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KARE

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DERGİSİ

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YAZARLARA BİLGİ

Ümraniye Pediatri Dergisi, uluslararası, periyodik ve açık erişimli akademik bir dergidir. Dergi; bağımsız, önyargısız ve çift-kör hakemlik ilkelerine uygun olarak Nisan, Ağustos ve Aralık aylarında yılda üç sayı yayınlanmaktadır. Derginin yayın dili Türkçe ve İngilizce'dir.

Değerlendirilmek üzere gönderilen yazılar Türkçe ya da İngilizce olarak kabul edilmekte ve yayınlanmaktadır.

Dergide makale değerlendirme ve yayın işlemleri için yazarlardan ücret talep edilmemektedir. Dergi arşivi www.umraniyepediatri.com üzerinden ücretsiz olarak okuyucuların erişimine açıktır.

Ümraniye Pediatri Dergisi çocuk sağlığı ve hastalıkları alanında yayınladığı özgün araştırma, nadir görülen olgu sunumları, derleme ve editöre mektup türündeki yazılar ile tıp bilimine katkı sağlamayı amaçlamaktadır. Derginin hedef kitlesi çocuk sağlığı ve hastalıkları konusunda çalışan uzmanlar, akademisyenler ve ilgili diğer dal uzmanlarıdır.

Derginin yazıları değerlendirme 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) kılavuzlarına uygun olarak şekillendirilmiş olup 'Principles of Transparency and Best Practice in Scholarly Publishing' (doaj.org/bestpractice) ilkelerine uygun olarak yürütülmektedir.

Bir yazının yayına kabul edilmesindeki en önemli ölçütler; özgünlük, yüksek bilimsel kalite ve atıf potansiyelidir. Ümraniye Pediatri Dergisi'ne gönderilen yazıların daha önce başka bir elektronik ya da basılı dergide, kitapta ya da farklı bir mecrada sunulmamış ya da yayınlanmamış olması gerekir. Toplantılarda sunulan çalışmalar için, sunum yapılan kongrenin tam adı, tarihi, şehri ve ülkesi belirtilmelidir.

Ümraniye Pediatri Dergisi'ne gönderilen tüm yazılar çift-kör hakem değerlendirme sürecinden geçmektedir. Tarafsız değerlendirme sağlayabilmek için her yazı alanlarında uzman en az iki dış-bağımsız hakem tarafından değerlendirilir. Dergi Yayın Kurulu üyeleri tarafından gönderilecek yazıların değerlendirme süreçleri, davet edilecek dış bağımsız editörler tarafından yürütülecektir. Bütün yazıların karar verme süreçlerinde son karar yetkisi Baş Editör'dedir.

Klinik ve deneysel çalışmalar, ilaç ile cihaz araştırmaları ve bazı olgu sunumları için World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013, www.wma.net) çerçevesinde hazırlanmış Etik Kurul raporu gerekmektedir. Türkiye'de yapılan bu tür çalışmalar için Sağlık Bakanlığı'nın 3359 numaralı Sağlık Hizmetleri Temel Kanunu'na uygun olarak Sağlık Bakanlığı'ndan izin alınması gereklidir. Etik Kurul raporu ya da eşdeğeri olan resmi bir yazı taranarak sisteme yüklenmelidir. İnsanlar üzerinde yapılmış deneysel çalışmaların sonuçlarını bildiren yazılarda, çalışmanın yapıldığı kişilere uygulanan yöntemlerin niteliği tümüyle açıklandıktan sonra, onaylarının alındığına ilişkin bir açıklamaya metin içinde yer verilmelidir. Hayvanlar üzerinde yapılan çalışmalarda ise, hayvanlara ağrı, acı ve rahatsızlık verilmemesi için alınan önlemler yazıda açık olarak belirtilmelidir. Hasta onamları, Etik Kurul raporunun alındığı kurumun adı, onay belgesinin numarası ve tarihi ana metin dosyasında yer alan Gereç ve Yöntemler başlığı altında yazılmalıdır. İnsanlarda yapılan tıbbi araştırmalarda Dünya Tıp Birliği'nin Helsinki Bildirgesine uyularak araştırmanın yapıldığı belirtilmelidir. Hastaların kimliklerinin gizliliğini korumak yazarların sorumluluğundadır. Hastaların kimliğini açığa çıkarabilecek fotoğraflar için hastadan ya da hastanın yasal vasilerinden alınan imzalı izinlerin de dergiye gönderilmesi gereklidir.

Bütün yazıların benzerlik denetimi iThenticate yazılımı aracılığıyla yapılmaktadır.

Yayın Kurulu, dergiye gönderilen çalışmalar hakkındaki intihal, atıf yönlendirmesi ve veri sahteciliği iddiaları ya/ya da şüpheleri karşısında COPE kılavuzunda belirtilen ilkelere göre hareket edecektir.

Yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık ölçütlerini karşılaması gerekmektedir. ICMJE, yazarların aşağıdaki 4 ölçütü karşılamasını önermektedir:

Çalışmanın düşüncesine/tasarımına ya da çalışma için verilerin toplanmasına, incelenmesine ve yorumlanmasına önemli ölçüde katkı sağlamış olmak; VE

Yazı taslağını hazırlamış ya da düşünsel içeriğin eleştirel incelemelerini yapmış olmak; VE

Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak; VE

Çalışmanın herhangi bir bölümünün geçerliliğine ve doğruluğuna ilişkin soruların uygun şekilde incelenip çözümlendiğini sağlamak amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Bir yazar, çalışmada katkı sağladığı kısımların sorumluluğunu almasının yanı sıra diğer yazarların çalışmanın hangi kısımlarından sorumlu olduğunu da saptayabilmelidir. Ayrıca, yazarlar birbirlerinin katkılarının bütünlüğüne güven duymalılardır.

Yazar olarak belirtilen herkes yazarlığın dört ölçütünü karşılamalı ve bu dört ölçütü karşılayan herkes yazar olarak tanımlanmalıdır. Dört ölçütün tamamını karşılamayan kişilere yazının başlık sayfasında teşekkür edilmelidir.

Sorumlu yazarlar; yazarlık haklarına uygun hareket etmek ve hayalet ya da lütuf yazarlığın önüne geçmek amacıyla yazıların yükleme sürecinde, www.umraniyepediatri.com adresinden erişilebilen Yazar Katkı Formu'nu imzalamalı ve bu formun taranmış şeklini yazıyla birlikte göndermelidir. Yayın Kurulu'nun gönderilen bir yazıda "lütuf yazarlık" olduğundan şüphelenmesi durumunda söz konusu yazı değerlendirme yapılmaksızın reddedilecektir.

Ümraniye Pediatri Dergisi gönderilen yazıların yazarları ile yazıların değerlendirme sürecinde olan kişilerin potansiyel çıkar çatışmasına ya da önyargıya yol açabilecek mali, kurumsal ve diğer ilişkilerini ya da potansiyel çıkar çatışmalarını bildirmelerini talep ve teşvik eder.

Bir çalışma için bir birey ya da kurumdan alınan her türlü mali destek ya da diğer destekler Yayın Kurulu'na bildirilmelidir. Potansiyel çıkar çatışmalarını bildirmek amacıyla ICMJE Potansiyel Çıkar Çatışmaları Formu katkı sağlayan tüm yazarlar tarafından ayrı ayrı doldurulmalıdır. Editörler, yazarlar ve hakemler ile ilgili potansiyel çıkar çatışmaları derginin Yayın Kurulu tarafından COPE ve ICMJE kılavuzları kapsamında çözülmektedir.

Derginin Yayın Kurulu, itiraz ve şikayet olaylarını, COPE rehberleri kapsamında işleme almaktadır. Yazarlar, itiraz ve şikayetleri için doğrudan Yayın Sekreterliği ile temasa geçebilirler. Gereksinim duyulduğunda Yayın Kurulu'nun kendi içinde çözemediği konular için tarafsız bir temsilci atanmaktadır. İtiraz ve şikayetlerle ilgili karar verme süreçlerinde son kararı Baş Editör verecektir.

Ümraniye Pediatri Dergisi her yazının www.umraniyepediatri.com adresinden erişilebilen Telif Hakkı Sözleşmesi ile beraber gönderilmesini talep eder. Yazarlar, yazıda yer alan resimler, tablolar ya da diğer her türlü içerik dahil daha önce yayınlanmış içeriği kullanırken telif hakkı sahibinden izin almalılardır. Bu konudaki yasal, mali ve cezai sorumluluk yazarlara aittir. Yazarlar, Telif Hakkı Sözleşmesini imzalayarak, Ümraniye Pediatri Dergisi'nde yayınlanacak yazıların Creative Commons 4.0 Uluslararası Atıf Lisansı (CC-BY-NC) kapsamında lisanslanacağını kabul ederler.

Dergide yayınlanan yazılarda ifade edilen görüşler Ümraniye Pediatri Dergisi, Baş Editör, Editörler, Yayın Kurulu ve Yayıncı'nın değil, yazar(lar)ın bakış açılarını yansıtır. Baş Editör, Editörler, Yayın Kurulu ve Yayıncı bu içeriklere dair hiçbir sorumluluk ya da yükümlülük kabul etmemektedir. Yayınlanan içerik ile ilgili tüm sorumluluk yazarlara aittir.

Yazıların Hazırlanması

Yazılar, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje. org/icmje-recommendations.pdf) ile uyumlu olarak hazırlanmalıdır. Randomize çalışmalar CONSORT, gözlemsel çalışmalar STROBE, tanısal değerli çalışmalar STARD, sistematik derleme ve meta-analizler PRISMA, hayvan deneyli çalışmalar ARRIVE ve randomize olmayan davranış ve halk sağlığıyla ilgili çalışmalar TREND kılavuzlarına uyumlu olmalıdır.

Yazılar sadece www.umraniyepediatri.com adresinde yer alan derginin online yazı yükleme ve değerlendirme sistemi üzerinden gönderilebilir.

Gönderilen yazıların dergi yazım kurallarına uygunluğu ilk olarak dergi yayın kurulu tarafından kontrol edilecek, dergi yazım kurallarına uygun hazırlanmamış yazılar teknik düzeltme talepleri ile birlikte yazarlarına geri gönderilecektir.

Yazarların; Telif Hakkı Sözleşmesi, Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışmaları Formu'nu (bu form, tüm yazarlar tarafından doldurulmalıdır) ilk gönderim sırasında online yazıların yüklenme sistemine yüklemeleri gerekmektedir. Bu formlara www.umraniyepediatri.com adresinden erişilebilmektedir.

Başlık sayfası: Gönderilen tüm yazılar ile birlikte ayrı bir başlık sayfası da gönderilmelidir. Bu sayfa;

Yazının Türkçe ve İngilizce başlığını ve 50 karakteri geçmeyen kısa başlığını,

Yazarların isimlerini, kurumlarını, eğitim derecelerini, e-mail adreslerini ve ORCID ID numaralarını,

Mali destek bilgisi ve diğer destek kaynakları hakkında ayrıntılı bilgiyi,

Sorumlu yazarın ismi, adresi, telefonu (cep telefonu dahil), faks numarası ve e-posta adresini,

Yazıların hazırlama sürecine katkıda bulunan ama yazarlık ölçütlerini karşılamayan bireylerle ilgili bilgileri içermelidir.

Özet: Editöre Mektup ve Uzmanından Yorum türündeki yazılar dışında kalan tüm yazıların Türkçe ve İngilizce özetleri olmalıdır. Özgün Araştırma yazılarının özetleri "Amaç", "Gereç ve Yöntemler", "Bulgular" ve "Çıkarımlar" alt başlıklarını içerecek biçimde hazırlanmalıdır. Kelime kısıtlamaları için Tablo 1'i inceleyiniz.

Anahtar Sözcükler: Tüm yazılar en az 3 en fazla 10 anahtar kelimeyle birlikte gönderilmeli, anahtar sözcükler özetin hemen altına yazılmalıdır. Kısaltmalar anahtar sözcük olarak kullanılmamalıdır. Anahtar sözcükler National Library of Medicine (NLM) tarafından hazırlanan Medical Subject Headings (MeSH) veritabanından seçilmelidir.

Yazı Türleri

Yazı ana dosyaları Microsoft Office Word programı kullanarak hazırlanmalı ve türlerine göre aşağıdaki yapıda düzenlenmelidir.

Özgün Araştırma: Ana metin "Giriş", " Gereç ve Yöntemler", "Bulgular" ve "Tartışma" alt başlıklarını içermelidir. Özgün Araştırmalarla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Sonucu desteklemek için istatiksel çözümleme genellikle gereklidir. İstatistiksel çözümleme, tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatiksel çözümleme ile ilgili bilgi, Gereç ve Yöntemler bölümü içinde ayrı bir alt başlık olarak yazılmalı ve kullanılan yazılım kesinlikle tanımlanmalıdır. Araştırma makalelerinde örneklem sayısına karar verilirken yapılan hesaplamanın belirtilmesi gerekir. Sürekli değişkenlerin karşılaştırılmasında parametrik testler kullanıldığı zaman, verilerin ortalama±standart sapmalarıyla bildirilmesi gerekir. Parametrik olmayan testler için de ortanca (en düşük-en yüksek) ya da ortanca (25 ve 75. persantil) değerleri olarak bildirilmesi gerekir. İleri ve karmaşık istatistiksel çözümlemelerde, göreceli risk (RR-Relative Risk), olasılık (OR-Odds Ratio) ve tehlike (HR-Hazard Ratio) oranları, güven aralıkları (Confidence Intervals) ve p değerleri ile desteklenmelidir.

Birimler, uluslararası birim sistemi olan 'International System of Units' (SI)'a uygun olarak hazırlanmadır.

Uzmanından Yorum: Dergide yayınlanan bir araştırmanın, o konunun uzmanı olan ya da üst düzeyde değerlendirme yapan bir hakemi tarafından kısaca yorumlanması amacını taşımaktadır. Yazarları, dergi tarafından seçilip davet edilir. Uzmanından Yorum yazıları ile ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Derleme: Konusunda birikimi olan ve bu birikimleri uluslararası dizine yayın ve atıf sayısı olarak yansımış yazarlar Editörler Kurulu tarafından derleme yazmak üzere davet edilir. Derlemeler, bir bilgi ya da konunun klinikte kullanılması için vardığı son düzeyi anlatan, tartışan, değerlendiren ve gelecekte yapılacak olan çalışmalara yön veren bir şekilde hazırlanmalıdır. Ana metin "Giriş", "Klinik ve Araştırma Etkileri" ve "Sonuç" bölümlerini içermelidir. Derleme türündeki yazılarla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Olgu Sunumu: Olgu sunumları için sınırlı sayıda yer ayrılmakta ve sadece nadir görülen tanı ve tedavisi güç olan hastalıklarla ilgili yeni bir yöntem öneren, kitaplarda yer verilmeyen bilgileri yansıtan, ilgi çekici ve öğretici özelliği olan olgular yayına kabul edilmektedir. Özette genel bilgiler değil olgu anlatılmalıdır. Ana metin; "Giriş", "Olgu" ve "Tartışma" alt başlıklarını içermelidir. Olgu sunumu türündeki yazılar için hasta(lar)dan ya da hastanın yasal vasilerinden bilgilendirilmiş yazılı hasta onamı alınması ve yazının başvurusu sırasında dergimize gönderilmesi zorunludur. Olgu Sunumlarıyla ilgili kısıtlamalar için lütfen Tablo 1'i inceleyiniz.

Editöre Mektup: Dergide daha önce yayınlanan bir yazının önemi, gözden kaçan bir ayrıntısı ya da eksik kısımları tartışabilir. Ayrıca derginin kapsamına giren alanlarda okurların ilgisini çekebilecek konular ve özellikle eğitici olgular hakkında da editöre mektup türünde yazılar yayınlanabilir. Okuyucular da yayınlanan yazılar hakkında yorum içeren editöre mektup türünde yazılarını sunabilirler. Editöre mektup türündeki yazılarda özet, anahtar sözcük, tablo, şekil ve diğer görseller kullanılmaz. Ana metin alt başlıksız olmalıdır. Hakkında mektup yazılan yayına ait cilt, yıl, sayı, sayfa numaraları, yazı başlığı ve yazarların adları açık bir şekilde belirtilmeli, kaynak listesinde yazılmalı ve metin içinde kaynak gösterilmelidir.

Tablolar

Tablolar ana dosyaya eklenmeli, kaynak listesi sonrasında sunulmalı ve ana metin içerisindeki geçiş sıralarına uygun olarak numaralandırılmadır. Tabloların üzerinde tanımlayıcı bir başlık yer almalı ve tablo içerisinde geçen kısaltmaların açılımları tablo altında alfabetik sıraya göre tanımlanmalıdır. Tablo dipnotlarında üst simge olarak harfler kullanılmalıdır. Tablolar Microsoft Office Word dosyası içinde "Tablo Ekle" komutu kullanılarak hazırlanmalı ve kolay okunabilir şekilde düzenlenmelidir. Tablolarda sunulan veriler ana metinde sunulan verilerin tekrarı olmamalı, ana metindeki verileri destekleyici nitelikte olmalılardır. Tablolarda kullanılan kısaltmalar tablo altlarında alfabetik sıraya göre tanımlanmalıdır.

Resim ve Resim Altyazıları

Resimler, grafikler ve fotoğraflar (TIFF ya da JPEG formatında) ayrı dosyalar şeklinde sisteme yüklenmelidir. Görseller bir Word dosyası dokümanı ya da ana doküman içerisinde sunulmamalıdır. Alt birimlere ayrılan görseller olduğunda, alt birimler tek bir görsel içerisinde verilmemelidir. Her bir alt birim sisteme ayrı bir dosya olarak yüklenmelidir. Resimler alt birimleri belli etme amacıyla etiketlenmemelidir (a, b, c vb.). Resimlerde altyazıları desteklemek için kalın ve ince oklar, ok başları, yıldızlar, asteriksler ve benzer işaretler kullanılabilir. Yazıların geri kalanında olduğu gibi resimlerde de çift-kör değerlendirmeyi sağlamak için kişi ve kurum bilgileri gizlenmelidir. Görsellerin çözünürlüğü en az 300DPI olmalıdır. Değerlendirme sürecindeki aksaklıkları önlemek için gönderilen bütün görsellerin çözünürlüğü net ve boyutu büyük (En küçük boyutlar 100x100 mm) olmalıdır. Resim altyazıları ana metnin sonunda yer almalıdır.

Özel Kurallar

Çift-kör hakem değerlendirmesinin yapılabilmesi için dergiye gönderilen yazı dosyaları ve görseller çalışmanın yapıldığı kurum ve kişilere ait bilgiler içermemelidir.

Türkçe ve İngilizce başlık ve kısa başlıklarda cümlenin ilk harfi büyük, diğer tüm harfler küçük olmalıdır. Başlık ve metinde eğer ":" dan sonra cümle geliyorsa ilk harfi büyük, cümle gelmiyor ise küçük harfle yazılmalıdır. Çok kullanılar sözcükler kısaltılabilir. Ancak özette kısaltma kullanılmamalıdır. Yazı içerisinde geçen tüm kısaltmalar ana metinde ilk kez kullanıldıkları yerde tanımlanarak kısaltma tanımın ardından parantez içerisinde verilmeli, yazı içinde cümle başlarında kısaltma kullanılmamalı, cümle içinde kısaltma kullanılmalıdır.

Ana metin içerisinde cihaz, yazılım, ilaç vb. ürünlerden bahsedildiğinde ürünün ismi, üreticisi, üretildiği şehir ve ülke bilgisini içeren ürün bilgisi parantez içinde verilmelidir; "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)". İlaç isimleri etken madde adı ile yazılmalıdır.

Tüm kaynak, tablo ve şekillere ana metin içinde uygun olan yerlerde sırayla numara verilerek kaynak gösterilmelidir. Tablo ve şekil başlıklarında ve bunların yazı içinde anılmasında Roma rakamları kullanılmamalıdır.

Dört ve üzeri haneli sayılarda binlik basamaklar arasında boşluk bırakılmalıdır [Örn: 1 000 000]. Çift haneli sayılar, yazı içinde rakamla, tek haneli sayılar ise yazıyla verilmelidir. Ancak değerleri belirten ifadelerde tek haneler rakamla verilmelidir (Örn: 1 cm). Yazı içinde ve tablolarda yüzdelik değerler virgülden sonra iki basamak, p değerleri virgülden sonra üç basamak olarak verilmelidir. Yazı, tablo ve şekillerde yer alan ondalık sayılar Türkçe yazılarda virgül ile İngilizce yazılarda nokta ile ayrılmalıdır.

Özgün araştırmaların kısıtlamaları, engelleri ve yetersizliklerinden Sonuç paragrafı öncesi "Tartışma" bölümünde bahsedilmelidir.

Kaynaklar

Kaynak gösterirken en yeni ve güncel yayınlar tercih edilmelidir. Kaynak gösterilen erken çevrimiçi yazıların DOI numaraları mutlaka belirtilmelidir. Kaynakların doğruluğundan yazarlar sorumludur. Dergi isimleri Index Medicus/Medline/PubMed'de yer alan dergi kısaltmaları ile uyumlu olarak kısaltılmalıdır. Altı ya da daha az yazar olduğunda tüm yazar isimleri listelenmelidir. Eğer 7 ya da daha fazla yazar varsa ilk 3 yazar yazıldıktan sonra Türkçe kaynaklarda "ve ark." ve İngilizce kaynaklarda 'et al.' ifadesi eklenmelidir. Ana metinde kaynaklara atıf yapılırken ilgili kaynak kullanılma sırasına göre parantez içinde numaralandırılmalıdır. Farklı yayın türleri için kaynak gösterme biçimleri aşağıdaki örneklerde sunulmuştur:

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ORIGINAL RESEARCH
Neonatology

Mortality and associated risk factors in neonates with critical congenital heart disease: A retrospective single-center study

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ABSTRACT

Objective: Congenital heart diseases (CHDs) include congenital structural and functional abnormalities of the cardiovascular system and are associated with a high risk of mortality and morbidity. To evaluate early outcomes in infants with congenital heart disease (CHD), with a particular focus on critical CHD (CCHD), and to identify factors associated with mortality in patients with CCHD.

Material and Methods: Patients were grouped into five categories according to echocardiographic findings and clinical presentations: normal, non-significant, important, serious, and critical. In addition, all patients who underwent surgery for CHD were evaluated according to the RACHS-1 classification.

Results: CCHD (serious/critical) constituted 11.6% (71/608) of CHD cases. Mortality occurred in 32 of 71 neonates with CCHD (45.1%). Antenatal diagnosis (OR: 3.1), inoperability (OR: 4.6), ventilation requirement (OR: 8.1), and postoperative arrhythmia (OR: 8.4) were identified as risk factors for mortality in patients with CCHD. In multiple logistic regression analysis, genetic syndrome (OR: 17.3, 95% CI [1.04–28.7], p=0.010) and postoperative arrhythmia (OR: 42.6, 95% CI [4.1–44.09], p=0.002) were the strongest risk factors for mortality.

Conclusion: Integration of echocardiographic and risk-based classifications may guide better clinical decision-making in patients with CCHD. Early identification, antenatal diagnosis, and preoperative stabilization are key to improving outcomes. The risk of mortality was higher in patients who required mechanical ventilation, had genetic anomalies, or developed postoperative arrhythmias.

Keywords: Cardiac surgery; congenital heart diseases; mortality; neonatal intensive care unit.

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Kritik konjenital kalp hastalığı olan yenidoğanlarda mortalite ve ilişkili risk faktörleri: Retrospektif tek merkezli bir çalışma

ÖZET

Amaç: Konjenital kalp hastalıkları (KKH), kardiyovasküler sistemdeki konjenital yapısal ve işlevsel anormallikleri içerir ve yüksek mortalite ve morbidite riski taşır. Bu çalışmanın amacı, konjenital kalp hastalığı (KKH) olan bebeklerde erken dönem sonuçlarını, özellikle kritik KKH'ye (KKKH) odaklanarak değerlendirmek ve KKKH olan hastalarda mortalite ile ilişkili faktörleri belirlemektir.

Gereç ve Yöntemler: Hastalar, ekokardiyografi sonuçları ve klinik bulgularına göre normal, önemsiz, önemli, ciddi ve kritik olmak üzere beş kategoriye ayrılmıştır. Ayrıca, KKH nedeniyle ameliyat geçiren tüm hastalar RACHS-1 sınıflandırmasına göre değerlendirilmiştir.

Bulgular: KKKH (ciddi/kritik) vakaları, KKH vakalarının %11,6'sını (71/608) oluşturdu. KKKH olan 71 yenidoğanın 32'sinde mortalite görüldü (%45,1). Doğum öncesi tanı (OR: 3,1), ameliyat edilemezlik (OR: 4,6), ventilasyon ihtiyacı (OR: 8,1) ve ameliyat sonrası aritmi (OR: 8,4), KKKH'de mortalite için risk faktörleri olarak belirlendi. Çoklu lojistik regresyon analizinde, genetik sendrom (OR: 17,3; %95 CI [1,04–28,7]; p=0,010) ve ameliyat sonrası aritmi (OR: 42,6; %95 CI [4,1–44,09]; p=0,002) mortalite açısından en önemli risk faktörleri olarak saptandı.

Tartışma: Ekokardiyografik ve risk temelli sınıflandırmaların birleştirilmesi, KKKH olan hastalarda daha iyi klinik karar verme sürecine yol gösterebilir. Erken teşhis, doğum öncesi tanı ve ameliyat öncesi stabilizasyon, sonuçların iyileştirilmesinde kilit öneme sahiptir. Mekanik ventilasyona ihtiyaç duyan, genetik anomalileri olan veya ameliyat sonrası aritmi gelişen hastalarda mortalite riski daha yüksekti.

Anahtar Kelimeler: Kardiyak cerrahi girişim; konjenital kalp hastalıkları; mortalite; siyanotik kalp hastalığı; yenidoğan.

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INTRODUCTION

Congenital heart diseases (CHDs) include congenital structural and functional abnormalities of the cardiovascular system (1, 2). The prevalence of CHD among live births is approximately 0.8–1% (3–5). Despite modern diagnostic and treatment methods, CHD is associated with a high risk of mortality and morbidity.

There are many studies on the neonatal mortality rate during the first year of life. Although the mortality rate has gradually decreased over the last 40 years, an analysis conducted in the USA in 2012 reported a neonatal mortality rate of 0.32% (6–8). In Türkiye, this rate was 1.07% according to 2015 data from the Turkish Statistical Institute (9–11). Mortality in the neonatal period is associated with many causes, such as prematurity-related diseases, congenital malformations, sepsis, and congenital heart diseases (12–17).

In the United States, between 1999 and 2006, 0.21% of all reported deaths were associated with congenital heart disease (CHD), and the CHD-related mortality rate during the first year of life was reported as 41.48 per 100,000 live births (18). Similarly, a 20-year study conducted in the United Kingdom reported that 10.3% of deaths occurring within the first year of life were attributed to CHD (7). Other studies conducted in Türkiye have reported that the incidence of CHD in NICUs ranges from 1.6% to 15% (19–21).

CHDs that require surgical and/or catheter intervention in the first year of life and can cause death in the neonatal period are called critical CHDs (CCHDs) and account for approximately 25% of all CHDs (22). In a recent study conducted in the USA, the overall prevalence of CCHD was 19.6 per 10,000 live births (23).

Neonatal intensive care units (NICUs) with experienced staff, sufficient equipment, and adequate supplies are critical for these patients. Data on the epidemiology, mortality, and morbidity of newborns with CHD followed up in NICUs are quite limited in Türkiye. Currently, neonatal cardiac surgery is a developing field and can be performed in only a few centers in Türkiye.

A recent study covering the years 2018–2021 found that, among 41,490 infant deaths nationwide, 4,083 were due to CCHD, accounting for approximately 9.8% of infant deaths (24). The study reported that CCHD accounts for approximately 8% of neonatal deaths, with a neonatal mortality rate due to CCHD of 4.6 per 10,000 live births. The report also identified regional differences within Türkiye; for example, the mortality rate due to CCHD per 10,000 births was 8.4 in the Western region and approximately 9.0 in the Central, Southern, and Eastern regions (24).

Prematurity, low birth weight, sepsis, and pulmonary hypertension, along with poor preoperative clinical condition and low Apgar scores, are major factors that increase mortality in

Table 1. Grouping study population according to echocardiographic and clinical findings (40)

Group number	Group name	Description
Group 1	Normal	Normal echocardiography findings
Group 2	Insignificant	Lesions that do not cause clinical symptoms and resolve spontaneously within six months. For example, small PDA, PFO, small ASD, muscular VSD.
Group 3	Important	Lesions not classified as serious or critical but require medication or follow-up longer than six months
Group 4	Serious	Lesions that require intervention within the first year of age are not classified as critical
Group 5	Critical	All lesions that died within the first 28 days or that require intervention.

ASD: Atrial septal defect; PDA: Patenat ductus arteriosus; PFO: Patent foramen ovale; VSD: Venticular septal defect.

neonates with CHD (25–32). Additionally, high RACHS-1 scores, prolonged bypass time, preoperative mechanical ventilation, and postoperative complications, such as low cardiac output syndrome and infections, significantly increase the risk of death (33). Genetic syndromes, congenital airway anomalies, and the presence of perinatal stroke are also additional risk factors that negatively affect survival (26, 34–36).

The Risk Adjustment in Congenital Heart Surgery (RACHS-1) score is a widely used system for predicting surgical mortality in pediatric cardiac procedures and classifies surgeries into six categories based on their complexity (37). RACHS-1 scores can predict CCHD-related mortality by category as follows: category 1, 0.4%; category 2, 3.8%; category 3, 8.5%; category 4, 19.4%; category 5, insufficient number; and category 6, 47.7% (37).

Determining the factors affecting prognosis will play a role in developing approaches to reduce mortality and morbidity in patients with CHD. In this cross-sectional retrospective study, we aimed to evaluate both the prevalence and mortality rate of CCHDs and to identify the risk factors affecting mortality.

MATERIALS AND METHODS

Newborns with CHD were identified by reviewing the electronic records of all patients hospitalized in the NICU of Ege University Pediatric Hospital between January 2014 and December 2015. Approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee for this study (Decision Number: 16-11.1/14; Date: 01.12.2016). The study was conducted in accordance with the Declaration of Helsinki.

The present retrospective study included 750 patients from 2014 and 902 from 2015, for a total of 1,652 patients hospitalized in the Ege University NICU. Demographic characteristics, the presence of antenatal diagnosis, clinical features at the time of diagnosis, disease-related or independent risk factors affecting morbidity and mortality, such as renal failure, heart failure, other organ failures, immunological and genetic conditions, medical treatments, angiographic catheter interventions, surgical procedures, time of surgical decision, and time of death were examined from the patient files.

Patients were categorized into five CHD groups (normal, non-significant, important, serious, and critical) based on echocardiographic findings and clinical severity using the classification terms of Ewer et al. (38). Group 1 (Normal) included patients with no structural abnormalities. Group 2 (Insignificant) comprised minor defects such as small PDAs or patent foramen ovales (PFOs) that were asymptomatic and typically resolved spontaneously within six months. Group 3 (Important) involved conditions requiring prolonged follow-up or medication but not meeting the criteria for more severe classifications. Group 4 (Serious) included lesions requiring intervention within the first year of life, excluding those considered critical. Finally, Group 5 (Critical) encompassed defects necessitating urgent intervention or resulting in death within the neonatal period (the first 28 days). These groups are presented in Table 1 (38). Premature infants with PDA were excluded from the study.

CCHDs were defined as serious (Group 4) and critical (Group 5) according to this classification after screening with pulse oximetry before postnatal discharge.

In addition, the same treatment group was scored using the RACHS-1 classification system. The RACHS-1 classification is a scoring system used to predict the short-term mortality of congenital heart surgery in patients under 18 years of age (39). The risk categorization system for surgical procedures is divided into six different risk categories (39). Appendix 1 shows the RACHS-1 risk categories and related operations in the supplementary data.

Mortality rates in the study were calculated separately for CHD groups according to diagnoses and RACHS-1 classification categories. The risk factors that might affect mortality were determined by comparing the demographic, clinical, and interventional characteristics of patients with CCHD (serious [Group 4] and critical [Group 5]).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows, version 19.0 (IBM Corporation, Armonk, NY, USA). Numerical variables with a normal distribution were analyzed using the t-test and ANOVA, whereas those that were not normally distributed were evaluated using the Mann–Whitney U test and Kruskal–Wallis test. Mean±standard deviation and median (minimum–maximum) values were calculated as appropriate. The chi-square test and Fisher's exact test were used for comparisons between categorical variables. After determining the risk

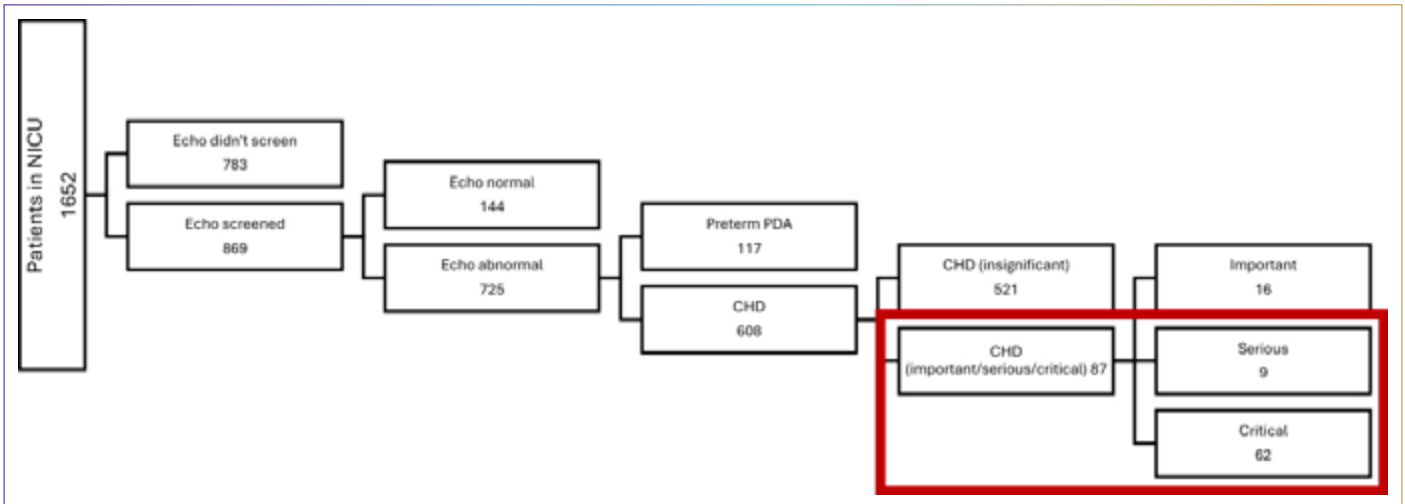

Figure 1. Echocardiographic evaluations of patients followed in the NICU between 2014 and 2015 and distribution of CHD.

CHD: Congenital heart disease; Echo: Echocardiography; NICU: Neonatal intensive care unit; PDA: Patients ductus arteriosus.

factors, univariate logistic regression analysis was performed, and parameters found to be significant were analyzed using multivariate regression analysis (full model, stepwise forward selection, and backward selection). Values of $p<0.05$ were considered statistically significant. Data analyses were carried out at the Department of Biostatistics, Ege University Faculty of Medicine.

RESULTS

This study included a cohort of 869 patients who underwent echocardiographic screening. Echocardiographic examinations were normal in 144 patients, while abnormalities were detected in the remaining 725 patients (83.4%). Among patients with abnormal echocardiographic findings, 117 (16.1%) had isolated PDA detected in preterm infants, while the remaining 608 patients (83.9%) had CHDs (Fig. 1). After excluding isolated PDA cases in preterm infants, a total of 608 patients remained, corresponding to 36.8% of all NICU patients. Echocardiographic abnormalities were classified as "insignificant" in 521 patients (31.6% of NICU patients), while the remaining patients were classified as "important" (n=16, 0.96% of NICU patients, 16/1652), "serious" (n=9, 0.54% of NICU patients, 9/1652), and "critical" (n=62, 3.75% of NICU patients, 62/1652) CHDs.

During the screening period, 6,440 live births were recorded at our center. In other words, 87 of 6,440 (1.3%) live births had CHD (important/serious/critical). The most common lesions in the "important," "serious," and "critical" CHD groups were TGA in 14 patients (2.3%, 14/608) and CoA in 14 patients (2.3%, 14/608). CHDs (important/serious/critical) were classified as cyanotic and acyanotic diseases in 54 (62%) and 33 (38%) patients, respectively. The numbers of cyanotic and acyanotic patients are shown in Appendix 2 in the supplementary data. In the acyanotic group, the most common diagnosis was aortic coarctation, observed in 16% of patients (14/87), as shown in Appendix 2. Similarly, in the cyanotic group, the most frequent diagnosis was transposition of the great arteries (TGA), also comprising 16% of the cohort (14/87), as detailed in Appendix 2.

In our study population, the mean gestational age was 37.1±2.4 (29–41) weeks, and the mean birth weight was 2,887±643 (1,010–4,230) g among the 87 patients with important/serious/critical CHD. Twenty-six patients (29%) were preterm (<37 weeks), and the median chronological age on the day of hospitalization was 1 day (IQR, 2; min, 1; max, 41). These demographic data are shown in Appendices 3, 4.

Serious/Critical Congenital Heart Diseases (CCHD): Demographic Data

Seventy-one of the 87 patients had serious/critical CHD. Demographic data, clinical features, and interventional characteristics of patients with CCHD are provided in the supplementary data (Appendices 3–5).

Among patients with CCHD, 43 had an antenatal fetal echocardiographic diagnosis of critical congenital heart disease, while 28 had no previous diagnosis during the fetal period. Among the patients who died, 24 had an antenatal diagnosis, while 8 had no antenatal diagnosis. This difference was statistically significant (p=0.024).

Seven patients with CCHD had genetic syndromes, including DiGeorge syndrome in one patient, LACTH syndrome in one patient, Turner syndrome in one patient, trisomy 18 in one patient, situs inversus totalis in one patient, and Johanson–Blizzard syndrome in one patient (Appendices 6, 7).

Mortality in Congenital Heart Diseases

The total number of neonatal deaths in the NICU was 132 during the two-year period (2014–2015), and patients who died with a diagnosis of CHD accounted for 24.2% (32/132) of all deaths. Other deaths were due to complications of prematurity, sepsis, and genetic and metabolic diseases. Of the 71 neonates with CCHD, 32 died, yielding an overall mortality rate of 45.1%.

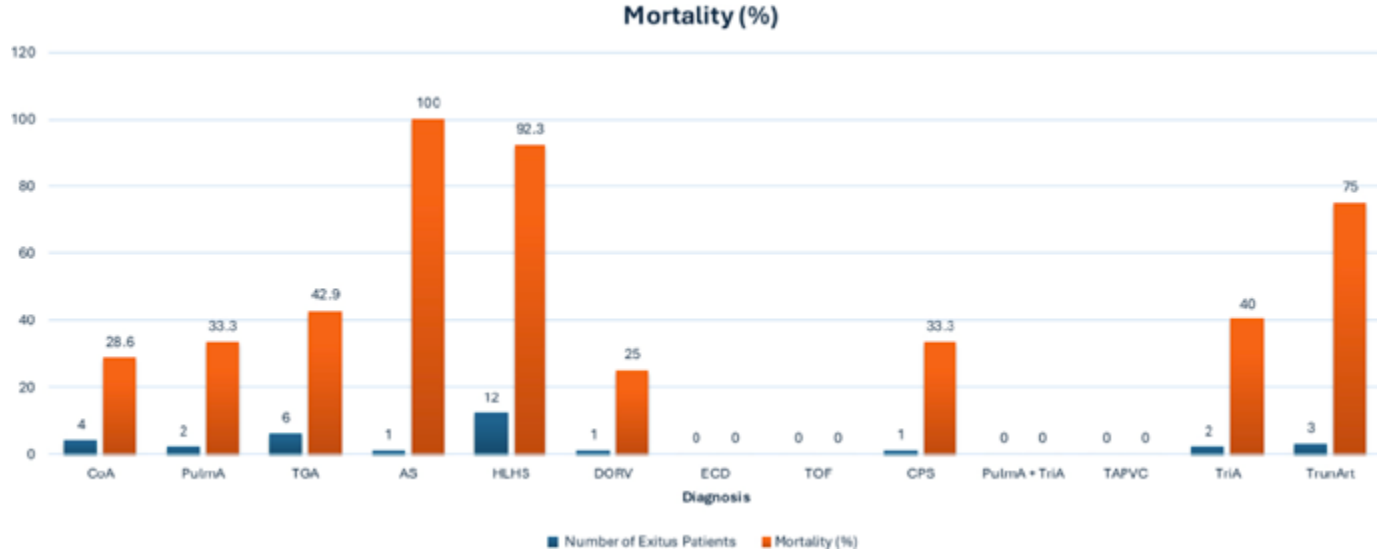

Figure 2. Mortality rates according to the diagnosises of CCHD.

AS: Aortic stenosis; CoA: Aortic coarctation; CPS: Critical pulmonary stenosis; DORV: Double output right ventricule; ECD: Endocardial cushion defect; HLHS: Left hypoplastic heart syndrome; PulmA: Pulmonary atresia; PTA: Truncus arteriosus; VSD: Ventricular septal defect; TAPVS: Total anomalous pulmonary venous connection; TOF: Tetralogy of fallot; TriA: Tricuspid atresia; CPS: Critical pulmonary stenosis.

Mortality was evaluated across the CHD groups. As expected, no patient in Group 4 (serious) died, whereas the mortality rate in Group 5 (critical) was 51.6% (32/62), which was statistically significant (p=0.003).

Fifty-three (74%) of the 71 patients with CCHD who underwent surgery were evaluated based on the RACHS-1 score. Eleven patients were classified as category 2, 26 as category 3, 7 as category 4, and 9 as category 6.

Among the 32 neonates who died, 10 (31%) died before surgery, while 6 (19%) and 16 (50%) died within 72 hours and after 72 hours following surgery, respectively. Four of the six early postoperative deaths occurred intraoperatively. The mean time to late postoperative death was 32.6±6.8 days (min–max, 4–90). The distribution of deceased patients according to diagnosis is summarized in Figure 2. The mortality of the 53 operated patients was evaluated using the RACHS-1 scoring system. Based on the RACHS-1 score, no patient died in category 2; the mortality rate was 34.6% in category 3, 42.9% in category 4, and 88.9% in category 6 (Appendix 8). A statistically significant difference was observed among the three groups (p=0.022).

Mortality rates were relatively high in patients diagnosed with aortic valve stenosis, HLHS, and truncus arteriosus. Early 3-month mortality in patients with CCHD according to surgical status was demonstrated by Kaplan–Meier analysis in Figure 3.

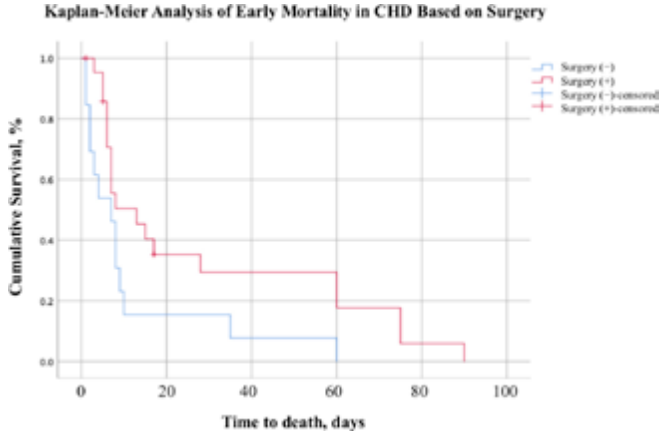

Figure 3. Kaplan-Meier curves demonstrating cumulative survival in CHD patients with and without surgical intervention. The x-axis indicates time to death (days), and the y-axis shows cumulative survival (%). Patients undergoing surgery exhibited higher early survival rates, particularly within the first 20 days. Censored observations are indicated on the curves.

Characteristics of Patients Who Died and Possible Risk Factors Associated with Mortality

Risk factors associated with mortality were investigated by comparing the demographic, clinical, and interventional characteristics of surviving and deceased neonates (Table 2).

When risk factors for mortality were compared between the groups, the need for mechanical ventilation during the preoperative period was significantly higher among patients who died (87% vs. 46%, p=0.004). Among the 71 patients with CCHD, 19 (26.7%) developed multiple organ failure (MOF) during the postoperative period. All patients who developed MOF died (p<0.001). Liver failure developed in 9 patients (12%), with a mortality rate of 66.6% (6/9). All 10 patients who developed renal failure died (p<0.001). Dialysis was performed in 5 patients, all of whom died. The mortality rate was 100% and was statistically significant (p<0.001). Among patients with CCHD, 17 of the 28 patients with sepsis survived, while 11 died. There was no statistically significant association between mortality in CHD and sepsis (p=0.156).

Table 2. Mortality-demographic data in CCHD

Demographics	Survived (n=39)	Died (n=32)	p
Gestational week, week, mean (±SD), min–max	37 (±1.9), 32–41	36 (±2.2), 31–40	0.143
Birth weight	3.021 (±547), 1590–4230	2.771 (±722), 1010–4000	0.186
Gender, n (%)			0.619
Male	27 (70)	20 (62.5)	
Female	12 (30)	12 (37.5)	
Antenatal diagnosis, n (%)	19 (48%)	24 (75%)	**0.024**
Age at diagnosis, days, mean (± SD), min–max	0 (IQR 5), 0–28	0 (IQR 0), 0–22	0.091
Those born in the outer center, n (%)	12 (30)	5 (15)	0.141
Gestational week <37, n (%)	7 (17.9)	11(34)	0.303
Birth Weight <2500, n (%)	7 (17.9)	10 (31)	0.369
Genetic Syndrome, n (%)	3 (7.6)	4 (12.5)	0.449
Clinical Findings			
Cyanosis, n (%)	26 (66)	28 (87)	0.166
Mechanical Ventilation, n (%)	18(46)	28 (87)	**0.004**
Mechanical Ventilation Time, median (IQR) min–max	7 (IQR 12), 1–31	9(IQR 15), 1–90	0.319
Ventilator-Associated Pneumonia, n (%)	4 (10)	4(12.5)	0.770
Sepsis, n (%)	17 (43.5)	11 (34)	0.156
MOF, n (%)	0	19 (59)	**<0.001**
Renal Insufficiency, n (%)	0	10 (31)	**<0.001**
Liver Failure, n (%)	3 (7.6)	6 (18.7)	0.285
Hematological Insufficiency, n (%)	2 (5.1)	2 (6.2)	0.839
Genetic abnormality, n (%)	3 (7.6)	4 (12.5)	0.502
Length of stay, median, n (%)	16 (IQR 24), 1–90	7.5 (IQR), 1–90	0.407
Interventional characteristics			
Prostaglandin Infusion, n (%)	23 (44)	30 (56%)	**0.003**
Atrial septostomy, n (%)	4	3	0.166
Atrial septostomy age, median (IQR) min–max	3 (IQR 15), 1–20	1 (IQR 0), 1–2	0.358
Surgical operation, n (%)	34 (87)	19 (60)	**0.007**
RACHS-1-2	11	0	**0.020**
RACHS-1-3	17	9	
RACHS-1-4	4	3	
RACHS-1-6	1	8	
Postoperative takeover time, median day (IQR) min–max	1(IQR 3), 0–14	2.5 (IQR 7.5), 1–12	0.232
Multiple inotrop requirements, n (%)	25 (52)	23 (48)	0.802
Preoperative arrhythmia, n (%)	1 (2.9)	5 (26)	0.830
Postoperative arrhythmia, n (%)	2 (5.8)	9 (47)	**0.009**

C/S: Cesarean section; IQR: Interquartile range; MOF: Multiple organ failure; RACHS-1: Risk adjustment for congenital heart surgery-1.

Initially, mortality risk in our study population was assessed, and then factors frequently reported in the literature were analyzed using univariate logistic regression for each variable, followed by multivariate logistic regression analysis to evaluate their combined effects. This approach allowed us to clearly distinguish the individual and collective impacts of these factors on mortality risk. The presence of an antenatal diagnosis, PGE1 infusion, inoperability, the need for invasive mechanical ventilation before surgery, and postoperative arrhythmia were identified as factors associated with an increased risk of mortality (Appendix 5).

Table 3. Risk and mortality relationship in CCHD

Features*	OR	95% CI	p (<0.05)
Prematurity (<37 weeks of gestational age)	2.898	0.315- 26.635	0.347
Birth Weight <2500 gr	5.271	0.668- 41.574	0.057
Genetic Syndrome	**17.310**	**1.043-28.716**	**0.010**
Having Antenatal Diagnosis	4.358	0.819- 23.185	0.084
PGE1 treatment requirement	3.720	0.468- 29.598	0.214
Ventilation before surgery	2.606	0.418- 16.250	0.305
Pre-operative arrhythmias	5.834	0.348-97.699	0.220
Post-operative arrhythmias	**42.664**	**4.128-44.968**	**0.002**

OR: Odds ratio; CI: Confidence interval; PGE1: Prostaglandin E1; *: Variables performed in Full Model Multiple Logistic Regression Analysis.

Table 4. Cox regression analysis of risk factors associated with mortality

Variables	B	SE	Wald	df	p	Exp(B) HR	95% CI for Exp(B)
Post-operative arrhythmias	0.807	0.800	1.018	1	0.313	2.242	0.467–10.756
Inoperability	0.938	0.433	4.684	1	0.030*	2.554	1.093–5.969
Genetic syndrome	0.317	0.627	0.256	1	0.613	1.374	0.402–4.699
Mechanical ventilation before surgery	0.609	0.617	0.973	1	0.324	1.839	0.548–6.166

B: Regression coefficient; SE: Standard error; Wald: Wald chi-square statistic; df: Degrees of freedom; Exp(B): Exponentiated B; HR: Hazard ratio; CI: Confidence interval; *: Among the variables analyzed, inoperability was significantly associated with an increased risk of mortality (p=0.030). Other factors did not reach statistical significance.

Forty-six of the 71 patients (64%) with CCHD received preoperative invasive mechanical ventilation. Among the patients who died, a higher proportion required preoperative mechanical ventilation than among survivors (87% vs. 46%, p=0.004). The median duration of mechanical ventilation was 7 days (IQR 12 [min–max: 1–31]) for survivors and 9 days (IQR 15 [min–max: 1–90]) for nonsurvivors, with no statistically significant difference between the two groups (p=0.319).

In the multivariate logistic regression analysis conducted for patients with CCHD (Table 3), postoperative arrhythmias were found to be the strongest predictor of mortality (OR: 42.6, 95% CI: 4.1–44.09, p=0.002). The presence of a genetic syndrome was also significantly associated with an increased risk of mortality (OR: 17.3, 95% CI: 1.04–28.7, p=0.010). Although other variables, such as low birth weight, antenatal diagnosis, RACHS-1 score, and preoperative mechanical ventilation, showed elevated odds ratios, they did not reach statistical significance.

Among the variables analyzed in the Cox regression model, inoperability was the only factor significantly associated with an increased risk of mortality (p=0.030; HR=2.55; 95% CI: 1.09–5.97). Postoperative arrhythmias, genetic syndromes, and preoperative mechanical ventilation did not reach statistical significance (Table 4).

DISCUSSION

In this retrospective single-center cohort, we evaluated the clinical characteristics, mortality outcomes, and factors associated with mortality among neonates with congenital heart disease admitted to a tertiary neonatal intensive care unit (NICU), with a particular focus on critical congenital heart disease (CCHD). Among 608 neonates with CHD identified after exclusion of isolated patent ductus arteriosus in preterm infants, 71 (11.7%) were classified as having critical CHD. The proportion of CCHD among neonates with CHD was 11.7%, rather than representing the population-based incidence of CCHD. Thirty-two of the 71 patients with CCHD died, corresponding to an overall mortality rate of 45.1% within the CCHD group. Importantly, CCHD accounted for 24.2% of all neonatal deaths occurring in our NICU during the study period, emphasizing the substantial contribution of severe cardiac disease to neonatal mortality in a tertiary-care setting.

Previous studies have emphasized that undiagnosed or late-diagnosed CCHD remains a significant cause of neonatal death, underlining the need for early detection and intervention (40). In particular, neonates with CCHD account for a disproportionately high proportion of ICU mortality compared with other patient groups, reflecting the severity and complexity of their condition (41). Furthermore, the American Heart Association and the American Academy of Pediatrics have jointly stated that accurate estimation of the burden of CCHD-related mortality is critical for shaping effective screening policies and guiding healthcare resource allocation (42). Therefore, presenting the proportion of CCHD-related deaths among all NICU deaths in our study provides clinically

relevant insight into the disease burden and supports the importance of early diagnosis and specialized care pathways.

In this study, almost all patients (n=32) who died were in the CCHD group. Only one patient with a diagnosis of ASD in the non-CCHD group died due to intracranial hemorrhage associated with a vein of Galen aneurysm. Forty percent of the patients who died had complex cardiac pathologies, such as hypoplastic left heart syndrome (HLHS), while others had TGA and CoA.

It has been reported that 24% of patients with important/severe/critical CHD had acyanotic heart disease, while the remaining 76% had cyanotic heart disease, and 73% of these patients had duct-dependent circulation. Prostaglandin infusion was initiated preoperatively in patients requiring urgent surgery. In our study, 28 (87%) of the patients who died had cyanotic CHDs. Cyanotic CHDs account for approximately one-third of fatal cases among all CHDs (43).

Considering our study cohort, antenatal diagnosis, PGE1 infusion, inoperability, the need for preoperative mechanical ventilation support, and postoperative arrhythmia were associated with an increased risk of mortality. Üstün et al. (44) identified significant independent variables associated with mortality, including gestational age, the presence of associated disease, preoperative mechanical ventilation requirement, pulmonary hypertension, sepsis, RACHS-1 score, postoperative low cardiac output, and heart failure. Cheng et al. (30) identified independent risk factors associated with mortality in 174 patients undergoing cardiac intervention, including 5-minute Apgar scores <7, preoperative mechanical ventilation requirement, and RACHS-1 scores >4. In our study, only two infants had Apgar scores <7. The mean 5-minute Apgar score was 8.9±0.93 (min–max, 6–10). The results did not support a strong association between the Apgar score and mortality in our cohort (p=0.072).

Several risk-scoring systems are used in the field of CHD surgery, and RACHS-1 has been accepted as one of the most reliable scoring systems. The degree of surgical complexity has been recognized as one of the factors associated with increased mortality both in Türkiye and worldwide. In the current study, the majority of patients (49%, 26/53) were classified as category 3. The highest mortality rate was observed in RACHS-1 risk category 6, at 88.9%. There was a significant association between mortality and RACHS-1 score (p=0.020). In addition, contemporary studies increasingly use alternative risk-adjustment systems, including the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality categories (45). Therefore, direct comparisons of surgical mortality across studies should take into account differences in risk-adjustment methodology.

Previous studies from different parts of the world have reported 1-year mortality rates of approximately 24.1%–25.5% among neonates with CCHD (11, 46).

In a nationwide study covering 2018–2021, Çaylan et al. (24) reported that CCHD-related deaths accounted for 9.8% of all infant deaths and 8.0% of all neonatal deaths, with a CCHD-specific infant mortality rate of 8.8 per 10,000 live births. Although these population-based mortality estimates cannot be directly compared with the 45% mortality observed within the first three months of life among neonates with CCHD admitted to our tertiary NICU, this rate was higher than the 35.2% reported by Üstün et al. (44) in another Turkish cohort, highlighting the substantial mortality burden associated with CCHD in this population. However, more recent Turkish data suggest a substantial improvement in outcomes over time. Dilli et al. (45) recently reported the results of a multicenter study involving 488 neonates with CCHD treated at nine tertiary centers in Türkiye between October 2021 and November 2022. In that cohort, in-hospital mortality was 20.1% and postoperative mortality was 19.6%, considerably lower than the mortality observed in our 2014–2015 cohort. This difference may reflect advances in prenatal diagnosis, neonatal stabilization, cardiac surgical techniques, perioperative management, intensive care practices, and access to advanced postoperative support over the intervening years. It may also reflect differences in case mix and referral patterns between a single-center historical cohort and a multicenter registry. Therefore, the difference in mortality should not be interpreted as a direct comparison of center performance but rather as evidence of the evolving outcomes of neonatal CCHD care in Türkiye. Despite the difference in overall mortality, the two Turkish cohorts demonstrated important similarities in the factors associated with adverse outcomes. In our study, preoperative PGE1 use was associated with increased mortality, and PGE1 requirement was also identified as an independent risk factor in the multicenter study by Dilli et al (45). PGE1 requirement is likely to represent the underlying physiological severity of the cardiac lesion, particularly ductal-dependent systemic or pulmonary circulation, rather than a direct harmful effect of the treatment itself. This concordance between two cohorts from different periods supports the importance of underlying disease severity and ductal dependency as persistent determinants of neonatal outcomes. A comparison of the two cohorts is presented in Table 5.

The specific postoperative predictors differed between the two studies. In our cohort, postoperative arrhythmia was the strongest independent predictor of mortality in multivariable logistic regression, while the presence of a genetic syndrome was also independently associated with increased mortality. In contrast, Dilli et al. (45) identified higher vasoactive-inotropic support (VIS>17.5), major postoperative complications, and early postoperative extracorporeal membrane oxygenation as independent predictors of mortality. These apparently different predictors may represent different manifestations of a common underlying pathway: greater disease severity, hemodynamic instability, and postoperative organ dysfunction.

Thanks to advances in NICU technology and healthcare, as well as the development of mechanical ventilators, the survival rate and prognosis of children with chronic conditions such as congenital heart disease have improved over time (43). Previous studies, such as that by Üstün et al. (44), have also reported an association between preoperative mechanical ventilation and

Table 5. Comparison of mortality outcomes and associated risk factors in two Turkish CCHD cohorts

Characteristic	Present study	Dilli et al. (45)
Study period	2014–2015 (two years)	2021–2022 (one year)
Study design	Retrospective, single-center	Multicenter
Number of centers	1	9
CCHD cohort	71	488
Cardiac surgery	53/71 (74.6%)	325/488 (66.6%)
Mortality outcome	32/71 (45.1%)	20.1% in-hospital
CCHD-related deaths among all NICU deaths	32/132 (24.2%)	—
Surgical risk scores	RACHS-1	STAT
Preoperative PGE1 infusion	Associated with mortality	Independent mortality risk factor
Preoperative mechanical ventilation	Associated with mortality	Not reported as an independent major predictor
Postoperative arrhythmia	Strongest multivariable predictor	—
Genetic syndrome	Independent predictor	Extracardiac anomalies reported in 12.9%
High vasoactive support	—	VIS >17.5 associated with mortality
Major postoperative complications	—	Independent mortality risk factor
Early postoperative ECMO	—	Independent mortality risk factor
Cox regression	Inoperability	Not the principal analysis
Main contribution	Detailed mortality-risk assessment in a tertiary NICU cohort	Contemporary multicenter Turkish epidemiology and outcomes

CCHD: Critical congenital heart disease; ECMO: Extracorporeal membrane oxygenation; NICU: Neonatal intensive care unit; PGE1: Prostaglandin E1; RACHS-1: Risk adjustment for congenital heart surgery-1; STAT: Society of thoracic surgeons–european association for cardio-thoracic surgery congenital heart surgery mortality categories; VIS: Vasoactive-inotropic score.

increased mortality in patients with CCHD undergoing cardiac intervention. However, it is important to consider that this association likely reflects the severity of the patients' underlying cardiac conditions rather than complications directly related to mechanical ventilation. Factors such as poor cardiac function, resistance to medical therapy, and the need for high-dose inotropes contribute significantly to this outcome. Although patients requiring mechanical ventilation had higher mortality, the focus should not solely be on limiting its use. Instead, the goal should be to avoid unnecessary mechanical ventilation while recognizing that invasive mechanical support can be life-saving in critically ill patients when appropriately indicated. Reducing the duration of mechanical ventilation remains an important treatment goal, but clinical judgment must prioritize patient stability and survival.

Limitations

This study has several limitations. First, its retrospective and single-center design limits generalizability and introduces the possibility of selection and information bias. Second, the relatively small number of patients with CCHD limits statistical power and results in wide confidence intervals for some multivariable estimates, particularly for postoperative arrhythmia and genetic syndromes. Third, the study period predates major advances in neonatal cardiac surgery, intensive care, and extracorporeal support; therefore, the mortality estimates should not be considered representative of current national outcomes. Fourth, RACHS-1 was used for surgical risk adjustment, whereas contemporary multicenter studies may use alternative systems such as STAT, limiting direct comparisons between studies. Finally, our definition of CCHD was operationalized according to the serious/critical classification used in this study and should therefore be interpreted in the context of that classification rather than assumed to be directly equivalent to all contemporary definitions of CCHD.

CONCLUSION

In conclusion, CCHD was associated with substantial mortality in this tertiary NICU cohort, accounting for nearly one-quarter of all neonatal deaths. Higher surgical complexity, poor preoperative clinical condition, PGE1 requirement, postoperative arrhythmia, genetic syndromes, and postoperative organ dysfunction were associated with adverse outcomes. Importantly, comparison with multicenter Turkish data suggests a marked improvement in CCHD survival over time. Nevertheless, the persistence of disease severity and postoperative physiological instability as major determinants of outcome underscores the importance of early diagnosis, timely referral, appropriate preoperative stabilization, and high-quality perioperative cardiac intensive care. These findings provide a benchmark and may help contextualize the evolution of neonatal CCHD outcomes in Türkiye.

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Appendix 1. RACHS-1 risk categories*

RACHS-1 risk category	Category operation
Risk category -1	- Atrial septal defect surgery (secundum, sinus venosus, PFO closure) - Aortopexy - Patent ductus arteriosus surgery (>30 days) - Coarctation repair (>30 days) - Partially anomalous pulmonary venous connection surgery
Risk category -2	- Aortic valvotomy or valvuloplasty (>30 days) - Subaortic stenosis resection - Pulmonary valvotomy or valvuloplasty - Pulmonary valve replacement - Right ventricular infundibulectomy - Pulmonary outflow tract augmentation - Repair of coronary artery fistula - Atrial and ventricular septal defect repair - Atrial septal defect primum repair - Ventricular septal defect repair - VSD closure + pulmonary valvotomy/infundibular resection - VSD closure + pulmonary artery band removal - Repair of unspecified septal defect - Total repair of tetralogy of Fallot - Repair of total anomalous pulmonary veins (>30 days) - Glenn shunt - Vascular ring surgery - Repair of aorta-pulmonary window - Coarctation repair (≤30 days) - Repair of pulmonary artery stenosis - Transection of pulmonary artery - Common atrium closure - Left ventricular to right atrial shunt repair
Risk category -3	- Aortic valve replacement - Ross procedure - Left ventricular outflow tract patch - Ventriculomyotomy - Aortoplasty - Mitral valvotomy or valvuloplasty - Mitral valve replacement - Valvectomy of tricuspid valve - Tricuspid valvotomy or valvuloplasty - Tricuspid valve replacement - Tricuspid valve repositioning for Ebstein anomaly (>30 days) - Repair of anomalous coronary artery (without intrapulmonary tunnel) - Repair of anomalous coronary artery (with Takeuchi intrapulmonary tunnel) - Closure of semilunar valve (aortic or pulmonary) - Right ventricular to pulmonary artery conduit - Left ventricular to pulmonary artery conduit - Repair of double-outlet right ventricle (+/- RV obstruction repair) - Fontan procedure - Repair of transitional/complete AV canal (+/- valve replacement) - Pulmonary artery banding - Repair of tetralogy of Fallot with pulmonary atresia - Repair of cor triatriatum - Systemic-to-pulmonary artery shunt - Atrial switch operation - Arterial switch operation - Reimplantation of anomalous pulmonary artery - Annuloplasty - Repair of coarctation + VSD closure - Excision of intracardiac tumor

Appendix 1 (cont). RACHS-1 risk categories*

RACHS-1 risk category	Category operation
Risk category -4	- Aortic valvotomy or valvuloplasty (≤30 days) - Konno procedure - Repair of complex anomaly (single ventricle) with VSD enlargement - Repair of total anomalous pulmonary veins (≤30 days) - Atrial septectomy - Rastelli repair (transposition, VSD, subpulmonary stenosis) - Atrial switch + VSD closure - Atrial switch + repair of subpulmonary stenosis - Arterial switch + pulmonary artery band removal - Arterial switch + VSD closure - Arterial switch + repair of subpulmonary stenosis - Repair of truncus arteriosus - Repair of hypoplastic/interrupted arch without VSD closure - Repair of hypoplastic/interrupted arch with VSD closure - Transverse arch graft - Unifocalization for tetralogy of Fallot + pulmonary atresia - Double switch
Risk category -5	- Tricuspid valve repositioning for neonatal Ebstein anomaly (≤30 days) - Repair of truncus arteriosus + interrupted arch
Risk category -6	- Stage 1 repair of hypoplastic left heart syndrome (Norwood) - Stage 1 repair of nonhypoplastic left heart conditions - Damus-Kaye-Stansel procedure

*: Adapted from article written by Jenkins et al. (39)

Appendix 2. Types of congenital heart diseases within the study group

Acyanotic heart diseases (N=33)	N	% (n/87)	Cyanotic heart diseases (N=54)	N	% (n/87)
Coarctation of aortica	14	16	D-Great Artery Transposition	14	16
Severe pulmonary stenosis	3	3.4	HLHS	13	14.9
AVSD	6	6.8	Pulmonary valve atresia	5	5.7
ASD	4	4.4	Tricuspid valve atresia	6	6.8
VSD	3	3.4	Pulmonary valve atresia + Tricuspid valve atresia	3	3.4
Tricuspid insufficiency	2	2.2	DORV	5	5.7
Aortic stenosis	1	1.1	Persistant truncus arteriosus	4	4.5
			TAPVC	2	2.2
			TOF	2	2.2

ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; DORV: Double output right ventricule; HLHS: Left hypoplastic heart syndrome; VSD: Ventricular septal defect; TAPVC: Total anomalous pulmonary venous connection; TOF: Tetralogy of Fallot.

Appendix 3. Demographics, clinical findings, and interventional characteristics of the patients with CCHD

Demographics	n=71
Gestational age, week, mean (±SD), min–max	37.2 (±1.9), 32–41
Birth weight, gr	2.900 (±640), 1010–4230
Gender, n (%)	
Female	24 (33)
Male	47 (66)
Hospitalization day, day, mean (±SD), min–max	55 (77)
Antenatal diagnosis, n (%)	0 (IQR 1), 0–34
Those born in the outer center, n (%)	43 (60)
Maternal age	17 (23)
Hospitalization day, day, mean (±SD), min–max	28.5 (±6.3), 17–52
Age at diagnosis	
Ege University birth	2.3 (±1.9), 1–7
Eccentric birth	8.2 (±7.4), 1–22
Age at diagnosis, days, mean (±SD), min–max	4.4 (±3.6), 1–22
Clinical findings	
Cyanosis N, %	54 (76)
Mechanical ventilation, n (%)	46 (64%)
Mechanical ventilation time, median	8 (IQR 25), 1–90
Ventilator-associated pneumonia, n (%)	8 (17)
Sepsis	28 (39)
Early sepsis	12 (17)
Late sepsis	16 (22)
Proven sepsis	8 (11)
MOY	19 (26)
Renal insufficiency	10 (14)
Liver failure	9 (12)
Hematological Insufficiency	4 (5.6)
Immunodeficiency	2 (2)
Genetic abnormality	7 (9.8)
Length of stay	13 (IQR 19), 1–90
Interventional characteristics	
Prostaglandin infusion, n (%)	52 (73)
Atrial septostomy, n (%)	7 (9.8)
Atrial septostomy age, days, median (IQR)	1 (IQR 19)
The surgical operation, n (%)	53 (74)
RACHS-1-2	11 (21)
RACHS-1-3	25 (48)
RACHS-1-4	7 (13.4)
RACHS-1-6	9 (17)
Operation Day, mean±(min–max)	13.9±4.5 (0–90)
Postoperative takeover time, days, mean±(min–max)	3.48±3.6 (0–14)
Need of multiple inotrope drugs, n (%)	47 (90)
Preoperative arrhythmia, n (%)	6 (8.4)
Postoperative arrhythmia, n (%)	11 (21)
Mortality, n (%)	32 (45)

CCHD: Critical congenital heart disease; IQR: Interquartile range; MOY: Multiple organ failure; RACHS-1: Risk adjustment in congenital heart surgery-1; SD: Standard deviation.

Appendix 4. Demographic data in patients with congenital heart disease

Characteristics	Patients with (important/severe/critical) CHD (n= 87)	Patients with CCHD (severe/critical) (n=71)
Gestational age, weeks, mean±SD (min–max)	37.1±2.4 (29–41)	37.2 (±1.9), 32–41
Birth weight, g, mean±SD (min–max)	2.887±643 (1010–4230)	2.900±640 (1010–4230)
Gender, n (%)		
Female	32 (36)	24 (33)
Male	55 (63)	47 (66)
Cesarean delivery, n (%)	69 (79)	55 (77)
Preterm birth (<37 weeks), n (%)	28 (32.1)	26 (36.6)
Multiple pregnancy (twins, triplets), n (%)	8 (9.1)	7 (9.8)
Assisted reproductive technology (ART), n (%)	6 (6.8)	6 (8.4)
Maternal age, years, mean±SD (min–max)	28.7±6.2 (17-–52)	28.5±6.3 (17–52)

ART: Assisted reproductive technology; CCHD: Critical congenital heart disease; CHD: Congenital heart disease; SD: Standard deviation.

Appendix 5. Risk and mortality relationship in CCHD as a result of univariate model in logistic regression analysis

Features	OR	95% CI	p
Prematurity (<37 weeks of gestational age)	1.926	0.55–6.69	0.303
Birth weight ≤ 2500 gr	2.300	0.95–7.16	0.118
Type of Delivery, C / S	1.500	0.74–1.10	0.461
Gender, male	1.300	0.53–3.60	0.551
Antenatal diagnosis	**3.100**	**1.14–8.73**	**0.024**
Length of hospital stay (days)	1.000	0.87–1.10	0.930
Age at diagnosis of CHD	1.100	0.97–1.22	0.116
Assisted reproductive techniques (ARTs)	1.900	0.39–12.2	0.493
Apgar 5, <7	1.400	0.96–2.20	0.251
Genetic syndrome	1.871	0.37–9.46	0.449
Acyanotic heart defects	2.400	0.74–7.70	0.143
Prostaglandin infusion before surgery	**6.700**	**1.70–25.90**	**0.006**
Inoperability	**4.600**	**1.40–15.00**	**0.010**
After surgery admission time to NICU	1.000	0.77–1.80	0.311
Need of mechanical ventilation	**8.100**	**2.40–27.70**	**0.001**
Ventilation time	0.970	0.93–1.00	0.278
Ventilator-associated pneumonia	1.200	0.94–1.10	0.541
Clinical Sepsis	1.800	0.75–5.00	0.203
Proven Sepsis	2.200	0.36–13.70	0.382
Need of inotropic drugs	1.200	0.40–3.30	0.681
Preop. Arrhythmias	7.037	0.77–63.69	0.830
Postop. Arrhythmias	**8.409**	**1.60–41.00**	**0.009**

ART: Assisted reproductive technology; C/S: Cesarean section; CCHD: Critical congenital heart disease; CHD: Congenital heart disease; CI: Confidence interval; NICU: Neonatal intensive care unit; OR: Odds ratio; Postop: Postoperative; Preop: Preoperative.

Appendix 6. Neurological findings in CCHD

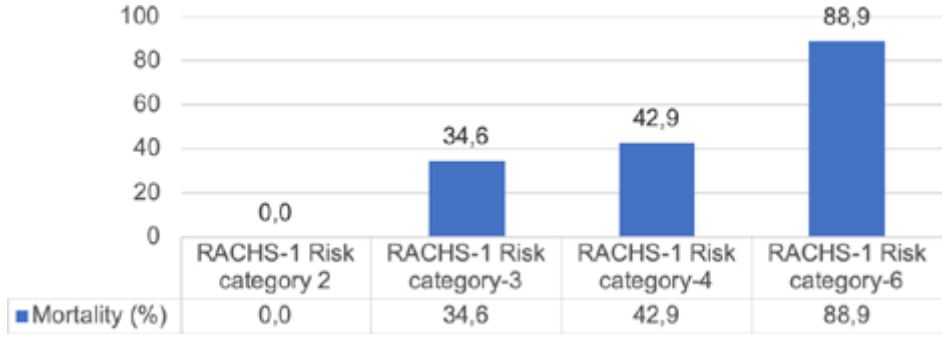
Features	N=71, %
Seizures	16 (22)
Intracranial hemorrhage	3 (4.2)
Ischemia	2 (2.8)
Cerebral Infarct	2 (2.8)
Diffuse Cerebral Atrophy	2 (2.8)
Abnormal USG	17 (23)
Abnormal CT	4 (5.6)
Abnormal MRI	9 (12.6)

CCHD: Critical congenital heart disease; CT: Computed tomography; MRI: Magnetic resonance imaging; USG: Ultrasonography.

Appendix 7. Patients diagnosed with genetic syndromes in CHD

Genetic syndrome	Diagnosis	Prognosis
Turner syndrome	Aortic coarctation	Discharged
Situs inversus totalis	DORV + TGA	Discharged
LACHT syndrome	Endocardial cushion defect	Discharged
Trisomy 18	Hypoplastic left heart syndrome	Deceased
Johanson-Blizzard syndrome	TGA	Deceased
Noonan syndrome	Pulmonary atresia	Deceased
DiGeorge syndrome	Hypoplastic left heart syndrome	Deceased

DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome; TGA: Transposition of the great arteries.



Appendix 8. Mortality in CCHD patients according to RACHS-1 risk categories.

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ORIGINAL RESEARCH
Pediatrics Emergency

Extended-spectrum beta-lactamase-producing gram-negative urinary tract infections in children: A retrospective children's hospital experience

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ABSTRACT

Objective: Extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria are an increasing concern in pediatric urinary tract infections (UTIs), contributing to antimicrobial resistance, limited treatment options, and higher recurrence rates. This study aimed to identify the risk factors associated with ESBL-positive Gram-negative UTIs in children and evaluate antimicrobial susceptibility patterns.

Material and Methods: Medical records of pediatric patients aged 1 month to 18 years with culture-confirmed ESBL-producing Gram-negative UTIs were retrospectively reviewed between January 2015 and December 2020 at a tertiary pediatric hospital in Istanbul. Both inpatient and outpatient cases were included. Data extracted from electronic records included demographic characteristics, clinical presentation, comorbidities, recent antibiotic use, prior hospitalization or surgery, intensive care unit (ICU) admission, use of urinary or central venous catheters, and total parenteral nutrition (TPN).

Results: Among 4,722 positive pediatric urine cultures, ESBL-producing Gram-negative organisms were identified in 215 cases (4.6%). After applying the inclusion criteria, 184 patients were analyzed. The cohort showed a female predominance (80.4%), with a median age of 57 months. Presentations included cystitis (60.9%) and pyelonephritis (39.1%). Common risk factors were recent antibiotic use (44%) and prior hospitalization (12.5%). Antimicrobial susceptibility testing demonstrated high in vitro activity for meropenem, fosfomycin, and amikacin (>90%). No treatment failure or urosepsis occurred during the initial episode. Recurrent UTIs were observed in 10.3% of cases.

Conclusion: ESBL-producing Gram-negative UTIs highlight the need for risk-based evaluation and antimicrobial stewardship. Fosfomycin and nitrofurantoin may be suitable oral options pending culture results, while meropenem remains effective for severe infections.

Keywords: Antibiotic resistance; children; *Enterobacteriaceae*; extended-spectrum beta-lactamases; urinary tract infections.

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Genişlemiş spektrumlu beta-laktamaz üreten gram-negatif idrar yolu enfeksiyonları olan çocuklar: Retrospektif bir çocuk hastanesi deneyimi

ÖZET

Amaç: Genişlemiş spektrumlu beta-laktamaz (ESBL) üreten Gram-negatif bakteriler, pediatrik idrar yolu enfeksiyonlarında (İYE) giderek artan bir sorun olup antimikrobiyal direnç, sınırlı tedavi seçeneklerine ve daha yüksek nüks oranlarına katkıda bulunmaktadır. Bu çalışmanın amacı, çocuklarda ESBL pozitif Gram-negatif İYE ile ilişkili risk faktörlerini belirlemek ve antimikrobiyal duyarlılık paternlerini değerlendirmektir.

Gereç ve Yöntemler: İstanbul'daki üçüncü basamak bir çocuk hastanesinde Ocak 2015 ile Aralık 2020 tarihleri arasında kültürle doğrulanmış ESBL üreten Gram-negatif İYE tanısı alan 1 ay–18 yaş arası pediatrik hastaların tıbbi kayıtları retrospektif olarak incelendi. Hem yatan hem de ayaktan başvuran hastalar çalışmaya dahil edildi. Elektronik kayıtlardan elde edilen veriler; demografik özellikler, klinik başvuru şekli, komorbiditeler, yakın zamanda antibiyotik kullanımı, önceki hastaneye yatış veya cerrahi öyküsü, yoğun bakım ünitesi (YBÜ) yatışı, üriner veya santral venöz kateter kullanımı ve total parenteral beslenme (TPN) durumunu içermektedir.

Bulgular: Toplam 4.722 pozitif pediatrik idrar kültürü arasında ESBL üreten Gram-negatif mikroorganizmalar 215 olguda (%4,6) saptandı. Dahil edilme kriterlerinin uygulanmasının ardından 184 hasta analiz edildi. Kohortta kadın cinsiyet baskındı (%80,4) ve medyan yaş 57 aydı. Klinik başvurular sistit (%60,9) ve piyelonefrit (%39,1) şeklindeydi. En sık risk faktörleri yakın zamanda antibiyotik kullanımı (%44) ve önceki hastaneye yatış (%12,5) idi. Antimikrobiyal duyarlılık testleri, meropenem, fosfomisin ve amikasin için yüksek in vitro etkinlik göstermiştir (>%90). İlk enfeksiyon epizodu sırasında tedavi başarısızlığı veya ürosepsis gözlenmemiştir. Olguların %10,3'ünde tekrarlayan İYE gelişmiştir.

Tartışma: ESBL üreten Gram-negatif İYE'ler, risk temelli değerlendirme ve antimikrobiyal yönetimin önemini vurgulamaktadır. Kültür sonuçları beklenirken fosfomisin ve nitrofurantoin uygun oral tedavi seçenekleri olabilirken ağır enfeksiyonlarda meropenem etkinliğini korumaktadır.

Anahtar Kelimeler: Antibiyotik direnci; çocuklar; *Enterobacteriaceae*; genişlemiş spektrumlu beta-laktamazlar; idrar yolu enfeksiyonları.

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INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in children and are most frequently caused by *Enterobacteriaceae* species such as *Escherichia coli* and *Klebsiella* spp. Over recent decades, resistance to β-lactam antibiotics among Gram-negative bacteria has significantly increased, largely due to the emergence of extended-spectrum β-lactamases (ESBLs) (1, 2). ESBL-producing *Enterobacteriaceae* (ESBL-PE) are now increasingly prevalent worldwide, affecting both adults and children and posing a serious therapeutic challenge in both community and hospital settings (3–6). With the World Health Organization warning about a "post-antibiotic era," healthcare providers must carefully balance the effective treatment of ESBL-PE infections with efforts to prevent further antibiotic resistance (7).

While a recent meta-analysis reported a pooled ESBL-UTI prevalence of 14% in children (8), findings from individual studies vary substantially, with reported rates ranging from 3.8% to 15.5%, depending on local epidemiology, patient demographics, and healthcare practices (9, 10).

Despite the growing body of research on ESBL-PE in pediatric populations, knowledge gaps remain, particularly regarding the identification of clinical and demographic risk factors. A summary of the identified risk factors for ESBL-positive infections, categorized by study, population, and reported determinants, is presented in Table 1.

However, findings vary significantly across populations and settings, and the consistency and predictive value of these risk factors remain uncertain. Understanding these predictors is essential for guiding empirical treatment and infection control strategies. Although multiple recent studies have examined similar risk factors in pediatric populations, data from different regions remain limited. Therefore, the primary aim of this study was to identify the risk factors associated with pediatric ESBL-positive UTIs, while the secondary aim was to evaluate antibiotic susceptibility patterns in urine cultures of affected children, thereby contributing region-specific evidence to the existing literature.

MATERIAL AND METHODS

A single-center retrospective study was conducted using medical records collected between January 1, 2015, and December 31, 2020. The study included children aged 1 month to 18 years who were either hospitalized or presented to the pediatric outpatient

Table 1. Summary of risk factors for ESBL-positive infection categorized by study, population, and the major risk factors reported

Study	Population	Significant risk factors for ESBL-positive infection
Çelebi (Türkiye, 2009) (17)	Pediatric	PICU stay, hospital-acquired infection broad/prolonged antibiotic use, immunosuppressive therapy, blood transfusion, central venous catheter, TPN, prolonged hospitalization
Dayan (Israel, 2013) (31)	Pediatric	Longer hospital stay, recent hospitalization, previous UTI, urinary tract anomalies, cephalexin prophylaxis, *Klebsiella* spp. infection
Biehl (2016) (32)	Mixed (adult and pediatric)	Prior antimicrobial use, recent hospitalization, recent/repeated surgery
Flokas (USA, 2016) (8)	Pediatric	Prior antibiotic use, hospitalization, surgical interventions, healthcare contact
Park (Korea, 2017) (26)	Pediatric	Previous hospitalization, high recurrence rate, prolonged pre-onset hospitalization
Tüzün (Türkiye, 2019) (33)	Adult/mixed	Healthcare-associated UTI, antibiotics in past 6 months
Lu (China, 2022) (34)	Pediatric	Age <12 months, urological anomalies (VUR), urodynamic changes, neurologic disorders, undernutrition, recent antibiotic use (past 3 months), previous UTI (past 3 months)
Collingwood (2023) (4)	Adult	Male sex, history of urology care, previous antibiotic exposure
Bousseta (Tunisia, 2023) (19)	Pediatric	Antibiotic use (past 3 months), prophylaxis, hospitalization (past year), outpatient care (past 6 months), age >6 years
Bursal (Türkiye, 2025) (14)	Pediatric	Blood in urine, high CRP

ESBL: Extended spectrume beta lactamases; PICU: Pediatric intensive care unit; UTI: Urinary tract infection; VUR: Vesicourethral reflux.

clinics of our tertiary referral hospital in Istanbul. All cases involved urinary tract infections (UTIs) caused by ESBL-producing Gram-negative bacteria, confirmed by urine culture. Both inpatient and outpatient cases were analyzed. No additional follow-up was conducted beyond the documented clinical encounter. The study was approved by the Institutional Research Ethics Committee of the hospital (05.05.2021/108). As this study was conducted retrospectively using previously recorded data, obtaining informed consent from participants was not required.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) age between 1 month and 18 years, (2) diagnosis of UTI confirmed by a positive urine culture, and (3) isolation of ESBL-producing Gram-negative bacteria.

The exclusion criteria included the following: (1) urine samples collected using urine bags, (2) polymicrobial growth in cultures, (3) bacterial counts below diagnostic thresholds, and (4) missing key clinical or laboratory data in patient records.

Data Collection

The following variables were analyzed: patient demographic data, type of clinical encounter (inpatient or outpatient), presence of systemic or urinary tract comorbidities, and underlying conditions such as congenital or acquired urogenital system anomalies, chronic endocrine or congenital diseases, and immunodeficiency. Additional variables included recent antibiotic use (within the previous 30 days), use of nasogastric tubes (NGTs), presence of indwelling urinary catheters or central venous lines, and presenting symptoms (e.g., fever, vomiting, diarrhea, anorexia, dysuria, lumbar or flank pain, and urinary incontinence). Physical examination findings (e.g., costovertebral angle tenderness and suprapubic pain), ICU (intensive care unit) admission, total parenteral nutrition (TPN) administration, and duration of hospitalization were also recorded.

Definitions

Acute pyelonephritis and cystitis were defined based on standard clinical guidelines (11, 12). Acute upper UTI was defined as bacteriuria accompanied by either fever ≥38°C or a lower-grade fever with flank pain or tenderness. Lower UTI (cystitis) was defined as bacteriuria without systemic symptoms. The diagnosis of UTI was confirmed via urine culture, with thresholds defined as $\geq 10^3$ CFU/mL for suprapubic aspiration, $\geq 10^4$ CFU/mL for bladder catheterization, and $\geq 10^5$ CFU/mL for clean-catch midstream samples (12).

Microbiological Analysis

Urine samples were incubated on 5% blood agar plates (BAPs) and chromogenic plates for ESBL (CPSE, ChromID® ESBL Agar; bioMérieux, Hazelwood, MO, USA) at 37°C for 18–24 hours. Urinary pathogen identification and antimicrobial susceptibility testing were performed using the VITEK® 2 Compact automated system (bioMérieux).

ESBL production was confirmed by the hospital microbiology laboratory in accordance with EUCAST guidelines (13). The diagnosis of comorbidities and device usage was validated through clinical documentation and imaging reports.

Table 2. Risk factors associated with ESBL-positive urinary tract infections

Risk factors	n (%)
History of hospitalization in last 3 months	23 (12.5)
History of antibiotic use in last 3 months	81(44)
History of surgery in last months	6 (3.3)
Immunosuppression	1 (0.5)
Malnutrition	1 (0.5)
Presence of gastrostomy	1 (0.5)
Presence of a central venous catheter	2 (1.1)
Presence of indwelling urinary catheters	3 (1.6)

ESBL: Extended spectrume beta lactamases.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Numerical variables are presented as mean±standard deviation (SD), as well as median, minimum, and maximum values. Categorical variables are expressed as frequencies (n) and percentages (%).

RESULTS

During the study period, 4,722 urine cultures from children aged between 1 month and 18 years were positive. ESBL-positive Gram-negative microorganisms were isolated in 215 cultures (4.6%). Of the 215 cases initially identified, 31 were excluded due to incomplete medical records. The final study population comprised 184 patients with culture-confirmed ESBL-producing Gram-negative urinary tract infections, of whom 148 (80.4%) were female and 36 (19.6%) were male. The median age at diagnosis was 57 months (range: 1–203 months).

Urine culture samples were obtained during hospitalization in 13.0% (n=24) of patients and during outpatient clinic visits in 87.0% (n=160). Among the hospitalized patients, 20 were managed in pediatric wards and 4 were admitted to the intensive care unit. The median length of hospital stay among inpatients was 9 days (range: 4–48 days).

According to the retrospective chart review, the most frequently reported reasons for urine sample collection included dysuria (46.2%), fever (39.1%), nausea or vomiting (28.3%), hematuria (16.3%), suprapubic pain (10.3%), increased urinary frequency (3.8%), urinary incontinence (3.3%), flank pain (2.2%), restlessness (2.2%), and constipation (1.1%). In terms of risk factors, 12.5% of patients had a prior history of hospitalization, 44.0% had received antibiotics within the previous three months, and 3.3% had undergone surgery in recent months. These risk factors are summarized in Table 2.

Urinary system comorbidities among the patients included vesicoureteral reflux (4.9%), neurogenic bladder (4.3%), spina bifida (4.3%), enuresis (2.7%), hydronephrosis (2.2%), perineal fissure (1.6%), posterior urethral valves (1.1%), nephrolithiasis (0.5%), solitary kidney (0.5%), horseshoe kidney (0.5%), and hypospadias (0.5%). Additionally, 19 patients (10.3%) had a documented history of recurrent urinary tract infections.

The most commonly isolated ESBL-producing pathogen was *Escherichia* spp., identified in 158 cases (85.8%), followed by *Klebsiella* spp. in 21 cases (11.4%), *Proteus* spp. in 2 cases (1.1%), *Morganella morganii* in 2 cases (1.1%), and *Citrobacter* spp. in 1 case (0.5%). A total of 115 patients (62.5%) were diagnosed with cystitis, while 72 (39.1%) were diagnosed with pyelonephritis.

The antibiotic susceptibility profiles of *E. coli* and *Klebsiella* spp. isolates were analyzed based on the available data and are summarized in Table 3.

DISCUSSION

The increasing prevalence of antimicrobial resistance in ESBL-producing *Enterobacteriaceae* (ESBL-PE) represents a significant global health concern. This issue is driven by the transmission of resistance mechanisms and the widespread, often inappropriate, use of antimicrobials (14). In Türkiye, ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* have been identified as significant causative agents of both hospital-acquired and community-acquired (CA) infections. It has been reported that over half of hospital-acquired UTIs and approximately one-fourth of CA infections are attributable to ESBL-producing strains (15, 16).

Table 3. Susceptibility patterns of *E. coli* and *Klebsiella* spp. to commonly used antibiotics

Antibiotic	*Escherichia coli*		*Klebsiella* spp.	
	Sensitive	Resistant	Sensitive	Resistant
TMP-SMX (n=176)[1]	87	68	8	13
Piperacillin-tazobactam (n=144)	92	36	8	8
Amikacin (n=176)	146	9	18	3
Nitrofurantoin (n=143)	123	8	9	3
Fosfomycin (n=139)	127	0	11	1
Ciprofloxacin (n=169)	95	53	14	7
Meropenem (n=141)	123	0	18	0

1: Not all total number equal to 184 in each column because not all isolates had all the antibiotic susceptibility result; TMP-SMX: Trimethoprim-sulfamethoxazole.

A five-year surveillance study conducted among hospitalized pediatric patients reported an *E. coli* infection rate of 15.3 per 1,000 hospitalizations, with 62.5% of the isolates derived from urine samples. Among these, 54.4% were ESBL-producing *E. coli* strains, and notably, 83.7% (62 out of 74) of them were hospital-acquired infections (17). In our cohort, most ESBL-positive urine cultures (87%) were obtained during outpatient clinic visits, with the remaining samples collected from inpatients.

In the study by Akgül et al. (18), which evaluated pediatric patients aged 1 month to 18 years with UTIs over a three-year period, ESBL production was detected in approximately half of both *E. coli* and non-*E. coli* isolates. While their analysis assessed the proportion of ESBL positivity within each microorganism group, our study examined the distribution of pathogens among ESBL-producing isolates. In our cohort, *E. coli* accounted for 85.8% of ESBL-PE strains, followed by *Klebsiella* species (11.4%).

Upon examining the risk factors in children diagnosed with ESBL-positive UTIs (mean age, 57 months), we identified a high prevalence of recent antibiotic use and hospitalization within the past three months (antibiotic use: 44%; hospitalization: 12.5%). Additionally, 3.3% of the patients had undergone surgery in the last month. In our cohort, 62.5% of patients presented with acute cystitis and 37.5% with pyelonephritis. Hospitalization was required in 13% of the cases, with a median length of stay of 9 days. Consistent with our findings, Collingwood et al. (4) reported that children with ESBL-producing *E. coli* UTIs are more likely to experience prolonged hospital admissions. Understanding the epidemiological profile and risk factors for ESBL-producing UTIs, including ESBL-producing *E. coli*, in the pediatric population could improve the therapeutic approach (19).

Recent antibiotic exposure was the most prominent risk factor identified in our cohort, supporting previous evidence that inappropriate or repeated antimicrobial use contributes to the emergence of ESBL-producing organisms through selective pressure. This finding further emphasizes the importance of antimicrobial stewardship programs aimed at reducing unnecessary broad-spectrum antibiotic exposure, particularly in pediatric outpatient settings, where most of our cases were identified (20).

Although our study did not evaluate treatment practices or clinical outcomes, the antibiotic susceptibility patterns observed in our cohort highlight the importance of considering local resistance profiles when selecting empirical therapy. The wide regional variation in the detection rates of ESBL-producing *E. coli* makes it essential to consider local epidemiological data and institutional surveillance reports when determining initial treatment strategies. In regions with a high ESBL prevalence, empirical therapy may need to consider the possibility of ESBL-producing organisms, particularly in children with recognized risk factors such as recent antibiotic exposure or prior hospitalization (20). However, while carbapenems are regarded as the first-line treatment for serious and invasive ESBL-PE infections, their use may contribute to the emergence of carbapenem-resistant strains and should be avoided unless clearly indicated (5).

A multicenter study from Japan investigating febrile UTIs in children reported similar clinical outcomes in patients with ESBL-producing organisms. The study recommended postponing the use of broad-spectrum antibiotics until culture results are available (21, 22) and suggested that cephalosporins may remain effective for initial empirical therapy (21–24). Aminoglycosides, despite their variable efficacy, may serve as second-line agents when third-generation cephalosporins fail to provide bactericidal activity in ESBL-related UTIs, with amikacin showing the most promising results (25–27).

Several studies from Türkiye have assessed antibiotic resistance in *E. coli* and *Klebsiella* spp. isolates (14, 28). In general, *Klebsiella* spp. exhibited higher resistance levels compared with *E. coli*. Among Gram-negative isolates, the lowest resistance rates were observed for amikacin, meropenem, piperacillin, and oral nitrofurantoin (28).

Furthermore, fosfomycin has demonstrated higher susceptibility rates than nitrofurantoin against ESBL-PE and appears to be clinically comparable to intramuscular ertapenem. Nonetheless, it is not recommended for the treatment of pyelonephritis, as it does not achieve sufficient serum or renal tissue concentrations (27, 29, 30). The high susceptibility rates observed for fosfomycin, nitrofurantoin, and amikacin support the potential role of carbapenem-sparing strategies in selected patients, particularly in uncomplicated lower UTIs without systemic involvement (27). Culture-guided de-escalation and selective carbapenem use may help preserve the effectiveness of last-resort antibiotics while reducing selective pressure for further resistance development (20, 27).

At our institution, antibiotic usage patterns and resistance trends are closely monitored. In our study of pediatric patients with urine cultures growing ESBL-PE, 100% of the isolates were susceptible to meropenem. This antibiotic is administered under strict clinical oversight and in accordance with our institutional antibiogram guidelines, taking into account the patient's age and clinical condition.

Importantly, our study also revealed that ESBL-PE strains were highly susceptible to orally administered nitrofurantoin and fosfomycin. This suggests that these agents may represent potential oral treatment alternatives in selected cases of suspected lower UTI pending culture results (20, 27).

Although this study has certain limitations, including its retrospective design, possible gaps in medical documentation, and the risk of underestimating some cases due to prior antibiotic exposure or low bacterial loads, it also has notable strengths. Most importantly, urine samples were collected under strict aseptic conditions, ensuring the reliability of the microbiological findings. No formal sample size calculation was performed due to the retrospective nature of the study. However, selection bias was mitigated by including only microbiologically confirmed cases with comprehensive clinical documentation.

CONCLUSION

Our findings highlight the growing clinical relevance of ESBL-producing *Enterobacteriaceae* in pediatric UTIs and emphasize the importance of local epidemiological surveillance and careful risk assessment. Recent antibiotic exposure emerged as a major associated factor, underscoring the need for strengthened antimicrobial stewardship strategies.

Ethics Committee Approval: This study followed the Declaration of Helsinki, and the University Faculty of Medicine Local Ethics Committee approved the study (Decision protocol no: 05.05.2021/108 Date: 05.05.2021).

Informed Consent: As this study was conducted retrospectively using previously recorded data, obtaining informed consent from participants was not required.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Authorship Contributions: Concept – NUK, MİN; Design – MİN, NUK; Supervision – NUK, MİN; Data Collection and/or Processing – MİN, NUK; Analysis and/or Interpretation – NUK, MİN; Literature Search – MİN, NUK; Writing – NUK, MİN; Critical Reviews – MİN, NUK.

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Hasta Onamı: Bu çalışma, daha önce kaydedilmiş veriler kullanılarak retrospektif olarak yürütüldüğünden, katılımcılardan bilgilendirilmiş onam alınması gerekli görülmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Bu makale için yapay zekadan herhangi bir destek alınmamıştır.

Yazarlık Katkıları: Fikir – NUK, MİN; Tasarım – MİN, NUK; Denetlemeler – NUK, MİN; Veri toplanması ve/veya işleme – MİN, NUK; Analiz ve/veya yorumlama – NUK, MİN; Literatür araştırması – TC, FKC, EES, NH; Yazım – NUK, MİN; Eleştirel incelemeler – MİN, NUK.

Hakemli inceleme: Harici olarak hakemli.

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ORIGINAL RESEARCH
Pediatric Cardiology

The impact of maternal age on congenital heart defects and their severity in Down syndrome

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ABSTRACT

Objective: Advanced maternal age is known to be a risk factor for Down syndrome. This study aimed to investigate whether maternal age affects the development and severity of congenital heart defects in patients with Down syndrome.

Material and Methods: A total of 394 patients with Down syndrome who presented to our center between 2018 and 2024 and underwent at least one echocardiographic examination in the pediatric cardiology outpatient clinic were included in the study. Maternal age, gravidity, parity, gestational age, and birth weight were retrospectively evaluated, and their relationships with the severity of congenital heart defects were analyzed.

Results: The study included 221 boys (53.6%) and 183 girls (46.4%). The mean gestational age was 36.85±2.46 weeks, and the mean birth weight was 2783.25±574.21 g. The mean maternal age among patients for whom this information was available was 37±5.96 years. The most common congenital heart defects were ventricular septal defect (24.87%), atrioventricular septal defect (16.49%), atrial septal defect (10.91%), and tetralogy of Fallot (4.56%). Of the cases, 41.6% required intervention, whereas 35.25% had no cardiac pathology.

Conclusion: No statistically significant correlation was found between maternal age and the type or severity of congenital heart defects. Investigating the influence of other factors and conducting multicenter studies, where possible, may be beneficial.

Keywords: Congenital heart defect; Down syndrome; echocardiography; maternal age.

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Down sendromlu bebeklerde doğuştan kalp kusurları ve şiddeti üzerine anne yaşının etkisi

ÖZET

Amaç: İleri anne yaşı, Down sendromu için bir risk faktörü olarak bilinmektedir. Bu çalışma, anne yaşının Down sendromlu hastalarda doğuştan kalp kusurlarının gelişimi ve şiddeti üzerindeki etkisini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: 2018–2024 yılları arasında merkezimize başvuran ve pediatrik kardiyoloji polikliniğinde en az bir kez ekokardiyografi yapılan 394 Down sendromlu hasta çalışmaya dahil edildi. Anne yaşı, gebelik ve doğum sayısı, doğum haftası ve doğum ağırlığı retrospektif olarak değerlendirildi ve bunların doğuştan kalp kusurlarının şiddetiyle ilişkisi analiz edildi.

Bulgular: Çalışmaya 221 erkek (%53,6) ve 183 kız (%46,4) hasta dahil edildi. Olguların ortalama doğum haftası 36,85±2,46 hafta, ortalama doğum ağırlığı ise 2783,25±574,21 g idi. Yaşları bilinen annelerin ortalama yaşı 37±5,96 yıldı. En sık görülen doğuştan kalp kusurları sırasıyla ventriküler septal defekt (%24,87), atriyoventriküler septal defekt (%16,49), atriyal septal defekt (%10,91) ve Fallot tetralojisi (%4,56) idi. Olguların %41,6'sına müdahale gerekti. Olguların %35,25'inde herhangi bir kalp patolojisi yoktu.

Tartışma: Anne yaşı ile doğuştan kalp kusurlarının türü ve şiddeti arasında istatistiksel olarak anlamlı bir ilişki bulunmadı. Diğer faktörlerin etkisinin araştırılmasının ve mümkünse çok merkezli çalışmalar yapılmasının yararlı olacağı sonucuna varıldı.

Anahtar Kelimeler: Anne yaşı; doğuştan kalp kusuru; Down sendromu; ekokardiyografi.

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INTRODUCTION

Down syndrome is the most prevalent chromosomal anomaly compatible with life, occurring in approximately 16 per 10,000 live births (1). Congenital heart defects are observed in 40%–60% of patients with Down syndrome (2–4). and approximately 50% of these defects are severe (5).

Advanced maternal age is generally accepted as a risk factor for Down syndrome (6). Age-related changes in oocyte quality are thought to play a role in this association (6). However, it remains unclear whether maternal age, gravidity, parity, and birth characteristics affect the risk and severity of congenital heart defects (6). This study aimed to investigate the relationships between maternal age, gravidity, parity, gestational age, birth weight, and the prevalence and severity of congenital heart defects in patients with Down syndrome.

Although advanced maternal age is a well-established risk factor for Down syndrome, its specific role in determining the phenotypic severity of associated cardiac defects remains poorly understood. This study addresses a critical gap in prenatal counseling by evaluating whether maternal age can serve as a predictor of the clinical management needs of these infants.

MATERIAL AND METHODS

This retrospective cohort study analyzed the effect of maternal age on the severity of congenital heart defects in patients with Down syndrome.

The study included patients with a genetic diagnosis of Down syndrome who presented to our center between 2018 and 2024 and underwent at least one echocardiographic examination in the pediatric cardiology outpatient clinic. Patients who did not undergo echocardiographic examination were excluded from the study. The patients' sex, gestational age, birth weight, maternal age, gravidity, parity, consanguinity, and the type and severity of congenital heart defects detected by echocardiography were evaluated.

The gestational ages of the patients were classified as <28 weeks, 28–32 weeks, 32–37 weeks, and >37 weeks. Birth weights were classified as 1000–1500 g, 1500–2500 g, and >2500 g. Cases with more than one congenital heart defect detected on echocardiography were classified according to the major defect. Congenital heart defects were classified into three groups according to their severity. Group 1 included cases with normal echocardiographic findings, patent foramen ovale, or physiological valvular insufficiency. Group 2 included moderately severe defects that did not require intervention or surgery but required follow-up, hemodynamically insignificant defects (e.g., small ventricular or atrial septal defects), and valvular insufficiencies (e.g., mild insufficiency requiring endocarditis prophylaxis during surgical procedures). Group 3 included cases with severe defects requiring medical, surgical, or catheter-based intervention or those with severe pulmonary hypertension.

A dataset comprising 394 patients with Down syndrome was analyzed to identify associations between congenital heart defect type and other patient characteristics. Maternal age was treated as a continuous variable, whereas sex, gestational age, birth weight, gravidity, parity, twin status, consanguinity, and echocardiographic findings were treated as categorical variables. Analyses were conducted using an available-case approach. Patients with missing data for a specific variable were excluded only from analyses involving that variable. Data entry and storage were performed using Microsoft Excel 2016. Data cleaning, recoding, descriptive summaries, and quality control procedures were performed using R version 4.4.0 with the "dplyr" and "summarytools" packages. All inferential statistical analyses and hypothesis tests were performed using SPSS version 30 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA).

Statistical Analysis

All formal statistical analyses and tests were conducted using SPSS version 30 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) on a personal computer. Data storage, preprocessing, and chart creation were performed using Microsoft Excel 2016. The normality of variable distributions was assessed using the Kolmogorov–Smirnov test, histograms, coefficients of variation, detrended Q–Q plots, and skewness and kurtosis analyses. A p-value of <0.05 was considered statistically significant. Group comparisons were performed using the independent-samples t-test and Mann–Whitney U test, as appropriate, because of the non-Gaussian distribution of the data.

Categorical variables were compared using Pearson's chi-square test when the assumptions of the test were satisfied, namely, when no more than 20% of the expected cell counts were <5 and no expected cell count was <1. For contingency tables larger than 2×2 in which these assumptions were violated because of sparse data or low expected cell frequencies, the Fisher–Freeman–Halton exact test was applied. Before the analyses, expected frequencies were examined for all contingency tables to determine the appropriate statistical test. The association between echocardiographic findings and sex was analyzed using Pearson's chi-square test, whereas comparisons involving variables with sparse categories, including gestational age, birth weight, gravidity, parity, twin status, and consanguinity, were evaluated using the Fisher–Freeman–Halton exact test when the assumptions of the chi-square test were not met. For statistically significant associations identified using the chi-square test, Cramér's V coefficient was calculated to assess the strength of the association between categorical variables.

Ethical Approval

This study was conducted in accordance with the ethical principles outlined in the 2013 revision of the Declaration of Helsinki. All participants provided written informed consent or, in the case of minors, written assent with parental consent before participation in the study.

Table 1. The frequency and percentages of birth weeks and birth weights

	n	%
Birth week	282	
<28 weeks	2	0.7
28–32 weeks	11	3.9
32–37 weeks	129	45.7
>37 weeks	140	49.6
Birth weight	286	
1–1.5 kg	6	2.1
1.5–2.5 kg	77	26.9
>2.5 kg	203	71.0

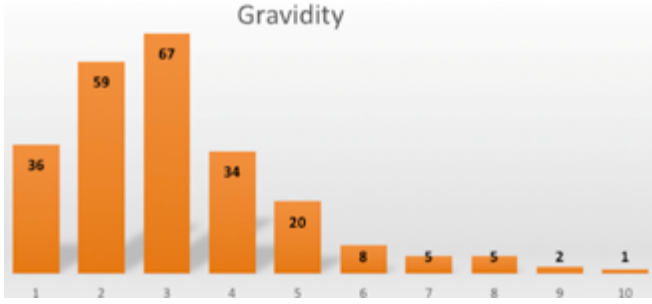

Figure 1. Distribution of gravidity.

Ethical approval was granted by the Clinical Research Ethics Committee of the University of Health Sciences Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital (approval number: 159; date: December 6, 2023).

RESULTS

The study included a total of 394 patients (221 boys [53.6%] and 183 girls [46.4%]) who were genetically and phenotypically diagnosed with Down syndrome. The boy-to-girl ratio was 1.15. The mean gestational age of the cases was 36.85±2.46 weeks, and their mean birth weight was 2783.25±574.21 g.

One hundred and forty cases (49.6%) were born at ≥37 weeks, 129 cases (45.7%) were born between 32 and 37 weeks, 11 cases (3.9%) were born between 28 and 32 weeks, and 2 cases (0.7%) were born before 28 weeks of gestation (Table 1).

The mean age of the mothers whose ages were known was 37±5.96 years (minimum: 21; maximum: 48). Gravidity ranged from 1 to 10, and parity ranged from 1 to 10, as demonstrated in Figures 1 and 2, respectively. Eight cases were twins. Consanguineous marriage was present in the families of 21 cases (11.4%).

As shown in Figure 1, Down syndrome was most frequently observed in the third, second, first, fourth, and fifth pregnancies, respectively. Among 237 cases, 15.2% were G1, 24.9% were G2, 28.3% were G3, 14.3% were G4, 8.4% were G5, 3.4% were G6, 2.1% were G7, 2.1% were G8, 0.8% were G9, and 0.4% were G10. Gravidity data were unavailable for 157 cases.

Table 2. Type of congenital heart defect seen on echocardiography

Type of defect	n	%
Ventricular septal defect	98	24.87
Atrio ventricular septal defect	65	16.49
Atrial septal defect	43	10.91
Tetralogy of fallot	18	4.56
Patent ductus arteriosus	15	3.80
Coarctation of aorta	3	0.76
Hypoplastic left ventricular syndrome	1	0.25
Aortic arch anomaly	3	0.76
Coronary artery fistula	2	0.50
Mitral valve prolapse	1	0.25
Partial anomalous pulmonary venous return	1	0.25
Wolff-Parkinson-white syndrome	5	1.26
Normal/patent foramen ovale	139	35.27

As shown in Figure 2, which demonstrates the distribution of parity, third-, second-, and first-born children were the most common among the 240 cases in our study group. Parity data were unavailable for 154 cases.

Six cases had translocation-type trisomy, six had mosaic trisomy, one had 48,XXY,+21, and one had 48,XXX,+21.

The types of congenital heart defects observed are presented in Table 2. Cases with more than one defect were classified according to the major defect.

Although the most commonly observed congenital heart defect was ventricular septal defect (24.87%), only 53 defects were significant and required treatment, whereas the remaining defects were hemodynamically insignificant and expected to close spontaneously. Five cases of atrioventricular septal defect (AVSD) were accompanied by aortic coarctation, pulmonary stenosis, tetralogy of Fallot, or atrial isomerism. All AVSD cases except one were balanced. Six patients had intermediate or transitional AVSD. Atrioventricular septal defect was more common in girls than in boys (36 girls and 29 boys), whereas

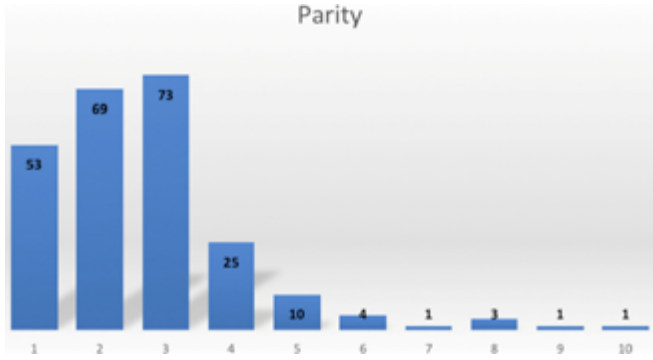

Figure 2. Distribution of parity.

tetralogy of Fallot was more common in boys (11 boys and 7 girls). Tetralogy of Fallot (ToF) was observed in 18 patients. One patient with ToF also had a ventricular septal defect (VSD) and pulmonary atresia.

When the cases were classified according to their echocardiographic findings, 139 cases (35.3%) were in Group 1, 91 cases (23.1%) were in Group 2, and 164 cases (41.6%) were in Group 3, as shown in Figure 3.

The distribution of congenital heart defect groups according to sex is presented in Table 3.

Maternal ages were classified as <35 years, 35–40 years, and >40 years to evaluate the frequency of each congenital heart defect group according to maternal age, as shown in Table 4.

Pearson's chi-square test was used to analyze the association between echocardiographic findings and sex because the assumptions of the chi-square test were satisfied. For variables with sparse categories and low expected cell frequencies, including gestational age, birth weight, gravidity, parity, twin status, and consanguinity, the Fisher–Freeman–Halton exact test was applied. No statistically significant associations were identified between echocardiographic findings and gestational age, birth weight, gravidity, parity, twin status, consanguinity, or maternal age categories ($p>0.05$).

A statistically significant relationship was found between echocardiographic findings and sex ($p<0.05$). The strength of this relationship, evaluated using Cramér's V, was relatively

Table 3. Distribution of congenital heart defect group

	Group 1		Group 2		Group 3		Total	
	n	%	n	%	n	%	n	%
Male	92	23	45	11	74	19	211	53
Female	47	12	46	12	90	23	183	47
Total	139	35	91	23	164	42	394	100

Group 1: Normal echocardiograms, Group 2: Moderately severe or hemodynamically insignificant defects (e.g., small VSD/ASD) and requiring follow-up but no immediate intervention. Group 3: Severe defects requiring medical, surgical, or invasive intervention, or presence of severe pulmonary hypertension. Row% represents the percentage within the gender; Total% represents the percentage within the entire cohort. $\chi^2(2)=14.222$, $p=0.000816$ (Pearson Chi-square); Cramer's V=0.1899926.

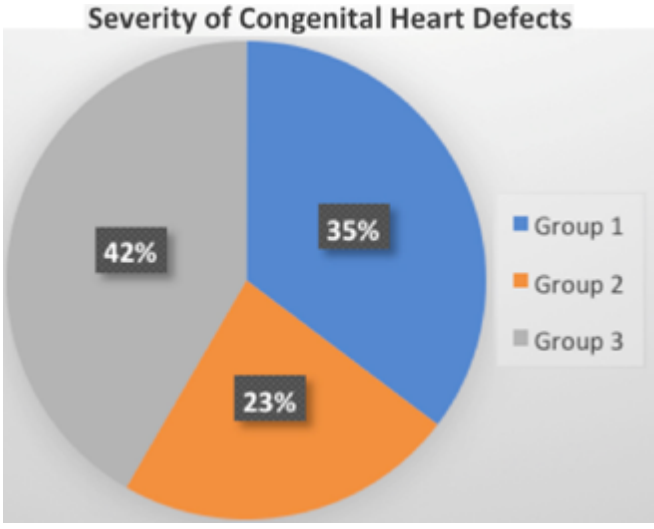

Figure 3. Distribution of congenital heart defects according to severity.

Group 1: Normal echocardiograms, Group 2: Moderately severe or hemodynamically insignificant defects (e.g., small VSD/ASD) and requiring follow-up but no immediate intervention. Group 3: Severe defects requiring medical, surgical, or invasive intervention, or presence of severe pulmonary hypertension.

weak despite being statistically significant (Cramér's V=0.190). Female patients had a higher proportion of severe congenital heart defects than male patients (Group 3: 23% vs. 19%; $p<0.05$).

The Kruskal–Wallis test was used to analyze the relationship between maternal age as a numerical variable and echocardiographic findings. No statistically significant difference was found among the groups ($p>0.05$).

DISCUSSION

The primary finding of this study is that maternal age does not significantly influence the type or severity of congenital heart defects in children with Down syndrome. Although advanced maternal age increases the risk of nondisjunction, our data suggest that it does not necessarily determine the subsequent cardiac phenotype.

It is widely accepted that the risk of Down syndrome increases with advanced maternal age, particularly after 35 years (7, 8). Approximately 88% of cases result from meiotic nondisjunction and are of maternal origin (9). The remaining cases are attributed to translocation (4.5%), mosaicism (2.3%), and, rarely, duplication (9).

The boy-to-girl ratio of 1.15 in our study was close to the average European ratio of 1.3 (10). Approximately half of the cases were premature births, most of which were late preterm. The birth weights of 70% of the cases were >2500 g. These findings were consistent with those of similar studies (11, 12). Most cases were conceived during the third pregnancy and were third-born children, which may be associated with the increasing risk of Down syndrome with advancing maternal age.

The prevalence of congenital heart defects in patients with Down syndrome is generally reported to be approximately 40%–60% (2–4, 13), ranging from 27% to 79% across different studies and populations (1). With advances in perinatology and the increase in voluntary pregnancy termination, the prevalence and types of congenital heart defects in Down syndrome have changed (14). In societies where pregnancy termination is culturally, religiously, or legally prohibited, however, no such change has been observed (12, 15). In our study, 65% of the cases had cardiac findings, and 42% had severe congenital heart defects.

Atrioventricular septal defect is usually reported as the most common type of congenital heart defect in Down syndrome (3, 6, 16, 17). In 1992, identified a narrow locus on chromosome 21 associated with atrioventricular septal defect (2, 9). However, the etiology of congenital heart defects in Down syndrome has not yet been fully elucidated and is thought to be multifactorial, with contributions from genetic factors and environmental exposures.

A smaller number of studies, however, have reported ventricular septal defect as the most common type of congenital heart defect in Down syndrome (11), with a particularly high prevalence among Asian patients (5, 6, 11). Similarly, ventricular septal defect was the most frequent type of congenital heart defect in our study. However, when hemodynamically insignificant ventricular septal defects were excluded, atrioventricular septal defect was more common.

A statistically significant but weak association was found between sex and congenital heart defect type. Consistent

Table 4. Distribution of congenital heart defect groups according to grouped maternal age

	Group 1		Group 2		Group 3		Total	
	n	%	n	%	n	%	n	%
<35	22	10.3	23	10.7	31	14.5	76	35.5
35-40	22	10.3	16	7.5	35	16.4	73	34.2
>=40	17	7.9	22	10.3	26	12.1	65	30.3
Total	61	28.5	61	28.5	92	43	214	100

Group 1: Normal echocardiograms, Group 2: Moderately severe or hemodynamically insignificant defects (e.g., small VSD/ASD) and requiring follow-up but no immediate intervention. Group 3: Severe defects requiring medical, surgical, or invasive intervention, or presence of severe pulmonary hypertension. p- value >0.05 (Pearson Chi-square). No statistically significant association was found.

with similar studies, atrioventricular septal defect was more common in girls, whereas tetralogy of Fallot was more common in boys (10, 18). Severe congenital heart defects classified as Group 3 were observed in two of the six patients with translocation-type Down syndrome and in two of the six patients with mosaic-type Down syndrome. These rates were not considerably different from those observed in patients with the classical type.

Interestingly, although the prevalence of Wolff–Parkinson–White syndrome has been reported to be 1–3 per 1000 individuals in large-scale general population studies (19), five patients in our study who had normal echocardiographic findings were diagnosed with Wolff–Parkinson–White (WPW) syndrome on electrocardiography. Although this association with WPW syndrome is noteworthy, it may be coincidental given the limited sample size of the present study. Further studies involving larger patient populations are required.

Although it is widely accepted that advanced maternal age increases the risk of Down syndrome, no association between advanced maternal age and the risk or severity of congenital heart defects in patients with Down syndrome has been reported in the literatüre (6, 9). Similarly, in our study, almost half of the congenital heart defects were severe and required intervention; however, no association was found between the severity of congenital heart defects and maternal age, gestational age, birth weight, gravidity, or parity. No formal sample size calculation was performed because all eligible patients during the study period were included. Consequently, analyses involving rare congenital heart defects may have been underpowered, and nonsignificant findings should be interpreted with caution.

This study has several limitations. First, its retrospective design and the relatively high proportion of missing maternal and perinatal data may have introduced selection bias. Although no significant differences were identified between patients with and without available maternal age data, residual bias cannot be completely excluded. In addition, data regarding certain maternal lifestyle factors were unavailable. Second, as this was a single-center study, the findings may not be fully generalizable to other populations. Third, because of the high proportion of missing data for several covariates, multivariable regression analysis was not performed. Consequently, residual confounding cannot be excluded, and the independent effect of maternal age should be interpreted with caution.

CONCLUSION

In conclusion, our study demonstrates that although maternal age is a critical factor in the occurrence of Down syndrome, it does not significantly influence the clinical severity or specific type of congenital heart defects in these patients. The findings suggest that the cardiac phenotype in trisomy 21 is likely determined by complex genetic and environmental interactions that are independent of maternal age. Within the limitations of this retrospective, single-center cohort, maternal age was not significantly associated with the type or severity of congenital heart defects. However, these findings should not be interpreted as definitive evidence of the absence of an association. Therefore, prenatal and postnatal cardiac management should focus on the specific anatomical defect rather than solely on maternal demographic risk factors. Future prospective, multicenter studies with larger cohorts are needed to further elucidate the multifactorial determinants of congenital heart defect severity in this population.

This study may contribute to the literature by classifying congenital heart defects and birth characteristics, including maternal age, birth weight, gestational age, gravidity, and parity, in patients with Down syndrome. The absence of a statistically significant correlation between these parameters and the severity of congenital heart defects highlights the need for further studies investigating the potential influence of other factors.

Ethics Committee Approval: This study was approved by the Ethics Committee of of University of Health Sciences, Zeynep Kamil Women's and Children's Diseases Training and Research Hospital (Date: Dec 6, 2023, Decision No. 159).

Informed Consent: All participants provided written informed consent or, in the case of minors, written assent with parental consent before participation in the study.

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Authorship Contributions: Concept – NE; Design – NE, ZEE; Supervision – NE, ÇE, AA, ZEE; Fundings – NE; Materials – NE; Data Collection and/or Processing – NE; Analysis and/or Interpretation – ÇE; Literature Search – NE; Writing – NE, ZEE; Critical Reviews – NE, AA.

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Hasta Onamı: Tüm katılımcılar, çalışmaya katılmadan önce yazılı bilgilendirilmiş onam vermiş; reşit olmayan katılımcılar ise ebeveynlerinin onayıyla yazılı rıza göstermiştir.

Çıkar Çatışması: Yazar, herhangi bir çıkar çatışması bulunmadığını beyan eder.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Bu makale için yapay zekadan herhangi bir destek alınmamıştır.

Yazarlık Katkıları: Fikir – NE; Tasarım – NE, ZEE; Denetlemeler – NE, ÇE, AA, ZEE; Kaynaklar – NE; Malzemeler – NE; Veri toplanması ve/veya işleme – NE; Analiz ve/veya yorumlama – ÇE; Literatür araştırması – NE; Yazım – NE, ZEE; Eleştirel incelemeler – NE, AA.

Hakemli inceleme: Harici olarak hakemli.

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ORIGINAL RESEARCH
Pediatric Intensive Care

Respiratory viral coinfections and clinical outcomes in critically ill children with acute lower respiratory tract infections

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ABSTRACT

Objective: To characterize the distribution of respiratory viruses, determine the frequency of multiple viral detection, and evaluate the association between viral detection patterns and clinical outcomes in children admitted to a pediatric intensive care unit (PICU) with acute lower respiratory tract infections (LRTIs).

Material and Methods: This retrospective observational cohort study included patients admitted to the PICU with LRTIs between September 2022 and December 2024 who underwent multiplex respiratory polymerase chain reaction (PCR) testing using nasopharyngeal specimens. Patients were evaluated according to respiratory panel positivity and viral burden. Demographic characteristics, laboratory findings, respiratory support requirements, length of stay, and mortality were compared.

Results: A total of 183 patients were included, with at least one virus detected in 126 (68.9%). Among virus-positive patients, 73 (57.9%) had single viral detection, and 53 (42.0%) had multiple viral detection. The most common viruses among patients with single viral detection were rhinovirus/enterovirus (17.8%), human bocavirus (15.1%), and respiratory syncytial virus (RSV) (15.1%); among those with multiple viral detection, they were rhinovirus/enterovirus (39.6%), RSV (37.7%), and human bocavirus (35.8%). Invasive mechanical ventilation was more frequent in patients with multiple viral detection than in those with single viral detection (52.8% vs. 34.2%, p=0.037), whereas hospital length of stay, PICU length of stay, and mortality did not differ significantly. Although PICU length of stay differed overall across the four viral-burden groups (p=0.029), no post hoc pairwise comparison remained significant after Bonferroni adjustment.

Conclusion: Multiple viral detection was common among virus-positive children with LRTIs and was associated with a higher frequency of invasive mechanical ventilation. No significant differences were observed in mortality or length of stay. Although PICU length of stay differed overall across viral-burden groups, pairwise comparisons were not significant; therefore, this finding should be considered exploratory. Larger prospective studies are needed to confirm these findings.

Keywords: Bronchiolitis; multiplex PCR; pediatric intensive care unit; pneumonia; respiratory syncytial virus; viral coinfection.

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Akut alt solunum yolu enfeksiyonu nedeniyle yoğun bakımda izlenen kritik hasta çocuklarda solunum yolu viral koenfeksiyonları ve klinik sonuçları

ÖZET

Amaç: Bu çalışmanın amacı, akut alt solunum yolu enfeksiyonu (ASYE) nedeniyle çocuk yoğun bakım ünitesine (ÇYBÜ) yatırılan çocuklarda solunum yolu virüslerinin dağılımını belirlemek, çoklu viral saptanma sıklığını değerlendirmek ve viral saptanma paternleri ile klinik sonuçlar arasındaki ilişkiyi incelemektir.

Gereç ve Yöntemler: Bu retrospektif gözlemsel kohort çalışmasına, Eylül 2022 ile Aralık 2024 tarihleri arasında akut alt solunum yolu enfeksiyonu tanısıyla ÇYBÜ'ye yatırılan ve nazofaringeal örneklerden multipleks solunum yolu polimeraz zincir reaksiyonu (PCR) testi yapılan hastalar dahil edildi. Hastalar, solunum yolu paneli pozitifliği ve viral yük açısından değerlendirildi. Demografik özellikler, laboratuvar bulguları, solunum desteği gereksinimleri, yatış süreleri ve mortalite karşılaştırıldı.

Bulgular: Toplam 183 hasta çalışmaya dahil edildi ve 126 hastada (%68,9) en az bir solunum yolu virüsü saptandı. Virüs pozitif hastaların 73'ünde (%57,9) tek, 53'ünde (%42,0) ise birden fazla virüs saptandı. Tek virüs saptanan hastalarda en sık rinovirüs/enterovirüs (%17,8), human bocavirus (%15,1) ve respiratuvar sinsityal virüs (RSV) (%15,1); birden fazla virüs saptanan hastalarda ise rinovirüs/enterovirüs (%39,6), RSV (%37,7) ve human bocavirus (%35,8) belirlendi. İnvaziv mekanik ventilasyon gereksinimi, birden fazla virüs saptanan hastalarda tek virüs saptananlara göre daha sıktı (%52,8'e karşı %34,2; p=0,037). Buna karşılık, hastanede ve ÇYBÜ'de yatış süreleri ile mortalite açısından gruplar arasında anlamlı fark saptanmadı. Saptanan virüs sayısına göre oluşturulan dört grup arasında ÇYBÜ yatış süresi genel analizde farklılık gösterdi (p=0,029); ancak Bonferroni düzeltmesi sonrasında ikili karşılaştırmaların hiçbiri istatistiksel olarak anlamlı değildi.

Tartışma: Solunum yolu virüsü saptanan ASYE'li çocuklarda birden fazla virüs saptanması sık görülmüş ve daha yüksek invaziv mekanik ventilasyon gereksinimi ile ilişkili bulunmuştur. Mortalite ve yatış süreleri açısından anlamlı fark saptanmamıştır. Saptanan virüs sayısına göre ÇYBÜ yatış süresi genel analizde farklılık gösterse de ikili karşılaştırmalar anlamlı bulunmadığından, bu sonuç keşifsel niteliktedir. Bulguların doğrulanması için daha geniş, prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bronşiolit; çocuk yoğun bakım ünitesi; multipleks PCR; pnömoni; respiratuvar sinsityal virüs; viral koenfeksiyon.

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INTRODUCTION

Among children, lower respiratory tract infections (LRTIs) are among the most frequent reasons for hospital admission and remain an important cause of morbidity and mortality, especially in early childhood. The majority of these infections are viral in origin, with respiratory syncytial virus (RSV), rhinovirus, influenza and parainfluenza viruses, human metapneumovirus, and human bocavirus among the pathogens most often implicated (1, 2).

Multiplex PCR platforms now allow several respiratory pathogens to be identified from a single nasopharyngeal sample, and their growing clinical use has markedly increased detection sensitivity relative to older single-target assays. As a result, coinfection with more than one respiratory virus is being reported more often among children hospitalized with LRTIs, with published detection rates ranging from approximately 10%-40% and occasionally exceeding this range in selected populations (3, 4). However, it remains uncertain whether the detection of multiple viruses represents true concurrent infection or reflects prolonged viral shedding or asymptomatic carriage.

Findings on this point are inconsistent: some individual studies link coinfection with longer hospital stays and more severe disease (4). Yet, pooled data from systematic reviews and meta-analyses have generally failed to show consistent differences between children with single versus multiple viral detections in terms of intensive care admission, the need for mechanical ventilation, length of stay, or mortality (3). Because of this inconsistency, research interest has shifted from simply asking whether multiple viral detection is present to examining the number and patterns of viruses detected, on the premise that these features may better characterize the heterogeneity of clinical outcomes. Previous studies have suggested that the number of detected viruses may be associated with disease severity and resource utilization, although the clinical significance of multiple viral detection remains uncertain (5, 6).

The present study aimed to characterize the distribution of respiratory viruses, determine the frequency of multiple viral detection, compare the clinical characteristics and outcomes of children with single and multiple viral detection, and explore the association between viral burden and clinical outcomes among patients admitted to a pediatric intensive care unit with acute LRTIs.

MATERIAL AND METHODS

Study Design and Patient Selection

This retrospective observational cohort study was conducted in a PICU between September 2022 and December 2024. During the study period, 782 patients were admitted to the PICU with LRTIs. Respiratory multiplex PCR testing was not routinely performed in all patients with LRTIs; testing was requested at the discretion of the treating physician based on clinical suspicion and was also influenced by test availability. Consequently, only patients who underwent respiratory multiplex PCR testing were eligible for the present study, resulting in a final study cohort of 183 patients. Because patients who were not tested were not included in the analytic cohort, the study population represents a selected subset of PICU patients with LRTIs rather than the entire LRTI population admitted during the study period.

The study was approved by the Scientific Research Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Approval No.: 2026/13; approval date: 14.01.2026). All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Owing to the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived by the ethics committee.

Patients admitted to the PICU with a diagnosis of LRTI who underwent multiplex respiratory PCR testing using nasopharyngeal specimens at admission or within the first 48 hours of hospitalization were eligible for inclusion. Patients with incomplete clinical records or unavailable PCR results were excluded from the study.

Definitions

A diagnosis of pneumonia required compatible clinical signs supported by radiographic evidence of pulmonary infiltration (7). Bronchiolitis was diagnosed clinically according to current pediatric guideline criteria, particularly in children younger than 2 years of age presenting with wheezing, tachypnea, and increased respiratory effort following a preceding viral upper respiratory illness (8).

Multiplex Respiratory PCR Analysis

Nasopharyngeal swab specimens were obtained as part of routine clinical practice and analyzed using a multiplex respiratory polymerase chain reaction (PCR) assay. Respiratory pathogens were detected using the Respiratory Pathogens Kit (24) (Laborant, Ref No.: LRP-01-24, AMT Medical Laboratory Equipment Industry and Trade Ltd. Co., Istanbul, Türkiye). The assay included rhinovirus/enterovirus, respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus types 1–4, adenovirus, human metapneumovirus, seasonal coronaviruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human bocavirus, and several bacterial and atypical bacterial pathogens.

For the purposes of the present study, analyses were restricted to viral pathogens. Although the multiplex panel also included bacterial and atypical bacterial targets, these organisms were excluded from multiple viral detection analyses because the primary objective was to evaluate the distribution and clinical significance of multiple respiratory viral detection and viral burden. Inclusion of bacterial targets would have introduced a biologically distinct category of mixed viral–bacterial infections requiring separate analysis.

Data Collection

Demographic and clinical data were extracted from electronic medical records, including age, sex, history of prematurity, presence of comorbidities, Pediatric Risk of Mortality III (PRISM III) score, admission diagnosis, respiratory PCR results, and identified viruses (9).

Laboratory variables included C-reactive protein (CRP), procalcitonin (PCT), white blood cell count, neutrophil count, lymphocyte count, pH, partial pressure of carbon dioxide ($PaCO_2$), and lactate levels.

Clinical outcome measures included the requirement for high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV), together with the duration of each respiratory support modality. Pediatric intensive care unit length of stay, total hospital length of stay, and mortality were also recorded. In addition, respiratory panel positivity, the distribution of detected viruses, viral burden, and seasonal patterns were evaluated.

Study Groups

Among PCR-positive patients, virus distribution was characterized according to the number of viral targets detected. Patients with one detected virus were classified as having single viral detection, whereas those with two or more detected viruses were classified as having multiple viral detection. For descriptive purposes, the number of viruses detected in each patient (one, two, three, or four) was defined as viral burden. Because multiplex PCR detects viral nucleic acid and does not establish active viral replication, the terms “single viral detection” and “multiple viral detection” were preferred over “single viral infection” and “viral coinfection” when referring specifically to PCR findings. Viral-burden analyses were considered exploratory.

Statistical Analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test together with visual inspection of histograms. Continuous variables were reported as median (IQR), and categorical variables were reported as counts and percentages. Because the continuous variables included in Tables 1 and 2 were non-normally distributed, comparisons between two independent groups were performed using the Mann–Whitney U test. Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test, as

Table 1. Comparison of demographic, clinical, and outcome characteristics according to respiratory panel positivity

	Negative (n=57)	Positive (n=126)	p
Age, months, median (IQR)	18.5 (4-52.75)	10 (2-29.5)	0.086
Male sex, n (%)	32 (56.1)	66 (52.4)	0.637
Comorbidity, n (%)	13 (22.8)	20 (15.9)	0.259
PRISM III score, median (IQR)	5 (0-9.25)	3 (0-6)	0.099
Hospital LOS, days, median (IQR)	8 (7-18)	9 (7-15)	0.861
PICU LOS, days, median (IQR)	8 (5.75-14.25)	9 (5-14)	0.762
Mortality, n (%)	3 (5.3)	3 (2.4)	0.377
IMV, n (%)	24 (42.1)	53 (42.1)	0.996
NIV, n (%)	30 (52.6)	79 (62.7)	0.199
HFNC, n (%)	30 (52.6)	71 (56.3)	0.640
Radiographic infiltrate, n (%)	41 (71.9)	99 (78.6)	0.326

Data are presented as median (IQR) or n (%). Percentages were calculated within each study group. Continuous variables were compared using the Mann–Whitney U test. Fisher's exact test was used for mortality; Pearson's chi-square test was used for all other categorical variables. PICU: Pediatric intensive care unit; LOS: Length of stay; IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation; HFNC: High-flow nasal cannula.

Table 2. Comparison of demographic, clinical, and outcome characteristics according to single and multiple viral detection

	Single viral detection (n=73)	Multiple viral detection (n=53)	p
Age, months, median (IQR)	12 (3-33)	9 (2-21.5)	0.143
Male sex, n (%)	41 (56.2)	25 (47.2)	0.318
Prematurity, n (%)	17 (23.3)	16 (30.2)	0.384
Comorbidity, n (%)	12 (16.4)	8 (15.1)	0.839
PRISM III score, median (IQR)	3 (0-6)	3 (0-7)	0.663
Hospital LOS, days, median (IQR)	9 (7-14)	10 (6-17)	0.789
PICU LOS days, median (IQR)	9 (6-13)	9 (5-15.5)	0.768
Mortality, n (%)	2 (2.7)	1(1.9)	1.000
IMV, n (%)	25 (34.2)	28 (52.8)	**0.037**
NIV, n (%)	43 (58.9)	36 (67.9)	0.301
HFNC, n (%)	45 (61.6)	26 (49.1)	0.160
Radiographic infiltrate, n (%)	56 (76.7)	43 (81.1)	0.550

Data are presented as median (IQR) or n (%). Continuous variables were compared using the Mann–Whitney U test. Fisher's exact test was used for mortality; Pearson's chi-square test was used for all other categorical variables. PICU: Pediatric intensive care unit; LOS: Length of stay; IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation; HFNC: High-flow nasal cannula.

appropriate. Comparisons across the four viral-burden groups were performed using the Kruskal–Wallis test. When the overall test was statistically significant, pairwise post hoc comparisons with Bonferroni adjustment for multiple testing were performed. A two-sided p value<0.05 was considered statistically significant.

RESULTS

Among the 183 patients with LRTIs who underwent respiratory multiplex PCR testing and were included in the study, at least one virus was detected in 126 (68.9%), whereas 57 (31.1%) had no viral target detected. Among virus-positive patients, 73 (57.9%) had single viral detection, and 53 (42.0%) had multiple viral detection.

No significant differences were observed between respiratory panel-positive and respiratory panel-negative patients with respect to age, sex, presence of comorbidities, PRISM III score, hospital length of stay, PICU length of stay, mortality, or respiratory support requirements (Table 1).

Respiratory panel positivity varied significantly according to the month of admission (p=0.001). The highest positivity rates were observed in December (91.7%), April (85.7%), and January (84.6%), whereas no positive cases were identified in July or August. Seasonal positivity rates were 80.6% in winter, 74.1% in

Table 3. Distribution of detected viruses and viral burden among patients with positive respiratory panels (n=126)

Variables	n	%
Single viral detection	73	57.9
Rhinovirus/Enterovirus	13	17.8
Human bocavirus	11	15.1
RSV	11	15.1
Adenovirus	7	9.6
Influenza B	6	8.2
Parainfluenza virus	6	8.2
Influenza A	5	6.8
Seasonal coronavirus	5	6.8
SARS-CoV-2	5	6.8
Human metapneumovirus	4	5.5
Number of detected viruses (n=126)		
1 virus	73	57.9
2 viruses	35	27.8
3 viruses	15	11.9
4 viruses	3	2.4
Most frequently detected viruses among patients with multiple viral detection (n=53)		
Rhinovirus/Enterovirus	21	39.6
RSV	20	37.7
Human bocavirus	19	35.8
Most common multiple viral detection combinations (n=53)		
RSV + Rhinovirus/Enterovirus	10	18.9
Human bocavirus + RSV	8	15.1
Human bocavirus + Rhinovirus/Enterovirus	6	11.3

Data are presented as n (%). Percentages for individual viruses in the single viral detection group were calculated among patients with single viral detection (n=73). Percentages for the number of detected viruses were calculated among all respiratory panel-positive patients (n=126). Percentages for viruses and viral combinations in the multiple viral detection group were calculated among patients with multiple viral detection (n=53). RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

spring, 47.8% in summer, and 47.1% in autumn. No significant differences in positivity rates were observed across the study years (p=0.395).

Among patients with single viral detection, the most frequently identified viruses were rhinovirus/enterovirus (17.8%), human bocavirus (15.1%), RSV (15.1%), and adenovirus (9.6%). Influenza B and parainfluenza viruses were each detected in 8.2% of cases, whereas influenza A, seasonal coronaviruses, and SARS-CoV-2 were each identified in 6.8% of cases. Human metapneumovirus was the least frequently detected virus among patients with single viral detection, accounting for 5.5% of cases (Table 3).

Comparison of patients with single and multiple viral detection revealed no significant differences in age, sex, prematurity, comorbidity status, PRISM III score, hospital length of stay, PICU length of stay, mortality, NIV requirement, HFNC requirement, or radiographic infiltrates. However, invasive mechanical ventilation was more frequent among patients with multiple viral detection than among those with single viral detection (52.8% vs. 34.2%, p=0.037) (Table 2).

The frequency of multiple viral detection did not differ significantly across seasons (p=0.472) or study years (p=0.396).

Among laboratory variables, lactate levels were higher in patients with multiple viral detection than in those with single viral detection (1.6 [1.17–2.27] mmol/L vs. 1.35 [0.91–1.76] mmol/L, p=0.028). HFNC duration was shorter in patients with multiple viral detection than in those with single viral detection [0 (0–3) days vs. 2 (0–4) days, p=0.043]. No statistically significant differences were observed in the other laboratory parameters or in IMV and NIV durations (Appendix 1).

When patients were stratified according to the number of detected viruses, PICU length of stay differed significantly across the four viral-burden groups in the overall Kruskal–Wallis analysis (H=9.018, df=3, p=0.029) (Appendix 2). Median PICU length of stay was 9 (6–13) days in patients with one detected virus, 7 (5–11) days in those with two viruses, 13 (7.5–18.25) days in those with three viruses, and 50 (11–NA) days in those with four viruses. However, none of the post hoc pairwise comparisons remained statistically significant after Bonferroni adjustment for multiple comparisons (all adjusted p≥0.136) (Appendix 3). These findings should be interpreted cautiously, particularly because the higher viral-burden subgroups were small and the four-virus group included only three patients.

Among patients with multiple viral detection, the most frequently detected viruses were rhinovirus/enterovirus (n=21, 39.6%), RSV (n=20, 37.7%), and human bocavirus (n=19, 35.8%). The most common multiple viral detection combinations were RSV–rhinovirus/enterovirus (n=10, 18.9%), human bocavirus–RSV (n=8, 15.1%), and human bocavirus–rhinovirus/enterovirus (n=6, 11.3%) (Table 3).

DISCUSSION

Among the selected cohort of PICU patients with LRTIs who underwent respiratory multiplex PCR testing, at least one respiratory virus was detected in 68.9%, and 42.0% of virus-positive patients had multiple viral detections. These proportions should be interpreted within the tested cohort and should not be considered estimates of viral positivity or multiple viral detection among all children admitted to the PICU with LRTIs. Multiple viral detection was associated with a higher frequency of invasive mechanical ventilation, whereas no statistically significant differences were detected in hospital length of stay, PICU length of stay, mortality, NIV requirement, or HFNC requirement.

As multiplex PCR testing has become routine, detecting more than one respiratory virus in a single pediatric sample is now

common, yet the clinical significance of this finding remains debated. In a systematic review including more than 17,000 children, Scotta and colleagues could not demonstrate any association between coinfection and hospital length of stay, PICU admission, ventilation requirement, or mortality (3). Asner et al. (10) reached a similar conclusion, reporting comparable hospitalization duration and mortality regardless of whether children carried one virus or several. Our findings were partly consistent with these reports, as multiple viral detection was not associated with differences in length of stay or mortality. However, IMV was more frequent among patients with multiple viral detection in our cohort. This finding suggests a possible association between multiple viral detection and the need for invasive respiratory support, although the retrospective design precludes causal inference, and residual confounding cannot be excluded.

Although HFNC duration was shorter in patients with multiple viral detection, this finding should be interpreted cautiously. Given the higher frequency of IMV in this group, differences in respiratory support trajectories may have influenced HFNC exposure; however, the timing and sequence of transitions between respiratory support modalities were not evaluated in the present study.

One important limitation in interpreting multiplex PCR results is that the detection of multiple viruses does not necessarily represent simultaneous active infections. Rhinovirus and human bocavirus, in particular, are known to persist in the airway well after symptoms resolve and can even be identified in children without respiratory complaints. Some cases we classified as multiple viral detection may therefore reflect one active infection alongside residual shedding of a second virus rather than genuine concurrent disease. This uncertainty complicates the interpretation of the observed associations between multiple viral detection and clinical outcomes. Accordingly, our findings should be interpreted as associations between viral detection patterns and outcomes rather than as evidence of causality (3, 4).

Among patients with single viral detection, rhinovirus/enterovirus, human bocavirus, and RSV were the most frequently detected viruses. Earlier work, especially in bronchiolitis cohorts, has repeatedly identified RSV as the leading respiratory pathogen, with rhinovirus close behind in frequency (2, 5). The relatively high frequency of human bocavirus observed in our cohort is consistent with earlier reports describing its common detection among hospitalized children (2). However, the role of human bocavirus in LRTIs remains incompletely understood. Because human bocavirus is frequently detected alongside other respiratory viruses and may exhibit prolonged viral shedding, PCR positivity does not necessarily indicate active disease (1, 2). Therefore, the clinical significance of human bocavirus detection should be interpreted in conjunction with the overall clinical and laboratory context.

Notably, rhinovirus/enterovirus, RSV, and human bocavirus were also the most commonly identified viruses among patients with multiple viral detection. This finding indicates that these viruses not only represent commonly detected viruses in patients with single viral detection but also contribute substantially to viral detection patterns in children with LRTIs. Consistent with this observation, the most frequent viral combinations in our cohort were RSV–rhinovirus/enterovirus, human bocavirus–RSV, and human bocavirus–rhinovirus/enterovirus. Similar coinfection patterns have been reported previously, with RSV–rhinovirus and RSV–human bocavirus among the most commonly described viral combinations in pediatric respiratory infections (2, 4). However, because rhinovirus and human bocavirus are also among the viruses most frequently associated with prolonged shedding, caution is warranted when interpreting the clinical significance of specific viral combinations or increasing viral burden.

Respiratory panel positivity showed clear seasonality, peaking in winter and spring—a pattern that mirrors the well-documented seasonal circulation of RSV and related viruses (1, 2). The frequency of multiple viral detection remained relatively stable across seasons. The mechanisms underlying this pattern could not be evaluated in the present study. Virus–virus interactions and differences in host susceptibility have been proposed as possible explanations, but these mechanisms remain hypothetical in the context of our data.

Patients with multiple viral detection also had modestly higher lactate levels than those with single viral detection; however, the clinical relevance of this isolated laboratory finding remains uncertain and may reflect residual confounding rather than a direct effect of multiple viral detection.

An exploratory analysis demonstrated an overall difference in PICU length of stay across viral-burden groups; however, none of the pairwise comparisons remained significant after Bonferroni adjustment, and the higher viral-burden groups were small. Previous studies have suggested that the number of detected viruses may be associated with clinical outcomes and resource utilization (5, 6). Bermúdez-Barrezueta et al. (6) reported progressively longer hospital stays with increasing numbers of detected viruses. However, their findings concerned hospital rather than PICU length of stay. Therefore, our finding should be considered exploratory rather than evidence of a dose–response or causal relationship.

Limitations

This study has several limitations. First, its single-center, retrospective design limits causal inference and generalizability. Of the 782 patients admitted to the PICU with LRTIs during the study period, only 183 underwent respiratory multiplex PCR testing and were included in the analysis. Testing was performed according to clinical judgment and test availability rather than through a systematic screening protocol. This may have preferentially selected patients with suspected viral disease or particular clinical presentations. Consequently, the observed 68.9% viral detection rate applies only to the tested cohort and cannot be extrapolated to the entire population of PICU patients with LRTIs. Because patients who were not

tested were not included in the analytic dataset, a systematic comparison of tested and untested patients was not possible, and residual selection bias cannot be excluded.

A second limitation is inherent to the technology itself: multiplex PCR identifies viral nucleic acid rather than active replication, so some positive results may reflect prolonged viral shedding, asymptomatic carriage, or concurrent active infection. These results should therefore be interpreted as descriptive associations between viral detection patterns and outcomes rather than as evidence of a causal relationship.

Third, all multiple viral detections were analyzed as a single group, although different viral combinations may differ biologically and clinically. The viral-burden subgroups with three or four detected viruses were also small, including only three patients with four detected viruses. Accordingly, findings from the viral-burden analysis should be considered exploratory and hypothesis-generating rather than confirmatory. In addition, the small number of deaths limited the statistical power to detect differences in mortality. More generally, the absence of statistically significant differences should not be interpreted as evidence of equivalence, particularly for infrequent outcomes and analyses involving small subgroups.

Finally, because quantitative viral load data were unavailable, the behavior of specific viral combinations could not be assessed, leaving the individual contribution of each virus within a multiple viral detection unresolved.

Notwithstanding these limitations, the present study provides real-world data on respiratory viral detection patterns and their associations with clinical outcomes in critically ill children with LRTIs.

CONCLUSION

Multiple respiratory viral detections were common among virus-positive children in this selected cohort of critically ill patients with LRTIs and were associated with a higher frequency of invasive mechanical ventilation. No statistically significant differences were detected in several other major clinical outcomes, including mortality and length of stay; however, the limited sample size and small number of outcome events preclude conclusions regarding equivalence between single and multiple viral detection. Although PICU length of stay differed across viral-burden groups in the overall analysis, none of the pairwise comparisons remained statistically significant after adjustment for multiple testing. Given the small number of patients with three or four detected viruses, this finding should be regarded as exploratory. Larger prospective studies using systematic respiratory testing are needed to clarify the clinical relevance of multiple viral detection, viral burden, and specific viral combinations.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital (Date: Jan 14, 2026, Decision No. 2026/13).

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Çıkar Çatışması: Yazar, herhangi bir çıkar çatışması bulunmadığını beyan eder.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Yazarlar, ChatGPT'yi (OpenAI) yalnızca makalenin dilini, dilbilgisini ve okunabilirliğini iyileştirmek amacıyla kullanmışlardır. Tüm bilimsel içerik, çalışma tasarımı, veri analizi, sonuçların yorumlanması ve makalenin nihai onayı yazarlar tarafından gerçekleştirilmiştir; yazarlar, içeriğin tüm sorumluluğunu üstlenmektedir.

Yazarlık Katkıları: Fikir – EGŞ, CD; Tasarım – FV, KBG; Denetlemeler – FV; Veri toplanması ve/veya işleme – BE, FT, KBG; Analiz ve/veya yorumlama – EBŞ, CD; Literatür araştırması – EGŞ, BE; Yazım – EGŞ, CD; Eleştirel incelemeler – FV, CD.

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Appendix 1. Laboratory parameters and respiratory support durations according to single and multiple viral detection

Variables	Single viral detection (n=73)	Multiple viral detection (n=53)	p
IMV durations, days	0 (0-4)	0 (0-7)	0.152
NIV durations, days	2 (0-4)	2 (0-4)	0.504
HFNC duration, days	2 (0-4)	0 (0-3)	**0.043**
CRP, mg/L	11.7 (2.5-61.6)	16.4 (6.8-50.6)	0.364
Procalcitonin, ng/mL	0.26 (0.12-1.02)	0.3 (0.15-2.98)	0.250
White blood cell count, /µL	9190 (6280-14040)	10190 (6865-16145)	0.229
Neutrophil count, /µL	6000 (2980-10560)	6600 (3685-11720)	0.322
Lymphocyte count, /µL	2110 (1220-3150)	2300 (1415-3845)	0.296
pH	7.33 (7.26-7.39)	7.31 (7.25-7.37)	0.313
$PaCO_2$, mmHg	42.8 (35.7-54.0)	41.2 (37.8-52.6)	0.465
Lactate, mmol/L	1.35 (0.91-1.76)	1.6 (1.17-2.27)	**0.028**

Data are presented as median (IQR). Comparisons were performed using the Mann–Whitney U test. IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation; HFNC: High-flow nasal cannula; CRP: C-reactive protein; $PaCO_2$: Partial pressure of carbon dioxide; n: Number of patients.

Appendix 2. PICU length of stay according to viral burden

Number of detected virus	n	PICU LOS, median (IQR), days
1 virus	73	9 (6-13)
2 viruses	35	7 (5-11)
3 viruses	15	13 (7.5-18.25)
4 viruses	3	50 (11-NA) *
Overall p value		**0.029**

Overall Kruskal–Wallis test: H=9.018, df=3, p=0.029. *: IQR could not be fully calculated for the four-virus group because of the small sample size (n=3). PICU: Pediatric intensive care unit; LOS: Length of stay; IQR: Interquartile range; df: Degrees of freedom; NA: Not applicable; n: Number of patients.

Appendix 3. Bonferroni-adjusted pairwise comparisons of PICU length of stay across viral-burden groups

Pairwise comparison	Test statistic	Standard error	Standardized test statistic	Unadjusted p value	Bonferroni-adjusted p value
Two viruses vs. one virus	7.685	7.411	1.037	0.300	1.000
Two viruses vs. three viruses	-25.750	11.461	-2.247	0.025	0.148
Two viruses vs. four viruses	-49.833	21.866	-2.279	0.023	0.136
One virus vs. three viruses	-18.065	10.617	-1.702	0.089	0.533
One virus vs. four viruses	-42.148	21.436	-1.966	0.049	0.296
Three viruses vs. four viruses	-24.083	23.150	-1.040	0.298	1.000

The overall Kruskal–Wallis test demonstrated a significant difference in PICU length of stay across the four viral-burden groups (H=9.018, df=3, p=0.029). Pairwise comparisons were subsequently performed with Bonferroni adjustment for multiple testing. None of the pairwise comparisons remained statistically significant after adjustment. Asymptotic two-sided p values are reported. Group sizes were 73, 35, 15, and 3 patients for the one-, two-, three-, and four-virus groups, respectively. PICU: Pediatric intensive care unit.

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ORIGINAL RESEARCH
Pediatric Surgery

Diagnostic value of selected hematological markers in differentiating acute appendicitis from reactive lymphoid hyperplasia in children: A retrospective single-center study

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic performance of selected hematological markers for differentiating histopathologically confirmed acute appendicitis (AA) from reactive lymphoid hyperplasia (RLH) in children and to investigate their independent associations with AA.

Material and Methods: This retrospective, single-center study included 195 children with histopathologically confirmed AA (n=45) or RLH (n=150) following appendectomy. Preoperative leukocyte, neutrophil, lymphocyte, and platelet counts were recorded, and the systemic immune-inflammation index (SII) was calculated as platelet count × neutrophil count/lymphocyte count. The discriminatory performance of the hematological markers was evaluated using receiver operating characteristic (ROC) curve analysis, and optimal cutoff values were determined using the Youden index. Multivariable logistic regression analyses were performed to identify factors independently associated with AA.

Results: Leukocyte, neutrophil, platelet, and SII values were significantly higher in the AA group than in the RLH group, whereas the lymphocyte count was significantly lower (all $p<0.05$). ROC analysis showed the highest discriminatory performance for neutrophil count (AUC=0.724; 95% CI: 0.648–0.800), followed by SII (AUC=0.712; 95% CI: 0.634–0.791) and leukocyte count (AUC=0.690; 95% CI: 0.611–0.769). At the optimal cutoff values, neutrophil count had a sensitivity of 84.4% and a specificity of 56.7%, whereas SII had a sensitivity of 82.2% and a specificity of 56.0%. In multivariable analysis, SII remained independently associated with AA after adjustment for age, sex, and leukocyte count (adjusted OR=1.258 per 1,000-unit increase; 95% CI: 1.068–1.482; p=0.006). In the conventional hematological model excluding SII, neutrophil and platelet counts were independently and positively associated with AA, whereas lymphocyte count was inversely associated.

Conclusion: Selected hematological markers may provide supportive information for differentiating AA from RLH in children. Although SII was independently associated with AA, it did not demonstrate a diagnostic advantage over the absolute neutrophil count. Therefore, SII and other routine hematological markers should be considered adjuncts to, rather than standalone substitutes for, clinical assessment and imaging findings.

Keywords: Appendicitis; biomarkers; child; leukocyte count; lymphoid tissue.

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Çocuklarda akut apandisit ile reaktif lenfoid hiperplazinin ayırıcı tanısında seçilmiş hematolojik belirteçlerin tanısal değeri: Retrospektif tek merkezli bir çalışma

ÖZET

Amaç: Bu çalışmanın amacı, çocuklarda histopatolojik olarak doğrulanmış akut apandisit (AA) ile reaktif lenfoid hiperplazinin (RLH) ayırıcı tanısında seçilmiş hematolojik belirteçlerin tanısal performansını değerlendirmek ve bu belirteçlerin AA ile bağımsız ilişkilerini araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli çalışmaya, apendektomi sonrası histopatolojik olarak AA (n=45) veya RLH (n=150) tanısı doğrulanan toplam 195 çocuk dahil edildi. Ameliyat öncesi lökosit, nötrofil, lenfosit ve trombosit sayıları kaydedildi ve sistemik immün-inflamasyon indeksi (SII), trombosit × nötrofil/lenfosit formülü kullanılarak hesaplandı. Hematolojik belirteçlerin ayırt edici performansı, alıcı işletim karakteristiği (ROC) eğrisi analizi ile değerlendirildi ve optimal eşik değerleri Youden indeksi kullanılarak belirlendi. AA ile bağımsız olarak ilişkili faktörleri değerlendirmek amacıyla çok değişkenli lojistik regresyon analizleri gerçekleştirildi.

Bulgular: Akut apandisit grubunda lökosit, nötrofil, trombosit ve SII değerleri RLH grubuna göre anlamlı olarak daha yüksek, lenfosit sayısı ise daha düşüktü (tümü p<0,05). ROC analizinde en yüksek ayırt edici performans nötrofil sayısında saptandı (AUC=0,724; %95 GA: 0,648–0,800); bunu SII (AUC=0,712; %95 GA: 0,634–0,791) ve lökosit sayısı (AUC=0,690; %95 GA: 0,611–0,769) izledi. Optimal eşik değerlerinde nötrofil sayısının duyarlılığı %84,4, özgüllüğü %56,7; SII'nin duyarlılığı %82,2, özgüllüğü %56,0 idi. Çok değişkenli analizde SII, yaş, cinsiyet ve lökosit sayısı için düzeltme yapıldıktan sonra AA ile bağımsız olarak ilişkili bulundu (düzeltilmiş OR=1,258/her 1000 birimlik artış; %95 GA: 1,068–1,482; p=0,006). SII'nin yer almadığı konvansiyonel hematolojik modelde ise nötrofil ve trombosit sayıları AA ile bağımsız ve pozitif yönde, lenfosit sayısı ise ters yönde ilişkiliydi.

Tartışma: Seçilmiş hematolojik belirteçler, çocuklarda AA ile RLH'nin ayırt edilmesinde destekleyici bilgiler sağlayabilir. SII, AA ile bağımsız olarak ilişkili bulunmasına rağmen mutlak nötrofil sayısına göre tanısal bir üstünlük göstermemiştir. Bu nedenle SII ve diğer rutin hematolojik belirteçler, tek başına tanısal testler olarak değil, klinik değerlendirme ve görüntüleme bulgularını tamamlayan yardımcı parametreler olarak değerlendirilmelidir.

Anahtar Kelimeler: Apandisit; biyobelirteçler; çocuk; lenfoid doku; lökosit sayımı.

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INTRODUCTION

Acute appendicitis (AA) is the most common pediatric abdominal surgical emergency, with a lifetime risk of approximately 7–8% and a peak incidence during the second decade of life (1). Despite advances in laboratory testing and imaging, diagnosis remains challenging because clinical manifestations are often nonspecific, particularly in younger children, who frequently lack the classic triad of right lower quadrant pain, fever, and leukocytosis (2). Although clinical scoring systems such as the Pediatric Appendicitis Score (PAS) and modified Alvarado score facilitate risk stratification, neither provides sufficient diagnostic accuracy when used alone (3).

Negative appendectomy continues to occur in approximately 10–20% of pediatric cases (4, 5). Reactive lymphoid hyperplasia (RLH), a frequent but underrecognized pathological finding in these patients, is characterized by lymphoid follicular enlargement with preservation of normal appendiceal architecture and the absence of acute inflammatory changes (5). Because RLH commonly develops in response to viral or other antigenic stimulation during periods of active lymphoid tissue growth, it is encountered predominantly in children and adolescents (6, 7). Importantly, RLH may cause appendiceal wall thickening and luminal distension that closely resemble AA on ultrasonography, increasing the likelihood of unnecessary appendectomy (8, 9). As definitive diagnosis relies on postoperative histopathological examination, additional preoperative diagnostic tools are needed (4).

Routine complete blood count (CBC) parameters and CBC-derived inflammatory indices have attracted increasing interest because they are inexpensive, rapidly available, and readily incorporated into emergency evaluation (10, 11). Conventional hematological parameters, particularly leukocyte and neutrophil counts, remain widely used in the assessment of suspected AA, while composite indices such as the neutrophil-to-lymphocyte ratio (NLR) have also demonstrated diagnostic and prognostic value (12). More recently, the systemic immune-inflammation index (SII), calculated as platelet count×neutrophil count/lymphocyte count, has emerged as a composite marker integrating different components of the inflammatory and immune responses (13).

Originally introduced as a prognostic marker for hepatocellular carcinoma, SII has subsequently been investigated in various inflammatory and surgical conditions (13).

Previous studies have investigated SII and other hematological markers in pediatric AA and have reported their potential diagnostic value and associations with disease severity (14–17). However, most studies have compared patients with AA with heterogeneous control populations, including those with negative appendectomy specimens or mesenteric lymphadenitis and elective surgical patients, rather than focusing specifically on histopathologically confirmed RLH (18, 19). This distinction is clinically relevant because RLH may mimic AA both clinically and radiologically and may itself be accompanied by alterations in inflammatory parameters.

Therefore, this study aimed to evaluate the diagnostic performance of selected hematological markers, including leukocyte, neutrophil, lymphocyte, and platelet counts and SII, for differentiating histopathologically confirmed AA from RLH in children undergoing appendectomy. We also sought to determine clinically relevant cutoff values for these markers and to assess their associations with AA after adjustment for potential confounding factors.

MATERIAL AND METHODS

Study Design

A retrospective diagnostic accuracy study was conducted at a tertiary pediatric surgery center in Türkiye between January 2020 and December 2024. The study was approved by the University of Health Sciences, UÜmraniye Training and Research Hospital Ethics Committee (approval no. 216; September 11, 2025) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design.

Patient Selection

Approximately 1,400 pediatric appendectomies were performed during the study period. Reactive lymphoid hyperplasia (RLH) was identified in 150 specimens. A randomly selected cohort of 45 children with acute appendicitis (AA) served as the comparison group. Therefore, the proportions of AA and RLH in this analysis were not intended to represent the institutional incidence of AA or the overall negative appendectomy rate.

The final diagnosis was established by histopathological evaluation of the resected appendix. Based on these findings, patients were assigned to either the AA group (n=45) or the RLH group (n=150). Only patients with histopathologically confirmed AA or RLH were included.

The exclusion criteria were incomplete preoperative complete blood count (CBC) data, concurrent systemic infection, chronic inflammatory, hematological, or immunological disease, malignancy, or preoperative treatment with corticosteroids or immunosuppressive agents.

Clinical Management

Children presenting with suspected AA underwent routine clinical evaluation supported by laboratory and imaging findings. The indication for appendectomy was determined according to the overall clinical assessment. Perioperative antibiotic therapy followed institutional treatment protocols, whereas postoperative management was individualized according to operative findings and clinical recovery.

Data Collection and Laboratory Measurements

Age and sex were recorded for all participants. Peripheral venous blood samples obtained before surgery were analyzed for white blood cell (WBC), neutrophil, lymphocyte, and platelet counts using automated hematology analyzers in the central laboratory under standardized quality-control procedures.

The systemic immune-inflammation index (SII) was calculated according to the method described by Hu et al. (13) SII=[platelet count ($\times10^3/\mu L$) × neutrophil count ($\times10^3/\mu L$)]/lymphocyte count ($\times10^3/\mu L$).

Individual CBC parameters and calculated SII values were subsequently compared between the two study groups.

Outcome Measures

The primary objective was to evaluate the diagnostic performance of selected hematological markers, including WBC, neutrophil, lymphocyte, and platelet counts and SII, for differentiating histopathologically confirmed AA from RLH. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of each marker by determining the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the optimal cutoff values.

A secondary objective was to evaluate whether the investigated hematological markers were independently associated with AA after adjustment for age and sex using multivariable logistic regression analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation (SD) and median, and categorical variables as number (n) and percentage (%). The distribution of continuous variables was assessed using the Shapiro–Wilk test together with visual inspection of histograms and Q–Q plots. Because continuous variables were not normally distributed, between-group comparisons were performed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of each hematological marker. Areas under the curve (AUCs) with 95% confidence intervals (CIs) were calculated, and optimal cutoff values were determined using the Youden index, with corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Table 1. Comparison of demographic characteristics between the acute appendicitis and reactive lymphoid hyperplasia groups

Gender, n (%)			0.793[a]
Male	**23 (51.1)**	**80 (53.3)**	
Female	22 (48.9)	70 (46.7)	
Age (years) mean±SD / median	11.7±4.3 / 12.0	10.7±5.2 / 11.0	0.308[b]

a: Chi-Kare (Chi-Square) test; b: Mann–Whitney U test; SD: Standard deviation.

Multivariable logistic regression analysis was performed to identify factors independently associated with acute appendicitis (AA) using three Enter models. Model 1 included age, sex, and SII; Model 2 additionally included WBC count. Because SII is derived from neutrophil, lymphocyte, and platelet counts, these components were evaluated separately in Model 3 together with age, sex, and WBC count. SII was scaled per 1,000-unit increase. Results are reported as adjusted odds ratios (aORs) with 95% CIs. Multicollinearity was assessed using variance inflation factors (VIFs), and model performance was summarized using Nagelkerke R^2. All tests were two-sided, with $p<0.05$ considered statistically significant.

RESULTS

Patient Demographics

The study included 195 children, comprising 45 patients with acute appendicitis (AA) and 150 with reactive lymphoid hyperplasia (RLH). Sex distribution was similar between the groups (51.1% vs. 53.3% male, respectively; p=0.793), as was age (median, 12.0 vs. 11.0 years, respectively; p=0.308) (Table 1). Because the AA cohort was randomly selected, the proportions of AA and RLH in the study population were not intended to represent the institutional incidence of AA or the overall negative appendectomy rate.

Laboratory Parameters

All evaluated complete blood count (CBC) parameters differed significantly between the two groups (Table 2). Leukocyte count was higher in the AA group than in the RLH group (mean±SD: 15.4±7.9 vs. 13.0±12.1 ×10³/μL; median: 14.2 vs. 10.5 ×10³/μL; p<0.001). Similar findings were observed for neutrophil count (11.50±4.06 vs. 8.22±4.77 ×10³/μL; median: 10.72 vs. 6.71 ×10³/μL; p<0.001) and platelet count (306.0±64.1 vs. 284.1±74.5 ×10³/μL; median: 301.0 vs. 281.0 ×10³/μL; p=0.034). In contrast, lymphocyte count was lower in the AA group (1.84±0.91 vs. 2.16±0.99 ×10³/μL; median: 1.61 vs. 2.06 ×10³/μL; p=0.039). SII values were also significantly higher in the AA group than in the RLH group (mean±SD: 2.625±2.119 vs. 1.634±2.139; median: 1.897 vs. 963; p<0.001).

Diagnostic Performance

Receiver operating characteristic (ROC) analysis demonstrated the highest AUC for neutrophil count (AUC=0.724; 95% CI: 0.648–0.800), followed by SII (AUC=0.712; 95% CI: 0.634–0.791) and leukocyte count (AUC=0.690; 95% CI: 0.611–0.769) (Table 3; Fig. 1). Platelet and lymphocyte counts showed lower discriminatory ability, with AUC values below 0.65. Thus, although SII demonstrated moderate discriminatory ability, its AUC did not exceed that of the absolute neutrophil count.

According to the Youden index, the optimal cutoff value was 7.715 ×10³/μL for neutrophil count and 1.081 for SII. At these thresholds, neutrophil count yielded a sensitivity of 84.4%, specificity of 56.7%, positive predictive value (PPV) of 36.9%, and negative predictive value (NPV) of 92.4%. For SII, the corresponding sensitivity, specificity, PPV, and NPV were 82.2%, 56.0%, 35.9%, and 91.3%, respectively (Table 3).

Multivariable Logistic Regression Analysis

The results of the multivariable logistic regression analyses are presented in Table 4. In Model 1, which included age, sex, and SII, SII remained independently associated with AA (aOR=1.264 per 1,000-unit increase; 95% CI: 1.072–1.490; p=0.005), whereas age and sex were not independently associated with AA.

In Model 2, after additional adjustment for leukocyte count, SII remained independently associated with AA (aOR=1.258 per 1,000-unit increase; 95% CI: 1.068–1.482; p=0.006). Leukocyte count was not independently associated with AA in this model (aOR=1.018; 95% CI: 0.991–1.046; p=0.200).

Table 2. Comparison of preoperative laboratory parameters between patients with acute appendicitis and those with reactive lymphoid hyperplasia

Parameters	Acute appendicitis (n=45) Mean±SD / Median	Reactive lymphoid hyperplasia (n=150) Mean±SD / Median	p
Leukocyte (×10³/μL)	15.4±7.9 / 14.2	13.0±12.1 / 10.5	<0.001
Neutrophil (×10³/μL)	11.50±4.06 / 10.72	8.22±4.77 / 6.71	<0.001
Platelet (×10³/μL)	306.0±64.1 / 301.0	284.1±74.5 / 281.0	0.034
Lymphocyte (×10³/μL)	1.84±0.91 / 1.61	2.16±0.99 / 2.06	0.039
SII	2.625±2.119 / 1.897	1.634±2.139 / 0.963	<0.001

*: Mann–Whitney U test. SII: Systemic Immune-Inflammation Index = (Platelet count×Neutrophil count) / Lymphocyte count.

Table 3. ROC curve analysis: discriminatory performance of preoperative laboratory parameters in differentiating acute appendicitis from reactive lymphoid hyperplasia

Neutrophil (×10³/µL)	7.715	0.724 (0.648–0.800)	84.4	56.7	36.9	92.4
SII	1.081	0.712 (0.634–0.791)	82.2	56.0	35.9	91.3
Leukocyte (×10³/µL)	10.985	0.690 (0.611–0.769)	84.4	53.3	34.9	91.9
Platelet (×10³/µL)	275.5	0.604 (0.516–0.693)	71.0	48.0	29.1	84.7
Lymphocyte (×10³/µL)	1.695	0.602 (0.510–0.693)	55.6	64.0	32.9	83.2

Cutoff values determined by the Youden index (maximum of sensitivity + specificity − 1). Top two performers (neutrophil count and SII) are highlighted. SII: Systemic Immune-Inflammation Index = (Platelet×Neutrophil) / Lymphocyte; AUC: Area under the ROC curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Table 4. Multivariable logistic regression analysis of factors associated with acute appendicitis

Model	Variables	aOR	95% CI	p
Model 1	Age at surgery (years)	1.075	0.993–1.164	0.074
	Sex (Ref: Male)	0.815	0.399–1.664	0.574
	SII (per 1,000-unit increase)	1.264	1.072–1.490	0.005
Model 2	Age at surgery (years)	1.083	0.999–1.174	0.054
	Sex (Ref: Male)	0.799	0.390–1.635	0.539
	SII (per 1,000-unit increase)	1.258	1.068–1.482	0.006
	WBC count (×10³/µL)	1.018	0.991–1.046	0.200
Model 3	Age at surgery (years)	1.119	1.021–1.227	0.017
	Sex (Ref: Male)	0.726	0.337–1.564	0.413
	WBC count (×10³/µL)	1.007	0.972–1.043	0.700
	Neutrophil count (×10³/µL)	1.162	1.065–1.267	<0.001
	Platelet count (×10³/µL)	1.006	1.001–1.012	0.039
	Lymphocyte count (×10³/µL)	0.653	0.437–0.976	0.038

The Enter method was used for all models. VIF ranges were 1.026–1.082 for Model 1, 1.027–1.100 for Model 2, and 1.063–1.230 for Model 3. Nagelkerke R^2 values were 0.084, 0.096, and 0.226 for Models 1, 2, and 3, respectively. aOR: Adjusted odds ratio; CI: Confidence interval; SII: Systemic immune-inflammation index; WBC: White blood cell; VIF: Variance inflation factor.

In Model 3, which evaluated conventional hematological parameters without SII, age (aOR=1.119; 95% CI: 1.021–1.227; p=0.017), neutrophil count (aOR=1.162; 95% CI: 1.065–1.267; p<0.001), and platelet count (aOR=1.006; 95% CI: 1.001–1.012; p=0.039) were independently and positively associated with AA, whereas lymphocyte count was inversely associated with AA (aOR=0.653; 95% CI: 0.437–0.976; p=0.038). Sex (p=0.413) and leukocyte count (p=0.700) were not independently associated with AA in this model. No evidence of relevant multicollinearity was observed, with VIF values ranging from 1.026 to 1.082 in Model 1, from 1.027 to 1.100 in Model 2, and from 1.063 to 1.230 in Model 3. Nagelkerke R^2 values were 0.084, 0.096, and 0.226 for Models 1, 2, and 3, respectively.

DISCUSSION

The present study evaluated selected hematological markers for differentiating histopathologically confirmed reactive lymphoid hyperplasia (RLH) from acute appendicitis (AA) in children undergoing appendectomy. Patients with AA had significantly higher leukocyte, neutrophil, platelet, and SII values and lower lymphocyte counts than those with RLH. Among the evaluated markers, neutrophil count had the highest discriminatory performance (AUC=0.724), followed by SII (AUC=0.712) and leukocyte count (AUC=0.690). In multivariable analysis, SII remained independently associated with AA after adjustment for age, sex, and leukocyte count. However, in a separate model evaluating conventional hematological parameters, neutrophil and platelet counts were independently and positively associated with AA, whereas lymphocyte count showed an inverse association. Taken together, these findings suggest that SII may provide supportive information in differentiating AA from RLH but does not demonstrate a clear diagnostic advantage over routinely available hematological parameters, particularly the absolute neutrophil count.

Differentiating AA from RLH before surgery remains challenging because both conditions may share overlapping clinical and

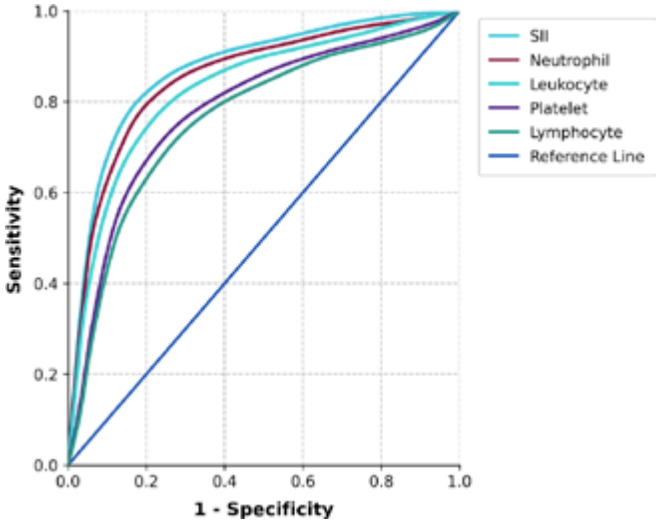

Figure 1. Receiver operating characteristic (ROC) curves showing the discriminatory performance of selected hematological markers for differentiating acute appendicitis from reactive lymphoid hyperplasia in children. Neutrophil count showed the highest area under the curve (AUC=0.724), followed by the systemic immune-inflammation index (SII; AUC=0.712), leukocyte count (AUC=0.690), platelet count (AUC=0.604), and lymphocyte count (AUC=0.602).

ultrasonographic features. RLH is characterized by lymphoid follicular enlargement within the appendiceal wall, usually related to viral infection or antigenic stimulation, and may produce mural thickening that resembles inflammatory appendicitis (8, 20). Previous studies have reported RLH in approximately 10–20% of pediatric appendectomy specimens, although this proportion varies according to patient selection and pathological criteria (7, 21). Because definitive differentiation between AA and RLH relies on histopathological examination of the resected appendix, the identification of preoperative parameters that may contribute to this distinction remains clinically relevant (8, 9).

The systemic immune-inflammation index integrates platelet, neutrophil, and lymphocyte counts into a single parameter and therefore reflects several components of the inflammatory and immune responses (13). The higher SII values observed in AA in the present study are consistent with the neutrophilia, relative lymphopenia, and platelet response that may accompany acute inflammation. RLH, in contrast, represents lymphoid proliferation associated with antigen-driven immune stimulation rather than the neutrophil-predominant inflammatory response characteristic of AA (5, 8). Nevertheless, these hematological changes are not specific to appendicitis and may occur in a variety of inflammatory conditions. Accordingly, SII should be regarded as a supportive inflammatory marker rather than a disease-specific biomarker.

The ROC findings provide important context for interpreting the potential role of SII. Neutrophil count showed the highest AUC (0.724), followed closely by SII (0.712), whereas leukocyte count had an AUC of 0.690. Therefore, although SII demonstrated moderate discriminatory ability, it did not outperform the absolute neutrophil count. Previous pediatric studies have also reported diagnostic or prognostic associations between SII and acute appendicitis. Firinci et al. (17) reported high diagnostic performance for SII when children with appendicitis were compared with elective surgical controls. Feier et al. (15) demonstrated associations between systemic inflammatory indices and appendicitis severity across different age groups. Siki et al. (16) also reported diagnostic value for SII in children with AA. Differences in diagnostic performance across studies may partly reflect differences in comparator populations. In the present study, the control group consisted exclusively of patients with histopathologically confirmed RLH, which represents a clinically relevant mimic of AA and may itself be associated with alterations in inflammatory parameters.

The multivariable analyses further clarify the relationship between SII and conventional hematological markers. SII remained independently associated with AA after adjustment for age and sex and retained this association after leukocyte count was added to the model. However, because SII is mathematically derived from neutrophil, lymphocyte, and platelet counts, its individual components were evaluated in a separate model to avoid simultaneously entering mathematically dependent variables. In this conventional hematological model, neutrophil and platelet counts were independently and positively associated with AA, whereas lymphocyte count was inversely associated; leukocyte count was not independently significant. These findings indicate that the association observed for SII likely reflects the combined contribution of its constituent hematological components and should not be interpreted as evidence of superiority over simpler CBC parameters. In particular, the strong independent association of neutrophil count, together with its numerically higher AUC, supports the continued clinical relevance of this readily available conventional marker.

At their optimal cutoff values, both neutrophil count and SII demonstrated sensitivities above 80% and NPVs above 90% in the present cohort, whereas specificity and PPV were comparatively modest. These findings suggest that lower values of these markers may provide supportive information when AA is considered less likely; however, they should not be used in isolation to exclude the diagnosis or determine management. Importantly, predictive values are influenced by disease prevalence, and the deliberately unequal composition of our study population (45 AA and 150 RLH cases) does not represent the prevalence of these diagnoses in routine clinical practice. Therefore, the PPV and NPV observed in this cohort should not be directly extrapolated to unselected pediatric populations. Rather than serving as standalone decision thresholds, these hematological markers may be most appropriately interpreted alongside clinical examination, established scoring systems, and imaging findings. Consistent with this approach, Guo et al. (22) reported improved diagnostic performance when SII was combined with the Pediatric Appendicitis Score, supporting the integration of laboratory markers with clinical assessment rather than their use in isolation.

A major strength of the present study is the use of histopathologically confirmed RLH as the comparison group. Previous investigations have often compared AA with heterogeneous populations, including normal appendices, negative appendectomy specimens, mesenteric lymphadenitis, or elective surgical controls (18, 19). Such comparator groups may not fully represent the specific diagnostic challenge posed by RLH, which can closely mimic AA. Similar to the studies by Kaya et al. (14) and Ucar Karabulut et al., (5) which evaluated hematological parameters in AA and lymphoid hyperplasia, the present study considered RLH as a distinct pathological entity. This approach provides a focused assessment of routinely available hematological markers in a clinically relevant differential diagnostic setting.

Limitations

This study has several limitations. First, its retrospective, single-center design introduces the possibility of selection bias. Only children who underwent appendectomy and had histopathologically confirmed AA or RLH were included; therefore, children with suspected RLH who were managed nonoperatively were not represented. Second, the AA cohort was randomly selected from the institutional appendectomy population, and the resulting distribution of AA and RLH was determined by the study design rather than by their prevalence in clinical practice. Consequently, PPV and NPV estimates should be interpreted within the context of this selected cohort and may not be directly generalizable to unselected populations. Third, laboratory parameters were evaluated only at admission, and potentially relevant variables such as C-reactive protein, clinical scoring systems, symptom duration, and imaging findings were not incorporated into the multivariable models. The relatively limited number of AA cases also restricted the number of variables that could be included in the regression analyses. Finally, the proposed cutoff values were derived from the same cohort in which diagnostic performance was assessed and were not externally validated.

Further prospective, multicenter studies incorporating clinical scores, inflammatory biomarkers, and imaging findings are needed to externally validate these results and determine whether combining routinely available hematological markers provides incremental diagnostic value in distinguishing pediatric AA from RLH.

CONCLUSION

Selected hematological markers may provide supportive information for differentiating acute appendicitis from reactive lymphoid hyperplasia in children. SII demonstrated moderate discriminatory performance and remained independently associated with acute appendicitis after adjustment for age, sex, and leukocyte count; however, it did not show a diagnostic advantage over the absolute neutrophil count. Conventional CBC parameters, particularly neutrophil count, also showed clinically relevant associations with acute appendicitis. Therefore, these readily available hematological markers should be considered adjuncts to, rather than substitutes for, clinical assessment and imaging findings. Prospective multicenter studies with external validation are needed to determine their incremental value in preoperative diagnostic assessment.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital (Date: Sep 11, 2025, Decision No. 216).

Informed Consent: The requirement for informed consent was waived because of the retrospective design.

Conflict of Interest: The author declare that there is no conflict of interest.

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Use of AI for Writing Assistance: No artificial intelligence (AI)-assisted technology was used to generate, interpret, analyze, or report the study data. AI-assisted language tools were used only to improve the clarity and grammatical quality of the manuscript. The authors reviewed and approved the final manuscript and take full responsibility for its content.

Authorship Contributions: Concept – NG, CŞ; Design – NG, CŞ, CG; Supervision – NG, CŞ; Data Collection and/or Processing – NG, CŞ, MSD, MA,CG; Analysis and/or Interpretation – NG, CŞ, MSD, CG; Literature Search – NG, CŞ, MSD, SLM, CG; Writing – NG; Critical Reviews – NG, CŞ, AK.

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Hasta Onamı: Çalışmanın geriye dönük tasarımı nedeniyle bilgilendirilmiş onam şartından feragat edildi.

Çıkar Çatışması: Yazar, herhangi bir çıkar çatışması bulunmadığını beyan eder.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Çalışma verilerinin oluşturulması, yorumlanması, analiz edilmesi veya raporlanmasında yapay zeka (AI) destekli hiçbir teknoloji kullanılmamıştır. AI destekli dil araçları, yalnızca makalenin anlaşılırlığını ve dilbilgisi kalitesini artırmak amacıyla kullanılmıştır. Yazarlar, nihai makaleyi gözden geçirip onaylamışlardır ve içeriği konusunda tüm sorumluluğu üstlenmektedirler.

Yazarlık Katkıları: Fikir – NG, CŞ; Tasarım – NG, CŞ, CG; Denetlemeler – NG, CŞ; Veri toplanması ve/veya işleme – NG, CŞ, MSD, MA,CG; Analiz ve/veya yorumlama – NG, CŞ, MSD, CG; Literatür araştırması – NG, CŞ, MSD, SLM, CG; Yazım – NG; Eleştirel incelemeler – NG, CŞ, AK.

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CASE REPORT
Pediatric Genetics

Progressive familial intrahepatic cholestasis type 3 (PFIC3), a rare chronic liver disease: A case report

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ABSTRACT

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a rare autosomal recessive chronic liver disease characterized by reduced secretion of bile phospholipids resulting from pathogenic variants in the *ABCB4* gene. In pediatric cases, it typically presents with jaundice, pruritus, hepatosplenomegaly, and elevated GGT levels and may progress to cirrhosis and liver failure with advancing age. This study presents a pediatric case diagnosed with PFIC3. A 7.5-year-old female patient presented with jaundice, fatigue, and pruritus. Physical examination revealed an icteric appearance, hepatosplenomegaly, and findings consistent with chronic liver disease. Laboratory findings showed cholestasis and elevated liver enzyme levels. Imaging studies also revealed findings consistent with chronic liver disease. Liver biopsy revealed inflammation, fibrosis, and a reduction in the number of bile ducts. Genetic testing identified compound heterozygous variants in the *ABCB4* gene, one of which was pathogenic and the other a variant of uncertain significance (VUS). In conclusion, genetic analysis is critically important in the diagnosis of PFIC3, alongside clinical, laboratory, and histopathological findings. Screening other family members is important for early diagnosis, disease management, and prognosis.

Keywords: *ABCB4*; child; cholestasis; PFIC3.

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Progresif familyal intrahepatik kolestaz tip 3 (PFIC3), nadir görülen kronik bir karaciğer hastalığı: Olgu sunumu

ÖZET

Progresif familyal intrahepatik kolestaz tip 3 (PFIC3), *ABCB4* genindeki patojenik varyantlara bağlı olarak gelişen, safra fosfolipit sekresyonunun azalmasıyla karakterize, nadir görülen ve otozomal resesif kalıtım gösteren kronik bir karaciğer hastalığıdır. Pediatrik olgularda genellikle sarılık, hepatosplenomegali, kaşıntı ve yüksek GGT düzeyleriyle seyreder ve ilerleyen yaşlarda siroz ve karaciğer yetmezliğine ilerleyebilir. Bu çalışmada, PFIC3 tanısı alan pediatrik bir olgu sunulmuştur. Yedi buçuk yaşında kız hasta, sarılık, halsizlik ve kaşıntı şikâyetleriyle başvurdu. Fizik muayenesinde ikterik görünüm, hepatosplenomegali ve kronik karaciğer hastalığı bulguları saptandı. Laboratuvar incelemelerinde kolestaz ve karaciğer enzim yüksekliği görüldü. Görüntüleme yöntemlerinde de kronik karaciğer hastalığını destekleyen bulgular izlendi. Karaciğer biyopsisinde inflamasyon, fibrozis ve safra duktuslarında azalma saptandı. Genetik incelemede *ABCB4* geninde patojenik bir varyant tespit edilerek PFIC3 tanısı doğrulandı. Sonuç olarak, PFIC3 tanısında klinik, laboratuvar ve histopatolojik bulgularla birlikte genetik analizler de kritik öneme sahiptir. Ailenin diğer bireylerinin de taranması, erken tanı, hastalık yönetimi ve prognoz açısından önemlidir.

Anahtar Kelimeler: *ABCB4*; çocuk; kolestaz; PFIC3.

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INTRODUCTION

Progressive familial intrahepatic cholestasis type 3 (PFIC3) is a chronic liver disease inherited in an autosomal recessive pattern, caused by pathogenic variants in the *ABCB4* gene, and characterized by reduced bile phospholipid secretion due to MDR3 protein deficiency (1, 2). Although the prevalence of the disease is not precisely known, it is estimated to account for approximately 10–15% of all cases of cholestasis observed in children (3). In pediatric cases, the clinical presentation typically includes jaundice, hepatomegaly, splenomegaly, pruritus, and acholic stools, along with elevated serum GGT levels on laboratory testing. Most patients develop cirrhosis, portal hypertension (PHT), and liver failure within the first 20 years of life (1, 4). In the differential diagnosis, infections in early childhood, as well as metabolic disorders such as Alagille syndrome, Wilson disease, autoimmune hepatitis, primary sclerosing cholangitis, cystic fibrosis, tyrosinemia, Gaucher disease, and glycogen storage diseases (types 3 and 4), should be considered and ruled out. Ursodeoxycholic acid (UDCA) is used for treatment, and studies have reported that UDCA improves liver survival (4). As progressive liver fibrosis, cirrhosis, and end-stage liver disease develop, liver transplantation becomes necessary (2).

CASE REPORT

A 7.5-year-old female patient with no known chronic illness presented with jaundice, fatigue, and pruritus. Physical examination revealed icteric skin and sclerae, facial telangiectasias, digital clubbing, and palmar erythema. Abdominal examination revealed hepatomegaly with hypertrophy of the left lobe and splenomegaly. The patient also had growth and developmental delay; her height was 115 cm (-1.9 SDS), and her weight was 19 kg (-1.7 SDS). Laboratory findings included a WBC count of 7,610/mm³, hemoglobin (Hb) level of 12.7 g/dL, mean corpuscular volume (MCV) of 91 fL, platelet (PLT) count of 132,000/mm³, alanine aminotransferase (ALT) level of 143 U/L, aspartate aminotransferase (AST) level of 275 U/L, albumin level of 3.8 g/dL, total bilirubin level of 3.3 mg/dL, direct bilirubin level of 3 mg/dL, gamma-glutamyl transferase (GGT) level of 353 U/L, creatine kinase (CK) level of 61 U/L, erythrocyte sedimentation rate (ESR) of 99 mm/h, prothrombin time of 16 seconds, INR of 1.2, total cholesterol level of 155 mg/dL, and HDL level of 13 mg/dL. Autoantibodies associated with autoimmune hepatitis, including anti-LKM-1, AMA, and ASMA, were negative. Portal Doppler ultrasonography revealed that the liver was enlarged to 120 mm. The parenchymal echotexture was heterogeneous and granular, and multiple hypoechoic nodular lesions were observed, the largest of which measured 10 mm in diameter. The portal vein diameter was normal, and blood flow was hepatopetal. The spleen was enlarged (118×54 mm), the sinusoids were prominent, and the splenic vein diameter and blood flow direction were reported as normal. Linear hyperechoic structures were also observed. Whole-abdominal MRI revealed enlargement of the left hepatic lobe, hypertrophy of the caudate lobe, and millimeter-sized hypointense nodular lesions in the parenchyma. These lesions were considered possible dysplastic nodules that had developed against a background of chronic liver disease. A liver biopsy was planned to determine the etiology of

Table 1. Molecular and clinical characteristics of variants identified in the *ABCB4* gene

Gene/transcript	Genomic position (hg19)	Variant (cDNA/protein)	Annotation	Zygosity	ACMG classification	ClinVar ID
ABCB4 NM_000443.4	Chr7:87069514 –	c.1560+1G>A	Intronic	Heterozygous	Pathogenic (PVS1, PM2, PP5)	1676065
ABCB4 NM_000443.4	Chr7:87082270 Exon 6	c.526C>T p.Arg176Trp	Missense	Heterozygous	VUS (PM2, PP5)	372802

VUS: Variant of uncertain significance.

the patient's chronic liver disease. Histopathological examination revealed mild-to-moderate inflammation in all portal areas, periportal and periseptal interface hepatitis (moth-eaten necrosis), and fibrosis extending into the portal areas, along with findings consistent with bile duct hypoplasia and glycogenosis. During the genetic evaluation, the patient underwent targeted PFIC panel analysis based on clinical exome sequencing (CES). Compound heterozygous variants in the *ABCB4* gene were identified, one of which was pathogenic and the other was a variant of uncertain significance (VUS) (Table 1). Because the patient voluntarily discontinued outpatient follow-up at our clinic, no additional information is available regarding her long-term prognosis or current clinical status.

Written informed consent was obtained from the patient's legal representative for publication of this case report and the accompanying clinical information.

CONCLUSION

Our case highlights the importance of considering PFIC3, a rare liver disease, in the differential diagnosis of patients presenting with signs of cholestasis. Establishing a definitive diagnosis requires molecular and genetic analyses as well as clinical, laboratory, and histopathological evaluations. Furthermore, screening other family members and providing genetic counseling are essential for early diagnosis and disease management.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient's legal representative for publication of this case report and the accompanying clinical information.

Conflict of Interest: No conflict of interest was declared by the authors.

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Use of AI for Writing Assistance: While preparing this case report, the authors utilized artificial intelligence (AI)-powered technologies to assist with proofreading and drafting; ultimately, all content was reviewed, edited, and approved by the authors.

Authorship Contributions: Concept – FKC, NG; Design – FKC, TK; Supervision – FKC, NG; Resources – FKC; Materials – FKC; Data Collection and/or Processing – FKC, NG; Analysis and/or Interpretation – FKC; Literature Search – FKC; Writing – FKC; Critical Reviews – YŞ; Genetic Analysis – BY.

Peer-review: Externally peer-reviewed.

Etik Kurul Onayı: Bu, tek bir vaka raporudur ve bu nedenle kurum politikaları uyarınca etik kurul onayı gerekli görülmemiştir.

Hasta Onamı (veya gönüllü onamı): Bu vaka raporunun ve beraberindeki klinik bilgilerin yayınlanması için hastanın yasal temsilcisinden yazılı bilgilendirilmiş onam alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Olgu sunumunun hazırlanması sırasında yazarlar, yazı dilini düzeltme ve taslak hazırlama desteği için yapay zeka (AI) destekli teknolojilerden yararlanmış olup, nihai olarak tüm içerik yazarlar tarafından incelenmiş, düzenlenmiş ve onaylanmıştır.

Yazarlık Katkıları: Fikir – FKC, NG; Tasarım – FKC, TK; Denetlemeler – FKC, NG; Kaynaklar – FKC; Malzemeler – FKC; Veri toplanması ve/veya işleme – FKC, NG; Analiz ve/veya yorumlama – FKC; Literatür araştırması – FKC; Yazım – FKC; Eleştirel incelemeler – FKC; Genetik Analiz – BY.

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CASE REPORT
Pediatric Cardiology

Aortopulmonary window closure with an amplatzer duct occluder 1 in a 13-year-old: A case report

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ABSTRACT

An aortopulmonary window (APW) is a rare congenital anomaly characterized by a septation defect between the ascending aorta and the main pulmonary artery, accounting for approximately 0.2%–0.6% of all congenital heart diseases. Clinical severity and management depend on the size of the defect, the magnitude of the left-to-right shunt, and the patient's age. Although surgical repair remains the standard treatment, transcatheter closure has emerged as a feasible alternative in selected patients with suitable anatomy. Herein, we report the percutaneous closure of an APW in a 13-year-old patient, representing an atypical presentation with respect to age. A 13-year-old boy was referred to our clinic for evaluation of a cardiac murmur. Physical examination, transthoracic echocardiography, and computed tomography angiography demonstrated a 6-mm APW between the ascending aorta and the main pulmonary artery. Transcatheter closure of the defect was performed under general anesthesia. Complete closure was successfully achieved using a 14/12-mm Amplatzer Duct Occluder I device. The postprocedural course was uneventful, and the patient was discharged the following day. Follow-up echocardiographic assessments revealed no residual shunt or vascular obstruction. In conclusion, APW is an uncommon congenital malformation resulting from incomplete septation between the aorta and pulmonary artery during embryogenesis. Echocardiography plays a pivotal role in diagnosis and anatomical assessment. Although surgical correction remains the gold standard, transcatheter closure may serve as a safe and effective therapeutic alternative in appropriately selected patients with favorable anatomical characteristics.

Keywords: Aortopulmonary window; echocardiography; transcatheter closure.

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13 yaşında amplatzer duct occluder 1 ile aortopulmoner pencerenin kapatılması: Olgu sunumu

ÖZET

Aortopulmoner pencere (APP), çıkan aort ile ana pulmoner arter arasında bulunan bir septasyon defekti olup tüm konjenital kalp hastalıklarının %0,2–0,6'sını oluşturan nadir bir anomalidir. Tedavi yaklaşımı; defektin çapına, soldan sağa şant miktarına ve hastanın yaşına göre değişmektedir. Primer tedavi cerrahi kapatma olmakla birlikte, uygun hastalarda transkateter kapatma da uygulanabilmektedir. Bu olguda, yaş açısından atipik olan 13 yaşındaki bir hastada perkütan APP kapatılması sunulmuştur. Üfürüm nedeniyle değerlendirilen 13 yaşındaki erkek hastanın fizik muayene, ekokardiyografi ve bilgisayarlı tomografi anjiyografi incelemelerinde çıkan aort ile ana pulmoner arter arasında 6 mm genişliğinde APP izlendi. Hastaya genel anestezi altında transkateter APP kapatma işlemi uygulandı. 14/12 mm ADO I cihazı kullanılarak başarılı bir şekilde kapatma sağlandı. Hasta işlem sonrasında sorunsuz olarak izlenerek bir gün sonra taburcu edildi. Takiplerde yapılan ekokardiyografik incelemelerde rezidüel şant veya vasküler obstrüksiyon saptanmadı. Sonuç olarak APP, embriyolojik dönemde aort ile pulmoner arter arasındaki septasyon kusuruna bağlı olarak gelişen nadir bir anomalidir. Tanıda ekokardiyografi büyük önem taşımaktadır. Cerrahi temel tedavi yöntemi olsa da uygun anatomik özelliklere sahip hastalarda transkateter kapatma güvenli ve etkili bir alternatif tedavi seçeneğidir.

Anahtar Kelimeler: Aortopulmoner pencere; ekokardiyografi; transkateter kapama.

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GİRİŞ

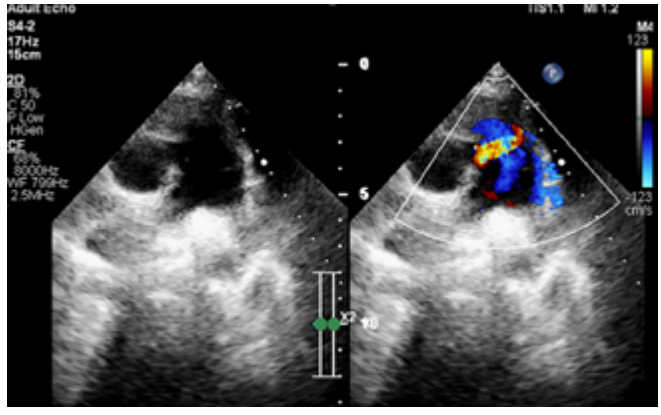
Aortopulmoner pencere (APP), çıkan aort ile ana pulmoner arter arasında bulunan bir septasyon defekti olup tüm konjenital kalp hastalıklarının %0,2–0,6'sını oluşturur (1).

Hastalığın ciddiyeti ve tedavisi; aortadan pulmoner artere uzanan defektin çapına, soldan sağa şantın derecesine ve çocuğun yaşına bağlı olarak değişir. APP'nin primer tedavisi cerrahi kapatma olsa da uygun hastalarda transkateter yolla kapatma da mümkündür.

Burada, muayenede devamlı üfürümü bulunan ancak 13 yaşına kadar tanı almamış, aynı zamanda defekt çapının bilgisayarlı toraks anjiyografisinde (BTA) ölçülenden daha büyük olmasına rağmen ciddi pulmoner hipertansiyon veya Eisenmenger sendromu gelişmemiş bir hastada perkütan yöntemle kapatılan bir APP olgusu sunulmaktadır.

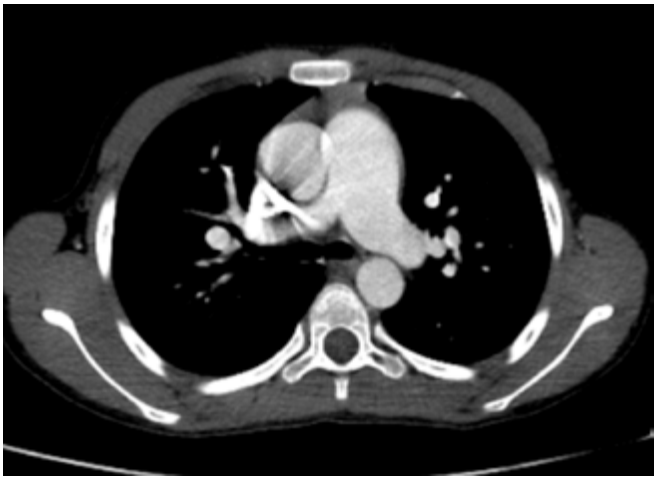
OLGU SUNUMU

On üç yaşında erkek hasta, üfürüm nedeniyle kliniğimize yönlendirildi. Başvuru sırasındaki fizik muayenesinde sternumun sol üst kenarında devamlı üfürüm mevcuttu. Oksijen satürasyonu %98 idi. Telekardiyografide kardiyotorasik oran 0,5 olarak ölçüldü. Ekokardiyografik incelemede çıkan aort ile ana pulmoner arter arasında 6 mm genişliğinde APP görüldü (Şekil 1). Sol kalp boşluklarında genişleme ve minimal mitral yetersizlik izlendi. Sol ventrikül diyastol sonu çapı 54 mm (z skoru: +7,74) idi. Çekilen BTA'da çıkan aort ile ana pulmoner arter arasında 6 mm genişliğinde APP görüldü (Şekil 2).

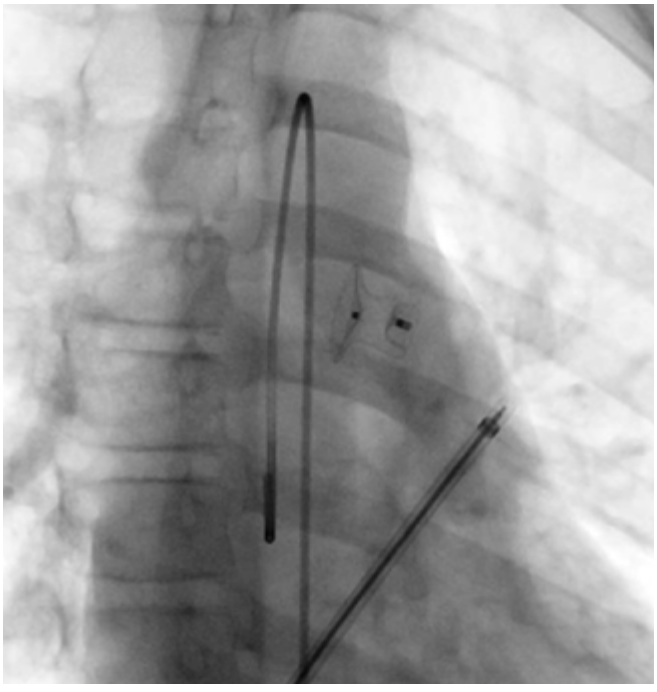


Şekil 1. APP EKO görüntüsü.

Hastaya transkateter APP kapatılması planlandı. Bilgilendirme yapılarak yazılı onam alındı. Kateterizasyon laboratuvarında, genel anestezi altında, 8 F kılıf sağ femoral vene ve 6 F kılıf sağ femoral artere perkütan teknikle yerleştirildi. Beş F pigtail kateter ve hidrofilik tel femoral arterden asendan aortaya kadar ilerletildi. Kontrast madde enjeksiyonu yapılarak aortopulmoner pencerenin çapı değerlendirildi. Defektin 8/6 mm ADO I cihazı ile kapatılmasının uygun olacağına karar verildi. Femoral venden 5 F JR4 kateter ve düz uçlu hidrofilik tel ile vena kava inferior, sağ atriyum, pulmoner arter ve APP geçilerek asendan aortaya, oradan da desendan aortaya ulaşıldı. Usulüne uygun şekilde hazırlanan uzun kılıf desendan aortada sabitlendi ve



Şekil 2. BTA APP görüntüsü.



Şekil 3. İşlem sonu anjiyo görüntüsü.

8/6 mm Amplatzer Duct Occluder I (ADO I) cihazı uzun kılıf içinden ilerletilerek önce aort tarafında açıldı. Ancak cihaz defekti kavrayamadığı için pulmoner arter içine düştü. Defektin 14/12 mm ADO I cihazı ile kapatılmasının daha uygun olacağı düşünüldü. İşlem bu cihazla tekrarlandı ve başarılı sonuç elde edildi. Cihaz tamamen serbestleştirilmeden önce kontrol anjiyogramı tekrarlandı. Pozisyonun uygun olduğu görülerek cihaz serbestleştirildi (Şekil 3).

Hasta işlemden bir gün sonra sorunsuz bir şekilde taburcu edildi. Altı ay süreyle antiagregan dozda asetilsalisilik asit kullanması önerildi. Poliklinik izlemlerinde yapılan ekokardiyografik kontrollerde rezidüel defekt bulunmadığı ve aort ile pulmoner arterde obstrüksiyon gelişmediği saptandı.

TARTIŞMA

APP, embriyonel dönemde nöral krest hücrelerinin göçündeki duraklama sonucu gelişen, aort ile pulmoner arter arasındaki septasyon defektidir.

Aortopulmoner pencere ilk olarak 1830 yılında Elliotson tarafından otopsi bulgusu olarak tanımlanmıştır (2).

Anatomik özellikleri göz önüne alındığında APP geleneksel olarak cerrahi yöntemle tedavi edilmektedir ve literatürde cerrahi sonuçlara ilişkin çok sayıda çalışma bulunmaktadır (3). Transkateter kapatma ile ilk tedavi, 1990'lı yıllarda çift şemsiye oklüder sistemi kullanılarak tanımlanmıştır (4).

O tarihten bu yana farklı cihazlarla transkateter APP kapatılmasına ilişkin olgular bildirilmiştir (5).

APP sıklıkla izole olarak görülmekle birlikte, olguların yaklaşık yarısına aortik ark anomalileri, patent duktus arteriozus, ventriküler septal defekt, Fallot tetralojisi ve diğer konjenital kalp defektleri eşlik edebilir. APP tanısında ekokardiyografinin rolü büyüktür. Trunkus arteriozustan ayırıcı tanısında iki ayrı semilunar kapağın bulunması önemlidir. Primer tedavi cerrahi kapatma olsa da yeterli rimlere sahip uygun hastalarda transkateter yolla APP kapatılması, cerrahiye alternatif, etkili bir yöntem olarak uygulanabilir.

Transkateter APP kapatma işleminde ekstrakorporeal dolaşıma gereksinim duyulmaması ve işlem sonrası hastanede kalış süresinin daha kısa olması önemli avantajlardır.

SONUÇ

Sonuç olarak, uygun hasta seçimi ve uygun cihaz kullanımıyla gerçekleştirilen transkateter yaklaşım, APP'li hastalarda cerrahiye alternatif olarak uygulanabilir.

Etik Kurul Onayı: Bu, tek bir vaka raporudur ve bu nedenle kurum politikaları uyarınca etik kurul onayı gerekli görülmemiştir.

Hasta Onamı (veya gönüllü onamı): Bilgilendirilmiş onam alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Bu makalenin yazımında yapay zeka kullanılmamıştır.

Yazarlık Katkıları: Fikir – TÖ, RÇ; Tasarım – TÖ, RÇ; Denetlemeler – TÖ, RÇ; Kaynaklar – TÖ, İCT; Malzemeler – TÖ; Veri toplanması ve/veya işleme – TÖ, RÇ; Analiz ve/veya yorumlama – RÇ; Literatür araştırması – RÇ; Yazım – RÇ, TÖ; Eleştirel incelemeler – TÖ, İCT; Girişimsel İşlemin Uygulanması – İCT, TÖ.

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LETTER TO THE EDITOR
Pediatric Cardiology

Prognosis in pediatric myocarditis: Inflammatory indices calculable from the complete blood count

Çocukluk çağı miyokarditinde prognoz: Hemogramdan hesaplanabilen inflamatuar indeksler

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Sayın Editör,

Bozkurt ve arkadaşlarının derginizin 2025 yılı 5. cilt, 3. sayısında, 98–105. sayfalarda yayımlanan "Çocukluk Çağı Miyokarditlerinde Klinik Seyir ve Tedavi Yaklaşımları: Tek Merkez Deneyimi" başlıklı çalışmasını ilgiyle okuduk (1). Yazarlar, 37 hastadan oluşan bir seride akut miyokarditin klinik seyrini ayrıntılı biçimde tanımlamış ve prognozu belirleyen etkenleri araştırmışlardır.

Çalışmanın dikkat çekici bulgularından biri, prognoz üzerindeki etkisi incelenen laboratuvar parametreleri arasında beyaz küre yüksekliğinin kötü prognozla anlamlı bir ilişki göstermesi ($p<0,001$), buna karşın C-reaktif protein yüksekliğinin anlamlı bulunmamasıdır ($p=0,920$). Bu ayrışma, miyokarditte hücresel inflamatuar yanıtın akut faz reaktanlarına kıyasla daha fazla prognostik bilgi sağlayabileceğini düşündürmektedir.

Bu noktada, aynı hemogramdan elde edilebilecek ek bilgilere dikkat çekmek isteriz. Beyaz küre sayısı toplam bir değerdir ve alt gruplarının dağılımını yansıtmaz. Oysa nötrofil, lenfosit ve monosit sayıları ile bunlardan türetilen bileşik indeksler—sistemik immün-inflamasyon indeksi (SII; nötrofil×trombosit/lenfosit) ve sistemik inflamatuar yanıt indeksi (SIRI; nötrofil×monosit/lenfosit) gibi—ek bir tetkik gerektirmeksizin hesaplanabilmektedir. Yazarların beyaz küre ve trombosit değerlerini zaten sunmuş olmaları, bu indekslerin geriye dönük olarak hesaplanabileceğini göstermektedir.

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Bu indekslerin pediyatrik miyokarditteki prognostik değeri daha önce gösterilmiştir. Yakın zamanda yayımlanan ve 122 çocuğu kapsayan tek merkezli bir kohortta, fulminan seyir gelişen 26 olguda başvuru sırasındaki SII ve SIRI değerleri anlamlı olarak yüksek bulunmuş ve her iki indeksin de fulminan seyrin bağımsız öngördürücüleri olduğu saptanmıştır (2). Bağımsız bir pediyatrik seride de SII'nin fulminan ve fulminan olmayan miyokarditi ayırt ettiği bildirilmiş (3). akut miyokardit serilerinde ise inflamatuar indeksler hastalık şiddetiyle ilişkilendirilmiştir (4). Bu bulgular, miyokardiyal hasarın derecesinin hücresel inflamatuar yanıtla ilişkili olduğunu gösteren mekanistik verilerle uyumludur (5).

Önerimizin bazı sınırlılıkları da bulunmaktadır. Söz konusu indekslerin çocuklarda yaşa göre referans aralıkları henüz tanımlanmamıştır ve tek bir indeksin ayırt edici gücü tek başına sınırlıdır. Ayrıca yazarların serisi ağırlıklı olarak adolesan yaş grubundan ve görece hafif seyirli olgulardan oluşmaktadır. Bu durum, indekslerin söz konusu popülasyondaki performansını etkileyebilir.

Bununla birlikte hemogram, her hastada rutin olarak değerlendirilen, ek maliyet gerektirmeyen ve sonucu dakikalar içinde elde edilebilen bir tetkiktir. Yazarların mevcut veri setinde bu indekslerin hesaplanması ve prognostik değerlerinin beyaz küre sayısıyla karşılaştırılması, bulgularına düşük maliyetli bir katkı sağlayabilir. Yazarları, ülkemiz verilerine dayanan bu değerli çalışma için kutlarız.

Çıkar Çatışması: Yazarlar, herhangi bir çıkar çatışması bulunmadığını beyan ederler.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Bu makale için yapay zekadan herhangi bir destek alınmamıştır.

Yazarlık Katkıları: Fikir – DK, EÖ; Tasarım – DK; Denetlemeler – EÖ; Analiz ve/veya yorumlama – DK, EÖ; Literatür araştırması – DK; Yazım – DK; Eleştirel incelemeler – EÖ.

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