exploring the potential relationship between paraquat and PD (94). Experimental evidence suggests that paraquat can cause significant damage to mitochondria in a dose-dependent manner, leading to oxidative stress, cytochrome C release, and caspase-9 activation, ultimately leading to

mitophagy and apoptosis (95). Similarly, it has been reported that paraquat produces radicals, including H2O2, O2, and HO-, using complex III of the electron transport chain in rat brains. In human SH-SY5Y neuroblastoma cells, paraquat induces oxidative stress through ROS production, leading to apoptosis and DNA fragmentation by increasing caspase-3 activation. Paraquat enters dopaminergic neurons via DAT and also enters astrocytes through organic cation transporter-3 (OCT3). Paraquat exposure has been associated with variable changes in mRNA levels of DAT and dopamine receptor D3 (DRD3), which are two components of the dopaminergic signaling pathway (84, 85). Paraquat exhibits neurotoxic effects, primarily showing synergistic and potent degeneration of dopaminergic neurons in the basal ganglia. Thus, this toxin-induced upregulation and accumulation of α-synuclein significantly contribute to the PD model. Considering these advantages of paraquat, this modeling provides a valuable contribution to clearly express the progression of PD. However, the disadvantages include the lack of motor impairment observed in the PD model and its limitation mainly to Lewy body pathology (86).

2.7. Genetic Models

It is believed that PD is a combination of genetic and environmental risk factors, making genetics play a significant role in PD pathogenesis (96). Drosophila melanogaster is a powerful organism for modeling human neurodegenerative diseases. Approximately 75% of all human disease genes have homologs in Drosophila. Through various studies conducted in the last 15 years, gene mutations associated with PD have been identified. These mutations can be mainly categorized into autosomal dominant and autosomal recessive mutations. The autosomal dominant mutations include SNCA, LRRK2 (PARK8), HTRA2 (PARK13), and others. On the other hand, the autosomal recessive mutations include PARKIN, DJ-1, PINK1, and others (as shown in the Table 1). In a recent study, it has been reported that mitochondrial dysfunction and oxidative stress play a significant role in PD pathogenesis, and genes like PINK1, PARKIN, and DJ-1 have important roles in mitochondrial function and oxidative stress resistance (97). Therefore, these genes associated with PD are of great importance in the pathophysiology of the disease.

SNCA is the first gene identified in familial PD. The first transgenic mouse model with α-synuclein was generated by Masliah et al. however, this initial transgenic mouse model could not fully replicate the human pathology (98, 99). Subsequently, more α-synuclein models were produced through expression via the tyrosine hydroxylase (TH) promoter. On the other hand, a model containing a double mutant (A30P/A53T) showed a phenotype of motor deficits and neuronal aggregation due to significant neurite dystrophy (100). While these models are useful in shedding light on the neurodegeneration associated with α-synuclein, their clinical relevance to PD can be questioned. LRRK2, specifically the G2019S and R1441C/G mutations, are the most common two LRRK2 mutations. Most LRRK2 transgenic animal models have failed to explain the major distinguishing features of PD. In one published study, BAC-LRRK2-R1441G transgenic mice showed motor impairments and axonal pathology in the striatum, but no significant dopamine cell loss or α-synuclein aggregations were observed (101). Similarly, other LRRK2 models have been created using viral vectors such as herpes simplex virus (HSV) and adenoviral vectors. As a result, HSV-LRRK2-G2019 infection in the mouse striatum was found to induce approximately 50% degeneration of dopaminergic neurons (102). PARKIN, associated with about 50% of familial and 20% of idiopathic cases of early-onset PD, is one of the most common autosomal recessive mutations. PARKIN is an E3 ubiquitin ligase and plays a significant role in proteasomal degradation. Although numerous PARKIN knockout models have been produced, none have successfully summarized the typical PD phenotype. However, in primary midbrain cultures prepared from PARKIN knockout lines, increased sensitivity to rotenone was demonstrated, while overexpression of PARKIN prevented dopaminergic neurodegeneration in rats treated with 6-OHDA and in mice treated with MPTP. From these screenings, it is concluded that the PARKIN model is not yet an ideal animal model for PD, but PARKIN remains a potential therapeutic target. DJ-1 is thought to be an antioxidant protein that is beneficial in protecting dopamine neurons from oxidative stress. It is believed that DJ-1 deficiency can trigger motor dysfunction even in the absence of nigral neurodegeneration. Additionally, DJ-1 has been shown to play a neuroprotective role in our neural system. Therefore, DJ-1 knockout mice could be a valuable tool for investigating the molecular mechanism of PD. PINK1 is a neuroprotective kinase mainly found in mitochondria and cytosolic compartments, and it plays a role in neuronal differentiation. In a study conducted in SH-SY5Y cells, increased PINK1 expression was associated with neurite growth and induction of dendrite length in dopaminergic neurons. Thus, it was noticed that PINK1 and PARKIN mutants have similar phenotypes. Although studies have been conducted on PINK1 knockout mouse models, there is no clear PD pathology observed in the brain. However, the studies have shown that PINK1 knockout mice are sensitive to oxidative stress and ROS production (6, 19, 86, 103).

Table 1. Molecular Models Associated with PD [97, 108].

PD gene/locus	Mutation	Phenotypic Expression in Mammals/ Mice	Trusted PD Gene
SNCA /PARK	Missense or multiplication	Expression of Human α-Syn (A53T, A30P): ↑ Accumulation of α-synuclein, ND and leading to cell death. Progressive motor disorder accompanied by accumulation of α synuclein in the soma and neurite	+++
PARK /PARK2	Missense or loss of function	Motor deficit, nigrostriatal degeneration, α-synuclein accumulation	+++
UCH-L1/PARK5	Missense	Rotenone induced mouse models: ↑ α-synuclein aggregation	+
DJ-1 /PARK7	Missense	Loss of DA neurons in SN of brain	+++
LRRK2 /PARK8	Missense	Progressive motor deficit with immobility by 10-12 months	+++
ATP13A2 /PARK9	Missense or loss of function	Impairment in lysosomal degradation, α-synuclein accumulation and neurotoxicity	+++
GIGYF2/PARK11	Missense	Exhibits motor dysfunction by 12-15 months	+
HTRA2/PARK13	Missense	☒Climbing ability, movement disorders, and tremor	+
PLA2G6/PARK14	Missense or loss of function	Loss of DA neurons in SN	+++
FBOX7/PARK15	Missense	↓ Proteasome activities and early-onset motor deficit	+++
VPS35/PARK17	Missense	Mitochondrial fusion and cellular respiration function impairments and neuronal loss	+++
EIG4G1/PARK18	Missense	Impairment in oxidative stress resistance	+
DNAJC6/PARK19	Missense or loss of function	Early postnatal mortalities, and weight loss of surviving pups	++
SYNJ1/PARK20	Missense or loss of function	Progressive PD-like behavioral alterations and DA neurodegeneration	++

Symbols indicate; +++: Very high, ++: High, and +: Low.

Genetic PD animal models are mostly initially generated in mice due to their practicality and suitability compared to other models. However, most genetic mouse models of PD fail to achieve damage to over 50% of nigral dopaminergic neurons (104). Many behavioral, physiological, and biochemical differences are known between mice and rats. Additionally, there are significant differences in their genetic sequence and expression. For example, rats have lower LRRK2 expression in the SN compared to mice (105). As a result of reviews conducted for PD, 90 independent common genetic risk factors and associated phenotypes have been identified, which could be valuable qualities for future PD biomarker studies (106).

Various software and studies are available in neurodegenerative diseases and genome-wide association studies. Methylation Genome-wide Association Studies (MWAS) methods have emerged to investigate the impact of differentially methylated positions (DMPs) on complex diseases. Recently, the OmicS-based Complex Trait Analysis (OSCA) software has been developed, and both the Mixed linear model-based omics association (MOA) and mixed-linear model method (MOMENT) software are used to test the relationship between each DNA methylation region and traits (107).

3. Conclusion

It is important to acknowledge that no single animal model perfectly replicates all aspects of human PD. In order to carry out the experimental processes successfully, researchers should choose the experimental PD model to be used in accordance with the study design. In candidate drug molecule or active ingredient research, an experimental PD model should be selected for the symptoms or mechanism for which the drug is expected to be indicated. Each model has its limitations, and findings from animal studies must be carefully interpreted and validated in human clinical trials. Nonetheless, animal models remain invaluable tools in the quest to unravel the complexities of PD and develop effective treatments for this challenging condition.

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Review Article/ Derleme Makalesi

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Does Artificial Intelligence Guided Approach to Cardiac Arrest Increase Survival Rate? Will Neurological Outcomes Improve?

Yapay Zekâ Eşliğinde Kardiak Arreste Yaklaşım Sağ Kalım Oranını Artırır mı? Nörolojik Sonuçlar İyileşir mi?

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ABSTRACT

Interest in the use of Artificial intelligence (AI) in in-hospital and out-of-hospital emergency situations has increased in recent years. In this review, we present a summary of recent studies using in-hospital and out-of-hospital AI for cardiac arrest management. Cardiac arrest is known as a life-threatening cessation of cardiac activity, and early diagnosis and intervention are crucial. For this reason, AI technologies are being used more and more nowadays as they allow for earlier identification of patients at risk.

Keywords: artificial intelligence, cardiac arrest, prediction

ÖZ

Hastane içi ve hastane dışı acil uygulama gerektiren durumlarda Yapay zekâ (Artificial intelligence (AI)) kullanımına olan ilgi son yıllarda artış göstermiştir. Bu derlemede, kardiyak arrest yönetimi için hastane içi ve hastane dışı yapay zekâ ile yapılmış güncel çalışmaların bir özeti sunulmaktadır. Kardiyak arrest kalpteki aktivitenin hayatı tehdit eden bir şekilde durması olarak bilinir ve erken teşhis ve müdahale oldukça önemlidir. Bu nedenle, AI teknolojileri risk altındaki hastaların daha öncesinde belirlenmesine imkân sağlamasından dolayı günümüzde daha fazla kullanılmaktadır.

Anahtar kelimeler: Yapay zekâ, kardiyak arrest, tahmin

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Giriş

Ani kardiyak ölüm olarak da bilinen kardiyak arrest beyin ve kalbin kan akışından mahrum kalmasından dolayı oldukça sık görülen ve mortal bir durumdur (1). Beyin ve kalp gibi hayati organlar kan akışından mahrum kalması nedeniyle bu akut durum acil müdahale gerektirir. Müdahalede gecikme yaşam boyu komplikasyonlara ve hatta ölüme yol açabilir (1). Kalp durması sonrası küresel ölüm oranı oldukça yüksektir ve hastane dışı kalp durması (Out-of-hospital cardiac arrest, (OHCA)) vakalarının %78'i hastaneye ulaşamadan hayatını kaybetmektedir (1,2).

Kardiyak arrest anından taburcu anına kadar OHCA için hayatta kalma oranı dünya genelinde %2 ila %11 arasında değişmektedir (3). Hastane ortamında meydana gelen kardiyak arrest ölümlerinin sayısı da önemlidir. Yalnızca Amerika Birleşik Devletleri'nde, yıllık olarak 290.000'in üzerinde kardiyak arrestte meydana gelmektedir ve sağkalım oranları ortalama %18,1 ve bu oranın çok küçük bir yüzdesi olumlu nörolojik prognoza sahip olmaktadır (1,4).

Başarılı bir resüsitasyon yapmak, sağ kalım oranını artırmak ve iyi bir nörolojik iyileşme elde etmek, acil servis çalışanlarının ortak hedefi ve amacıdır. Bu nedenle bu yönde birçok çalışma yapılmaya devam edilmektedir. Günümüzde bu çalışmaların yoğunlaştığı alanlardan biri de AI kullanımıdır.

AI Teknolojisinin Acil Çağrı Merkezinde Kullanımı

Erken tanı ve müdahale, yüksek kaliteli kardiyopulmoner resüsitasyon (CPR), defibrilasyon, post-resüsitasyon bakımı, komplikasyonların önlenmesi ve tedavisi, altta yatan hastalık, yaş ve sosyo-ekonomik faktörler, sağ kalımı ve nörolojik iyileşmeyi etkileyecek önemli faktörlerdendir. Son yıllarda kardiyak arrestin erken tanınma ve erken müdahalesi (arrestin ön görülmesi, arrestin erken tanınması, erken göğüs basılarına başlanması), defibrilasyon (doğru zamanda, doğru yöntemle, göğüs basılarını kesintiye uğratmaksızın, ölümcül ritimlerin erken tanınması, defibrilatör ulaşımını kolaylaştırma), ve post-resüsitatif sonuçları ön görmede AI'nın kullanılması önemli rol oynayabilir.

Blomberg ve arkadaşları tarafından Kopenhag'da kardiyak arrestin erken tanınması ile ilgili acil yardım hattına yapılan 108.607 acil çağrı incelenmiş ve bu çağrılardan 918'inin kardiyak arrest ile ilişkili olduğunu tespit edilmiştir. Gelen çağrılar üzerinden kardiyak arresti tanımak için makine öğrenimi ile geliştirdiği AI programı ile hastane dışı kardiyak arresti tanımak için duyarlılık, özgüllük ve pozitif prediktif değer hesaplanmıştır. AI programının performansı, tıbbi sevk görevlileri tarafından kardiyak arrestin gerçek tanıma süresiyle karşılaştırılmıştır. Çalışmanın sonucunda işlenmemiş ve düzenlenmemiş ses dosyalarını analiz eden AI'nın acil yanıt sistemi çalışanlarına göre kardiyak arrest durumunu daha hızlı ve daha doğru tespit ettiği, kurtarıcıya daha hızlı destek sağlanabildiği, olay yerine acil yardım ekiplerinin daha hızlı sevk edilebileceği sonucuna ulaşılmıştır (5). Byrsell ve arkadaşları, önceden tanımlanmış ayara bağlı olarak az yâda çok OHCA'nın önceden tespit edilebilmesi için makine öğrenimi ile geliştirdiği AI programı ile İsveç acil çağrı merkezine yapılan 851 OHCA vakasını incelenmiştir. Bu vakalarda OHCA tanı oranı AI destekli programda %36 iken, acil yanıt sistemi çalışanlarında bu oranı %25 olarak tespit etmiştir. Hem AI programı, hem de acil yanıt sistemi çalışanları tarafından tanınan OHCA'lar arasında AI programı lehine 28 saniyelik bir ortalama fark bulunmuş ve bu çalışmada kardiyak arrestin AI destekli programlar ile ortalama 72 saniyede, acil yanıt sistemi çalışanları tarafından ortalama 94 saniyede tespit edildiği belirlenmiştir (6). Bu çalışmanın sonucunda AI destekli programların gelen çağrıların daha erken ve doğru tanınmasına ve temel yaşam desteğinin daha erken başlanmasına imkân sağlayabileceğini göstermiştir.

AI Teknolojisi ile Kardiyak Arrestin Erken Belirlenmesi

Kardiyak arrestin erken tanınması kadar erken ön görülmesi de sağ kalımı etkileyecek durumlardan biridir. Son zamanlarda geliştirilen derin öğrenme tabanlı erken uyarı puanının (DEWS), durumu kötüleşen hastaları tahmin etme potansiyeli olup olmadığını araştıran Lee ve arkadaşları hastane içi kalp durması (In-hospital cardiac arrest, IHCA) riski taşıyan hastaları belirlemek için Deep Learning-Based Early Warning Score (DEWS) erken uyarı puanıyla Modified Early Warning Score (MEWS) karşılaştırmışlardır. Bu çalışmaya 1 yıl boyunca beş hastanenin genel servislerine başvuran 173.368 yetişkin hasta dâhil edilmiştir. Hastaların vital bulgularının takibi ile yapılan bu çalışmada vakalardan 224'nin IHCA olduğu ve DEWS'in MEWS'ten daha başarılı olduğu belirlenmiştir (7). Kwon ve arkadaşları da hastanede yatarak tedavi alan hastaların sistolik kan basıncı, nabız, solunum hızı ve vücut ısısını sık aralıklarla ölçerek kardiyak arresti ön görmeye yönelik bir AI programı kullanmış ve bu programın IHCA riski taşıyan hastaların %50'sinden fazlasını olaydan 14 saat önce tespit edebildiğini göstermiştir (8). Park ve arkadaşları vital bulgular aracılığı ile kardiyak arresti ön görmeye yönelik geliştirdikleri AI programı ile 50.019 pediatrik vakadan kardiyak arrest gelişen veya pediatrik yoğun bakıma ihtiyacı olan hastalar için geliştirdikleri AI programı ile 24 saat öncesinde yatan hastalarda IHCA ve beklenmedik çocuk yoğun bakım ünitesi (ÇYBÜ) transferleri öngörmede iyi bir performans gösterdiğini belirlemişlerdir (9). Jang ve arkadaşları acil servis başvurularında gelişecek kardiyak arrest durumunu erken tanımak için yaptıkları çalışmada 374.605 acil servis başvurusunu incelemiş ve acil serviste kardiyak arrest geçiren 1.097 hastanın demografik bilgileri (yaş ve cinsiyet), ana şikâyetleri, vital bulguları ve bilinç düzeyleri (AVPU (A: uyanıklık hali V: sözlü uyarılara yanıtlılık P: ağrıya tepki verme ve U: tepkisizlik) ölçeğine göre) AI destekli bir programa tanımlanmış ve kardiyak arrest gelişecek vakaları ön görüp göremeyeceği incelenmiş ve AI programının geleneksel risk skorlarından daha başarılı bir şekilde kardiyak arrest vakalarını ön gördüğü sonucuna ulaşılmıştır (10). Alonso ve arkadaşları bu konuyu biraz daha detaylandırarak AI programına 8.321 hastanın Adenozin Miyokardiyal Perfüzyon (Single-photon emission computed tomography, SPECT) görüntülerini ve kardiyak arrest risk faktörleri tanımlayarak kardiyak arresti ön görme yetisini değerlendirmiş ve bu vakalardan 551'i için kardiyak arrest geliştiğini belirlemişlerdir. AI programının hastalarda gelişecek kardiyak arrest riskinin önceden belirlenmesinde önemli bir rol oynayabileceğini göstermiştir (11).

Kardiyak arrest vakalarına erken müdahale edilmesi sağ kalımı ve iyi nörolojik iyileşmeyi olumlu etkiler. Bu konuda yapılan halk eğitimlerine rağmen, kardiyak arrest vakalarına müdahale etme oranları oldukça düşüktür. Bu oranların arttırılması için birçok eğitim yapılmaktadır. Bu konuda AI'nin etkilerini araştıran çalışmalar teknoloji ile ilerlemeye devam etmektedir. İlk olarak acil yardım ekiplerinin görüntülü aranmasının erken müdahaleye etkisi üzerine yapılmış çalışmalara göz atmak gerekmektedir. Lee ve arkadaşlarının 1.720 OHCA vakası ile yaptıkları bir çalışmada 1.489 sesli, 231 arama ise görüntülü olarak acil yardım ekipleri tarafından yönlendirildi. Görüntülü olarak yardım alan hastalarda sağ kalım ve iyi nörolojik iyileşmenin daha fazla olduğu görüldü (12). Teknolojik ilerlemeler ile hayatımıza giren Chatbotların kardiyak arrest vakalarında kurtarıcıya yardım edip edemeyeceğini inceleyen Agra ve arkadaşlarının, çalışmasında ise kurtarıcılar karşılaştıkları kardiyak arrest durumunda Chatbotlardan yardım isteyerek durumu yönetmişler ve Chatbotlar ile katılımcıların %91'i temel yaşam desteği basamaklarındaki tüm sıralamayı

doğru olarak yerine getirmişlerdir. Katılımcıların tamamı olay yerinin güvenliğini kontrol edip 112'yi aramayı ihmal etmemiş ve katılımcılardan %62'si doğru kompresyon yapmıştır. Tüm süreçte 158 saniyelik bir ortalama süre, hızı için ise ortalama 100 kompresyon belirlendi. Kurtarıcıların %33'ü Chatbotlar aracılığı ile yüksek kalitede CPR elde etmiştir (13). Acil yardım ekiplerinin özellikleri kadar kurtarıcının özellikleri de erken resüsitasyon için önemli bir faktördür. Soğukkanlılığını koruyabilen, duygusal açıdan daha kontrollü işbirlikçi kurtarıcılar, erken resüsitasyona başlama açısından daha faydalı olacaklardır. AI'nin bu tür kurtarıcıları ses kaydından tanıyarak müdahale için yönlendirdiği bir çalışmada, AI'nin belirlediği kurtarıcıların diğer kurtarıcılar göre resüsitasyona daha erken başlanıldığı görülmüştür (14).

AI'nin CPR Esnasında Kullanımı

Resüsitasyon esnasında göğüs kompresyonlarında kesintilerin olması resüsitasyonun kalitesini düşürmesi, sağ kalımı ve iyi nörolojik iyileşmeyi engellemektedir. Bu nedenle temel hedeflerden biri de kesintisiz göğüs kompresyonudur. Ancak defibrilasyonda artefaktlardan kurtulmak ve doğru karar verebilmek için çoğu zaman göğüs basıları kesintiye uğratılır. Bu sorunu çözme adına yapılan bir çalışmada Isasi ve arkadaşları 3.319 elektrokardiyografi (EKG) ile geliştirilen AI ile CPR esnasında artefaktlardan arındırmaya çalıştı. Böylece şoklanabilir ve şoklanamaz ritimleri göğüs basısı yaparken de ayırt edebilmelerine imkân sağlamıştır (15). Jekova ve arkadaşları ise otomatik eksternal defibrilatörleri artefaktlardan kurtarmak için AI'yi kullanmış ve çalışma sonunda göğüs kompresyonları esnasında bile otomatik eksternal defibrilatörlerin doğru karar verdiğini gözlemlemiştir (16).

AI ile Ölümcül Ritimlerin Önceden Belirlenmesi

Ölümcül taşikardilerin erken tanınması ve erken müdahale edilmesi resüsitasyonun başarısını artıracak önemli faktörlerdendir. Bu nedenle çeşitli yöntemler ile hastalarda taşikardilerin ön görülmesi sağlanması için AI programı kullanılabilmektedir. Liu ve arkadaşlarının yaptığı bir çalışmada AI programına 5.699 hasta için yaş, cinsiyet, yatış nedenini içeren elektronik sağlık kayıtları ve kardiyovasküler hastalık öyküsü tanımlandıktan sonra hastalarda kalp atış hızı, solunum hızı ve kan oksijen satürasyonu değerleri takip edildi. AI programı ile takip edilen hastalarda taşikardilerin 6 saat öncesinde tespit edilebileceği belirlenmiştir (17). Benzer şekilde Alanis ve arkadaşları AI programı ile implante edilebilen kardiyoverter defibrilatör (ICD)'li hastalarda kalp hızı değişkenliği, Prematür Ventriküler Kompleks (PVC) endeksleri, ani kardiyak ölüm ve ölümcül taşiaritmiyi önceden tespit edebileceğini göstermişlerdir (18). Thannhauser ve arkadaşları benzer şekilde AI programı kullanarak 206 ICD'li hastada akut Miyokard Enfarktüsü (MI) ve Ventriküler Fibrilasyonu (VF) erken evrede tanıyarak tedaviye erken başlanabileceğini göstermişlerdir (19).

AI ile Otomatik Ekstrenal Defibrilatörlerin Taşınması

Taşiaritmilerin erken tanınması kadar defibrilatöre erken ulaşmak da önemlidir. Bunun için Otomatik Ekstrenal Defibrilatörlerin (OED) yerini bilmek gerekir. Bunu sağlamak amacıyla son on yılda, OED'leri haritalamak ve bulmak için çok sayıda mobil uygulama ve web sitesi geliştirildi. Bu uygulamalar akıllı telefonun coğrafi konum özelliği sayesinde kullanıcının konumunu gerçek zamanlı olarak bulabilmekte ve yakındaki OED'leri, en yakın olana ulaşma talimatlarıyla birlikte görüntüleyebilmektedir. Ülkelerin %78'inde mevcut olan OED'leri haritalandırmaya yönelik uygulamalar ve web siteleri, OHCA durumunda en yakın OED'nin yerini tespit etmeye yardımcı olur. Dahası, bu sistemler vatandaşların yeni OED'ler eklemesine veya topluluklar halinde mevcut olanların ayrıntılarını güncellemesine olanak tanır. Güncel bir OED kaydının oluşturulması ve sürdürülmesi toplumdaki farkındalığı artırır. Vatandaşların ilk müdahale ekiplerini uyarmak için acil sevk merkezleri ve uygulamalarıyla koordine edildiğinde etkinlik oranı daha yüksek olabilir (20). Defibrilatöre erken ulaşmak için denenmiş yöntemlerden biri de uçan göz kullanmaktır. Claesson ve arkadaşları OHCA simülasyonunda OED'yi kurtarıcıya ulaştırmada uçan göz kullanımının acil yardım ekiplerinden daha hızlı gerçekleştiğini gözlemlemişlerdir (21). Ancak drone (uçan göz) uçuşlarının maliyeti, kaza olasılığı, uçan gözün ambulanstan sonra gelme olasılığı, uçan gözün önceki görevden dönünceye kadar sonraki OHCA'lar için kullanılamaması gibi dezavantajları da vardır. Bu sorunların çözümü için Chu ve arkadaşları ambulans sevk merkezlerine benzer şekilde AI destekli uçan göz sevk merkezi kurulmasıyla OED sevkinin kısa sürede ve başarılı bir şekilde yapılabileceğini savunmuştur (22).

AI programı yapılan resüsitasyonun sonucunu ön görme konusunda da yardımcı olabilir. Kajino ve arkadaşları OHCA vakalarında resüsitasyonun sonlandırılmasına karar vermeye yönelik bir AI programı geliştirmiş ve retrospektif vakalarda bu program ile evrensel resüsitasyonu sonlandırma kurallarını karşılaştırmışlar ve AI programının evrensel resüsitasyonu sonlandırmada iyi bir performans gösterdiğini belirlemiştir (23). IHCA vakalarında resüsitasyon sonucunu ön görme için yapılmış çalışmalardan biri de Amacher ve arkadaşlarına aittir. Bu çalışmada Chatbotlardan biri olan ChatGPT programına hasta ile ilgili veriler girilerek bu hastanın IHCA sonrası prognozu soruldu. OHCA skoru, Kardiyak Arrest Hastane Prognozu (Cardiac Arrest Hospital Prognosis, CAHP) skoru ve erken evrelerdeki seçilmemiş yetişkin kardiyak arrest hastaları için logistik regresyon modeli kullanılarak prognostikasyon (PROgnostication using LOGistic regression model for Unselected adult cardiac arrest patients in the Early stages, PROLOGUE score) skoru ile kıyaslandı. ChatGPT-4'ün mortaliteyi ve kötü nörolojik sonuçları tahmin etme konusundaki prognostik performansının iyi olduğunu göstermişlerdir (24). AI yalnızca akut durumlarda değil aynı zamanda kronik iyileşme sürecini ön görmede de yardımcı olabilmektedir. Heo ve arkadaşları yaptıkları çalışmada 1.207 (IHCA ve OHCA sonrası spontan dolaşımın geri döndüğü) vakayı değerlendirdi. Geliştirdikleri 4 AI programına hasta ile ilgili tıbbi kayıtları girerek 1 yıllık beyin performansı kategorisi (cerebral performance category, CPC) skoru ile karşılaştırdı. Geliştirdikleri programların hastaların 1 yıllık nörolojik durumlarını ön görmede CPC skoru kadar efektif olduğu gözlenmiştir (25).

Sonuç:

Tüm bu çalışmalar göz önüne alındığında yapay zekâ;

1. IHCA'nin öngörebilir ve kötüleşen hastaların belirlenmesini sağlayabilir,
2. Yaşamsal belirtilere ve laboratuvar sonuçlarına göre hastadaki bozulmayı daha erken tespit ederek IHCA'nin daha erken tahmin edilmesini sağlayabilir,
3. Tek derivasyonlu EKG kullanarak kalp durmasını tahmin etme olanağı sağlar,
4. Kalp ritmi bozukluğunu altı saate kadar önceden tahmin edebilir ve kalp durmasını öngörebilir
5. Uçan göz ile teslim edilen OED'ler, OED'nin sahaya ulaşması için gereken süreyi önemli ölçüde azaltabilir,
6. Tüm OHCA'lara uçan göz gönderen bir politika geliştirilebilir,
7. Resüsitasyon sırasında CPR'yi durdurma ihtiyacını ve şok vermenin optimum zamanlamasını ortadan kaldırabilir,

8. Yoğun bakımın ilk üç gününden itibaren klinik faktörleri ve biyobelirteçleri kullanarak OHCA sonrası hastalarda nörolojik prognozu iyiden mükemmele doğru tahmin etmede yardımcı olabilir,

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Dynamic Shifts in Vitamin D Status Following Liposuction: Implications for Patient Monitoring and Health

Liposuction Sonrası D Vitamini Durumundaki Dinamik Değişimler: Hasta İzleme ve Sağlık Açısından Etkileri

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We have read with great interest the research article by Kandulu, titled "Dynamic Shifts Vitamin D Status in Following Liposuction: Implications for Patient Monitoring and Health" published in the first issue of Ağrı Medical Journal in 2024 (1). We extend our gratitude to the author and the editorial team for their valuable contribution. Through this letter, we aim to highlight specific elements that we believe will enrich the ongoing discourse surrounding the article.

As underscored by Kandulu, vitamin D exerts influence not only on the musculoskeletal system but also on various other physiological pathways (2). Therefore, it is recommended to maintain serum 25 hydroxy (25-OH) vitamin D levels, which are the major circulating form, particularly above 20 ng/mL. Since vitamin D is a fat-soluble vitamin, investigating its fluctuation in patients undergoing liposuction is intriguing. Such an approach not only facilitates the identification of replacement needs in this patient cohort but also holds promise for effectively managing vitamin D deficiency/insufficiency during liposuction procedures. Considering these facets, we commend the significance of Kandulu's study.

However, we wish to address a concern regarding the exclusion criteria of the study. As it is not stated in the methods section, it appears that patients receiving vitamin D supplementation were not excluded from the study cohort, which may pose challenges in accurately evaluating the changes of 25-OH vitamin D levels after liposuction.

It is well-established that sources of vitamin D include sunlight exposure, dietary intake, and supplements (3). When administered as a supplement, cholecalciferol is metabolized in the liver by the hepatic enzyme 25-hydroxylase, leading to the formation of 25-OH vitamin D (calcidiol) (4). The half-life of calcidiol is approximately 2-3 weeks (5). Consequently, if patients received vitamin D supplementation at any point during the study period, the results could be prone to misinterpretation. For instance, preoperative vitamin D replacement administered approximately 2-3 weeks prior to surgery may initiate a decline in levels, potentially confounding the findings. In the study, postoperative 25-OH vitamin D levels decreased from 27.70 to 15.196 prompting the author to emphasize the statement "Furthermore, we observed increased rates of Vitamin D deficiency following the surgery, indicating the necessity of a closer follow-up of this parameter in the patient group". Notably, 25-OH vitamin D levels in patients increased during the postoperative 3rd and 6th months. Moreover, while 3 patients had adequate 25-OH vitamin D levels postoperatively, this number increased to 12 patients at the 1-month mark, raising questions about the ongoing replacement therapy in these individuals. If replacement therapy was not administered, the underlying reasons of increasing vitamin D levels of patients should be explored.

In conclusion, while acknowledging the merits of Kandulu's study, we believe that addressing the aforementioned concerns regarding the exclusion criteria and interpretation of results would further enhance the scientific rigor and clinical relevance of the findings. We appreciate the opportunity to provide feedback and eagerly anticipate further advancements in this area of research. Additionally, we extend our heartfelt thanks to the author, Kandulu, again for their valuable contribution to the field of research.

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