e-ISSN: 2149-8059
ISSN: 1017-6616

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Selçuk Tıp Dergisi, Türkiye Atıf Dizini, Index Copernicus, International Citation Index, Türk Atıf Dizini (ULAKBİM) ve EBSCO tarafından indekslenmektedir.

Cilt: 38 Sayı: 3 EYLÜL 2022

SELCUK TIP DERGİSİ

Cilt: 38 Sayı: 3 EYLÜL 2022

e-ISSN: 2149-8059

ISSN: 1017-6616

Haberleşme (Communication)
Selçuk Tıp Dergisi Editörlüğü
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi 42080
Meram, KONYA
Tel: 0332 223 60 00 Fax: 0332 223 61 81
e-posta:info@selcukmedj.org
Web adresi: www.selcukmedj.org

Selçuk Tıp Dergisi yılda dört sayı (Mart, Haziran, Eylül, Aralık) yayınlanan "peer review" yöntemi ile çalışan hakemli bir dergidir. Selçuk Tıp Dergisi Türkiye Atıf Dizini, Index Copernicus, International Citation Index, Türk Atıf Dizini (ULAKBİM) ve EBSCO arafından indekslenmektedir.

Grafik-Tasarım
İlkay KURT, 0332 223 62 54

Araştırma Makalesi / Research Article

Derleme / Review

DERGİ HAKKINDA

İlk olarak 1984 yılında yayın hayatına başlayan Selçuk Tıp Dergisi (Selcuk Med J) (ISSN: 1017-6616, e-ISSN: 2149-8059), Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi'nin bağımsız, çift kör, hakemli bilimsel yayın organıdır. Dergimiz Mart, Haziran, Eylül ve Aralık aylarında üç ayda bir yayımlanmaktadır.

Derginin sayılarına tam erişim aşağıdaki adresten temin edilebilir.

http://www.selcukmedj.org

Selçuk Tıp Dergisi (Selcuk Med J) dünya genelinden yayınları kabul etmektedir. Yayınlar en az iki hakem tarafından orijinal bilgi, fikir ve sunum açısından değerlendirilmektedir.

Selçuk Tıp Dergisi (Selcuk Med J), Türkçe ve/veya İngilizce makaleleri yayınlar, dergi içeriklerine ücretsiz erişim sağlar (Open Access) ve yazarların makalelerin son kabul edilmiş halini OAI uyumlu kurumsal / konu bazlı bir havuzda kendi arşivleyebilmelerine izin verir.

Selçuk Tıp Dergisi (Selcuk Med J) tıp doktorları, araştırmacılar ve bilim adamlarından oluşan bir kitleye yönelik çok disiplinli bir dergidir.

Etik Kurallara Uygunluk

Derginin yayın 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.

Dergimiz 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) (doaj.org/bestpractice) uygundur.

Makalelerin daha önce hiçbir yerde yayınlanmamış ve yayın için başka bir dergiye gönderilmemiş olması gerekir. Selçuk Tıp Dergisi'nde intihal programı (iThendicate) kullanılmaktadır. Akademik atıf sınırını aşan benzerlik taşıyan makaleler ve yayın kurallarına uygun olarak hazırlanmamış makaleler değerlendirmeye alınmayacaktır. Tüm çalışmalarda etik kurul onayı gerekmektedir ve bu onamın belgelendirilmesi yazıların yayınlanmasında esas teşkil edecektir.

Tüm çalışmalarda yazarların çalışmaya katkı düzeyi ve onayı bildirilmelidir. Çalışmada veri toplanması, deney aşaması, yazım ve dil düzenlemesi dahil olmak üzere herhangi bir aşamasında finansal çıkar çatışması olmadığı bildirilmelidir. Çalışmada varsa ticari sponsorluk bildirilmelidir.

Yazarlardan Selçuk Tıp Dergisi'nde yayımlanacak makaleleri için herhangi bir ödeme istenmez.

Bütün makaleler editor ve yayın kurulu tarafından üç ay içerisinde sonuçlandırılacaktır. Fakat elde olmayan gecikmelerden dolayı bu süre uzayabilir.

Dergi Amaç ve Kapsamı

Selçuk Tıp Dergisi amacı, genel tıp alanında tanı ve tedavideki güncel gelişmeler, cerrahi yenilikler ve bilim dünyasına katkıda bulunacak deneysel çalışmaların ulusal ve uluslararası literatürde paylaşımının sağlanmasıdır.

Selçuk Tıp Dergisi, sağlık bilimlerindeki tüm etik yönergelere uygun olarak hazırlanmış klinik ve deneysel araştırma makaleleri, olgu bildirileri, derleme makaleleri, teknik notlar ve editöre mektupları yayınlamaktadır.

Bu Sayıda Görev Alan Hakemler

1. Prof. Dr. Ekrem ÜNAL
2. Prof. Dr. Neslihan YILMAZ
3. Prof. DR. Ruhuşen KUTLU
4. Doç. Dr. Sadık Ahmet UYANIK
5. Doç. Dr. Ahmet YILDIRIM
6. Doç. Dr. Celalettin KORKMAZ
7. Doç. Dr. Funda GÖK
8. Doç. Dr. Hülya VATANSEV
9. Doç. Dr. Pembe OLTULU
10. Doç. Dr. Özge Metin AKCAN
11. Doç. Dr. Mustafa ÖZER
12. Dr. Öğr. Üyesi Ahmet ÇİZMECİOĞLU
13. Dr. Öğr. Üyesi Bülent IŞIK
14. Dr. Öğr. Üyesi Enver MİRZA
15. Dr. Öğr. Üyesi Fakih Cihat ERAVCI
16. Dr. Öğr. Üyesi Filiz TAŞPINAR
17. Dr. Hasan ÇANAKCI
18. Dr. Öğr. Üyesi Sinem Suner KEKLİK
19. Dr. Şefika AKYOL

YAZARA AÇIKLAMA

Selçuk Tıp Dergisi (Selcuk Med J) Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi Dekan'lığının yayın organıdır. Dergimize yazı hazırlanırken aşağıdaki açıklamaları lütfen bütünüyle okuyunuz.

Selçuk Tıp Dergisi (Selcuk Med J) tıp bilimine ve akademik çalışmalara katkısı olan, klinik ve deneysel çalışmaları, editoryal yazıları, kısa raporları, klinik olgu bildirimlerini, teknik ve eğitici derlemelerini, tıp konusundaki son gelişmeler ile orijinal görüntü raporlarını, görüntülü hastalık tanımlama sorularını ve editöre mektupları yayınlar. Ayrıca daha önce yayınlanmış makale ve deneysel çalışmalarla ilgili okuyucu soru ve katkıları kısaca yayınlanır. Yayına kabul edilme, editöryal komite ile en az iki hakem kararı ile alınır. Bir hakem, hakemlik talebini kabul etmeye karar vermeden önce, hakem değerlendirme süreci ve gözden geçirmenin nasıl yapılacağı hakkında daha fazla bilgi edinmek isteyebilir.

Hakemler, Selçuk Tıp Dergisi'nin gereklerine, önceden tanımlanmış kriterlere ve sunulan araştırmanın kalitesine, eksiksizliğine ve doğruluğuna dayanarak makale gönderimini değerlendirir. Hakemler makale hakkında geri bildirimde bulunur, iyileştirmeler önerir ve makalede yapılan değişiklikleri kabul edip etmeme, talep etme veya reddetme konusunda editöre tavsiyede bulunur. Nihai karar her zaman baş editöre aittir, ancak hakemler sonucu belirlemede önemli bir rol oynamaktadır. Bir hakemin makaleyle çıkar çatışması varsa, editöre bildirmesi gerekir. Hakemler, hakem gözden geçirme sistemine katılarak bilimsel sürecin katı standartlarını sağlamalıdır. Ayrıca, geçersiz araştırmaları tespit ederek ve derginin kalitesini korumaya yardımcı olarak derginin bütünlüğünü korumalıdırlar. Hakemler, intihal, araştırma sahtekarlığı ve diğer sorunları tespit ederek etik konuların ihlal edilmesini önlemeye gönüllü olmalıdır.

Yayına kabul edilen yazıların her türlü yayın hakkı dergiye aittir. Bu hak özel düzenlenmiş yayın hakkı devir formu ile bütün yazarların imzası ile tespit edilir. Dergi 3 ayda bir, yılda 4 kez yayınlanır. Derginin yayın dili Türkçe ve/veya İngilizcedir. Gönderilen yazılar daha önce herhangi bir dergide yayınlanmamış olmalıdır (Bilimsel kongrelerde sunulan sözlü bildiri ve posterler bildirmek kaydı ile hariçtir). Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal vb.) yazarlara aittir. Yazım kurallarına uygun olarak hazırlanmamış olan yazıların incelenmeye alınıp alınmaması Yayın Kurulu'nun insiyatifindedir.

Makalelerin daha önce hiçbir yerde yayınlanmamış ve yayın için başka bir dergiye gönderilmemiş olması gerekir. Selçuk Tıp Dergisi'nde intihal programı (iThendicate) kullanılmaktadır. Akademik atıf sınırını aşan benzerlik taşıyan makaleler ve yayın kurallarına uygun olarak hazırlanmamış makaleler değerlendirmeye alınmayacaktır. Tüm çalışmalarda etik kurul onayı gerekmektedir ve bu onamın belgelendirilmesi yazıların yayınlanmasında esas teşkil edecektir.

Tüm çalışmalarda yazarların çalışmaya katkı düzeyi ve onayı bildirilmelidir. Çalışmada veri toplanması, deney aşaması, yazım ve dil düzenlemesi dahil olmak üzere herhangi bir aşamasında finansal çıkar çatışması olmadığı bildirilmelidir. Çalışmada varsa ticari sponsorluk bildirilmelidir.

Derginin editöryal ve yayın süreçleri International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE) ve National Information Standards Organization (NISO) organizasyonlarının kılavuzlarına uygun olarak biçimlendirilmiştir. Selçuk Tıp Dergisi'nin editöryal ve yayın süreçleri, Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice) ilkelerine uygun olarak yürütülmektedir. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında COPE kurallarına uygun olarak hareket edecektir.

Derginin Yayın Kurulu, itiraz ve şikayet vakalarını, COPE rehberleri kapsamında işleme almaktadır. Yazarlar, itiraz ve şikayetleri için doğrudan baş editör veya yayın kurulu ile temasa geçebilirler. İhtiyaç duyulduğunda Yayın Kurulu'nun kendi içinde çözemediği konular için tarafsız bir temsilci atanmaktadır. İtiraz ve şikayetler için karar verme süreçlerinde nihai kararı Baş Editör verecektir. Yayıncı ve editör gerektiğinde düzeltmeler, açıklamalar, geri çekilmeler ve özürler yayınlamaya her zaman hazırdır.

Selçuk Tıp Dergisi (Selcuk Med J) ile ilgili tüm yazışmalar, makale gönderme, makalenin takibi, danışman raporları, düzeltmelerin yapılıp yüklenmesi, kabul yazısı gönderimi ve diğer tüm makale ile ilgili formların yüklenmesi https://www.selcukmedj.org sayfasından yapılacaktır. Bu site üzerinden yüklenecek makaleler için kurallar aşağıda belirtilmiştir.

YAZIM KURALLARI

Yayına gönderilen yazılar Microsoft Word programında yazılmalıdır. Yazı, şekil ve grafilerin tamamı elektronik ortamda https://www.selcukmedj.org word ve pdf formatında gönderilmelidir.

Tüm yazılar:

1. Başlık sayfası,
2. Türkçe özet,
3. İngilizce özet,

4. Makale kısmı,
5. Kaynaklar,
6. Tablolar,
7. Şekiller ve resimler,
8. Alt yazılar şeklinde dizilmelidir.

Araştırma inceleme yazılarının makale kısmı (özet, referanslar, tablo, şekil ve alt yazılar hariç) toplam 4000 kelimeyi, özet kısmı 400 kelimeyi, referanslar 60'ı, tablo ve şekil sayısı 10'u geçmemelidir. Özet amaç, gereç ve yöntemler, bulgular ve sonuç bölümlerini içermelidir.

Olgu bildirileri şu bölümlerden oluşmalıdır: Başlık, İngilizce başlık, Türkçe ve İngilizce özet, giriş, olgunun/olguların sunumu, tartışma ve kaynaklar. Olgu sunumları toplam 8 sayfayı geçmemeli ve 3 resimden fazla olmamalıdır. Özet 200 kelimeyi geçmemeli ve tek bir paragraf şeklinde olmalıdır.

Derlemeler İngilizce ve Türkçe özet içermeli ve özet kelime sayısı 300'ü aşmamalıdır. Tablo sayısı ve şekiller (veya resimler) toplam 6 adedi aşmamalıdır. REferanslar 80'i geçmemelidir. Özet tek bir paragraf şeklinde olmalıdır. Editöre mektup, kısa raporlar, görüntü raporları, teknik ve tıp alanındaki gelişmelere ait yazılar ve orijinal konulara ait görüntü sunumları 2 sayfayı geçmemelidir. Kısa bir (100 kelime) İngilizce ve Türkçe özet içermelidir.

YAZILARIN HAZIRLANMASI

Yazının başlığı hem İngilizce hem de Türkçe olarak yazılmalıdır. Yazıda çalışmaya katkısı olan yazarların ad ve soyadları açık olarak yazılmalı. Yazıların altına çalışmanın yapıldığı kurumun açık adresi yazılmalıdır. Çalışma daha önce herhangi bir kongrede sunulmuş ise kongre adı, zamanı (gün-ay-yıl olarak) belirtilmelidir. Başlık sayfasının en altına iletişim kurulacak yazarın adı, soyadı, açık adresi, posta kodu, telefon ve faks numaraları ile e-posta adresi yazılmalıdır.

Özetler

Ayrı bir sayfa olarak verilmelidir. İngilizce özetin başında İngilizce başlık bulunmalıdır. Araştırma inceleme yazılarında 400, olgu sunumlarında 200 kelimeyi geçmemelidir. Araştırma makalelerinde özet amaç, gereç ve yöntemler, bulgular ve sonuç bölümlerini içermelidir. Araştırma ve inceleme yazılarında özetlerden sonra Türkçe ve İngilizce anahtar kelimeler verilmelidir. Anahtar kelime sayısı 5'i geçmemelidir. Anahtar Kelimelerin İngilizcesi Index Medicus'daki Medical Subjects Headings'e uygun olmalı, Türkçe Anahtar kelimeler ise Türkiye Bilim Terimleri'nden (http://www.bilimterimleri.com) seçilmelidir. Özetlerde kısaltma olmamalıdır.

Makale

Yazı Giriş, Gereçler ve Yöntem, Bulgular ve Tartışma bölümlerinden oluşur.

Giriş: Konuyu ve çalışmanın amacını açıklayacak bilgilere yer verilir.

Gereçler ve Yöntem: Çalışmanın gerçekleştirildiği yer, zaman ve çalışmanın planlanması ile kullanılan elemanlar ve yöntemler bildirilmelidir. Verilerin derlenmesi, hasta ve bireylerin özellikleri, deneysel çalışmanın özellikleri ve istatistiksel metotlar detaylı olarak açıklanmalıdır. Çalışma klinik bir çalışma ise başlık 'Hastalar ve Yöntem' şeklinde olmalıdır.

Bulgular: Elde edilen veriler istatistiksel sonuçları ile beraber verilmelidir.

Tartışma: Çalışmanın sonuçları literatür verileri ile karşılaştırılarak değerlendirilmelidir.

Tüm yazımlar Türkçe yazım kurallarına uymalı, noktalama işaretlerine uygun olmalıdır. Kısaltmalardan mümkün olduğunca kaçınılmalı, eğer kısaltma kullanılacaksa ilk geçtiği yerde ( ) içerisinde açıklanmalıdır. Kaynaklar, şekil tablo ve resimler yazı içerisinde geçiş sırasına göre numaralandırılmalıdır. Metin içerisindeki tüm ölçüm birimleri uluslararası standartlara uygun biçimde verilmelidir.

Kaynaklar

Kaynaklar iki satır aralıklı olarak ayrı bir sayfaya yazılmalıdır. Kaynak numaraları cümle sonuna nokta konmadan ( ) içinde verilmeli, nokta daha sonra konulmalıdır. Kaynak yazar isimleri cümle içinde kullanılıyorsa ismin geçtiği ilk yerden sonra ( )
içinde verilmelidir. Birden fazla kaynak numarası veriliyorsa arasına ",", ikiden daha
fazla ardışık kaynak numarası veriliyor ise rakamları arasına ",-" konmalıdır [ör.(1,2), (1-3)gibi]. Kaynak olarak dergi kullanılıyorsa: yıl, cilt, başlangıç ve bitiş sayfaları verilir. Kaynak olarak kitap kullanılıyorsa: sadece yıl, başlangıç ve bitiş sayfaları verilir. Kaynaklarda yazarların soyadları ile adlarının baş harfleri yazılmalıdır. Dergi isimleri Index Medicus'a göre kısaltılmalıdır. Kaynak yazılma şekli aşağıdaki örnekler gibi olmalıdır. Yazar sayısının üçten fazla olması durumunda ise ilk üç yazarın ismi yazılmalı, sonrasında "et al." eklenmelidir.

Dergiler için

1) Kocakuşak A, Yücel AF, Arıkan S. Karına nafiz delici-kesici alet yaralanmalarında rutin abdominal eksplorasyon yönteminin retrospektif analizi. Van Tıp Dergisi 2006;13(3):90-6.

2) Vikse BE, Aasard K, Bostad L, et al. Clinicalprognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant 2003;18:517-23.

Kitaplar için

1) Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Kitaptan Bölüm İçin

1) Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.

2) Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.

Tablolar

Tablolar ayrı sayfaya iki satır aralıklı yazılmalı, her tablonun üzerinde numara ve açıklayıcı ismi olmalıdır. Tabloda kısaltmalar varsa tablonun altında alfabetik sıraya göre açılımları yazılmalıdır. Örnekler: PS: pulmoner stenoz, VSD: ventriküler septal
defekt. Tablolar yazı içindeki bilgilerin tekrarı olmamalıdır.

Şekil ve Resimler

Şekil ve resimler mutlaka isimlendirilmeli ve numaralandırılmalıdır. Resimler minimum 300 dots per inch (dpi) çözünürlüğünde ve net olmalıdır. Resimler makaleden ayrı bir şekilde makale gönderimi esnasında elektronik olarak JPEG formatında gönderilmelidir.

Makale içerisinde geçen resimler kabul edilmeyecektir. Renkli resimlerin basımı ancak yazarın basım ücretini kabul etmesi ve bu ücreti ödemesi halinde mümkün olacaktır. Aksi takdirde resim siyah-beyaz olarak basılır. Şekil ve resim altlarında kısaltmalar kullanılmış ise, kısaltmaların açılımı alfabetik sıraya göre alt yazının altında belirtilmelidir. Mikroskobik resimlerde büyütme oranı ve tekniği açıklanmalıdır. Yayın kurulu, yazının özünü değiştirmeden gerekli gördüğü
değişiklikleri yapabilir.

HAKEM RAPORU SONRASINDA DEĞERLENDİRME

Yazarlar hakem raporunda belirtilen düzeltme istenen konuları maddelendirerek bir cevap olarak kendilerine ayrılan cevap bölümüne yazmalıdırlar ve ek bir dosya şeklinde yüklenmelidir https://www.selcukmedj.org. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak) online olarak tekrar göndermelidirler.

SON KONTROL

1. Yayın hakkı devir ve yazarlarla ilgili bildirilmesi gereken konular formu gereğince
doldurulup imzalanmış,
2. Özet makalede 400, olgu sunumunda 200 kelimeyi aşmamış,
3. Başlık Türkçe ve İngilizce olarak yazılmış,
4. Kaynaklar kurallara uygun olarak yazılmış,
5. Tablo, resim ve şekillerde bütün kısaltmalar açıklanmış olmalıdır.

ONLİNE YÜKLEME BASAMAKLARI

https://www.selcukmedj.org sayfasında
1. Makale şekli *
2. Türkçe ve İngilizce başlık *
3. Kısa başlık *
4. Türkçe ve İngilizce özet*
5. Türkçe ve İngilizce anahtar kelimeler *
6. Yüklenmesi gerekli bölümler (word makale dosyası, makale dosyasının pdf
formatı, Başlık sayfası, copyright formu, ek dosyalar (resim, şekil ve tablolar) şeklinde
5 basamakta tamamlanmalıdır.

INSTRUCTIONS FOR AUTHORS

Selcuk Medical Journal (Selcuk Med J) is a scientific publication of Necmettin Erbakan University, Meram Faculty of Medicine.

Please entirely read the instructions discussed below before submitting your manuscript to the journal. Selcuk Medical Journal publishes original articles on clinical or experimental work, case histories reporting unusual syndromes or diseases, brief reports, technical and educative reviews, recent advancement of knowledge of the medical sciences with original images, questionnaires of defining disease, and letters to the editor.

Final recommendation for publication is made by the editorial board and at least two independent reviewers. Before reviewers decide to accept a request to review, they might want to know more about the peer review process and how to conduct a review. Reviewers evaluate article submissions to journal based on the requirements of Selcuk Medical Journal, predefined criteria, and the quality, completeness and accuracy of the research presented. Reviewers provide feedback on the paper, suggest improvements and make a recommendation to the editor about whether to accept, reject or request changes to the article. The ultimate decision always rests with the chief editor but reviewers play a significant role in determining the outcome.

If a reviewer has conflict of interest regarding article, he should inform it to the editor. Reviewers should ensure the rigorous standards of the scientific process by taking part in the peer-review system. Also they should uphold the integrity of the journal by identifying invalid research, and helping to maintain the quality of the journal. Reviewers should be volunteer to prevent ethical breaches by identifying plagiarism, research fraud and other problems by dint of their familiarity with the subject area. The copyrights of articles accepted for publication is belonged to journal. This is determined by the assignment of copyright statement, signed by all authors.

The journal is published four times in a year. The language of the journal is Turkish and/or English. Manuscripts submitted to the journal should not be published before or not under consideration elsewhere (in the case of previous oral or poster presentation of the paper at scientific meetings author should inform the journal). The full responsibility of the articles (ethic, scientific, legal, etc.) published in the journal belong to the authors. If the paper is not prepared in conformity with the writing instructions, decision for its evaluation will be made by the members of the editorial board. The articles have not been published anywhere before and no other journal has been sent for the publication. Plagiarism program (iThendicate) is used in Selcuk Medical Journal. Articles with similarities that exceed the academic citation limit and/or articles that are not prepared in accordance with the publication rules will not be evaluated. All studies require approval of the ethics committee and certification of this certificate will be the basis for the publication of the manuscripts.

All studies should be informed of the level of authors' contribution and approval. The study should also be informed that there is no financial conflict of interest at any stage, including data collection, experimentation, writing and language editing. Commercial sponsorship should be reported if it is in work.

The editorial and publication processes of the journal include the International Committee of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE) and the National Information Standards Organization (NISO). The editorial and publishing processes of the Selcuk Medical Journal are conducted in accordance with the principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The Editorial Board will act in accordance with COPE rules in the face of claims and suspicions of plagiarism, citation manipulation and data forgery of works submitted to our journal. The Editorial Board of the journal handles cases of objections and complaints within the scope of COPE guidelines. Authors can contact the Chief Editor or Editorial Board directly for objections and complaints. When necessary, an impartial representative is appointed for issues that the Editorial Board cannot solve within itself. The Chief Editor will make the final decision in the decision-making process for appeals and complaints.

Publisher and editor always be willing to publish corrections, clarifications, retractions and apologies when needed.

The all correspondences (manuscript submission, follow up, reviewers reports, revision files, ac- ceptance form and other forms about publications) about Selcuk Medical Journal should be made online at https://www.selcukmedj.org. The rules about the manuscripts that would be submitted are given below.

WRITING INSTRUCTIONS

Submitted manuscripts should be prepared using Microsoft Word program. All manuscripts, figures and pictures must be submitted electronically as word and pdf format h https://www.selcukmedj.org . Authors should ensure that (apart from the title page) the manuscript should contain no clues about the identity of authors and institution where the study was performed.

All papers should be arranged on the basis of following sequence: 1. Title page, 2. Turkish abstract, 3. English abstract, 4. Text of the article, 5. References, 6. Table(s), 7. Figure(s) and illustration(s), 8. Figure legend(s). In the original (research) articles number of words should not exceed 4000 (except abstract, references, tables, figures and legeds) for the text of article and 400 for the abstract. Upper limit for reference number is 60, and this limit is 10 for tables and figures. The abstracts should include objec- tive, materials and methods, results and conclusion sections. Case reports should be composed of Turkish and English title, Turkish and English abstracts, introduction, case report, discussion and references. The number of typewritten pages should not exceed 8 pages and 3 picture in case reports. In abstract, numbers of words should not exceed 200 and should be written as a paragraph.

Reviews should be composed of Turkish and English title. In abstract, numbers of words should not exceed

400. In reviews number of tables and figures (or pictures) should not exceed 6. Upper limit for reference number is 80. Abstracts should be written as a paragraph.

Letter to editor, brief report, image report, advancements in technical and medical topics and questionnaires of original issues should not exceed 2 typewritten pages. Its should be composed of Turkish and English abstracts (100 words).

PREPARATION OF MANUSCRIPT

Title Page

Title of the article should be written both in English and Turkish. The first and last names for all contributors designated as author should be written clearly. Subsequently, address of the institution where the study was performed should be written clearly. If the study was previously presented in any scientific meeting, name and date (as day-month-year) of the organization should be written. The name and mailing address of the corresponding author, accompanied by telephone and fax numbers, and e-mail should be written at the bottom of title page.

Abstracts

Abstracts should be given in separate sheets. English title should be used for English abstracts. The abstracts should not exceed 400 words in original articles and 200 words in case reports. The abstract should include objective, materials and methods, results and conclusion sections in research articles. Turkish and English key words should be listed at the bottom of the abstract page in original articles and should not be more than 5 words. In selecting key words, authors should strictly refer to the Medical Subject Headings (MeSH) list of the Index Medicus. Turkish key words should be selected from Turkish Science Term ((http://www.bilimterimleri.com). The abbreviations should not be used in the abstract.

Text

Text is composed of Introduction, Materials and Methods, Results and Discussion.

Introduction: The matter and purpose of the study is clearly defined.

Materials and Methods: This should include the date and design of the study, the setting, type of participants or materials involved, a clear description of all interventions and comparisons, and the statistical analysis. If the study is a clinical study the title should be 'Patients and Methods'.

Results: Collected data and results of statistical analysis should be outlined in this section.

Discussion: The discussion section should include interpretation of study findings and results should be considered in the context of results in other trials reported in the literature. All written content should be prepared in conformity with grammar and punctuation rules. Avoid abbreviations whenever possible; in case of necessary, it should be given in parentheses when they are first used. References, figures, tables and illustrations should be consecutively numbered in the order in which they have been cited in the text. All measurement units in the text should be used in accordance with international standards for units of measurement.

References

References should be given in a separate sheet with double spaced. References should be consecutively numbered in the order in which they are first mentioned in the text using Arabic numerals (in parentheses). If the author names in references are used in a sentence, it should be given in parentheses when they are first used. Reference number should be placed at the end of sentence before the period. If there are multiple references number use "," between them and "- " should be inserted between digits when three or more consecutive references are used [e.g. (1,2), (1,3)]. Journal references should include the following information: year, volume, first and last pages of article. Book references should include only year and first and last pages of the article. Authors in the references should be cited with last names and first initials. Journal's title should be abbreviated in conformity with the Index Medicus system. References should be cited as per the examples below. If there are more than 3 authors, only first 3 may be listed followed by "et al" for references.

Journal references:

1) Kocakuşak A, Yücel AF, Arıkan S. Karına nafiz kesici-delici batın yaralanmalarında rutin abdominal eksplorasyon yönteminin retrospektif analizi. Van Tıp Dergisi 2006;13(3):90-6.

2) Vikse BE, Aasard K, Bostad L, et al. Clinicalprognostic factors in biopsyproven benign nephrosclerosis. Nephrol Dial Transplant 2003;18:517-23.

Book references:

1) Danovitch GM. Handbook of kidney transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8. Chapter in book references:

1) Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III, İstanbul Üniversitesi, Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999: 1635-50.

2) Davison AM, Cameron CS, Grünfeld CF, et al. Oxford textbook of clinical nephrogology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.

Tables

Tables should be printed on a separate sheet with double spaced. Each table should contain a table number in the order in which they are first mentioned in the text and title that summarizes the whole table. All abbreviations used in the table should be alphabetically arranged and defined under the table (e.g., PS; pulmonary stenosis, VSD: ventricular septal defect).

Figures and Illustrations

Figures and illustrations should be named and numbered. Figures should be provided with a mini- mum of 300 dots per inch (dpi) in JPEG format and should be clear. Figures must be submitted online during manuscript submission. Figures embedded into article will not be accepted. If authors accept to charge extra cost, colored publication of the illustrations is possible; otherwise all illustrations will be published as black and white. All abbreviations used in the figures and illustrations should be alphabetically arranged and defined under the footnote. Technique and ratio of magnification for

photomicrographs should be indicated. The editorial board has the right to make any revisions on the manuscript unless such changes interfere with the scientific data presented.

REVISION AFTER REFEREE REPORT

Authors should point by point reply the items on which revision is demanded via referee report to the reserved box in the online system and as additional files should be uploaded https://www.selcukmedj.org. Additionally they should do necessary changes in article and highlight them and submit online again.

FINAL CHECKING

1. All pages have been numbered beginning form first page of the text. 2. Assignment of copyright form has been properly filled and signed. 3. The abstract should not exceed 400 words in original articles and 200 words in case reports. 4. The title has been separately written in Turkish and in English. 5. References is in conformity with the instructions. 6. All abbreviations used in tables, figures and illustrations have been defined.

ONLINE STEPS

At https://www.selcukmedj.org
1. Article Type *
2. Article Title in English *
3. Running Title *
4. Manuscript Abstract in English *
5. Key Words in English and Turkish *
6. This sections should be uploded at 5 steps(Article File, Article File in PDF

Format, Title Page,

Form of Matters Related to Copyright Transfer Agreement and Instructions for Authors, Uploaded Main Files, Additional Files (figures, pictures and tables).

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 106-113
DOI: 10.30733/std.2022.01557

NEÜ YAYINEVİ

Kinesiophobia, Physical Activity, Fear of COVID-19, and Fatigue in Adult Individuals: A Cross-Sectional Study

Yetişkin Bireylerde Kinezyofobi, Fiziksel Aktivite, COVID-19 Korkusu ve Yorgunluk: Kesitsel Çalışma

Gulsah Bargi[1], Merve Koku[1]

[1]*Izmir Democracy University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey*

Address correspondence to: Gulsah Bargi, Izmir Democracy University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey
e-mail: gulsahbargi@gmail.com

Geliş Tarihi/Received: *27 January 2022*
Kabul Tarihi/Accepted: *24 July 2022*

Öz

Amaç: Yeni koronavirüs hastalığının (COVID-19) uzamış süreci ve ilgili kısıtlamalar bireylerde fiziksel inaktiviteye, COVID-19 korkusuna ve yorgunluğa neden olmaktadır. Pandemi sürecinde, hastalarda kinezyofobi ölüm korkusu ve fiziksel inaktiviteyi artırabilmektedir. Ancak bireylerde kinezyofobi ve kinezyofobinin fiziksel aktivite, COVID-19 korkusu ve yorgunlukla ilişkisi henüz bilinmediğinden mevcut çalışmada araştırılması amaçlanmıştır.
Hastalar ve Yöntem: Çalışmaya yetişkin bireyler (n=166, 36,3±15,37 yıl) dâhil edildi. Kinezyofobi (Tampa Kinezyofobi Ölçeği), fiziksel aktivite düzeyleri (Uluslararası Fiziksel Aktivite Anketi-Kısa Formu), COVID-19 korkusu (COVID-19 Korkusu Ölçeği (CKÖ-19)) ve yorgunluk (Sayısal Derecelendirme Ölçeği) 3 Haziran 2021 ve 30 Haziran 2021 arasında çevrimiçi platform üzerinden uzaktan değerlendirildi.
Bulgular: Bireylerin 91'inde (%54,8) yüksek derecede kinezyofobi vardı, 55'i (%33,1) inaktif, 84'ü (%50,6) minimal aktif ve 27'si (%16,3) çok aktifti. Kinezyofobi puanı yaş, vücut ağırlığı, vücut kütle indeksi, eğitim düzeyi, yürüme, toplam fiziksel aktivite, CKÖ-19 ve yorgunluk puanları ile anlamlı olarak ilişkiliydi (p<0,05).
Sonuç: Bireylerin çoğunluğunda kinezyofobi ve fiziksel inaktivite yaygındır. COVID-19 pandemisi boyunca bireylerin hastalığı olmamasına rağmen, yürüme, fiziksel aktiviteler ve eğitim düzeyi azaldıkça bireylerde kinezyofobi artmaktadır. Yaş, vücut ağırlığı, vücut kütle indeksi, COVID-19 korkusu ve yorgunluk arttıkça da kinezyofobi artmaktadır. Kinezyofobinin ve uzamış pandemi sürecinin olumsuz etkileri düşünüldüğünde, bireyler acilen fiziksel aktivite danışmanlığı programlarına yönlendirilmelidir.

Anahtar Kelimeler: COVID-19, fiziksel aktivite, korku, yetişkinler, yorgunluk

Abstract

Aim: The prolonged process of new coronavirus disease (COVID-19) and related restrictions cause physical inactivity, fear of COVID-19, and fatigue in individuals. During the pandemic, kinesiophobia may raise fear of death and physical inactivity in patients. However, kinesiophobia and its relationship with physical activity (PA), fear of COVID-19, and fatigue in individuals have not been known yet, which was therefore aimed to investigate in the current study.
Patients and Methods: Adult individuals (n=166, 36.3±15.37 years) were included in the study. Kinesiophobia (Tampa Scale of Kinesiophobia), PA levels (International Physical Activity Questionnaire-Short Form), fear of COVID-19 (Fear of COVID-19 Scale (FCS-19)), and fatigue (Numeric Rating Scale) were evaluated remotely between 3 June 2021 and 30 June 2021 through an online platform.
Results: Of the individuals, 91 (54.8%) had a high level of kinesiophobia, 55 (33.1%) were inactive, 84 (50.6%) were minimally active, and 27 (16.3%) were very active. Kinesiophobia score was significantly correlated with age, weight, body mass index, education level, and walking, total PA, FCS-19, and fatigue scores (p<0.05).
Conclusion: Kinesiophobia and physical inactivity are prevalent in many individuals. Although individuals have no disease during the COVID-19 pandemic, their kinesiophobia level increases as walking, physical activities, and education levels decrease. Kinesiophobia also increases as age, weight, body mass index, fear of COVID-19 and fatigue increase. Considering the negative effects of kinesiophobia and the prolonged pandemic process, individuals should be urgently directed to PA counseling programs.

Key words: COVID-19, physical activity, fear, adults, fatigue,

Cite this article as: Bargi G, Koku M. Kinesiophobia, Physical Activity, Fear of COVID-19, and Fatigue in Adult Individuals: A Cross-Sectional Study. Selcuk Med J 2022;38(3): 106-113

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

When the first new coronavirus disease-2019 (COVID-19) cases started to appear in Turkey, the World Health Organization declared this newly emerging outbreak a pandemic. Since then, many measures have been taken to protect public health against the pandemic all over the world (1). In this process, as a result of the restrictions and measures that have been put into effect rapidly, people have been forced to stay at home. With the long-term implementation of strict quarantine measures, many radical changes have occurred in the lifestyle of societies. The leading radical changes include a decrease in physical activity levels, withdrawal from daily routines, and deterioration in mood. Therefore, the quality of life of individuals has gradually decreased (2). Compared to the pre-pandemic period, physical activity levels of the individuals have decreased significantly during the pandemic period (3), while their sedentary behaviors have increased (4,5). In addition, increased levels of depression, anxiety disorder, fear, and stress have been observed in individuals living under social isolation conditions due to the pandemic (6,7).

In extraordinary conditions caused by pandemic diseases like COVID-19, a sense of fear may occur in individuals. Depending on this fear, some individuals may feel sick and even commit suicide even though they have not been infected with the COVID-19 disease (8). During the pandemic, most individuals feel a moderate level of fear of COVID-19 (9,10). Fear of COVID-19 in adolescent children negatively affects adolescent mental health and well-being (11). During the restrictions due to the COVID-19 pandemic, kinesiophobia seen in patients can also bring on concerns such as fear of death. The most critical aspect of COVID-19 is the unknown course of the pandemic, the uncertainty of when the disease will be brought under control, and the ever-increasing number of cases. This situation can further increase the anxiety of the masses with some analyses and disinformation (12,13). It is also known that 64.1% of the individuals have become physically and mentally tired during the pandemic period (14).

The negative effects of the COVID-19 pandemic, which has been going on for about 1.5 years today, on human health continue to increase. Due to the increasing number of cases and restrictive measures, the individuals are seriously affected by this process both psychologically and physically. It is known that physical inactivity, fatigue, and fear of COVID-19 develop in the individuals during the COVID-19 pandemic. However, the kinesiophobia status of these individuals during the COVID-19 pandemic and the relationship of kinesiophobia with physical activity levels, fear of COVID-19, and perception of fatigue have not been known, yet. Therefore, this study was conducted to investigate the kinesiophobia, physical activity levels, fear of COVID-19, and perceived fatigue in adults during the COVID-19 pandemic process and relationships between these parameters.

PATIENTS AND METHODS

This prospective and cross-sectional study was approved by the Izmir Democracy University Non-Interventional Clinical Research Ethics Committee on May 26, 2021 (Decision no. 2021/06-13). The study consisted of adult individuals who could understand and respond to the questionnaires, had a smartphone, a computer, or an electronic device to access the questionnaires, and volunteered to participate in the study. Individuals who had any physical, mental problems, or chronic disorders that may prevent physical activity, had been diagnosed with COVID-19, had had COVID-19, and/or were pregnant were not included in the study. The individuals were first informed about the study, and then their informed consents were obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The participants filled out all the questionnaires on their smartphones or computers between 3 June 2021 and 30 June 2021 through a form created on an online platform (Microsoft Forms). Within the scope of the study, the socio-demographic characteristics of the individuals (age, gender, height, body weight, body mass index, education level, history of disease and infection, and presence of a chronic disease) were recorded. While primary outcome was physical activity, secondary outcomes were kinesiophobia, fear of COVID-19, and fatigue.

The Tampa Scale of Kinesiophobia

This scale was developed by Vlaeyen et al. to measure the fear of movement or re-injury (15). There are 17 items on this scale measuring parameters, such as injury, re-injury, fear, and avoidance in work-related activities (15). The Turkish version of the scale is valid and reliable (16). It uses a 4-point Likert-type scale (1: strongly disagree, 2: disagree, 3: agree, 4: strongly agree). The total score of the scale is calculated after the scores of the answers to the 4th, 8th, 12th, and 16th questions are reversed. The

minimum and maximum scores from the scale range between 17 and 68. High scores indicate a high level of kinesiophobia (15,16). The cut-off score for a high degree of kinesiophobia is 37 (15).

The International Physical Activity Questionnaire-Short Form

This questionnaire, which has a valid and reliable Turkish version (17), was developed by Craig et al. (18). It provides knowledge about the daily sitting time and the time spent on walking and doing moderate and vigorous physical activities in the last week. The questionnaire measures the frequency (days) and duration (minutes) of physical activities performed in the last seven days. Then, the amount of weekly physical activity (MET-min/week) spent on these physical activities is calculated by using the appropriate metabolic equivalents (MET) for vigorous (8 METs) and moderate (4 METs) activities and walking (3.3 METs). The scores are used to classify individuals as physically inactive, minimally active, and very active (19).

The Fear of COVID-19 Scale

This scale was developed by Ahorsu et al. (7) to measure the fear of COVID-19. The Turkish version of the scale is valid and reliable (20). It is a single-factor scale and consists of seven items. It is scored using a 5-point Likert type scale (1: strongly disagree; 2: disagree; 3: neither agree nor disagree; 4: agree; 5: strongly agree). A minimum of seven and a maximum of 35 points can be obtained from the scale. It is considered that the higher the total score obtained from the scale is, the higher the fear of COVID-19 is (9).

The Numeric Rating Scale

The scale is a single-item measurement tool that evaluates the severity of fatigue. Fatigue is graded between zero (energetic/no fatigue) and 10 (unbearable fatigue). The scale has horizontal and vertical forms, and the horizontal form was used in this study (21).

Statistical Analyses

The population of the study (459 individuals) was estimated by using the Raosoft sample size calculator (22), and the necessary sample size was calculated as at least 166 individuals based on a physical inactivity response rate of 39%, a 90% confidence level, and a maximum margin of error of 5% (23). All statistical analyses were conducted using the "Statistical Package for the Social Sciences" version 15.0 software package. The fit of variables to normal distribution was analyzed by using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were represented by frequency (n), percentage (%), mean (×), standard deviation (SD), median and percentiles (25%-75%) values. Relationships between variables that either fit or did not fit the normal distribution were determined using the Pearson or Spearman correlation analysis methods, respectively. The probability of a Type I error in statistical analyses was determined as $p<0.05$.

RESULTS

Of the 195 individuals who responded to the questionnaires, 29 were excluded from the study due to having COVID-19 (n=24) and being pregnant (n=5) (Figure 1). The results of 166 individuals who met the inclusion criteria were analyzed. The socio-demographic characteristics of these individuals are presented in Table 1.

There was a high level of kinesiophobia in 91 (54.8%) individuals (Figure 2). In addition, 55 (33.1%) individuals were inactive, 84 (50.6%) were minimally active, and 27 (16.3%) were very active (Figure 3, Table 2). Also, 162 (97.6%) of the individuals were found to feel tired recently.

There was a statistically significant correlation between the kinesiophobia scores of the individuals and their age, body weight, body mass index,

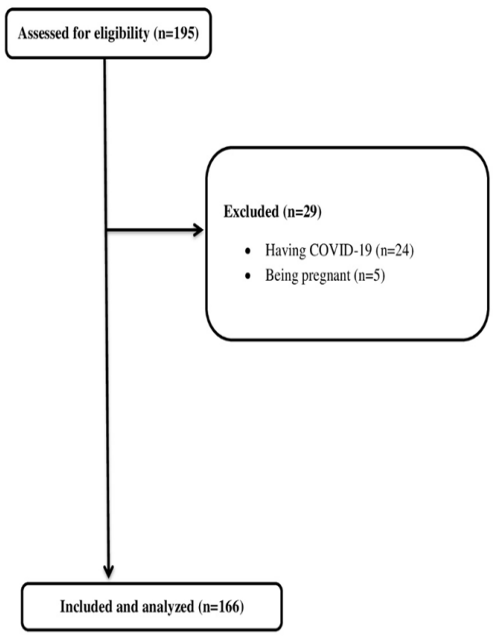


Figure 1. Flow diagram of the study

Table 1. Social and demographic characteristics of the individuals.

	Individuals (n=166) ×±SD / Median (25%-75%) / n; %
Age (year)	36.3±15.37
Male / Female	52; 31.3% / 114; 68.7%
Weight (kg)	68.92±14.85
Height (m)	1.68±0.09
Body mass index (kg/m^2)	24.2±4.06
Daily sleeping duration (hour)	7.5±1.28
Education level	
Elementary school	10; 6%
Secondary school	7; 4.2%
High school	18; 10.8%
College	83; 50%
Postgraduate	33; 19.9%
Doctorate	15; 9.1%
Total Score of Tampa Scale of Kinesiophobia (17-68)	37.93±6.06
Total Score of Fear of COVID-19 Scale (7-35)	18.29±5.39
Vigorous physical activity (MET-min/week)	489.01±1196.09 / 0 (0-320)
Moderate-intensity physical activity (MET-min/week)	288.96±477.17 / 70 (0-360)
Walking (MET-min/week)	822.91±921.97 / 495 (247.5-1188)
Total physical activity (MET-min/week)	1600.89±1804.12 / 1005 (396-2123.25)
Daily sitting duration (hour)	15.09±1.56
Score of Fatigue Numerical Rating Scale (0-10)	4.69±2.23

kg: kilogram, m: meter, MET: metabolic equivalent, min: minute. Descriptive analyses were presented using ×±SD (mean±standard deviation), median, percentiles (25%-75%), n (frequency) and % (percentage).

education level, time spent on walking, time spent on total physical activity, fear of COVID-19 and fatigue scores (Figure 4-5, Table 3, $p<0.05$). On the other hand, there was no statistically significant correlation between kinesiophobia scores and height, daily sitting and sleeping times, time spent on vigorous physical

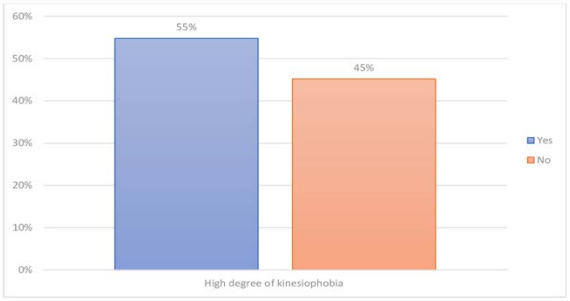


Figure 2. Presence of high degree of kinesiophobia in the individuals

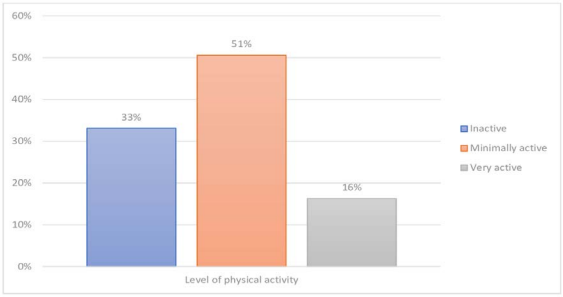


Figure 3. Rate of physical activity levels in the individuals

Table 2. The incidence of high degree of kinesiophobia and physical inactivity in the individuals.

	Individuals (n=166)	
	n	%
Presence of high degree of kinesiophobia	91	54.8%
Level of physical activity		
Inactive	55	33.1
Minimal active	84	50.6
Very active	27	16.3

Descriptive analyses were presented using n (frequency) and % (percentage).

Table 3. Relationship between kinesiophobia and other outcomes in the individuals.

	Total Score of Tampa Scale of Kinesiophobia	
	r value	p value
Age (year)	0.328	<0.001#
Weight (kg)	0.192	0.013#
Height (m)	0.099	0.203
Body mass index (kg/m^2)	0.190	0.014#
Daily sleeping duration (hour)	0.091	0.241
Education level (from elementary school to doctorate)	-0.349	<0.001*
Total Score of Fear of COVID-19 Scale (7-35)	0.296	<0.001#
Vigorous physical activity (MET-min/week)	-0.106	0.174
Moderate-intensity physical activity (MET-min/week)	-0.147	0.059
Walking (MET-min/week)	-0.327	<0.001*
Total physical activity (MET-min/week)	-0.299	<0.001*
Daily sitting duration (hour)	0.076	0.333
Score of Fatigue Numerical Rating Scale (0-10)	0.188	0.015#

kg: kilogram, m: meter, MET: metabolic equivalent, min: minute, r: correlation coefficient, p: p value. Spearman correlation analysis, *p<0.05 and Pearson correlation analysis, #p<0.05.

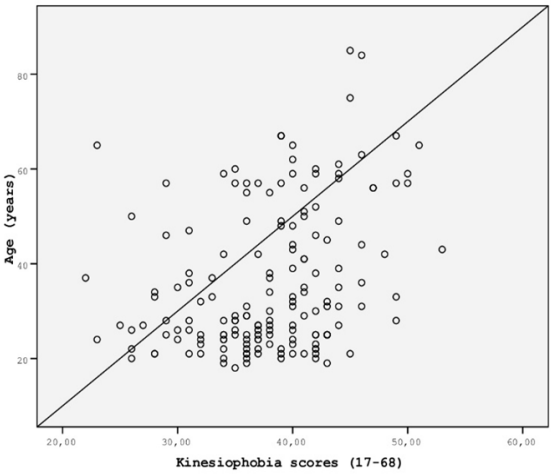


Figure 4. Correlation between age and kinesiophobia scores in the individuals

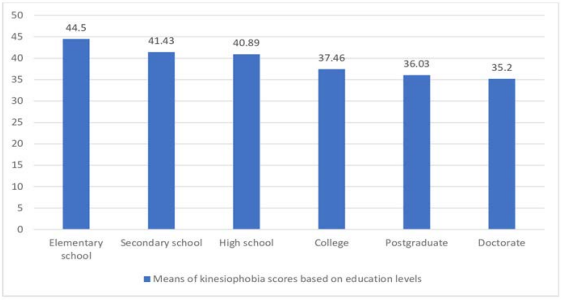


Figure 5. Comparison of means of kinesiophobia scores according to education levels of the individuals

activity and time spent on moderate physical activity (Table 3, p>0.05). A statistically significant correlation was found between the fear of COVID-19 scores and time spent on total physical activity (r=-0.186; p=0.017), fatigue scores (r=0.156; p=0.045). There was also a statistically significant correlation between the fatigue scores and the time spent on walking (r=-0.167; p=0.031).

DISCUSSION

The most important results of our study, which was carried out during the prolonged COVID-19 pandemic, were the existence of a high level of kinesiophobia in many individuals (54.8%) and the inadequate physical activity in the majority of these individuals (83.7%). In addition, the kinesiophobia scores of these individuals, who did not have any diseases that prevented them from doing physical activity during the COVID-19 pandemic, increased as their time spent on walking and total physical activities in a week and their education level decreased. Another important result was that the kinesiophobia score increased as the age, body weight, body mass index, fear of COVID-19 and fatigue increased.

While the total kinesiophobia score and the incidence of kinesiophobia were found to be significantly higher in individuals with low back pain who worked actively from home due to the COVID-19 pandemic restrictions, the physical activity score and sitting time were found to be similar (24).

Kinesiophobia was observed in 49.51% of all these individuals working from home. In addition, the kinesiophobia scores of the employees increased as their low back pain increased (24). The mean age, gender distribution, and total kinesiophobia scores of the individuals included in our study were similar to the characteristics of the individuals working from home included in this study. The individuals in our study had a higher level of kinesiophobia (54.8%) than the rate reported in the study of Bahar Özdemir (49.51%) (24). In addition, while all individuals included in the study of Bahar Özdemir (24) were physically active minimally, 83.7% of the individuals participating in our study were found to be inactive and minimally active. Unlike the results of the study of Bahar Özdemir, it was found that the increase in the kinesiophobia scores of the individuals participating in our study was directly affected by the decrease in the time spent on weekly physical activities and the decrease in the level of education. The high level of kinesiophobia observed in more individuals in our study can be attributed to the fact that our study was conducted during the prolonged period of the COVID-19 pandemic and that individuals who were not actively working in this process were also included in the study. In addition, the transformation of the virus into a more severe form through mutation (25) may have caused a higher rate of kinesiophobia in our individuals reflecting the general population. In this sense, our study is very valuable in that it has shown that kinesiophobia can develop in the individuals who do not have a problem that prevents them from moving physically in extraordinary processes such as pandemics. Consistent with the results of our study related to physical inactivity, studies published to date have reported that physical inactivity is seen in all segments of society due to the COVID-19 pandemic and the accompanying restrictions (2-7). In fact, it has been shown that physical activities have generally decreased in individuals, sedentary behaviors, such as spending long periods in front of the screen or lying down throughout the day, have increased, and accordingly, the quality of life has decreased, and the levels of depression, anxiety disorder, anxiety, fear, and stress have increased (2-7). Unlike these studies published in the literature, it was shown in our study that kinesiophobia increased with the decrease in the time spent on weekly walks and total physical activities in the individuals who did not have any diseases that prevented physical activity. This result is important because kinesiophobia is defined as the excessive avoidance of physical movement and activity by individuals who experience injuries or painful situations due to the fear of recurrence of the problem (26). In addition, it is known that kinesiophobia increases as physical activities decrease in individuals with chronic diseases (27). Therefore, it is necessary to consider kinesiophobia and the relationship of kinesiophobia with physical activities, body weight, and fear of COVID-19 in both patients and healthy individuals during the COVID-19 pandemic. In this process, while directing individuals to physical activities, it is beneficial to evaluate their kinesiophobia status and to direct them to both private physical activity counseling (11) and psychological counseling when necessary.

In the ongoing COVID-19 pandemic since the beginning of 2020, individuals all over the world have accessed a variety of worrying videos or news about the pandemic, which can be speculative, via smartphones and computers. Due to all these negative pieces of news, some individuals who were highly afraid of the process committed suicide though they were not infected with COVID-19 (8). The mean scores of the individuals included in our study from the fear of COVID-19 scale were close to a moderate level. Moreover, as the fear of COVID-19 increased, it was determined that physical activities decreased, fatigue and kinesiophobia increased in these individuals, who participated in our study, and it was shown that one of the most important determinants of kinesiophobia was the fear of COVID-19 score. The fear scores of the individuals in our study were similar to the fear scores of university students in the study conducted by Duman (9). Duman reported that students had a moderate level of fear of COVID-19 and that this fear was even higher in students who lost their relatives due to COVID-19 (9). In another study, similar to this result of our study, it was reported that individuals living in Çorum province experienced a fear of COVID-19, close to a moderate level (10). In another study conducted in the United Kingdom during the quarantine period due to the pandemic, it was reported that fear of COVID-19 affected adolescents' mental health and well-being negatively, while physical activity positively affected their mental health and well-being (11). Therefore, if we consider the linear relationship between fear of COVID-19 and kinesiophobia shown in our study, we see that more importance should be given to community-based physical activity counseling in this process. For this reason, individuals should be directed to

physical activities by experts, taking into account the COVID-19 measures, both through media channels such as television and radio and through social media platforms. In this way, kinesiophobia seen in individuals can be reduced by decreasing the fear of the long-standing COVID-19 pandemic. Further studies are needed to investigate the effects of physical activity counseling in this regard.

Of the individuals participating in our study, 97.6% stated that they had been tired recently, and their fatigue was moderate according to their mean fatigue scores. It was reported that individuals living in Istanbul during the pandemic period experienced psychological fatigue (64.1%) at a lower rate than this rate, found in our study (14). In addition, when psychologically normal individuals were compared with those who were tired, the belief that the pandemic would be controlled, the satisfaction with the preventive measures taken by the authorities, and the confidence that the COVID-19 pandemic would be overcome were found to be higher in psychologically normal individuals (14). Another important result of our study was that as fatigue score increased, the time spent on walking decreased, and fear of COVID-19 along with kinesiophobia increased. Therefore, perceived physical and mental fatigue, which is a psychological outcome, may be due to fear and anxiety about the COVID-19 pandemic (8,14). For this reason, within the framework of the pandemic measures, physical activity counseling can reduce individuals' fatigue, fears of movement, and fears of COVID-19. Further studies are urgently needed because it is uncertain when the pandemic will end.

The population of our study mostly consisted of the individuals belonging to the younger age group. Considering that being a middle-aged and/or an older individuals is a major risk factor for the COVID-19 virus, the middle and older age group may have been more affected in terms of kinesiophobia, physical activities, fatigue, and fear although there was no COVID-19 transmission during the pandemic process. For this reason, it is recommended to include the middle-aged and older population in future studies which was our main limitation.

CONCLUSION

In conclusion, 54.8% of the adult individuals who were healthy during the prolonged COVID-19 pandemic had a high level of kinesiophobia, 83.7% had physical inactivity, and 97.6% had a feeling of fatigue in recent days. During the COVID-19 pandemic, kinesiophobia is directly affected by the decrease in the time spent on physical activities, advanced age, increase in body weight, decrease in education level, and increase in fear of COVID-19 and fatigue negatively. In addition, the factors that increase the fear of COVID-19 in this process include the decrease in the time spent on physical activities and the increase in perceived fatigue. Considering that perceived fatigue also increases with the decrease in the time spent on walking, it is recommended to give more importance to counseling of physical activity to prevent the long-term negative effects of the pandemic. In this context, scientific and cultural programs that inform, educate, and direct the society, including physiotherapists, should be organized as soon as possible.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Gulsah Bargi, Izmir Democracy University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Izmir, Turkey*
e-mail: *gulsahbargi@gmail.com*

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33.
2. Tural E. Covid-19 pandemi dönemi ev karantinasında fiziksel aktivite düzeyinin yaşam kalitesine etkisi. Van Sag Bil Derg 2020;13(Özel Sayı):10-8.
3. Ünlü H, Öztürk B, Aktaş Ö, et al. Bireylerin COVID-19 sürecinde fiziksel aktivite düzeylerindeki değişimin incelenmesi. TUSBİD Türkiye Spor Bilimleri Dergisi 2020;4(2):79-87.
4. Gallè F, Sabella EA, Ferracuti S, et al. Sedentary behaviors and physical activity of Italian undergraduate students during lockdown at the time of CoViD−19 pandemic. Int J Environ Res Public Health 2020;17(17):6171.
5. Amini H, Isanejad A, Chamani N, et al. Physical activity during COVID-19 pandemic in the Iranian population: A brief report. Heliyon 2020;6(11):e05411.
6. Brooks K, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. Lancet 2020;395(10227):912-20.
7. Ahorsu DK, Lin CY, Imani V, et al. The fear of COVID-19 scale: Development and initial validation. Int J Ment Health Addict 2020;1-9.
8. Goyal K, Chauhan P, Chhikara K, et al. Fear of COVID 2019: First suicidal case in India. Asian J Psychiatr 2020;49:101989.
9. Duman N. Üniversite öğrencilerinde COVID-19 korkusu ve belirsizliğe tahammülsüzlük. TJSS (The Journal of Social Science) 2020;4(8):426-37.
10. Gencer N. Pandemi sürecinde bireylerin koronavirüs (KOVİD-19) korkusu: Çorum örneği. USBAD Uluslararası

Sosyal Bilimler Akademi Dergisi 2020;2(4):1153-73.
11. Wright LJ, Williams SE, Veldhuijzen van Zanten JJCS. Physical activity protects against the negative impact of coronavirus fear on adolescent mental health and well-being during the COVID-19 pandemic. Front Psychol 2021;12:580511.
12. Verwoerd AJH, Luijsterburg PAJ, Koes BW, et al. Does kinesiophobia modify the effects of physical therapy on outcomes in patients with sciatica in primary care? Subgroup analysis from a randomized controlled trial. Phys Ther 2015;95(9):1217-23.
13. Bao Y, Sun Y, Meng S, et al. 2019-nCoV epidemic: Address mental health care to empower society. Lancet 2020;395(10224):37-8.
14. Morgul E, Bener A, Atak M, et al. COVID-19 pandemic and psychological fatigue in Turkey. IJSP International Journal of Social Psychiatry 2021;67(2):128-35.
15. Vlaeyen JWS, Kole-Snijders AMJ, Boeren RGB, et al. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain 1995;62(3):363-72.
16. Tunca Yılmaz Ö, Yakut Y, Uygur F, et al. Tampa Kinezyofobi Ölçeği'nin Türkçe versiyonu ve test-tekrar test güvenirliği. Fizyoter Rehabil 2011;22(1):44-9.
17. Sağlam M, Arikan H, Savci S, et al. International physical activity questionnaire: Reliability and validity of the Turkish version. Percept Mot Skills 2010;111(1):278-84.
18. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12 country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-95.
19. IPAQ Research Committee. (2004). Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)- Short Form. Çevrimiçi https://www.physio-edia.com/images/c/c7/Quidelines_for_interpreting_the_IPAQ.pdf
20. Ladikli N, Bahadır E, Yumuşak FN, et al. The reliability and validity of Turkish version of coronavirus anxiety scale. INJOS Uluslararası Sosyal Bilimler Dergisi 2020;3(2):71-80.
21. Gladman D, Nash P, Goto H, et al. Fatigue numeric rating scale validity, discrimination and responder definition in patients with psoriatic arthritis. RMD Open 2020;6(1):e000928.
22. http://www.raosoft.com/samplesize.html., Erişim tarihi: 21 Nisan 2021.
23. Alsalhe TA, Aljaloud SO, Chalghaf N, et al. Moderation effect of physical activity on the relationship between fear of COVID-19 and general distress: A pilot case study in Arabic countries. Front Psychol 2020;11:570085.
24. Bahar Özdemir Y. Investigation of low back pain in the white-collar population working from home due to the COVID-19 pandemic. J PMR Sci 2021;24(2):135-42.
25. Khateeb J, Li Y, Zhang H. Emerging SARS-CoV-2 variants of concern and potential intervention approaches. Crit Care 2021;25(1):244.
26. Turhan B, Usgu G, Usgu S, et al. Alt ekstremitede bağ yaralanması veya kırık geçmişi olan bireylerde kinezyofobi, durumluluk ve sürekli kaygı düzeylerinin incelenmesi. Turk J Sports Med 2019;54(3):175-82.
27. Wasiuk-Zowada D, Knapik A, Szefler-Derela J, et al. Kinesiophobia in stroke patients, multiple sclerosis and parkinson's disesase. Diagnostics (Basel) 2021;11(5):796.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 114-120
DOI: 10.30733/std.2022.01561

NEÜ YAYINEVİ

Awareness Among Otorhinolaryngologists of Literature Resources: Survey Research

Kulak Burun Boğaz Hekimlerinin Bilgi Kaynaklarına Yönelik Farkındalığının Anket Yoluyla Değerlendirilmesi

Nurullah Ture[1], Yesim Tunc[2], Cemal Aksoy[1]

[1]*Kutahya Health Sciences University, Department of Otorhinolaryngology, Kutahya, Turkey*
[2]*Kutahya Health Sciences University, Department of Biostatistics, Kutahya, Turkey*

Address correspondence to: Nurullah Ture, Kutahya Health Sciences University, Department of Otorhinolaryngology, Kutahya, Turkey.
e-mail: nurullah.ture@ksbu.edu.tr

Geliş Tarihi/Received: *26 May 2022*
Kabul Tarihi/Accepted: *15 August 2022*

Öz

Amaç: Bu çalışmada, ulusal ölçekte kulak burun boğaz hekimleri arasında podcast farkındalığının ve kullanım sıklığının araştırılması amaçlanmıştır.
Hastalar ve Yöntem: Çevrimiçi anket türündeki çalışmamız, 2021-2022 yılları arasında 'Google forms' (Mountain View, CA) açık web adresi üzerinden yapılmıştır. Hedef kitle, ulusal ölçekteki her yaş ve deneyim seviyesinden kulak burun boğaz hekimleridir. Anketimiz yirmi sorudan oluşmaktadır.
Bulgular: Anket çalışmamızda, sorularımıza cevap veren kişi sayısı 112'dir. Bu 112 kişinin 92' si erkek (%82,1), 20' si kadın (%17,9)'dır. Kulak burun boğazla ilgili mesleki alanda podcast dinleyen %20,5 (n=23), dinlemeyen %79,5 (n=89) olarak izlendi. Pandemi öncesi en sık başvurulan kaynakların %40,2 (n=45) ile kitap ve %31,3 (n=35) ile e-kitap olurken, pandemide %30,4 (n=34) çevrimiçi toplantı ve %27,7 (n=31) e-kitap olduğu izlenmiştir. Pandemi öncesi ve pandemi dönemi başvurulan kaynakların sıklık karşılaştırılmasında istatistiksel anlamlı fark bulunmuştur (p<0,001).
Sonuç: Süregelen pandemi bilgi kaynaklarına başvuru sıklığını etkilemiş olmasına rağmen, podcast kullanımında anlamlı bir değişikliğe neden olmamıştır. Yazarlar, bu makalenin kulak burun boğaz alanında Türkçe podcast üretmek için bir farkındalık oluşturacağını umuyorlar.

Anahtar Kelimeler: Podcast, otolaringoloji, asenkron öğrenme, pandemi

Abstract

Aim: It was aimed to investigate podcast awareness and frequency of use among otorhinolaryngologists on a national scale.
Patients and Methods: This study was conducted via the open web address of 'Google forms' (Mountain View, CA) between 2021-2022. On a national scale, the intended audience consisted of otorhinolaryngologists of all ages and levels of experience. Our survey consisted of twenty questions.
Results: In our study, the number of people who answered our questions was 112 (92 men (82.1%), 20 women (17.9%). When asked if they had listened to podcasts about otorhinolaryngology, 23 people (20.5%) answered that they had listened and 89 people (79.5%) had not. When people want to learn about a topic in the field of Otorhinolaryngology before pandemic, the most frequently used literature resources are 40.2% (n=45) books and 31.3% (n=35) e-books. It was observed that the most frequently used literature sources in the pandemic were 30.4% (n=34) online meetings and 27.7% (n=31) e-books. There was a statistically significant difference between the frequency distribution of resources consulted before and during the pandemic (p<0.001).
Conclusion: Although the ongoing pandemic has affected the frequency of consulted to literature resource, it has not caused a significant change in podcast usage. The authors hope that this article will create an awareness for producing Turkish podcasts in the field of otolaryngology.

Key words: Podcast, otolaryngology, asynchronous learning, pandemic

Cite this article as: Ture N, Tunc Y, Aksoy C. Awareness Among Otorhinolaryngologists of Literature Resources: Survey Research. Selcuk Med J 2022;38(3): 114-120

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Otorhinolaryngologists must continuously improve their skills, to to acquire and maintain expertise in their field. Even though traditional methods of study, such as books and articles, have continued to be useful, Internet-based learning has become increasingly prevalent over the past decade (1). A study of residents and medical students reported that 58% of them preferred using only electronic learning methods (2). It is evident from the increasing of online courses, video images, and podcasts podcasts that the amount of professional knowledge is expanding exponentially and changing constantly (1). Podcasts have been found to be an effective method for modern medical education (3). However, few studies have investigated the use and effects of podcasts in specific fields (4, 5).

A study of residents in emergency medicine found that more than 80% reported listening to podcasts on a regular basis (6). It has been reported that approximately three-quarters of residents in otorhinolaryngology (ENT) listen to ENT podcasts (7). According to Malka et al., podcasts in the field of ENT can facilitate rapid dissemination of content knowledge and current trends (8). Reports have also indicated that podcasts significantly increase the recall of medical information when compared to traditional means (9).

Several international studies that have examined the reasons for and frequency of the use of podcasts in the field of ENT (7, 8, 10). However, it has not been possible to identify a study that has focused on understanding the awareness and usage characteristics of podcasts among otorhinolaryngologists on a national scale. The present study aims primarily to determine the level of awareness and frequency of podcast use among otorhinolaryngologists, as well as to encourage the creation of Turkish language podcasts in the field of ENT.

PATIENTS AND METHODS

This study was approved by the ethics committee of Kutahya Health Sciences University's non-interventional clinical research, with number 2021/10-03. A preliminary study was conducted to clarify the questions in our study, and 10 otorhinolaryngologists were asked to respond to this. After receiving feedback from the otorhinolaryngologists who filled out the questionnaire, necessary corrections were made and the questionnaire was put into its final form.

This study was carried out on the open web address of ‘‘Google forms’’ (Mountain View, CA) between 2021-2022. The target audience was otorhinolaryngologists of all ages and levels of experience. There were twenty (20) questions, and it took about 10 minutes to complete the survey. The survey was open to participation for three months. A call for participation was made from the KanalKBB news source, and the link address was shared three times over KanalKBB. Each participant had the right to complete the survey only once. Participants were not given the right to see the answers of others, which were obtained from ‘‘Google forms’’.

The participants were asked to provide the following information: Email addresses, ages, genders, academic titles, how long they had worked in medicine, and the characteristics of the hospitals where they worked. They also answered questions about their use of the literature: their first sources (books, journals, podcasts, electronic books, or online meetings), the frequency of their applications to literature sources (once a week, once a month, or once a year), the literature sources they had used most frequently during the pandemic (online meetings, podcasts, books, journals, or electronic books), the literature sources they would reference most frequently in the near future (books, journals, online meetings, podcasts, or e-books), whether their literature sources included information about podcasts (I know or have never heard of), whether they had ever listened to podcasts (I have listened or have not), whether they had listened to podcasts in the professional field (about ENT) (I have listened or have not), how many times they had listened to podcasts in the previous month (0, 1–3, 4–7, 8–11, or ‘‘12 or more’’), for how many years they had used podcasts as a medical information transfer tool (0–2 years, 3–5 years, 6–8 years, 8–10 years, or 10 years or more), and their knowledge of the podcasts (easy to access, reproducible, web-based, reliable source of information, and paid content). The participants were asked questions about the following as well: for what parts of ENT certain podcasts will be most useful and able to be applied (in diagnosis, treatment, both diagnosis and treatment, or surgery-surgical techniques), whether podcasts will be used as a common information transfer tool in the future (strongly disagree, disagree, undecided, agree, or strongly agree), the usefulness of podcast-supported education for the professional development of ENT physicians (strongly disagree, disagree, undecided, agree, or strongly agree), and whether podcasts are

more useful than other key information transfer tools (strongly disagree, disagree, undecided, agree, or strongly agree) (Appendix 1).

SPS statistical software (SPSS Inc., version 21.0, Chicago, IL, USA) was used for statistical analysis. Frequency distributions and percentages of categorical variables are provided. Cronbach's Alpha value (0.839) and reliability value were calculated in the part that was evaluated with a Likert scale. The Chi-square test was used for comparisons between qualitative variables. Continuity corrected Chi-square, Fisher exact probability test, Mc Nemar Bowker test, and likelihood ratio values were used when appropriate, according to the characteristics of the data. A value of $P<0.05$ was considered to be significant.

RESULTS

There were 112 people who responded to our questions. Among these participants, 92 (82.1%) were men, and 20 (17.9%) were women. The age ranges of the participants were 17 people (15.2%) from 20-to-29 years of age, 50 people (44.6%) from 30-to-39, 20 people (17.9%) from 40-to-49, 15 people (13.4%) from 50-to-59, and 10 people (8.9%) who were more than 60 years old. There were 13 professors (11.6%), 10 associate professors (8.9%), 12 faculty members (10.7%), 53 operator doctors (47.3%), and 24 residents (14.1%). Among those within the field of otorhinolaryngology, 25 people (22.3%) had worked in it for 1-to-5 years, 35 people (31.3%) for 6-to-10 years, 14 people (12.5%) for 11-to-15 years, nine people (8%) for 16-to-20 years, and 29 people (25.9%) had more than 20 years of experience in otorhinolaryngology. Demographic data is summarized in Table 1.

When asked "Do you know the podcast," 64 (57.1%) people replied "I do" and 48 (42.9%) reported that they had never heard of it. With regard to the question about how many times they had listened to podcasts in the past month, 33 people answered 1-to-3 times (29.5%), eight people answered 4-to-7 times (7.1%), six people answered 8-to-11 times (5.4%), three people answered (2.7%) over 12 times, and 62 people (55.4%) responded that they had never listened to podcasts. In response to the question about whether they had listened to podcasts about otorhinolaryngology, 23 individuals (20.5%) said that they had. However, 89 respondents (79.5%) said that they did not listen to podcasts.

When asked to respond to five true-or-false statements about their knowledge of podcasts, 61 respondents (54.5%) said that they are easily accessible, 59 (52.7%) stated that they are repeatable, 65 (58%) said that they are Internet-based, 12 (10.7%) responded that they are reliable information sources,

Table 1. Demographic Information

Total	112
Gender	Man= 92 (%82,1) Women=20 (%17,9)
Term of study	
1-5 Years	25 (%22,3)
6-10 Years	35 (%31,3)
11-15 Years	14 (%12,5)
16-20 Years	9 (%8,0)
>21 Years	29 (%25,9)
Age	
20-29 Age	17 (%15,2)
30-39 Age	50 (%44,6)
40-49 Age	20 (%17,9)
50-59 Age	15 (%13,4)
>60 Age	10 (%8,9)
Title	
Resident	24 (%21,4)
Operator Doctor	53 (%47,3)
Faculty member	12 (%10,7)
Associate professor	10 (%8,9)
Professor	13 (%11,6)
Institution	
University Hospital	36 (%32,1)
Training and Research Hospital	32 (%28,6)
Public Hospital	14 (%12,5)
Private Hospital	23 (%20,5)
Private Clinics	7 (%6,3)

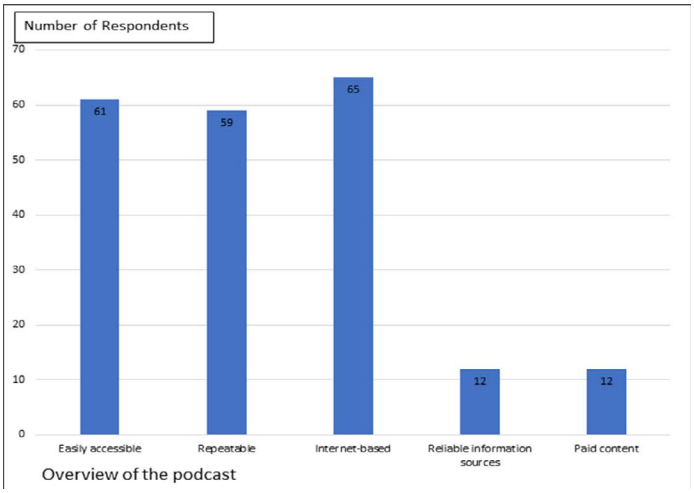


Figure 1. Answers to questions regarding the features of podcasts

Table 2. Answers to questions relating to education and the increased usefulness of podcasts in the near future

	Strongly agreed	Agreed	Undecided	Disagreed	Strongly disagreed
Q-Is podcast-based education helpful to otorhinolaryngologists' professional development?	17 (15.2%)	65 (58%)	21 (18.8%)	5 (4.5%)	4 (3.6%)
Q-Are podcasts more useful than other literature tools (books, journals, or online meetings)?	9 (8%)	13 (11.6%)	53 (47.3%)	29 (25.9%)	8 (7.1%)
Q-Will podcasts become a common tool for information sharing in the near future?	21 (18.8%)	42 (37.5%)	36 (32.1%)	10 (8.9%)	3 (2.7%)

and 12 (10.7%) stated that they include paid content (Figure 1).

In response to the question about whether podcast-based education is helpful for the professional development of otorhinolaryngologists, 65 (58%) respondents agreed, and 21 (18.8%) respondents were undecided (Table 2). Based on the otorhinolaryngologists' responses after being asked whether the "podcast is more useful than other literature tools (books, journals, online meetings), 53 people (47.3%) said they were undecided, and 29 (25.9%) disagreed (Table 2).

When asked if podcasts will become a common tool for sharing information in the near future, 37.5% (n=42) responded that they agreed, and 32.1% (n=36) were undecided (Table 2).

With regard to how frequently they referred to literature resources, 48 respondents (42.9%) answered once a week, and 40 respondents said they did so (35.7%9) daily (Table 3). In response to the question about which area of ENT could benefit from podcasts, 73 people (65.2%) answered that these would be useful for diagnosis and treatment, and 33 people (29.5%) cited surgery-surgical techniques (Table 3). For the question regarding how long the podcast has been used as a medical transmission tool, 47 people (42%) responded that they had been using it for 0-to-2 years, and 34 (30.4%) indicated 3-to-5 years (Table 3).

In response to the question about the most frequently consulted source in otolaryngology before the pandemic, 45 people (40.2%) said books, 35 people (31.3%) e-books, 25 people (22.3%) journals, five people (4.5%) online meetings, and two people (1.8%) cited podcasts (Figure 2). When asked what resource was most frequently consulted during the pandemic period, 34 people (30.4%) said online meetings, 31 people (27.7%) e-books, 26 people (23.2%) journals, 18 people (16.1%) books, and three people (2.7%) cited podcasts (Figure 2). There was a statistically significant difference between the resources consulted before the pandemic and those to which people referred during the pandemic using the Mc Nemar Bowker test ($p<0.001$).

In response to the question about their beliefs regarding the most frequently used source of literature in the near future, 60 people (53.6%) answered e-books, 20 (17.9%) online meetings, 18

Table 3. Answers to questions about the frequency and the areas of ENT for which medical transmission tools are used

Q-Regarding the frequency of referral to literature resources	**Daily** 40 (35.7%) respondents	**Once a week** 48 (42.9%) respondents	**Once a month** 21 (18.8%) respondents	**Once a year** 3 (2.7%) respondents	
Q-Concerning which areas of ENT could benefit from the podcast	Diagnosis and treatment 73 (65.2%) respondents	Surgery-surgical techniques 33 (29.5%) respondents	Diagnosis 30 (26.8%) people	Only treatment 10 (8.9%) people	
Q-About how long the podcast has been used as a medical transmission tool	0-2 years 47 (42%) people	3-5 years 34 (30.4%) people	6-8 years 10 (8.9%) people	8-10 years 8 (7.1%) people	>10 years 13 (11.6%) people

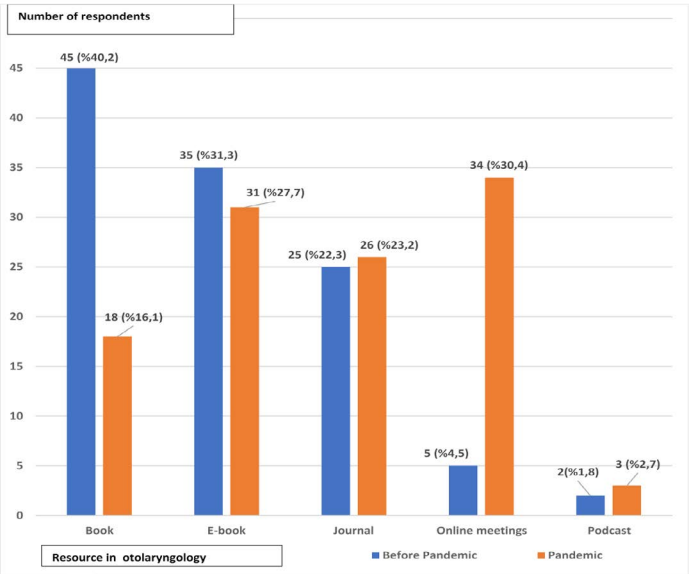


Figure 2. The frequency with which literature sources were consulted before and during the pandemic

(16.1%) journals, seven (6.7%) books, and seven (6.7%) podcasts. There was no significant difference between the age groups with regard to the distribution of podcast information (p=0.408). In addition, there was no significant difference between the genders in terms of podcast awareness (p=0.593).

DISCUSSION

The podcast is an online audio program to which people listen via subscription. Because of the ease of use, convenience, and repeatability of podcasts, they have become an increasingly popular asynchronous educational method (4). A podcast provides listeners with a unique opportunity to take part in learning while they are also engaging in their daily routine activities (exercise, commuting, etc.), regardless of the time of day or night or where they are. According to the literature, this opportunity to learn is frequently selected by those in areas such as emergency medicine and internal medicine. Podcasts are also employed in surgical branches of medicine, such as orthopedics, obstetrics, and anesthesia (11).

In the past ten years, there has been an increase in the amount of podcast content that is available in the field of ENT (8). However, in spite of the increasing interest in podcasts at the global level, no study has been found that quantifies the opportunity, advantages, awareness, and contributions of podcasts to continuing education on a national scale. This is the first study that has been conducted on the podcast at the national level.

We received 121 responses to our online questionnaire from otolaryngologists, including 82.1% (n=92) males and 17.9% (n=20) females. Most of the participants in our study (59.8%) were aged from 20 and 39. With regard to their titles, the group with the highest number of responses was the operator doctors 47.3% (n=53). According to Vanstrum et al.'s study (7), 73 otolaryngology residents were included in the study, and their median age was reported as 30 years.

According to study by Riddell that investigated the use of podcasts by emergency room residents, 65.5% (n=233) of the 352 participants were male, and 33.4% (n=119) were female (12). There were more male than female participants, as was the case in our study, which provides the first national data of titles and age groups.

There were 64 people (57,1%) who were aware of podcasts, while 48 (42,9%) were not. Another study that reported on a national scale in the United States found that 55% of participants, approximately 155 million people, had listened to podcasts at least once (13). The level of recognition, which is very similar to that of the literature, is expected to increase over time.

Although 45% (n=50) had listened to podcasts in the previous month, 55.4% (n=62) had not listened to them. In a study of 73 residents in the field of otolaryngology, 83% reported that they listened to podcasts at least once a month (7). Another study conducted on emergency room residents reported that the majority of them listened to podcasts at least once a month (88.8%; 316/356) (12). In addition, a study of 91 ENT residents reported that they listened to podcasts only 10% of the time that they spent learning (13). In response to the question about whether they had listened to podcasts about otolaryngology, 23 people (20.5%) responded in the affirmative, and 89 people (79.5%) responded negatively. Another study reported that three-quarters of the otolaryngology residents listened to podcasts regarding their field (7). Although podcasts are a preferred method of education at the international level, it has been found that the degree to which this method is preferred is still low at the national level. This is similar with regard to otorhinolaryngologists, among whom the preference for podcasts on a national scale is low but is higher globally. This low rate may be due to the absence of

Turkish podcasts on ENT.

When asked about the validity of podcasts, 12 individuals (10.7%) answered that these are reliable literature. When podcast content is developed, information security needs to be taken into consideration, including reliability, content, and design evaluation, which is similar to other educational methods that use peer review. If podcasts can be standardized, it may be possible for them to become accredited as continuing medical education in the near future.

In our study, 72.4 percent of the participants responded that the podcast has been used as a medical communication tool for five years. However, our results show that the podcast is relatively new in the professional field in Turkey. In addition, since podcasts are a new method, further research is needed with regard to their use.

Podcast-supported education is considered by 63.2% (n=82) of the respondents to be a useful tool for otolaryngologists to maintain and develop their professional skills. Studies have reported that, when compared to classical literature sources, podcasts are effective and adequate methods for supporting the learning process (14). The results of our study are, then, consistent with the literature.

According to the results of our survey, 56.3% of the respondents believed that podcasts will be widely used to transfer information. In response to the question about what educational methods will be most common in the near future, e-books were the most frequently cited, with 53.6% (n=60), and podcasts were the least, with 6.3% (n=7). The podcast continues to rank low among educational methods (7). Many authors consider that the ability of the podcast to increase accessibility, the production of Turkish content, and the provision of high-quality information can add to and at times replace traditional learning methods. However, this will depend on podcasts providing the right information, as well as on professionalism, and universal accessibility (15).

With regard to the question about the areas of otorhinolaryngology where podcasts would be most useful, 73 respondents (65.2%) indicated that they would contribute to diagnosis and treatment, and 33 respondents (29.5%) cited surgery-surgical techniques. The literature contains reports that listening to podcasts affects clinical practice (7). However, further studies are needed to determine the levels of contribution and benefit. Otolaryngologists have also reported using podcasts to communicate with patients (16).

Before the pandemic, 40.2% (n=45) used books as the first source of literature when learning about topics in otorhinolaryngology. However, during the pandemic period the most frequently used literature source, as cited by with 30.4% (n=45), was the online meeting. In addition, before the pandemic, 31.3% (n=35) used electronic books, while 27.7% (n=31) did so during the pandemic. Before the pandemic, 22.3% (n=25) of otolaryngologists consulted journals, while 23.2% (n=26) consulted these during the pandemic. Also, before the pandemic, 1.8% (n=2) listened to podcasts, but 2.7% (n=3) did so during the pandemic. There was a statistically significant difference between the frequency distribution of resources that were consulted before and during the pandemic ($p<0.001$). The coronavirus disease 2019 pandemic has not only affected our professional activities and social lives but also the frequencies in the use of otolaryngology literature. Our study provides the first data to be reported in the literature. Although the literature reports that the use of podcasts has increased with the pandemic (7), it also indicates that podcasting was not preferred in the pandemic period on a national scale, in spite of the great opportunity it offers for unprecedented learning conditions (10).

Our study had a number of limitations. Although we tried to reach all ENT physicians registered within the KanalKBB system, access remained restricted. In addition, the answers were based on statements and were therefore subject to human error. However, the study was conducted on the Internet, and the sample was randomly selected.

CONCLUSION

It has been observed that otolaryngologists throughout Turkey do not prefer using podcasts rather than other methods of learning. Even though the pandemic has affected the frequency with which otolaryngologists consult literature sources, the use of podcasts has not changed significantly. It is hoped that the content presented in this paper will encourage those in teaching positions at universities, colleges, and professional associations to produce ENT podcasts in Turkish.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Nurullah Ture, Kutahya Health Sciences University, Department of Otorhinolaryngology, Kutahya, Turkey.*
e-mail: *nurullah.ture@ksbu.edu.tr*

REFERENCES

1. Tsai Do BS. Reflections on the changing platform of education for the budding otolaryngologist. Otolaryngol Head Neck Surg 2015;153(5):706-7.
2. Egle JP, Smeenge DM, Kassem KM, et al. The internet school of medicine: Use of electronic resources by medical trainees and the reliability of those resources. J Surg Educ 2015;72(2):316-20.
3. Malecki SL, Quinn KL, Zilbert N, et al. Understanding the use and perceived impact of a medical podcast: Qualitative study. JMIR Med Educ 2019;5(2):e12901.
4. Cho D, Cosimini M, Espinoza J. Podcasting in medical education: A review of the literature. Korean J Med Educ 2017;29(4):229.
5. Clarke CGD, Nnajiuba U, Howie J, et al. Giving radiologists a voice: A review of podcasts in radiology. Insights Imaging 2020;11(1):1-9.
6. Mallin M, Schlein S, Doctor S, et al. A survey of the current utilization of asynchronous education among emergency medicine residents in the United States. Acad Med 2014;89(4):598.
7. Vanstrum EB, Badash I, Wu FM, et al. The role of educational podcast use among otolaryngology residents. Ann Otol Rhinol Laryngol 2022:00034894211072996.
8. Malka R, Villwock J, Faucett EA, et al. Podcast-based learning in otolaryngology: Availability, breadth, and comparison with other specialties. Laryngoscope 2021;131(7):E2131-8.
9. Back DA, von Malotky J, Sostmann K, et al. Superior gain in knowledge by podcasts versus text-based learning in teaching orthopedics: A randomized controlled trial. J Surg Educ 2017;74(1):154-60.
10. Barnes JH, Choby G, Carlson ML. How to create a subspecialty podcast: Headmirror's ENT podcast series. Med Educ 2020;54(10):956-7.
11. Little A, Hampton Z, Gronowski T, et al. Podcasting in medicine: A review of the current content by specialty. Cureus 2020;12(1).
12. Riddell J, Swaminathan A, Lee M, et al. A survey of emergency medicine residents' use of educational podcasts. West J Emerg Med 2017;18(2):229.
13. Catalano DJ, Yin LX, Bisco SE, et al. Accuracy and misrepresentation of reported publications among otolaryngology residency applicants professional/personal. Professional and personal development. Otolaryngol Head Neck Surg 2021;165(1_suppl):P317-27.
14. Edmond M, Neville F, Khalil HS. A comparison of teaching three common ear, nose, and throat conditions to medical students through video podcasts and written handouts: A pilot study. Adv Med Educ Pract 2016;7:281.
15. Lin M, Thoma B, Trueger NS, et al. Quality indicators for blogs and podcasts used in medical education: Modified Delphi consensus recommendations by an international cohort of health professions educators. Postgrad Med J 2015;91(1080):546-50.
16. Abreu DV, Tamura TK, Sipp JA, et al. Podcasting: Contemporary patient education. Ear Nose Throat J 2008;87(4):208-11.

Araştırma Makalesi / Research Article

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
Selcuk Med J 2022;38(3): 121-127
DOI: 10.30733/std.2022.01559

Covid-19 Pandemisinde Çocuk Acilden İstenen Cerrahi Konsültasyonlar

Consultations to Surgical Departments in Pediatric Emergency Department in Covid-19 Pandemic

Alper Yıldırım[1], Abdullah Yazar[1], Fatih Akın[1], Ahmet Osman Kılıç[1], Mehmet Uyar[2], Ayşegül Zaimoğlu[3]

[1]Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Konya, Türkiye
[2]Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi Halk Sağlığı Anabilim Dalı, Konya, Türkiye
[3]Türkiye Cumhuriyeti Sağlık Bakanlığı, Şarkikaraağaç Dr. Sadettin Bilgiç Devlet Hastanesi, Isparta, Türkiye.

Yazışma Adresi: Alper Yıldırım, Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Konya, Türkiye
e-posta: aalperyildirim86@hotmail.com

Geliş Tarihi/Received: *24 Mart 2022*
Kabul Tarihi/Accepted: *28 Mayıs 2022*

Öz

Amaç: Çalışmanın amacı pandemi döneminde çocuk acil servisten cerrahi branşlara danışılan hastaların klinik özelliklerinin ve konsültasyon sürecinin değerlendirilmesi, elde edilen bulguların pandemi öncesi verilerle kıyaslanmasıdır.
Hastalar ve Yöntem: Araştırma 11.03.2020-11.03.2021 tarihleri arasında hastanemizin çocuk acil servisinde yapılmıştır. 0-18 yaş grubundaki hastalar geriye dönük olarak cinsiyet, yaş, tanı, konsültasyon sonucu, konsültasyon yanıt süresi açısından değerlendirildi. Elde edilen bulgular 01.01.2019-31.12.2019 tarihleri arasındaki pandemi öncesi verilerle karşılaştırıldı.
Bulgular: Hastaların; %42,4'ü kadın, %57,6'sı erkektir. Ortalama yaş 6,9±4,9 yıldır. Hastalarımızın %27,3'ünün cerrahi kliniklerden birine yabancı cisim, %22,2'sinin akut karın, %10,6'sının yabancı cisim aspirasyonu tanısı ile başvurduğu belirlendi. Hastaların %38,5'inin çocuk cerrahisi, %33,9'unun kulak burun boğaz ve %11,4'ünün göğüs cerrahisi bölümüne konsülte edildiği belirlendi. Ortalama konsültasyon yanıt süresi 72,2±48,8 dakikaydı. Pandemi sırasında acil servise başvuran hastaların tanı dağılımı, konsültasyon yanıtlanma süresi, konsültasyon yapılan cerrahi bölüm dağılımı, konsültasyon sonuçları, cerrahi bölümlere göre konsültasyon yanıt sürelerinin dağılımı pandemi öncesi döneme göre istatistiksel olarak anlamlı bulundu (p<0,05).
Sonuç: Çalışmamızda pandemi döneminde çocuk acil servisine başvuran hasta sayısının azaldığı, yatış sayısının arttığı, travma ve yakın fiziksel temasla ilişkili tanıların azaldığı, epididimoorşit tanılarının arttığı saptandı. Bununla beraber konsültasyon yanıtlanma sürelerinin oldukça uzadığı görüldü.

Anahtar Kelimeler: Covid-19, çocuk acil servisi, konsültasyonlar

Abstract

Aim: The aim of the study was to evaluate the clinical features and consultation process of the patients who were consulted from the pediatric emergency department to the surgical departments during the pandemic period, and to compare the findings with the data before the pandemic.
Patients and Methods: The research was conducted between 11.03.2020-11.03.2021 in the pediatric emergency department of our hospital. The enrolled patients at 0-18 years of age were retrospectively evaluated in terms of gender, age, diagnosis, consultation result, consultation response time. Our study was compared with the prepandemic data between 01.01.2019 and 31.12.2019.
Results: Of the patients; 42,4% were female and 57,6% were male. The mean age was 6,9±4,9 years. It was determined that 27,3% of our patients were consulted to one of the surgical clinics with the diagnosis of foreign body, 22,2% acute abdomen, 10.6% foreign body aspiration. It was found that 38,5% of the patients were consulted to the pediatric surgery department, 33,9% to the otolaryngology department and 11,4% to the thoracic surgery department. The mean consultation response time was 72,2±48,8 minutes. The distribution of diagnoses, consultation response time, consulted surgical departments, consultation results by age groups, and distribution of the consultation response times by surgical departments during the pandemic were found to be statistically significant compared to the pre-pandemic period (p<0,05).
Conclusion: In our study, it was found that the number of patients admitted to the pediatric emergency department decreased during the pandemic period, the number of hospitalizations increased, the diagnoses associated with trauma and close physical contact decreased, and the diagnosis of epididymorchitis increased. In addition consultation response times were observed to be considerably longer.

Key words: Covid-19, pediatric emergency department, consultations

Atıf yapmak için: Yıldırım A, Yazar A, Akın F, Kılıç AO, Uyar M, Zaimoğlu A. Covid-19 Pandemisinde Çocuk Acilden İstenen Cerrahi Konsültasyonlar. Selcuk Med J 2022;38(3): 121-127

Açıklama: *Yazarların hiçbiri, bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi. Yazarlar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedirler.*

GİRİŞ

COVID-19, ilk olarak Çin'in Vuhan kentinde 2019 yılı Aralık ayının sonlarında solunum yolu semptomları (ateş, öksürük, nefes darlığı) gelişen bir grup hastada yapılan araştırmalar sonucunda tanımlanan bir virüstür. Salgın ilk olarak bu bölgedeki deniz ürünleri ve hayvan pazarında bulunanlarda tespit edilmiştir. Daha sonra insandan insana bulaşarak Vuhan başta olmak üzere Hubei eyaletindeki diğer şehirlere ve Çin Halk Cumhuriyeti'nin diğer eyaletlerine ve diğer ülkelere yayılmıştır. Ülkemizde ilk vaka 11 Mart 2020 tarihinde görülmüştür (1,2).

Konsültasyon tanım olarak hekimin hastasının farklı uzmanlık alanlarının değerlendirmesine ve uygulamalarına ihtiyaç olduğuna karar vermesi durumunda başka bir uzmanlık dalından meslektaşına danışmasıdır (3). Çocuk acil servisleri (ÇAS) çok büyük bir hasta grubuna hizmet vermektedir. Acil servislere başvuruların yaklaşık üçte birini çocuklar oluşturmaktadır (4). Geniş bir hasta grubuna hizmet veren ÇAS'ların iş yükünün büyük kısmını konsültasyonlar oluşturmaktadır.

Bizim çalışmada pandemi döneminde ÇAS'tan cerrahi branşlara danışılan hastaların klinik özelliklerinin ve konsültasyon sürecinin değerlendirilmesi, elde edilen bulguların pandemi öncesi verilerle kıyaslanması amaçlanmıştır.

HASTALAR VE YÖNTEM

Çalışmamızda 2021/2035 sayılı etik kurul izni ile, hastanemizin ÇAS'a 11.03.2020-11.03.2021 tarihleri arasında başvuran, 0 ile 18 yaş arasındaki hastaların cinsiyet, yaş, tanı, konsültasyon sonucu ve cevaplanma süreleri incelenmiştir. Pandemi dönemi verileri otomasyon sistemi kayıtlarından elde edilmiştir. Pandemi öncesi veriler ise üniversitemizde 2020 yılında yapılan bir uzmanlık tezinden elde edilmiştir (5). Çalışmamızda elde edilen veriler değerlendirilirken SPSS (Statistical Package for Social Sciences) 18.0 programı kullanıldı. Tanımlayıcı analizlerde frekans verileri sayı (n) ve yüzde (%) olarak, sayısal veriler ise ortalama ± standart sapma, minimum-maksimum kullanılarak gösterildi. Kategorik veriler Ki-kare (χ^2) ve Fisher'ın kesin ki-kare testleri ile karşılaştırıldı. Tüm istatistik analizlerde anlamlılık düzeyi $p<0.05$ olarak kabul edildi.

BULGULAR

COVID-19 pandemi döneminde hastanemizin ÇAS'ına başvuran ve cerrahi kliniklerden birine konsülte edilen 879 hasta çalışmaya dahil edildi. Çalışmaya alınan hastaların 506'sı (%57,56) erkek, 373'ü (%42,44) kızdı. Tüm hastaların yaş ortalaması 6,88±4,85 yıl olarak bulundu. Pandemi öncesi dönemde ise 1212 hasta izlendi. Hastaların

Tablo 1. COVID-19 Öncesi ve COVID-19 Döneminde Başvuran Hastaların Tanılarının Dağılımı

	COVID-19 öncesi n (%)	COVID-19 dönemi n (%)	χ^2	p
Yabancı cisim	277 (22,9)	240 (27,3)		
Akut karın	222 (18,3)	195 (22,2)		
Yabancı cisim aspirasyonu	127 (10,5)	93 (10,6)		
Kulak burun boğaz acilleri	60 (5,0)	70 (8,0)		
Kırmızı göz	197 (16,3)	49 (5,6)		
Hidrosefali- Şant bozukluğu	39 (3,2)	46 (5,2)		
Koroziv madde içimi	85 (7,0)	44 (5,0)		
Testis torsiyonu ve epididimoorşit	4 (0,3)	37 (4,2)		
Prepisyum hastalıkları	3 (0,2)	23 (2,6)	75,63	0,001
Septik artrit	40 (3,3)	21 (2,4)		
Epistaksis	31 (2,6)	17 (1,9)		
Periferik fasiyal paralizi	14 (1,2)	9 (1,0)		
Apse	10 (0,8)	7 (0,8)		
Rektal prolapsus	-	5 (0,6)		
Pelvik inflamatuar hastalık	5 (0,4)	5 (0,6)		
Pnömotoraks ve pnömomediastinum	4 (0,3)	4 (0,5)		
Reaktif artrit	16 (1,3)	3 (0,3)		
Gözün kimyasal yanıkları	40 (3,3)	3 (0,3)		
Nefrolitiyazis	7 (0,6)	3 (0,3)		
Sünnet	2 (0,2)	2 (0,2)		
Derin ven trombozu	4 (0,3)	1 (0,1)		
Kolelitiyazis	-	1 (0,1)		
Beyin tümörü	4 (0,3)	1 (0,1)		

Tablo 2. COVID-19 Öncesi ve COVID-19 Döneminde Başvuran Hastaların Konsülte Edildiği Cerrahi Bölümlerin Dağılımı

	COVID-19 öncesi n (%)	COVID-19 dönemi n (%)	χ^2	p
Beyin ve sinir cerrahi konsültasyonu	43 (3,5)	46 (5,2)		
Çocuk cerrahisi konsültasyonu	307 (25,3)	338 (38,5)		
Göğüs cerrahi konsültasyonu	131 (10,8)	100 (11,4)		
Göz hastalıkları konsültasyonu	258 (21,3)	56 (6,4)		
Kadın hastalıkları konsültasyonu	5 (0,4)	3 (0,3)		
Kalp ve damar cerrahi konsültasyonu	4 (0,3)	1 (0,1)		
Kulak burun boğaz konsültasyonu	382 (31,5)	298 (33,9)	113,61	0,001
Ortopedi konsültasyonu	56 (4,6)	23 (2,6)		
Plastik cerrahi konsültasyonu	12 (1,0)	3 (0,3)		
Üroloji konsültasyonu	14 (1,2)	11 (1,3)		

%43,48'i kız, %56,52'si erkekti ve yaş ortalaması 7 yıldı. Her iki dönemde de ÇAS'tan cerrahi bölümlere konsülte edilen hastaların aldığı ilk iki sıradaki tanının yabancı cisim ve akut karın olduğu belirlendi. COVID-19 öncesi dönemde başvuran hastaların %16,3'ü kırmızı göz ile cerrahi bölümlere konsülte edilirken COVID-19 döneminde sadece %5,6'sının kırmızı göz nedeni ile cerrahi bölümlere konsülte edildiği görüldü. COVID-19 öncesi dönemde testis torsiyonu ve epididimoorşit tanısı alan hasta oranı %0,3 iken COVID-19 döneminde testis torsiyonu ve epididimoorşit tanısı alan hasta oranı %4,2 olarak tespit edildi. Hasta tanıları COVID-19 öncesi ve COVID-19 döneminde karşılaştırıldığında istatistiksel olarak anlamlı fark tespit edildi (p=0,001). COVID-19 döneminde yabancı cisim, akut karın, kulak burun boğaz acilleri, hidrosefali-şant bozukluğu tanıları ile başvurular COVID-19 öncesi döneme göre daha yüksek iken; kırmızı göz, koroziv madde içimi, epistaksis, periferik fasiyal paralizi, septik artrit tanıları ile başvurular COVID-19 öncesi döneme göre daha düşük olarak bulundu (Tablo 1). ÇAS'a COVID-19 öncesi ve COVID-19 döneminde başvuran hastaların konsülte edildiği cerrahi bölümlerin dağılımı incelendi. COVID-19 öncesi dönemde çocuk cerrahi konsültasyon oranı %25,3 iken COVID-19 döneminde %38,5 olduğu saptandı. COVID-19 öncesi dönemde göz hastalıkları konsültasyon oranı %21,3 olarak, COVID-19 döneminde %6,4 olarak tespit edildi. Hastaların konsülte edildikleri cerrahi branşlar COVID-19 öncesi ve COVID-19 döneminde karşılaştırıldığında istatistiksel olarak anlamlı fark tespit edildi (p=0,001). Bu fark COVID-19 döneminde göz hastalıklarına konsülte edilen hasta sayısının COVID-19 öncesi döneme göre daha düşük olmasından kaynaklanmaktaydı (Tablo 2). ÇAS'a bölümüne COVID-19 öncesi ve COVID-19 döneminde başvuran hastaların konsültasyon istemlerinin cevaplanma süreleri incelendi. COVID-19 öncesi dönemde 61 dakika ve üzerinde konsültasyona cevap verilme oranı %29,3 iken, COVID-19 döneminde bu oranın %48,5'e yükseldiği görüldü. Diğer konsültasyon cevaplanma sürelerinin oranları COVID-19 öncesi döneme göre düşük bulundu. Hastaların konsülte edildikleri cerrahi branşlar tarafından konsültasyonlarının cevaplanma süreleri karşılaştırıldığında istatistiksel olarak anlamlı fark tespit edildi (p=0,001). Bu fark COVID-19 döneminde daha fazla hastanın konsültasyonunun 61 dakika ve üzerinde yanıtlanmasından kaynaklanmaktaydı (Tablo 3). Pandemi öncesi ve pandemi döneminde başvuran hastaların cerrahi bölümler tarafından konsültasyon sonuçları değerlendirildi. COVID-19 öncesi dönemde servis yatışı yapılan hasta oranı %13,5 iken pandemi

Tablo 3. COVID-19 Öncesi ve COVID-19 Döneminde Başvuran Hastaların Konsültasyon İstemlerinin Cevaplanma Sürelerinin Dağılımı

	COVID-19 öncesi n (%)	COVID-19 dönemi n (%)	χ^2	p
0-15 dakika	214 (17,7)	77 (8,8)		
16-30 dakika	247 (20,4)	129 (14,7)		
31-45 dakika	213 (17,6)	139 (15,8)	94,56	0,001
46-60 dakika	183 (15,1)	105 (11,9)		
61 dakika ve üzeri	355 (29,3)	429 (48,8)		

Tablo 4. COVID-19 Öncesi ve COVID-19 Döneminde Başvuran Hastaların Konsültasyon Sonuçlarının Dağılımı

	COVID-19 öncesi n (%)	COVID-19 dönemi n (%)	χ^2	p
Servis yatışı yapılan	164 (13,5)	205 (23,3)		
Medikal tedavi verilen	406 (33,5)	202 (23)		
Sevk edilen	47 (3,9)	4 (0,5)		
Tedaviyi kabul etmeyen	100 (8,3)	83 (9,4)		
Yatış yapılmadan ayakta girişimsel işlem	178 (14,7)	128 (14,6)	74,22	0,001
Klinik izlem	311 (25,7)	253 (28,8)		
Opere edilen merkeze yönlendirme	6 (0,5)	4 (0,5)		
Toplam	**1212 (100,0)**	**879 (100,0)**		

döneminde bu oranın %23,3'e yükseldiği bulundu. COVID-19 öncesi dönemde medikal tedavi verilen hasta oranı %33,5 iken COVID-19 döneminde bu oranın %23,0'a düştüğü belirlendi. Hastaların konsültasyon sonuçları COVID-19 öncesi ve COVID-19 döneminde karşılaştırıldığında istatistiksel olarak anlamlı fark tespit edildi (p=0,001). Bu fark pandemi döneminde servis yatışı yapılan hasta sayısının pandemi öncesine göre daha yüksek bulunmasından kaynaklanmaktaydı (Tablo 4). COVID-19 öncesi ve COVID-19 döneminde başvuran hastaların aldıkları tanılar cinsiyetlerine göre değerlendirildi. Her iki cinsiyette hem pandemi öncesinde hem de pandemide ilk iki sıradaki hastalıklar aynı bulundu. COVID-19 öncesi dönemde erkeklerde testis torsiyonu, epididimoorşit oranı %0,6 iken COVID-19 döneminde bu oranın %7,3'e yükseldiği görüldü. COVID-19 öncesi dönemde gözün kimyasal yanıklarının görülme oranının her iki cinsiyette de COVID-19 döneminde azaldığı belirlendi. COVID-19 öncesi ve COVID-19 dönemindeki acil başvurularının cinsiyete göre dağılımı anlamlı derecede farklı bulundu (p=0,001). Bu fark kırmızı göz ile başvuran kız ve erkek cinsiyetinin COVID-19 döneminde daha düşük olmasından kaynaklanmaktaydı (Tablo 5). ÇAS'a başvuran hastaların yaş gruplarına göre aldıkları tanıların dağılımı incelendi. Yaş gruplarına göre acile başvuru tanıları arasında istatistiksel olarak anlamlı bir fark tespit edildi (p=0,001). 0-5 yaş

Tablo 5. COVID-19 Öncesi ve COVID-19 Döneminde Başvuran Hastaların Cinsiyete Göre Tanılarının Dağılımı

	COVID-19 öncesi		COVID-19 dönemi		χ^2	p
	Kız n (%)	Erkek n (%)	Kız n (%)	Erkek n (%)		
Kırmızı göz	85 (16,10)	112 (16,4)	25 (6,7)	24 (4,7)		
Prepisyum hastalıkları	-	3 (0,4)	-	23 (4,5)		
Yabancı cisim	117 (22,2)	160 (23,3)	116 (31,1)	124 (24,5)		
Kolelitiyazis	-	-	-	1 (0,2)		
Yabancı cisim aspirasyonu	61 (11,6)	66 (9,6)	34 (9,1)	59 (11,7)		
Nefrolitiyazis	-	7 (1,0)	1 (0,3)	2 (0,4)		
Akut karın	102 (19,3)	120 (17,5)	90 (24,1)	105 (20,8)		
Kulak burun boğaz acilleri	26 (4,9)	34 (5,0)	31 (8,3)	39 (7,7)		
Pnömotoraks ve pnömomediastinum	-	4 (0,6)	2 (0,5)	2 (0,4)	85,65	0,001
Testis torsiyonu ve epididimoorşit	-	4 (0,6)	-	37 (7,3)		
Koroziv madde içimi	37 (7,0)	48 (7,0)	14 (3,8)	30 (5,9)		
Hidrosefali- şant bozukluğu	12 (2,2)	27 (3,9)	23 (6,2)	23 (4,5)		
Epistaksis	15 (2,8)	16 (2,3)	9 (2,4)	8 (1,6)		
Periferikfasiyal paralizi	8 (1,5)	6 (0,9)	3 (0,8)	6 (1,2)		
Rektal prolapsus	-	-	4 (1,1)	1 (0,2)		
Septik artrit	16 (3,0)	24 (3,5)	10 (2,7)	11 (2,2)		
Reaktif artrit	4 (0,8)	12 (1,8)	1 (0,3)	2 (0,4)		
Gözün kimyasal yanıkları	27 (5,8)	34 (4,9)	1 (0,3)	2 (0,4)		
Apse	6 (1,1)	4 (0,6)	4 (1,1)	3 (0,6)		
Pelvik inflamatuar hastalık	5 (0,9)	-	5 (1,3)	-		
Derin ven trombozu	2 (0,4)	2 (0,3)	-	1 (0,2)		
Sünnet	-	2 (0,3)	-	2 (0,4)		
Beyin tümörü	2 (0,4)	2 (0,3)	-	1 (0,2)		

Tablo 6. Yaş Gruplarına Göre Hasta Tanılarının Dağılımı

	0-5 yaş n (%)	6-10 yaş n (%)	11 yaş ve üzeri n (%)	χ^2	p
Kırmızı göz	20 (4,4)	17 (9,0)	12 (5,2)		
Prepisyum hastalıkları	15 (3,3)	6 (3,2)	2 (0,9)		
Yabancı cisim	182 (39,7)	39 (20,7)	19 (8,2)		
Kolelitiyazis	-	-	1 (0,4)		
Yabancı cisim aspirasyonu	76 (16,6)	14 (7,4)	3 (1,3)		
Nefrolitiyazis	1 (0,2)	1 (0,5)	1 (0,4)		
Akut karın	38 (8,3)	45 (23,9)	112 (48,1)		
Kulak burun boğaz acilleri	24 (5,2)	27 (14,4)	19 (8,2)		
Pnömotoraks ve pnömomediastinum	-	-	4 (1,7)		
Testis torsiyonu ve epididimoorşit	7 (1,5)	10 (5,3)	20 (8,6)		
Koroziv madde içimi	40 (8,7)	2 (1,1)	2 (0,9)		
Hidrosefali-şant bozukluğu	35 (7,6)	6 (3,2)	5 (2,1)	210,09	0,001
Epistaksis	3 (0,7)	4 (2,1)	10 (4,3)		
Periferik fasiyal paralizi	1 (0,2)	4 (2,1)	4 (1,7)		
Rektal prolapsus	4 (0,9)	1 (0,5)	-		
Septik artrit	4 (0,9)	7 (3,7)	10 (4,3)		
Reaktif artrit	-	2 (1,1)	1 (0,4)		
Gözün kimyasal yanıkları	3 (0,7)	-	-		
Apse	2 (0,4)	3 (1,6)	2 (0,9)		
Pelvik inflamatuar hastalık	-	-	5 (2,1)		
Derin ven trombozu	1 (0,2)	-	-		
Sünnet	2 (0,4)	-	-		
Beyin tümörü	-	-	1 (0,4)		

grubunda en sık tanı %39,7 ile yabancı cisim, 6-10 yaş grubundaki en sık tanı %23,9 ile akut karın, 11 yaş ve üzeri grubundaki en sık tanı %48,1 ile akut karın olarak tespit edildi (Tablo 6).

TARTIŞMA

Acil servisler iş yükünün ve hasta başvurusunun çok fazla olduğu birimlerdir. Bu nedenle işleyiş hızlı ve etkin olmalıdır. Konsültasyonlar bu işleyişin önemli bir parçasını oluşturur. Kliniğimizde COVID-19 öncesi ÇAS'lara başvuran hastaların cerrahi konsültasyonlarının değerlendirildiği bir tez çalışması yürütülmüştür. Çalışmamızda benzer şekilde ÇAS'lardaki işleyiş değerlendirilmiş olup pandemi sürecinde konsültasyon yanıtlanma sürelerinin oldukça arttığı görülmüştür.

Çalışmamızda hastaların yaş gruplarının dağılımı değerlendirildiğinde 458 hasta (%52,10) 0-5 yaş grubunda, 188 hasta (%21,38) 6-10 yaş grubunda, 233 hasta ise (%26,50) 11 yaş ve üzerindeydi. Bununla beraber ÇAS'a COVID-19 öncesi ve sonrasında başvuran ve cerrahi bölümlere konsülte edilen hastaların cinsiyetlerine göre yaş gruplarının dağılımının benzer oranlarda olduğu görüldü. Kliniğimizde 2018 yılında yapılan bir çalışmada da hastanemiz ÇAS'ına başvuran hastaların çoğunluğunun erkek ve 5 yaş altında olduğu görülmüştür (6). Çalışmamızda dikkat çeken bir diğer husus ise pandemi döneminde öncesine göre acil başvurular ve istenen cerrahi konsültasyonların sayısında azalma olmasıdır. Bu durum sokağa çıkma yasakları ve zorunlu kalınmadıkça hastane başvurularının ertelenmesi gibi sebeplere bağlanabilir. Literatür incelendiğinde pandemi döneminde diğer ülkelerde yapılan çalışmalarda da hastanelerin acil servislerine başvuruların azaldığı görülmüştür (7). Ülkemizde yapılan bir çalışmada da benzer şekilde pandemi döneminde acil servise başvuru sayısının azaldığı ve servise yatış oranının arttığı bulunmuştur (8).

Çocuklarda en sık aspire edilen yabancı cisimlerin boncuk, düğme, kılçık gibi gıda artıkları, kuruyemiş parçaları, oyuncaklar, su maymuncuğu adı verilen ve su aldıkça şişip solunum yolunu tıkayabilen objeler olduğu görülmektedir. Solunum yolu tıkanıklıkları derecesine göre hayati öneme sahip olabilmektedir ve ivedilikle müdahale edilmesi gereken acillerdir. Vakaların acil trakeotomi ihtiyacı olabildiğinden solunum işi dikkatlice değerlendirilmelidir. 2017 yılında ülkemizde yapılan bir çalışmada yabancı cisim aspirasyonlarının %80'inin 3 yaşından küçük hastalarda meydana geldiği görülmüştür (9). Benzer şekilde çalışmamızda yabancı cisim aspirasyonu tanısı konulan hastaların %75,83'ü 5 yaşından küçük

olduğu bulundu.

Literatüre baktığımızda 2011 yılında yaptığı bir çalışmada hastanelerin acil servisinden göz hastalıkları kliniğine danışılan hastaların en sık aldığı ilk iki tanının sırasıyla oküler travma ve konjonktivitler olduğu görülmüştür (10). Bizim çalışmamızda COVID-19 öncesinde başvuran hastaların %16,3'ü kırmızı göz ön tanısıyla göz hastalıkları bölümüne konsülte edilirken COVID-19 döneminde sadece %5,6'sının kırmızı göz nedeni ile konsülte edildiği görülmüştür. Her iki cinsiyette de göz konsültasyonlarında ve kırmızı göz tanısında azalma vardır. Aradaki bu fark pandemi döneminde viral ve bakteriyel konjonktivitlerdeki bulaş oranının azalmasına bağlanabilir. Yine okulların kapalı olması ve sokağa çıkma yasakları da çocukları travma gibi gözde selülitlere yol açabilen çevresel sebeplerden ve özellikle adenovirüs bulaşlarından korumuş olduğu sonucuna ulaşılabilir. Bu düşüncemizi destekleyen diğer bulgularımız ise pandemide epistaksis, septik artrit, periferik fasiyal paralizi gibi travma ile ilişkilendirilebilecek tanılarda da azalma olmasıdır.
Pandemi öncesinde testis torsiyonu ve epididimoorşit tanısı alan hasta oranı %0,3 iken bizim çalışmamızda %4,2 olarak tespit edildi. Ülkemizde yapılan bir çalışmada COVID-19 ile testiküler ağrı, epididimit ve orşit arasındaki ilişki değerlendirildiğinde COVID-19 ile ilişkili testis ağrısına beklenenden daha sık rastlanılmış, ancak bu konuda kesin bir kanıya ulaşmak için COVID-19'un genitoüriner sistemden izole edildiği ileri çalışmalara gerek olduğu vurgulanmıştır (11). Bununla beraber pediatrik hastalarda testis torsiyonu ve epididimit, orşit ile COVID-19 arasındaki ilişkiyi ispatlayacak geniş kapsamlı çalışmalara ihtiyaç vardır.

ÇAS'a COVID-19 öncesi ve sonrasında başvuran hastaların konsülte edildiği cerrahi bölümlerin dağılımına bakıldığında COVID-19 döneminde çocuk cerrahisinden istenen konsültasyon oranının arttığı, göz hastalıkları konsültasyonunun ise istatistiksel olarak anlamlı derecede azaldığı görüldü. Pandemi döneminde sağlık kuruluşlarına başvuruların mümkün oldukça ertelenmeye çalışılması ve klinik durumun giderek ağırlaşması çocuk cerrahisi konsültasyonlarının büyük kısmını oluşturan akut karın gibi tanıların artmasına sebep olmuş görünmektedir. Servis yatışlarının artmış olması da benzer bakış açısıyla açıklanabilir. Daha önce bahsedildiği gibi pandemi dönemindeki sokağa çıkma yasakları ve temas oranının azalması göz hastalıkları konsültasyonunda bu anlamlı farka sebep olmuş görünmektedir. Yine benzer düşünce ile ortopedi konsültasyonlarının da azaldığı görülmektedir.

Konsültasyon süreleri incelendiğinde COVID-19 öncesi dönemde 61 dakika ve üzerinde konsültasyona cevap verilme oranı %29,3 iken, pandemide bu oranın %48,5'e yükseldiği görüldü. Diğer konsültasyon cevaplanma sürelerinin oranları COVID-19 döneminde öncesine göre düşük bulundu. Bazı durumlarda sözel olarak konsülte edilen hastaların konsültasyon cevaplarının sisteme yazılması bir süre gecikebilmektedir. Özellikle pandemi döneminde artmış iş yükü, cerrahi servislerin bir kısmının pandemi servisi haline getirilmesi, ilgili branşlardaki hekimlerin bir kısmının pandemi servislerinde görevlendirilmesiyle oluşan personel eksikliği bu uzamış konsültasyon cevaplanma sürelerine sebep olabilir. Uzun konsültasyon yanıtlanma sürelerinin tedavi başarısı, erken tanı ve hasta maliyetlerini olumsuz etkileyeceği açıktır. Konsültasyon cevaplanma süresinin kısaltılması için bazı sağlık kuruluşlarında kısa mesaj uygulaması kullanılmaktadır. Bu uygulamayı kullanan hastanelerden birinde yapılan çalışmada hem cerrahi hem de dahili birimlerde konsültasyon cevaplanma sürelerinin kısaldığı görülmüştür (12).

Çalışmamızda ÇAS'tan cerrahi konsültasyon istenen hastaların %5'ini koroziv madde içen hastalar oluşturmaktadır. Evlerde uygun şekilde muhafaza edilmeyen temizlik malzemeleri, deterjanlar, asidik veya bazik muhteviyatta ve sindirim sistemine ciddi hasar verebilecek kimyasal maddeler büyük risk oluşturmaktadır. Küçük yaştaki hastaların merakı ve çevreyi keşfetme arzusu en büyük risk faktörleri olarak görülmektedir. Erkek çocuklarının daha hareketli olması da bu tanının bariz bir şekilde erkek hastalara daha çok koyulmasına sebep olmaktadır. 2006 yılında ülkemizde yapılan çalışmada koroziv madde içen 102 hasta değerlendirilmiş ve hastaların 67'sinin erkek ve yaş ortalamasının 5,5 olduğu görülmüştür (13). Bizim çalışmamızda da benzer şekilde hastalarımızın %68'i erkek ve %90'ı 5 yaş altındaydı. En önemli engellenebilir ölüm nedenlerinin başında gelen yabancı cisim aspirasyonu ve koroziv madde içimi vakalarının azaltılabilmesi için çocuklara güvenli bir çevre oluşturulması önem arz etmektedir. Çocukların yaşam alanlarında, özellikle evlerde güvenlik için gerekli düzenlemeler yapılmalı, lüzum halinde uygun güvenlik araçları kullanılmalıdır. Ayrıca eğitimciler ve sağlık profesyonelleri tarafından çocuklara ve ebeveynlere yaralanma-korunma programları çerçevesinde düzenli eğitimler verilmelidir.

Yaş gruplarına göre hastaların aldıkları tanılar

değerlendirildiğinde her üç yaş grubunda ilk sıralardaki tanıların 0-5 yaş arasında yabancı cisim ve diğer iki yaş grubunda akut karın olduğu görüldü. COVID-19 öncesi dönemde de bu durum aynıydı. Kliniğimizde 2017 yılında yaptığımız çalışmamızda da yabancı cisim aspirasyonu tanısı konulan hastaların %90,5'inin 5 yaş altında olduğu görüldü (14). Bu yaş grubunda çevreyi keşif ve merak duygusu sonuçları ağır olabilecek yabancı cisim aspirasyonlarına neden olabilmektedir. Bu konuda sosyal mecralarda ailelere bilgi verilmeli ve Hemlich manevrası gibi hayat kurtarıcı uygulamalardan bahsedilmelidir.

Sonuç olarak COVID-19 pandemisi döneminde cerrahi branşlardaki hekim sayısının yetersizliği ve acillerde artan iş yükü gibi nedenler konsültasyon yanıtlama sürelerinin uzamasına yol açmıştır. Acil servislere başvuruların azalmasına rağmen servis yatış oranları da artmıştır. Bu bağlamda kesintisiz sağlık hizmeti veren acil servislerde ve ilgili cerrahi birimlerde yeterli sayıda hekim bulundurulmalı, konsültasyon işleyişini kolaylaştıracak ekipman ve uygulamalar sağlanmalıdır.

Çıkar Çatışması: *Çalışmada herhangi bir çıkar çatışması yoktur.*

Finansal Çıkar Çatışması: *Çalışmada herhangi bir finansal çıkar çatışması yoktur.*

Yazışma Adresi: *Alper Yıldırım, Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Konya, Türkiye*
E-mail: *aalperyildirim86@hotmail.com*

KAYNAKLAR

1. Huang C, Wang Y, Li X, et al. Clinicalfeatures of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
2. Öğütlü H. Turkey's response to COVID-19 in terms of mental health. Ir J PsycholMed 2020;37(3):222-5.
3. Holliman CJ. The art of dealing with consultants. J EmergMed 1993;11(5):633-40.
4. Institute of Medicine Committee on the Future of Emergency Care in the U.S. Health System. The future of emergency care in the United States health system. Ann Emerg Med 2006;48(2):115-20.
5. Zaimoğlu AG. Çocuk acilden cerrahi bölümlere danışılan hastaların değerlendirilmesi (Uzmanlık tezi). Konya: Necmettin Erbakan Üniversitesi; 2020.
6. Eraslan E. Meram tıp fakültesi hastanesi çocuk acile başvuran hastaların klinik ve demografik özelliklerinin incelenmesi (Uzmanlık tezi). Konya: Necmettin Erbakan Üniversitesi; 2018.
7. Giamello JD, Abram S, Bernardi S, et al. The emergency department in the COVID-19 era. Who are we missing? Eur J EmergMed 2020;27(4):305-6.
8. Alataş ÖD, Gökçek K. Pandemi döneminde ve pandemi öncesi dönemde acil servise başvuran hastaların karşılaştırılması. Medical Journal of Mugla Sitki Kocaman University 2021;8(3):195-8.
9. İlhan H. Çocuklarda yabancı cisim aspirasyonları. Çocuk Cerrahisi Dergisi 2017;31(Ek sayı):40-5.
10. Alotaibi AG, Osman EA, Allam KH, et al. One month out come of ocular related emergencies in a tertiary hospital in Central SaudiArabia. SaudiMed J 2011;32(12):1256-60.
11. Ediz C, Tavukcu HH, Akan S, et al. Is the reany association of COVID-19 with testicular pain and epididymo-orchitis? Int J ClinPract 2021;75(3):e13753.
12. Özyurt E, Aykutluğ M, Uğurlu D, et al. Acil servis konsültasyon sürecinde SMS uygulaması Dışkapı hastanesi modeli. Sağlık Akademisyenleri Dergisi 2018:5-4.
13. Kayaalp L, Gurkan O, Burak D, et al. Endoskopik izlem gerektiren korozif yanıkları olan çocuk ve ergenlerde kazanın meydana geliş şekli ve aile özelliklerinin değerlendirilmesi. Türk Pediatri Arşivi 2006;41:24-30.
14. Yazar A, Akın F, Türe E, et al. Çocuk acil kliniğine başvuran adli vakaların değerlendirilmesi. Dicle Tıp Dergisi / Dicle Medical Journal 2017;44(4):345-53.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 128-135
DOI: 10.30733/std.2022.01558

NEÜ YAYINEVİ

Does Experimental Morphine Addiction in Rats Change Physiological and Histological Characteristics of the Heart?

Sıçanlarda Deneysel Morfin Bağımlılığı Kalbin Fizyolojik ve Histolojik Özelliklerini Değiştirir mi?

Hande Cagliyan[1], Z. Isik Solak Gormus[2], Hatice Solak[3], Raviye Ozen Koca[2], Burcu Gultekin[4]

[1]Istanbul Arel University, Faculty of Medicine, Department of Physiology, Istanbul, Turkey
[2]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Physiology, Konya,Turkey
[3]Kutahya Health Sciences University, Faculty of Medicine. Department of Physiology, Kutahya, Turkey
[4]Necmettin Erbakan University, Meram Faculty of Medicine, Department of Histology, Konya, Turkey

Address correspondence to: Z. Isik Solak Gormus, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Physiology, Konya,Turkey
e-mail: igormus@gmail.com

Geliş Tarihi/Received: *28 January 2022*
Kabul Tarihi/Accepted: *11 July 2022*

Öz

Amaç: Morfin, kronik ağrı tedavisinde tercih edilen opioidlerdendir. Tekrarlayan kullanımı bağımlılığa neden olabilir. Opioid bağımlılığının kalp kontraksiyonuna olan etkilerini araştırmak amacıyla deneysel morfin bağımlılığı/yoksunluğu oluşturulan sıçanlarda miyokardiyal kontraktilite/histolojik değişiklikler araştırıldı.
Gereçler ve Yöntem: Resmi olarak 28.05.2021'de tamamlanan çalışmada kullanılan 32 yetişkin erkek Wistar albino sıçan, Kontrol(C), Morfin(M), Morfin+Nalokson(MN) gruplarına ayrıldı. GrupC'ye 10mg/kg %0,9 NaCl, GrupM'ye 10mg/kg morfin 7 gün subkutan uygulandı. Son morfin uygulamasından sonra C-M gruplarına 3mg/kg NaCl, GrupMN'ye 3mg/kg nalokson intraperitoneal verildi. 30dk morfin yoksunluğu belirtileri puanlandı. 3-4mm atriyum şeritleri izole organ banyosu haznelerine asıldı. 2g gerimle adrenalin kaynaklı kasılmalar(0,001M) gözlemlendi. Gerim değişiklikleri kaydedildi. İstatistiksel analizde SAS University Edition 9.4 programı kullanıldı.
Bulgular: MN grubunda morfin yoksunluğu davranışları gözlendi. GrupM-MN'de adrenalin öncesi gerim değerleri GrupC'ye göre daha yüksekti. Adrenalin kaynaklı verilerden 15 dakika öncesi/sonrası kasılmadaki en büyük artış GrupC'de tesbit edildi.
Sonuç: Morfin bağımlılığı-yoksunluğu, sıçanlarda inotropik/kronotropik etkilerde değişikliğe neden olmadı. Mast hücrelerinde histolojik farklılık gözlenmedi. Çalışma morfin bağımlılarında, sistem analizi açısından kalp için olumlu bir kaynak oluşturabilir.

Anahtar Kelimeler: İzole organ banyosu, sıçan, miyokardiyal kasılma, morfin bağımlılığı, morfin çekilmesi

Abstract

Aim: Morphine is one of the most preferred opioids in treatment of chronic pain. Recurrent use can cause addiction. There is no consensus on cardiovascular system treatment/side effects of opioids. In order to investigate effects of opioid addiction on heart, myocardial contractility/histological changes were investigated in rats via experimental morphine addiction/withdrawal.
Materials and Methods: 32 adult male Wistar albino rats used for study, which was officially completed on 28-05-2021, were divided into Control(C), Morphine(M), Morphine+Naloxone(MN) groups randomly. In GroupC 10mg/kg 0.9% NaCl solution, in GroupM-MN 10mg/kg morphine were administered subcutaneously for 7 days. After the last administration of morphine, 3mg/kg NaCl was given to GroupC-M, 3mg/kg naloxone was given to GroupMN intraperitoneally. Signs of morphine withdrawal were observed for 30 minutes and scored. 3-4mm strips of atria were hung in isolated organ bath chambers. Tension was adjusted to 2g. Adrenaline-induced contractions (0.001M) were observed. Changes in tension were recorded. SAS University Edition 9.4 program was used for statistical analysis.
Results: Morphine withdrawal behaviours were observed in GroupMN. There was no statistically significant difference between atrial contractility tension values of GroupC-M-MN($p>0.05$). Pre-adrenaline tension values were higher in GroupM-MN than in GroupC. But the greatest contraction increase between 15minutes before/after adrenaline-induced data was in GroupC.
Conclusion: Morphine addiction/withdrawal didn't cause inotropic/chronotropic changes. No histological differences were observed in mast cells. These results may constitute a positive resource for the heart for systems analysis in morphine addicts.

Key words: Isolated organ bath;rat, myocardial contractility, morphine addiction, morphine withdrawal.

Cite this article as: Cagliyan H, Solak Gormus ZI, Solak H, Ozen Koca R, Gultekin B. Does Experimental Morphine Addiction in Rats Change Physiological and Histological Characteristics of the Heart? Selcuk Med J 2022;38(3): 128-135

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Morphine is a powerful analgesic and a natural opioid. Opium (poppy) plant is the dried form of the juice obtained by drawing the fresh fruit capsule (13). Morphine, which is a Mu receptor agonist, is one of the most preferred opioids in the treatment of chronic pain. When used repeatedly, they can cause addiction (9). Naloxone is an opioid antagonist used to reverse the effects of opioid overdose. It causes withdrawal syndrome (5).

Specific receptors to which opioids bind in the central nervous system are also found in many organs including cardiovascular tissue. The heart controlled by the autonomic nervous system has a cardiac nervous system composed of cardiac ganglia, sensory afferents, pre- and postganglionic parasympathetic and postganglionic sympathetic efferents. It has been observed in rats that μ, κ, δ receptors are expressed as mRNA and converted into specific receptor proteins on different components of the cardiac nervous system (28).

Morphine is used for pain relief during postoperative cardiac surgery and myocardial ischemia. Due to the high affinity for mu receptors, stimulation of mu opioid receptors is responsible for respiratory and cardiovascular side effects (7). The mechanism of opioids in the pathogenesis of cardiovascular disease is unclear. It is said that long-term opioid intake causes cardiovascular risk. Studies have found a relationship between cardiovascular death, MI, and opioid use. In recent studies, when prescription opioid use and non-steroidal anti-inflammatory drugs were compared, it was stated that the risk of coronary artery revascularization and MI risk increased, and cardiac death was higher in those treated with opioids. After MI, opioids affect myocardial conduction, reperfusion, and contractility (2).

Morphine and its analogues decrease sympathetic activity and increase parasympathetic activity. It causes hypotension and cardiac arrhythmias by histamine release from mast cells. In addition, morphine causes peripheral vasodilation and orthostatic hypotension. With naloxone deprivation, heart rate and systolic pressure increased with a decrease in cardiac vagal tone (14). The riskiest cardiac side effect of opioids is prolongation of the QT interval, as it causes Torsades de Pointes (a specific type of ventricular tachycardia), which can result in sudden death (2).

The effects of opioids vary according to the duration of use. acute and chronic opioid use does not have the same cardiac effect (4). Morphine was frequently preferred in the treatment of heart failure and heart attack in the previous periods. It is said that this improves myocardial function by relieving pain, decreasing respiratory rate, effective in anxiety, and dilating venous vessels. Also, long-term use of opioids is a risk factor for acute myocardial infarction. Because of its pain-relieving properties, it hides the symptoms, leads to the progression of the lesion and causes the development of coronary atherosclerosis (17). Although there are few studies on chronic activation of these receptors, it has been reported that chronic morphine use has cardioprotective effects. Morphine has been shown to have a cardioprotective role with delta-1 opioid receptor agonists. Recent studies have shown that other opioids such as morphine can exert a protective effect in ischemia induced heart (26). By administering intrathecal morphine to rats with ischemia-reperfusion damage, infarction decreased as a result of activation of central opioid receptors, resulting in cardioprotective effects (35).

While there are many studies on addiction and tolerance in the central nervous system, there are not enough studies yet on the effects of opioid addiction on cardiac functions. Data regarding the cardiac side effects of chronic opioid administration are currently limited. The aim of the present study is to examine the chronotropic, inotropic effects and myocardial histology in rats with a morphine dependence and withdrawal model.

MATERIALS AND METHODS

Ethics Statement

The protocols of animal experiments were approved by the Local Ethics Committee of Application and Research Center of Experimental Medicine, Necmettin Erbakan Universty No. 2020-006, on 16.01.2020.

In this study, 32 adult (300-350gr), male Wistar albino rats were randomly divided into 3 different groups. The care and feeding of the rats were done at Experimental Medicine Application and Research Center. They were housed in plastic cages where they could move freely with food and water containers, their food and water were given as ad-libitum. The animals were stored at room temperature 22 ± 1˚C for 12 hours light/dark period under standard laboratory conditions.

Creation and evaluation of morphine addiction

Control group (Group C, n=10): 10mg/kg saline solution (0.9% NaCl solution) was injected subcutaneously once a day for 7 days. On the 7th day

at 08:00, 2 hours after the last saline administration a single dose of 3 mg/kg saline was administered intraperitoneally, and the behavior of the animals was observed.

Morphine group (Group M, n=11): 10mg/kg of morphine was injected subcutaneously once a day for 7 days. On the 7th day at 08:00, 2 hours after the last dose of morphine was administered, a single dose of 3 mg/kg saline (0.9% NaCl solution) was administered intraperitoneally, and the behavior of the animals was observed.

Morphine+Naloxone group (Group MN, n=11): 10mg/kg of morphine was injected subcutaneously once a day for 7 days. On the 7th day at 08:00, 2 hours after the last dose of morphine was administered, a single dose of 3 mg/kg naloxone was administered intraperitoneally and the behavior of the animals was observed (18).

After naloxone and saline injection, the animals were placed in plexiglass transparent cylinder observation cages with a diameter of 25 cm and a height of 65 cm and were observed for 30 minutes. Their weight was included in the scoring by measuring 1.5 hours before and half an hour after the naloxone and saline (0.9% NaCl solution) injections. The Withdrawal score was calculated for each animal using the modified Gellert and Holtzman scale (Table 1) (8). The numbers of withdrawal behaviors were compared between groups. Later, cervical dislocation was applied to the rats under mild ether anesthesia. The heart was included in Krebs-Henseleit solution [composed of (mM): NaCl 119, MgSO4 1.50, KCl 4.70, CaCl2 2.50, KH2PO4 1.20, Glucose 11, NaHCO3 25].

Preparation of isolated Organ Bath

3-4 millimeters long incisions were made from the atrium. Tissues were hung in the isolated organ bath with silk thread. Its tension was set to 2g. The krebs solution temperature is 37˚C and is continuously gassed (95% O_2 and 5% CO_2). Isometric tension values of the atrium sections were recorded with a transducer (MAY IOBS 99 Isolated Tissue Bath Stand Set Integrated Tissue Bath System, Turkey). After a 45-minute adaptation period, spontaneous isometric contractions were observed. 1 hour after hanging, contractions were induced with 0.001 M adrenaline solution. Tensions at the 15th minute before the administration of adrenaline and the 15th, 30th and 45th minutes after the administration were evaluated.

Histological Evaluation

The heart tissue of the rats was taken and placed in 10% formaldehyde. Tissue samples were embedded in paraffin. 5 µm thick sections were taken with microtom. Hematoxylene Eosin and Toluidine blue staining methods were applied to the sections. The prepared preparations were examined with light microscopy. The sections were histologically examined for myofibril loss in heart muscle, intracytoplasmic vacuolization, eosinophilic stained, picnotic nucleated cells and congestion. Mast cell and degranulation were investigated in preparations stained with Toluidine blue.

Statistical Method

Atrial contractions and withdrawal behaviors were evaluated. Mean and standard deviations were given for symmetrically distributed numeric data, while median values (25. percentile- 75. percentile) were given for non-symmetric numeric data. A mixed effect model was created to analyze the change of tension values between groups and over time. Group, Time and Group×Time effects were investigated. Poisson mixed effect models were used in the analysis of withdrawal findings. SAS University Edition 9.4 program was used for analyzes. $p<0.05$ was considered statistically significant.

RESULTS

Morphine Withdrawal Findings

In the analysis of morphine withdrawal score, a

Table 1. Modified Gellert and Holtzman Behavior Scale

Behavior or finding	Score	Behavior or finding	Score
1% body weight loss for each	1	Abnormal postures	3
Escape attempts 2-4 times	1	Squinting eyes	1
Escape attempts 5-9 times	2	Sneeze	1
Escape attempts 10-∞ times	3	Rolling movements	2
Wet dog shaking 1-2 times	2	Rearing	1
Wet dog shaking 3-4 times	4	Jumping	2
The number of defecations (diarrhea) per each	2	Body grooming	1
		Profuse salivations	7
Teeth chattering	2		

significant increase was observed in the comparison of the Group MN with the Group C and Group M (p<0.001). In the weight loss analysis, a significant increase was observed in the Group MN compared to the Group M (p<0.05). In the defecation number analysis, a significant increase was observed in the Group MN compared to the Group M and Group C (p <0.001). A significant increase was observed in the MN group compared to the Group C and Group M in the analysis of the number of cracking teeth (p <0.001). No significant differences were seen between the groups in the number of prancing, embellishment and escape attempts (p>0.05) There was an increase in the number of eyes squint in the Group MN compared to the Group M and Group C (p<0.05). An increase was seen in the comparison of the Group MN with the Group M and Group C in the number of abnormal posture (p<0.001). The number of genital grooming was higher in the Group MN than in the Group C and Group M (p<0.05). Wet dog shaking and rolling movements were more observed in the Group MN. But it was not statistically significant (p>0.05). Profuse salivations and sneeze were not observed in Group K and Group M, and were observed in Group MN. But it was not statistically significant (p>0.05) (Table 2).

Isolated Organ Bath Findings

The tension values before adrenaline administration were found to be higher in the Group M and Group MN compared to the Group C. However, the highest increase in the tension value between the 15th minute before induction with adrenaline and the 15th minute after the induction was in the Group C. In the other two groups, the amount of increase in these time periods and the tension value at the 15th minute after adrenaline were observed less (Fig. 1). There was no statistically significant difference in inotropic and chronotropic effects in the Group C, Group M and Group MN. As a result of the mixed effect model analysis, p=0.7085 for group-time, p=0.0005 for time, and p=0.9383 for the group, the result shows that the groups were similar to each other.

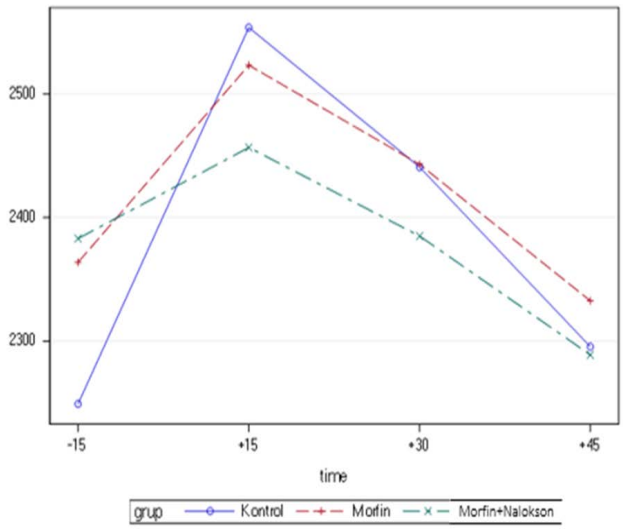


Figure 1. Comparison of induced in vitro atrial contractility in the Group C, Group M and Group MN by time.

Histological Findings

The heart muscle of Group C was monitored in a normal histological view (Fig. 2a). The heart muscle in the Group M and Group MN showed similar

Table 2. Social and demographic characteristics of the individuals.

	Control (10)	Morphine (11)	Morphine + naloxone (11)
Weight	258,60±41	302,55±25,99	303,64±33,95
Weight loss (g)	8,40±7,76	4,45±3,11	10,18±3,89
Escape Attempt	7,80±6	9,91±6,55	5,18±2,32
Wet dog shaking	0,00(0,00-0,00)	0,00±0,00	1,82±1,17
Defecation	1,50(0-3)	0,00(0,00-0,00)	7,73±3,04
Teeth chattering	0,00(0,00-0,00)	0,00(0,00-0,00)	4,91±1,92
Rolling movements	0,00±0,00	0,00(0,00-0,00)	0,00(0-1,00)
Profuse salivations	0,00±0,00	0,00±0,00	0,00(0,00-2,00)
Rearing	2,20±2,20	2,00(0-4,00)	0,00(0,00-0,00)
Body Grooming	5,10±1,60	3,18±1,66	4,09±2,47
Squinting eyes	1,80±1,48	1,00(0-2,00)	5,45±2,07
Sneeze	0,00±0,00	0,00±0,00	0,00(0-1,00)
Abnormal postures	0,00(0,00-0,00)	1,00(0-1,00)	3,09±1,30
Genital grooming	0,00(0,00-0,00)	0,00(0,00-0,00)	2,27±1,90
Withdrawal Score	14,80±6,05	10,64±2,62	34,09±4,28

Values are expressed as mean ± standard error.

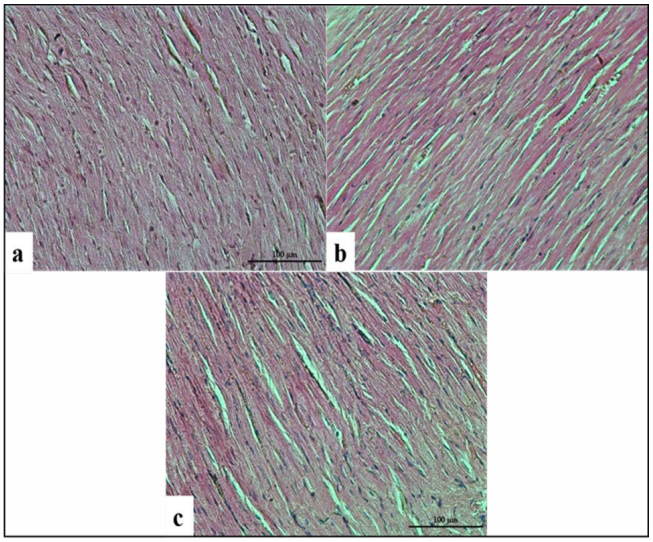


Figure 2. Hematoxylin-Eosin image **a)** Group C, **b)** Group M, **c)** Group MN

characteristics to the Group C (Fig. 2b, c). In Toluidine blue-dyed preparations, there was no difference in the number of mast cells of the Group C (Fig. 3a), Group M (Fig. 3b) and Group MN (Figure 3c). Degranulated mast cells were found in the Group MN (Fig. 3c).

DISCUSSION

The cardiovascular effects of opioids are controversial. Due to the connection between the heart and the central nervous system, adaptive changes that drugs make in the brain affect the heart pathways, neurotransmitters and adrenergic receptors expressed in the heart. Heart also has an intrinsic cardiac plexus that works independently, taking inferences from the cardiac sympathetic nervous system and the parasympathetic nervous system. Cardiac changes that occur after medication may be due to changes in intrinsic cardiac neurons (16).

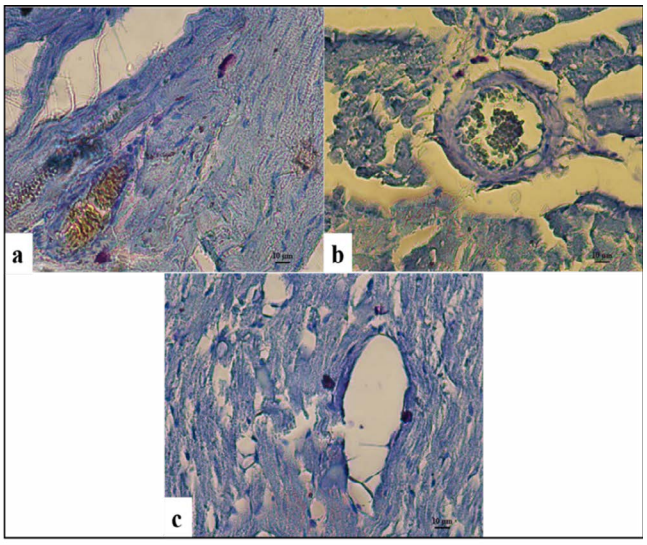


Figure 3. Toluidine Blue image **a)** Group C **b)** Group M **c)** Group MN

Scientific research about morphine is mostly in the central nervous system. In recent years, interest in the cardiovascular system has increased due to the cardioprotective effect of opioid endogenous and exogenous compounds in ischemic preconditioning (IPC). Opioids cause IPC, reduce apoptosis and ischemic reperfusion injury in myocytes. Thus, it improves ventricular function by reducing the infarct. In addition, μ-opioid receptor stimulation supports improvement of myocardial contractility in the post-ischemia period. Despite this therapeutic and protective effects during ischemic event, the chronic consumption effects of opioids are complicated (20).

Morphine is responsible for cardiovascular complications with histamine release. It leads to decreased cardiac output, hypotension, vasodilation, bradycardia (3). In the study conducted on dogs, it has been observed that morphine caused a decrease in systemic blood pressure, cardiac output, heart rate with histamine release and increased vagal effect (6).

There is evidence of a negative or positive inotropic effect of opioid receptor agonists on the myocardial function (31). There are also studies that say there is no direct effect on myocardial contractility (25). The inotropic effect that morphine does not alter contractions has been said to be unique to Kappa-type opioid agonists. It has been said that μ and δ opioid receptor agonists have no effect on contraction, whereas stimulation of κ opioid receptors reduces contraction through g (i/o) proteins (34). In another study, it has been observed that δ and κ opioid receptor agonists had a negative inotropic effect on left ventricular myocytes by causing changes in cell Ca homeostasis and IP3 production. It has been said that μ-opioid receptor stimulation has no significant effect on contractility (32).

There are also studies stating that μ-opioid receptor activation decreases the frequency of myocardial infarction with increased action potential duration and negative inotropic effects (21). In the study where morphine and noradrenaline were given cumulatively

to the atrium preparation in an isolated organ bath, it has been recorded that morphine increased the power of noradrenaline. It has been concluded that morphine acts presynaptically to increase noradrenaline release (30).

Morphine and heroin have been administered to the rabbit heart perfused in Langendorff device. It has been said that there is no significant change in contractility, chronotropic effect, systolic and diastolic ventricular pressure (6). It has been said that most opioids do not have a direct effect on cardiac contractility (4). While the endogenous opioid system is active in cardiac hypertrophy, it has been found that opioid receptor antagonists are not effective on contractility (33).

Morphine did not significantly affect inotropy and action potential in guinea pig, rabbit and human ventricular preparations. In a previous study examining the effects of morphine on rabbits, a small negative inotropic effect was observed that was eliminated by the addition of naloxone. However, morphine-induced negative inotropy was not seen in the presence of atenolol. Based on these results, it has been said that the effect of morphine on cardiac contractility mediates presynaptically by affecting the release of noradrenaline or acetylcholine from nerve termin. Another study has showed that the negative inotropic effects induced by opioids given in cumulative doses in organ baths were not antagonized by opioid antagonists. Thus, it has been suggested that cardiac effects are not mediated by opioid receptors and these effects may be due to sodium channel blocking actions (15).

It has been found that the cumulatively administered morphine in the organ bath does not cause a significant electrophysiological effect, but has little negative inotropic effect. Morphine has been thought to have no direct cardiac effects (11). In a study comparing the inotropic effects of morphine and ketamine on the canine right ventricle, it has been recorded that morphine did not make any significant inotropic changes even at high concentrations (29). In our study, morphine dependence and morphine withdrawal were performed in rats. Rat hearts were studied in an isolated organ bath. There was no statistically significant difference in myocardial contractility. It did not cause changes in chronotropic and inotropic effects.

Opioids have different arrhythmogenicity and data on morphine are scarce. Most of the studies confirm its safety for cardiac electrical activity when used in routine doses and are said to be low risk (3). There are also studies saying that morphine causes minimal cardiac arrhythmias and coagulation abnormalities by inducing histamine release (10). The frequency of atrial contraction has been investigated by intravenous administration of 30 mg/kg of morphine on the last day to rats treated with implantation of pellets (75 mg of morphine) for 7 days. It was concluded that acute administration of morphine to rats treated with morphine reduced the frequency of atrial contraction by leading to inhibition of neuronal catecholamine activity in the heart (23). No difference was observed in our study.

In a study, slight irregularities in the atrial and ventricular structures were observed in histological specimens, both after heroin and after administration of morphine (19). As a result of chronic opioid exposure, decreased sensitivity of the neurons in the respiratory center in the brainstem has caused a decrease in respiratory rate. Hypoxia has been observed in the heart tissue due to this decrease. Thus, the accumulation of fibrous connective tissue has caused thickening of the walls and stiffness of the tissue, leading to impairment cardiac contractility (27). In our study, the heart muscle was seen in normal histological appearance in all three groups. However, degranulated mast cells were found in places in the group that we created withdrawal.

Naloxone administration increased heart rate, mean aortic pressure, cardiac output, and myocardial contractility in dogs with congestive heart failure (12). In another study, two in vitro models were used to test the hypothesis that naloxone has a direct positive inotropic effect on heart muscle. In the first experiment, the isolated perfused rat heart has been given naloxone to the isolated rat atrium in the organ bath in the other. Both have been observed to provide a significant increase in the contraction amplitude. It has been said that this effect of naloxone is not related to opioid receptors, as it is not affected by pre-treatment with morphine (24).

While the main effects of opioids are on the autonomic and central nervous system, they affect many organ systems, including the respiratory and cardiovascular systems. The treatment and side effects of opioids on cardiovascular system are discussed. However, there are not many studies done to prove or refute these ideas (1). In a comprehensive animal model study by Schultz and Gross, it has been proven that finding different opioid receptors in the heart and minimizing the cardioprotective effects and

infarction size of opioid drugs such as morphine (26). However, many different studies have been stated that opioid use is a strong risk factor for cardiovascular problems (22).

CONCLUSION

Different opinions have been put forward in studies on the effect of opioids on myocardial contractility. Studies on the effect of opioids given in cumulative doses in organ baths on myocardium are available in the literature. However, there are deficiencies in the literature regarding the investigation of myocardiums with morphine addiction and withdrawal. In the present study, a morphine dependence model was established with 7 days of morphine administration and withdrawal with a single dose of naloxone administration. Chronotropic and inotropic effects, myocardial histology, behavioral changes caused by withdrawal were examined. Morphine withdrawal behaviors were seen in naloxone-treated rats. There were no statistically significant differences in inotropic and chronotropic effects. The heart muscle of the groups was observed in normal histological appearance. No change was seen in the number of mast cells. However, degranulated mast cells were found in places in the group that we created withdrawal.

It is thought that different results could be obtained by increasing the number of days and dose of morphine. The present study can provide insight into the literature as a primary source of inotropic chronotropic effects of opioid dependence and withdrawal on the cardiovascular system. These results may constitute a positive resource for the heart for systems analysis in morphine addicts. Further more and different scientific researches should be carried out with different parameters in order to obtain further information about the effects of addiction on the heart.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Z. Isik Solak Gormus, Necmettin Erbakan University, Meram Faculty of Medicine, Department of Physiology, Konya,Turkey*
e-mail: *igormus@gmail.com*

REFERENCES

1. Aghadavoudi O, Eizadi-Mood N, Najarzadegan M. Comparing cardiovascular factors in opium abusers and non-users candidate for coronary artery bypass graft surgery. Adv Biomed Res 2015;6(4):12.
2. Barkin RL, Barkin SJ, Barkin DS. Propoxyphene (Dextropropoxyphene): A critical review of a weak opioid analgesic that should remain in antiquity. Am J Ther 2006;13(6):534-42.
3. Behzadi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: A literature review. Med Princ Pract 2018;27(5):401-14.
4. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Med 2015;16(1):27-31.
5. Dorp ELA, Yassen A, Dahan A. Naloxone treatment in opioid addiction: The risks and benefits. Expert Opin Drug Saf 2007;6(2):125-32.
6. Frishman WH, Del Vecchio A, Sanal S, et al. Cardiovascular manifestations of substance abuse: Part 2: Alcohol, amphetamines, heroin, cannabis, and caffeine. Heart Dis 2003;5(4):253-71.
7. Fuardo M, Lemoine S, Lo Coco, et al. [D-Ala2,D-Leu5]-enkephalin (DADLE) and morphine-induced postconditioning by inhibition of mitochondrial permeability transition pore, in human myocardium. Exp Biol Med 2013;238(4):426-32.
8. Gellert VF, Holtzman S. Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. J Pharmacol Exp Ther 1978;205(3):536-46.
9. Grenald SA, Largent-milnes TM, Vanderah TW. Animal models for opioid addiction drug discovery. Expert Opin Drug Discov 2014;9(11):1345-54.
10. Guedes AGP, Rudé EP, Rider MA. Evaluation of histamine release during constant rate infusion of morphine in dogs. Vet Anaesth Analg 2006;33(1):28-35.
11. Helgesen KG, Refsum H. Arrhythmogenic, antiarrhythmic and inotropic properties of opioids. Effects of piritramide, pethidine and morphine compared on heart muscle isolated from rats. Pharmacology 1987;35(3):121-9.
12. Himura Y, Liang CS, Imai N, et al. Short-term effects of naloxone on hemodynamics and baroreflex function in conscious dogs with pacing-induced congestive heart failure. J Am Coll Cardiol 1994;23(1):194-200.
13. Koob GF, Moal ML. Addiction and the brain antireward system. Annu Rev Psychol 2008;59:29-53.
14. Levin CJ, Wai JM, Jones JD, et al. Changes in cardiac vagal tone as measured by heart rate variability during naloxone-induced opioid withdrawal. Drug Alcohol Depend 2019;1:204.
15. Llobell F, Laorden ML. Characterization of the opioid receptor subtypes mediating the negative ınotropic effects of DAMGO, DPDPE and U-50, 488H in isolated human right atria strips. Neuropeptide 1995;29(2):115-9.
16. Martínez-Laorden E, Navarro-Zaragoza J, Milanés MV, et al. Cardiac protective role of heat shock protein 27 in the stress induced by drugs of abuse. Int J Mol Sci 2020;21(10):1-12.
17. Masoudkabir F, Sarrafzadegan N, Eisenberg MJ. Effects of opium consumption on cardiometabolic diseases. Nat Rev Cardiol 2013;10(12):733-40.
18. Mishra PR, Barik M, Ray SB. Effect of nimodipine on morphine-related withdrawal syndrome in rat model: An observational study. J Pediatr Neurosci 2017;12(1):7-14.
19. Paterna S, Pasquale PDi, Montaina G, et al. Effect of heroin

and morphine on cardiac performance in isolated and perfused rabbit heart: Evaluation of cardiac haemodynamics, myocardial enzyme activity and ultrastructure features. Cardiologia 1991;36(10):811-5.
20. Peart JN, Gross ER, Gross GJ. Opioid-induced preconditioning: Recent advances and future perspectives. Vascul Pharmacol 2005;42(5-6):211-18.
21. Peart JN, Gross ER, Reichelt ME, et al. Activation of kappa-opioid receptors at reperfusion affords cardioprotection in both rat and mouse hearts. Basic Res Cardiol 2008;103(5):454-63.
22. Pur-Shahrıarı AA, Mills RA, Hoppin FG, et al. Comparison of chronic and acute effects of morphine sulfate on cardiovascular function. Am J Cardiol 1967;20(5)654-9.
23. Rabadan JV, Mılanés MV, Laorden ML. Effects of acute administration of morphine on right atrial catecholamine content and heart rate in chronically morphine-treated rats. Br J Anaesth 1997;78(4):439-41.
24. Sagy M, Shavit G, Oron Y, et al. Nonopiate effect of naloxone on cardiac muscle contractility. J Cardiovasc Pharmacol 1987;9(6):682-5.
25. Saunders WS, Thornhill JA. No inotropic action of enkephalins or enkephalin derivatives on electrically-stimulated atria isolated from lean and obese rats. Br J Pharmac 1985;85(2):513-22.
26. Schultz JE, Gross GJ. Opioids and cardioprotection. Pharmacol Ther 2001;89(2):123-37.
27. Seltenhammer MH, Marchart K, Paula P, et al. Micromorphological changes in cardiac tissue of drug-related deaths with emphasis on chronic illicit opioid abuse. Addiction 2013;108(7):1287-95.
28. Sobanski P, Krajnik M, Shaqura M. The presence of mu-, delta-, and kappa-opioid receptors in human heart tissue. Heart Vessels 2014;29(6):855-63.
29. Urthaler F, Walker AA, James TN. Comparison of the inotropic action of morphine and ketamine studied in canine cardiac muscle. J Thorac Cardiovasc Surg 1976;72(1):142-9.
30. Valcarcel MI, Ruiz F, Laorden ML. Interaction between morphine and noradrenalıne on isolated heart muscle. Gen Pharmacol 1991;22(4):577-9.
31. Vasko JS, Henney RP, Brawley RK, et al. Effects of morphine on ventricular function and myocardial contractile force. Am J Physiol 1966;210(2):329-34.
32. Ventura C, Spurgeon H, Lakatta EG, et al. Kappa and delta opioid receptor stimulation affects cardiac myocyte function and Ca+2 release from an intracellular pool in myocytes and neurons. Circ Res 1992;70(1):66-81.
33. Weil J, Zolk O, Griepentrog J, et al. Alterations of the preproenkephalin system in cardiac hypertrophy and its role in atrioventricular conduction. Cardiovasc Res 2006;69(2):412-22.
34. Wenzlaff H, Stein B, Teschemacher H. Diminution of contractile response by kappa-opioid receptor agonists in isolated rat ventricular cardiomyocytes is mediated via a pertussis toxin-sensitive G protein. Naunyn Schmiedebergs Arch Pharmacol 1998;358(3):360-6.
35. Wong GTC, Ling JL, Irwin MG. Activation of central opioid receptors ınduces cardioprotection against ıschemia-reperfusion ınjury. Anesth Analg 2010;111(1):24-8.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 136-142
DOI: 10.30733/std.2022.01560

NEÜ YAYINEVİ

The Effect of Waiting Time for Surgery after Hip Fractures and the Covid-19 Pandemic on Mortality

Kalça Kırıkları Sonrası Cerrahi Zamanlamanın ve Covid-19 Pandemisinin Mortaliteye Etkisi

Ahmet Fevzi Kekec[1], Alper Kirilmaz[1], Haluk Yaka[1], Tahsin Sami Colak[1], Halil Sezgin Semis[2]

[1]*Necmettin Erbakan University, Meram Faculty of Medicine, Department of Orthopaedics and Traumatology, Konya, Turkey*
[2]*Buhara Private Hospital, Department of Orthopaedics and Traumatology, Erzurum, Turkey*

Address correspondence to: Ahmet Fevzi Kekec, Necmettin Erbakan University, Meram Faculty of Medicine, Departmant of Orthopedics and Traumatology, Konya, Turkey
e-mail: afkekec@hotmail.com

Geliş Tarihi/Received: *24 June 2022*
Kabul Tarihi/Accepted: *25 July 2022*

Öz

Amaç: Bu çalışmanın amacı, kalça kırığı tanısı almış yaşlı hastalarımızda pandemi öncesi ve sonrasında ameliyata alınma süresinin değişip değişmediğini ve bu durumun mortalitede artışa neden olup olmadığını incelemektir.
Hastalar ve Yöntem: Mart 2019-Mart 2020 tarihleri arasında kalça kırığı tanısı ile opere edilen hastalar pandemi öncesi dönem, Nisan 2020-Nisan 2021 tarihleri arasında kalça kırığı tanısı ile opere edilen hastalar ise pandemi dönemi olarak kabul edildi. Her iki grup; yaş, cinsiyet, cerrahiye kadar geçen süre, hastanede kalış süresi ve bir yıllık mortalite açısından karşılaştırıldı.
Bulgular: Mortaliteyi etkileyen tüm faktörler incelendiğinde, ameliyata kadar geçen sürenin mortaliteyi anlamlı olarak artırdığını gösterdi. Ameliyat için ortalama bekleme süresi tüm hastalarda 27,6±19,4 saat iken Grup 1'de 25,7±19,1 saat ve Grup 2'de 29,6±19,6 saat olup iki grup arasında anlamlı fark vardı. (p=0.043). Mortaliteye neden olan cerrahi bekleme süresinin cut-off değeri "23.35" saat olarak hesaplandı. Grup 1'de mortalitede anlamlı artış saptanmazken (p=0.340), Grup 2'de cerrahi gecikmenin artması mortaliteyi anlamlı olarak etkiledi (p=0.027).
Sonuç: Bu çalışmada, yaşlı popülasyonda kalça kırığı sonrası 23.35 saatin üzerinde cerrahi başvuru gecikmesindeki artışın bir yıllık mortalite ile doğrudan ilişkili olduğu gösterilmiştir, ayrıca pandemi koşullarında ameliyat için bekleme süresindeki artışın direkt olarak mortaliteyi olumsuz etkileyen faktörlerden biri olduğu düşünülmektedir.

Anahtar Kelimeler: Kalça kırığı, mortalite, cerrahi zamanlama, covid-19 pandemisi

Abstract

Aim: The aim of this study is to examine whether the timing of surgery in our elderly patients with a diagnosis of hip fracture changed before and after the pandemic, and whether this situation caused an increase in mortality.
Patients and Methods: The patients who were operated with the diagnosis of hip fracture between March 2019 and March 2020 in our hospital database were accepted as in the pre-pandemic period, and the patients who were operated with the diagnosis of hip fracture between April 2020 and April 2021 were considered as in pandemic period. Both groups were statistically compared in terms of age, gender, waiting time for surgery, length of hospital stay and one year mortality.
Results: When the factors affecting mortality were examined, the time elapsed until surgery significantly increased mortality. While the mean waiting time for surgery was 27.6±19.4 hours in all patients, it was 25.7±19.1 hours in Group 1 and 29.6±19.6 hours in Group 2 and there was a significant difference between the two groups (p=0.043). The cut-off value of the waiting time for surgery, which caused mortality, was determined as "23.35" hours. While no significant increase in mortality was found in Group 1 (p=0.340), the increased delay for surgery in Group 2 affected mortality significantly (p=0.027).
Conclusion: In this study, it was found that the increase in the delay of admission for surgery over 23.35 hours in the elderly population after hip fractures was directly associated with one year of mortality and also we think that the waiting time for surgery in the pandemic conditions is one of the factors that negatively affect mortality in these patients.

Key words: Hip fracture, mortality, surgery timing, covid-19 pandemic

Cite this article as: Kekec AF, Kirilmaz A, Yaka H, Colak TS, Semis HS. The Effect of Waiting Time for Surgery after Hip Fractures and the Covid-19 Pandemic on Mortality. Selcuk Med J 2022;38(3): 136-142

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Hip fractures are serious health problem that incidence is constantly increasing with the increase in the elderly population. Studies show that 86% of patients who suffer hip fractures are in the 65 years and older group. Generally, low-energy traumas such as simple indoor falls are the most important etiological factor in hip fractures in the elderly population. One-year mortality in patients with hip fractures after 65 years of age ranges from 15% to 36% (1,2).

Health systems in many countries were adversely affected by the 2019 Coronavirus Disease Pandemic (Covid-19) (3). Many elective surgical procedures have also been postponed in our country to prevent the spread of the virus and to provide necessary care to infected patients. Even emergent surgical procedures were hampered by a lack of human resources and operating rooms. However, despite the mandatory quarantine measures during the Covid-19 Pandemic, the incidence of hip fracture did not change (4,5). In a few cohort studies with a limited number of patients, it was reported that there was no significant difference between the pandemic and pre-pandemic period in terms of surgical delay, treatment methods, complications, and 30-day mortality in hip fracture. (6,7). In a study by Cha et al., (8) it was shown that three-quarters of the delays in the timing of surgery are caused by factors related to the hospital, not the patient.

According to our clinical experience, since our intensive care beds were full due to virus infected patients during the Covid-19 pandemic, we often had problems in the timing of surgery due to the lack of reserved intensive care beds in the orthogeriatric high-risk patient group. Although there are conflicting results in the literature regarding the timing of hip fractures for surgery and their relationship with mortality, meta-analyses of these studies have shown that mortality increases as a result of various complications in patients who wait longer than 48 hours (9-11).

The aim of this study is to examine whether the timing of surgery in our elderly patients with a diagnosis of hip fracture changed with pandemic, and whether this situation caused an increase in mortality.

PATİENTS AND METHOD

The study was planned as a single-centered observational, descriptive, retrospective design. Ethics Committee Approval was obtained from Necmettin Erbakan University Ethics Committee (2022/3605). The patients who were operated with the diagnosis of hip fracture between March 2019 and March 2020 in Necmettin Erbakan University, Meram Faculty of Medicine hospital database were accepted as in the pre-pandemic period, and the patients who were operated with the diagnosis of hip fracture between April 2020 and April 2021 were considered as in pandemic period. As the inclusion criteria for the study; Patients over 60 years of age with intracapsular, extracapsular and intertrochanteric proximal femur fractures with an ASA score of 3 were determined. Patients with ASA 2 and ASA 4 scores were not included in the study to determine a more homogeneous sample, since clinical status is directly related to mortality. In addition, only patients who underwent regional anesthesia were included in the study in order to eliminate the effect of anesthesia techniques on mortality. The period before the World Health Organization (WHO) officially recognized Covid-19 as an international emergency on 11 March 2020 was considered pre-pandemic (12). Patients who were operated in the pre-pandemic period were determined as Group 1, and those operated in the pandemic period were determined as Group 2. Patients with multiple trauma, open fractures, pathological fractures, periprosthetic fractures, and pandemic patients who could be operated on quite late due to Covid19 positivity were not included in the study. Since Covid 19 infection is a serious cause of mortality especially in the elderly population, at follow up, patients who died due to the coronavirus infection during the pandemic period were not included in the study.

Demographic data of the patients, waiting time to surgery, ASA scores, surgical procedures, length of hospital stay were obtained from the hospital database records, while their one year mortality and causes of death were obtained from the records of the Department of Population and Citizenship. The primary outcome of the study was to determine whether the time to surgery affects mortality and whether there is a significant difference in terms of time to surgery and mortality in this patient group in the pre-pandemic and pandemic period.

In both patient groups, many variables were detected that could affect the delay in admission to surgery and their mortality. While these variables may be demographic variables such as age and gender, there may be additional diseases detected in the preoperative evaluation and preoperative clinical status (ASA score). In addition, there may be

institution-related factors, including the avaliability of surgical team and the operating theater, and especially the disruptions experienced in the provision of reserved intensive care for patients who will likely need intensive care during the pandemic period.

Data were analyzed by the International Business Machines Statistical Package for the Social Sciences (IBM SPSS) software package version 22.0 (IBM; Armonk, New York, USA). Qualitative data were defined using numbers and percentages. The Shapiro Wilk test was used to confirm the normality of the distribution. Quantitative data were defined using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). Mann-Whitney U-test and Pearson Chi Square test were used for statistical analysis between groups that did not fit normal distribution. The ROC curve was used to evaluate whether the time to surgery could be used as a predictor of mortality. Logistic regression analysis was made to evaluate causes of mortality. P-value of ≤ 0.05 was considered statistically significant.

RESULTS

The demographic data of the patients are summarized in Table 1. While the mean age of all patients included in the study was 81.9±6.9 (66-98), it was calculated as 82.7±7.1 in Group 1 and 81.2±6.7 in Group 2. Both groups are homogeneous in terms of age. While the time to surgery was 27.6±19.4 (1.1-114.1) hours in all patients, it was 25.7±19.14 hours (1.1-98.7) in Group 1 and 29.6±19.6 hours (10.8-114.1) in Group 2, and there was statistical difference between the two groups (p=0.043).

There was no significant difference between the two groups in terms of total hospital stay (p=0.405). Another parameter with significant difference between Group 1 and Group 2 is gender. While the male/female ratio was 1.17 in the pre-pandemic period, it was calculated as 0.63 during the pandemic period. The density of female patients in Group 2 was significantly higher than the patients in Group 1 (p=0.023). In terms of gender, both groups are not homogeneous. In terms of one year mortality, there is a statistically insignificant increase in the pandemic group (p=0.255).

All the patients included in the study in both groups are evaluated together in order to determine the main cause of mortality with logistic regresssion anlysis, the waiting time to surgery was found to be only significant cause of deaths (Table 2). When regression analysis was performed to find out the

Table 1. Characteristics of patient groups and demographic variables

Variables	Total n=217	Group 1 (Pre-pandemic) n=111	Group 2 (Pandemic) n=106	p
Age, mean ± SD (range)	81.9±6.9 (66-98)	82.7 ± 7.1 (66-98)	81.2 ± 6.7 (67-97)	0.139
Male, n, (%)	101 (%46.5)	60 (54%)	41 (35%)	0,023**
Female, n, (%)	116 (53.5%)	51 (46%)	65 (65%)	
Time to surgery, hour, mean ± SD (range)	27.6±19.4 (1.1-114.1)	25.7±19.1 (1.1-98.7)	29,6±19.6 (10,8-114,1)	0,043*
Length of stay, days, mean ± SD (range)	4.9±4,3 (0-57)	5.2±5.5 (0-57)	4.7±2.6 (2-19)	0,405
Mortality, n (%)	54 (%33)	24 (%28)	30 (%39)	0,255

Mann-Whitney U Test*, Pearson Chi square**

Table 2. Logistic regression analysis of factors affecting mortality in all patients

	Living (n=163)	Dead (n=54)	AOR	95% CI	p
Age, mean ± SD	81.6±6.9	83.1±6.9	1.037	0.989-1.087	0.137
Gender, n, M/F	77/86	24/30	0.823	0.432-1.568	0.554
Time to surgery, hour, mean ± SD	25.3±17.6	34.7±22.7	1.023	1.007-1.039	0.004*
Length of stay, days, mean ± SD	4.8±4.6	5.5±3.0	1.005	0.937-1.078	0.889
Pre-pandemic / Pandemic, n	87/24	76/30	1.407	0.733-2.701	0.304

Table 3. Logistic regression analysis of factors affecting mortality in the pre-pandemic and pandemic period

	Pre-pandemic Period (Group-1)					Pandemic Period (Group-2)				
	Living (n=87)	Dead (n=24)	AOR	95% CI	p	Living (n=76)	Dead (n=30)	AOR	95% CI	p
Age, mean±SD	82.4±7.3	83.9±6.3	1.036	0.969-1.107	0.306	82.4±7.3	83.9±6.3	1.047	0.976-1.123	0.201
Gender, M/F	47/40	12/12	0.787	0.313-1.979	0.610	30/46	12/18	1.030	0.399-2.659	0.951
Time to surgery, hour, mean±SD	24.9±19.1	28.6±19.2	1.011	0.988-1.035	0.340	25.6±15.8	39.4±24.4	1.027	1.000-1.054	0.027*
Length of stay, days, mean±SD	5.3±6.0	5.0±2.4	0.967	0.847-1.104	0.618	4.2±1.9	5.9±3.5	1.183	0.964-1.453	0.108

factors that cause mortality in Group 1 and Group 2 separately, no significant risk factor associated with mortality was detected in the prepandemic period, while increased delay of surgery during the pandemic period significantly increased mortality (p=0.027). (Table 3)

The cut-off value of the waiting time to surgery, which predicted mortality, was determined as “23.35” hours with a Sensitivity of 61.1% and a Specificity of 60.7% (Area Under the Curve = 0.644) when all patients were evaluated together. The mean waiting time to surgery in the pre-pandemic period was close to this cut-off (25.7±19.1 hours), it is remarkable that delay for surgery was increased by approximately 4 hours in the pandemic period and 6 hours away from the calculated cut-off value (29.6±19.6 hours) (Figure 1).

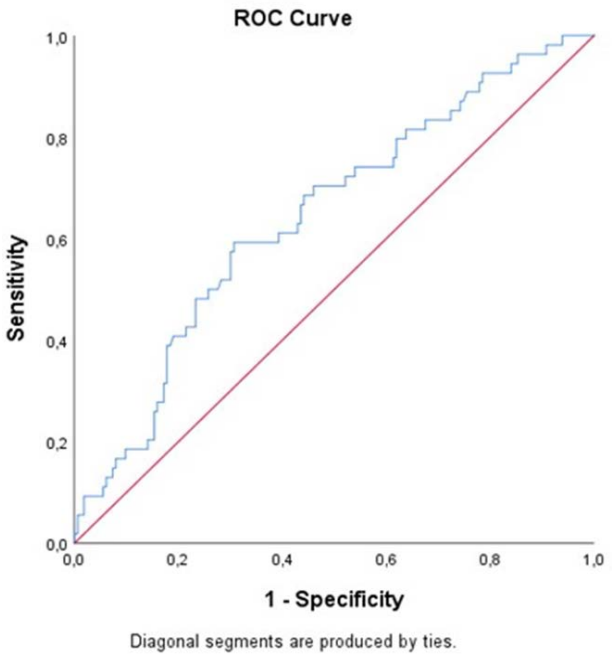


Figure 1. Roc analysis of the relationship between mortality and waiting time for surgery.

DISCUSSION

This study was conducted to examine whether the Covid-19 pandemic affects the waiting time for surgery in hip fractures associated with high morbidity and mortality in the elderly patient group, and the effects of this situation on mortality. Since hip fractures usually occur with low-energy traumas such as indoor simple falls in the elderly population, they were not affected by the measures and social isolation during the pandemic period, and the incidence of these fractures increased (13,14). The most important result of our study is that the mortality increased statistically with the increase in the waiting time for surgery and the Covid-19 Pandemic caused surgical delays in this patient group.

Although there are conflicting results in the literature regarding the time of hip fractures for surgery and their relationship with mortality, meta-analyses of these studies have shown that mortality increases as a result of various complications in patients who wait longer than 48 hours (9-11,15).

Some studies have revealed that the main reason for increasing mortality is the comorbidities and preoperative conditions of the patients rather than the waiting period (16). These delays in surgical timing have been explained by many reasons, including preoperative medical evaluations, optimization of patients' preoperative cardiovascular and pulmonary problems, access to the operating room room, and lack of reserved intensive care beds. In many countries with highly developed health systems, it has been reported that elderly patients with hip fractures are operated at least 24 hours after their admission to the emergency department (17). In a study conducted in France in 2010, the proportion of patients who were operated after 48 hours was around 47% - 60%, which is close to that observed in the United Kingdom (49%) (18). Even in protocols that accept hip fracture in the elderly as an indication for emergency surgery,

the rate of patients who underwent surgery after 48 hours exceeds 13% (19). In addition, delay in surgical timing does not only cause mortality; It has been shown in various studies that it also increases morbidities such as pressure ulcers, urinary system infections, deep vein thrombosis/embolism and the risk of cerebrovascular events (20,21). In a study by Cha et al., (8) it was shown that three-quarters of the delays in the timing for surgery are caused by factors related to the hospital resources, not the patient.

From the point of view of the Covid-19 Pandemic, we experienced some periods of semi-closure and some periods of full-closure in our country. During these periods, many hospitals throughout the country, including our hospital, were declared Pandemic hospitals and elective outpatient clinic applications and surgeries were suspended. Since elective surgery was not performed for a long time in our hospital, it can be said that more time can be allocated to emergent trauma cases and the delays are not due to access to the operating theater in this sense. However, patients infected with the Covid-19 virus filled the intensive care capacities of the hospital, and we experienced surgical delays in elderly hip fracture patients especially who may needed intensive care. In the literature, there are also studies in some cohort studies reporting that there is no significant difference in surgical delay, treatment methods, complications and 30-day mortality in hip fracture between the pandemic and pre-pandemic period (3,4), however, in our study 4 hours delay in waiting time for surgery during the pandemic period was detected (p=0.043). This delay in admission to surgery did not seem to increase mortality when the two groups were compared with each other (p=0.255). Although both groups are homogeneous in terms of age and ASA scores, they are not homogeneous in terms of gender (p=0.023). While the male/female ratio was 1.17 in the pre-pandemic period, it was calculated as 0.63 during the pandemic period. Long-term survival analyzes reveal that mortality is strongly higher for men than for women, even when factors such as age and comorbidities are controlled (22). Considering the mortality-increasing effect of male gender, the fact that we did not detect an increase in mortality during the pandemic period compared to the pre-pandemic period may be due to the heterogenity of our groups in this sense. When both groups are evaluated separately in terms of surgical timing and mortality, although surgical delays in the pre-pandemic period did not increase mortality, in the post-pandemic period mortality may have increased significantly since the cut-off value we obtained was exceeded by approximately 6 hours (p=0.027). There are studies in the literature showing that long-term (12-month) mortality increases statistically significantly when the cut-off value is calculated in 24 hours, similar to our study (20,23,24). In this sense, our results support the literature.

When Polimerase Chain reaction (PCR) tests for Covid-19 and variants became standardized in the pandemic period, PCR test samples were routinely taken from patients who admitted to Emergeny Department. If the result was positive, we transferred these patients to Infectious Disease Ward for their treatment. At the end of the treatment, after the PCR results were negative, we performed the surgeries in accordance with the Covid-19 protection rules against virus transmission. In an international study published in The Lancet Journal, higher mortality rates were reported in patients operated on with co-existing Covid-19 infection (25), so preoperative waiting times of approximately 15 days have to be occurred in these patients. Since we have a few patients who were treated in this way, and in terms of the mortality of the virus infection rather than the long waiting times of these patients, we excluded these patients in order not to deviate from the focus of the study. The mortality of these group of patients can be an another subject of a study.

As another outcome of our study, the length of hospital stay was not found to be associated with mortality when both groups were evaluated together. The increase in the length of hopital stay was affected by the time spent preoperatively for optimization of patient for surgery, hospitalizations in the intensive care unit and the orthopaedic ward postoperatively. In the pre-pandemic period, we could not find a positive relationship with surgical delay in mortality, and no relationship was found between length of hospital stay and mortality. However, it has been shown that our patients who were mortal during the Pandemic were hospitalized for a longer time but results were not statistically significant (p=0.108). There are conflicting views on this issue in the literature. Nikkel et al. (26) conducted a study in the American population and lower early mortality was found in elderly hip fractures who stayed in the hospital for less than 5 days compared to those who stayed in the hospital for 10-15 days, on the contrary, in a study conducted in the Swedish population fewer hospitalization time caused an increased mortality in patients who were

stay in hospital less than 10 days (27). It is thought that discharge protocols in different country health systems and some other comorbidities are more associated with mortality.

The most important limitation of the study is that it was designed retrospectively. In addition, although the groups are homogeneous in terms of factors such as chronic diseases (ASA scores) and age, which may affect mortality, both groups are not homogeneous in terms of gender. Since our sample size would not allow for meaningful statistical analysis, subgroup analyzes were not performed in terms of factors such as age, gender, physical condition, comorbid diseases, surgical technique, surgical duration, and amount of bleeding etc. In addition, patients with a very small number of Covid positive diagnoses in the pandemic and who had serious surgical delays (over 10 days) due to Covid-19 treatment were not included in the study because it would cause a serious deviation in the means and this disease is a cause of high mortality in this age group. Although these deaths due to Covid-19 infection were not included in the study, they may have an indirect effect of this disease on the increase in mortality rates, since Covid-19 has serious morbidity and PCR negative deaths are not recorded as Covid deaths in the records of the Department of Population and Citizenship. When calculating the delays in the time of admission for surgery, the extra time spent by patients admitted from other centers was ignored. Data analysis was not conducted on whether the number of referred patients during the pandemic period differed from the pre-pandemic period.

As a conclusion, despite all it's limitations, in this study, it was found that the increase in the delay of admission for surgery over 23.35 hours in the elderly population after hip fractures was directly associated with one yaer mortality and also we think that the delay in time for surgery in the pandemic conditions is one of the factors that negatively affect mortality in these patients.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Ahmet Fevzi Kekec, Necmettin Erbakan University, Meram Faculty of Medicine, Departmant of Orthopedics and Traumatology, Konya, Turkey*
e-mail: *afkekec@hotmail.com*

REFERENCES

1. Civinini R, Paoli T, Cianferotti L, et al. Functional outcomes and mortality in geriatric and fragility hip fractures-results of an integrated, multidisciplinary model experienced by the "Florence hip fracture unit". Int Orthop 2019;43(1):187-92.
2. Mariconda M, Costa GG, Cerbasi S, et al. The determinants of mortality and morbidity during the year following fracture of the hip: A prospective study. Bone Joint J 2015;97-B(3):383-90.
3. WHO. Coronavirus disease (COVID-19) pandemic. 2020. Available from: http://www.who.int/covid-19
4. Das De S, Puhaindran ME, Sechachalam S, et al. Sustaining a national surgical training programme during the COVID-19 pandemic. Bone Jt Open 2020;1(5):98-102.
5. Mathai NJ, Venkatesan AS, et al. COVID-19 and orthopaedic surgery: Evolving strategies and early experience. Bone Jt Open 2020;1(5):160-6.
6. Chui K, Thakrar A, Shankar S. Evaluating the efficacy of a two-site ('COVID-19' and 'COVID-19-free') trauma and orthopaedic service for the management of hip fractures during the COVID-19 pandemic in the UK. Bone Jt Open 2020;1(6):190-7.
7. Segarra B, Ballesteros Heras N, Viadel Ortiz M, et al. Are hospitals safe? A prospective study on SARS-CoV-2 Prevalence and outcome on surgical fracture patients: A closer look at hip fracture patients. J Orthop Trauma 2020;34(10):e371-6.
8. Cha YH, Ha YC, Yoo JI, et al. Effect of causes of surgical delay on early and late mortality in patients with proximal hip fracture. Arch Orthop Trauma Surg 2017;137(5):625-30.
9. Shiga T, Wajima Z, Ohe Y. Is operative delay associated with increased mortality of hip fracture patients? Systematic review, meta-analysis, and meta-regression. Can J Anaesth 2008;55(3):146-54.
10. Moja L, Piatti A, Pecoraro V, et al. Timing matters in hip fracture surgery: Patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. PLoS One 2012;7(10):e46175.
11. Klestil T, Röder C, Stotter C, et al. Impact of timing of surgery in elderly hip fracture patients: A systematic review and meta-analysis. Sci Rep 2018;8(1):13933.
12. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report. Updated 12 January 2021 Accessed March 21, 2021.7
13. Oguzkaya S, Misir A, Ozcamdalli M, et al. Impact of the COVID-19 pandemic on orthopedic fracture characteristics in three hospitals in Turkey: A multi-center epidemiological study. Jt Dis Relat Surg 2021;32(2):323-32.
14. Kamacı S, Göker B, Çağlar Ö, et al. The effect of the COVID-19 pandemic on orthopedic surgeries in a tertiary referral center. Jt Dis Relat Surg 2021;32(2):333-9.
15. Simunovic N, Devereaux PJ, Sprague S, et al. Effect of early surgery after hip fracture on mortality and complications: Systematic review and meta-analysis. CMAJ 2010;182(15):1609-16.
16. Greve K, Modig K, Talbäck M, et al. No association between waiting time to surgery and mortality for healthier patients with hip fracture: A nationwide Swedish cohort of 59,675 patients. Acta Orthop 2020;91(4):396-400.
17. Hip fracture accelerated surgical treatment and care track (HIP ATTACK) investigators. Accelerated care versus

standard care among patients with hip fracture: The HIP ATTACK pilot trial. CMAJ 2014;186(1):E52-60.
18. White SM, Griffiths R, Holloway J, et al. Anaesthesia for proximal femoral fracture in the UK: First report from the NHS hip fracture anaesthesia network. Anaesthesia 2010;65(3):243-248.
19. Boddaert J, Cohen Bittan J, Khiami F, et al. Postoperative admission to a dedicated geriatric unit decreases mortality in elderly patients with hip fracture. PLoS One 2014;9(1):e83795.
20. Al Ani AN, Samuelsson B, Tidermark J, et al. Early operation on patients with a hip fracture improved the ability to return to independent living. A prospective study of 850 patients. J Bone Joint Surg Am 2008;90(7):1436-42.
21. Mariconda M, Costa GG, Cerbasi S, et al. The determinants of mortality and morbidity during the year following fracture of the hip: A prospective study. Bone Joint J 2015;97-B(3):383-90.
22. Kannegaard PN, van der Mark S, Eiken P, et al. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing 2010;39(2):203-9.
23. Orosz GM, Magaziner J, Hannan EL, et al. Association of timing of surgery for hip fracture and patient outcomes. JAMA 2004;291(14):1738-43.
24. Maggi S, Siviero P, Wetle T, et al. A multicenter survey on profile of care for hip fracture: Predictors of mortality and disability. Osteoporos Int 2010;21(2):223-31.
25. COVID surg collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: An international cohort study [published correction appears in Lancet 2020 Jun 9;:]. Lancet 2020;396(10243):27-38.
26. Nikkel LE, Kates SL, Schreck M, et al. Length of hospital stay after hip fracture and risk of early mortality after discharge in New York state: Retrospective cohort study. BMJ 2015;351:h6246.
27. Nordström P, Gustafson Y, Michaëlsson K, et al. Length of hospital stay after hip fracture and short term risk of death after discharge: A total cohort study in Sweden. BMJ 2015;350:h696.

Araştırma Makalesi / Research Article

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
Selcuk Med J 2022;38(3): 143-147
DOI: 10.30733/std.2022.01562

Evre II Sarkoidoz'lu Hastalarda Ana Pulmoner Arter Çapının Çok Kesitli Bilgisayarlı Tomografi ile Değerlendirilmesi

Evaluation of Main Pulmonary Artery Diameter by Multislice Computed Tomography in Patients with Stage II Sarcoidosis

Pınar Diydem Yılmaz[1], Sevinç Kalın[2], Mevlüt Hakan Göktepe[3]

[1]Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Radyoloji Anabilim Dalı, Konya, Türkiye
[2]Sağlık Bilimleri Üniversitesi, İstanbul Ümraniye Eğitim ve Araştırma Hastanesi, Radyoloji Anabilim Dalı, İstanbul, Türkiye
[3]Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Konya, Türkiye

Yazışma Adresi: Pınar Diydem Yılmaz, Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Radyoloji Anabilim Dalı, Konya, Türkiye
e-posta: pinardidemyilmaz@hotmail.com

Geliş Tarihi/Received: *25 Mayıs 2022*
Kabul Tarihi/Accepted: *8 Temmuz 2022*

Öz

Amaç: Non- kazeifiye granülomlar ile karakterize sistemik granülomatöz bir hastalık olan sarkoidozun tanısında ve prognozunu belirlemede akciğer grafisi ve toraks bilgisayarlı tomografi (BT) önemli bir yer tutmaktadır. Hastalığın nadir bir komplikasyonu olan pulmoner hipertansiyon tüm evrelerde görülebilmektedir. Pulmoner hipertansiyon (PH) ile ana pulmoner arter çapındaki (APAÇ) artış arasında güçlü bir ilişki bulunmaktadır. Bu çalışmamızda evre II sarkoidozlu hastalarda erken dönemde PH tanısı için çok kesitli BT incelemesi ile APAÇ' ı değerlendirmeyi amaçladık.
Hastalar ve Yöntem: Görüntülemelerinde hiler lenfadenopati ve parankimal değişikliklerin olduğu, ocak-2018 ile aralık-2021 tarihleri arasında hastanemizde sarkoidoz tanısı ile takip edilen Evre II sarkoidozlu hastalarda toraks BT'de ana pulmoner arter çapını ölçerek akciğer grafisi normal olup nonspesifik semptomlarla toraks BT çekilmiş kontrol grubu ile karşılaştırdık. Evre II sarkoidozlu hastaların Ekokardiyografi (EKO) ile elde edilmiş pulmoner arter basınçları ile ana pulmoner arter çapı arasındaki ilişkiyi değerlendirdik.
Bulgular: Sarkoidozlu hastalarda kontrol grubuna kıyasla APAÇ artışı ve EKO ile ölçülen pulmoner arter basıncı ile bu grup hastalardaki BT'den ölçülmüş olan pulmoner arter çapı arasında anlamlı bir ilişki tespit ettik.
Sonuç: Sarkoidozlu hastalarda BT ile pulmoner arter çapının değerlendirilmesinin PH gelişimi konusunda yol gösterici olabileceği dolayısıyla erken dönemde müdahele fırsatı sunacağı kanısındayız.

Anahtar Kelimeler: Sarkoidoz, pulmoner arter çapı, bilgisayarlı tomografi

Abstract

Aim: Chest radiography and thoracic computed tomography (CT) play an important role in the diagnosis and prognosis of sarcoidosis, a systemic granulomatous disease characterized by non-caseating granulomas. Pulmonary hypertension, a rare complication of the disease, can be seen in all stages. There is a strong correlation between pulmonary hypertension (PH) and an increase in the diameter of the main pulmonary artery (MPAD). In this study, we aimed to evaluate MPAD with multislice computed tomography (CT) examination for the early diagnosis of PH in patients with stage II sarcoidosis.
Patients and Methods: We measured the diameter of the main pulmonary artery on thorax CT in patients with stage II sarcoidosis, who were followed up in our hospital with a diagnosis of sarcoidosis between January-2018 and December-2021, with hilar lymphadenopathy and parenchymal changes in their imaging, and compared them with the control group, whose chest X-ray was normal and thorax CT scan was performed with nonspecific symptoms. We evaluated the relationship between the pulmonary artery pressures obtained by echocardiography and the diameter of the main pulmonary artery in patients with stage II sarcoidosis
Results: We found a significant correlation between the increase in MPAD and pulmonary artery pressure measured by ECHO in patients with sarcoidosis compared to the control group, and the pulmonary artery diameter measured by CT in this patient group.
Conclusion: We think that CT evaluation of pulmonary artery diameter in patients with sarcoidosis can guide the development of PH and therefore offer an opportunity for early intervention.

Key words: Sarcoidosis, pulmonary artery diameter, computed tomography

Atıf yapmak için: Yılmaz PD, Kalın S, Göktepe MH. Evre II Sarkoidoz'lu Hastalarda Ana Pulmoner Arter Çapının Çok Kesitli Bilgisayarlı Tomografi ile Değerlendirilmesi. Selcuk Med J 2022;38(3): 143-147

Açıklama: *Yazarların hiçbiri, bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi. Yazarlar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedirler.*

GİRİŞ

Sarkoidoz non-kazeifiye granülomlarla seyreden nadir sistemik granülomatöz bir hastalıktır (1), hedef organ %90 akciğerdir (1,2). Hastaların yaklaşık yarısı asemptomatiktir. Akciğer tutulumu olan semptomatik hastalarda en sık öksürük ve dispne görülür. Akciğer grafisi ve toraks BT; tanıda, hastalığın prognozunun belirlenmesinde ve bazı durumlarda gereksiz biyopsiden kaçınılmasında önemli bir yere sahiptir (1). Tanı, tipik klinik bulguların varlığı ve histopatolojik olarak non-kazeifiye granülomların gösterilmesi ile benzer klinik özelliklere ve patolojiye sahip hastalıkların dışlanması ile konulur (2,3). Sarkoidozda prognostik değerlendirme dört aşamalı bir evreleme sistemine dayanmaktadır (3). Scadding tarafından yaklaşık altmış yıl önce 1961'de tasarlanan radyografik görünüme dayalı bu evreleme tablo 1'de özetlenmiştir.

Pulmoner hipertansiyon (PH), ciddi akciğer tutulumu olan hastalarda sarkoidozun nadir bir komplikasyonu olarak görülebilir. Henüz pulmoner fibrozis gelişmemiş sarkoidozlu hastalarda da önemli bir dispne nedenidir (4). Dünya Sağlık Örgütü (WHO) pulmoner hipertansiyon sınıflamasına göre sarkoidoza bağlı PH Grup 5'te yer almaktadır. 5. Grup başlığı belirsiz/multifaktöriyel mekanizmalarla ilişkili diğer PH'lardır (5). Sarkoidoz ile ilişkili PH, artan mortalite oranları ile ilişkilidir. Her evrede görülebilmesine rağmen sıklığı sarkoidozun şiddetine bağlıdır (6,7). Vasküler hastalık, pulmoner emboli, postkapiller PH, eksternal kompresyon ve sarkoidozla ilişkili diğer komorbiditeler gibi mekanizmalar PH'a katkıda bulunabilir (8). Evre II sarkoidozlu hastalarda bilateral hiler lenadenopatiye, parankimal nodüller ve parankimal infiltratlar eşlik eder (9). Evre 2 sarkoidozlu hastalarda pulmoner hipertansiyon etiyolojisinde hiler lenfadenopatilerin eksternal kompresyonu ve parankimal tutuluma bağlı artmış postkapiller basınç yer alır.

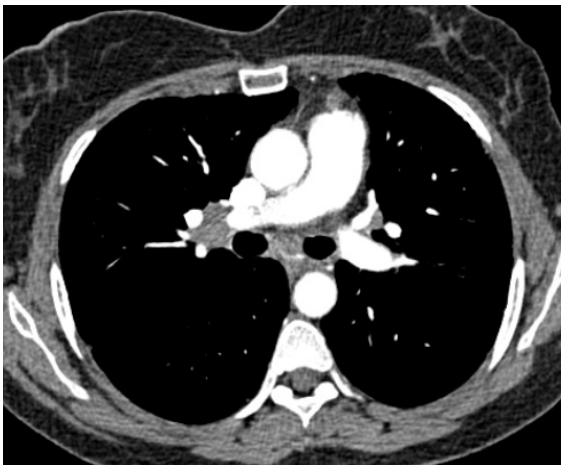
Pulmoner hipertansiyon tanısı, sağ kalp kateterizasyonu ile ana pulmoner arterden elde edilen basıncın 25 mmHg'nin üzerine çıkması ile konur (10, 11). Pulmoner arter basıncı ekokardiyografi (EKO) ile de ölçülebilir, ancak tanı için etkili bir yöntem değildir. Non-invaziv bir yöntemdir ve hastalığın ayırıcı tanısında ve takibinde kullanılır (5). Ek olarak, hangi hastalara sağ kalp kateterizasyonu yapılması gerektiğine karar vermek için EKO kullanılmaktadır (10).

Pulmoner hipertansiyonlu hastalarda ana pulmoner arter çapında artış gösterilmiştir (12). Toraks BT'de pulmoner arter çapı; aksiyel kesitlerden, bifurkasyon düzeyinde uzun eksene dik olarak ölçülür. PH'de ana pulmoner arter çapı genellikle 29 mm'den büyük ve aynı seviyedeki çıkan aortadan daha geniştir. Pulmoner arter/aorta oranı >1'dir (13). Bu çalışmamızda evre II sarkoidozlu hastalarda erken dönemde PH tanısı için çok kesitli BT incelemesi ile APAÇ' ı değerlendirmeyi amaçladık.

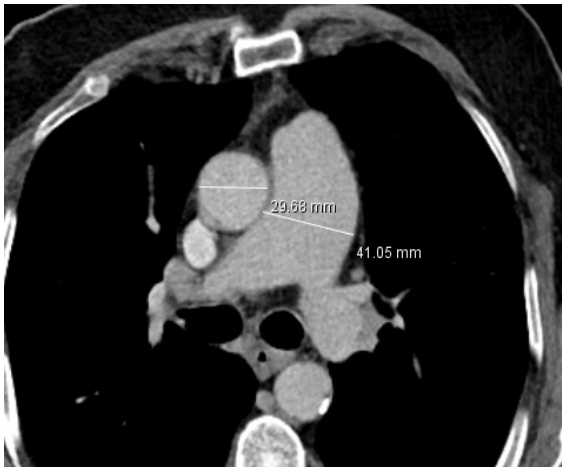
HASTALAR VE YÖNTEM

Ocak-2018 ile Aralık-2021 tarihleri arasında hastanemizde sarkoidoz tanısı ile takip edilen, görüntülemelerinde hiler lenfadenopati ve parankimal değişikliklerin olan evre II sarkoidozlu hastaların toraks BT'de ana pulmoner arter çapını ölçerek akciğer grafisi normal olup nonspesifik semptomlarla toraks BT çekilmiş kontrol grubu ile karşılaştırdık. Evre II sarkoidozlu hastaların Ekokardiyografi (EKO) ile elde edilmiş pulmoner arter basınçları ile ana pulmoner arter çapı arasındaki ilişkiyi değerlendirdik. Hastaların akciğer grafileri Scadding sınıflamasına göre sınıflandırıldı. Sarkoidoz tanısı ile takip edilen hastaların akciğer grafilerinin (Şekil 1) değerlendirilmesi sonucunda evre II sarkoidoz olarak sınıflandırılan 28 hasta çalışma grubumuza alındı. Kontrol grubuna, radyoloji kliniğimize nonspesifik semptomlarla başvuran, akciğer grafisi normal ve toraks BT'si olan 34 hasta dahil edildi. Geçirilmiş akciğer ya da kardiyak cerrahisi hikayesi bulunan hastalar, toraksa yönelik radyoterapi uygulanmış

Şekil 1. 63 yaşında Evre 2 sarkoidozlu hastanın PA Akciğer Grafisi; Hiler lenfadenopatiler ve akciğer parankiminde retiküler patern



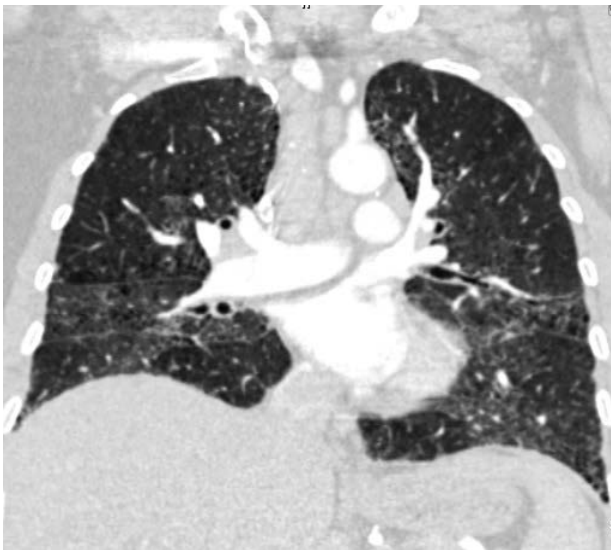
Şekil 2. Evre 2 Sarkoidozu olan 45 y kadın hastanın aksiyel kontrastlı toraks BT incelemesinde lenfadenopatiler



Şekil 4. 70y Evre 2 sarkoidozlu hastada pulmoner arter çapının ölçümü ve artmış pulmoner arter/ aorta oranı

hastalar, belirgin kifoz yada skolyoz deformitesi bulunan hastalar çalışmaya dahil edilememiştir.

Tüm toraks BT çekimleri Somatom Drive (Siemens Healthineers) ile yapılmış olup Kontrastlı BT incelemesi akciğer apeksi ile bazali arasını içine alacak şekildedir. Tarama parametreleri: tüp voltajı, 120 kV; tüp current-time product, 50 - 100 mAs; pitch, 0,6; matrix, 512×512; kesit kalınlığı, 3 mm, rekonstrukte kesit kalınlığı, 1,5 mm. Görüntüler Syngo Via Workstation (Siemens Healthineers)da mediasten penceresinde (width: 300 - 350 HU, level: 30 - 40 HU) değerlendirildi. Ölçümler toraks radyolojisi konusunda 8 yıllık deneyimi bulunan radyoloji uzmanı tarafından yapılmıştır. Kontrastlı toraks BT tetkiklerinde mediasten penceresi kullanılarak 3 mm kesitler kullanılarak pulmoner arter bifurkasyonu düzeyinde uzun eksene dik en geniş transvers çap ölçülerek (Şekil 2-4) not edildi. Daha sonra elde edilen ortalama değer hem sarkoidozlu hasta grubu hem de kontrol grubu için karşılaştırıldı.



Şekil 3. Evre 2 Sarkoidozu olan 45 y kadın hastanın koronal reformat toraks BT parankim penceresinde akciğer parankiminde izlenen değişiklikler

Sarkoidoz tanısı bulunan hastaların arşiv dosyaları taranmasını takiben 28 hastanın EKO ile elde edilmiş pulmoner arter basınç ölçüm sonuçlarına ulaşıldı ve bu değerler ile BT'de ölçümü yapılan pulmoner arter çapı arasındaki ilişki karşılaştırıldı. Ayrıca yine sarkoidozlu hasta grubunda yer alan erkek ve kadın hastalar için hem PA basıncı hem de pulmoner arter çapı karşılaştırıldı. Çalışma için 2022/3676 sayılı lokal etik kurul onayı alındı.

İstatistiksel analiz SPSS 20.0. Versiyonu ile yapılmıştır. Verilerin homojen bir dağılım gösterip göstermediği Kolmogorov-Smirnov testi ile değerlendirildi. Homojen veriler student t- testi, homojen olmayan veriler ise Mann-Whitney U-testi ile değerlendirildi. <0,05 P değeri anlamlı kabul edildi.

BULGULAR

Evre II sarkoidozlu hasta grubunda ortalama yaş 37,33 ± 12,4, kontrol grubunda ise ortalama yaş 39,1 ± 13,2 idi. Sarkoidoz hasta grubunda 23 kadın ve 11 erkek hasta yer almaktaydı. Her iki grupta yaş ve cinsiyet dağılımları arasında anlamlı fark

Tablo 1. Scadding Sarkoidoz Evrelemesi

Evre	Bulgular (PAAG [1])	Tanı anında hasta %si
0	Normal	-
1	Lenf nodu büyümesi	%5-15
2	1. + Parankimal değişiklikler	%45-65
3	Parankimal değişiklikler	%30-40
4	Fibrozis	%5

PAAG [1]: Posteroanterior akciğer grafisi

bulunmamaktaydı (p=0.022). Sarkoidoz tanısı ile takip edilen hastalardan oluşan ilk grupta ortalama APAÇ 30.6 ±2.7 mm, kontrol grubunda ise 24.4 ±2.2 mm olarak ölçülmüştür. Elde edilen değerler karşılaştırıldığında sarkoidozlu hastalarda kontrol grubuna kıyasla APAÇ artışı tespit edilmiş olup bu fark, istatistiksel olarak anlamlı bulunmuştur (p<0.05). Çalışmaya dahil edilen sarkoidoz tanılı hastaların dosya taramasını takiben 28 hastada EKO yapıldığı tespit edilmiş olup ortalama PA basıncı 28.18±5.26 mmHg (min-max: 23 ve 43) olarak saptanmıştır. Ayrıca EKO ile ölçülen pulmoner arter basıncı ile bu grup hastalardaki BT'den ölçülmüş olan pulmoner arter çapı arasında anlamlı bir ilişki tespit edilmiştir (p<0.001). Sarkoidoz tanısı bulunan hasta grubundaki kadın ve erkek hastalar arasında pulmoner arter çapı ve EKO incelemesi bulunan hasta grubunda ise pulmoner arter basınçları arasında anlamlı fark bulunmamaktaydı.

TARTIŞMA

Sarkoidozda PH'nin tanısının konulması ve tedavisi oldukça karmaşıktır ve bu nedenle sarkoidoz konusunda deneyimli bir merkezde multidisipliner yaklaşımla uzman ekip tarafından yapılmalıdır (14,15). Sarkoidoz tanısı olan ve PH gelişime riski taşıyan hastaları tespit etmek hala büyük bir problemdir. PH şüphesi olan bir hastanın tanı ve tedavi sürecinin algoritması konusunda onaylanmış bir protokol yoktur. Ayrıca sarkoidoz tanısı olan hastalarda da PH için belirlenmiş bir tedavi yoktur. (15).

Sarkoidozlu hastalarda, kronik hipoksi ve fibrozise bağlı olarak distal kapiller yatakta oluşan vazokonstriksiyon ve arter duvarında kazeifiye olmayan granülomların birikmesi sonucu PH gelişebilir (9). Ayrıca perivasküler fibrozis ve lenfadenopatiler pulmoner artere bası yapmaktadır (14). Sarkoidozlu hastalarda öksürük ve dispne semptomlarının altında bazı hastalarda pulmoner hipertansiyon yatmaktadır. Pulmoner hipertansiyona bağlı pulmoner arter çapı artışı önemli bir radyolojik bulgudur. Huitema (15) sarkoidoz tanılı hastalarda yaptığı çalışmada; pulmoner arter çapının 29 mm'den büyük olmasının, pulmoner arter/aorta çapına oranının 1'den büyük ya da eşit olmasını PH'nin bulgusu olduğunu ifade etmiştir. Bizim çalışmamızda sarkoidozlu hasta grubunda elde ettiğimiz değerler Huitema'nın çalışmasının sonuçları ile korelasyon göstermektedir. Yine Galie (10) sarkoidozlu hastalarda yaptığı çalışmasında pulmoner arter çapındaki artıştan bahsetmektedir. Pulmoner arter çapı birçok çalışmaya konu olmuştur. Kuriyama (16) pulmoner arter çapını 24,2 ± 2,2 mm, Gunthaner (17) ise 28 ± 0,3 mm olarak belirlemiştir. Çalışmamızda kontrol grubunda ortalama ana pulmoner arter çapı 24,4 ± 2,2 mm olarak saptandı ve bu değer normal popülasyon sonuçlarıyla uyumludur. Ekokardiyografi, PH analizinde bilgisayarlı tomografi ile birlikte önemli rol oynar (7,15). Ekokardiyografik incelemede PH tanısı için kullanılan parametreler içinde doppler inceleme ile ölçülebilen pik triküspit regürjitasyon hızı (TRV) ve sağ atriyum basıncına dayanan sistolik PA basıncı değerlidir. Burada önemli olan bu ölçülen değerin kateterizasyon ile elde olunan gerçek değerden daha fazla veya daha az tahmin

Tablo 2. Evre 2 Sarkoidoz tanılı hasta grubu ve kontrol grubu verileri

	Evre 2 Sarkoidoz hasta grubu	Kontrol grubu	
Yaş ortalaması	37,33±12,4	39,1±13,2	
Ana pulmoner arter çapı (APAÇ)[1]	30,6±2,7	24,4±2,2	p<0.05
Pulmoner arter basıncı (PAB)[2]	28.18±5.26		

[1]Ana pulmoner arter çapı mm olarak ölçülmüştür.
[2]Pulmoner arter basıncı EKO ile ölçülen verilere dayanmaktadır.

edebilir olduğu gerçeği göz önünde bulundurulmalıdır (13,15).

Sarkoidoz ve diğer fibrotik akciğer hastalıklarında PH için erken teşhis yönteminin geliştirilmesine ihtiyaç vardır (6). Bu komplikasyonu öngörebilecek non-invaziv yöntemlerin başında ise BT yer almakta olup bizim çalışmamızda da BT ile PH gelişme olasılığını takipte APAÇ ölçümünün önemli olduğu vurgulanmaktadır.

Sonuç olarak; Sarkoidozlu hastalarda PH olası komplikasyonlardan biri olup invaziv bir yöntem olan sağ kalp kataterizasyonu ile ana pulmoner arter basıncının ölçülmesi tanı koydurucudur. Çalışmamızda evre II sarkoidozlu hastalarda BT eşliğinde ana pulmoner arter çapının arttığı sonucunu elde ettik. Sarkoidozlu hastalarda BT ile pulmoner arter çapının değerlendirilmesinin PH gelişimi konusunda yol gösterici olabileceği dolayısıyla erken dönemde müdahele fırsatı sunacağı kanısındayız. Seçilmiş hastalar, ekokardiyografi ve BT'de ölçülen pulmoner arter çapının birlikte kullanılması ile pulmoner hipertansiyon tanısında sağ kalp kateterizasyonuna yönlendirilebilir.

Çıkar Çatışması: *Çalışmada herhangi bir çıkar çatışması yoktur.*

Finansal Çıkar Çatışması: *Çalışmada herhangi bir finansal çıkar çatışması yoktur.*

Yazışma Adresi: *Pınar Diydem Yılmaz, Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Radyoloji Anabilim Dalı, Konya, Türkiye*
E-mail: *pinardidemyilmaz@hotmail.com*

KAYNAKLAR

1. Arkema EV, Cozier YC. Epidemiology of sarcoidosis: Current findings and future directions. Ther Adv Chronic Dis 2018;9(11):227-40.
2. Ianuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Egl J Med 2007;357:2153-65.
3. Scadding, JG. Prognosis of intrathoracic sarcoidosis in England Br Med J 1961;2(5261):1165-72.
4. Diaz-Guzman E, Farver C, Parambil J, et al. Pulmonary hypertension caused by sarcoidosis Clin Chest Med 2008;29(3):549-63.
5. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1):1801-913.
6. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 2008;32:296-302.
7. Sulica R, Teirstein AS, Kakarla S, et al. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis related pulmonary hypertension. Chest 2005;128:1483-9.
8. Huitema MP, Mathijssen H, Johannes J, et al. Post. sarcoidosis-associated pulmonary hypertension. Semin Respir Crit Care Med 2020;41(05):659-72.
9. Criado E, Sanchez M, Ramirez J, et al. Pulmonary sarcoidosis: Typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 2010;30:1567-86.
10. Galiè N, Humbert M, Vachiery JL, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2015;(37):67-119.
11. Boucly A, Cottin V, Nunes H, et al. Management and long-term outcomes of sarcoidosis associated pulmonary hypertension. Eur Respir J 2017;50(4):1-12.
12. Kuriyama K, Gamsu G, Stern RG, et al. CT-determined pulmonary artery diameters in predicting pulmonary hypertension Investigative Radiology 1984;19(1):16-22.
13. Jaramillo FA, Gutierrrez FR, Telli FGD, et al. Approach to pulmonary hypertension: From CT to clinical diagnosis. Radiographics 2018;38(2):357-73.
14. Marloes P, Huitema, Marcela Spee, et al. Pulmonary artery diameter to predict pulmonary hypertension in pulmonary sarcoidosis. European Respiratory Journal 2016;47:673-6.
15. Huitema MP, Grutters JC, Rensing BJ, et al. Pulmoner hypertension complicating pulmonary sarcoidosis. Neth heart J 2016;24:390-9.
16. Spagnolo P, Rossi G, Trisolini R, et al. Pulmonary sarcoidosis. Lancet Respir Med 2018;6(5):389-402.
17. Guthaner DF, Wexler L, Harell C. CT demostration of cardiac structures. AJR 1979;133:75-81.

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 148-155
DOI: 10.30733/std.2022.01563

NEÜ YAYINEVİ

Autologous Hematopoietic Stem Cell Transplantation in Pediatric Malignant Diseases: 12 Years of Experience

Pediatrik Malign Hastalıklarda Otolog Hematopoietik Kök Hücre Nakli-12 Yıllık Deneyim

Ibrahim Kartal[1], Ayhan Dagdemir[1], Oguz Salih Dincer[1], Murat Elli[2], Canan Albayrak[1]

[1]*Ondokuz Mayıs University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Samsun, Turkey*
[2]*Medipol University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, İstanbul, Turkey*

Address correspondence to: İbrahim Kartal, Ondokuz Mayıs University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Samsun, Turkey
e-mail: ibrahim_kartal28@hotmail.com

Geliş Tarihi/Received: *27 June 2022*
Kabul Tarihi/Accepted: *1 September 2022*

Öz

Amaç: Bu çalışmada yüksek riskli pediatrik solid tümör hastalarında uyguladığımız otolog hematopoietik kök hücre tedavisinin (OHKHT) etkinlik ve güvenilirliğini 12 yıllık tecrübemizle paylaşmayı amaçladık.
Hastalar ve Yöntem: Ocak 2009-Temmuz 2021 tarihleri arasında Çocuk Kemik İliği Nakil Ünitesi'nde 18 yaş altı OHKHT yapılan pediatrik maligniteli hastaların verileri retrospektif olarak değerlendirildi.
Bulgular: Ortanca yaşı 7,8 (0,5-18) yıl olan 51 hasta (24 kız, 27 erkek) çalışmaya dahil edildi: sırasıyla nöroblastom, ewing sarkomu, hodgkin lenfoması, hodgkin dışı lenfoma, germ hücreli tümör ve yumuşak doku sarkomu olan 20, 15, 8, 4, 2 ve 2 hasta vardı. Hastaların nötrofil ve trombosit engraftman ortanca süreleri sırasıyla 11 (8-45) gün ve 16 (4-62) gün ve ortanca hastanede kalış süresi 38 (17-67) gün idi. Tüm hastalarda ortanca takip süresi 2.83 (0.12-10.81) yıl ve genel sağkalım %51.3±10.3; Ewing sarkomu ve nöroblastom olgularının ortanca takip süreleri ve sağkalım oranları sırasıyla 2,63 (0,12-10,55) yıl ve % 64,2 ±14,9 ve 2,81 (0,31-7,91) yıl ve %42,8±12 idi. Nöroblastom hastalarında; karboplatin, etoposid, melfalan (CEM) hazırlık rejimi olarak alan 4 hastanın tümü ölürken, hazırlık rejimi olarak busulfan ve melfalan (Bu/Mel) rejimi alan 16 hastanın 6'sı öldü: Bu/Mel grubunun ortanca takip süresi 3.08 (0.32-7.91) yıl ve genel sağkalım %55,1±13,8 idi (p:0,001).
Sonuç: Hasta sayımızın sınırlı olmasına rağmen, kliniğimizde Ewing sarkomu ve nöroblastom olgularımızda elde edilen verilerde ve literatürde OHKHT'nin yapılmayan hastalara göre daha iyi sağkalım sağladığı görülmektedir.

Anahtar Kelimeler: Otolog hematopoietik kök hücre nakli, nöroblastom, Ewing sarkomu, pediatri, onkoloji.

Abstract

Aim: In this study, we discuss the efficacy and safety of autologous hematopoietic stem cell transplantation (AHSCT) for high-risk pediatric solid-tumor patients based on 12 years of experience.
Patients and Methods: The data of patients aged < 18 years with pediatric malignancies who underwent AHSCT between January 2009 and July 2021 at the Pediatric Bone Marrow Transplant Unit were evaluated retrospectively.
Results: Fifty-one patients (24 girls and 27 boys; median age, 7.8 years; range: 0.5–18 years) were enrolled in the study; 20, 15, 8, 4, 2, and 2 patients had diagnoses of neuroblastoma, Ewing's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, germ cell tumor, and soft tissue sarcoma, respectively. The median neutrophil and platelet engraftment times were 11 (8–45) and 16 (4–62) days, respectively, and the median hospital stay was 38 (17–67) days. The median follow-up time was 2.83 (0.12–10.81) years and the overall survival (OS) rate was 51.3 ± 10.3% for all patients; the median follow-up times and survival rates for the Ewing's sarcoma and neuroblastoma cases were 2.63 (0.12–10.55) years and 64.2 ± 14.9%, and 2.81 (0.31–7.91) years and 42.8 ± 12%, respectively. All four patients who received the conditioning regimen of carboplatin, etoposide, and melphalan (CEM) died; 6 of 16 neuroblastoma patients who received the busulfan and melphalan (Bu/Mel) regimen as a conditioning regimen died: the median follow-up period of the Bu/Mel neuroblastoma patients was 3.08 (0.32–7.91) years and the OS rate was 55.1 ± 13.8%.
Conclusion: Although the number of patients in this study was limited, AHSCT resulted in better survival for Ewing's sarcoma and neuroblastoma cases than reported for those who did not undergo AHSCT in our clinic.

Key words: Autologous hematopoietic stem cell transplantation, neuroblastoma, Ewing's sarcoma, pediatrics, oncology

Cite this article as: Kartal I, Dagdemir A, Dincer OS, Elli M, Albayrak C. Autologous Hematopoietic Stem Cell Transplantation in Pediatric Malignant Diseases: 12 Years of Experience. Selcuk Med J 2022;38(3): 148-155

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

The prognosis of pediatric solid tumors has improved greatly due to the use of multi-agent chemotherapy, aggressive surgery, and targeted radiation therapy. However, patients with metastatic, refractory, or recurrent disease still have a poor prognosis and are candidates for aggressive treatments, such as autologous hematopoietic stem cell transplantation (AHSCT) (1-3). High-dose chemotherapy with AHSCT is a potentially curative treatment, particularly in patients with chemotherapy-sensitive malignancies; it can eliminate minimal residual disease and is suitable for children with high-risk solid tumors for whom conventional multimodal therapy may not be sufficient (1-3).

AHSCT is suitable for high-risk pediatric patients with solid tumors who respond to chemotherapy, and have harvestable stem cells and a clinical condition suitable for this aggressive treatment (4). AHSCT allows doses of chemotherapeutic agents to be increased above those used in the context of myeloablation. Therefore, most preparative regimens consist of combinations of chemotherapeutic agents administered at high dosages to maximize antitumor cytotoxicity (4). Transplant-related mortality has decreased with advances in supportive care, the use of growth factors, and good infection management. Disease recurrence remains the most common cause of treatment failure in patients undergoing AHSCT (5).

In this study, we discuss the efficacy and safety of AHSCT treatment for high-risk pediatric solid tumor patients based on 12 years of experience.

PATIENTS AND METHODS

Patients

Pediatric patients aged < 18 years with malignancy, and who were scheduled for AHSCT at the Pediatric Bone Marrow Transplant Unit between January 2009 and July 2021, were included in the study. Eligibility criteria, other than the indication for transplantation, included a Lansky's performance status of 0.70%, left ventricular ejection fraction of 0.50%, and normal liver and kidney function. Written informed consent was obtained from the parents or legal guardians in all cases involving high-dose chemotherapy, AHSCT therapy, or peripheral blood stem cell (PBSC) mobilization and collection. Ethics committee approval was obtained for the study (KAEK No: 2022/256).

Peripheral blood stem cell mobilization and collection

PBSCs mobilized with granulocyte colony-stimulating factor (G-CSF; filgrastim) were administered for 4 days before starting the subcutaneous (SC) collection (6, 7). PBSCs were collected using the Spectra Optia apheresis device through a double-lumen central venous catheter. G-CSF (filgrastim) was administered subcutaneously for 4 days in patients who failed the PBSC collection. Then, the stem cells were collected from the bone marrow under operating room conditions (7).

Conditioning regimen and supportive treatment

The busulfan/melphalan (Bu/Mel) regimen consisted of 12.8 mg/kg Bu, provided as 6-hourly doses over 4 days (between days −6 and −3 before transplant); 140 mg/m^2 Mel was administered by intravenous (IV) infusion on day −2 (8, 9). IV levetiracetam was given from day 1 of Bu to the last day of infusion to prevent Bu-related neurologic toxicity. The carboplatin, etoposide, melphalan (CEM) protocol consisted of carboplatin at a dose of 300 mg/m^2/day and etoposide at a dose of 200 mg/m^2/day between days −5 and −2, and Mel at a dose of 45 mg/m^2 on days −8, −7, −6, and −5 (10, 11). The carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen consisted of carmustine at a dose of 300 mg/m^2/day on day −7, 300 mg/m^2/day etoposide in two doses, and 400 mg/m^2/day cytarabine in two doses on days −6 to −3, and 140 mg/m^2 Mel on day −2 IV (12, 13). Transplants were performed in reverse barrier isolation rooms. Cryopreserved PBSCs were infused after rapid thawing at 37°C on day 0. Diphenhydramine (1 mg/kg) and methylprednisolone (2 mg/kg) were administered to prevent dimethylsulfoxide toxicity. All patients received G-CSF (10 mg/kg/day) from day 1 until neutrophil engraftment. Oral antibiotic therapy was started empirically and IV antibiotic therapy was started in cases of fever. Irradiated blood products devoid of leukocytes were used to maintain a hemoglobin level > 8 g/l and platelet count > 10 × 109/l.

Statistical analysis

Median and range values were calculated for numerical parameters, and frequencies and percentages for categorical parameters. Patient age, sex, diagnosis, transplant type, stem cell source, priming regimen, and transplantation-related adverse event data were summarized. Survival analyses were performed with the Kaplan-Meier method and survival curves were drawn. The log-rank test was used to compare survival between subgroups in the

survival analyses. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS software (ver. 22.0; IBM Corp., Armonk, NY, USA) software. Event-free survival (EFS) was defined as the time from day 0 (day of transplant) to disease progression or relapse, or death from any cause. Overall survival (OS) was defined as the time from day 0 (day of transplant) to last contact with the healthcare team or death.

RESULTS

Fifty-one malignant pediatric patients with an indication who received AHSCT were included in the study. The median age of the patients was 7.8 (0.5–18) years; there were 24 females and 27 males. The characteristics of the patients and transplantations are given in Table 1. The median follow-up period after transplantation was 2.83 (0.12–10.81) years.

Hematopoietic recovery

The median number of CD34 cells infused was 3.25 × 106/kg (0.3–26). All patients experienced severe myelosuppression. Hematopoietic recovery was defined as achieving an absolute neutrophil count > 0.5 × 109/l and unsupported platelet count > 20 × 109/l for at least 3 days. These values were calculated after a median of 11 (8–45) and 16 (4–62) days, respectively. The median number of days with fever was 5 (1–15 days), and the median number of IV antibiotic days was 14 (5–25 days). The patients were hospitalized for a median of 38 (17–67) days from the day of the stem cell infusion until discharge.

Non-hematological toxicities

All patients experienced moderate nausea and vomiting during the conditioning regimen. A short-term generalized convulsion was observed in one patient. During the myelosuppression period, 21 patients had gastrointestinal complaints, manifested as mucositis and diarrhea, which required pain relief. Twelve patients needed total parenteral nutrition (TPN), which was applied to the patients for a median of 7 (2–27) days. Grade I and II acute graft-versus-host disease with skin involvement was observed in two patients. Five patients developed hepatic veno-occlusive disease, which was severe in one case. Acinetobacter baumannii growth was detected in the catheter of one patient. No transplantation-related deaths were recorded.

Survival

As of May 2022, 32 patients were alive and disease-free, one is living with relapsed disease, and 18 have died. No transplantation-related deaths were reported; relapse and progressive disease were the only causes of death. The median relapse time after transplantation was 8.93 (1.41–94.94) months. The

Table 1. Characteristics of patients and transplantation

Characteristics	Value
Age (years) (median)	7,8 (0,5-18)
Gender	
Female	24 (% 47)
Male	27 (% 53)
Diseases	
Neuroblastoma	20 (% 39)
Ewing Sarcoma	15 (% 29)
Hodgkin Lymphoma	8 (% 16)
Non-Hodgkin lymphoma	4 (% 8)
Soft tissue sarcoma	2 (% 4)
Germ Cell Tumor	2 (% 4)
Stem cell source	
Peripheral blood	49 (% 96)
Bone marrow	2 (% 4)
Conditioning Regime	
Busulfan/Melphalan (Bu/Mel)	33 (% 64)
Carmustine/Cyt/Eto/Mel (BEAM)	8 (% 16)
Carboplatin/Eto/Mel (CEM)	6 (% 12)
Others(Bu/Cyc, Bu/Eto/Cyc, Cyc/Eto/carbo)	4 (% 8)
Neutrophil engraftment time (median days)	11 (8-45)
Platelet engraftment time (median days)	16 (4-62)
Hospitalization period (median days)	38 (17-67)

Abbreviations
Cyc: Cyclophosphamide, Cyt: Cytarabine, Eto: Etoposide, , carbo: Carboplatin.

Table 2. Comparison of Neuroblastoma Conditioning Regimes

	Total Patient	Dead patient	Alive patient
BU/MEL	16	6	10 (%62,50)
CEM	4	4	0 (%0,00)
Total	20	10	10 (%50,00)

Abbreviations:
BU/MEL: Busulfan/Melphalan, CEM: Carboplatin/Etoposide/Melphalan

EFS rate for the entire group was 57.4 ± 7.9% at 2 years. The EFS rate at 2 years was 64.2% ± 14.9% for the Ewing's sarcoma patients, 40.8% ± 12.5% for the neuroblastoma patients, 87.5 ± 11.7% for the Hodgkin's lymphoma patients, and 87.5 ± 11.7% for the non-Hodgkin's lymphoma patients. The OS rate was 51.3 ± 10.3% for the entire group, with a median follow-up of 2.83 (0.12–10.81) years. The OS rate for Ewing's sarcoma was 64.2 ± 14.9%, with a median follow-up duration of 2.63 (0.12–10.55) years. The OS rate for neuroblastoma was 42.8 ± 12%, with a median follow-up time of 2.81 (0.31–7.91) years. The OS rate for Hodgkin's lymphoma was 58.3 ± 25.1%, with a median follow-up of 6.42 (0.5–10.81) years. The OS rate for non-Hodgkin's lymphoma was 75 ± 21.7%, with a median follow-up of 3.49 (0.25–6.23) years (Figure 1). The OS rate was 55.1 ± 13.8% for the neuroblastoma patients using the Bu/Mel regimen, in respect to the receiving CEM that no living rest, with a median follow-up of 3.08 (0.32–7.91) years (p = 0.001) (Table 2 and Figure 2).

DISCUSSION

Although childhood cancer accounts for only a small proportion of the global cancer burden, it remains one of the leading causes of death in children and adolescents (14). OS has improved in recent years, due to remarkable progress in the diagnosis and treatment of childhood cancers. According to 2014 statistics from the American Cancer Society, 5-year survival rates for pediatric cancer exceed 80% in developed countries (14).

The prognosis of relapsed/progressed childhood cancers remains unfavorable, particularly for certain solid tumors such as neuroblastoma, and bone and soft tissue sarcomas (15). Numerous attempts have been made to improve the prognosis, and high-dose chemotherapy and AHSCT have played an important

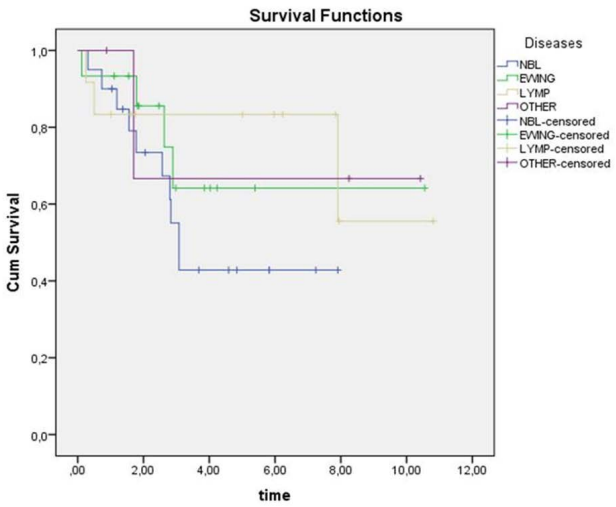


Figure 1. Overall survival curve of patients undergoing autologous hematopoietic stem cell transplantation

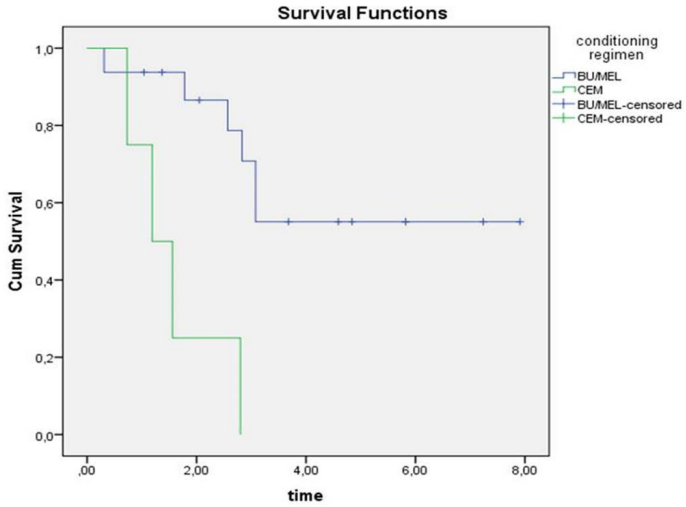


Figure 2. Comparison of the overall survival curve of neuroblastoma patients treated with the BU/MEL and CEM conditioning regimens

role in some cases (3, 4). However, survival rates for most relapsed/progressed solid tumors have generally been stable for almost 30 years (16).

The ability to safely collect, store, and reinfuse the patient's hematopoietic stem cells has led to bone marrow tolerance of cytotoxic therapy, allowing for more intensive treatment of some malignancies (17). Improvements in supportive care, the use of growth factors, and improved management of infectious complications have reduced mortality due to cytotoxic regimens. Unfortunately, disease recurrence remains the most common cause of treatment failure in patients undergoing AHSCT (5).

Hematopoietic stem cell-assisted high-dose chemotherapy was evaluated in a randomized clinical trial of patients with Ewing's sarcoma (European Ewing Tumor Working Initiative of National Groups [Euro-EWING] 99 and EWING 2008). In that study, 287 patients with isolated pulmonary (lung or pleural) metastatic disease received six courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) and one course of vincristine, dactinomycin, and ifosfamide (VAI). Next, the patients were randomly assigned to groups receiving one course of Bu plus Mel high-dose chemotherapy followed by autologous stem cell rescue, or seven cycles of conventional chemotherapy with VAI followed by whole-lung irradiation. During a median follow-up of approximately 8 years, no significant difference in the 8-year EFS rates was detected between the two groups (53% vs. 43%). The 8-year OS rates were 54% vs. 55%, respectively. In addition, infection rates, as well as gastrointestinal and liver toxicities, were higher in the high-dose chemotherapy and AHSCT groups; there were four deaths in this group, and none in the conventional chemotherapy group (18).

In an open-label phase III study (Ewing 2008R3), 109 patients with metastatic Ewing's sarcoma (excluding those with pulmonary metastases only) received six cycles of VIDE and eight cycles of consolidation therapy with vincristine, actinomycin D, and cyclophosphamide. Patients were then randomly assigned to groups receiving treosulfan plus Mel followed by hematopoietic stem cell support or no other treatment. After a median follow-up of almost 3.5 years, the addition of hematopoietic stem cell support and high-dose chemotherapy did not improve 3-year EFS (21% vs. 19%). However, posthoc analysis of a subset of 41 patients aged < 14 years of age demonstrated a potential benefit of this approach for 3-year EFS (39% vs. 9%) (19).

In a thesis study that evaluated 71 patients with Ewing's sarcoma, which was completed in 2022 at our institution, the OS rate was 43.4 ± 0.65%. AHSCT was applied in 19 of 71 cases (26.7%). The OS of the patients who did not undergo AHSCT (n = 52; 73.2%) was 36.2% ± 0.69%, and the OS of the patients who underwent AHSCT was 66.7 ± 1.61% ($p < 0.05$) (20). In our study, the EFS rate of patients with Ewing's sarcoma (metastatic, undergoing inadequate surgery, tumor volume > 200 ml) was 64.2% ± 14.9% at 2 years. The OS rate was relatively high for Ewing's sarcoma compared to the literature, at 64.2 ± 14.9%. The median follow-up was 2.63 (0.12–10.55) years. No transplantation-related deaths were recorded.

Consolidation therapy with stem cell salvage improves EFS, but not OS, according to a Cochrane review of three randomized trials of 739 children with high-risk neuroblastoma. In that analysis, high-dose chemotherapy and hematopoietic stem cell transplantation improved EFS and tended to improve OS in two studies compared with conventional therapy, although the results were not significant. No difference in secondary malignant disease or treatment-related deaths was observed between the two treatment groups, but significantly higher rates of treatment-related toxicities, such as renal damage, interstitial pneumonia, and veno-occlusive disease, were seen in those treated with stem cell transplantation compared with those treated with conventional chemotherapy (21).

The clinical features and prognoses of 458 children with high-risk neuroblastoma were assessed at a single center. The 5-year EFS rate was 31.2 ± 2.6% and the 5-year OS rate was 43.9 ± 3.2%. The 5-year EFS and OS rates in 142 AHSCT patients with bone marrow metastases (38.1 ± 5.5% and 35.7 ± 4.7%, respectively) were better than those of 196 patients with bone marrow metastases who did not undergo transplantation (26.5 ± 4.5% and 25.1 ± 3.6%, respectively) ($p = 0.001$). The EFS and OS rates of patients with bone metastases who underwent AHSCT were significantly better than those of patients who did not (22).

The results of the Turkish Pediatric Oncology Group (TPOG) national protocol were evaluated in a study that included 272 high-risk neuroblastoma patients. The EFS and OS rates were 28% and 36% at 5 years, respectively. The EFS rate after induction was 41% (n = 138) in the conventional chemotherapy arm and 29% in the AHSCT group (n = 47) ($p = 0.042$); the OS rates were 45% and 39%, respectively (p =

0.05) (10). The OS rate was 54.5%, and the EFS rate was 39%, at a median follow-up of 20.7 (7.8–105.6) months in a study conducted by Yılmaz et al., in which 11 patients with a diagnosis of refractory/ultra-high-risk neuroblastoma underwent tandem MIBG scans and AHSCT (23).

A thesis study of neuroblastoma patients evaluated at our institution in 2017 reported that the 5-year OS and EFS rates were 52% and 34%, respectively, in 33 patients treated according to the TPOG 2009 neuroblastoma protocol. AHSCT was performed in 10 of 22 stage 4 patients. The 3-year OS rate was 71.1%, and the 5-year OS rate was 35.6%, in patients who underwent AHSCT. The 3-year OS rate was 37.5% in patients who did not undergo AHSCT. No significant difference in OS was detected between patients who received and did not receive AHSCT (p = 0.164). However, the OS of patients who underwent AHSCT was better (24). In this study, the 2-year EFS was 40.8 ± 12.5%, the OS was 42.8 ± 12%, and the median follow-up was 2.81 (0.31–7.91) years for 20 neuroblastoma patients who underwent AHSCT.

Bu/Mel improved EFS, and caused fewer serious adverse events, than CEM in an international, randomized, multi-arm, open-label phase III study (HR-NBL1/SIOPEN) comparing CEM vs. Bu/Mel as high-dose chemotherapy in high-risk neuroblastoma. The median follow-up time was 7.2 (5.3–9.2) years. At 3 years, 146 of 296 patients in the Bu/Mel group and 188 of 302 in the CEM group had an event. The 3-year EFS rates were 50% and 38% (p = 0.0005) (25). In our study, the OS rate for neuroblastoma patients who underwent the Bu/Mel regimen was 55.1 ± 13.8%, which was better than the OS rate of all neuroblastoma patients (42.8 ± 12%). Despite the limited number of cases, the OS of patients transplanted with Bu/Mel was better than that of CEM protocol and non-transplanted patients, and transplantation with Bu/Mel significantly contributed to survival.

Second-line chemotherapy followed by high-dose chemotherapy and AHSCT is the regimen of choice for patients with Hodgkin's lymphoma who develop refractory disease during treatment or relapse < 1 year after completing treatment (26, 27). A study of 82 patients with refractory Hodgkin's lymphoma reported that, after aggressive second-line therapy (high-dose chemoradiotherapy), AHSCT resulted in a 49% 5-year OS rate (28). In another study, the 10-year EFS and OS rates were 41% and 51%, respectively, for primary refractory Hodgkin's lymphoma patients treated with chemotherapy plus radiation therapy (29). In a Turkish study by Hazar et al., in which patients with recurrent or refractory pediatric Hodgkin's lymphoma who underwent AHSCT with a median follow-up period of 39 months were evaluated, the 5-year OS and EFS rates were 63.1% and 54.3%, respectively (12). In another study from Turkey, the 3-year OS rates for patients with Hodgkin's lymphoma and an indication for AHSCT were 100% for late relapse (relapsed 1 year after treatment completion) and for early relapse (relapsed 3–12 months after completing the treatment); the respective rates for those with resistant disease were 83.3% and 57.6% (p = 0.003) (30). Autologous and allogeneic hematopoietic stem cell therapy can be applied in patients with non-Hodgkin's lymphoma, and long-term remission can be achieved in relapsed patients (31). In our study, the 2-year EFS rate was 87.5 ± 11.7% for Hodgkin's lymphoma and 75 ± 21.7% for non-Hodgkin's lymphoma. The OS rate was 58.3 ± 25.1% for Hodgkin's lymphoma with a median follow-up of 6.42 (0.5–10.81) years, and 75 ± 21.7% for non-Hodgkin's lymphoma with a median follow-up of 3.49 (0.25–6.23) years. Although the survival rates of our patients were high, it was not possible to draw any definitive conclusions due to the low number of cases.

This study had several limitations, including the single-institution retrospective design and small sample size. Also, the different therapeutic protocols used during the study period may have affected the treatment results, particularly the comparison between neuroblastoma patients who received Bu/Mel and those who did not. However, all of the protocols were based on various combinations of the same induction chemotherapeutic agents used today; therefore, differences between protocols are unlikely to affect our findings over the long term.

CONCLUSION

The efficacy and toxicity of AHSCT combined with multi-agent chemotherapy, radiation, and surgery for solid tumors remain controversial. Our study involved a small number of patients. Although the use of AHSCT in children and adolescents with high-risk solid tumors has shown promising results, disease recurrence remains a major challenge. AHSCT should be used in specific subsets of patients, along with post-transplant immunomodulatory maintenance or vaccine, cytokine, or antibody therapies. Prospective randomized multicenter clinical trials of pediatric patients with solid tumors should be conducted.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *İbrahim Kartal, Ondokuz Mayıs University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Samsun, Turkey*
e-mail: *ibrahim_kartal28@hotmail.com*

REFERENCES

1. Robinson L. General principles of the epidemiology of childhood cancer. Principles and practice of pediatric oncology 1993: 3-10.
2. Hawkins D, Barnett T, Bensinger W, et al. Busulfan, melphalan, and thiotepa with or without total marrow irradiation with hematopoietic stem cell rescue for poor-risk Ewing-sarcoma-family tumors. Medical and Pediatric Oncology: The Official Journal of SIOP-International Society of Pediatric Oncology (Societé Internationale d'Oncologie Pédiatrique 2000;34(5):328-37.
3. Perentesis J, Katsanis E, DeFor T, et al. Autologous stem cell transplantation for high-risk pediatric solid tumors. Bone Marrow Transplantation 1999;24(6):609-15.
4. Hale GA. Autologous hematopoietic stem cell transplantation for pediatric solid tumors. Expert review of anticancer therapy 2005;5(5):835-46.
5. Phillips GL. What is the best strategy for autologous hematopoietic stem cell transplantation in cancer? In: Armitage JO, Antman KH (Eds). High-dose Cancer Therapy: Pharmacology, Hematopoietins, Stem Cells. 3th ed. PA: Lippincott Publishing, 2000: 69-75.
6. Kawano Y, Takaue Y, Watanabe T, et al. Efficacy of the mobilization of peripheral blood stem cells by granulocyte colony-stimulating factor in pediatric donors. Cancer research 1999;59(14):3321-4.
7. Karakukcu M, Unal E. Stem cell mobilization and collection from pediatric patients and healthy children. Transfus Apher Sci 2015;53(1):17-22.
8. Diaz MA, Vicent MG, Madero L. High-dose busulfan/melphalan as conditioning for autologous PBPC transplantation in pediatric patients with solid tumors. Bone Marrow Transplant 1999;24(11):1157-9.
9. Hartmann O, Valteau-Couanet D, Vassal G, et al. Prognostic factors in metastatic neuroblastoma in patients over 1 year of age treated with high-dose chemotherapy and stem cell transplantation: A multivariate analysis in 218 patients treated in a single institution. Bone marrow transplantation 1999;23(8):789-95.
10. Aksoylar S, Varan A, Vergin C, et al. Treatment of high-risk neuroblastoma: National protocol results of the Turkish Pediatric Oncology Group. J Cancer Res Ther 2017;13(2):284-90.
11. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. New England Journal of Medicine 1999;341(16):1165-73.
12. Hazar V, Kesik V, Aksoylar S, et al. Outcome of autologous hematopoietic stem cell transplantation in children and adolescents with relapsed or refractory Hodgkin's lymphoma. Pediatr Transplant 2015;19(7):745-52.
13. Argiris A, Seropian S, Cooper DL. High-dose BEAM chemotherapy with autologous peripheral blood progenitor-cell transplantation for unselected patients with primary refractory or relapsed Hodgkin's disease. Ann Oncol 2000;11(6):665-72.
14. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64(2):83-103.
15. Shankar AG, Ashley S, Craft AW, et al. Outcome after relapse in an unselected cohort of children and adolescents with Ewing sarcoma. Med Pediatr Oncol 2003;40(3):141-7.
16. Ceschel S, Casotto V, Valsecchi MG, et al. Survival after relapse in children with solid tumors: A follow-up study from the Italian off-therapy registry. Pediatr Blood Cancer 2006;47(5):560-6.
17. Barrett D, Fish JD, Grupp SA. Autologous and allogeneic cellular therapies for high-risk pediatric solid tumors. Pediatric Clinics 2010;57(1):47-66.
18. Dirksen U, Brennan B, Le Deley MC, et al. High-dose chemotherapy compared with standard chemotherapy and lung radiation in ewing sarcoma with pulmonary metastases: Results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008. J Clin Oncol 2019;37(34):3192-202.
19. Koch R, Gelderblom H, Haveman L, et al. High-dose treosulfan and melphalan as consolidation therapy versus standard therapy for high-risk (metastatic) ewing sarcoma. J Clin Oncol 2022:Jco2101942.
20. Demir G. Ewing sarkomu tanısı ile izlenen çocuk hastaların retrospektif değerlendirilmesi. Tıpta Uzmanlık Tezi, Ondokuz Mayıs Üniversitesi Tıp Fakültesi 2022.
21. Yalçin B, Kremer LC, Caron HN, et al. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev 2013;(8):Cd006301.
22. Su Y, Ma XL, Wang HM, et al. [Clinical characteristics and prognostic analysis of 458 children with high-risk neuroblastoma in a single center]. Zhonghua Er Ke Za Zhi 2020;58(10):796-801.
23. Yilmaz E, Samur MB, Ozcan A, et al. Transplantation for ultra high-risk neuroblastoma patients: Effect of tandem autologous stem cell transplantation. Journal of Health Sciences and Medicine 2021;4(6):943-8.
24. Bekar E. 2000-2015 Arasında tanı alan çocukluk çağı nöroblastom hastalarında 2003 İle 2009 TPOG kemoterapi protokollerinin retrospektif karşılaştırılması. Tıpta Uzmanlık Tezi, Ondokuz Mayıs Üniversitesi 2017.
25. Ladenstein R, Pötschger U, Pearson ADJ, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): An international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol 2017;18(4):500-14.
26. Lieskovsky YE, Donaldson SS, Torres MA, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation for recurrent or refractory pediatric Hodgkin's disease: Results and prognostic indices. J Clin Oncol 2004;22(22):4532-40.
27. Harris RE, Termuhlen AM, Smith LM, et al. Autologous peripheral blood stem cell transplantation in children with

refractory or relapsed lymphoma: Results of children's oncology group study A5962. Biol Blood Marrow Transplant 2011;17(2):249-58.
28. Morabito F, Stelitano C, Luminari S, et al. The role of high-dose therapy and autologous stem cell transplantation in patients with primary refractory Hodgkin's lymphoma: A report from the gruppo Italiano per lo studio dei linfomi (GISL). Bone Marrow Transplant 2006;37(3):283-8.
29. Schellong G, Dörffel W, Claviez A, et al. Salvage therapy of progressive and recurrent Hodgkin's disease: Results from a multicenter study of the pediatric DAL/GPOH-HD study group. J Clin Oncol 2005;23(25):6181-9.
30. Kesik V, Ataş E, Karakükcü M, et al. Prognostic factors and a new prognostic index model for children and adolescents with hodgkin's lymphoma who underwent autologous hematopoietic stem cell transplantation: A multicenter study of the Turkish pediatric bone marrow transplantation study group. Turk J Haematol 2016;33(4):265-72.
31. Gross TG, Hale GA, He W, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 2010;16(2):223-30.

Derleme / Review

SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
Selcuk Med J 2022;38(3): 156-164
DOI: 10.30733/std.2022.01556
NEÜ YAYINEVİ

SARS-CoV-2 Enfeksiyonu ile İlişkili Yetişkinlerde Multisistemik İnflamatuar Sendrom (MIS-A); Literatür İncelemesi

Adult Multisystem Inflammatory Syndrome (MIS-A) Associated with SARS-CoV-2 Infection; Literature Review

Duygu İlke Yıldırım[1]

[1]*Selçuk Üniversitesi, Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, Konya, Türkiye*

Yazışma Adresi: Duygu İlke Yıldırım, Selçuk Üniversitesi, Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, Konya, Türkiye
e-posta: azrailla@hotmail.com

Geliş Tarihi/Received: *23 Kasım 2021*
Kabul Tarihi/Accepted: *2 Şubat 2022*

Öz

SARS-CoV-2'nin tanımlanmasından bu yana COVID-19 hastalığı sonrası çocuklarda ortaya çıkan ve Kawasaki hastalığını taklit eden multisistem inflamatuar bir sendrom (MIS-C) İngiltere'de Nisan 2020'de bildirilir iken, yetişkinlerde ortaya çıkan COVID-19 ile ilişkili multisistem inflamatuar sendrom (MIS-A) Haziran 2020'de bildirilmiştir. MIS-A hastalarının literatürde 50 yaşına kadar olduğu bildirilmiş olup MIS-C ile karşılaştırıldığında altta yatan bazı sağlık koşullarına sahip olma ve yakın dönemde tanımlanabilir bir solunum yolu hastalığı geçirmiş olma olasılığı daha yüksektir. Diğer yandan MIS-A hastaları ile MIS-C hastaları örtüşen birçok klinik özelliğe sahiptir fakat MIS-A'da kardiyak disfonksiyonun ciddiyeti, tromboz insidansı ve MIS-A mortalitesi daha yüksek olabilir. MIS-C/A'da nötrofili, lenfopeni ve trombositopeninin yaygın olarak bulunduğu açık olmakla beraber bu özellikler troponin ve BNP/NT-proBNP'deki yükselmelerle birlikte hastalık aktivitesinin ölçüleri olarak kabul edilmiştir.

Anahtar Kelimeler: Multisistem inflamatuar sendrom, çocuk, yetişkin, MIS-C, MIS-A, COVID-19

Abstract

Since the identification of SARS-CoV-2, a multisystem inflammatory syndrome (MIS-C) that appears in children after COVID-19 disease and mimics Kawasaki disease was reported in the UK in April 2020, while it is associated with Covid-19 in adults. Multisystem inflammatory syndrome (MIS-A) was reported in June 2020. MIS-A patients have been reported to be up to 50 years of age in the literature and are more likely to have some underlying health condition and have recently had an identifiable respiratory disease compared to MIS-C. On the other hand, MIS-A patients and MIS-C patients have many overlapping clinical features, but the severity of cardiac dysfunction, incidence of thrombosis, and MIS-A mortality may be higher in MIS-A. While it is clear that neutrophilia, lymphopenia, and thrombocytopenia are common in MIS-C/A, these features, together with elevations in troponin and BNP/NT-proBNP, have been considered measures of disease activity.

Key words: Multisystem inflammatory syndrome, child, adult, MIS-C, MIS-A, COVID-19

Atıf yapmak için: Yıldırım Dİ. SARS-CoV-2 Enfeksiyonu ile İlişkili Yetişkinlerde Multisistemik İnflamatuar Sendrom (MIS-A); Literatür İncelemesi. Selcuk Med J 2022;38(3): 156-164

Açıklama: *Yazar bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi.Yazar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedir.*

GİRİŞ

İnsan koronavirüsleri ilk olarak 1960'larda keşfedilmiş olup ismini bulaştırıcılıklarında rol oynayan yüzeylerinde bulunan başak proteinlerinin taç benzeri yapısından almaktadır (1). Tüm insan koronavirüsleri hayvan kökenlerine kadar izlendiğinde; HCoV-229E, HCoV-OC43, HCoV-NL63 ve HCoV-HKU1'in ''soğuk algınlığına'' benzer hafif solunum semptomlarına neden olduğu bilinmektedir (2). Yeni bir koronavirüs olan SARS-CoV-2 Aralık 2019'da ortaya çıkarak, ilk olarak Çin'in Wuhan kentinde salgına neden oldu (3). Amerika Birleşik Devletleri Hastalık Kontrol ve Korunma Merkezlerine (CDC) göre, virüsün bulaşması yakın ve zamana bağlı bir şekilde doğrudan temas veya solunum damlacıkları yolu ile gerçekleşmektedir. Bulaşın olması genellikle 15 dakika veya daha uzun süre boyunca 1.82 metre içinde yakın temas gerektirir (4). Dünya çapında vaka sayısı 13 Nisan 2021 tarihi itibari ile 2,961,931 ölümle 136 milyonu aşmıştır (5). Tüm dünyada görülen bu hastalığı Dünya Sağlık Örgütü 11 Mart 2020 tarihinde pandemi olarak ilan etti (6).

SARS-CoV-2'nin tanımlanmasından bu yana COVID-19 hastalığı sonrası çocuklarda ortaya çıkan ve Kawasaki hastalığını taklit eden multisistem inflamatuar bir sendrom (MIS-C) İngiltere'de Nisan 2020'de bildirilir iken, yetişkinlerde ortaya çıkan COVID-19 ile ilişkili multisistem inflamatuar sendrom (MIS-A) Haziran 2020'de bildirilmiştir. Etyolojide rol alan faktörler hala iyi tanımlanmamış olsa da adaptif bağışıklığın sorumlu olduğu düşünülmektedir (7). MIS-C'li çocukların halihazırda veya yakın zamanda hastalığa maruz kalma öyküleri mevcuttur. Bildirilen semptomlar arasında ateş veya titreme, gastrointestinal semptomlar, taşikardi, konjonktivit ve göreceli olarak ciddi solunum hastalığı ile mukozal değişiklikler yer alır. Bu hastaların büyük bir çoğunluğu, yoğun bakım ünitesi düzeyinde bakım gerektiren şok ve kardiyak disfonksiyon geliştirir (8). Klinik özellikler çoğunlukla farklılıklar göstermekle birlikte ateş MIS-A sendromunun ana bulgusudur. Çoğunlukla şok, kardiyak disfonksiyon, gastrointestinal sistemle ilgili şikayetler (karın ağrısı, bulantı, kusma) ve ferritin, D-dimer, C-reaktif protein, IL-6 dahil olmak üzere yüksek inflamatuar belirteçler görülen diğer bulgulardır (9).

MIS-A'nın Temel, Demografik, Klinik ve Tanısal Özellikleri

MIS-C tanımlandıktan sonra, yetişkinlerde benzer bir form olan MIS-A, ayrı bir klinik tablo olarak tanımlanmıştır (10-12). MIS-A; ≥21 yaşında bir kişide, laboratuvar kanıtı ile tanımlanmış olan mevcut veya 12 hafta içinde geçirilmiş SARS-CoV-2 enfeksiyonu varlığı, şiddetli ekstrapulmoner organ disfonksiyonu (tromboz dahil), laboratuvar olarak kanıtlanmış hiperinflamasyon, ciddi solunum yolu hastalığının yokluğu ile karakterize hastaneye yatış gerektiren ciddi bir hastalık olarak kabul edilmiştir (10). MIS-A hastalarının literatürde 50 yaşına kadar olduğu bildirilmiş olup MIS-C ile karşılaştırıldığında altta yatan bazı sağlık koşullarına sahip olma ve yakın dönemde tanımlanabilir bir solunum yolu hastalığı geçirmiş olma olasılığı daha yüksektir. Diğer yandan MIS-A hastaları ile MIS-C hastaları örtüşen birçok klinik özelliğe sahiptir fakat MIS-A'da kardiyak disfonksiyonun ciddiyeti, tromboz insidansı ve MIS-A mortalitesi daha yüksek olabilir (10).

SARS-CoV-2'nin Patofizyolojisi

Akut COVID-19; çoklu organ yetmezliğini ve hızlı klinik bozulmayı tetikleyerek, hem lokal hem sistemik bir sitokin fırtınası ve akut solunum sıkıntısı sendromu (ARDS) ile karakterize şiddetli bir tablo gösterebilir. Hem ARDS'li ciddi birincil COVID-19 hem de MIS-C/A hiperinflamasyon ve sitokin salınımı ile karakterize edilirken, kayda değer bazı patolojik farklılıklar da kaydedilmiştir. SARS-CoV-2 enfeksiyonuna karşı insan bağışıklık tepkisini tam olarak karakterize etmeye yönelik agresif çabaların şimdiye kadar bildirilmiş olanları aşağıda özetlenmiş olup bu konak ve patojen ilişkisi hakkında öğrenilecek hala çok fazla şey vardır (13).

COVID-19

Bir Betacoronavirüs olan SARS-CoV-2; zarflı, tek sarmallı, pozitif duyarlı bir RNA virüsüdür (14). Yüzeyindeki S (sivri uçlu) gliko-protein, anjiyotensin dönüştürücü enzim 2'ye (ACE-2) bağlanır, akciğerlerdeki vasküler endotel hücrelerinde ve diğer birçok organda bulunan yüksek oranda eksprese edilen bir transmembran protein viral girişe izin verir (15,16). Bu durumun sonucunda baskın bir sitokin salınımı ve monosit aktivasyonu ile doğuştan gelen immün yanıtın aktivasyonu tetiklenir (17). Lokal ve periferik monositler, proinflamatuar sitokinlerin artan sekresyonu yoluyla şiddetli COVID-19 sırasında oluşan sitokin fırtınasından sorumlu gibi görünmektedir (14,18).

COVID-19 hastalarında nötralize edici antikor yanıtları saptanmış olup SARS-CoV-2 antikor seviyeleri ile hastalık şiddeti arasındaki ilişki hala tartışmalıdır (19-22). SARS-CoV-2 S proteini IgM ve IgG seviyeleri şiddetli ve iyileşmiş COVID-19 hastalarında daha yüksektir ve semptomların başlangıcından bu yana

geçen süre ile orantılı olup bu durum güçlü bir SARS-CoV-2 spesifik humoral yanıtı yansıtır (22). SARS-CoV-2 IgG ve IgM antikorları asemptomatik SARS-CoV-2 pozitif bireylerde COVID-19 hastalarına kıyasla daha düşük seviyelerde bulunmuştur (23). COVID-19'u takiben uzun süreli koruyucu nötralize edici antikor bağışıklığının oluşup oluşmadığı henüz netlik kazanmamıştır (23,24).

COVID-19 hastalarında, sağlıklı donörlere ve iyileşmiş COVID-19 hastalarına kıyasla şiddetli COVID-19 hastalarında B hücre plazmablastları genişlemiştir (21,25). Genişletilmiş plazmablastlar ekstra foliküler B hücresi aktivasyonunu yansıtabilir ve bu uyumsuz inflamatuar yanıt, doku hasarını artırabilen immün aracılı hasardan sorumlu olabilir (21,26).

Lenfopeni, SARS-CoV-2 enfeksiyonunun ciddiyeti ve mortalitesi ile ilişkilidir; bu lenfopeni, hem CD4 + hem de CD8 + T hücre alt gruplarındaki azalmaların bir sonucudur (27). Bu azalmaların etiyolojisi belirsizliğini koruyor ve Orta Doğu Solunum Sendromu koronavirüsünde (MERS-CoV) olduğu gibi T hücrelerinin doğrudan viral enfeksiyonu veya inflamatuar ortamın etkileriyle veya son organlarda T hücresinin sekestrasyonu ile ilişkili olabilir (17,27,28). T hücreleri muhtemelen SARS-CoV-2 enfeksiyon kontrolü için temeldir ve akut SARS-CoV-2'ye özgü T hücreleri yüksek düzeyde aktive olmuş sitotoksik fenotip sergilemiştir (29). T hücre bağışıklığının indüksiyonu etkili virüs kontrolü için gerekliyken, düzensiz T hücre yanıtları birincil COVID-19'da hiperinflamasyona katkıda bulunabilir. Kritik hastalığı olan COVID-19 hastalarında, önemli ölçüde ex vivo inflamatuar sitokin üretimi yapabilen belirli CD4 + T hücrelerinin artan frekansları tanımlanmıştır (30). Bu alt küme daha önce inflamatuar hastalıklarda ve sepsiste kötü sonuçlarla ilişkilendirilmiştir (31). Şiddetli COVID-19 vakalarında, regülatör T hücrelerinin azaltılmış sıklığı da tanımlanmıştır, bu da hiperinflamasyonu şiddetlendirebilir (27,32).

MIS-C

MIS-C'de hiperenflamasyona yol açan moleküler mekanizmalar bu aşamada büyük ölçüde bilinmemektedir ve fenotipik karakterizasyonlarla sınırlıdır. MIS-A'da henüz benzer çalışmalar rapor edilmemiştir. MIS-C sırasında bağışıklık tepkisinin profilini çıkarmaya odaklanan son çalışmalar bazı potansiyel mekanizmaları aydınlatmış olup incelenen hasta sayısı hala azdır ve bu şiddetli inflamatuar bozukluğa yol açan immünopatoloji keşfedilmeyi beklemektedir.

MIS-C hastalarının çoğu pozitif anti-S IgG'ye sahiptir ve bu seviyeler şiddetli COVID-19'dan sağ kurtulan yetişkin bireylerle karşılaştırılabilir, bu da MIS-C'nin güçlü bir bağışıklık tepkisi ile ilişkili olduğunu düşündürür (28,33,34). Bu gözlem doğrultusunda ve şiddetli COVID-19'un aksine MIS-C; düşük ve hatta negatif viral yüklerin yanı sıra düşük veya anti-S IgM yokluğu ile karakterize edilir ve bu da postenfeksiyöz bir fenomen fikrini destekler (34,35).

Ayrıca immünomodülasyona mükemmel yanıt, MIS-C'nin doğrudan virüsten ziyade enfeksiyon sonrası immün düzensizlik tarafından yönlendirildiğini ileri sürer.

İlginç bir şekilde, anti-S IgG nötralize edici aktivite karşılaştırıldığında; MIS-C hastaları, COVID-19 ARDS'li yetişkin hastalara ve iyileşen plazma donörlerine kıyasla azalmış aktivite sergiler iken, COVID-19'lu diğer çocuklara kıyasla artmış aktivite sergilemiştir (28,33,34). Bu bulgular, MIS-C pediatrik immün yanıtında anormal bir nötralize edici aktivite olduğunu düşündürmektedir.

MIS-C hastalarındaki lenfopeninin, CD4+ ve CD8+ T lenfositleri ve NK hücrelerinin sayısının azalmasına bağlı olduğu gösterilmiştir (36,37). MIS-C hastalarının immüno-profillemesi, belirgin T hücresi aktivasyonunu ve çarpık T hücresi alt kümelerini ortaya çıkarmıştır (28,36,37). MIS-C'de T hücreleri daha aktif görünürken, monositler, dendritik hücreler ve B hücreleri gibi antijen sunan hücreler daha düşük aktivasyon belirteçlerine sahiptir, bu da antijen sunumunda olası bir eksikliği düşündürür (38).

MIS-C hastalarında saptanabilen birkaç element, daha yüksek çözünür kompleman bileşenleri C5b-9'a eğilim dahil olmak üzere bir endotel disfonksiyonu ve mikroanjiyopatiyi düşündürür (35). Bu bulgu, kan yaymalarında daha yüksek sitokin seviyeleri ve daha yüksek ekinosit ve çapak hücresi sıklığı ile koreledir; bu durum, COVID-19 ARDS hastalarında olduğu gibi endotelyal disfonksiyonun inflamasyonun sürmesine katkıda bulunabileceğini düşündürmektedir (35).

MIS C/A için Ayırıcı Tanılar

Ortaya çıkan kanıtlar, MIS-C hastalarının sunum sırasındaki ana özelliklerine göre farklı kümelere ayrılabileceğini düşündürmektedir. MIS-C'nin en sık karşımıza çıkan bir formu; neredeyse evrensel olarak kardiyak ve gastrointestinal sistemler dahil olmak üzere daha fazla organ sisteminin de dahil olduğu ve daha yüksek oranda şokun, lenfopeninin ve miyokarditi gösteren yüksek kardiyak biyobelirteçlerin olduğu adölesanlarda görülen bir tablo şeklindedir (9). MIS-C geliştiren çocukların ilk raporlarından bu yana,

hastalığın iyi bilinen çocukluk hastalığı olan Kawasaki Hastalığı'nın (KH) bazı klasik semptomlarıyla ortaya çıktığı açıktı (9,39-41). Ayrıca yetişkinlerde KH normalde çok nadir görülmesine rağmen, MIS-A'lı hastaların da benzer özelliklere sahip olduğu bildirilmiştir (10).

Kawasaki Hastalığı

İlk tanınmasından itibaren, MIS-C ve KH arasındaki benzerliklerin (Tablo 1), özellikle şiddetli Kawasaki Şokunun (KŞ) gözden kaçırılması imkansız olmuştur. KH tanısı, başka yerlerde tanımlandığı gibi klinik bulgulara ve laboratuvar kriterlerine dayanır (42,43). KH ve KŞ'ye benzer şekilde, MIS-C/A'nın spesifik bir tanı testi yoktur. Bu nedenle, MIS-C ve KH/KŞ arasındaki başlıca ayırt edici semptomların vurgulanması, MIS-C/A'nın klinik vaka tanımının anlaşılmasını zenginleştirebilir.

MIS-C hastalarının sunumunda gastrointestinal semptomlar baskın olma eğilimindeyken, geleneksel KH veya KŞ durumunda (yani SARS-CoV-2 ile ilişkili olmayan vakalarda) abdominal ağrı, kusma ve ishal nadirdir (44). MIS-C ve KH arasındaki diğer farklılıklar da ortaya çıkmaya başlamıştır. MIS-C'li hastalar ortalama olarak KH hastalarından daha yaşlıdır (ortalama yaş 8-9 yıl ve 2-3 yıl). Obezite, KH'nda belirtilmeyen MIS-C'ye yatkınlık yaratan altta yatan bir tıbbi durum olabilir (9,40,41). MIS-C için mevcut vaka tanımlarını karşılayabilen sadece bir günlük ateşle başvuran çocuklar, 5 günlük ateş gerektiren tam KH kriterlerini hiçbir zaman karşılamayabilir. Minör laboratuvar kriterleri dahil olmak üzere eksik KH formları tanı durumunu daha da karmaşık hale getirir, ancak artan kanıtlar MIS-C'de daha yüksek C reaktif protein ve diğer inflamatuar belirteçler (ferritin ve D-dimer) ile, daha fazla anemi, lenfopeni ve trombositopeni durumlarının görüldüğünü göstermektedir (9,39-41,45).

Geleneksel KH hastalarında tipik olarak iskemi olmaksızın miyokardiyal ödem ve kardiyomiyosit nekrozu vardır (42,45). Bu nedenle, KH'nda ki troponin seviyeleri çok yüksek değildir. Aksine, MIS-C'nin kardiyak tutulumu sıklıkla yüksek troponin seviyelerine ve yüksek kardiyak disfonksiyon frekansları ile birlikte yüksek beyin natriüretik proteini (BNP) veya N Terminal-pro BNP'ye (NT-proBNP) yol açar (41,45-48). MIS-C hastalarında ayrıca sıklıkla miyokardit ile uyumlu elektrokardiyogram değişiklikleri olur (42,48). Yoğun bakım gerektiren, solunum desteği ihtiyacı olan ve şok ile başvuran MIS-C hastalarına kıyasla şok ile başvuran KH'nın sıklığı oldukça düşüktür, %5 civarındadır (45-48). MIS-C vakaları, KH'nın bir özelliği olan koroner arter dilatasyonunu içerebilir, ancak bu vakaların az bir kısmında görünmektedir (9,39-41,45). Uzun vadeli sonuçlar henüz mevcut olmadığından, MIS-C hastalarının uzun vadeli koroner sekel riskinin olup olmadığı açık değildir, ancak miyokardit tanısı olan hastaların çoğu ilk ayaktan takiplerinde başlangıca dönmüş görünmektedir (49,50).

MIS-C/MIS-A ile İlgili Diğer Görüşler

MIS-C/A'nın sunumu diğer birçok koşul ile de örtüşerek ayırt edici demografik, klinik, laboratuvar ve görüntüleme özelliklerinin tanınmasını hayati hale getirir. Geniş bir yelpazede enfeksiyöz, inflamatuar ve alerjik/reaktif etiyolojiler mutlaka düşünülmelidir. Yönetim önemli ölçüde değişebileceğinden, MIS-C/A'yı alternatif tanılardan ayırt etmek oldukça önemlidir. Maruziyet geçmişine dayalı yüksek klinik şüphenin eşlik ettiği kapsamlı bir öykü, fizik muayene ve laboratuvar incelemesi bir dereceye kadar klinik kesinlik sağlayabilir.

MIS-C/MIS-A mukokutanöz semptom kompleksleri, özellikle stafilokok ve streptokok toksik şok sendromu (TSS) ile ortak özellikler gösterir. Ateş ve şok her iki sendromun da baskın özellikleridir. Hem stafilokok hem de streptokok TSS'si döküntü ile ortaya çıkabilirken, konjonktivit TSS'de daha sık görülür. Gastrointestinal semptomlar MIS-C/A'nın baskın özellikleridir ve hipotansiyonun izlediği aşırı prodromal diyare ise stafilokok TSS'sinde daha sıklıkla görülmektedir. Kardiyak disfonksiyon ise; MIS-C/A'da görülür iken TSS'de görülmemektedir9,46,47,51,52. MIS-C/A'nın ek semptomları olan baş ağrısı ve solunum semptomları ise TSS'de daha az olasılıkla görülmektedir (9,47,53).

MIS-C/A ile ilişkili döküntü ''polimorfiktir''

Table 1. MIS-C ve KH'nın karşılaştırılması

Özellikler	MIS-C	KH
Yaş (ortalama)	8,5 yıl	3 yıl
Ateş	+++	+++
Döküntü	++	+++
Konjonktivit	++	++
Oromukozal değişiklik	++	++
Ekstremite değişimi	+/-	+
Servikal LAP	+/-	+
Koroner dilatasyon	+	++
Kardiyak disfonksiyon	++	-
GI semptomlar	+++	+
Şok/Hipotansiyon	++	+/-
Ölüm	%2	%0,17

MIS-C: Çocuklarda multisistem inflamatuar sendrom; KH: Kawasaki Hastalığı; LAP: Lenfadenopati.

(39). Bu nedenle ateş, döküntü ve mukokutanöz özellikler ile başvuran diğer antiteler düşünülmelidir. Staphylococcal Haşlanmış Deri Sendromu (SSSS), kızıl hastalığı ve diğer A Grubu beta-hemolitik streptokok enfeksiyonları dahil olmak üzere diğer stafilokok ve streptokok sendromları ise ayırt edici özelliklere sahiptir. SSSS ve diğer stafilokokal eksfolyatif toksin sendromları, akut faz sırasında deskuamasyon ile Nikolsky'nin ayırt edici işaretini gösterebilir. Kızıl ile ilişkili döküntü; tipik olarak Pastia işaretiyle birlikte papüler eritrodermadır ("zımpara kağıdı döküntüsü"). MIS-C/A ve KH'de görüldüğü gibi streptokok enfeksiyonları çilek dilini gösterebilirken, dudaklar genellikle normaldir ve orofarenks tonsiller eksüda ve palatal peteşi gösterir.

Yaygın viral enfeksiyonlar, MIS-C/A'nın bazı özelliklerini taklit edebilir, ancak tam bir uyum bulmak nadirdir. Ateş, hem viral enfeksiyonların hem de MIS-C/A'nın ortak bir belirtisidir. Ekzantemler, örneğin enterovirüs, adenovirüs, parvovirüs ve kızamıkta ve ayrıca MIS-C/A'da sıklıkla gözlenir. Konjonktival enfeksiyon kızamık, adenovirüs, hantavirüs ve kızamıkçıkta görülebilir (54). MIS-C/A'lı hastaların çoğunda bulunan gastrointestinal semptomlar, aynı zamanda adenovirüs, enterovirüs, rotavirüs ve Norwalk virüsü ile de ilişkilidir, ancak MIS-C/A'daki karın ağrısı, akut apandisite benzer bir şiddete sahiptir (45).

MIS-C/A vakalarının çoğunda kardiyak disfonksiyon bildirilmiştir (10,44-46,48). Kalp yetmezliğine yol açan miyokardit; parvovirus, adenovirus, HIV, influenza, echovirus, coxsackieviruses, EBV ve CMV gibi birçok virüsle ilişkili olabilir (55). Bu durumlarda, kardiyak miyositlere yönelik doğrudan viral toksisite patolojik sürecin bir parçasıdır, ancak bunun MIS-C/A'da doğru olup olmadığı henüz bilinmemektedir. MIS-C/A ile ilişkili kardiyak disfonksiyonun, vakaların çoğunda normal fonksiyona geri dönüşle birlikte geçici bir durum olması daha olası görünmektedir (45).

MIS-C/A'nın bazı kutanöz ve sistemik belirtileri, Stevens-Johnson sendromu (SJS), toksik epidermal nekroliz (TEN) ve eozinofili ve sistemik semptomlarla (DRESS) ilaç reaksiyonu gibi hastalıklarla da örtüşmektedir, ayrıca ilaca bağlı aşırı duyarlılık sendromu (DIHS) olarak da adlandırılır (56,57). Bu varlıklara çeşitli ilaçlar ve daha az yaygın olarak bulaşıcı ajanlar neden olabilir. MIS-C/A'da olduğu gibi mukokutanöz tutulum ve ateş sıktır, ancak cilt tutulumu SJS ve TEN'de çok daha belirgindir ve Nikolsky'nin işareti sıklıkla mevcuttur. Şok ile birlikte MIS-C/A'yı tanımlayan çoklu organ tutulumu, özellikle DRESS'te her birinde görülebilir. Genel olarak, bu antiteler dikkatli bir öykü ile ve gerekirse deri biyopsisi ile ayırt edilebilir (56,57).

Aşı Sonrası MIS-C/MIS-A

Brighton ve ark. tarafından 2017 yılında yapılan sistematik bir incelemede KH takibine ilişkin 27 gözlemsel çalışma ve vaka raporları belirlenmiştir. Bunlar; difteri-tetanoz-boğmaca (DTP) içeren aşılar, Haemophilus influenzae tip b (Hib) konjuge aşısı, grip aşısı, hepatit B aşısı, 4 bileşenli meningokok serogrup B (4CMenB) aşısı, kızamık-kabakulak-kızamıkçık dahil olmak üzere bir dizi aşı (MMR)/MMR-varisella aşıları, pnömokok konjuge aşısı (PCV), rotavirüs aşısı (RV), sarı humma aşısı ve Japon ensefaliti aşısıdır. İnceleme, yukarıdaki bağışıklamalardan herhangi birinin ardından KH riskinde artış olduğuna dair kanıt bulamadı (58).

Popülasyona dayalı çalışmalar, KH (Kawasaki Hastalığı) ve PCV aşıları arasındaki ilişkileri değerlendirmiştir. Erken bir çalışma, 7-değerli PCV (PCV7) ve KH arasında bir ilişki bulamamıştır59. Bir 2013 Aşı Güvenliği Veri Bağlantısı çalışması, PCV7 ile karşılaştırıldığında 13-değerli PCV'den (PCV13) sonra KH riskinde istatistiksel olarak anlamlı olmayan bir artış olduğunu kaydetmiştir (göreceli risk 1.94, %95 GA 0.79-4.86) (60). Bununla birlikte, daha yeni araştırmalar Amerika Birleşik Devletleri'nde KH ve PCV13 aşılaması ile Birleşik Krallık'ta PCV (7- veya 13-değerli) ya da 4CMenB aşıları arasında bir ilişki olduğuna dair kanıt bulamamıştır (61,62). Yazarlar PCV13'ün ilk dozunu takiben PCV13 ile tam KH arasında anlamlı bir ilişki olduğunu belirtse de, Singapur'daki bir çalışma da benzer şekilde PCV13'ün genel KH ile ilişkili olmadığını bildirmiştir (63).

MIS-C/A'nın klinik spektrumu ayrıca bakteriyel enfeksiyon kanıtı olmaksızın şok ve çoklu organ yetmezliğini de içerir. Canlı suçiçeği, herpes zoster ve sarı humma aşılarını takiben aşı ile ilişkili hastalık geliştiren bağışıklığı baskılanmış hastalarda nadiren şok ve çoklu organ yetmezliği bildirilmiştir (64-67). HIV ve romatoid artritli bir hastada adjuvan H1N1 aşılamasından sonra şok ve çoklu organ yetmezliği vakası bildirilmiştir, ancak aşı ile nedensel bir ilişki doğrulanmamıştır (68).

MIS-C/A, hem KH hem de TSS'den farklı olsa da, bunlar şiddetli inflamatuar durumlardır. Patogenezleri henüz anlaşılmamıştır, ancak COVID-19'un enfeksiyon sonrası bir tezahürü gibi görünmektedir.

MIS-C/A'nın Mevcut Vaka Tanımları

MIS-C ilk olarak Birleşik Krallık'ta Nisan 2020'de tanımlandı. Çocuk hastaların hiperinflamatuar şok

Tablo 2. Multi İnflamatuar Sendromların Mevcut Vaka Tanımları

Özellikler	Pediatrik:RCPCH	Pediatrik:CDC	Pediatrik:WHO	Yetişkin:CDC
Yaş (Yıl)	''çocuk''	<21	0-19	≥21
Ateş	Sürekli	≥1 gün	≥3 gün	-
Hastaneye Yatış	+	-	+	-
Tutulan organların sayısı	≥1	≥2	≥2	≥1 akciğer dışı
Adlandırılan organ sistemleri	Şok, kardiyak, respiratuar, nefritik, gastrointestinal, nörolojik,	Kardiyak, nefritik, respiratuar, hematolojik, gastrointestinal, dermatolojik, nörolojik	Mukokutanöz, hipotansiyon /şok, kardiyak, gastrointestinal	Hipotansiyon/şok, kardiyak, tromboz/ tromboembolizm, akut karaciğer hasarı,
(+) SARS-CoV-2 RT-PCR/ antijen/seroloji	-	+	+	+ (12 hafta içinde)

RCPCH, Royal College of Paediatrics and Child Health; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

ve SARS-CoV-2 enfeksiyonu kanıtı ile başvurdukları görülerek bu duruma MIS-C adı verildi (39,40). Bu hastaların klinik görünümleri ile bir süre sonra bildirilen diğer hastalar; Kawasaki Hastalığı, toksik şok sendromu ve makrofaj aktivasyon sendromu (MAS)/ sekonder hemofagositik lenfohistiyositoz (HLH) gibi bilinen hastalıklarla benzerlikler gösterdiği saptandı. Bu ilk raporların ardından MIS-C ile ilgili CDC ve WHO tarafından raporlar yayınlandı (Tablo 2) (70-71).

MIS-C için RCPCH (Royal College of Paediatricians and Child Health), CDC (United States Centers for Disease Control and Prevention) ve WHO (The World Health Organization) vaka tanımlarının bazı farklı varyasyonları vardır (Tablo 2) (69-71). Hastaların yaşı, ateşin uzunluğu ve SARS-CoV-2 pozitif test veya maruz kalma durumu temel farklılıklardır. CDC tanımı ayrıca hastaneye yatmayı da gerektirir. Şu anda, CDC tarafından kullanılan MIS-A için ön vaka tanımındaki 5 kriter, MIS-A için tek vaka tanımıdır (Tablo 2).

MIS-C/MIS-A Vaka Tanımı İhtiyacı

SARS-CoV-2 ve MIS-C'nin immünopatolojisine ilişkin mevcut veriler sınırlı olmasına rağmen artmaktadır. MIS-C ve MIS-A'nın benzer immünopatolojiye sahip olup olmadığı ise hala açık değildir. Doğal SARS-CoV-2 enfeksiyonunu takiben MIS-C/MIS-A'yı neyin tetiklediği belirlenmemiştir. Ayrıca SARS-CoV-2 için çeşitli aşı türleri geliştirilmektedir. Bu durum, aşılamadan sonra MIS-C/A gelişme olasılığını tahmin etmeyi zorlaştırmaktadır. Üç potansiyel aşılama sonrası senaryolar düşünülmelidir. İlk olarak, SARS-CoV-2 enfeksiyonunu hiç geçirmemiş ve SARS-CoV-2'ye karşı aşılanmış olan hastalar belirli bir süre sonra MIS-C/A için değerlendirildikleri bir hastalık geliştirebilirler. İkinci durum olarak, COVID-19 hastalığını geçirmiş hastalar daha sonra SARS-CoV-2'ye karşı aşılanmış olup sonrasında bir hastalık geliştirdiklerinde MIS-C/A için tekrar değerlendirilebilirler. Son olarak, SARS-CoV-2'ye karşı aşılanmış olup (önceden COVID-19 olsun ya da hiç olmasın) daha sonra SARS-CoV-2 ile enfekte olabilir/yeniden enfekte olabilir ve daha sonra MIS-C/A için değerlendirildiği bir hastalık geliştirebilir. Ayrıca, çocuklar genellikle COVID-19'a karşı asemptomatik olduğundan bir çocuğun aşılamadan önce SARS-CoV-2 ile önceden bir enfeksiyon geçirip geçirmediğini bilmek mümkün olmayabilir (69,71).

MIS-C/A için Klinik Bulgular

Alınan çalışma grubunda bulunan hastaların çoğunda MIS-C/A'nın mukokutanöz ve gastrointestinal bulguları ile birlikte şok/hipotansiyon eğilimi mevcuttur (9,10,39,45-47,51). Nörolojik bulgular MIS-C/A'da daha düşük olasılıkla görülmesine rağmen, MIS-C/A taklitlerinde bulunma olasılıkları daha da düşük olduğundan bu bulgular MIS-C/A'ya dahil edilmiştir. Tüm mukokutanöz bulguları içeren bir klinik kategori, bir KH ile örtüşme olasılığını da azaltacaktır. Kardiyak ve hematolojik tutulum, hastalığın laboratuvar kanıtlarına dahil edilir. Böbrek tutulumu yaygın ve ayırt edici bir bulgu olmadığı için dahil edilmemiştir. Solunum sistemi ile ilgili bulgulara da çalışma grubunda rastalanılmamıştır. MIS-C hastalarının bir kısmında görülen solunum semptomları ise tipik olarak hafiftir. CDC ön vaka tanımına göre şiddetli

solunum semptomlarının varlığı, MIS-A tanısını dışlar (9,46,47). Bu nedenle, hafif solunum semptomlarına sahip olmak MIS-C/A vakasını hariç tutmaz iken, şiddetli solunum semptomlarının varlığı MIS-C/A tanısını hariç tutar.

MIS-C/A için Laboratuvar Bulgular

MIS-C/A'da nötrofili, lenfopeni ve trombositopeninin yaygın olarak bulunduğu açık olmakla beraber bu özellikler troponin ve BNP/NT-proBNP'deki yükselmelerle birlikte hastalık aktivitesinin ölçüleri olarak kabul edilmiştir (9,10,39,45-47,51). Bu bulgular hematolojik ve kardiyak belirtileri de açıklamaktadır. İnflamasyonun laboratuvar kanıtı; CRP, ESR, ferritin ve prokalsitonin yükselmeleri ile gösterilir. SARS-CoV-2 için pozitif serolojinin MIS-C/A hastalarının çoğunda bir bulgu olduğu daha açık hale gelmektedir (9,10). Ancak çalışma grubu; SARS-CoV-2 nükleik asit veya antijeninin laboratuvar kanıtlarını sadece laboratuvarlar arasında tutmayı seçmiştir. SARS-CoV-2'ye maruz kalmanın kesin zamanlamasından bu yana elde edilen bulgular ve MIS-C/A'nın gelişimi halen araştırılmakta olup, antikor testi halen birçok yerde rutin olarak yapılmamaktadır.

MIS-C/A'nın Diğer Benzer İlişkili Bozukluklardan Farklılaşma Durumları

Vaka tanımının kritik bileşenlerinden biri, yalnızca bildirilen olay için semptomların kombinasyonunu hesaba katacak açık bir alternatif tanı olmadığında uygulanacak olmasıdır, yani bu diğer varlıkların bir vaka için hariç tutulacağı anlamına gelir. Özellikle vaka tanımı, klinik özelliklerde MIS-C ve KH'nın örtüşmesini azaltacak şekilde yapılandırılmıştır. Döküntü, oromukozal değişiklikler, konjonktivit ve ekstremite değişiklikleri gibi ikisi arasında daha yaygın örtüşen klinik özellikler sadece bir klinik özelliğe dahil edilmiştir. Vaka tanımını karşılamak için, KH'de çok daha az yaygın olan gastrointestinal semptomlar, şok/hipotansiyon veya nörolojik semptomların ek bir klinik özelliğinin mevcut olması gerekir. Son olarak, vaka tanımı, kişisel bir geçmiş veya SARS-CoV-2'ye maruz kalma geçmişi veya SARS-CoV-2'ye karşı bir aşı gerekliliğini içerir ve bu da MIS-C/A'yı diğer benzer bozukluklara göre tanımlamayı daha olası kılar8,15,21,68-71.

Çıkar Çatışması: *Çalışmada herhangi bir çıkar çatışması yoktur.*

Finansal Çıkar Çatışması: *Çalışmada herhangi bir finansal çıkar çatışması yoktur.*

Yazışma Adresi: *Duygu İlke Yıldırım, Selçuk Üniversitesi, Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, Konya, Türkiye*
e-mail: *azrailla@hotmail.com*

KAYNAKLAR

1. DA Tyrrell, ML Bynoe. Cultivation of a novel type of commoncold virus in organ cultures. Br Med J 1965;(1):1467-70.
2. DX Liu, JQ Liang, TS Fung. Human corona virus-229E,OC43,-NL63, and-HKU1 (Coronaviridae). Encylopedia of Virology 2021;428-40.
3. C Huang, Y Wang, X Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. Lancet 2020;(395):497-506.
4. M Jayaweera, H Perera, B Gunawardana, et al. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res 2020;(188):109819.
5. Worldometer, COVID-19 Coronavirus Pandemic, https:// www.worldometers.info/ coronavirus/ 2021 (accessed on 13 April 2021).
6. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. https://www.who.int/ director- general/speeches/ detail/who-director-general-s-opening-remarks-at-the-media briefing-on-covid-19---11-march- 2020. (accessed on 24 December 2020).
7. Kabeerdoss J, Pilania RK, Karkhele R, et al. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: Immunological mechanisms, clinical manifestations and management. Rheumatol Int 2021;41(1):19-32.
8. Amato MK, Hennessy C, Shah K, et al. Multisystem inflammatory syndrome in an adult. J Emerg Med 2021;41(1): 19-32.
9. Godfred-Cato S, Bryant B, Leung J, et al. California MIS-C Response Team. COVID-19–associated multisystem inflammatory syndrome in children-United States, MarchJuly 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074–80.
10. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69(40):1450–6.
11. Weatherhead JE, Clark E, Vogel TP, et al. Inflammatory syndromes associated with SARS-CoV-2 infection: Dysregulation of the immune response across the age spectrum. J Clin Invest 2020;130(12):6194–7.
12. Most ZM, Hendren N, Drazner MH, et al. The striking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: Overlapping manifestations of COVID-19. Circulation 2021;143(1):4-6.
13. Vogel TP, Top KA, Karatzios C, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2021;39(22):3049.
14. Zhou P, Yang X, Shi Z, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.
15. Sungnak W, Huang N, Becavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26 (5):681–7.
16. Walls AC, Park Y, Tortorici M, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181(2):281–92.
17. Vabret N, Britton G, Gruber C, et al. Immunology of COVID-19: Current state of the science. Immunity 2020;52(6):910-41.

18. Guo C, Li B, Ma H, et al. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumabresponding cytokine storm. Nat Commun 2020;11(1):3924.
19. Liu L, Wang P, Nair M, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature 2020;584(7821):450-6.
20. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730-41.
21. Kuri-Cervantes L, Pampena MB, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol 2020;5(49):7114.
22. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis 2020;71(16):2027-34.
23. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS- CoV-2 infections. Nat Med 2020;26(8):1200-4.
24. Iyer AS, Jones FK, Nodoushanı A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5(52):3-67.
25. Wilk AJ, Rustagi A, Zhao NQ, et al. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. Nat Med 2020;26(7):1070–6.
26. Woodruff M, Ramonell RP, Cashman KS, et al. Critically ill SARS-CoV-2 patients display lupus-like hallmarks of extrafollicular B cell activation. Med Rxiv 2020;10;29-20083717.
27. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130(5):2620–9.
28. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020;183(4);982-95.
29. Sekine T, Perez-Potti A, Rivere-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell 2020;183(1):158-68.e14.
30. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Proc Natl Acad Sci Rev 2020;7(6);998-1002.
31. Huang H, Wang S, Jiang T, et al. High levels of circulating GM-CSF(+)CD4(+) T cells are predictive of poor outcomes in sepsis patients: A prospective cohort study. Cell Mol Immunol 2019;16(6):602–10.
32. Guo C, Li B, Wang X, et al. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumabresponding cytokine storm. Nat Commun 2020;11(1):3924.
33. Anderson EM, Diorio C, Goodwin EC, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19. J Pediatric Infect Dis Soc 2020.
34. Weisberg SP, Connors T, Zhu Y, et al. Antibody responses to SARS-CoV2 are distinct in children with MIS-C compared to adults with COVID-19. Medrxiv 2020.
35. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest 2020;130(11):5967-75.
36. Consiglio CR, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183:968-81.
37. Vella LA, Giles JR, Baxter AE, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Medrxiv: The preprint server for health sciences 2021:57(6):7570.
38. Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med 2020;26(11);1701-7.
39. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet 2020;395(10239):1771–8.
40. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607–8.
41. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV- 2. JAMA 2020;324(3):259–69.
42. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):927-99.
43. Ayusawa M, Sonobe T, Uemura S, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int 2005;47(2):232–4.
44. Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19–related multisystem inflammatory syndrome in children. J Clin Investig 2020;130(11):5619-21.
45. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 2020;13(4);271.
46. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334-46.
47. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347-58.
48. Niaz T, Hope K, Fremed M, et al. Role of a pediatric cardiologist in the COVID-19 pandemic. Pediatr Cardiol 2021;42(1):19-35.
49. Jhaveri S, Ahluwalia N, Kaushik S, et al. Longitudinal echocardiographic assessment of coronary arteries and left ventricular function following multisystem inflammatory syndrome in children. J Pediatr 2020;228:290-3.
50. Minocha PK, Phoon CKL, Verma S, et al. Cardiac findings in pediatric patients with multisystem inflammatory syndrome in children associated with COVID-19. Clin Pediatr 2021;60(2):119-26.
51. Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child Adolesc Health 2020;4(9):669–77.
52. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-CoV-2- induced multisystem inflammatory syndrome in children. J Clin Invest

2020;130(11):5942-50.
53. Moraleda C, Serna-Pascual M, Soriano-Arandes A, et al. Multi-inflammatory syndrome in children related to SARS- CoV-2 in Spain. Clin Infect Dis 2021;72(9):397-401.
54. Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. N Engl J Med 1994;330(14):949–55.
55. Schultz JC, Hilliard AA, Cooper Jr LT, et al. Diagnosis and treatment of viral myocarditis. Mayo Clin Proc 2009;84(11):1001–9.
56. Hsu DY, Brieva J, Silverberg NB, et al. Pediatric Stevens- Johnson syndrome and toxic epidermal necrolysis in the United States. J Am Acad Dermatol 2017;76(5):811–7.
57. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: A literature review. Am J Med 2011;124(7):588–97.
58. Phuong LK, Bonetto C, Buttery J, et al. Kawasaki disease and immunisation: A systematic review. Vaccine 2017;35(14):1770–9.
59. Center KJ, Hansen JR, Lewis E, et al. Lack of association of Kawasaki disease after immunization in a cohort of infants followed for multiple autoimmune diagnoses in a large, phase-4 observational database safety study of 7-valent pneumococcal conjugate vaccine: Lack of association between Kawasaki disease and seven-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2009;28 (5):438–40.
60. Tseng HF, Sy LS, Liu ILA, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine 2013;31(22):2578-83.
61. Baker MA, Baer B, Kulldorff M, et al. Kawasaki disease and 13-valent pneumococcal conjugate vaccination among young children: A self-controlled risk interval and cohort study with null results. PLoS Med 2019;16(7):1002844.
62. Stowe J, Andrews NJ, Turner PJ, et al. The risk of Kawasaki disease after pneumococcal conjugate & meningococcal B vaccine in England: A self-controlled case-series analysis. Vaccine 2020;38(32):4935–9.
63. Yung CF, Ma X, Cheung YB, et al. Kawasaki disease following administration of 13-valent pneumococcal conjugate vaccine in young children. Sci Rep 2019;9(1):14705.
64. Gershman MD, Staples JE, Bentsi-Enchill AD, et al. Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2012;30(33):5038–58.
65. Italiano CM, Toi CS, Chan SP, et al. Prolonged varicella viraemia and streptococcal toxic shock syndrome following varicella vaccination of a health care worker. Med J Aust 2009;190(8):451–3.
66. Costa E, Buxton J, Brown J, et al. Fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient. J Clin Virol 2015;70:19.
67. Schrauder A, Henke-Gendo C, Seidemann K, et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. Lancet 2007;369(9568):1232.
68. De Nardo P, Bellagamba R, Corpolongo A, et al. Septic shock after seasonal influenza vaccination in an HIV- infected patient during treatment with etanercept for rheumatoid arthritis: A case report. Clin Vaccine Immunol 2013;20(5):761–4.
69. Royal college of paediatrics and child health. guidance - paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS). 2020; Available from: https://www.rcpch.ac.uk/resources/guidancepaediatricmultisystem-inflammatory-syndrome-temporally-associated- covid-19-pims.
70. Centers for disease control and prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available from: https://emergency. cdc.gov/han/2020/ han00432.asp. (accessed on 27 March 2020).
71. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. (accessed on 15 May 2020).