Muğla Tıp Dergisi
Mugla Medical Journal

ISSN: 2148-8118
e-ISSN: 2618-6020

# Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

## MEDICAL JOURNAL OF MUGLA SITKI KOCMAN UNIVERSITY

İndeks / Indexing



https://dergipark.org.tr/tr/pub/muskutd

Cilt/Volume: 12 Sayı/Number: 1 Nisan/April 2025


**Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi**

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

Medical Journal of Mugla Sitki Kocman University

# Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

*Medical Journal of Mugla Sitki Kocman University*

Muğla Tıp Dergisi

*Mugla Medical Journal*

ISSN:2148-8118

e-ISSN: 2618-6020

**Sahibi**
***Owner***
Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi adına
*On Behalf of Mugla Sitki Kocman University School Of Medicine*

Prof. Dr. Süleyman Cüneyt KARAKUŞ (Dekan / *Dean*)

**Yayın Dili**
***Language of the Journal***
İngilizce / *English*

**Yayın Türü**
***Type of Publication***
Ulusal Hakemli Dergi / *Periodical Publication*

**Baskı**
***Printing***
Muğla Sıtkı Koçman Üniversitesi Matbaası
*Mugla Sitki Kocman University Printing Office*

**Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, yılda 3 sayı (Nisan, Ağustos, Aralık) yayımlanır.**
*Medical Journal of Mugla Sitki Kocman University is published 3 times (April, August, December) per year.*



***Abstracting & Indexing***



***İletişim / Correspondence***
Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi Kötekli Mahallesi Marmaris Yolu Bulvarı No:50 48000/Menteşe/MUĞLA/TURKEY
***Tel*** :+90 252 211 48 00

***Faks / Fax*** :+90 252 211 13 45

***e-posta / e-mail*** : muglatipdergisi@mu.edu.tr

***İnternet Adresi / URL***: https://dergipark.org.tr/tr/pub/muskutd

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

Medical Journal of Mugla Sitki Kocman University

# Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

*Medical Journal of Mugla Sitki Kocman University*

Muğla Tıp Dergisi

*Mugla Medical Journal*

ISSN:2148-8118

e-ISSN: 2618-6020

## Yayın Kurulu / Publication Committee

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
Medical Journal of Mugla Sitki Kocman University

# Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
*Medical Journal of Mugla Sitki Kocman University*
Muğla Tıp Dergisi
*Mugla Medical Journal*
ISSN:2148-8118
e-ISSN: 2618-6020

## Danışma Kurulu / Advisory Board

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
Muğla Tıp Dergisi
*Medical Journal of Mugla Sitki Kocman University*
*Mugla Medical Journal*

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

## AMAÇ VE KAPSAM

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesinin süreli yayın organıdır ve Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanmaktadır. Derginin yayın dili Türkçe ve İngilizcedir.

Dergide, tıbbın her dalı ile ilgili prospektif, retrospektif ve deneysel araştırmalar, olgu sunumu ve derlemeler yayınlanır. Yayınlanan makalelerde konu ile ilgili en yüksek etik ve bilimsel standartlarda olması ve ticari kaygılarda olmaması şartı gözetilir. Yayın için gönderilen çalışmalar; orijinal, başka bir dergide değerlendirme sürecinde olmayan ve daha önce basılmamış olması koşullarıyla kabul edilir.

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi; TR Dizin, Google Akademik, Crossref, Türkiye Atıf Dizini, Türk Medline, Academic Keys ve Research Bible Index tarafından indekslenmektedir.

Dergide yayınlanacak olan yazılar http://dergipark.gov.tr/muskutd web sayfası üzerinden gönderilmelidir. Yazım kuralları, teknik bilgiler ve diğer gerekli formlara bu sayfadan erişilebilir. Gönderilen yazılardaki tüm içerikler yazarların sorumluluğundadır.

Bu dergide yer alan yazı, makale, fotoğraf ve illüstrasyonların elektronik ortamlarda dahil olmak üzere kullanma ve çoğaltma hakları Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'ne aittir. Yazılı ön izin olmaksızın materyallerin tamamının ya da bir bölümünün çoğaltılması yasaktır. Her hakkı saklıdır. Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'nde yayınlanan içerikler yazar(lar)a aittir. Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, dergi editörleri, çalışanları ve yayıncı bu yazılar için mali, hukuki ve diğer yönlerden sorumluluk kabul etmemektedir.

## AIMS AND SCOPE

Medical Journal of Mugla Sitki Kocman University is a periodical of Medical School of Mugla Sitki Kocman University and is published three times per year; in April, August, and December. The Medical Journal of Mugla Sitki Kocman University's publication languages are both Turkish and English.

The articles which could be prospective or retrospective on investigational studies, case reports and reviews of every aspect of medicine are published. The studies should have paramount ethical and scientific standards as well as no commercial concerns. Articles are accepted for publication on the condition that they are original, are not under consideration by another journal, or have not been previously published.

The Medical Journal of Mugla Sitki Kocman University is indexed by TR Dizin, Google Scholar, Crossref, Türkiye Atıf Dizini, Türk Medline, Academic Keys and Research Bible.

All manuscripts must be submitted electronically on the http://dergipark.gov.tr/muskutd. Instructions for authors, technical information, and other necessary forms can be accessed over this web page. Authors are responsible for all content of the manuscripts.

Rights to the use and reproduction, including in the electronic media, of all communications, papers, photographs and illustrations appearing in this journal belong to the Medical Journal of Mugla Sitki Kocman University without prior written permission of part or all of and material is forbidden. All rights are reserved. Published content of the journal is in authors' own responsibility. Mugla Sitki Kocman University School of Medicine, editors, employees and the publisher do not accept any financial, legal or any other liability for the published material.



**Adres / *Address:*** Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi Kötekli Mahallesi Marmaris Yolu Bulvarı No:50 48000/Menteşe/MUĞLA/TURKEY
**Tel:** + 90 252 211 48 00 **Faks / *Fax:*** +90 252 211 13 45
**e-posta / *e-mail:*** muglatipdergisi@mu.edu.tr
**İnternet Adresi / *URL:*** https://dergipark.org.tr/tr/pub/muskutd

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
Muğla Tıp Dergisi
*Medical Journal of Mugla Sitki Kocman University*
*Mugla Medical Journal*

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

## YAZARLARA BİLGİ

http://dergipark.gov.tr/muskutd/page/4152

**Genel Bilgiler**

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesinin süreli yayın organı olup özel sayılar hariç düzenli olarak yılda üç sayı olarak yayımlanır. Tıbbın her dalı ile ilgili prospektif, retrospektif ve deneysel araştırmalar, olgu sunumu ve derlemeler yayınlanmak için değerlendirilmektedir. Konu ile ilgili etik ve bilimsel standartlar olması ve ticari kaygıların olmaması şartı gözetilir. Yazarlar tarafından, başka bir dergide değerlendirme sürecinde olmayan ve daha önce basılmadığı beyan edilen yazılar incelemeye alınır. Editör onayı sonrasında en az yurt içi-yurt dışı iki hakem incelemesinden geçip gerek görüldüğü takdirde istenen değişiklikler yazarlar tarafından yapılıp hakemlerce kabul edildikten sonra yayımlanır.

**Bilimsel Sorumluluk**

Yazar olarak belirtilmiş tüm kişiler çalışmayı planlamalı veya gerçekleştirmeli, çalışmanın yazılmasında, gözden geçirilmesinde ve son halinin onaylanmasında rol almış olmalıdır. Kriterleri karşılayan bir metnin ortaya çıkması tüm yazarların sorumluluğudur.

**Etik Sorumluluk**

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, etik ve bilimsel standartlara uygun yazıları yayımlayarak bilimin doğru bir şekilde ilerlemesine katkı sağlamayı hedeflemektedir. Bu kapsamda, çalışmaların bilimsel etiğe uygunluğu önemlidir. Etik ilkeler COPE (Committee on Publication Ethics) tarafından hazırlanan yönerge (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors) temel alınarak Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi tarafından benimsenmiş ve yazarlar, hakemler ve editörler tarafından da benimsenmesi önerilmektedir. Bu önerilerin bir kısmı aşağıda verilmiştir.

**Yazarların Etik Sorumlulukları:**

- Çalışmayla ilişkili veri kayıtlarını düzenli tutmak ve olası bir talep üzerine bu verilere erişim verebilmelidir.
- Gönderdiği makalenin başka bir yerde yayınlanmadığından veya kabul edilmediğinden emin olmalıdır.
- İnsan veya hayvan denek içeren tüm çalışmalar için ulusal ve uluslararası yasalara ve yönergelere uygun olmasını sağlamak, (örneğin, WMA Helsinki Bildirgesi, NIH Laboratuar Hayvanlarının Kullanımına İlişkin Politika, Hayvanların Kullanımına İlişkin AB Direktifi) gerekli onayların alındığını onaylamak, denek mahremiyete saygı göstermek. Çalışmasına dair ilgili etik kurul onaylarını ve araştırma detaylarını çalışmanın "Gereç ve Yöntem" kısmında belirtmek.
- Herhangi bir çıkar çatışması durumunda, makalesiyle ilgili etik bir ihlal tespit ettiğinde bunu editör ve yayıncı ile paylaşmak, hata beyanı, zeyilname, tazminat bildirimi yayınlamak veya gerekli görüldüğü durumlarda çalışmayı geri çekmelidir.

**Hakemlerin Etik Sorumlulukları:**

- Editörün karar verme sürecine katkıda bulunmak için makaleyi objektif olarak zamanında incelmeli ve sadece uzmanlık alanı ile ilgili çalışma değerlendirmeyi kabul etmelidir.
- Değerlendirmeyi nesnel bir şekilde sadece çalışmanın içeriği ile ilgili olarak yapmalıdır.
- Dini, siyasi ve ekonomik çıkarlar gözetmeden çalışmayı değerlendirmelidir.
- Yayınlanacak makalenin kalitesini yükseltmeye yardımcı olacak yönlendirmelerde bulunmalı ve çalışmayı titizlikle incelemelidir. Yorumlarını yapıcı ve nazik bir dille yazara iletmelidir.
- Editör ve yazar tarafından sağlanan bilgilerin gizliliğini korumalı, kör hakemliğe aykırı bir durum varsa editöre bildirmeli ve çalışmayı değerlendirmemelidir.
- Potansiyel çıkar çatışmalarının (mali, kurumsal, işbirlikçi ya da yazar ve yazar arasındaki diğer ilişkiler) farkında olmalı ve gerekirse bu yazı için yardımlarını geri çekmek konusunda editörü uyarmalıdır.

**Editörlerin Sorumlulukları:**

- Cinsiyet, dini veya politik inançlar, yazarların etnik veya coğrafi kökenleri üzerine ayrım yapılmaksızın görevlerini yerine getirirken dengeli, objektif ve adil bir şekilde hareket etmelidir.
- Dergiye gönderilen çalışmaları içeriğine göre değerlendirmeli, hiçbir yazara ayrıcalık göstermemelidir.
- Olası çıkar çatışmalarını önlemek adına gerekli önlemleri almalı ve varsa mevcut beyanları değerlendirmelidir.
- Etik ihlali niteliğinde bir şikayet olması durumunda, derginin politika ve prosedürlerine bağlı kalarak gerekli prosedürleri uygulamalıdır. Yazarlara, gelen şikâyete cevap vermek için bir fırsat vermeli, çalışma kime ait olursa olsun gerekli yaptırımları uygulamaktan kaçmamalıdır.
- Derginin amaç ve kapsamına uygun olmaması durumunda gelen çalışmayı reddetmelidir.

Tüm araştırma makalelerinde (retrospektif çalışmalarda dahil olmak üzere), çalışma için Etik Kurul Onayı alınmalı ve Etik Kurul Onayının alındığı yer, tarih (gün, ay ve yıl olarak) ve onay numarası Gereç ve Yöntem bölümünde belirtilmelidir. İnsan ile ilgili tüm çalışmalarda Helsinki Deklarasyonu'na (World Medical Association Declaration of Helsinki http://www.wma.net/en/30/publications/10policies/b3/index.html) göre çalışmanın yapıldığı mutlaka belirtilmelidir. Olgu sunumlarında, hastadan (ya da yasal vasisinden) tıbbi verilerinin yayınlanabileceğine ilişkin yazılı hasta onam belgesi alındı cümlesinin hasta onam tarihi ile birlikte belirtilmesi gereklidir. Hayvan deneyleri için laboratuvar hayvanlarının bakım ve kullanımı konusunda kurumsal veya ulusal yönergelerin takip edilmeli ve bildirmelidirler. Yazarların çalışmalarında kullandıkları cümlelerinden editör ve yayın kurulu sorumlu değildir. Bilimsel, hukuki ve etik sorumluluğu yazarlara aittir.

Sorumlu yazar, gönderilen çalışmanın başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını belirtmelidirler. Çalışmanın bir kısmı kongrede sözlü veya poster bildiri olarak sunuldu ise başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

Kabul edilen yazının tüm kullanım ve yayın hakkı derginin olur ve izinsiz olarak başka bir yerde yayınlanamaz.

**Değerlendirme:** Tüm makaleler çift-kör değerlendirme yöntemi kullanılarak en az iki yerli veya yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayına kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir.

**İntihal taraması:** Dergiye gönderilen makaleler format ve intihal açısından kontrol edilir. Formata uygun olmayan veya intihal benzerlik oranı yüksek (%20'den az olmalıdır) makaleler değerlendirilmeden sorumlu yazara geri gönderilir.

**Çıkar çatışması:** Çalışmaları ile ilgili taraf olabilecek tüm kişisel, ticari bağlantı veya çalışma için doğrudan veya dolaylı olarak maddi destek veren kurum var ise yazarlar; kullanılan ticari ürün, ilaç, firma ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar vs.), editöre sunum sayfasında bildirmek zorundadır. Herhangi bir çıkar çatışmasının olmadığı durumda metin içerisinde 'Yazarlar çıkar ilişkisi olmadığını beyan eder' şeklinde ifade edilmelidir.

**Lisan**

Derginin yayın dili İngilizcedir. Gönderilmiş makalelerdeki tüm yazım ve imla hataları, anlam ve verileri değiştirmeksizin editör tarafından düzeltilebilir. Metnin kurallara uygun olarak düzenlenmesi yazarların sorumluluğundadır.

**Telif Hakkı Bildirimi**

Telif hakkı devrini bildirmek için kapak mektubunda 'Bu makalenin telif hakkı; çalışma, basım için kabul edilmesi koşuluyla Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'ne devredilir' şeklinde belirtilmelidir. Yazarlara ücret ödenmez.

**Yazı Tipleri**

***Derleme:*** Derlemeler yeni veya tartışmalı alanlarda olmalıdır. İngilizce ve Türkçe başlık olmalı ve özet 250 kelimeyi geçmemelidir. Derleme içeriği 5000 kelimeyi aşmamalı ve kaynak sayısı en fazla 70 olmalıdır.

***Orijinal makaleler:*** Orijinal makaleler temel veya klinik çalışmalar veya klinik denemelerin sonuçlarını bildirir. Makale Türkçe özet, İngilizce özet, giriş, gereç ve yöntemler, bulgular/sonuçlar, tartışma, teşekkür (gerekliyse), çıkar çatışması bildirimi, etik kurul onayı (yer/tarih/sayı), fon bildirimi, kaynaklar ve şekiller ve tablolardan oluşmalıdır.

***Olgu Sunumu:*** Tıbbın her alanındaki önemi olan olgu sunumlarını yayınlanır. Türkçe özet, İngilizce özet, giriş, olgu, tartışma, kaynaklardan oluşmalıdır.

**Yazı Gönderimi**

Tüm yazılar elektronik ortamda http://dergipark.gov.tr/muskutd adresi üzerinden gönderilmelidir.

**Yazının Hazırlanması**

Yazı hazırlığı iki satır aralıklı, satır numaraları verilmiş ve Times New Roman 12 punto karakter büyüklüğünde yapılmalıdır. Sayfalar başlık sayfasından başlamak üzere, sağ alt köşesinden numaralandırılmalıdır. Makale sistemine yüklenen word (*.doc, *.docx) dosyasının başlık sayfasında yazarlara ait isim ve kurum bilgileri yer almamalıdır.

***Kapak Mektubu:*** Kapak mektubu gönderilen makalenin kategorisini, daha önce başka bir dergiye gönderilmemiş olduğunu, çıkar ilişkisi bildirimini, yayın hakkı devri bildirimini ve varsa çalışmayı maddi olarak destekleyen kişi ve kurumların adlarını mutlaka içermelidir.

***Başlık sayfası:*** Bu sayfada çalışmanın tam Türkçe ve İngilizce ismi ve kısa başlığı olmalıdır. Katkıda bulunanların tüm yazarların isimleri, çalıştıkları kurumları ve ORCID numaraları listelenmelidir. Ücretsiz olarak bireysel ORCID numaraları http://orcid.org adresinden alınabilmektedir. Basım sürecinde dergi editörü ile iletişimde bulunacak olan yazışma yazarı belirtilmelidir. Çalışmanın bir kısmı kongrede sözlü veya poster bildiri olarak sunuldu ise başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

***Özet ve Anahtar Kelimeler:*** Özet 250 kelimeyi geçmemelidir. Çalışmanın amacını, yöntemi, bulgu ve sonuçları özetlemelidir. Çalışma 3 - 5 anahtar kelime içermelidir. Kelimeler birbirlerinden virgül (,) ile ayrılmalıdır. İngilizce kelimeler Index Medicus'taki Medical Subjects Headings listesine uygun olmalıdır www.nlm.nih.gov/mesh/MBrowser.html. Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne uygun olarak verilmelidir www.bilimterimleri.com

***Giriş:*** Kısa ve açık olarak çalışmanın amaçlarını tartışmalı, çalışmanın neden yapıldığına dair temel bilgileri içermeli ve hangi hipotezlerin sınandığını bildirmelidir.

***Gereç ve Yöntemler:*** Açık ve net olarak yöntem ve gereçleri açıklanmalıdır. İlk vurgulamada kullanılan araç ve cihazların model numaraları, firma ismi ve adresi (şehir, ülke) mutlaka belirtilmelidir. Tüm ölçümler metrik birim olarak verilmeli ve ilaçların jenerik adları kullanılmalıdır.

***İstatistiksel Değerlendirme:*** Tüm çalışma makaleleri istatistiksel olarak değerlendirilmeli ve uygun plan, analiz ve bildirimde bulunmalıdır. p değeri yazı içinde belirtilmelidir. Kullanılan istatistik yöntem açıkça belirtilmelidir.

***Sonuçlar:*** Sonuçlar metin, tablo ve şekiller kullanılarak sunulmalıdır. Tablo ve metinler tekrarlanmamalıdır. p değeri yazı içinde belirtilmelidir (p=0.014 gibi).

***Tartışma:*** Çalışmanın farklılıklarına ve sonuçlarına vurgu yapılmalıdır. En önemli bulgu kısa ve net bir şekilde belirtilmeli, gözlemlerin geçerliliği tartışılmalı, aynı veya benzer konulardaki yayınların ışığında bulgular yorumlanmalı ve yapılan çalışmanın olası önemi belirtilmelidir. Çalışmanın esas bulgularının kısa ve özlü bir paragrafla vurgulanması önerilir.

***Teşekkür:*** Yazarlar araştırmaya katkıda bulunan ancak yazar olarak yer almayan kişilere teşekkür etmelidir.

***Tablo, Resim, Şekil ve Grafikler:*** Tüm tablo, resim, şekil, grafik ve diğer görseller ana metnin içinde geçiş sıralarına uygun şekilde, ardışık olarak numaralandırılmalıdır. Kullanılan görsellerde hasta ve doktor kimlikleri içeren bilgiler ve kurum adları görülmeyecek şekilde hazırlanmalıdır. Tablolar ana metin içinde kaynak listesinin sonrasında sunulmalıdır. Tablolar JPEG, TIFF veya diğer görsel formatlarda gönderilmemelidir. Mikroskopik şekillerde açıklayıcı

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

bilgilere ek olarak, büyütme oranı ve kullanılan boyama tekniği de belirtilmelidir. Görseller sisteme minimum 300 DPI çözünürlükte yüklenmelidir. Şekil, resim, grafik ve fotoğrafların her biri ayrı *.jpg* veya *.gif* dosyası olarak sisteme eklenmelidir. Şekiller metin içinde kullanım sıralarına göre Arabik (1, 2, 3, v.b.) rakamla numaralandırılmalı ve metinde parantez içinde gösterilmelidir. Grafiklerde kullanılan çizgiler yayın hazırlığı aşamasında yeniden boyutlandırma sırasında meydana gelecek bozulmaları engellemek amacıyla yeterli kalınlıkta olmalıdır. Tablolarda kullanılan kısaltmalar tablo altlarında tanımlanmalıdır. Tablo ve şekil başlıklarında ve tablonun yazı içinde anılmasında Roma (I, II, II, v.b.) rakamları kullanılmamalıdır.

***Kaynaklar:*** Kaynaklar metin içinde alıntılanma sırasına uygun olarak doğal sayılar kullanılarak numaralandırılmalı ve cümlenin sonunda parantez içinde verilmelidir. Kaynaklar listesinde yazar sayısı üç veya daha az ise hepsi, üçten fazla ise sadece ilk üç ismi yazılmalı ve 've ark.' ilave edilmelidir. Kaynak ve kısaltılmış dergi adları yazımları Index Medicus'a veya aşağıda verilen örneklere uygun olmalıdır. Çalışmaya yazılan kaynakların okunmuş olması ve talep edildiğinde sunulması gerekmektedir.

***Dergi makaleleri için örnek***

Murtaugh TJ, Wright LS, Siegel FL. Calmodulin plus cyclic AMP-dependent phosphorylation of a Mr 22,000 pituitary protein. J Biol Chem. 1985;260(29):15932-7.

***Komite veya yazar grupları için örnek***

The Standard Task Force, American Society of Colon and Rectal Surgeons: Practice parameters for the treatment of haemorrhoids. Dis Colon Rectum 1993;36:1118-20.

***Kitaptan konu için örnek***

Milson JW. Haemorrhoidal disease. In: Beck DE, Wexner S, eds. Fundamentals of Anorectal Surgery. 1 1992; 192-214. 1a ed. New York: McGraw-Hill

***Kitap için örnek***

Bateson M, Bouchier I. Clinical Investigation and Function, 2nd edn. Oxford: Blackwell Scientific Publications Ltd, 1981.

**Kontrol Listesi**

Kontrol listesinde eksiklik(ler) olduğu takdirde çalışmanız değerlendirme sürecine alınmayacaktır.

- Kapak Mektubu
- Başlık sayfası
- Türkçe başlık
- İngilizce başlık
- Öz (250 kelimeden az olmalı)
- Abstract (250 kelimeden az olmalı)
- Anahtar kelimeler (En fazla 5 kelime olmalı)
- Keywords (En fazla 5 kelime olmalı)
- Tüm yazarların e-posta ve iletişim adresleri, Tüm yazarlar sisteme girilmelidir
- Sorumlu yazar belirtilmelidir.
- Metin içindeki ondalık sayılar nokta (.) ile ayrılmalıdır (0.25 gibi)
- Alt indisler uygun şekilde yazılmalıdır ($SpO_2$ gibi)
- P değerleri metin içerisinde tam olarak verilmelidir (p=0.035 gibi)
- Tablo açıklamaları yapılmalıdır
- Şekil, resim, grafik açıklamaları yapılmalıdır
- Kaynaklar dergi yazım kurallarına uygun şekilde yazılmalıdır
- Kaynaklar metin içerisinde parantez içerisinde yazılmalıdır (1,3,5-8) gibi
- Makalelerde etik kurul onayının alındığı yer, tarih ve sayı belirtilmelidir
- Olgu sunumlarında hasta onamının alındığı tarih yazılmalıdır.

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
Muğla Tıp Dergisi
*Medical Journal of Mugla Sitki Kocman University*
*Mugla Medical Journal*

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

**INSTRUCTIONS FOR AUTHORS**

http://dergipark.gov.tr/muskutd/page/4152

**General Information**

Medical Journal of Mugla Sitki Kocman University is a periodical of Medical School of Mugla Sitki Kocman University. The journal is published quadmonthly. The articles which could be prospective or retrospective on investigational studies, case reports and reviews of every aspect of medicine are published. The studies should have paramount ethical and scientific standards as well as no commercial concerns Articles are accepted for publication on the condition that they are original, are not under consideration by another journal, or have not been previously published. The studies that are sent to the journal provided that the study is appropriate for formal principles are evaluated by the editor and two peer reviewers. The study is published once the approvals of the reviewers have been taken. Hence, the authors should make the necessary changes in accordance with the reviewers' comments.

**Scientific Responsibility**

All authors should have contributed to the article directly either academically or scientifically. All persons designated as authors should plan or perform the study, write the paper or review the versions, approve the final version. It is the authors' responsibility to prepare a manuscript that meets scientific criteria.

**Ethical Responsibility**

The Medical Journal of Muğla Sıtkı Koçman University aims to contribute to the advancement of science by publishing articles that comply with ethical and scientific standards. It is important to adhere to ethical norms in scientific research. Ethical principles, based on the directive prepared by COPE (Committee on Publication Ethics) (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors), have been adopted by the Medical Journal of Muğla Sıtkı Koçman University and it is recommended to be adopted by authors, reviewers and editors. Some of these suggestions are given below.

**Ethical Responsibilities of Authors:**

- Authors should be able to keep the data records related to the research and give access to this data upon a possible request.
- Make sure that the article is not published or accepted elsewhere.
- To ensure compliance with national and international laws and guidelines for all reseach involving human or animal subjects (for example, the WMA Helsinki Declaration, the NIH Laboratory Animal Policy, the EU Directive on Animal Use), to confirm that the necessary approvals have been obtained, to respect the subject's privacy. To specify the relevant ethics committee approvals and research details regarding the research in the "Materials and Methods" section of the study.
- In the event of any conflict of interest, whenever the author detects an ethical violation related to article, should share it with the editor and publisher, publish a bug addendum, compensation notice, or withdraw the work when deemed necessary.

**Ethical Responsibilities of Reviewers:**

- To contribute to the decision-making process of the editor, they should review the article objectively in time and only accept the evaluation of the research related to his/her area of expertise.
- Evaluate objectively only on the content of the study.
- They should consider working without regard to religious, political and economic interests.
- They should provide guidance to help improve the quality of the article to be published and scrutinize the study. Reviewer should convey the comments constructively and kindly to the author.
-They should protect the confidentiality of the information provided by the editor and the author.
- Be aware of potential conflicts of interest (financial, institutional, collaborative, or other relationship between the author and the author) and, if necessary, alert the editor to withdraw their help for this article.

**Ethical Duties and Responsibilities of Editors:**

- They should act in a balanced, objective and fair manner while performing their duties, without discrimination on gender, religious or political beliefs, and ethnic or geographical origin of the authors.
- They should evaluate the studies submitted according to their content and should not show any privilege to any author.
- Take the necessary precautions to prevent possible conflicts of interest and evaluate existing statements.
- In case of an ethical complaint, they should follow the journal's policies and procedures and follow the necessary procedures. They should give the authors an opportunity to respond to the complaint, and should not avoid applying the necessary sanctions regardless of whoever the study belongs to.
- If the submitted study is not in line with the purpose and scope of the journal, it must be rejected.

In all research articles (including retrospective studies), Ethics Committee Approval must be obtained for the study and the location, date (day, month and year) and approval number of the Ethics Committee Approval must be specified in the Materials and Methods section. It should be noted that the study was carried out according to the Helsinki Declaration (World Medical Association Declaration of Helsinki http://www.wma.net/en/30/publications/10policies/b3/index.html) in all studies involving human participants. In case reports, the sentence ''written informed consent was obtained from the patient (or from the legal guardian), which indicates that medical data can be published'' must be stated together with the informed consent date. For experimants on animals, institutional or national guidelines on the care and use of laboratory animals should be followed and reported. The editor and editorial board are not responsible for the sentences used by the authors in their study. Scientific, legal and ethical responsibility belongs to the authors.

The corresponding author should state that the submitted manuscript is not published elsewhere and is not in the process of being evaluated in another journal at the same time. If part of the study was presented as an oral or poster presentation in the congress, the title page should be specified by giving the name of the congress, place

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

and date. Accepted manuscripts become the permanent property of the journal and may not be published elsewhere without permission.

**Evaluation:** All articles are evaluated by at least two reviewers using double-blind evaluation. The evaluation of the articles is done by considering their scientific importance and originality. Manuscripts accepted for publication can be edited by the editorial board by informing the authors without changing the content.

**Check for Plagiarism:** Articles submitted are checked for format and plagiarism. Articles that are not suitable for format or have high plagiarism similarity rate (should be less than 20%) are sent back to the responsible author for evaluation.

**Conflict of interest:** If there is an institution directly or indirectly providing financial support for any personal, commercial connection or study that may be a party to their work, the authors; must notify the editor on the presentation page of the commercial product, drug, or commercial relationship with the company. If there is no conflict of interest, the authors should state that 'Authors declare that there is no conflict of interest'.

**Language**

The official languages of the Journal is English. All spelling and grammar mistakes in the submitted articles are corrected by the editor without changing the data presented. It is the authors' responsibility to prepare a manuscript that meets spelling and grammar rules.

**Copyright Statement**

A copyright transfer statement indicating that the 'The copyright to this article is transferred to Medical Journal of Mugla Sitki Kocman University and will be effective if and when the article is accepted for publication' should be sent in the content of cover letter. No payment is done to authors for their articles.

**Article Types**

***Reviews:*** Reviews should shed light on new or controversial areas. It should include English and Turkish titles and the abstract should not exceed 250 words. The review content should not exceed 5000 words and the number of references should not exceed 70.

***Original articles:*** Original articles describe the results of basic or clinical studies or clinical trials. Original articles should follow the basic structure of an abstract, introduction, materials and methods, results, discussion, acknowledgement (if necessary), conflict of interest statement, ethics committee approval (place/date/number), funding statement, references and tables and figures (as appropriate).

***Case Reports:*** The Journal publishes significant case reports related to every aspect of medicine. Case reports should follow the basic structure of an abstract, introduction, case report, discussion, references, and tables and figures (as appropriate).

**Manuscript Submission**

All manuscripts must be submitted electronically on the http://dergipark.gov.tr/muskutd

**Preparation of Manuscripts**

Submissions should be doubled-spaced and typed in Times New Roman 12 points with line numbers. All pages should be numbered consecutively in the bottom right-hand corner, beginning with the title page. The title page should not include the names and institutions of the authors. Manuscript must be prepared as a word file (*.doc, *.docx).

***Cover letter*:** Cover letter should include statements about manuscript category designation, single-journal submission affirmation, conflict of interest statement, copyright transfer statement, sources of outside funding, equipments (if so).

***Title Page:*** On the title page, provide the complete title and a running title. List each contributor's name, institutional affiliation and ORCID number. The individual ORCID number can be obtained from http://orcid.org. Corresponding Author is the contributor responsible for the manuscript and proofs. This is the person to whom all correspondence and reprints will be sent. The corresponding author is responsible for keeping the Editorial Office updated with any change in details until the paper is published. If part of the study was presented as an oral or poster presentation in the congress, the title page should be specified by giving the name of the congress, place and date.

***Abstract and Keywords:*** The abstract must not exceed 250 words. It should summarize the aim of the study and describe the work undertaken, results and conclusions. The study should include 3 - 5 keywords. The words should be separated by comma (,) from each other. English key words should be appropriate to "Medical Subject Headings (MESH)" www.nlm.nih.gov/mesh/MBrowser.html Turkish key words should be appropriate to "Türkiye Bilim Terimleri (TBT)" www.bilimterimleri.com

***Introduction:*** The Introduction should briefly discuss the objectives of the study and provide the background information to explain why the study was undertaken, and what hypotheses were tested.

***Materials and Methods:*** Clearly explain the methods and the materials in detail to allow the reader to reproduce the results. Equipment and apparatus should cite the make and model number and the company name and address (town, county, and country) at first mention. Give all measurements in metric units. Use generic names of drugs.

***Statistically Evaluation:*** All retrospective, prospective and experimental research articles must be evaluated in terms of biostatics and it must be stated together with appropriate plan, analysis and report. p values must be given in the manuscripts.

***Results:*** Results must be presented in a logic sequence with text, tables and illustrations. Tables and text should not duplicate each other. p values must be given in the manuscripts (as p=0.014).

***Discussion:*** This section should be concise. Emphasize only the new and most important aspects of the study and their conclusions. The Discussion should include a brief statement of the principal findings, a discussion of the validity of the observations, a discussion of the findings in light of other published work dealing with the same or closely related subjects, and a statement of the possible significance of the work. Authors are encouraged to conclude with a brief paragraph that highlights the main findings of the study.

***Acknowledgements:*** Authors must acknowledge individuals who do not qualify as Authors but who

**ISSN: 2148-8118**
**e-ISSN: 2618-6020**

contributed to the research. Abbreviations: The abbreviation of a word or word sequence is given in the first appearance within a bracket after the word or word sequence. The abbreviation is used through the main text

***Tables, Figures and Graphs:*** All tables, figures, graphs and other visual media must be numbered in order of citation within the text and must not disclose the names of the patients, doctors or institutions. Tables must be placed at the end of the references section in the main document. Tables should not be submitted in JPEG, TIFF or other visual formats. In microscopic images, magnification and staining techniques must be specified in addition to figure captions. All images should be in high resolution with minimum 300 DPI. All illustrations (including line drawings and photographs) are classified as figures. Figures must be added to the system as separate *.jpg* or *.gif* files. Figures should be numbered consecutively in Arabic numbers and should be cited in parenthesis in consecutive order in the text. Lines in the graphs must be in adequate thickness. Therefore, loss of details would be minimal if reduction is needed during press. Abbreviations used in tables must be defined in alphabetical order at the bottom of the tables. Roman numerals should be avoided while numbering the Tables and Figures, or while citing the tables in the text.

***References:*** References in the text must be numbered in the order of citation and must be given with natural numbers within a bracket at the end of the sentence. List all Authors when three or fewer; when four or more, list only the first three and add 'et al'. Journal titles should be cited in full. The style of references and abbreviated titles of journals must follow that of Index Medicus or one of the examples illustrated below:

***Format for Journal Articles*:**

Murtaugh TJ, Wright LS, Siegel FL. Calmodulin plus cyclic AMP-dependent phosphorylation of a Mr 22,000 pituitary protein. J Biol Chem. 1985;260(29):15932-7.

***Format for Committees and Groups of Authors:***

The Standard Task Force, American Society of Colon and Rectal Surgeons: Practice parameters for the treatment of haemorrhoids. Dis Colon Rectum 1993;36:1118-20.

***Format for Chapter from a Book:***

Milson JW. Haemorrhoidal disease. In: Beck DE, Wexner S, eds. Fundamentals of Anorectal Surgery. 1 1992; 192-214. 1a ed. New York: McGraw-Hill

***Format for Books and Monographs:***

Bateson M, Bouchier I. Clinical Investigation and Function, 2nd edn. Oxford: Blackwell Scientific Publications Ltd, 1981.

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi
*Muğla Tıp Dergisi*

*Medical Journal of Mugla Sitki Kocman University*
*Mugla Medical Journal*

ISSN: 2148-8118
e-ISSN: 2618-6020

İÇİNDEKİLER / CONTENTS
Cilt/Volume: 12 Sayı/Number: 1 Ay/Month: Nisan/April Yıl/Year: 2025

***ORİJİNAL MAKALE / ORIGINAL ARTICLE***



***OLGU SUNUMU / CASE REPORT***



***DERLEME / REVIEW***

*Doi: 10.47572/muskutd.1503098*

# Ostracism in Adolescent Cancer Patients and Predictors (OSTRACA Study): A Pilot Study of the Palliative Care Working Committee of the Turkish Oncology Group (TOG)

# Adolesan Kanser Hastalarında Ostrasizm ve Prediktörleri (OSTRACA çalışması): Bir Türk Onkoloji Grubu Destek Tedaviler Çalışma Grubu Pilot Çalışması

**Ali ALKAN[1], Zeynep Gülsüm GÜÇ[2], Gül ERGÜN[3] Teoman ŞAKALAR[4], Güliz ÖZGÜN[5], Arzu YAŞAR[6], Yusuf KARAKAŞ[7], Tuğba YAVUZŞEN[2], Berna ÖKSÜZOĞLU[5], Özgür TANRIVERDİ[1], Filiz ÇAY ŞENLER[6]**

[1]Muğla Sıtkı Koçman University School of Medicine, Medical Oncology, Muğla
[2]Dokuz Eylul University School of Medicine, Medical Oncology, İzmir
[3]Mehmet Akif Ersoy University, Faculty of Health Sciences, Department of Nursing, Burdur
[4]Erciyes University School of Medicine, Medical Oncology, Kayseri
[5]Dr. Abdurrahman Yurtaslan Training and Research Hospital, Medical Oncology, Ankara
[6]Ankara University School of Medicine, Medical Oncology, Ankara
[7]Bodrum Acıbadem Hospital, Medical Oncology, Muğla

**Öz**

Ostrasizm, başkaları tarafından görmezden gelinmek veya dışlanmak olarak tanımlanır. Bu çalışmanın amacı, adölesan kanser hastalarında dışlanmayı değerlendirmek ve bunun prediktörlerini belirlemektir. Ergen kanser hastaları değerlendirildi. Ergenler için Ostrasizm Deneyim Ölçeği'nin (OES-A) Türkçe versiyonu ve Kutcher eadölesan depresyon ölçeği (KADS) kullanıldı. Ayrıca, karşılaştırma amacıyla kanser hastalığı olmayan bir adölesan kontrol grubu değerlendirildi. Aralık 2017 ve Nisan 2018 tarihleri arasında 4 farklı kanser merkezinde 52 hasta değerlendirildi. Çalışma popülasyonunda medyan OES-A skoru kontrol grubuna kıyasla daha yüksekti (23.5 vs 19.0, p=0.04). Çok değişkenli analizde, kadın olmak yüksek OES-A skorları ile ilişkilendirildi (OR: 7.4, CI (95%) 1.3-41.1, p=0.023). Üniversite öğrencisi olmak (OR: 0.16, CI (95%) 0.03- 0.84, p=0.036) ve aktif olarak çalışmak (OR: 0.07, CI (95%) 0.008- 0.7, p=0.031) düşük OES-A skorları ile ilişkilendirildi. Yüksek OES-A skorları yüksek KADS skorları ile ilişkilendirildi (9.0 vs 7.5, p=0.16). Adölesan kanser hastaları, kanser olmayan ergenlere kıyasla daha fazla dışlanmaktadır. Kadın cinsiyeti dışlanma riski ile ilişkilendirilirken, çalışmak ve üniversite öğrencisi olmak koruyucu faktörlerdir. Ergen kanser hastalarında dışlanma daha geniş bir seride incelenmelidir.

**Anahtar Kelimeler:** Adölesan, Depresyon, Kanser, Ostrasizm, Sosyal Dışlanma

**Abstract**

Ostracism is defined as being ignored or excluded by others. The purpose of the study is to evaluate ostracism in adolescent cancer patients and to determine the predictors of it. Adolescent cancer survivors were evaluated. Turkish version of the Ostracism Experience Scale for Adolescents (OES-A) and Kutcher adolescent depression scale (KADS) were used. In addition, a control cohort of adolescents without cancer was evaluated for comparison. Between December 2017 and April 2018, 52 patients were evaluated in 4 different cancer centers. The median OES-A score was higher in the study population when compared with the control cohort (23.5 vs 19.0, p=0.04). In MRA, being female was associated with high OES-A scores (OR: 7.8, CI (95%) 1.4-42.9, p=0.018). In multiple regression analysis, being female was linked to higher OES-A scores (OR: 7.4, 95% CI: 1.3-41.1, p=0.023). Being a university student (OR: 0.16, 95% CI: 0.03-0.84, p=0.036) and being actively employed (OR: 0.07, 95% CI: 0.008-0.79, p=0.031) were associated with lower OES-A scores. Higher OES-A scores were related to high KADS scores (9.0 vs 7.5, p=0.16). Adolescent cancer patients are more ostracized when compared with adolescents without cancer. While the female gender was associated with the risk of ostracism, working and being university students were protective. Ostracism in adolescent cancer patients should be studied in more extensive series.

**Keywords:** Adolescent, Depression, Cancer, Ostracism, Social exclusion

## Introduction

The word "Ostracism" originated around 500 B.C. in Greece. Athenians used shards of clay (Ostraca) to vote and decide whether a community member was banished. The term has been used to define "being ignored and excluded" (1-3). It critically impacts one's sense of belonging, self-worth, autonomy, and meaningful presence (4). The enduring impact of long-term ostracism is profound and destructive (1). In addition, it leads to a collapse in psychological drive and functioning, manifesting in suicidal thoughts or actions, eating disorders, depression, and a sense of hopelessness. Even short-term exposure has been associated with emotional stability and anger (5). Suppose one is exposed to ostracism in the short term. In such instances, there are notable rises in blood pressure and cortisol levels, alongside increased activation of dorsal anterior cingulate cortex which is a part of brain associated with responses to physical pain (6, 7).

| | ORCID No |
|---|---|
| Ali ALKAN | 0000-0002-8253-5046 |
| Zeynep Gülsüm GÜÇ | 0000-0001-8960-2208 |
| Gül ERGÜN | 0000-0002-1292-2040 |
| Teoman ŞAKALAR | 0000-0003-2749-9414 |
| Güliz ÖZGÜN | 0000-0002-9575-8214 |
| Arzu YAŞAR | 0000-0002-0545-1383 |
| Yusuf KARAKAŞ | 0000-0003-0205-4590 |
| Tuğba YAVUZŞEN | 0000-0001-9375-8133 |
| Berna ÖKSÜZOĞLU | 0000-0002-2756-8646 |
| Özgür TANRIVERDİ | 0000-0002-0598-7284 |
| Filiz Çay ŞENLER | 0000-0002-7156-4650 |

Başvuru Tarihi / Received: 09.07.2024
Kabul Tarihi / Accepted : 27.03.2025

Adres / Correspondence : Ali ALKAN
Muğla Sıtkı Koçman University School of Medicine, Medical Oncology, Muğla
e-posta / e-mail : alkanali@yahoo.com

*Doi: 10.47572/muskutd.1503098*

Furthermore, research on ostracism has uncovered correlations with depression, physical health issues, and even mortality rates (8, 9).

During adolescence, a pivotal stage of development, individuals grapple with understanding themselves within the social sphere. Experiencing exclusion during this period can lead to a range of behavioral issues and emotional disturbances. Ostracism among adolescents specifically has detrimental effects on anxiety levels, self-esteem, sense of belonging, perceived control, and the pursuit of meaningful existence (10, 11). Moreover, it serves as a social risk factor contributing to the intensification of depressive symptoms during early adolescence (12).

In addition to the problems of cancer itself and its consequences on social life, cancer patients are prone to psychosocial issues, such as social exclusion and social disconnection (13). Adolescent cancer patients are unaware of social failure after a cancer experience. The type of the tumor, younger ages, neurotoxic medications, and educational status have been associated with impaired social interactions (14). Social exclusion is a significant problem that is usually ignored or not discussed. Kim et al. demonstrated that 49.7% of adolescent cancer survivors experienced social exclusion in school (15). In addition, exclusion and victimization were associated with higher depressive symptoms. According to data on adolescent and adult cancer patients, we hypothesized that adolescent cancer patients are also prone to ostracism. The aim of this pilot study was to evaluate ostracism among adolescent cancer patients and identify the factors that contribute to it.

## Material and Method

The multicenter study was carried out by the Palliative Care Working Committee members of the Turkish Oncology Group (TOG) in four oncology centers in Turkey. The study protocol received approval from the Ethical Committee of the Institution and the study followed the ethical guidelines set in the 1964 Declaration of Helsinki. All the participants gave their informed consent to be included in the research.

*Participants*

Between December 2017 and April 2018, the patients who admitted and evaluated in outpatient clinic were included. Patients between the ages of 14-24, had cancer diagnosis, and ones who were in remission, were invited. In this pilot study, we aimed to study patients under remission to exclude the psychosocial distress related to the process of therapy and its complications, which could be an important confounder. In addition, the patients with a clinical suspicion of recurrence of neuropsychiatric illness (active psychotic symptoms or severe suicidal ideation and/or intent) causing difficulty participating in the survey and who were illiterate were excluded. A control cohort was studied to compare the group's results with those of healthy adolescents. The university students at Mehmet Akif Ersoy University were invited to the study. The adolescents between 18-22 were invited, and those diagnosed with cancer were excluded.

*Procedures/Measures*

After outpatient visits, the patients were invited to study. Suitable patients were assessed through either in-person interviews or online questionnaires. We sent an invitation e-mail to participants, and they filled out the survey online. To assess the factors associated with ostracism, the risk factors defined in the literature have been described and studied. The questionnaire included questions on demographic information, sociocultural background (such as presence of siblings and monthly household income), comorbidities, educational background, parental employment status, history of psychiatric admissions, and details about primary illnesses. To evaluate the ostracism, the Ostracism Experience Scale for adolescents (OES-A) was used (2). The OES-A is an 11-item self-report instrument that uses a five-point Likert scale to evaluate two subtypes of ostracism: exclusion and ignorance. Exclusion is social rejection and inappropriate actions a group performs against an individual. (e.g., physical or verbal aggression, behavioral disruption, gossip spreading) can lead to exclusion. Ignorance is social neglect and doesn't display the behaviors that elicit active exclusion(2). The total score from 11 items ranges between 11 and 55, with higher scores indicating a greater level of ostracism experienced. Mercan (16) and akın et al. (17). The test showed validity with an internal consistency reliability coefficient of 0.93 for the ignored subscale, .90 for the excluded subscale, and .89 for the overall scale. In addition, to assess the effects of ostracism depressive symptoms, the Adolescent depression scale (KADS) was used. KADS is an 11-item self-report scale for assessing depression, with each item scored from 0 to 3 based on the frequency of symptom occurrence: 0 (hardly ever), 1 (much of the time), 2 (most of the time), and 3 (all of the time). The total score, ranging from 0 to 33, is the sum of the scores for all 11 items(18). A questionnaire evaluated the characteristics of the control cohort, and OES-A was used to assess the level of ostracism.

*Statistical analysis*

The baseline characteristics of the patient group were described using frequencies and proportions for dichotomous and categorical variables. Normality testing was performed by evaluating histogram, using Skewness/ Kurtosis results and Kolmogorov- Smirnov/ Shapiro-Wilk tests. After evaluation all those results, distribution of numerical

**Table 1.** Characteristics of patients and control cohort

| Characteristics | With cancer (52) n (%) | Without cancer (206) n (%) |
|---|---|---|
| Median age (range) | 21 (14-24) | 20 (18-22) |
| Age<21 | 23 (44.2) | |
| Male | 31 (59.6) | 117 (56.8) |
| Educational status | | |
| in university | 23 (44.2) | |
| other | 29 (55.8) | |
| Living in | | |
| City center | 44 (84.6) | 175 (84.9) |
| Other (town, village…) | 8 (15.4) | 31 (15.1) |
| Living | | |
| With parents | 40 (76.9) | 149 (72.3) |
| With friends/dormitory | 12 (23.1) | 57 (27.7) |
| Parents alive | 42 (80.8) | 195 (94.7) |
| Parents divorced | 2 (3.8) | 8 (3.9) |
| Educational status- father | | |
| Illiterate | 6 (11.5) | 0 (0) |
| Primary school | 8 (15.4) | 115 (55.8) |
| Middle school | 13 (25.0) | 6 (2.9) |
| High school | 11 (21.2) | 48 (23.3) |
| University | 14 (26.9) | 37 (18.0) |
| Educational status- mother | | |
| Illiterate | 7 (13.5) | 8 (3.9) |
| Primary school | 1 (1.9) | 136 (66.0) |
| Middle school | 20 (38.5) | 11 (5.3) |
| High school | 6 (11.5) | 37 (18.0) |
| University | 12 (23.1) | 14 (6.8) |
| Sibling present | 50 (96.2) | 199 (96.6) |
| Household income (monthly) | | |
| Less than 2000tl | 20 (38.3) | 82 (39.8) |
| More than 2000tl | 32 (61.5) | 124 (60.2) |
| Working full/part-time | 9 (17.3) | 23 (11.2) |
| Time to follow up (range), months | 45 (3-267) | |
| Long follow-up (≥45 months) | 26 (50) | |
| Diagnosis | | |
| Bone- soft tissue malignancy | 15 (28.8) | |
| CNS malignancy | 11 (21.2) | |
| Testis/ Ovarian malignancy | 13 (25.0) | |
| Hematological malignancy | 4/7.7) | |
| Other | 9 (17.3) | |
| Comorbidity present | 14 (26.9) | |
| History of Psychiatry Admission | 8 (15.4) | |
| History of antidepressant/ antipsychotic | 5 (9.6) | |

data was determined and further analysis was performed. The Kruskal-Wallis test was employed for univariate analysis of predictors of OES-A scores. A median score of 23.5 was used to categorize OES-A scores into high and low groups. Age was divided based on the median age of 21 into two groups: <21 and ≥21. The income parameter was categorized as low or high according to the average wage in Turkey (2000 Turkish liras). The length of follow-up was classified as long or short, based on the median follow-up time of 45 months. The factors associated with OES-A scores were tested by Mann-Whitney U test and the factors associated with high OES-A scores were analyzed using Chi-square test. Parameters with a p-value of less than 0.10 were further explored in multiple regression analysis(MRA). Variables such as female sex, age under 21, university student status, active employment, and low income were examined using a logistic regression model in the MRA. All analyses were performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY). *P*- value of less than 0.05 was considered as statistically significant. Power analysis was not performed at the beginning of the study. A posterior power analysis was performed and calculated. The G*Power 3.1.9.2 program was used to perform the power analysis and the frequency of high OES-A cancer patients were used for calculation. Post hoc power was found to be 92.4% with 0.3 effect size.

## Results

*Demographics*

Between December 2017 and April 2018, 70 patients with a diagnosis of cancer were invited, and

**Table 2.** Factors associated with OES-A scores and high OES scores in adolescents with cancer

| Characteristics | OES-A score (median, range) | p | OES-A high n (%) | p |
|---|---|---|---|---|
| Sex | | | | |
| Male (n=31) | 19.0(11-41) | | 11 (35.5) | |
| Female (n=21) | 28.0(12-36) | 0.008 | 15 (71.4) | 0.011 |
| Age | | | | |
| <21 (n=23) | 25 (11-41) | | 15 (65.2) | |
| ≥21 (n=29) | 21 (11-36) | 0.182 | 11 (37.9) | 0.046 |
| Educational status | | | | |
| in university (n=14) | 18.5 (11-30) | | 7 (30.4) | |
| other (n=38) | 27.0 (11-41) | 0.011 | 19 (65.5) | 0.012 |
| Living in | | | | |
| City center (n=44) | 24.0 (11-36) | | 24 (54.5) | |
| Other (town, village…) (n=8) | 17.5 (11-41) | 0.103 | 2 (25.0) | 0.121 |
| Living | | | | |
| With parents (n=40) | 22.0(11-41) | | 22 (46.8) | |
| Others (n=12) | 35.0 (18-36) | 0.012 | 4 (80.0) | 0.173 |
| Both parents alive (n=42) | 23.0 (11-41) | | 21 (50.0) | |
| One/two parents dead (n=10) | 20.5 (16-36) | 0.776 | 5 (50.0) | 0.632 |
| Parents divorced | | | | |
| Yes (n=2) | | | 1 (50.0) | |
| No (n=50) | NC | | 25 (50.0) | 0.755 |
| Educational status- father | | | | |
| Illiterate (n=6) | 28.5 (21-41) | | 5 (83.3) | |
| Primary school (n=8) | 21.0 (15-32) | | 4 (50.0) | |
| Middle school (n=13) | 23.0 (11-36) | | 6 (46.2) | |
| High school (n=11) | 19.0 (17-32) | | 4 (36.4) | |
| University (n=14) | 22.5 (11-30) | 0.482 | 7 (50.0) | 0.281 |
| Educational status- mother | | | | |
| Illiterate (n=7) | 28.0 (21-41) | | 6 (85.7) | |
| Primary school (n=1) | 25.0 (15-36) | | 1 (100) | |
| Middle school (n=20) | 18.5 (16-32) | | 12 (60.0) | |
| High school (n=6) | 20.0 (11-27) | | 2 (33.3) | |
| University (n=12) | 17.5 (11-30) | 0.086 | 2 (33.3) | 0.592 |
| Sibling | | | | |
| Present (n=50) | | | 26 (52.0) | |
| Absent (n=2) | NC | | 0 (0) | 0.247 |
| Household income (monthly) | | | | |
| Low (<2000tl) (n=20) | 28.0 (11-41) | | 15 (75.5) | |
| High (>20000tl) (n=32) | 21.0 (11-32) | 0.029 | 11 (34.4) | 0.005 |
| Working full/part-time (n=9) | 19.0 (11-30) | | 1 (11.1) | |
| Not working (n=43) | 25.0 (11-41) | 0.08 | 25 (58.1) | 0.012 |
| Follow-up | | | | |
| Long (n=26) | 26.0 (12-36) | | 14 (53.8) | |
| Short (n=26) | 21.0 (11-41) | 0.153 | 12 (46.2) | 0.394 |
| Diagnosis | | | | |
| Bone- soft tissue malignancy (n=15) | 21.0 (11-40) | | 5 (33.3) | |
| CNS malignancy (n=11) | 25.0 (11-36) | | 7 (63.6) | |
| Testis/ Ovarian malignancy (n=13) | 23.0 (15-30) | | 6 (46.2) | |
| Hematological malignancy (n=4) | 28.0 (20-29) | | 3 (75.0) | |
| Other (n=9) | 21.5 (16-32) | 0.534 | 4 (50) | 0.983 |
| History of Psychiatry Admission | | | | |
| Present (n=8) | 21.0 (11-41) | | 5 (62.5) | |
| Absent (n=43) | 26.5 (19-32) | 0.235 | 21 (47.7) | 0.354 |
| History of antidepressant/ antipsychotic | | | | |
| Present (n=5) | 20.0 (19-32) | | 2 (40.0) | |
| Absent (n=47) | 23.5 (11-41) | 0.624 | 24 (51.1) | 0.501 |

52 (74.2%) patients participated in 4 different cancer centers. In addition, 206 adolescents without a history of cancer were evaluated as a control cohort. The analysis of characteristics of patients with cancer showed a median age of 21 (14-24), 40.4% of them were female, and most of them were university students (23, 44.2%) (Table 1). While 96.2% had at least one sibling, 3.8% had parents divorced. 17.3% of them were actively working part-time or full-time. Soft tissue/ bone tumors (28.8%) and germ cell tumors (25.0%) were the most common diagnoses, and median follow-up was 45 months (3-267). In

addition, 14 (26.9%) had at least one comorbidity, and 8 (15.4%) had a history of psychiatry admission.

*Ostracism scores and the predictors of ostracism*
The median OES-A scores were 23.5 (range: 11.0-41.0) for adolescents with cancer and 19.0 (range: 11-49) for the control cohort (p=0.040). Further analysis of OES-A scores in adolescents with cancer revealed median scores of 16.0 (range: 6-30) for the exclusion subscale and 6.0 (range: 5-13) for the ignorance subscale (Table 2). Factors associated with higher ostracism included female sex (71.4% vs. 35.5%, p=0.011), age under 21 (65.2% vs. 37.9%, p=0.046), and low household income (75.5% vs. 34.4%, p=0.005). Conversely, patients working full/part-time (11.1% vs. 58.1%, p=0.012) and university students (30.4% vs. 65.5%, p=0.012) experienced less ostracism. In MRA, being female was linked to higher OES-A scores (OR: 7.4, 95% CI: 1.3-41.1, p=0.023). Being a university student (OR: 0.16, 95% CI: 0.03-0.84, p=0.036) and being actively employed (OR: 0.07, 95% CI: 0.008-0.79, p=0.031) were associated with lower OES-A scores. Additionally, higher OES-A scores correlated with higher KADS scores (9.0 vs. 7.5, p=0.166) (Table 3).

**Table 3.** Multiple regression analysis of factors associated with high OES-A scores in adolescents with cancer

| | High OES-A scores | | |
|---|---|---|---|
| | **OR** | **CI (95%)** | **p** |
| Female | 7.4 | 1.3-41.1 | 0.023 |
| Being university student | 0.16 | 0.03-0.84 | 0.036 |
| Working | 0.07 | 0.008-0.79 | 0.031 |
| Low income | 3.2 | 0.6-16.2 | 0.152 |
| Age <21 | 1.5 | 0.3-7.0 | 0.565 |

## Discussion

In this study, we aimed to evaluate the level of ostracism in adolescent cancer patients and identify the predictors of ostracism. To the best of our knowledge, this is the first data on ostracism in cancer patients. We concluded that OES-A scores were higher in adolescent cancer patients compared to adolescents without a history of cancer. Female adolescent patients were found to be at higher risk of ostracism, while being employed and being university students appeared to be protective factors against ostracism.

Adolescence is an essential period of time for psychological development. During this period, individuals have healthy social relations and understand and improve their perspectives. However, adolescents are socially more sensitive and have unique problems; exposure to ostracism and social exclusion can cause irreversible issues (19). Being a group member in adolescence is essential, so being excluded from the group may result in disappointment, psychological stress and sorrow. In addition, social isolation and problems in getting touch with the social group may cause numerous behavioral problems and emotional disturbances (20). The ostracism in adolescents and its effects on adolescents have been studied in numerous studies. We found more OES-A scores in our study population than in the control cohort. The comparison with the historical data was difficult because of the data presented in the previous studies (11, 21). The survey by Gurler et al. found that younger adolescents are more ostracized. We also saw similar data, but there was statistical significance in MRA and correlation analysis (11). The studies on ostracism have not found gender as a risk factor for ostracism (21). Unlike the previous data, we demonstrated that gender is an essential predictor of ostracism. Female adolescents with cancer were exposed to a 7.4-fold increased risk of ostracism. Previous data has shown income level as a risk factor for social exclusion (22). In our study, low income was associated with a 3.2-fold increased risk of ostracism (p= 0.15). However, there are many determinants of socioeconomic parameters, and a more specific study can clarify them. Consistent with the literature, studies with adolescents showed a positive correlation between ostracism scores and depression (23, 24). As a clinical impact of ostracism, we evaluated KADS scores and found worse depression scores in ostracized adolescents. Some of the literature has shown social exclusion as a risk factor for cyber addiction (25). As a part of clinical impacts, we evaluated the impacts of social media exposure on ostracism. However, there was no correlation between them.

The study has inevitable limitations. Firstly, because we evaluated patients with questionnaires, the data were subjective. In addition, some of the participants completed the survey online. There was no previous data about ostracism in cancer patients. So, further analysis could be done using the median score of OES-A. There is a limited number of adolescent cancer patients who are in remission. So, we could reach only 52 patients. Due to the limited number of patients, we couldn't further evaluate the effects of "working" and "being a university student."

## Conclusion

The study found that OES-A scores were higher than those of adolescents without cancer. While female adolescent patients are more prone to ostracism, working and being university students were protective against ostracism. Ostracism in adolescent cancer patients should be studied in a more extensive series with a control group of non-cancer patients.

## Acknowledgements

None

## Conflict of interest statement

The authors have nothing to declare

**Ethics Committee Approval:** The study has been approved by Çukurova University Ethical committee with a approval number of 02.02.2018/74

**Funding:** The study was not funded

## References

1. Saylor CF, Williams KD, Nida SA, et.al. Ostracism in pediatric populations: review of theory and research. J Dev Behav Pediatr. 2013;34(4):279-87.
2. Gilman R, Carter-Sowell A, Dewall CN, et.al.Validation of the ostracism experience scale for adolescents. Psychol Assess. 2013;25(2):319-30.
3. Williams KD. Ostracism. Annu Rev Psychol. 2007;58:425-52.
4. Hartgerink CH, van Beest I, Wicherts JM, et.al. The ordinal effects of ostracism: a meta-analysis of 120 Cyberball studies. PLoS One. 2015;10(5):e0127002.
5. Zadro L, Williams, K.,& Richardson, R. How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. J Exp Soc Psychol. 2004;40(4):560-7.
6. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167-202.
7. Stroud LR, Tanofsky-Kraff M, Wilfley DE, et.al. The Yale Interpersonal Stressor (YIPS): affective, physiological, and behavioral responses to a novel interpersonal rejection paradigm. Ann Behav Med. 2000;22(3):204-13.
8. Baumeister RF, Leary MR. The Need to Belong - Desire for Interpersonal Attachments as a Fundamental Human-Motivation. Psychol. Bull. 1995;117(3):497-529.
9. Cacioppo JT, Hawkley LC. Social isolation and health, with an emphasis on underlying mechanisms. Perspect. Biol. Med. 2003;46(3):S39-S52.
10. Sebastian C, Blakemore SJ, Charman T. Reactions to ostracism in adolescents with autism spectrum conditions. J Autism Dev Disord. 2009;39(8):1122-30.
11. Abdullah Gürler CD. The relationship between ostracısm and self-esteem In adolescents J. Soc. Sci. 2017;4(11):941-51.
12. Witvliet M, Brendgen M, van Lier PA, et.al. Early adolescent depressive symptoms: prediction from clique isolation, loneliness, and perceived social acceptance. J Abnorm Child Psychol. 2010;38(8):1045-56.
13. Heiney SP. Social disconnection in African American women with breast cancer. Oncol Nurs Forum. 2014;41(1):E28-34.
14. Bonneau J, Dugas K, Louis A, et.al. Educational and social outcome after childhood cancer]. Bull Cancer. 2015;102(7-8):691-7.
15. Kim MA, Park JH, Park HJ, et al. Experiences of peer exclusion and victimization, cognitive functioning, and depression among adolescent cancer survivors in South Korea. Am J Orthopsychiatry. 2018;88(4):441-9.
16. CS M. Ostracısm experıence scale for adolescents: turkısh validity and reliability. HAYEF: Journal of Education. 2016;13(25):175-86.
17. Akın A UR, Akın Ü. The validity and reliability of turkish version of the ostracism experience scale for adolescents. Kastamonu Eğitim Dergisi. 2014;24(2):895-904.
18. Brooks SJ, Krulewicz SP, Kutcher S. The Kutcher Adolescent Depression Scale: assessment of its evaluative properties over the course of an 8-week pediatric pharmacotherapy trial. J Child Adolesc Psychopharmacol. 2003;13(3):337-49.
19. Laursen B, Hafen C. Future Directions in the Study of Close Relationships: Conflict is Bad (Except When It's Not). Soc Dev. 2010;19(4):858-72.
20. Greenberg MT, Siegel JM, Leitch CJ. The nature and importance of attachment relationships to parents and peers during adolescence. J Youth Adolesc. 1983;12(5):373-86.
21. U O. Ostracism among Gifted Adolescents: A Preliminary Study in Turkey. Ed Process Int J. 2015;4(1-2):18-30.
22. Karatasoglu S IE. A Research on Relationship between Income Level and Social Exclusion. Journal of Labour Relations. 2016;7(1):12-41.
23. Niu GF SX, Tian Y, Fan CY,et.al. Resilience moderates the relationship between ostracism and depression among Chinese adolescents. Pers Individ Dif. 2016;99:77-80.
24. Bowker JC AR, Fredstrom BK, Gilman R. Being Ignored by Peers During Late Adolescence: Linkages to Psychological Maladjustment. WSU Press. 2014;60(3):328-54.
25. Suissa AJ. Cyber addictions: toward a psychosocial perspective. Addict Behav. 2015;43:28-32.

*Doi: 10.47572/muskutd.1522772*

# Evaluation of the Relationship of Maternal Feeding Style with Fetal Sex

# Maternal Beslenme Tarzının Fetal Cinsiyetle İlişkisinin Değerlendirilmesi

**Mehmet Alican SAPMAZ[1]*, Murat POLAT[1], Sait ERBEY[1], Ömer Osman EROĞLU[1], Ayşe Sena KÜÇÜKKAYIKÇI[1], Nilüfer AKGÜN[2]**

[1]Ankara Etlik Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Ankara
[2]Ankara Etlik Zübeyde Hanım Doğumevi, Kadın Hastalıkları ve Doğum Kliniği, Ankara

**Öz**

Çalışmanın ana amacı gebelik öncesi diyet tarzı ile fetal cinsiyet arasındaki ilişkiyi belirlemektir. Gebelik öncesi ve sırasında Akdeniz diyetine bağlılık düzeyi ve fetal cinsiyet değerlendirildi. Fetal cinsiyetin gebelik sırasında maternal vücut kitle indeksi değişimine etkisi de değerlendirildi. Tanımlayıcı anket çalışmasına Etlik Şehir Hastanesi'nde doğum yapan 412 hasta dahil edilmiştir. Çalışma kapsamında, güç analizi ile örneklem sayısı hesaplanmıştır. 2 gruplu çalışmada G Power (Version 3.1.9.6) ile yapılan güç analizi sonucunda güvenirlik %95, etki düzeyi 0,50 ve güç %90 alınmıştır. Bu kapsamda en düşük örneklem sayısı her bir grup için 86 olmak üzere toplamda 172 olarak hesaplanmıştır. Ancak sonuçların güvenilirliği için erkek çocuklardan 192 ve kız çocuklardan 220 örneklem alınmıştır. Akdeniz diyet ölçeği anketi ilk trimester takibi sırasında ve doğum sırasında doldurulmuştur. Hastaların gebelik öncesi ve doğum sırasındaki kilo, boy ve vücut kitle indeksleri karşılaştırıldı. Çalışmaya dahil edilen hastalar doğumdan sonra bebeğin cinsiyetine göre iki gruba ayrıldı. Gebelik öncesi Akdeniz diyeti uyum puanı ortalaması erkek bebek annelerinde 6.98±2.21, kız bebek annelerinde 4.89±2.08'dir ve iki grup arasında anlamlı fark vardır. Gebelik süresince BKİ'deki ortalama değişim erkek bebeklerin annelerinde 2.83±1.70 ve kız bebeklerin annelerinde 3.60±1.84'tür ve bu fark istatistiksel olarak anlamlıdır. Gebelik öncesinde Akdeniz diyetine bağlı kalan hastaların gebelik süresince de bu diyete sadık kaldıkları gözlemlenmiştir. Akdeniz diyeti ile beslenenlerin anlamlı olarak daha fazla erkek bebeğe sahip olduğu sonucuna varılmıştır. Akdeniz diyetine uyum sonucunda, gebelik öncesi ve gebelikte bu diyete uyan hastaların vücut kitle indeksinin anlamlı olarak daha düşük olduğu, gebelikte kilo alımına bağlı olarak vücut kitle indeksindeki değişimin anlamlı olarak daha az arttığı sonucuna varıldı.

**Anahtar Kelimeler:** Akdeniz Diyeti, Fetal Cinsiyet, Gebelikte Beslenme

**Abstract**

The main aim of the study was to determine the relationship between pre-pregnancy dietary style and fetal sex. The level of adherence to the Mediterranean diet and fetal gender were assessed before and during pregnancy. The effect of fetal gender on maternal body mass index change during pregnancy was also evaluated. Descriptive survey study included 412 patients gave birth in Etlik City Hospital. The Mediterranean diet scale questionnaire was completed during first trimester follow-up and at time of delivery. Weight, height and body mass index of the patients before pregnancy and at delivery were compared. The included patients were divided into two groups according to sex of baby after delivery. Mean pre-pregnancy Mediterranean diet compliance score was 6.98±2.21 in mothers of male infants and 4.89±2.08 in mothers of female infants, and there was significant difference between the two groups. Mean change in BMI during pregnancy was 2.83±1.70 in mothers of male infants and 3.60±1.84 in mothers of female infants and this difference was statistically significant. It was observed that patients adhered to Mediterranean diet before pregnancy remained loyal to this diet during pregnancy. It was concluded that those fed with Mediterranean diet had significantly more male babies. Result of compliance with Mediterranean diet, it was concluded that body mass index of patients who adhered to this diet before and during pregnancy was significantly lower and change in body mass index increased significantly less due to weight gain during pregnancy.

**Keywords:** Mediterranean Diet, Fetal Sex, Nutrition in Pregnancy

## Introduction

Pregnancy is a complex process that requires physiological adaptation of the mother and changes in nutritional needs and regular intake of macro and micronutrients to ensure fetal growth and development. Pregnancy is a 40-week period of life with different nutritional requirements for mother and child, and it is an important period of life for both (1). Diet and other lifestyle factors such as smoking and alcohol consumption before and during pregnancy and lactation have been shown to affect child health (2). In addition, an unbalanced diet during pregnancy has been associated with serious pregnancy complications (3). The baby's physiology and metabolism can be permanently altered and shaped by the intrauterine environment (4). One of the most important reasons for these changes is undoubtedly maternal diet . Several studies have investigated the association between the intake of various nutrients, foods or food groups during pregnancy and maternal and fetal diseases (5).

There are also hypotheses that assess the relationship between environmental factors and maternal physiological status and fetal sex. One of

| | ORCID No |
|---|---|
| Mehmet Alican SAPMAZ | 0000-0003-3812-3455 |
| Murat POLAT | 0009-0002-2964-729X |
| Sait ERBEY | 0009-0007-1950-9041 |
| Ömer Osman EROĞLU | 0000-0001-6764-0131 |
| Ayşe Sena KÜÇÜKKAYIKÇI | 0000-0002-5106-3349 |
| Nilüfer AKGÜN | 0000-0003-0414-9470 |

Başvuru Tarihi / Received: 26.07.2024
Kabul Tarihi / Accepted : 26.01.2025

Adres / Correspondence : Mehmet Alican SAPMAZ
Ankara Etlik Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Ankara
e-posta / e-mail : dr.alicansapmaz@hotmail.com

the most well-known of these is The Trivers - Willard hypothesis. The Trivers – Willard hypothesis (TWH) predicts that, when one sex exhibits more variation in reproductive value, then mothers in good condition should 'prefer' offspring of that sex, while mothers in poor condition should 'prefer' offspring of the other sex (6).

There are other studies evaluating the relationship between diet and maternal body type on fetal sex. A large group of African women, most of whom were malnourished as determined by their height and weight, for example, produced more daughters than sons (7). A study examining birth rates of women from rural Ethiopia also demonstrated that a positive correlation existed between women who were in better nutritional state, as determined by body mass and muscle indices, and percent of male births (8). Analysis of over 10 000 children born in Modena, Italy, revealed that thinner mothers were less likely to give birth to sons (9). In humans, males appear to have higher in utero caloric demands than females (10). Vulnerability of male offspring to in utero malnutrition and other environmental stressors might, therefore, have arisen through natural selection, by maximizing the mother's reproductive success, so that she tends to give birth to the more energy-demanding male offspring during auspicious environmental cycles (11).

The Mediterranean diet, with its low intake of meat products and high-fat foods, is a balanced, nutritious diet that is considered a standard for diet quality because of its components such as vegetables, cheese, olive oil, fish, shellfish and little meat (12).

Mediterranean diet is accepted as a healthy nutrition program all over the world. The positive effects of the Mediterranean diet are known especially in the prevention of many disease groups such as cardiovascular diseases, diabetes, obesity and cancer. Mediterranean diet, which is applied before and during pregnancy, is a suitable and sufficient nutrition option for expectant mothers. It is distinguished by its high methyl donor content for one-carbon metabolism, which is engaged in growth and programming activities, notably during the periconceptional period (13).

During pregnancy, the mother has an excessive desire for some foods, while there is a desire to avoid some foods due to hypersensitivity and disgust. Although the cause of this situation is not known exactly, it is estimated that there are changing physiological and hormonal conditions during pregnancy. It is known that traditional behaviors and practices are frequently used in some cultures during this period. One of the conditions thought to be effective on the sex of the baby is the mother's diet. One of the traditional beliefs of Turkish society is that a woman who eats sour food will have a girl child and a woman who eats sweet food will have a boy child (14).

The primary aim of this study is to determine the relationship between pre-pregnancy dietary intake and infant gender. The extent to which the patients included in the study adhered to the Mediterranean diet style before and during pregnancy will also be evaluated, considering the fetal gender. In addition, the effect of fetal sex on maternal body mass index change during pregnancy will be investigated.

## Material and Method

The aim of this prospective descriptive questionnaire study was to investigate the effect of a Mediterranean diet on the prediction of fetal sex. The study was conducted in the Department of Obstetrics and Gynecology and included patients presenting to the outpatient clinic between 1 October 2023 and 1 July 2024. Patients were excluded if they were under 18 years of age, had pre-existing systemic diseases, multiple pregnancies, history of malignancy before pregnancy, active smoking, alcohol consumption or illicit drug use, HIV, HCV or HBV infection or any pre-existing chronic disease.

A total of 412 pregnant patients who applied to the pregnancy outpatient clinic in the 1st trimester were included in the study. Within the scope of the study, the sample size was calculated by power analysis. In the 2-group study, because of the power analysis performed with G Power (Version 3.1.9.6), reliability was 95%, effect level was 0.50 and power was 90%. In this context, the minimum sample size was calculated as 86 for each group, totaling 172. However, for the reliability of the results, 192 samples were taken from boys, and 220 samples were taken from girls. Informed consent was obtained from the participants that they wanted to be included in the study. Patients were asked to fill out questionnaire adapted to Turkish version of the Mediterranean Dietary Adherence Scale (MEDAS) (figure 1) considering their nutritional attitudes in the last 1 month before conception. Height, weight and body mass index of the patients were recorded in their files. When the patients were admitted to the hospital for delivery, they were asked to consider their dietary habits during pregnancy and questionnaire adapted to Turkish version of the Mediterranean Dietary Adherence Scale (MEDAS) was filled out again.

Height, weight and body index of the patients were re-evaluated and recorded in their files. The Mediterranean diet adherence scale is a test consisting of 14 questions and a score of 1 or 0 for each question. A total score of 7 and above indicates that the individual has acceptable compliance with the Mediterranean diet, and a score of 9 and above indicates that the individual has strict compliance with the Mediterranean diet (15).

| | | |
|---|---|---|
| 1. | **Yemeklerde temel yağ olarak zeytinyağı kullanıyor musunuz?** | **Haftada en az 2 kez salata, sebze, et veya balık yemeklerinde kullanıyorsa 1 puan** |
| 2. | Günde ne kadar zeytinyağı tüketiyorsunuz? (Kızartmalarda, salatalarda, ev dışında yenilen yemeklerde kullanılanlarda vb.) (1 yemek kaşığı=13.5 g*) | Günde 48 g'dan fazla tüketiyorsa 1 puan |
| 3. | Günde kaç porsiyon sebze tüketiyorsunuz? (1 porsiyon= 200 g) | Günde 2 porsiyon ve fazlası tüketiyorsa 1 puan |
| 4. | Günde kaç porsiyon meyve (taze sıkılmış meyve suları dahil) tüketiyorsunuz? (Toplam meyve porsiyonu= Total meyve g/80) (Taze meyve suyu porsiyonu= Her 100 ml** için 1 porsiyon) | Günde 3 porsiyon ve üzerinde tüketiyorsa 1 puan |
| 5. | Günde kaç porsiyon kırmızı et tüketiyorsunuz? | Günde 100 g altında tüketiyorsa 1 puan |
| 6. | Günde kaç porsiyon tereyağı veya margarin tüketiyorsunuz? (1 yemek kaşığı=12 g) | Günde 1 porsiyonun altında tüketiyorsa 1 puan |
| 7. | Günde ne kadar şekerli ya da tatlandırılmış içecekler tüketirsiniz? (1 porsiyon=100 ml) | Günde 1 porsiyonun altında tüketiyorsa 1 puan |
| 8. | Şarap içer misiniz? Haftada ne kadar tüketiyorsunuz? (1 kadeh= 125 ml) | Haftada 7 kadeh ve fazlası ise 1 puan |
| 9. | Haftada kaç porsiyon bakliyat tüketiyorsunuz? (1 porsiyon= 150 g) | Haftada 3 porsiyon ve fazlası ise 1 puan |
| 10. | Haftada kaç porsiyon balık / deniz ürünü tüketiyorsunuz? (1 porsiyon = 100-150 g balık veya 4-5 adet veya 200 g kabuklu deniz ürünleri) | Haftada 3 porsiyon ve fazlası ise 1 puan |
| 11. | Haftada kaç kez işlenmiş tatlı ya da hamur işi (ev yapımı olmayan) tüketiyorsunuz? | Haftada 3 den az ise 1 puan |
| 12. | Haftada kaç defa fındık (yer fıstığı dahil) tüketiyorsunuz? (1 porsiyon = 30 g) | Haftada 3 porsiyon ve fazlası ise 1 puan |
| 13. | Sığır eti, domuz eti, hamburger veya sosis yerine tavuk, hindi veya tavşan eti yemeyi mi tercih edersiniz? | Beyaz et tüketimi, kırmızı et tüketiminden gramaj olarak fazla ise 1 puan |
| 14. | Haftada kaç kere haşlanmış sebze, makarna, pilav veya diğer yemeklerinize domates, sarımsak, soğan veya pırasa soslu zeytinyağı kullanırsınız? | Haftada 2 defa ve daha fazla ise 1 puan ver |

**Figure 1.** Questionnaire adapted to Turkish version of the Mediterranean Dietary Adherence Scale (MEDAS)

Mediterranean diet compliance scores of the patients were also divided into 3 groups for both sexes. Those with a Mediterranean diet nutritional score of 0-6 were defined as level 1, 7-8 as level 2, and 9 and above as level 3.

The patients included in the study were divided into two groups according to the sex of the baby after delivery. The completed questionnaires and body mass indexes that changed during pregnancy were evaluated according to the sex of the baby. The analyses were performed with SPSS 26.0 programmed and 95% confidence level was used. In the analyses, mean and standard deviation values for measurements, frequency and percentage values for categorical variables were given. Since the skewness and kurtosis values obtained from the measurements were between +1 and -1, normality was ensured and the analysis in terms of gender was analyzed with the Independent groups t test. The relationship between gender and MEDAS level before pregnancy was analyzed by Chi-square test. Since the skewness and kurtosis values obtained from the measurements are between +1 and -1, normality is ensured and parametric test techniques will be used in the analyses (Table 1).

**Table 1.** Normality Test

| | **Skewness** | **Kurtosis** |
|---|---|---|
| Pre-pregnancy MEDAS level | 0,356 | -0,173 |
| Pre-pregnancy BMI | 0,526 | 0,407 |
| During Pregnancy Medas level | 0,380 | -0,481 |
| During Pregnancy BMI | 0,199 | 0,815 |
| In pregnancy BMI Change | 0,372 | -0,586 |

## Results

The mean pre-pregnancy Mediterranean diet compatibility score was 6.98±2.21 in mothers of male infants and 4.89±2.08 in mothers of female infants, and there was a significant difference between the two groups (p<.001). The mean Mediterranean diet compliance level before pregnancy was 1.52±0.71 in mothers of male infants and 1.13±0.38 in mothers of female infants, and this difference was statistically significant (p<.001). The mean Mediterranean diet compliance score during pregnancy was found to be 6.81±1.78 and 5.09±2.15 in mothers of male and female infants, respectively, and this difference was statistically significant (p<.001). Mediterranean diet compliance level during pregnancy was found to be 1.46±0.61 in mothers of male infants and 1.20±0.48 in mothers of female infants and there was a significant difference between them (p=0.020). The mean pre-pregnancy BMI was found to be 24.19±4.17 in mothers of male infants and 26.20±4.14 in mothers of female infants, with a statistically significant difference (p=0.013). The mean BMI at the end of pregnancy was 27.02±3.98 and 29.96±3.56 in mothers of male and female infants, respectively, and the difference between them was statistically significant (p<.001). The mean change in BMI during pregnancy was 2.83±1.70 in mothers of male infants and 3.60±1.84 in mothers of female infants, and this difference was statistically significant (p=0.032) (Table 2).

**Table 2.** Comparison of the values of patients grouped according to sex (MEDAS: Mediterranean Diet Adherence Scale)

| | Group | Mean±ss | P Value |
|---|---|---|---|
| Pre-pregnancy MEDAS | Boy(n=192) Girl (n=220) | 6.98±2.21 4.89±2.08 | 0.000 |
| Pre-pregnancy MEDAS level | Boy (n=192) Girl (n=220) | 1.52±0.71 1.13±0.38 | 0.000 |
| During Pregnancy MEDAS | Boy (n=192) Girl(n=220) | 6.81±1.78 5.09±2.15 | 0.000 |
| During Pregnancy MEDAS level | Boy(n=192) Girl(n=220) | 1.46±0.61 1.20±0.48 | 0.020 |
| Pre-pregnancy BMI | Boy (n=192) Girl(n=220) | 24.19±4.17 26.20±4.14 | 0.013 |
| End of Pregnancy BMI | Boy(n=192) Girl(n=220) | 27.02±3.98 29.96±3.56 | 0.000 |
| In pregancy BMI Change | Boy(n=192) Girl(n=220) | 2.83±1.70 3.60±1.84 | 0.032 |

When classified according to MEDAS level in mothers of male infants, there were 116 patients in incompatible, 52 patients in moderately compatible, and 24 patients in tightly compliant group. In mothers of baby girls, there were 196, 20 and 4 patients, respectively (Table 3).

**Table 3.** Gender distribution in patients grouped according to pre-pregnancy MEDAS level (MEDAS: Mediterranean Diet Adherence Scale)

| Sex | Pre-pregnancy MEDAS level | n (%) | p |
|---|---|---|---|
| Boy | Group 1(incompatible) | 116 (%60,4) | |
| | Group 2 (moderately compliant) | 52 (%27,1) | |
| | Group 3 (tightly matched) | 24 (%12,5) | 0,000 |
| Girl | Group 1(incompatible) | 196 (%89,1) | |
| | Group 2 (moderately compliant) | 20 (%9,1) | |
| | Group 3 (tightly matched) | 4 (%1,8) | |

## Discussion

Healthy nutrition during pregnancy is important for fetal development and maternal health. Many expectant mothers recognize that the right diet during pregnancy is important for the health of their baby. There are also different cultural beliefs that diet and a strong preference for certain foods are related to the sex of the baby. Expectant mothers are concerned about the health of their baby as well as the sex of the baby. Maternal diet is one of the important parameters thought to be associated with fetal sex.

Mothers that experience different individual or environmental conditions may produce different proportions of male to female offspring (16). Mammals usually produce approximately equal numbers of sons and daughters, but there are exceptions to this general rule, as has been observed in ruminant ungulate species, where the sex-allocation hypothesis of Trivers and Willard has provided a rational evolutionary underpinning to adaptive changes in sex ratio (17). In a laboratory study on mice, it was shown that maternal age and maternal diet, rather than maternal body condition, play a guiding role in controlling sex ratio (17). They concluded that a diet high in saturated fat but low in carbohydrate resulted in the birth of significantly more male offspring than female offspring in mature laboratory mice, while female offspring were more dominant when calories were provided in the form of carbohydrate rather than fat (17).

The Mediterranean diet is a term based on the traditional diet in countries bordering the Mediterranean Sea. Interest in the Mediterranean diet began in the 1950s. This interest arose from the realization that heart disease was less common in people living in Mediterranean countries than in wealthier Western countries. In addition, the Mediterranean diet has become one of the most preferred dietary styles during pregnancy. Many studies have been undertaken to investigate the effect of Mediterranean diet on maternal health and offspring health. For instance, the Mediterranean diet is associated with a higher chance of clinical pregnancy and live birth after IVF, and a lower incidence of infertility (18,19). There are studies showing the effective power of the Mediterranean diet in preventing gestational diabetes mellitus, pre-eclampsia, metabolic syndrome and syndromic infant birth during pregnancy. In our country, this diet style, which was previously preferred especially in the Mediterranean and Aegean regions, has started to be adopted in all regions today.

In previous studies, the importance of Mediterranean diet during pregnancy has been emphasized, but the relationship with fetal sex has not been mentioned. In our study, we aimed to evaluate the relationship between the Mediterranean dietary pattern preferred in the preconceptional period and fetal sex. The effect of adherence to the Mediterranean diet during pregnancy on body mass index has also been investigated. The pre-pregnancy Mediterranean diet adherence score was significantly higher in mothers who gave birth to male infants. The pre-pregnancy Mediterranean diet adherence level was significantly higher in mothers who gave birth to a male baby. However, when both scores and compliance levels were evaluated, it was observed that both groups of mothers did not have an

acceptable level of compliance with the Mediterranean diet. Both the score and the level of adherence to the Mediterranean diet during pregnancy were significantly higher in mothers who gave birth to male infants. It is noteworthy that the pre-pregnancy diet score of mothers of male infants was higher than the pre-pregnancy score. On the other hand, the Mediterranean diet score during pregnancy was found to be higher than the pre-pregnancy diet score in mothers of female infants. This contrast between the groups suggests that the compliance with the Mediterranean diet decreased with pregnancy in mothers of male infants, whereas mothers of female infants adopted a healthier eating style and turned to the Mediterranean diet. Body mass index was found to be significantly lower in mothers of male infants than in mothers of female infants before and at the end of pregnancy. At the same time, the increase in body mass index during pregnancy was found to be higher in mothers of female infants.

This study provides valuable information on the effects of a Mediterranean diet in predicting changes in body mass index and fetal sex. However, it is important to recognize some limitations of the study. Sample size, errors in completing the Turkish adapted questionnaire of the Mediterranean dietary adherence scale and patient selection may lead to inherent bias. One of the limitations of the study is that the influence of paternal factors on fetal sex was ignored. This limitation narrows the results of the study and does not sufficiently examine the potential effects of paternal genetic and environmental factors.

Despite these limitations, the fact that the association of Mediterranean diet with fetal sex was not evaluated makes our study original. In the light of these findings, it is thought that larger and more prospective studies and investigations should be carried out to confirm the relationships defined and to elucidate the underlying mechanisms.

## Conclusion

In the Trivers - Willard hypothesis, the prediction that expectant mothers with good fitness and environmental factors have a high potential to give birth to a male baby of the opposite sex can be associated with the conclusion that adherence to the Mediterranean diet will also lead to a male baby by providing good fitness and physiology in the mother.

## Acknowledgements

We would like to thank professor Levent Keskin for guiding us throughout the study process.

## Conflict of interest statement

Our study has not conflict of interest

**Ethics Committee Approval:** Ethics committee approval dated 18/10/2023 and numbered AEŞH-Ek1-2023-637

**Funding:** No financial support was received from any organization in our study

## References

1. Çobanoğullari H, Ergoren MC, Dundar M, et al. Periconceptional Mediterranean diet during pregnancy on children's health. *J Prev Med Hyg.* 2022;63(2 Suppl 3).
2. Koletzko B, Godfrey KM, Poston L, et al. Nutrition during pregnancy, lactation and early childhood and its implications for maternal and long-term child health: the early nutrition project recommendations. *Ann Nutr Metab.* 2019;74(2):93-106.
3. Danielewicz H, Myszczyszyn G, Dębińska A, et al. Diet in pregnancy—more than food. *Eur J Pediatr.* 2017;176:1573-9.
4. Abdou RM, El Hawary GS, Saab AA. Effect of gestational Mediterranean diet intervention on newborn fat mass and cord blood leptin level. *Gaz Egypt Paediatr Assoc.* 2020;63:30.
5. Peraita-Costa I, Gonzalez AL, Perales-Marin A, et al. Retrospective cross-sectional population-based study on prenatal levels of adherence to the Mediterranean diet: maternal profile and effects on the newborn. *Int J Environ Res Public Health.* 2018;15:1530.
6. Trivers RL, Willard DE. Natural selection of parental ability to vary the sex ratio of offspring. *Science.* 1973;179:90-2.
7. Andersson R, Bergstrom S. Is maternal malnutrition associated with a low sex ratio at birth? *Hum Biol.* 1998;70:1101-6.
8. Gibson MA, Mace R. Strong mothers bear more sons in rural Ethiopia. *Proc R Soc Lond B Biol Sci.* 2003;7.
9. Cagnacci A, Renzi A, Arangino S, et al. Influences of maternal weight on the secondary sex ratio of offspring. *Hum Reprod.* 2004;19:442-4.
10. Tamimi RM, Lagiou P, Mucci LA, et al. Average energy intake among pregnant women carrying a boy compared with a girl. *BMJ.* 2003;326:1245-6.
11. Wells JC. Natural selection and sex differences in morbidity and mortality in early life. *J Theor Biol.* 2000;7:65-76.
12. Fischer M, Stronati M, Lanari M. Mediterranean diet, folic acid, and neural tube defects. *Ital J Pediatr.* 2017;43:74.
13. Corsello G, Giuffrè M. Congenital malformations. *Matern Fetal Neonatal.* 2012;25:25-9.
14. Yalçın H, Koçak N. Gebelikle ilgili geleneksel inanç ve uygulamalar ve Karaman örneği. *Kent Akademisi.* 2013;6(13):18-34.
15. León-Muñoz LM, et al. Adherence to the Mediterranean diet pattern has declined in Spanish adults. *J Nutr.* 2012;142(10):1843-50.
16. Shyu E, Caswell H. Frequency-dependent two-sex models: a new approach to sex ratio evolution with multiple maternal conditions. *Ecol Evol.* 2016;6(19):6855-79.
17. Rosenfeld CS, Roberts RM. Maternal diet and other factors affecting offspring sex ratio: a review. *Biol Reprod.* 2004;71(4):1063-70.
18. Karayiannis D, Kontogianni MD, Mendorou C, et al. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. *Hum Reprod.* 2018;33:494-502.
19. Toledo E, Lopez-del Burgo C, Zambrana AR, et al. Dietary patterns and difficulty conceiving: a nested case-control study. *Fertil Steril.* 2011;96:1149-53.

*Doi: 10.47572/muskutd.1579237*

# Investigation of the Cost Impact of Chirality Status of the Most Commonly Consumed Drugs in Turkey

# Türkiye'de En Sık Tüketilen İlaçların Kiralite Durumunun Maliyete Yansımasının İncelenmesi

**Ahmet AKICI[1], Caner VIZDIKLAR[1], Şeyhmus GAVAŞ[1], Nazım HASPOLAT[2], Dieudonne HAVYARİMANA[1], Selcan TÜLÜ ÇOLAK[1], Volkan AYDIN[3]**

[1]Marmara University School of Medicine, Department of Medical Pharmacology, İstanbul, Turkey
[2]Bursa Uludağ University School of Medicine, Department of Medical Pharmacology, Bursa, Turkey
[3]İstanbul Medipol University International School of Medicine, Department of Medical Pharmacology, İstanbul, Turkey

**Öz**

Kiralite, terapötik veya advers etkiler yönünden ilaç aktivitesini etkileyen faktörler arasındadır. Yeni ilaç geliştirilmesinde, bu kavram doğrultusunda daha fazla fayda sağladığı düşünülen saf enantiyomer ilaçlar tavsiye edilmiştir. Bu çalışmada Türkiye'de sık tüketilen ilaçların kiralite durumları ve bunların maliyete yansımaları incelendi. Çalışmada IQVIA Türkiye biriminden alınan satış verileri kullanılarak ülke genelinde en fazla satılan ilk 200 etkin madde değerlendirildi ve 173'ünün kiralite durumu tespit edildi. Bu ilaçlar "kiral karışım", "akiral" ve "saf enantiyomer" olmak üzere üç gruba ayrılmalarının ardından kiralite durumlarına göre dağılımları ve ortalama kutu başına düşen (KBD) maliyetleri incelendi. Kiral dönüşümün maliyete yansımasını incelemek amacıyla dönüşüme uğrayan kiral karışımlarla bu işlem sonucunda meydana gelen saf enantiyomerler bu parametreler yönünden karşılaştırıldı. Kiralite durumu incelenen 173 etkin maddenin %35.8'i akiral, %22.0'ı kiral karışım ve %42.2'si saf enantiyomerdi. Toplam maliyet 2.09 milyar $ iken, maliyetin %46.4'ünü saf enantiyomerler, %22.0'ını ise kiral karışımlar oluşturmaktaydı. KBD maliyet ortalamaları bakımından saf enantiyomerler (2.8±3.5 $), akiral ilaçlar (2.3±2.5 $) ve kiral karışımlar (1.7±0.9 $) istatistiksel olarak benzerdi (p>0.05). Kiral dönüşüme uğrayan ilaçlarda kiral karışımların ortalama KBD maliyeti (1.4±0.4 $), saf enantiyomerlerinki (1.7±1.2 $) ile benzerdi (p>0.05). Kiral dönüşüme uğrayan ilaçların yarısında KBD maliyeti, kiral karışımda daha yüksekken diğer yarısında ise saf enantiyomerde daha yüksekti. Bu çalışmada Türkiye'de en çok satan ilaçlar arasında saf enantiyomerlerin önemli ölçüde yer tuttuğu ortaya konuldu. Sık kullanılan saf enantiyomer ve kiral karışımların maliyet yönünden benzer olması, saf enantiyomerlerin piyasada tercih edilme durumunun devam edebileceğini düşündürmektedir.

**Anahtar Kelimeler:** İlaç Harcamaları, Kiralite, Kiral Dönüşüm Kiral Karışım, Saf Enantiyomer

**Abstract**

Chirality is among the factors impacting drug activity in terms of therapeutic or adverse effects. Pure enantiomeric drugs, presumed to offer greater benefits in accordance with this concept, have been recommended for new drug development. We aimed to analyse the chirality status of the commonly consumed drugs in Turkey and assess their cost implications. We evaluated top-selling 200 active substances using nationwide sales data from IQVIA Turkey, identifying chirality status of 173. These were categorized into "chiral mixtures", "achiral", and "pure enantiomers", and their distribution and mean cost per unit (CPU) values by chirality status were examined. To examine the impact of chiral switching on expenses, CPUs of chiral-switched mixtures and resulting pure enantiomers, were compared. Among 173 compounds, 35.8% were achiral, 22.0% were chiral mixtures and 42.2% were pure enantiomers. Total cost was $2.09b, with pure enantiomers accounting for 46.4% and chiral mixtures 22.0%. Mean CPUs for pure enantiomers ($2.8±3.5), achiral drugs ($2.3±2.5), and chiral mixtures ($1.7±0.9) were similar (p>0.05). For drugs that underwent chiral switching, mean CPU of chiral mixtures ($1.4±0.4) was similar to that of pure enantiomers ($1.7±1.2), (p>0.05). Half of the chiral pairs that underwent switching had higher CPU for chiral mixture, while the other half had higher CPU for pure enantiomer. We demonstrated that pure enantiomers occupy a significant portion of top-selling drugs in Turkey. The observed cost similarity between commonly used pure enantiomers and chiral mixtures suggests that pure enantiomers may continue to gain preference in the market.

**Keywords:** Drug Expenditure, Chirality, Chiral Switch, Chiral Mixture, Pure Enantiomer

## Introduction

Chirality, defined as the property of a molecule being non-superimposable on its mirror image, is among the important geometric properties of objects in biological systems (1). Each of a chiral molecule and its mirror image is called an enantiomer. Chiral compounds may consist of a single enantiomer or a mixture of two enantiomers, including racemates, which are 50:50 mixtures (2). The proportion of pure enantiomers in newly approved drugs has gradually increased over the years, and recent studies have reported that more than two-fifths of drugs on the market are pure enantiomers (3,4). In contrast to chiral molecules, molecules that can superimpose on their mirror image are defined as "achiral" (2).

In medicines that are present as chiral mixtures, each enantiomer may exhibit different levels of activity in terms of therapeutic or adverse effects. The variability in activity has also been linked to adverse reactions associated with one enantiomer of a drug, as

| | ORCID No |
|---|---|
| Ahmet AKICI | 0000-0002-8593-0818 |
| Caner VIZDIKLAR | 0000-0002-9558-1914 |
| Şeyhmus GAVAŞ | 0000-0002-2691-6485 |
| Nazım HASPOLAT | 0009-0004-8064-0346 |
| Dieudonne HAVYARİMANA | 0000-0002-4818-6313 |
| Selcan TÜLÜ ÇOLAK | 0000-0002-6383-7591 |
| Volkan AYDIN | 0000-0002-8511-6349 |

Başvuru Tarihi / Received: 05.11.2024
Kabul Tarihi / Accepted : 05.04.2025

Adres / Correspondence : Volkan AYDIN
Department of Medical Pharmacology, İstanbul Medipol University International School of Medicine, İstanbul, Turkey
e-posta / e-mail : volkan.aydin@medipol.edu.tr

evidenced by the thalidomide tragedy (5,6). Consequently, this observation has prompted the view that drugs composed of a single enantiomer might more effectively achieve the desired outcomes with fewer side effects (7). Pharmaceutical regulatory authorities such as the US Food and Drug Administration (FDA) have also recommended, although not mandated, the development of new drugs as pure enantiomers (8). In this context, the process of chiral switch, i.e. development of a single enantiomer from a chiral drug that has been marketed as a chiral mixture, has been initiated (4). The theoretical advantages of a chiral switch include lower dosage requirements for treatment, less variation in individual drug response, prevention of adverse effects potentially due to an inactive enantiomer, and a competitive advantage in the market (9). However, there are also arguments that chiral switch practices do not always yield significant benefits in clinical practice (10). While there are studies reporting a higher cost burden associated with pure enantiomeric drugs compared to chiral mixtures, due to the additional steps required in drug development, there are also opinions suggesting that the cost differences between drugs in different chiral statuses may diminish with increased mass production (11-13). In order to assess the impact of these developments on the chirality of medicines, it is necessary to identify how these practices affect consumption trends in the pharmaceutical market and the resulting financial burden. This study aimed to analyse the chirality status of the most commonly consumed drugs in Turkey and their impact on costs.

## Material and Method

This study evaluated the chirality and chiral switch status of the most commonly used drugs in Turkey, along with their impact on consumption and costs. The study was initiated following the approval of İstanbul Medipol University Non-Interventional Clinical Studies Ethics Committee (approval number: 565, approval date: 23.06.2022).

The study utilized nationwide pharmaceutical sales data for 2021 at the wholesale level (i.e., sale from pharmaceutical warehouses to community pharmacies), obtained from the Turkey office of IQVIA (14). The 200 active substances with the highest number of units sold as single-ingredient preparations throughout the year were evaluated. Among these, inorganic substances, proteins, polymers, herbal products, vaccines, epimers, and products whose chirality status could not be evaluated (n=26) were excluded. The data regarding cefuroxime and its prodrug, cefuroxime axetil, which were listed as separate drugs in the dataset, have been combined for evaluation as a single active substance. After these steps, the remaining 173 active substances were included in the study (Figure 1).

The active substances were assigned into one of the three categories according to their chirality status: “achiral”, “chiral mixture” or “pure enantiomer”. The chirality status of the drugs were determined using the information in the US National Center for Advancing Translational Sciences (NCATS) Inxight Drugs database on 1-15 September 2022 (15). Of these active substances, the total number of single-ingredient preparations registered in the Turkish Medicines and Medical Devices Agency (TMMDA) database during the same timeframe were identified. Additionally, the distribution of the number of units (i.e., boxes) sold and their costs was analysed by chirality status of the active substances (16). The cost per unit (CPU) values of the active substances, based on their wholesale price, were calculated using the average US Dollar ($) exchange rate for the year 2021 (17).

The distribution of the number and CPU of active substances by chirality status, both overall and stratified at the first level of the Anatomical Therapeutic Chemical classification (ATC-1) by World Health Organization (WHO) were assessed (18). In addition, these assessments were also specifically made for certain widely used drug groups (acid suppressants, antidiabetics, antihypertensives, dermatological preparations, systemic antibiotics, analgesics [analgesic/anti-inflammatory/antirheumatics], antidepressants and systemic antihistamines). The consumption levels of the drugs were standardized according to “Defined Daily Dose” (DDD) parameter established by the WHO, in order to minimize the effect of differences in package contents on these results. For this purpose, the consumption and DDD values per unit were determined according to the chirality status of the active substances with an assigned DDD value in milligrams (89.0%). Among the drugs included in the study, the chirality status of the top 20 best-selling drugs and their costs were also analysed in more detail at ATC-5 level (18).

In order to examine the implications of chiral switch on drug expenses; sales volumes, costs, the number of single-ingredient preparations registered in TMMDA database, and the approval years of the first-registered preparations were compared (16). This analysis included chiral mixtures known to undergo chiral switching (n=8) and pure enantiomers produced by chiral switching (n=5) against their respective chiral counterparts. The active substances constituting the chiral pairs were categorized based on the list of the drugs under the ATC/DDD system (19). Of the 13 drugs analysed, six were included in the study alongside their chiral counterparts, while the remaining seven were included solely as chiral mixtures or pure enantiomers. Specifically, for this analysis, the chiral counterparts of these seven active substances were also included (Figure 1). In addition, a subgroup comparison was conducted for oral solid formulations of chiral drug pairs with assigned DDD

values to evaluate standardized consumption levels along with CPU. In order to calculate the consumed DDD levels for oral solid formulations, the number of units sold was multiplied by the strength and the number of tablets per pack of the preparations, and then divided by the DDD value assigned to the active substance.

Statistical analyses were performed using IBM SPSS 29.0 and GraphPad Prism 10.0 software. Data were expressed as numbers and percentages for categorical variables and mean ± standard deviation or median with interquartile range (IQR) for continuous variables. The Shapiro-Wilk test was used to determine whether the data was normally distributed. Depending on the presence of normal distribution, either Student's t-test or Mann-Whitney U test was used to compare continuous variables between two groups. Kruskal-Wallis test was employed for comparing more than two groups as the relevant data were not normally distributed. Type 1 error values below 0.05 were considered statistically significant.

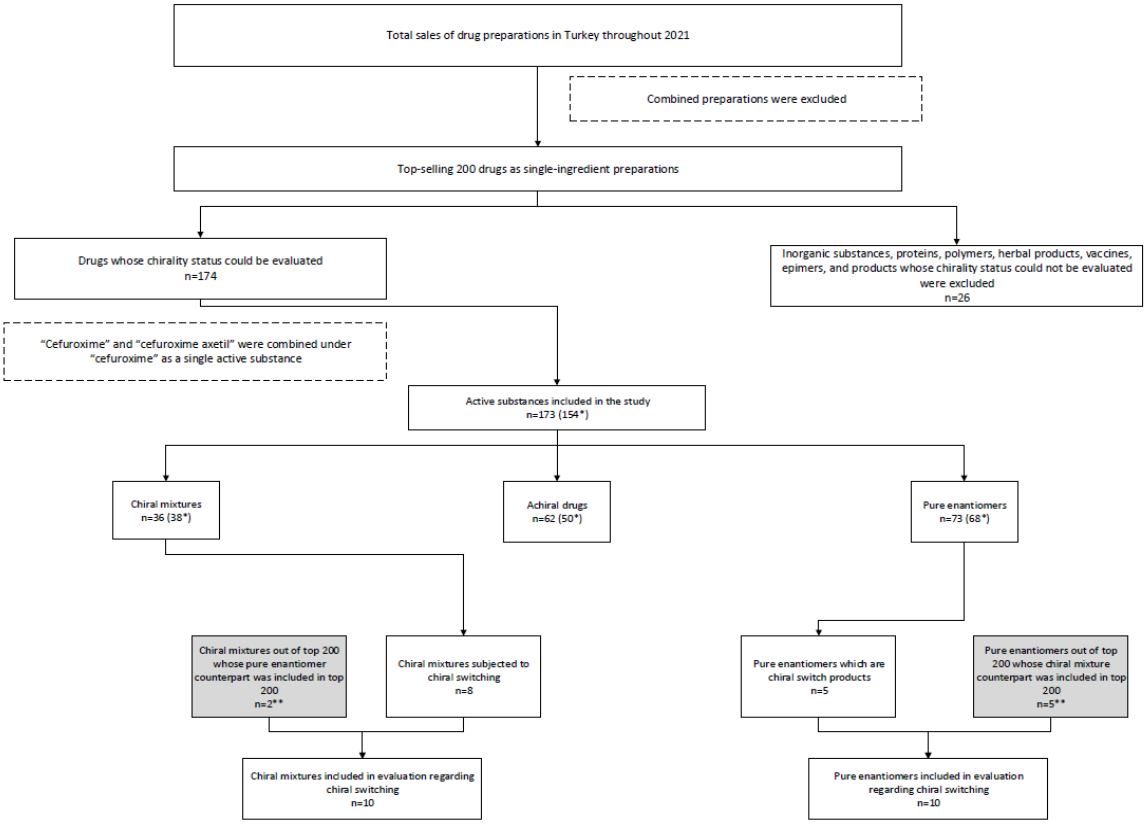



**Figure 1.** Flowchart of the study.
*: active substances with assigned DDD values. **: active substances not among top-selling 200 drugs but included in the study only for chiral switch analyses

## Results

Of the 173 active substances examined in the study, 35.8% (n=62) were achiral, 22.0% (n=38) were chiral mixtures, and 42.2% (n=73) were pure enantiomers. The total number of units sold for all the active substances was 1,259,296,936, with achiral drugs comprising 37.9% of them. The total consumption of drugs with a defined DDD value was 29,163,894,917.9 DDD, with pure enantiomers accounting for 56.7% of this consumption. While the total cost of all drugs examined was $2.09 billion, pure enantiomers accounted for 46.4% of the cost, and chiral mixtures for 22.0% (Figure 2).

The means of CPU values of pure enantiomers ($2.8±3.5; median: 1.5, IQR: 1.0-2.3), achiral drugs ($2.3±2.5; median: 1.5, IQR: 1.1-1.9), and chiral mixtures ($1.7±0.9; median: 1.7, IQR: 1.2-2.4) were statistically similar ($p>0.05$ in pairwise comparisons). In seven of the 13 ATC-1 classes examined, pure enantiomers produced the highest CPU. The ATC-1 class in which pure enantiomers yielded the highest CPU was "S-Sensory organs". The greatest CPU difference among the chiral categories was observed in "C-Cardiovascular system" where achiral drugs were more expensive than pure enantiomers. In "P-Antiparasitic products" class, both achiral drugs and chiral mixtures were found to be more expensive than pure enantiomers (Table 1).

The top 20 largest-selling pharmaceuticals accounted for 46.5% of the total number of units

sold and 29.7% of the total cost. Of the units sold, 26.5% were achiral drugs, 33.0% were mixtures, and 40.5% were pure enantiomers. In terms of total cost, achiral drugs accounted for 40.3%, mixtures for 28.2%, and pure enantiomers for 31.5%. Based on the number of packages sold, the most commonly sold drug was paracetamol, constituting 7.1% of all pharmaceuticals examined. The drug generating the highest cost was diclofenac, accounting for 3.1% of the total cost of all drugs examined. Both the top-selling and the highest-costing drugs were achiral (Supplementary Table 1). When the examined pharmaceuticals were categorized into widely-used pharmacological drug groups, it was observed that achiral drugs were most prevalent in analgesics (60.0%), chiral mixtures in antihypertensives (62.5%), and pure enantiomers predominantly in systemic antibiotics (73.9%). In four of these eight groups, pure enantiomers generated the highest CPU, whereas in three groups, chiral mixtures generated the highest CPU. In antidiabetics, which had the highest CPU ($4.1), pure enantiomers were the chiral category with the highest cost ($8.3) (Table 2).

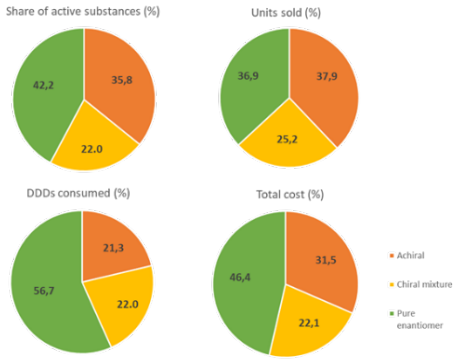



**Figure 2.** Distribution, sold units, consumed defined daily doses (DDDs), and total costs of top-selling active substances in Turkey by chirality status.
**Only active substances with known DDD values were included (n=154).*

**Table 1.** Distribution and cost per unit of top-selling active substances in Turkey by chirality status at the first level of Anatomical Therapeutic Chemical (ATC) classification.

| | Total | | | Achiral | | | Chiral mixtures | | | Pure enantiomers | | | Delta -1** | Delt a-2*** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ATC-1 classes | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | | |
| A – Alimentary tract and metabolism | 28 | 100.0 (16.2) | 2.1 | 9 | 32.1 (14.5) | 1.7 | 7 | 25.0 (18.4) | 1.6 | 12 | 42.9 (16.4) | 2.7 | +1.1 | +1.0 |
| N – Nervous system | 24 | 100.0 (13.9) | 1.7 | 13 | 54.2 (21.0) | 1.4 | 5 | 20.8 (13.2) | 1.8 | 6 | 25.0 (8.2) | 2.6 | +0.8 | +1.2 |
| C – Cardiovascular system | 22 | 100.0 (12.7) | 1.7 | 4 | 18.2 (6.5) | 2.3 | 10 | 45.5 (26.3) | 1.6 | 8 | 36.3 (11.0) | 1.6 | 0 | -0.7 |
| J – Antiinfectives for systemic use | 20 | 100.0 (11.6) | 1.4 | 5 | 25.0 (8.1) | 1.3 | 1 | 5.0 (2.6) | 1.6 | 14 | 70.0 (19.2) | 1.4 | -0.2 | +0.1 |
| R – Respiratory system | 21 | 100.0 (12.1) | 1.5 | 9 | 42.9 (14.5) | 1.5 | 5 | 23.8 (13.2) | 1.3 | 7 | 33.3 (9.6) | 1.8 | +0.5 | +0.3 |
| M – Musculo-skeletal system | 17 | 100.0 (9.8) | 1.0 | 8 | 47.1 (12.9) | 1.0 | 5 | 29.4 (13.2) | 1.1 | 4 | 23.5 (5.5) | 1.1 | 0 | +0.1 |
| D - Dermatologicals | 16 | 100.0 (9.3) | 1.7 | 9 | 56.2 (14.5) | 1.9 | 2 | 12.5 (5.3) | 1.4 | 5 | 31.3 (6.8) | 1.5 | +0.1 | -0.4 |
| B – Blood and blood forming organs | 7 | 100.0 (4.0) | 1.6 | 2 | 28.6 (3.2) | 0.9 | 1 | 14.3 (2.6) | 1.1 | 4 | 57.1 (5.5) | 3.5 | +2.4 | +2.6 |
| G – Genitourinary system and sex hormones | 7 | 100.0 (4.0) | 4.5 | 1 | 14.3 (1.6) | 4.5 | 1 | 14.3 (2.6) | 1.4 | 5 | 71.4 (6.8) | 5.1 | +3.7 | +0.6 |
| H – Systemic hormonal preparations | 5 | 100.0 (2.9) | 1.1 | - | - | - | - | - | - | 5 | 100.0 (6.8) | 1.1 | NA | NA |
| S – Sensory organs | 4 | 100.0 (2.3) | 7.3 | 2 | 50.0 (3.2) | 3.4 | - | - | - | 2 | 50.0 (2.7) | 11.4 | NA | +4.1 |
| L – Antineoplastic and immunomodulating agents | 1 | 100.0 (0.6) | 3.8 | - | - | - | - | - | - | 1 | 100.0 (1.4) | 3.8 | +3.8 | 0 |
| P – Antiparasitic products | 1 | 100.0 (0.6) | 1.9 | - | - | - | 1 | 100.0 (2.6) | 1.9 | - | - | - | -1.9 | -1.9 |
| Total | 173 | 100.0 (100.0) | 1.7 | 62 | 100.0 (35.8) | 1.4 | 38 | 100.0 (22.0) | 1.5 | 73 | 100.0 (42.2) | 2.1 | +0.6 | +0.4 |

*: Column percentage. **: Cost per unit difference between pure enantiomers and chiral mixtures. ***: Cost per unit difference between pure enantiomers and achiral drugs.

When the DDD values of achiral drugs, chiral mixtures, and pure enantiomer drugs were examined, the percentage distribution of these values was found to be 21.3%, 22.0%, and 56.7%, respectively (Figure 2).

Among the active substances examined, a total of 13 (7.5%) were involved in chiral switching process, including 8 chiral mixtures (amlodipine, cetirizine, citalopram, ibuprofen, ketoprofen, lansoprazole, rabeprazole, and salbutamol) and 5 pure enantiomers (dexketoprofen, esomeprazole, escitalopram,

levocetirizine, and levodropropizine). These pharmaceuticals accounted for 10.1% of the total number of units sold and 10.5% of the total cost. There were six chiral drug pairs in which both the chiral mixture and the pure enantiomer forms were available on the market. Among the chiral drug pairs that involved in switching, there were three gastric acid suppressants, two analgesics, one antidepressant, one antihypertensive, one beta-2 agonist, one antihistamine, and one antitussive (Figure 3). Among the drugs that underwent chiral switching, the pure enantiomer preparations of three (dexibuprofen, S-amlodipine, dexlansoprazole) and the preparation of dropropizine, the form before chiral switching of levodropropizine, were registered in the TMMDA database; however, the 2021 IQVIA sales data did not record any sales data for these drugs.

**Table 2.** Distribution and cost per unit of selected drug groups among top-selling active substances in Turkey, categorized by chirality status.

| | **Total** | | | **Achiral** | | | **Chiral mixtures** | | | **Pure enantiomers** | | | **Delta -1**** | **Delta-2***** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug groups | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | n | % (%)* | Cost per unit (US $) | | |
| Systemic antibiotics | 18 | 100.0 (10.4) | 1.3 | 3 | 21.1 (1.6) | 1.1 | 1 | 5.2 (2.6) | 1.6 | 14 | 73.9 (19.2) | 1.4 | -0.2 | +0.3 |
| Drugs used to treat hypertension (C03-C09) | 16 | 100.0 (9.2) | 1.6 | 2 | 12.5 (3.2) | 1.4 | 10 | 62.5 (26.2) | 1.6 | 4 | 25.0 (5.5) | 1.3 | -0.3 | -0.1 |
| Dermatologicals (D) | 16 | 100.0 (9.2) | 1.7 | 9 | 53.3 (12.7) | 2.1 | 2 | 13.4 (5.3) | 1.4 | 5 | 33.3 (6.8) | 1.5 | +0.1 | -0.6 |
| Analgesics/Anti-inflammatories / Antirheumatics | 15 | 100.0 (8.7) | 0.9 | 9 | 60.0 (14.3) | 0.8 | 4 | 26.7 (10.5) | 1.0 | 2 | 13.3 (2.7) | 1.1 | +0.1 | +0.3 |
| Drugs used to treat depression (N06) | 10 | 100.0 (5.8) | 1.8 | 3 | 20.0 (3.2) | 1.4 | 4 | 40.0 (10.5) | 2.0 | 4 | 40.0 (5.5) | 1.9 | -0.1 | +0.5 |
| Drugs used in diabetes (A10) | 8 | 100.0 (4.6) | 4.1 | 2 | 25.0 (3.2) | 1.7 | 2 | 25.0 (5.5) | 2.3 | 4 | 50.0 (5.5) | 8.3 | +6.0 | +6.6 |
| Antihistamines for systemic use | 8 | 100.0 (4.6) | 1.5 | 4 | 50.0 (6.3) | 1.5 | 3 | 37.5 (7.9) | 1.3 | 1 | 12.5 (1.4) | 1.8 | +0.5 | +0.3 |
| Drugs for acid related disorders (A02) | 7 | 100.0 (4.1) | 1.3 | 2 | 28.6 (3.2) | 1.2 | 3 | 42.8 (7.9) | 1.2 | 2 | 28.6 (4.0) | 1.3 | +0.1 | +0.1 |
| Others | 75 | 100.0 (43.4) | 2.1 | 19 | 39.5 (47.6) | 2.9 | 9 | 11.8 (23.7) | 1.5 | 37 | 48.7 (50.7) | 2.4 | +0.9 | -0.5 |
| Total | 173 | 100.0 (100.0) | 1.7 | 63 | 36.2 (100.0) | 1.4 | 38 | 21.8 (100.0) | 1.5 | 73 | 42.0 (100.0) | 2.1 | +0.6 | +0.7 |

**: Column percentage. **: Cost per unit difference between pure enantiomers and chiral mixtures. ***: Cost per unit difference between pure enantiomers and achiral drugs.*

Although the pure enantiomer formulations of three drugs that are chiral switch products (dexibuprofen, S-amlodipine, and dexlansoprazole) and the pre-chiral switch form of levodropropizine (dropropizine) were listed in the TMMDA database, no sales data for these drugs were recorded in the 2021 IQVIA sales data. Among the remaining six chiral drug pairs, it was observed that the consumption of rabeprazole, cetirizine, and salbutamol, both in terms of the number of units sold and the cost, was higher than that of the pure enantiomers of these drugs. In contrast, the opposite was observed for the other three chiral pairs (i.e., escitalopram, esomeprazole, and dexketoprofen were predominant) (Figure 3). The time periods between the approval of the first preparations of chiral mixtures and their pure enantiomer counterparts varied, ranging from 2 to 37 years. For the chiral mixtures that are predominant in terms of sales and costs, the average time to switch to pure enantiomers and the number of preparations were 20.0±14.7 years and 28.7±11.0 preparations, respectively, while for predominant pure enantiomers, these averages were 17.7±14.6 years and 70.7±36.6 preparations (Table 3).

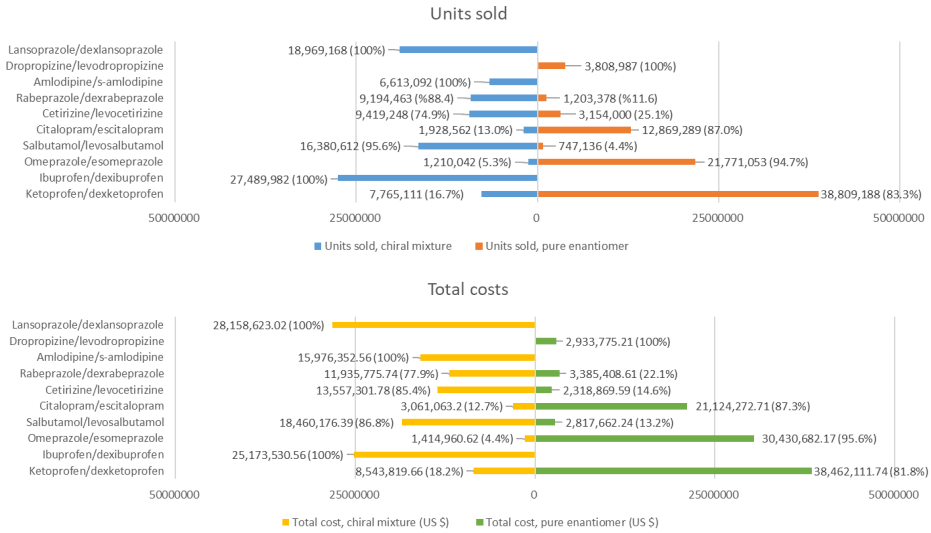



**Figure 3.** Units sold and total costs of active substance pairs subjected to chiral switching.

For chiral drug pairs with both chiral mixtures and pure enantiomer formulations were available in Turkey, the average CPU of chiral mixtures ($1.4±0.4) was similar to that of pure enantiomers ($1.7±1.2 USD), (p>0.05). In half of these chiral drug pairs, the CPU was higher for chiral mixture, while in the other half, it was higher for pure enantiomer. There was no statistically significant difference in the average number of preparations between chiral mixtures and pure enantiomers (45.7±30.7 vs. 36.7±39.1, p>0.05) (Table 3).

When the oral solid formulations of chiral drug pairs were compared, an increase in consumption after chiral switching was observed in the pure enantiomers of all pharmaceuticals except levocetirizine, with the highest increase seen in esomeprazole (approximately 24-fold) (Table 4).

The distribution of top-selling drugs by chirality status was found to be similar to that of the recent global drug market, especially with regard to pure enantiomers (3). Previous studies have revealed that the market share of pure enantiomer drugs was around one-quarter in the 1990s and increased to three-eighths by 2005 (2,20). The 42.2% share in our study, along with the 56.7% consumption by DDD amount for pure enantiomers, indicates a growing trend in the market share of these formulations. A previous study listed various factors influencing the high sales of a drug, including order of entry and quality (21). It can be considered that the leadership of pure enantiomers in sales figures in our study is not solely related to chirality. In fact, the majority of the 73 pure enantiomers among the most consumed drugs were originally introduced to the market in their current form. This might be related to the potential influence of recommendations and trends for producing new drugs as pure enantiomers on the most frequently preferred drugs in the market. In accordance with recommendations from various health authorities, particularly the FDA, to develop new pharmaceuticals as pure enantiomers whenever possible, a study published in 2000 predicted that consumption of pure enantiomers could increase by as much as 8% annually (22). The predominance of pure enantiomers among new pharmaceuticals introduced in subsequent years may be a contributing factor to this increase (20,23).

**Table 3.** Cost per unit values and number of single-ingredient preparations approved in Turkey for the drug pairs subjected to chiral switching.

| Chiral mixture (Year**) | Cost per unit (US $) | No of approved preparations (%)* | Pure enantiomer (Year**) | Cost per unit (US $) | No of approved preparations (%)* | Delta 1*** | Delta 2**** |
|---|---|---|---|---|---|---|---|
| Ketoprofen (1975) | 1.10 | 24 (25.3) | Dexketoprofen (2006) | 0.99 | 73 (74.7) | -0.11 | 31 |
| Ibuprofen (1973) | 0.92 | 100 (98.0) | *Dexibuprofen* (2009) | NA | 2 (2.0) | NA | 36 |
| *Omeprazole* (1991) | 1.17 | 23 (41.1) | Esomeprazole (2011) | 1.40 | 33 (58.9) | 0.23 | 20 |
| Salbutamol (1975) | 1.13 | 36 (97.3) | *Levosalbutamol* (2012) | 3.77 | 1 (2.7) | 2.64 | 37 |
| Citalopram (2003) | 1.59 | 38 (26.4) | Escitalopram (2005) | 1.64 | 106 (73.6) | 0.05 | 2 |
| Cetirizine (1996) | 1.44 | 34 (63.0) | Levocetirizine (2008) | 0.74 | 20 (37.0) | -0.70 | 12 |
| Rabeprazole (2002) | 1.30 | 16 (94.1) | *Dexrabeprazole* (2013) | 2.81 | 1 (5.9) | 1.51 | 11 |
| Amlodipine (1991) | 2.42 | 95 (97.9) | *S-amlodipine* (2011) | NA | 2 (2.1) | NA | 20 |
| *Dropropizine* (-) | NA | NA | Levodropropizine (2000) | 0.77 | 23 (100.0) | NA | NA |
| Lansoprazole (1996) | 1.48 | 45 (91.8) | *Dexlansoprazole* (2012) | NA | 4 (8.2) | NA | 16 |

*Active substances not among top-selling 200 drugs were italicized.* * Percentage among all preparations of the chiral drug pair (i.e., of both chiral mixture and pure enantiomer). ** Year of approval for the first approved preparation. *** Difference between cost per unit values of chiral mixture and pure enantiomer of the chiral drug pair. **** Difference between the years of approval for the first approved preparations of chiral mixture and pure enantiomer of the chiral drug pair.

## Discussion

This study, which investigated the chiral characteristics of the 200 most frequently used drugs in Turkey, revealed that pure enantiomers hold the highest share, consumption level, and cost among the 173 active substances where stereoisomerism could be examined. The fact that nearly one out of every two pharmaceuticals is a pure enantiomer, coupled with similar findings when this descriptive analysis was narrowed to the top 20 most commonly used pharmaceuticals, suggests that these drugs are widely preferred in clinical practice.

In our study, no significant difference was found among the three chirality categories in terms of CPU. Considering that pure enantiomers are generally more expensive than chiral mixtures (24,25), this unexpected result might be influenced by factors such as local pricing of medical formulations, the scope of drug-specific promotional activities, and the number of generic drugs. The high number of generics for commonly used active substances might have obscured the CPU differences between drugs. Indeed, in our study, for commonly used drugs with chiral pairs, 24 and 73 preparations were identified for ketoprofen and dexketoprofen, 23 and 33 for omeprazole and esomeprazole, and 38 and 106 for citalopram and escitalopram, respectively. This situation, combined with the strict drug price control policy in Turkey (26), may have contributed to the fact that the higher costs of pure enantiomers reported in the literature were not reflected in our study. Another reason could be the optimization of the production processes for pure enantiomers over time. While more complex steps were required to purify chiral mixtures when synthetic production of pure enantiomers was still new, the innovation and increasing optimization of new purification methods such as crystallization, chromatography, membrane-based chiral separation, and biochemical reactions may have helped close the cost gap between chiral mixtures and pure enantiomers (27,28).

**Table 4.** Distribution of units sold, consumption, and cost figures of the drug pairs subjected to chiral switching.

| Active substance (DDD*)<br>Total units sold (%)<br>Total consumed DDD (%) | Chiral switch | Strength | Tablets per pack | Units sold (%) | Consumed DDD (%) | Cost | |
|---|---|---|---|---|---|---|---|
| | | | | | | Per unit | Per DDD |
| ***Cetirizine (10)*** | Before | 10 | 10 | 1,312,248 (20.1) | 13,122,480.0 (11.2) | 0.9 | 0.09 |
| 6,519,852 (100) | | 10 | 20 | 5,207,604 (79.9) | 104,152,080.0 (88.8) | 1.7 | 0.08 |
| 117,274,560.0 (100) | | | | | | | |
| ***Levocetirizine (5)*** | After | 5 | 20 | 3,121,426 (99.0) | 62,428,520.0 (98.0) | 0.9 | 0.04 |
| 3,154,000 (100) | | 5 | 40 | 32,574 (1.0) | 1,302,960.0 (2.0) | 1.6 | 0.03 |
| 63,731,480.0 (100) | | | | | | | |
| ***Citalopram (20)*** | Before | 20 | 28 | 1,576,924 (81.8) | 44,153,872.0 (68.5) | 1.4 | 0.05 |
| 1,928,562 (100) | | 20 | 56 | 21,864 (1.1) | 1,224,384.0 (1.9) | 2.3 | 0.04 |
| 64,485,176.0 (100) | | 40 | 28 | 318,353 (16.5) | 17,827,768.0 (27.6) | 2.3 | 0.04 |
| | | 40 | 56 | 11,421 (0.6) | 1,279,152.0 (2.0) | 1.0 | 0.01 |
| ***Escitalopram (10)*** | After | 5 | 28 | 897,803 (7.1) | 12,569,242.0 (4.8) | 1.3 | 0.10 |
| 12,713,071 (100) | | 10 | 28 | 7,430,657 (58.4) | 7,430,657.0 (2.9) | 1.5 | 0.05 |
| 260,303,347.0 (100) | | 10 | 56 | 175,852 (1.4) | 9,847,712.0 (3.8) | 2.9 | 0.05 |
| | | 10 | 84 | 28,136 (0.2) | 2,363,424.0 (0.9) | 4.5 | 0.05 |
| | | 15 | 28 | 907,780 (7.1) | 38,126,760.0 (14.6) | 3.1 | 0.07 |
| | | 20 | 28 | 3,188,584 (25.1) | 178,560,704.0 (68.6) | 1.5 | 0.03 |
| | | 20 | 56 | 75,474 (0.6) | 9,928,968.0 (3.8) | 3.4 | 0.03 |
| | | 20 | 84 | 8,785 (0.1) | 1,475,880.0 (0.6) | 5.6 | 0.03 |
| ***Omeprazole (30)*** | Before | 20 | 14 | 212,351 (17.6) | 2,972,914.0 (9.6) | 0.7 | 0.11 |
| 1,209,852 (100) | | 20 | 28 | 997,501 (82.4) | 27,930,028.0 (90.4) | 1.3 | 0.11 |
| 30,902,942.0 (100) | | | | | | | |
| ***Esomeprazole (30)*** | After | 20 | 14 | 321,279 (1.5) | 2,998,604.0 (0.4) | 0.6 | 0.11 |
| 2,177,089 (100) | | 28 | 28 | 1,086,710 (5.0) | 20,285,253.0 (2.6) | 1.3 | 0.11 |
| 776,949,291.0 (100) | | 40 | 14 | 350,870 (1.6) | 6,549,573.0 (0.9) | 0.7 | 0.11 |
| | | 40 | 28 | 20,012,032 (91.9) | 747,115,861.0 (96.2) | 1.4 | 0.11 |
| ***Ketoprofen (150)*** | Before | 100 | 20 | 1,515,025 (42.0) | 20,200,333.3 (49.2) | 1.3 | 0.09 |
| 3,603,148 (100) | | 150 | 10 | 2,088,123 (58.0) | 20,881,230.0 (50.8) | 1.3 | 0.13 |
| 41,081,563.3 (100) | | | | | | | |
| ***Dexketoprofen (75)*** | After | 25 | 20 | 33,146,478 (84.4) | 22,149,832.0 (71.8) | 0.9 | 0.13 |
| 37,489,757 (100) | | 50 | 30 | 4,343,279 (11.6) | 86,865,580.0 (28.2) | 1.8 | 0.09 |
| 109,015,412.0 (100) | | | | | | | |

* DDD value assigned by the World Health Organization.

The reflection of chiral switch process to the pharmaceutical market emerged as another important finding in our study. However, the debate about the practical benefits of chiral switching for commonly used drugs that are currently available as chiral mixtures is still ongoing (24). The fact that four out of the ten chiral drug pairs included in the study—both their chiral mixtures and pure enantiomers—are among the top-selling drugs nationwide suggests that the practical benefits of chiral switch products are not adequately reflected in the preferences of physicians and patients. As a previous study indicated, this may be due to factors such as competitive pricing and various similar drug marketing strategies (29). When an alternative to well-established drugs enters the market, even if it offers potential tangible advantages,

the brand effect created by general marketing, the brand value generated by the commercial name, and the longstanding preferences of physicians and patients pose substantial barriers to significant changes. This might account for why pure enantiomers developed through chiral switching do not completely replace older chiral mixtures in the Turkish market. Our study showed that except omeprazole, the market share of the top-selling chiral mixtures subjected to chiral switching did not dramatically decrease to the extent that they would fall out of the top 200 drugs. Indeed, three chiral drug pairs were able to remain among the top 200 most consumed drugs, both as chiral mixture and pure enantiomer. It might be argued that commercial name and brand equity, along with the familiarity of the active substance, have facilitated the establishment of these drugs' presence in the market. Consequently, as new versions of drugs that have undergone chiral switching emerge, their established brand recognition may help them maintain market presence despite competition from potentially superior alternatives. It is expected that the development of new drugs undergoing chiral switching will benefit from these experiences. On the other hand, the extent to which this observation made in frequently used drugs applies to less commonly used ones might be the subject of future research.

The cost increase in drugs that have undergone chiral switching becomes even more pronounced when considering factors such as their classification as new drugs, protection from generic competition, and the clinical research and licensing procedures involved (30). For these reasons, while an increase in costs might be expected after chiral switching, our study found no statistically significant difference in cost per DDD or CPU. It should be kept in mind that our analysis of chiral switching was conducted with the most frequently consumed drugs in the country. Given the large market share of such frequently consumed drugs, it can be considered that the cost increase associated with their status as new drugs has been cushioned by marketing strategies and even partially reversed to maintain financial competition. From this perspective, our study does not support the claim that products of chiral switching generate higher costs compared to their chiral mixtures. The observed situation in frequently used drugs and its possible relationship with marketing strategies could be a subject for future studies to determine whether this is applicable to less frequently used drugs undergoing chiral switching.

It was noteworthy that pure enantiomers predominated in 6 out of 13 ATC-1 classes, with "H-Systemic hormonal preparations" and "L-Antineoplastics and immunomodulating agents" consisting entirely of pure enantiomers. This predominance might be potentially related to these groups containing a relatively higher number of newer drugs. Indeed, it is known that a significant portion of new drug research is primarily focused on treatments for cancer and endocrine-related diseases (31-33). Our study also revealed that the ATC-1 class with the highest CPU produced by pure enantiomers is "S-Sensory organs". A similar finding in a previous study conducted in Turkey was attributed to the small number of generic drugs in this class (34). The high cost of pure enantiomers in sensory organ drugs, as revealed in this study, might be associated with the higher production, research, and development costs of these drugs, as well as the limited number of generic competitors in the market.

The findings of our study should be interpreted in light of the existing limitations. Firstly, drugs in Turkey are subject to price control policies. It should be considered that in cost comparisons of drug groups, differences based on chemical characteristics may not directly reflect the actual production costs. Additionally, the impact of regulations related to price control and drug marketing strategies on market dynamics was not evaluated in this study. Another limitation of our study was the exclusion of combination products. The decision to exclude was due to the complexity and difficulty of conducting analyses when the active substances involved belong to different chiral groups, making cost calculations more challenging.

## Conclusion

This study demonstrated that pure enantiomers hold a significant position in the Turkish pharmaceutical market. The cost similarity between commonly used pure enantiomers and chiral mixtures, observed both in overall drugs and chiral switch products, indicates that pure enantiomers may continue to be increasingly preferred in the market in the future. Although the theoretical advantages of these pharmaceuticals in terms of efficacy and safety suggest a cost-benefit balance in favour of pure enantiomers, it should be noted that this study was conducted on the most commonly utilized pharmaceuticals. These findings need to be validated by future studies that encompass all drugs on the market and consider the social, economic, legal, and geographical factors influencing drug use.

## Acknowledgements

We thank IQVIA Turkey for their contributions in data collection.

## Conflict of interest statement

The authors declare that they have no conflict of interest.

**Ethics Committee Approval:** The study was commenced following the approval of İstanbul Medipol University Non-Interventional Clinical

Studies Ethics Committee (approval number: 565, approval date: 23.06.2022).

**Funding:** This study did not receive any specific grant.

## References

1. McConathy J, Owens MJ. Stereochemistry in Drug Action. Prim Care Companion J Clin Psychiatry. 2003;5(2):70-3.
2. Hancu G, Modroiu A. Chiral Switch: Between Therapeutical Benefit and Marketing Strategy. Pharmaceuticals (Basel). 2022;15(2):240.
3. Aydin V, Bahar A, Vizdiklar C, et al. The association of chiral characteristic with drug withdrawal due to safety: A comparative analysis. Br J Clin Pharmacol. 2023;89(1):290-8.
4. Lin GQ, Zhang JG, Cheng JF. Overview of Chirality and Chiral Drugs. In: Lin GQ, Zhang JG, Cheng JF, eds. Chiral Drugs: Chemistry and Biological Action. 1st ed. John Wiley & Sons, Inc, pp 3-28, 2011.
5. Agranat I, Wainschtein SR, Zusman EZ. The predicated demise of racemic new molecular entities is an exaggeration. Nat Rev Drug Discov. 2012;11(12):972-3.
6. Simoens S, De Bruyn K, Bogaert M, et al. Pharmaceutical policy regarding generic drugs in Belgium. Pharmacoeconomics. 2005;23(8):755-66.
7. Hutt AJ. The development of single-isomer molecules: why and how. CNS Spectr. 2002;7(S1):14-22.
8. Food and Drug Administration (FDA). FDA's policy statement for the development of new stereoisomeric drugs. Chirality. 1992;4(5):338-40.
9. Agranat I, Caner H. Intellectual property and chirality of drugs. Drug Discov Today. 1999;4(7):313-21.
10. Gellad WF, Choi P, Mizah M, et al. Assessing the chiral switch: approval and use of single-enantiomer drugs, 2001 to 2011. Am J Manag Care. 2014;20(3):e90-7.
11. Carlson SC. Commentary: the case against market exclusivity for purified enantiomers of approved drugs. Yale Symp L & Tech. 1999;6.
12. Pifferi G, Perucca E. The cost benefit ratio of enantiomeric drugs. Eur J Drug Metab Pharmacokinet. 1995;20(1):15-25.
13. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis. 2006;24(1-2):11-46.
14. Kirmizi NI, Aydin V, Akici A. Utilization trend of gastric acid-suppressing agents in relation to analgesics. Pharmacoepidemiol Drug Saf. 2022;31(3):314-21.
15. Siramshetty VB, Grishagin I, Nguyễn ĐT, et al. NCATS Inxight Drugs: a comprehensive and curated portal for translational research. Nucleic Acids Res. 2022;50(D1):D1307-16.
16. KÜB/KT Listesi. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). Access date: 27 May 2024. https://www.titck.gov.tr/kubkt
17. EVDS Anasayfa. Türkiye Cumhuriyeti Merkez Bankası (TCMB). Access date: 30 May 2024. https://evds2.tcmb.gov.tr/
18. ATC Classification. World Health Organization (WHO). Access date: 12 Dec 2024 https://www.who.int/tools/atc-ddd-toolkit/atc-classification
19. ATC/DDD Index. World Health Organization (WHO). Access date: 27 May 2024, https://atcddd.fhi.no/atc_ddd_index/
20. Single-Enantiomer Drugs Poised for Further Market Growth. Pharmaceutical Technology. Access date: 6 June 2024, https://www.pharmtech.com/view/single-enantiomer-drugs-poised-further-market-growth
21. Fischer M, Leeflang PSH, Verhoef PC. Drivers of peak sales for pharmaceutical brands. Quant Mark Econ. 2010;8(4),429-60.
22. Stinson SC. Chiral Drugs. Chem. Eng. News. 2000;78(43),55-78.
23. McVicker RU, O'Boyle NM. Chirality of New Drug Approvals (2013-2022): Trends and Perspectives. J Med Chem. 2024;67(4):2305-20.
24. Long AS, Zhang AD, Meyer CE, et al. Evaluation of Trials Comparing Single-Enantiomer Drugs to Their Racemic Precursors: A Systematic Review. JAMA Netw Open. 2021;4(5):e215731.
25. Mansfield P, Henry D, Tonkin A. Single-enantiomer drugs: elegant science, disappointing effects. Clin Pharmacokinet. 2004;43(5):287-90.
26. 10 Temmuz 2015 Tarihli ve 29412 Sayılı Resmî Gazetede yayımlanan 2015/7752 Sayılı Beşeri Tıbbi Ürünlerin Fiyatlandırılmasına Dair Karar. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). Access date: 07 October 2024. https://www.titck.gov.tr/faaliyetalanlari/ilac/ilacta-fiyatlandirma#:~:text=E%C5%9F%20de%C4%9Fer%20%C3%BCr%C3%BCn%C3%BCn%20piyasa%20%C3%A7%C4%B1kmas%C4%B1,%80'ine%20kadar%20olabilir
27. Ciriani M, Oliveira RM, Afonso CA. Semi-continuous and continuous processes for enantiomeric separation. Green Chem. 2022;24(11),4328-62.
28. Kaspereit M, Swernath S, Kienle A. Evaluation of Competing Process Concepts for the Production of Pure Enantiomers. Org. Process Res. Dev. 2012;16(2),353-63.
29. Khoso I, Ahmed RR, Ahmed J. Pricing strategies in pharmaceutical marketing. Pharma Innovation. 2014;3(7):13-7.
30. Calcaterra A, D'Acquarica I. The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds. J Pharm Biomed Anal. 2018;147:323-40.
31. Brown DG, Wobst HJ. A Decade of FDA-Approved Drugs (2010-2019): Trends and Future Directions. J Med Chem. 2021;64(5):2312-38.
32. Dahlén AD, Dashi G, Maslov I, et al. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Front Pharmacol. 2022;12:807548.
33. Scott EC, Baines AC, Gong Y, et al. Trends in the approval of cancer therapies by the FDA in the twenty-first century. Nat Rev Drug Discov. 2023;22(8):625-40.
34. Tuna E, Yenilmez FB, Atikeler K, Kockaya G. Discount distribution analysis of original medicines which has no generics in Turkey. Value Health. 2015;18(7):A547.

*Doi: 10.47572/muskutd.1600240*

# An Investigation of TRIM36 Expression in Breast Cancer

## Meme Kanserinde TRIM36 Ekspresyonunun İncelenmesi

**Aycan CELIK[1], Sevim KARAKAS CELIK [2], Guldeniz KARADENIZ CAKMAK[3], Furuzan KOKTURK[4]**

[1]Zonguldak Bülent Ecevit University, Faculty of Science, Department of Molecular Biology and Genetics, Zonguldak
[2]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Medical Genetics, Zonguldak
[3]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of General Surgery, Faculty of Medicine Zonguldak
[4]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Biostatistics, Zonguldak

**Öz**

Meme kanseri, dünya genelinde en sık teşhis edilen kanser türü olup, kansere bağlı ölümler arasında ikinci sırada yer almaktadır. *TRIM36*'nın rolü prostat ve akciğer kanseri gibi bazı insan kanserlerinde araştırılmış olsa da bu proteinin işlevleri büyük ölçüde bilinmemektedir. Bu çalışmada, daha önce meme kanseri ile ilişkisi incelenmemiş olan *TRIM36*'nın ifade düzeyi ve meme kanseri patogeneziyle potansiyel ilişkisi analiz edilmiştir. Çalışma kapsamında, 45 meme kanseri hastasının normal ve tümör dokularından RNA izole edilmiştir. İzole edilen RNA'dan tamamlayıcı DNA (cDNA) sentezlenmiş ve *GAPDH* ile *TRIM36*'nın mRNA ifade düzeyleri qRT-PCR yöntemiyle ölçülmüştür. *TRIM36* ifadesinin meme dokularında gözlendiği tespit edilmiştir; ancak, *GAPDH*'ye normalize edilen *TRIM36* mRNA ifade düzeyleri açısından normal ve tümör dokuları arasında istatistiksel olarak anlamlı bir fark bulunamamıştır (p=0.731). Bu çalışma, meme kanseri dokularında *TRIM36* gen ifadesinin normal dokulardan farklı olmadığını öne sürse de sınırlı örneklem boyutu, *TRIM36* geni ile meme kanseri arasındaki ilişkinin daha kapsamlı çalışmalarla aydınlatılması gerekliliğini ortaya koymaktadır.

**Anahtar Kelimeler:** Gen Ekspresyonu, Meme Kanseri, *TRIM36*

**Abstract**

Breast cancer is the most frequently diagnosed cancer type worldwide and ranks 2nd among cancers that cause death. While the role of *TRIM36* has been investigated in certain human cancers, such as prostate and lung cancer, its functions remain largely unexplored. In this study, the expression level of *TRIM36*, whose role in breast cancer has not been previously examined, and its potential association with breast cancer pathogenesis were analyzed. RNA was isolated from normal and tumor tissues of 45 breast cancer patients. Complementary DNA (cDNA) was synthesized from the RNA, and mRNA expression levels of *GAPDH* and *TRIM36* were quantified using qRT-PCR. *TRIM36* expression was observed in breast tissues; however, no statistically significant difference was found in *TRIM36* mRNA expression levels, normalized to *GAPDH*, between normal and tumor tissues (p=0.731). Although this study suggests that *TRIM36* gene expression levels in breast cancer tissues do not differ from normal tissues, the limited sample size highlights the need for more comprehensive studies to elucidate the relationship between the *TRIM36* gene and breast cancer.

**Keywords:** Gene Expression, Breast Cancer, *TRIM36*

### Introduction

According to GLOBOCAN data for 2022, breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide, following lung cancer. It has the highest incidence among women (1). The heterogeneous nature of breast cancer, the incomplete understanding of tumorigenesis mechanisms, and the resulting limited availability of specific treatment options for most subtypes contribute to its high incidence and mortality rates. Consequently, the identification of biomarkers with strong diagnostic potential has gained significant attention for improving diagnostic and therapeutic strategies (2).

TRIM (tripartite motif) proteins are a family of E3 ubiquitin ligases comprising more than 70 members. (3,4). The TRIM protein family is defined by the presence of a RING domain, one or two B-box domains, a coiled-coil domain, and a variable C-terminal domain (5). Specific C-terminal domains of TRIM proteins include the COS domain, fibronectin type III repeat (FNIII), PRY domain, SPRY domain, acid-rich domain (ACID), filamin-type IG domain (FIL), NHL domain, PHD domain, bromodomain (BROMO), Meprin and TRAF-homology domain (MATH), ADP-ribosylation factor family domain (ARF), and transmembrane domain (TM) (6).

TRIM proteins are implicated in various diseases, including cancer, infectious diseases, developmental disorders, and neuropsychiatric conditions (7). Many TRIM proteins have been identified as playing dual roles in human cancers, functioning as both tumor suppressors and oncogenes. For instance, translocation of *TRIM19* is involved in acute promyelocytic leukemia (APL) (8). TRIM24 acts as an oncogenic transcription activator, promoting cell growth in prostate cancer cells and regulating proliferation in gastric cancer and hepatocellular carcinoma (9, 10). TRIM22 and TRIM24 target TP53 for degradation (11, 12), whereas TRIM13 overexpression stabilizes TP53, leading to apoptosis induction (13).

Additionally, *TRIM29* regulates the Wnt/β-catenin signaling pathway and acts as an oncogene in gastric cancer (14). In contrast, *TRIM8* is downregulated in glioma tissues and interacts with

| | ORCID No |
|---|---|
| Aycan CELIK | 0000-0003-0151-4081 |
| Sevim KARAKAS CELIK | 0000-0003-0505-7850 |
| Guldeniz KARADENIZ CAKMAK | 0000-0001-5802-4441 |
| Furuzan KOKTURK | 0000-0002-2580-7770 |

Başvuru Tarihi / Received: 12.12.2024
Kabul Tarihi / Accepted : 01.01.2025

Adres / Correspondence : Aycan CELIK
Zonguldak Bulent Ecevit University Faculty of Science, Department of Molecular Biology and Genetics, Zonguldak
e-posta / e-mail : aycan.celik@beun.edu.tr

activated STAT protein inhibitors, such as PIAS3, negatively regulating their activity (15, 16).

TRIM36 is an RBCC (RING, B-box, Coiled-Coil) protein that belongs to the C-I TRIM subfamily. It is encoded by a 55 kb genomic sequence comprising 10 exons, localized on chromosome 5q22.3. First identified in 2001 (5), *TRIM36* was cloned and characterized by Balint et al. in 2004. According to this study, the TRIM36 protein, consisting of 728 amino acids, includes a RING finger, two B-boxes, a coiled-coil domain, a fibronectin type III motif, and a C-terminal domain. Although TRIM36 contains a putative nuclear localization signal, it was exclusively detected in the cytoplasm (17).

*TRIM36* expression has been shown to be high in testis, prostate, and brain tissues, while being low in kidney, lung, and heart tissues. Despite being synthesized in many cell types, TRIM36 is notably absent in mitotic cells (17). Additionally, TRIM36 has been reported to be associated with homodimerization and microtubules (6). In a study conducted in 2009, TRIM36 overexpression was observed to decelerate the cell cycle and limit cell growth (18).

In this study, we investigated the expression levels of *TRIM36*, a gene that has not been previously studied in the context of breast cancer, and its potential association with breast cancer pathogenesis.

## Material and Method

*Tissue Samples*

Fine needle aspiration biopsies were collected from both tumor tissue and normal tissue (approximately 50 mg in weight) from the same individual, with normal tissue sampled at least 5 cm away from the tumor site. These samples were obtained from 45 breast cancer patients undergoing mastectomy at Zonguldak Bülent Ecevit University Faculty of Medicine, Department of General Surgery. The collected tissues were preserved in TRIzol™ reagent (Thermo Fisher Scientific) and stored at -80°C until RNA isolation. Written informed consent was obtained from all participants prior to their inclusion in the study. The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee on February 10, 2021 (Approval No. 2021/03).

*RNA Isolation*

RNA isolation from tissue samples was carried out using the PureLink™ RNA Mini Kit (Invitrogen, Thermo Fisher Scientific, Cat. No: 12183018A) according to the manufacturer's protocol. The concentration and purity of the isolated RNA samples were measured using a microplate and µDrop plate reader (Thermo Scientific Multiskan™ Sky, Cat. No: 51119600DP). Measurements were performed at 230, 260, and 280 nm wavelengths. RNase-free water provided in the PureLink™ RNA Mini Kit was used as a blank control. The isolated RNA samples were stored at -80°C until further use.

*cDNA Synthesis*

cDNA synthesis was carried out using the cDNA Synthesis Kit with RNase Inhibitor (High Capacity) (A.B.T.™). The reaction was prepared in a final volume of 20 µl according to the manufacturer's protocol, consisting of 1X Reaction Buffer, 2.5 mM dNTP mix, 50 µM random hexamers, 200 U/µl reverse transcriptase, 0.5 µl RNase inhibitor, 10 µl RNA, and 3.5 µl RNase-free water. The reaction mixture was incubated at 25°C for 10 minutes, 37°C for 120 minutes, and 85°C for 5 minutes. The resulting cDNA concentrations and purities were measured using the same microplate and µDrop plate reader (Thermo Scientific Multiskan™ Sky, Cat. No: 51119600DP) and stored at -80°C until further use.

*Real-Time PCR (qRT-PCR)*

Real-time PCR (qRT-PCR) experiments were conducted using the synthesized cDNAs and 2X qPCR SYBR-Green MasterMix (without ROX) (A.B.T.™) on a CFX96 Touch™ Real-Time PCR Detection System.

For the *GAPDH* gene, primer and template concentrations were optimized according to the manufacturer's instructions, and single-site amplification was confirmed through melting curve analysis. The reaction mixture included 1X Master Mix, 0.5 µM forward and reverse primers, and 2 µl cDNA in a total volume of 20 µl. The PCR cycling conditions were as follows: 95°C for 10 minutes, followed by 40 cycles of 15 seconds at 95°C and 45 seconds at 62°C. Primer sequences used; *GAPDH* forward: 5′-GGTGGTCTCCTCTGACTTCAACA-3′, *GAPDH* reverse: 5′-GTGGTCGTTGAGGGCAATG-3′

For the *TRIM36* gene, primer and template concentrations were similarly optimized, and single-site amplification was verified through melting curve analysis. The reaction mixture included 1X Master Mix, 0.4 µM forward and reverse primers, and 1.8 µl cDNA in a total volume of 20 µl. The PCR cycling conditions were as follows: 95°C for 5 minutes, followed by 40 cycles of 15 seconds at 95°C and 45 seconds at 62°C. Primer sequences used; *TRIM36* forward: 5′-CGTCGGTCCTCCTCCAGAGTTTGTG-3′, *TRIM36* reverse: 5′-GTGGCAAGTTCCGTCGTCGTCTTCC-3′

Primer sequences were designed using Primer3 software (19). All qRT-PCR experiments were performed in triplicate. The relative expression of *TRIM36* in tumor and normal tissues was calculated

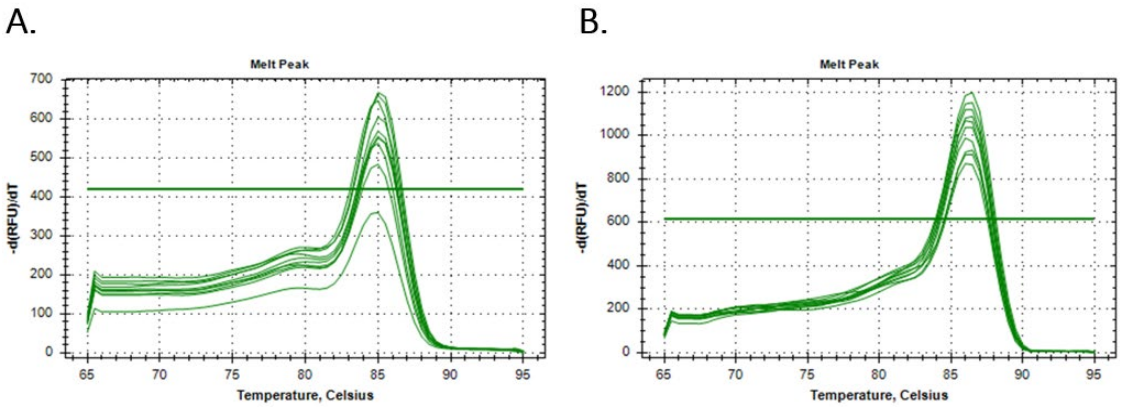



**Figure 1.** (A) Melting curve analysis showing the melting peak obtained from amplification using primers designed for the GAPDH gene. (B) Melting curve analysis showing the melting peak obtained from amplification using primers designed for the TRIM36 gene.

using the 2^-ΔΔCT method (20), with *GAPDH* serving as the reference gene.

*Statistical Analysis*

The sample size of the study was calculated using a medium effect size (Cohen's d = 0.5). A minimum of 78 samples (n = 39 per group) were required to achieve 80% power and a confidence level of α <0.05, as calculated using the GPower 3.1.9.7 software. However, we analyzed a total of 90 samples (n = 45 per group). Statistical analyses were performed using SPSS software (Version 29.0). The normality of the data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as median (minimum–maximum). The Wilcoxon signed-rank test was employed to compare *TRIM36* mRNA expression levels between the two paired groups. A p-value of <0.05 was considered statistically significant.

## Results

In this study, *TRIM36* expression levels were analyzed in tumor and adjacent normal breast tissues from 45 breast cancer patients. The primer pairs used for detecting *GAPDH* and *TRIM36* mRNA levels were validated for specificity by melting curve analysis, confirming single-site amplification (Figure 1).

The relative mRNA expression level of *TRIM36* was normalized to *GAPDH* mRNA expression levels in the same tissues. The median of fold change of *TRIM36* expression relative to *GAPDH* was 0.5218 (0.05-8.73) in normal tissues and 0.5775 (0.01-3.94) in tumor tissues. Desciptive statistics are presented in Table 1.

qRT-PCR results indicated that *TRIM36* is expressed in human breast tissue. However, no statistically significant difference was observed in *TRIM36* expression levels between normal and tumor tissues (p = 0.731, Table 1, Figure 2).

**Table 1.** Statistics of TRIM36 mRNA expression fold changes in normal and tumor tissues.

| Descriptive statistics | Normal tissue (n=45) | Tumor tissue (n=45) | Total (n=90) | p value / significance |
|---|---|---|---|---|
| Median | 0.5218 | 0.5775 | 0.5252 | |
| Minimum | 0.05 | 0.01 | 0.01 | 0.731[w] |
| Maximum | 8.73 | 3.94 | 8.73 | |

[w]Wilcoxon Signed ranks test.

*Doi: 10.47572/muskutd.1600240*

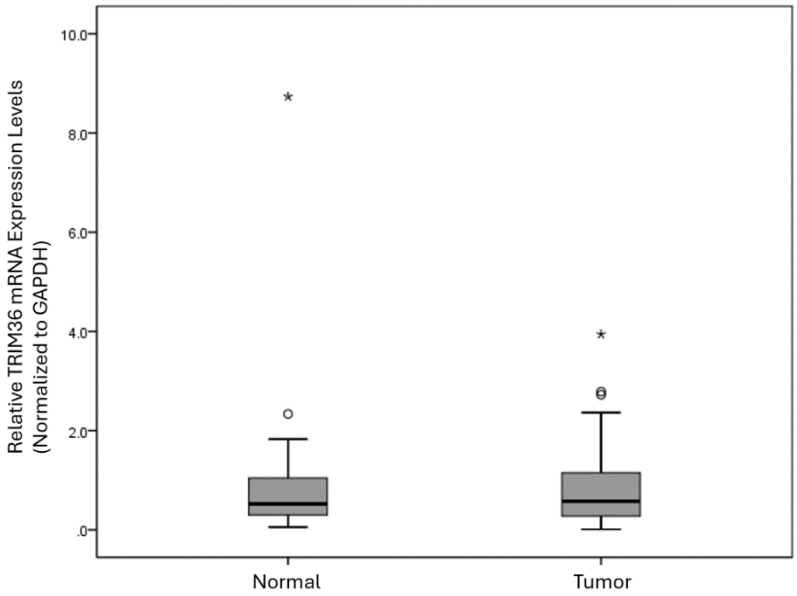



**Figure 2.** Fold changes in TRIM36 mRNA expression in normal and tumor tissues.

## Discussion

Breast cancer, the most commonly diagnosed and one of the most lethal cancers worldwide, is among the malignancies in which the roles of TRIM family members have been extensively studied. For instance, *TRIM25* is expressed in female organs through estrogen action (21). Its high expression levels in human breast cancer cells (MCF7) were shown to accelerate tumor growth, while its silencing slowed tumor progression. Additionally, overexpression of *TRIM25* was found to promote breast cancer development by degrading the cell cycle inhibitor 14-3-3σ (22).

Similarly, *TRIM24* overexpression has been associated with poor prognosis and reduced survival in breast cancer patients (23). TRIM29, which transcriptionally inhibits TP53 (24), has been shown to enhance cell proliferation and metastatic activity in pancreatic cancer cells (25). In contrast, decreased TRIM29 expression in MCF10A human breast cells led to increased cell growth, enhanced cell motility, and impaired 3D acinar formation in vitro. Conversely, in MCF7 cells, overexpression of TRIM29, which is normally expressed at low levels, resulted in reduced cell division rates (26).

Furthermore, silencing TRIM47 in breast cancer cell lines was found to inactivate the PI3K/Akt signaling pathway, leading to the inhibition of cell proliferation, migration, and invasion (27).

In addition, several TRIM proteins are known to play distinct roles in breast cancer. For example, TRIM3, TRIM6, TRIM11, TRIM14, TRIM27, TRIM32, TRIM37, TRIM39, TRIM44, TRIM59, and TRIM63 have been identified as oncogenic, whereas TRIM16, TRIM21, TRIM31, TRIM35, and TRIM62 function as tumor suppressors (28).

To date, no studies have specifically investigated the relationship between *TRIM36*, the focus of this study, and breast cancer. However, a study using tumor tissues from mice injected with human breast cancer cells reported a decrease in *TRIM36* expression levels in breast tissue (39).

Although the roles of *TRIM36* in human cancers are gradually being elucidated, further research is necessary. For instance, *TRIM36* expression has been found to be elevated in prostate cancer, suggesting a potential role in carcinogenesis (17). Interestingly, however, a study reported that high TRIM36 expression levels were associated with favorable prognosis in prostate cancer, inhibiting cell proliferation and migration. Furthermore, it was proposed that TRIM36, which also promotes apoptosis, functions as a tumor suppressor (30).

In another study published in the same year, high TRIM36 expression levels were observed in prostate cancer tissues. Interestingly, TRIM36 was shown to inhibit the MAPK/ERK phosphorylation pathway, which plays a critical role in tumor survival and development (31).

Conversely, *TRIM36* expression levels were reported to be significantly lower in non-small cell lung cancer and esophageal cancer compared to healthy controls (32,33). In human neuroblastoma patients, *TRIM36* was found to be hypermethylated and expressed at lower levels in individuals with a more aggressive disease course (34).

A study suggested that TRIM36 may influence glycolysis by regulating the expression of the glycolysis-related protein HK2 and neuroendocrine differentiation in prostate cancer. This regulatory mechanism was shown to be inhibited by glycolytic and HK2 inhibitors (35).

More recently, in 2023, TRIM36 was reported to directly interact with and suppress FOXA2, thereby activating the Nrf2/GPX4 ferroptosis signaling

pathway. This interaction suggests a tumor suppressor role for TRIM36 in colorectal cancer (36).

*TRIM36* is recognized as an androgen-responsive gene and has been shown to enhance the efficacy of anti-androgen drugs in prostate cancer (31). Androgen signaling is essential for the development and maintenance of male sexual characteristics, including muscle mass, strength, bone mineral density, prostate enlargement, spermatogenesis, hair distribution, and neuronal remodeling. Moreover, it plays a pivotal role in female physiology and reproduction.

Androgen signaling has been implicated in several diseases, including prostate cancer, breast cancer, diabetes, metabolic syndrome, and Alzheimer's disease (37). Notably, androgens have been reported to inhibit human breast cancer cell proliferation both in vitro and in vivo, and clinical observations suggest that androgens or androgenic compounds may exert protective effects against breast cancer growth in women (38).

In this context, TRIM36 may have significant and unexplored roles in breast cancer, potentially influenced by its interaction with androgen signaling pathways.

In this study, we analyzed the relative mRNA expression levels of *TRIM36* in female breast cancer patients by normalizing them to *GAPDH* mRNA levels. We evaluated whether *TRIM36* expression differs between tumor and normal breast tissues. Our findings confirm that *TRIM36* is expressed in breast tissues; however, no statistically significant difference was observed in its expression levels between normal and tumor tissues.

The qRT-PCR analyses further supported that *TRIM36* gene expression in breast cancer tissues does not significantly differ from that in normal tissues. These findings suggest that additional molecular mechanisms should be explored to elucidate the potential role of *TRIM36* in breast cancer development.

Notably, this study was conducted with a limited number of patient samples. Although no significant differences in *TRIM36* expression were identified, larger-scale studies are required to validate these findings in a broader patient population and to fully understand the involvement of *TRIM36* in breast cancer pathogenesis.

## Conclusion

In this study, the expression levels of *TRIM36* mRNA in normal and tumor breast tissues were investigated. While *TRIM36* was found to be expressed in breast tissues, no statistically significant differences were observed between normal and tumor tissues. These findings suggest that *TRIM36* may not play a direct role in breast cancer development. However, larger-scale studies with more comprehensive datasets are needed to further evaluate the potential involvement of *TRIM36* in breast cancer and its relationship with other molecular mechanisms.

## Acknowledgements

We thank Zonguldak Bülent Ecevit University Scientific Research Projects Unit for financial support of this study (Project no: 2021-50737594-03). We sincerely thank all the patients who participated in this study for their valuable contributions

## Conflict of interest statement

The authors declare no conflict of interest.

**Ethics Committee Approval:** The study protocol was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee. (Zonguldak / February 10, 2021/Approval No:2021/03).

**Funding:** This study was supported by the Scientific Research Projects Unit of Zonguldak Bülent Ecevit University (Project No: 2021-50737594-03).

## References

1. Bray F, Ferlay J, Soerjomataram I, et al. GLOBOCAN estimates of cancer incidence and mortality worldwide for 2022. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: CA Cancer J Clin, 2024;74(3):229–63.
2. Zhou W, Zhang Y, Zhong C, et al. Decreased expression of TRIM21 indicates unfavorable outcome and promotes cell growth in breast cancer. Cancer Manag Res. 2018;10:3687-97.
3. Hatakeyama S. TRIM family proteins: Roles in autophagy, immunity, and carcinogenesis. Trends Biochem Sci, 2017; 42(4):297–311.
4. Hatakeyama S. TRIM proteins and cancer. Nat Rev Cancer. 2011;11(11):792.
5. Reymond A, Meroni G, Fantozzi A, et al. The tripartite motif family identifies cell compartments. EMBO J. 2001;20(9):2140-51.
6. Short KM, Cox TC. Subclassification of the RBCC/TRIM superfamily reveals a novel motif necessary for microtubule binding. J Biol Chem. 2006;281(13):8970–80.
7. Watanabe M, Hatakeyama S. TRIM proteins and diseases. J Biochem. 2017; 1;161(2):135-44.
8. Goddard AD, Borrow J, Freemont PS, Solomon E. Characterization of a zinc finger gene disrupted by the t(15;17) in acute promyelocytic leukemia. Science. 1991;29;254(5036):1371-4.
9. Fang YY, Li JL, Ding H, et al Regulation of TRIM24 by miR-511 modulates cell proliferation in gastric cancer. J Exp Clin Cancer Res. 2017;23:36(1):17.
10. Groner AC, Cato L, de Tribolet-Hardy J, et al. TRIM24 Is an Oncogenic Transcriptional Activator in Prostate Cancer. Cancer Cell. 2016:13;29(6):846-58.
11. Appikonda S, Thakkar KN, Freeman WM. Regulation of gene expression in human cancers by TRIM24. Drug Discov Today Technol. 2016:19:57-63.
12. Obad S, dos Santos CO, Petri A, et al. Regulation of the interferon-inducible p53 target gene TRIM22 (Staf50) in

human T lymphocyte activation. J Interferon Cytokine Res. 2007:27(10):857-64.
13. Joo, HM, Kim JY, Jeong JB, et al. Ret finger protein 2 enhances ionizing radiation-induced apoptosis via degradation of AKT and MDM2. Eur J Cell Biol. 2011:90(5);420-31.
14. Qiu F, Xiong JP, Deng J, et al. TRIM29 functions as an oncogene in gastric cancer and is regulated by miR-185. Int J Clin Exp Pathol. 2015;8(5):5053-61.
15. Micale L, Chaignat E, Merla G. TRIM8 downregulation in glioma affects cell proliferation and it is associated with patients survival. BMC Cancer. 2015;15(6):470.
16. Okumura F, Matsunaga Y, Katayama Y, et al. TRIM8 modulates STAT3 activity through negative regulation of PIAS3. J Cell Sci. 2010;123(Pt 13):2238-45.
17. Balint I, Müller A, Nagy A, et al. Cloning and characterisation of the RBCC728/TRIM36 zinc-binding protein from the tumor suppressor gene region at chromosome 5q22.3. Gene. 2004;332(5):45-50.
18. Miyajima N, Maruyama S, Kasai H, et al. TRIM36 interacts with the kinetochore protein CENP-H and delays cell cycle progression. Biochem Biophys Res Commun. 2009;381(3):383–7.
19. Koressaar T, Remm M. Enhancements and modifications of primer design program Primer3. Bioinformatics. 2007;23(10):1289-91.
20. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8.
21. Ikeda K, Orimo A, Higashi Y, et al. Efp as a primary estrogen-responsive gene in human breast cancer. FEBS Lett. 2000;472(1):9-13.
22. Urano T, Saito T, Tsukui T, et al. Efp targets 14- 3-3 sigma for proteolysis and promotes breast tumour growth. Nature. 2002;417(6891):871–5.
23. Chambon M, Orsetti B, Berthe ML, et al. Prognostic significance of TRIM24/TIF-1α gene expression in breast cancer. Am J Pathol. 2011;178(4):1461-9.
24. Yuan Z, Villagra A, Peng L, et al. The ATDC (TRIM29) protein binds p53 and antagonizes p53-mediated functions. Mol Cell Biol. 2010;30(12):3004–15.
25. Wang L, Heidt DG, Lee CJ, et al. Oncogenic function of ATDC in pancreatic cancer through Wnt pathway activation and beta-catenin stabilization. Cancer Cell. 2009;15(3):207–19.
26. Liu J, Welm B, Boucher KM, et al. TRIM29 functions as a tumor suppressor in nontumorigenic breast cells and invasive ER+ breast cancer. Am J Pathol. 2012;180(2):839-47.
27. Wang Y, Liu C, Xie Z, et al. Knockdown of TRIM47 inhibits breast cancer tumorigenesis and progression through the inactivation of PI3K/Akt pathway. Chem Biol Interact. 2020;317:108960.
28. Cao J, Yang M, Guo D, et al. Emerging roles of tripartite motif family proteins (TRIMs) in breast cancer. Cancer Med. 2024;13(14):e7472.
29. Zheng M, Wang J, Ling L, et al. Screening and analysis of breast cancer genes regulated by the human mammary microenvironment in a humanized mouse model. Oncol Lett. 2016;12(6):5261-8.
30. Kimura N, Yamada Y, Takayama KI, et al. Androgen-responsive tripartite motif 36 enhances tumor-suppressive effect by regulating apoptosis-related pathway in prostate cancer. Cancer Sci. 2018;109(12):3840-52.
31. Liang C, Wang S, Qin C, et al. TRIM36, a novel androgen-responsive gene, enhances anti-androgen efficacy against prostate cancer by inhibiting MAPK/ERK signaling pathways. Cell Death Dis. 2018;9(2):1-13.
32. Zhan W, Han T, Zhang C, et al. TRIM59 promotes the proliferation and migration of non-small cell lung cancer cells by upregulating cell cycle-related proteins. PLoS One. 2015;10(11):e0142596.
33. Zhang H, Sun W, Qiao G, et al. The expression of tripartite motif protein 36 and β-catenin correlates with the prognosis of esophageal cancer. Gastroenterol Res Pract. 2020;2020(7641761):1-9.
34. Olsson M, Beck S, Kogner P, et al. Genome-wide methylation profiling identifies novel methylated genes in neuroblastoma tumors. *Epigenetics*. 2016;11(1):74-84.
35. Zhao X, Zhou T, Wang Y, et al. TRIM36 regulates neuroendocrine differentiation of prostate cancer via HK2 ubiquitination and GPx4 deficiency. Res Sq. 2022;Version 1:e2190616.
36. Liu X, Yan C, Chang C, et al. FOXA2 Suppression by TRIM36 Exerts Anti-Tumor Role in Colorectal Cancer Via Inducing NRF2/GPX4-Regulated Ferroptosis. Adv Sci (Weinh). 2023;10(35):e2304521.
37. Jiang M, Ma Y, Chen C, et al. Androgen-responsive gene database: integrated knowledge on androgen-responsive genes. Mol Endocrinol. 2009;23(11):1927-33.
38. Labrie F, Simard J, de Launoit Y, et al. Androgens and breast cancer. Cancer Detect Prev. 1992;16(1):31-8.

*Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi 2025;12(1):27-33* *Orijinal Makale/Original Article*
*Medical Journal of Mugla Sitki Kocman University 2025;12(1):27-33* *Altıntas and Eras*
*Doi: 10.47572/muskutd.1621921*

# Evaluation of Beta Globin Gene Mutations in Mersin, Turkey: A Single Center Experience

# Mersin, Türkiye'de Beta Globin Gen Mutasyonlarının Değerlendirilmesi: Tek Merkezli Bir Deneyim

**Zuhal ALTINTAS and Nazan ERAS**

Mersin University Faculty of Medicine, Department of Medical Genetics, Mersin, Turkey

**Öz**

Beta-talasemi, β-globin zincir sentezinin eksikliği veya yokluğundan kaynaklanan otozomal resesif kalıtım gösteren, dünya çapında en yaygın tek gen hastalığıdır. Çalışmamızın amacı Mersin ilinde beta talasemi tanısı alan hastaların mutasyon tiplerini ve sıklığını değerlendirmektir. 2017-2019 yılları arasında Mersin Üniversitesi Tıp Fakültesi hastanesinde hemoglobinopati taraması yapılan 292 hastanın klinik verileri retrospektif olarak incelendi. HBB geninde mutasyon bulunan 292 hastanın %55,5'inde (n=162) beta talasemi vardı. Beta talasemili hastalarda, 4'ü anormal Hb varyantı olmak üzere 32 farklı mutasyon ve bu hastaların 22'sinde 12 farklı bileşik heterozigot β-tal mutasyonu tespit edildi. En sık görülen alel %25.2 frekansla c.93-21G>A idi. En yaygın bileşik varyasyon HBB:c.*233G>C/HBB:c.92+6T>C/A, (%27,4) idi. Türkiye'de daha önce bildirilmemiş olan HBB:c.92+5G>A mutasyonunu tespit ettik. Beta-talasemi mutasyonlarının tipleri ve sıklıkları coğrafi bölgeler arasında farklılık göstermektedir. Bu çalışmada, beta-talasemi mutasyonlarının yaygınlığını moleküler düzeyde incelemiş ve DNA dizi analizi ile tanımlanamayan mutasyonların tespit oranını artırmıştır. Beta-talasemide yeni mutasyonların tanımlanması genetik danışmanlık, prenatal tanı, tarama programları ve literatür için yararlıdır.

**Anahtar Kelimeler:** Beta-talasemi, HBB geni, Mersin, Mutasyon, Türkiye

**Abstract**

Beta-thalassemia is the most common single gene disease worldwide with an autosomal recessive inheritance caused by the deficiency or absence of β-globin chain synthesis. The aim of our study is to evaluate the types and frequencies of mutations in patients diagnosed with beta thalassemia in the province of Mersin. Clinical data of 292 patients who underwent hemoglobinopathy screening at Mersin University Faculty of Medicine Hospital between 2017 and 2019 were retrospectively analysed. Of the 292 patients with mutations in the *HBB* gene, 55.5% (n=162) had beta thalassemia. In patients with beta thalassemia, 32 different mutations, including 4 abnormal Hb variants, and 12 different compound heterozygous β-tal mutations were detected in 22 of these patients. The most commonly seen allele was c.93-21G>A with a frequency of 25.2%. The most common compound variation was HBB:c.*233G>C/HBB:c.92+6T>C/A, (27.4%). We detected the mutation HBB:c.92+5G>A, which has not been previously reported in Turkey. The types and frequencies of beta-thalassemia mutations vary among geographic regions. This study examined the prevalence of beta-thalassemia mutations at the molecular level and enhanced the detection rate of unidentified mutations by DNA sequence analysis. Identification of new mutations in beta-thalassemia is useful for genetic counseling, prenatal diagnostic, screening programs, and literature.

**Keywords:** Beta-thalassemia, HBB gene, Mersin, Mutation, Turkey

## Introduction

Beta-thalassemia is a blood disorder caused by the absence (β0) or deficiency (β+) of the β globin chains in the two β globin chains and two alpha globin chains (alpha2beta2) that make up the hemoglobin (Hb) tetramer. One of the most common autosomal recessive disorders in the world, β-thalassemia, is highly prevalence in Cyprus (14%), Sardinia (12%), and Southeast Asia (1). While β-thalassemia carriage is seen at a rate of 5.1% worldwide, this rate was shown to be between 0.7% and 13.1% in study including 16 provinces in the Mediterranean, Aegean and Marmara regions in our country (2). Demographic events such as high birth rate, migration and high rates of consanguineous marriage have led to increased prevalence of β-thalassemia in some regions of Turkey.

| | ORCID No |
|---|---|
| Zuhal ALTINTAS | 0000-0001-9805-6624 |
| Nazan ERAS | 0000-0001-5475-1684 |

Başvuru Tarihi / Received: 17.01.2025
Kabul Tarihi / Accepted : 27.03.2025

Adres / Correspondence : Zuhal ALTINTAS
Mersin University Faculty of Medicine, Department of Medical Genetics, Mersin, Turkey
e-posta / e-mail : altintaszmert@gmail.com

The hemoglobin β-globin (HBB) gene situated in the short arm of chromosome 11 is approximately 1.6 Kb long, encodes 146 amino acids, contains 3 exons, 2 introns and 5' and 3' untranslated regions (UTRs), and is regulated by the 5' promoter region (3). A variety of molecular lesions, from point mutations to tiny deletions restricted to HBB to massive deletions of the complete β-globin cluster, can cause hemoglobin's β-globin chains to be down-regulated. Deletions cause α-thalassemia, while most mutations causing β-thalassemia are point mutations (4). Among the point mutations affecting the expression of the β-globin gene are mutations causing defective β-globin gene transcription (promoter and 5' UTR mutations), mutations affecting messenger RNA (mRNA) synthesis (splice junction and consensus sequence mutations, polyadenylation and other 3' UTR mutations), and mutations causing abnormal mRNA translation (start codon mutations, nonsense and frameshift mutations) (5).

β0-thalassemias, defined by the complete absence of β chain synthesis, result from deletion, nonsense, frameshift, start codon, and splicing

mutations, particularly at the splice junction. The polyadenylation signal and 5' or 3' UTR, mutations in the promoter region (CACCC or TATA box), or splicing abnormalities lead to a decrease in the synthesis of β chains, causing β+-thalassemias. There are three categories of β-thalassemia mutations: severe, mild, and silent. The classification is based on the degree of reduction in β chain synthesis1. So far, 486 β-thalassemia mutations have been reported in the IthaGenes database (6).

In the molecular analysis of β-thalassemia patients carried out in Turkey, it has been demonstrated that more than 40 different β-globin gene mutation types responsible for the disease represent 90% of the total mutations (7). This diversity reflects the heterogeneity of the Turkish population. Worldwide, in high-frequency carrier populations, there are a few common mutations specific to a particular region, as well as a varying number of rare mutations (8). It is helpful to identify the relationship between genotype and phenotype as well as to detect and categorize β-thalassemia mutations, which are very common in our nation. The objective of our study was to to determine the spectrum of β-globin gene mutations and frequency of patients diagnosed with β-thalassemia in Mersin province and to identify infrequent and rare β-thalassemia mutations. Knowing the spectrum of prevalent and rare mutations will help determine responsible mutations accurately and in a timely manner.

## Material and Method

In this study, Mersin University Medical Genetics Department Molecular Genetics Laboratory 292 patients who were referred from other clinics with preliminary diagnoses of anemia and β-thalassemia and whose mutation was detected as a result of *HBB* gene sequence analysis were retrospectively evaluated. These patients underwent *HBB* gene sequence analysis as part of the Hemoglobinopathy evaluation. Complete blood count parameters and HbA2 level at the time of diagnosis and demographic characteristics of these cases were obtained from file scans and computer data systems. Ethics committee approval for this study was obtained from Mersin University Local Ethics Committee with decision no: 650 dated 2022.

Reference ranges for HbA2 in normal subjects are usually between 2.0% and 3.3%, whereas HbA2 levels in β-thalassemia carriers are usually above 3.5%. HbA2 values between 3.1% and 3.5% are considered borderline. Mean corpuscular volume (MCV) <80 fL and/or mean corpuscular hemoglobin (MCH) <27 pg and HbA2 level >3.5% are interpreted in favor of thalassemia carrier status. For HbF values, <1% was considered normal, 1-5% slightly high and >5% high (9).

Before the β-thalassemia tests were performed, a consent form was acquired from all patients and genetic counseling was provided. Current classifications of the detected mutations were checked utilizing the Franklin by Genoox (10) and ClinVar (11) databases. Mutations are classified according to the ACMG (American College of Medical Genetics) Guidelines as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, and benign[12]. Age and gender data of the patients with β-thalassemia were obtained from the hospital and department archives (12).

*Statistical analysis*

Results were presented as mean ± standard deviation. Categorical variables were presented as numbers and percentages.

## Results

We evaluated the findings of 292 people who were referred to our laboratory from other clinics with preliminary diagnoses of anemia and β-thalassemia and underwent MCI gene screening. Since the incidence of β-thalassemia is high in our region, β-thalassemia was screened in the patient group in which anemia was investigated. Of 292 patients with HBB gene mutation, 130 (44.5%) had sickle cell anaemia alone, 27 had compound sickle cell anemia (9.2%) and 135 had beta-thalassemia (46.3%). This group with sickle cell anemia and compound sickle cell anemia were excluded from the statistical analysis in research. The results of 135 patients with β-thalassemia mutation were evaluated. In 135 patients who were diagnosed with anemia and underwent HBB gene mutation analysis, we detected a total of 32 different HBB mutations, 28 of which were β-globin gene mutations, together with 4 abnormal Hb variants, when HbS compound heterozygotes were excluded. In this study, a different β-globin gene mutation (HBB:c.92+5G>A), which has not been reported before in Turkey, was identified.

Ninety-nine (73.3%) of these individuals had heterozygous mutations, 22 (16.3%) had compound heterozygous mutations, and 14 (10.4%) had homozygous mutations. Of the 135 patients with β-globin gene mutation, 89 (66%) were under 18 years of age, and 46 (34%) were 18 years of age or older. The youngest patient with β-thalassemia was 1 year old, the oldest was 71 years old, and the average age of all patients was determined to be 16.1±12.4 years.

In this study, 90 cases with HbA2 elevation (>3.5%) were detected, and 86 of 90 cases had MCV <80 and/or MCH <27. Three of the four cases with high HbA2 had MCV>80 and MCH>27. However, in 1 case, MCV was high and MCH was normal. In 80 cases, HbF was >2%. Borderline HbA2 level was found in 6 cases. Of the 90 cases with elevated HbA2

**Table 1.** Distribution and frequency of beta globin gene mutations and some abnormal hemoglobins in Mersin, Turkey

| HGVS Name | Variation Name | HbName | rs ID | Clinical Significance | Homozygous/ Heterozygous (n/n) | Frequency n ( %) | Type | Mutation Type | Consequence |
|---|---|---|---|---|---|---|---|---|---|
| HBB:c.93-21G>A | IVS-I-110 G>A | | rs35004220 | Pathogenic | 6/42 | 48 (25.2) | β+ | SNV | Intronic |
| HBB:c.*233G>C | TTS +99 G>C 3′ UTR +101 (G>C) | | rs12788013 | Benign | 2/42 | 44 (23.1) | benign polymorphism | SNV | 3'UTR |
| HBB:c.92+6T>C | IVS-I-6 (T>C) | | rs35724775 | Pathogenic | 3/8 | 11 (5.6) | β+ | SNV | Intronic |
| HBB:c.92+1G>A | IVS I-1 G>A | | rs33971440 | Pathogenic | -/9 | 9 (4.7) | $\beta^0$ | SNV | Splice-D/A |
| HBB:c.135del | Codon 44 (-C) | | rs80356820 | Pathogenic | -/9 | 9 (4.7) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.25-26delAA | Codon8 (-AA) | | rs35497102 | Pathogenic | 1/7 | 8 (4.2) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.364G>C | Codon121 GAA>CAA | variant Hb D-LA | rs33946267 | Likely Pathogenic | -/8 | 8 (4.2) | variant Hb D-LA | SNV | Missense |
| HBB:c.315+1G>A | IVS-II-1 | | rs33945777 | Pathogenic | -/5 | 5 (2.7) | $\beta^0$ | SNV | Splice-D/A |
| HBB:c.-80T>A | -30 (T>A) | | rs33980857 | Pathogenic | 2/3 | 5 (2.7) | β+ | SNV | 5'UTR |
| HBB:c.68_74del | Codon 22-24 (-7 bp) | | rs281864898 | Pathogenic | -/4 | 4 (2.4) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.316-106C>G | IVS II-745 C>G | | rs34690599 | Pathogenic | 2/2 | 4 (2.4) | β+ | SNV | Intronic |
| HBB:c.118C>T | Codon 39 (C>T) | | rs11549407 | Pathogenic | -/4 | 4 (2.4) | $\beta^0$ | SNV | Stop gain |
| HBB:c.364G>A | Codon121GAA >AAA | variant Hb O-Arab | rs33946267 | Pathogenic | -/3 | 3 (1.6) | variant Hb O-Arab | SNV | Missense |
| HBB:c.17-18del | Codon 5( -CT) | | rs34889882 | Pathogenic | -/3 | 3 (1.6) | $\beta^0$ | SNV | Missense |
| HBB:c.92+5G>C | IVS1-5G>C | | rs33915217 | Pathogenic | 1/1 | 2 (1) | $\beta^0$ | SNV | Intronic |
| HBB:c.92+5G>A* | IVS I-5 G>A | | rs33915217 | Likely Pathogenic | -/1 | 1 (0.5) | β+ | SNV | Intronic |
| HBB:c.251delG | Codon 82/83 (-G) | | rs193922555 | Pathogenic | 1/1 | 2 (1) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.82G>T | Codon 27 (G>T) | | rs35424040 | Pathogenic | -/2 | 2 (1) | β+ | SNV | Missense |
| HBB:c.-31C>T | IVS II-745 C>G | | rs63750628 | Likely Benign | -/2 | 2 (1) | β+ | SNV | 5'UTR |
| HBB:c.112delT | Codon 36/37 (-T) | | rs63750532 | Pathogenic | -/2 | 2 (1) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.79G>A | Codon 26 (G>A) | Hb E | rs33950507 | Pathogenic | -/2 | 2 (1) | Hb E | SNV | Missense |
| HBB:c.135del | Codon 44 (–C) | | rs80356820 | Pathogenic | -/2 | 2 (1) | $\beta^0$ | Deletion | Frameshift |
| HBB:c.180G>A | Codon 59 (AAG>AAA) | | rs34621955 | Likely Benign | 1/- | 1 (0.5) | Neutral | SNV | Synonymous |
| HBB:c.*110T>C | Poly A (T>C) AATAAA>AACAAA | | rs33978907 | Pathogenic | -/1 | 1 (0.5) | β+ | SNV | 3'UTR |
| HBB:c.-78A>C | -28 (A>C) | | rs33931746 | Pathogenic | -/1 | 1 (0.5) | β+ | SNV | 5'UTR |
| HBB:c.-151C>T | -101 C>T | | rs63751208 | Pathogenic | -/1 | 1 (0.5) | β+ | SNV | 5'UTR |
| HBB:c.27dupG | Codon 8/9 (+G) | | rs35699606 | Pathogenic | -/1 | 1 (0.5) | $\beta^0$ | Duplication | Stop gain |
| HBB:c.151A>T | Codon 50 ACT>TCT | Hb Zürich-Langstrasse | rs63750336 | VUS | -/1 | 1 (0.5) | Hb Zürich-Langstrasse | SNV | Missense |
| HBB:c.47G>A | Codon 15 TGG>TAG | | rs63750783 | Pathogenic | -/1 | 1 (0.5) | $\beta^0$ | SNV | Stop gain |
| HBB:c.315+260A>G | IVS II-260 A>G | | rs111415391 | Likely Benign | -/1 | 1 (0.5) | β? | SNV | Intronic |
| HBB:c.315+74T/G | IVS II-74 T>G | | rs7480526 | Benign | -/1 | 1 (0.5) | benign polymorphism | SNV | Intronic |
| **HBB:c.96T>C | CAP + 1570 T>C | | rs34029390 | Benign | -/1 | 1 (0.5) | β? | SNV | 3'UTR |
| HBB:c.112delT | Codon 36/37 (-T) | | rs63750532 | Pathogenic | -/2 | 2 (1) | $\beta^0$ | Deletion | Frameshift |

HGVS: Human Genome Variation Society, ** New variation identified for the first time

(>3.5%), 67 were under 18 years of age, while 23 cases were 18 and over.

The patients were divided into two main groups according to their age: the pediatric group 15 years or younger (n=79; 58.5%) and the adult group older than 15 years (n=56; 41.5%).

The most prevalent allele frequency was found as 25.2% for HBB:c.93-21G>A, 23.1% for HBB:c.*233G>C, 5.6% for HBB:c.92+6T>C, 4.7% for HBB:c.92+1G>A and 4.7% for HBB:c.135del. These five mutations accounted for 63.3% of all mutations in the patients. The distribution and allele

prevalence of all noted mutations are provided in Table 1.

When the HbS compound was excluded, compound heterozygous mutation were detected in 12 different genotypes in 22 patients. The most prevalent of these mutations were compound heterozygous genotypes HBB:c.*233G>C/HBB:c.92+6T>C/A, which were found in six cases (27.4%). Others that are common are HBB:c.25-26delAA / HBB:c.*233G>C (18.2%); HBB:c.*233G>C/HBB:c.316-106C>G/HBB:c.-31C>T (9.2%); HBB:c.135delC/HBB:c.*233G>C (9,2%) and HBB:c.93-21G>A/HBB:c.*233G>C (4.5%), respectively. The genotypes of patients exhibiting compound heterozygous mutations are presented in Table 2.

**Table 2.** The distribution of compound heterozygous β-thalassemia mutations, in Mersin, Turkey

| Variations | Mutation Type | n | % |
|---|---|---|---|
| HBB:c.92+6T>C/A(rs35724775), HBB:c.*233G>C (rs12788013) | β+, benign polymorphism | 6 | 27.4 |
| HBB:c.25-26delAA (rs35497102), HBB:c.*233G>C (rs12788013) | β0, benign polymorphism | 4 | 18,2 |
| HBB:c.*233G>C (rs12788013), HBB:c.316-106C>G(rs34690599), HBB:c.-31C>T (rs63750628) | benign polymorphism, β+, β+ | 2 | 9.2 |
| HBB:c.135delC (rs80356820), HBB:c.*233G>C (rs12788013) | β0, benign polymorphism | 2 | 9.2 |
| HBB:c.93-21G>A (rs35004220), HBB:c.*233G>C (rs12788013) | β+, benign polymorphism | 1 | 4.5 |
| HBB:c.93-21G>A(rs35004220), HBB:c.135delC (rs80356820) | β+, β0 | 1 | 4.5 |
| HBB:c.-80T>A (rs33980857), HBB:c.93-21G>A(rs35004220), HBB:c.*233G>C (rs12788013) | β+, β+, benign polymorphism | 1 | 4.5 |
| HBB:c.92+5G>A(rs33915217), HBB:c.151A>T(rs63750336) | β+, β0 | 1 | 4.5 |
| HBB:c.92+6T>C/A(rs35724775), HBB:c.*233G>C (rs12788013), HBB:c.20A>T (rs334) | β+, benign polymorphism, βS | 1 | 4.5 |
| HBB:c.-80T>A (rs33980857), HBB:c.*233G>C (rs12788013) | β+, benign polymorphism | 1 | 4.5 |
| HBB:c.92+1G>A(rs33971440), HBB:c.93-21G>A (rs35004220) | β0, β+ | 1 | 4.5 |
| HBB:c.93-21G>A (rs35004220), HBB:c.*110T>C (rs33978907) | β+, β+ | 1 | 4.5 |
| **TOTAL** | | 22 | 100 |

HBB: c.*233G>C 42 of 44 cases with variation were heterozygous, and 23 of them carried only this variation. Of the 23 patients who were only HBB: c.*233G>C heterozygous, MCV<80 fL in 18 patients and MCV>80fL in 4 patients. Data could not be reached in 1 patient. While MCH was <27 pg in 16 patients with only HBB: c.*233G>C heterozygote, it was MCH>27 pg in 4 patients. In 3 patients, data could not be reached. Only in cases with HBB: c.*233G>C heterozygous, HbA2 was <3.5% in 15 cases, while in 1 patient, HbA2 was >3.5%. Data could not be obtained for 6 patients. Two cases were homozygous for the HBB:c.*233G>C variant. Homozygous cases and 19 heterozygous cases were found to be compound with other HBB gene mutations.

## Discussion

Hemoglobin disorders that affect the structure or function of hemoglobin are among the most common monogenic disorders in the world, and there are approximately 270 million thalassemia carriers worldwide (13). Thalassemia syndromes, including α-thalassemia, β-thalassemia, and hemoglobin-E disease, lead to a critical public health problem due to their high prevalence considering. Mersin province receives a lot of immigration due to its geographical location. Due to the high thalassemia carrier rate in Mersin, determining the mutation diversity and common mutations is very important in terms of informing the public, genetic counseling and public health. In short, it is important to identify regional mutations to create effective treatment and prevention programs.

In this study we detected 32 different β-globin gene mutations, 4 of which are abnormal Hb variants; HbE, Hb D-Los Angeles (Hb D-LA), Hb O-Arabic and Hb Zurich-Langstrasse (Table1).

HBB:c.93-21G>A mutation is reported at varying rates in numerous studies including different regions In Turkey, the HBB:c.93-21G>A mutation is seen with a frequency of nearly 52.3% in Central Anatolia Region Turkey (7). However, in the eastern and south-eastern Anatolian regions of Turkey, the frequency of the HBB:c.93-21G>A mutation has been shown to be 25-30% (14). Ince et al. reported the frequency of HBB:c.93-21G>A mutation as 27.8% in a study conducted in Diyarbakır province located in the southeastern region of Turkey (15). Beksaç et al. found it to be 49.01% in a study conducted in Ankara province located in the Central Anatolia region (16). In our study, as in other geographical regions of Turkey, the most frequent mutation is HBB:c.93-21G>A and constitutes 25.2% of all mutant alleles which was consistent with other studies.

The HBB:c.*233G>C variant has been temporarily included in the HbVar database based on a study conducted on Palestinians with β-

thalassemia disease or carrier status in the Gaza Strip (17). In their the study by of Smith et al. the allele frequency of the HBB:c.*233G>C variant was found to be 9.1% and they showed that this variant is a common benign polymorphism (18). In a study conducted in Malaysia, HBB: c.*233G>C (3' UTR+101 G>C) was reported to have the same protective role (19). In our study, we detected compound heterozygotes in 18 patients (13.3%). HBB: c.*233G>C (3' UTR+101 G>C) variation was not shown in the study conducted by Tadmuri et al. in our country (20). In our study, the HBB: c.*233G>C variant was the second most frequent variant with a frequency of 23.1% and was the most frequent compound heterozygous variant. HBB:c.*233G>C variation heterozygous have average HbA2 level of 23 cases was found to be 2.6 (±0.4) and HbF was 6.1 (±7.7). Parameters determined by whole blood count analysis were calculated with red the cell distribution width (RDW) index (MCVxRDW/RBC) formula. RDW index of <220 was interpreted in favor of thalassemia carrier status. The RDW index was <220 in 11 of 20 cases with the heterozygous HBB:c.*233G>C variation. In 2 cases with heterozygous HBB:c.*233G>C and heterozygous HBB:c.25-26delAA, RDW index was <220. In cases with heterozygous HBB:c.25-26delAA mutation, the RDW index was <220. In cases with homozygous HBB:c.92+6T>C mutation, the RDW index was >220. The RDW index was <220 in the case with homozygous HBB:c.92+6T>C and homozygous HBB:c.*233G>C and also in the case with heterozygous HBB:c.92+6T>C and heterozygous HBB:c.*233G>C. HBB: c.*233 G>C mutation has been reported as benign in previous studies. Therefore, these results show us that more detailed information about HBB:c.*233G>C is needed.

The reason why HBB:c.*233G>C was detected more in our study group may be because we used the DNA sequencing method. Furthermore, it may not have been detected in other groups due to differences in study methods or may not have been reported by laboratories because the HBB:c.*233G>C mutation is considered benign. It would be appropriate to evaluate this variation in more detail with clinical and laboratory data of patients in future studies. Also, any nucleotide changes (mutations or polymorphisms) found must be reported to the Hemoglobin Variant Database.

Turkey is one of them hotspots for variations in the globin genes. HBB:c.315+74T >G is one of the most frequently characterized polymorphic regions on the β-globin gene. Among the healthy controls, HBB:c.315+74T >G was commonly found in multiple investigations and was recognized as a polymorphism (21). Hocaoğlu et al. reported in their study that a HBB:c.315+74T >G homozygous change may be sufficient to cause the β-thalassemia carrier phenotype (21). It is thought that functional characterization of variants and elucidating their roles in the progression of the disease may provide a great advantage in designing appropriate treatment.

According to the Turkish registry study, HBB:c.92+6T>C (7.5%), which is linked to moderate $\beta^{+}$-thalassemia mutations, was the third most prevalent mutation in pediatric β-thalassemia major patients in Turkey (22). In our study, we detected the third most common HBB:c.92+6T>C mutation (5.6%), consistent with this study.

The HBB:c.92+1G>A mutation, which is very common in the Aegean and Marmara regions of Turkey, is one among the four most common mutations in the Mediterranean and Middle Eastern countries (23). Throughout the European countries, the HBB:c.92+1G>A mutation is observed with a frequency of 52.9% in the Czech Republic (24), and approximately 30% in Spain (25). Karaer et al. and Güvenç et al. reported that this variation 6.83% and 8.66%, respectively (26,27). The 4th most common mutation in our study was HBB:c.92+1G>A and the allele frequency was 4.7%.

In studies conducted in our country, HBB:c.135del mutation was found to be 3.23% by Karaer et al. and 4.7% in our study (26). While Güvenç et al. reported that HBB:c.25-26delAA mutation was 9.1% in Adana (27), Karaer et al. reported 4.9% in Southeastern Turkey (26). In our study, we reported the allele frequency of the HBB:c.25-26delAA mutation to be 4.2%.

In a study conducted in Syria, HBB:c.92+5G>C (4.1%) was reported as one of the common β-globin gene mutations (28). In our study, we found HBB:c.92+5G>C mutation (1%).

In our study, the β-globin gene mutation HBB: c.92+5G>A, which has not been previously reported in Turkey, was detected with a rate of 0.5%. Jarjour et al. reported the frequency of HBB:c.92+5G>A mutation as 3.2% in 189 Syrian β-thalassemia patients and carriers (29). There may also be co-inheritance of different mutations involving the β-thalassemia gene, which include gene structural variants that cause genotypic and phenotypic symptoms such as HbS-β-thalassemia (sickle-β-thalassemia) or HBB:c.79G>A-β-thalassemia (HbE-β-thalassemia or E-β-thalassemia). In our study, the group with HbS was not evaluated because it was excluded from this study. In several Asian nations, hemoglobin E (HbE), a structural hemoglobin variation, is prevalent and occurs at high frequency. HbE; the β chain is produced at a lower rate, causing a mild β thalassemia phenotype. While HbE by itself does not result in major clinical issues, it interacts with different types of α and β thalassemia to produce a variety of clinical syndromes that are co-inherited with β-thalassemia and range in severity. This condition, called HbE β-thalassemia, is the most common form of severe β-thalassemia in Asia and accounts for approximately 50% of clinically

severe β-thalassemia disorders worldwide (30). Güvenç et al. was detected the frequency of HbE to be 0.2% in Adana (27). In our study, we detected heterozygous HbE variation in 2 patients (1.1%). Although HbE is the second most common hemoglobinopathy globally, HBB:c.364G>C (HbD-Los Angeles) has been reported as the second most common abnormal hemoglobin among the Eti-Turks in Turkey, with a prevalence of 0.16-2.4% (31). While HbD-Los Angeles is more common in the Eastern Mediterranean and Southeastern Anatolia, is more common Hb E in the Western Mediterranean region and HBB:c.364G>A (Hb O Arab) is more common in the Thrace region (32). According to the researches, while HbD-Los Angeles was determined as 0.2% in Turkey, this abnormal hemoglobin is in the first place with a frequency of 57.8% in Denizli province (31,33). In our study, the frequency of HbD-Los Angeles was 3.6%. In the presence of Hb O-Arab, a clinical picture ranging from normal phenotype to mild anemia is observed. Hb O-Arab heterozygous variation does not show any clinical symptoms, whereas Hb O-Arab homozygous show mild hemolysis and mild splenomegaly. Co-inheritance of the hemoglobin O-Arab mutation in sickle cell disease patients causes a severe hemoglobinopathy with clinical and hematological features similar to sickle cell disease and may require frequent blood transfusions (33-36). Canatan et al. reported the HbO-Arab frequency as 0.4% in 2016 (32). In our study, this rate was 1.5%. Therefore, close follow-up of these patients in the clinic is important and people carrying this mutation should be recommended to undergo screening programs before marriage. Given that Turkish people have a wide spectrum of thalassemia syndromes and abnormal hemoglobin, all these results increase the importance of detecting Hb variant status.

HBB:c.315+1G>A is one of the mutations frequently detected in Arab countries, particularly in Erbil-Northern Iraq and Iran, Saudi Arabia, and Kuwait (29,37,38). Karaer et al. reported the prevalence of HBB:c.315+1G>A between 1-11% in an article in which they compared it with studies conducted in other regions of Turkey and Syria (26). In the current research, we observed the HBB:c.315+1G>A mutation as heterozygous in 6 patients (3.1%). The 5 most frequently inherited compound heterozygous variations in our research were HBB:c.*233G>C/HBB:c.92+6T>C/A (27.4%); HBB:c.25-26delAA/HBB:c.*233G>C (18.2%); HBB:c.*233G>C/HBB:c.316-106C>G/HBB:c.-31C>T (9.2%); HBB:c.135delC/HBB:c.*233G>C (9.2%); HBB:c.93-21G>A/HBB:c.*233G>C (4.5%).

In a study conducted in 1998, a total of 42 mutations were determined in Turkey (20). We identified a total of 32 different β globin gene mutations (4 of them are abnormal Hb variants), and 12 compound heterozygous variants. The molecular heterogeneity of Mersin province may be explained by its geographical location. In the study Abbasali et al. reported that the phenotype of heterozygous cases with the HBB: c*96T>C mutation was compatible with the silent carrier of β-thalassemia (39). In our study, we noted the HBB:c*96T>C mutation as heterozygous in one patient. Although this change is quite rare, it is a clinically significant β-globin gene mutation. This mutation, which can be categorized as a silent β-thalassemia defect and contributes to a decrease in β-globin chain synthesis, results in non-transfusion-dependent β thalassemia in compound heterozygosity. Even if one of the parents has a silent mutation such as the heterozygous HBB:c*96T>C gene mutation, screening the other one of the parents β-globin gene mutation carrier is essential in terms of the compound heterozygosity of future generations (40).

In our region, where the carrier rate is high, it is very important to first evaluate the complete blood count and perform hemoglobin electrophoresis to detect patients and carrier individuals. It is necessary to make a differential diagnosis of β thalassemia from diseases such as iron deficiency anemia, alpha thalassemia trait and anemia of chronic disease. In this study, the use of DNA sequencing was increased the detection percentage of undetectable mutations.

A multi-center study conducted by the Turkish Pediatric Hematology Association in 2018 demonstrated that the count of families with more than one affected child was high, the consanguineous marriage of the parents was high and, preventive measures were not implemented even in families where the risk. As an outcome of this the research carried out in 2018, Aydinok et al. express that the majority of families did not undergo premarital screening, and that prenatal diagnosis was either not offered to families at risk or was not accepted by the families (22).

## Conclusion

The main purpose of molecular diagnosis in β-thalassemia is to identify mutation profiles before marriage, and it is thought to be useful for prenatal molecular diagnostic tests and genetic counselling. Knowing the spectrum of prevalent and rare mutations in the national population is of great significance in terms of the identification of new mutations that causing a clinically significant disease, genetic counselling, informing the society and prenatal diagnosis, together with effectively controlling the disease.

*Limitations*

In this study, patients who underwent hemoglobinopathy screening in Mersin province during a certain period (2017-August 2019) were included in a cross-sectional design. Since our study was retrospective, laboratory parameters such as

hematological parameters, complete blood count and hemoglobin A2 levels could not be obtained in all cases in which *HBB* gene sequence analysis was performed. The results of our study reflect the genetic characteristics of this region and cannot be generalized to the entire population in Turkey.

## Conflict of interest statement

No potential conflict of interest was reported by the author(s)

**Ethics Committee Approval:** Mersin University Local Ethics Committee/650/2022.

**Funding:** The author(s) reported there is no funding associated with the work featured in this article

## References

1. Cao A, Galanello R. Beta-thalassemia. *ACMG*. 2010;12(2):61-76.
2. Yaprak I. Beta Talasemi Tanı ve Tedavisinde Güncel Yaklaşımlar. *STED.* 2004;13:58-9.
3. Origa R. β-Thalassemia. *ACMG*. 2017;19(6):609-619.
4. Thein SL. Molecular basis of β thalassemia and potential therapeutic targets. *BCMD.* 2018;70:54-65.
5. Jaing TH, Chang TY, Chen SH, et al. Molecular genetics of β-thalassemia: A narrative review. *Medicine.* 2021;100(45):e27522.
6. The HbVar Database. (http://globin.bx.psu.edu/cgi-bin/hbvar/ query_vars3). access date 22.09.2024.
7. Tadmouri GO, Başak AN. Beta-thalassemia in Turkey: a review of the clinical, epidemiological, molecular, and evolutionary aspects. *Hemoglobin*. 2001;25(2):227-39.
8. Weatherall DJ, Clegg JB. The Thalassemia Syndromes. England: Blackwell Science Ltd. 2001; 4th ed. Oxford
9. Republic of Turkey Ministry of Health, General Directorate of Public Health. *Hemoglobinopati Tanı Rehberi*. 2016 [cited 2024 May 13] Available from: https://hsgm.saglik.gov.tr/tr/tghsldb-rehberler/hemoglobinopati-tan%C4%B1-rehberi.html
10. Genoox. 'Franklin by Genoox'. https://franklin.genoox.com. access date 10.06.2024.
11. ClinVar. https://www.ncbi.nlm.nih.gov/clinvar/ access date 15.06.2024.
12. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med*. 2020;22(2):245-57.
13. Thalassemia Research Network. Interactive database for hemoglobin variants (ITHANET). Ithagene database. Available from: http://ithanet.eu/db/ithagenes.) access date. 25.08.2024.
14. Basak AN. The molecular pathology of beta-thalassemia in Turkey: The Boğaziçi university experience. *Hemoglobin*. 2007;31(2):233-41.
15. Ince HH, Ayyildiz O, Kalkanli S, et al. Molecular basis of beta-thalassemia mutations in Diyarbakir in the southeastern region of Turkey. *Hemoglobin.* 2003;27(4):275-8.
16. Beksac MS, Gumruk F, Gurgey A, et al. Prenatal diagnosis of hemoglobinopathies in Hacettepe University, Turkey. *PHO*. 2011;28(1):51-5.
17. Sirdah MM, Sievertsen J, Al-Yazji MS, et al. The spectrum of β-thalassemia mutations in Gaza Strip, Palestine. *BCMD.* 2013;50(4):247–51.
18. Smith DL, Mitui M, Park JY, et al. Characterization of the HBB: c.*233G > C Variant: No Evidence of a β-Thalassemic Phenotype. *Hemoglobin*. 2016;40(1):25-8.
19. Aziz, N.-A.; Taib, W.-R.W.; Kharolazaman, N.-K.; Ismail, I.; Al-Jamal, H.A.N.; Jamil, N.W.-A.W.A.; Esa, E.; Ibrahim, H. Evidence of new intragenic HBB haplotypes model for the prediction of beta-thalassemia in the Malaysian population. Sci. Rep. 2021, 11, 1–6.
20. Tadmouri GO, Tüzmen S, Ozçelik H, et al. Molecular and population genetic analyses of beta-thalassemia in Turkey. *AJH*. 1998;57(3):215-20.
21. Hocaoglu-Emre F, Yenmis G, Saribal D, et al. IVSII-74 T>G: As harmless as we thought? *TJB.* 2019;44(1): 41-6.
22. Aydınok Y, Oymak Y, Atabay B, et al. A National Registry of Thalassemia in Turkey: Demographicand Disease Characteristics of Patients, Achievements, and Challenges in Prevention. *Turk J Haematol.* 2018;35(1):12-8.
23. Dilmec F, Koc A, Akkafa F. Investigation of - SS globingene mutations in patients with β-thalassemia in Şanlıurfa province of Turkey. *Turkiye Klinikleri J Med Sci* 2010;30:514-9.
24. Indrak K, Brabec V, Indrakova J, et al. Molecular characterization of beta-thalassemia in Czechoslovakia. *Human genetics.* 1992; *88*(4):399–404.
25. Villegas A, Ropero P, González FA, et al. The thalassemia syndromes: molecular characterization in the Spanish population. *Hemoglobin.* 2001;25(3):273-83.
26. Karaer D, Sahinoglu B, Pekpak Sahinoglu E, et al. The Molecular Spectrum of Beta Thalassemia Mutations in Southeastern, Turkey. *GMJ.* 2023;34:63-7.
27. Guvenc B, Canataroglu A, Unsal C, et al. β-Thalassemia mutations and hemoglobinopathies in Adana, Turkey: results from a single center study. *Arch Med Sci.* 2012;8(3):411-4.
28. Murad H, Moasses F, Dabboul A, et al. Geographical distribution of β-globin gene mutations in Syria. *Hematology.* 2018;23(9):697-704.
29. Jarjour RA, Murad H, Moasses F, Al-Achkar W. Molecular update of β-thalassemia mutations in the Syrian population: identification of rare β-thalassemia mutations. *Hemoglobin.* 2014;38(4):272-6.
30. Fucharoen S, Weatherall DJ. The hemoglobin E thalassemias. *Cold Spring Harb Perspect Med*. 2012;2(8):a011734.
31. Akar E, Akar N. A review of abnormal hemoglobins in Turkey. Turk. J. Hematol. 2007; 24(4): 143-5.
32. Canatan D, Delibas S Report on Ten Years' Experience of Premarital Hemoglobinopathy Screening at a Center in Antalya, Southern Turkey. *Hemoglobin.* 2016 Aug;40(4):273-6.
33. Atalay EÖ, Koyuncu H, Turgut B, Atalay A, Yıldız S, Bahadır A, Köseler A. High incidence of Hb D- Los Angeles [β121(GH4) Glu>Gln] in Denizli province. *Hemoglobin*. 2005; 29(4): 307-10.
34. Zimmerman SA, O'Branski EE, Rosse WF, Ware RE. Hemoglobin S/O(Arab): thirteen new cases and review of the literature. *AJHl.* 1999;60(4):279-84.
35. Elbashir I, Elsayed Yousif TY. Molecular Detection of Hemoglobin O-Arab in the Sudanese Population. *Int J Gen Med.* 2023;16:3323-30.
36. Dror S. Clinical and hematological features of homozygous hemoglobin O-Arab [beta 121 Glu → Lys]. *Pediatr Blood Cancer.* 2013;60(3):506-7.
37. Al-Allawi NA, Hassan KM, Sheikha AK, et al. B-thalassemia mutations among transfusion-dependent thalassemia major patients in northern Iraq. *Mol Biol Int.* 2010;2010:479282.
38. Najmabadi H, Karimi-Nejad R, Sahebjam S, et al. The beta-thalassemia mutation spectrum in the Iranian population. *Hemoglobin.* 2001;25:285-96.
39. Abbasali FH, Mahmoud KS, Hengameh N, et al. Rare and New Mutations of B-Globin in Azari Population of Iran, a Considerable Diversity. *BJMG*. 2023;25(2):51-62.
40. Bilgen T, Canatan D, Arikan Y, Yeşilipek A, Keser İ. The effect of HBB:c.*+96T>C (3'UTR +1570 T>C) on the mild b-thalassemia intermedia phenotype. *Turk J Hemato*, 2011; 28(3), 219-22.

*Doi: 10.47572/muskutd.1490410*

# Predictors of In-Hospital Mortality in Patients with Acute Coronary Syndrome Referred from Non-Cardiology Clinics: A Comparison Between Medical Therapy and Percutaneous Coronary Intervention

# Kardiyoloji Dışı Kliniklerden Akut Koroner Sendrom İle Konsülte Edilen Hastalarda Hastane İçi Mortalite Öngördürücüleri: Tıbbi Tedavi Ve Perkütan Koroner Girişim Arasında Bir Karşılaştırma

**Gizem ÇABUK, Özgür KUŞ**

Izmir City Hospital, Department of Cardiology, Izmir, Turkiye

**Öz**

Akut koroner sendrom hastalarının, acil servise veya koroner yoğun bakım ünitesine doğrudan kabul edilenlere kıyasla, kardiyoloji dışı kliniklerde tedavi yönetimi daha zorlu olabilmektedir. Bu çalışmanın amacı, kardiyoloji dışı kliniklerde yatan akut koroner sendrom hastalarındaki hastane içi mortalite öngördürücülerini araştırmak ve sadece tıbbi tedavi ile veya ek olarak perkütan koroner girişim ile yönetilen hastalar arasındaki sonuçları karşılaştırmaktı. Bu retrospektif bir çalışmaydı. Ocak 2018 - Aralık 2023 arasında kardiyoloji dışı kliniklerden akut koroner sendrom olarak konsülte edilen hastalar (ST elevasyonlu miyokart enfarktüslü hastalar hariç) çalışmaya dahil edildi. Hastalar, tedavi yönetimine göre iki gruba ayrıldı: yalnızca tıbbi tedavi alanlar ve medikal tedaviye ek olarak koroner anjiyografi yapılanlar. Hastane içi mortalite açısından bağımsız öngördürücüler, ikili lojistik regresyon analizi kullanılarak belirlendi. Çalışmaya toplam 241 hasta dahil edildi. 112 hasta (%46.4) yalnızca tıbbi tedavi aldı (Grup 1), 129 hastaya (%53.6) koroner anjiyografi yapıldı (Grup 2) ve Grup 2'deki 69 hastaya perkütan koroner girişim uygulandı. Alt grup analizi, başlangıçtan itibaren medikal tedavi alan hastaların, perkütan koroner girişim uygulanan hastalara göre daha yüksek hastanede ölüm oranına sahip olduğunu gösterdi; medikal tedavi alan 172 hastadan 32'si (%18.6), perkütan koroner girişim uygulanan 69 hastadan 10'unda (%14.4) mortalite gelişti (p=0.040). İleri yaş, düşük serum albumin, yüksek bilirubin, üre ve kardiyak troponin seviyeleri ile COVID-19 enfeksiyonu artmış hastane içi mortalite ile ilişkili bulunurken, kardiyoloji dışı kliniklerden konsülte edilen akut koroner sendrom hastalarında perkütan koroner girişim, tek başına azalmış hastane içi mortalite ile ilişkiliydi.

**Anahtar Kelimeler:** Akut Koroner Sendrom, Mortalite, Perkütan Koroner Girişim

**Abstract**

The management of patients with acute coronary syndrome who are hospitalized in non-cardiology clinics can be more challenging compared to those admitted directly to the emergency department or coronary intensive care unit. The aim of this study was to investigate the predictors of in-hospital mortality in patients with acute coronary syndrome who were initially hospitalized in non-cardiology clinics, and to compare outcomes between those managed with medical therapy alone versus those who also underwent percutaneous coronary intervention. This was a retrospective study. We enrolled patients who were referred as acute coronary syndrome from non-cardiology clinics (excluding patients with ST elevation myocardial infarction) between January 2018 and December 2023. Patients were divided into two groups based on their management approach: those who received medical therapy only and those who also underwent coronary angiography. Independent predictors of in-hospital mortality were identified using binary logistic regression analysis. A total of 241 patients were included in this study. While 112 patients (46.4%) received medical therapy only (Group 1), 129 patients (53.6%) underwent coronary angiography (Group 2), and 69 of 129 patients underwent percutaneous coronary intervention. The subgroup analysis showed that patients receiving medical therapy from the onset after coronary angiography (CAG) had a higher in-hospital mortality rate (32 of 172 patients, 18.6%) than those undergoing percutaneous coronary intervention (PCI) (10 of 69 patients, 14.4%), with a p-value of 0.040. We found that while advanced age, low serum albumin, elevated bilirubin, blood urea nitrogen, and cardiac troponin levels, as well as COVID-19 infection were associated with increased in-hospital mortality; percutaneous coronary intervention was associated with reduced in-hospital mortality in patients with acute coronary syndrome who were referred from non-cardiology clinics.

**Keywords:** Acute Coronary Syndrome, Mortality, Percutaneous Coronary Intervention

## Introduction

The diagnosis of acute coronary syndrome (ACS) requires an elevation of cardiac troponin levels, and consultations from other clinics with suspicion of ACS always include this parameter. However, we are aware that various clinical conditions may lead to an increase in troponin levels (in the absence of coronary obstruction), such as ischemic or hemorrhagic cerebrovascular events, renal failure, severe infections causing sepsis, acidosis, extreme anemia, etc. Therefore, an additional finding related to cardiac ischemia (such as ischemic electrocardiographic or echocardiographic findings, ischemic symptoms, etc.) recommended in clinical guidelines is necessary (1). Managing patients with suspicion of ACS in the emergency department or outpatient clinic of cardiology is relatively straightforward for

| | ORCID No |
|---|---|
| Gizem ÇABUK | 0000-0002-3478-4611 |
| Özgür KUŞ | 0000-0001-8109-662X |

Başvuru Tarihi / Received: 28.05.2024
Kabul Tarihi / Accepted : 27.03.2025

Adres / Correspondence : Gizem ÇABUK
Izmir City Hospital, Department of Cardiology, Izmir, Turkiye

e-posta / e-mail : giizemcelik@gmail.com

a cardiologist. However, in clinics outside of cardiology, patients referred with suspicion of ACS often have multiple comorbidities that can impact our assessment and final decision. Current guidelines may not cover all scenarios for this specific population.

For example, when a patient hospitalized for an ischemic stroke event is referred from a neurology critical care unit with a high level of high-sensitive troponin T (hs-TnT), it is necessary to differentiate whether this elevation is due to acute coronary syndrome (ACS) or stroke. Patients with acute ischemic stroke and myocardial infarction share similar risk factors, leading to a high risk for subsequent ACS in stroke patients and vice versa (2). Up to 60% of ischemic stroke patients exhibit hs-TnT levels above the upper reference limit for defining myocardial injury. Diagnosing ACS becomes more challenging when other parameters, such as ECG or echocardiographic findings, are normal, especially in patients who are unable to communicate their symptoms (e.g., intubated). Furthermore, the addition of heparin to medical therapy for ACS increases the risk of hemorrhagic transformation of vulnerable ischemic brain tissue in this specific population. In conclusion, the diagnosis and therapeutic decision-making for such patients are complex and critical.

Patients at other clinics, such as surgery departments (referred in the perioperative period), gastroenterology (e.g., a patient with massive gastrointestinal bleeding), nephrology (e.g., a patient with atypical chest pain during hemodialysis and elevated hs-TnT level), and the anesthesiology intensive care unit (e.g., an intubated patient with metabolic acidosis, lobar pneumonia, and elevated hs-TnT level), should also be carefully evaluated for the final decision. When a patient's diagnosis is accepted as ACS (only unstable angina or non-ST elevation myocardial infarction for this study), they need to be treated medically or undergo percutaneous coronary intervention (PCI).

In this study, we aimed to determine the predictors of in-hospital mortality for high-risk patients diagnosed with ACS at non-cardiology clinics who were managed medically and/or underwent coronary angiography with/without PCI.

## Material and Method

*Study Design*

This was a retrospective single-center study. This study was carried out in accordance with the conditions of the declaration of Helsinki and approved by our local ethical committee.

*Study Population*

We enrolled patients who were referred as acute coronary syndrome from non-cardiology clinics (excluding patients with ST elevation myocardial infarction) between January 2018 and December 2023. Patients with relative contraindications to CAG (e.g., septic shock, active gastrointestinal bleeding), patients who refused coronary intervention or had a lack of recorded data, those with excessive exposure to contrast media (>500 mL) during percutaneous intervention, acute liver failure, recent hemorrhagic stroke (within 15 days), thyrotoxicosis, and patients who underwent coronary artery bypass surgery as a result of CAG (including ≥ 50% stenosis of the left main coronary artery) were excluded from the study. We analyzed digitally recorded data for demographic characteristics, risk factors, comorbidities, laboratory and echocardiographic findings, angiography findings and amount of contrast media, medications, and primary diagnosis of patients. We divided the patients into two groups: those who received medical therapy only (Group 1, n=112) and those who underwent coronary angiography in addition to medical therapy (Group 2, n=129). To determine the independent effect of interventional treatment and other possible factors on mortality, the study population was analyzed by dividing it into two subgroups: patients who survived (n=199) and those who experienced in-hospital exitus (n=42).

*Coronary Angiography, Monitorization and Further Management*

All coronary angiography procedures were performed via the femoral or radial (mostly radial) approach. Patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) pectoris underwent coronary angiography within 24 hours after diagnosis, according to the recommendations of recent guidelines (3). We used the Global Registry of Acute Coronary Events (GRACE) score to identify the risk category of patients, and the result of the score was one of the main factors in decision-making for our therapeutic choice (4). We used a non-ionic and low-osmolality contrast agent (Optiray© [Ioversol]) and administered it manually to all patients in our institution, and the amount of contrast media used was obtained from the digitally recorded data at the end of each intervention. All patients received acetylsalicylic acid and ticagrelor or clopidogrel, high-dose statin, heparin (before and during PCI), a beta-blocker (if possible), and an angiotensin-converting enzyme inhibitor (if possible). The second antiplatelet agent was loaded when it was decided to perform PCI. In cases where percutaneous coronary intervention (PCI) was deemed necessary, we used drug-eluting stents for all patients. The choice of stent size and type was based on the characteristics of the lesion and the vessel size. In cases where the lesion was considered complex or calcified (e.g. left main coronary lesions), we used intravascular ultrasound (IVUS) to guide our intervention.

We closely monitored all patients during the procedure for any signs of complications such as contrast-associated acute kidney injury (CA-AKI), hypotension, or arrhythmias. Immediate complications were managed promptly according to established protocols in our institution.

After the procedure, all patients were transferred to the coronary care unit for further monitoring and management. We provided detailed instructions to patients regarding their medications, lifestyle modifications, and follow-up appointments.

Overall, our approach to coronary angiography and PCI in patients with NSTEMI or UA pectoris was guided by evidence-based guidelines and individual patient characteristics. Our goal was to provide timely and effective treatment to improve outcomes and reduce the risk of future cardiovascular events.

*Statistical Analysis*

SPSS 21.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was applied to the variables to determine whether or not they were normally distributed. Categorical variables were presented as number and percentage, and all continuous variables were presented as median and percentiles due to the non-parametric distribution. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate.

**Table 1.** Baseline characteristics of Group 1 and 2.

| Parameter | Group 1 (n = 112) | Group 2 (n = 129) | p value |
|---|---|---|---|
| Age (years) | 70 (61.5 - 73.5) | 71.0 (64.5 - 81.0) | 0.052 |
| Gender (female), n (%) | 46 (41.1) | 58 (44.9) | 0.058 |
| Heart rate (bpm) | 86 (58 - 116) | 89 (54 - 121) | 0.074 |
| SBP (mmHg) | 126.8 (95.6 - 148.8) | 123.5 (92.6 - 145.9) | 0.158 |
| BMI (kg/m$^2$) | 24.4 (19.6 - 28.8) | 23.8 (19.1 - 27.6) | 0.452 |
| Smoking, n (%) | 31 (27.6) | 42 (32.5) | 0.126 |
| Hypertension, n (%) | 72 (64.3) | 83 (64.4) | 0.993 |
| Diabetes mellitus, n (%) | 54 (48.2) | 70 (54.2) | **0.044** |
| Dyslipidemia, n (%) | 45 (40.1) | 58 (44.9) | 0.096 |
| History of CHD, n (%) | 15 (13.3) | 18 (13.9) | 0.882 |
| Ejection fraction (%) | 50.5 (42.5 - 55.0) | 45.5 (40.5 - 50.5) | **0.008** |
| GRACE score | 112.3 (82.5 - 131.8) | 132.7 (94.4 - 168.4) | **0.004** |
| Glucose (mg/dl) | 147.0 (112.0 - 196.0) | 134.0 (100.5 - 214.5) | 0.546 |
| BUN (mg/dl) | 89.0 (55.5 - 127.0) | 61.5 (36.5 - 100.0) | **< 0.001** |
| Creatinine (mg/dl) | 1.5 (1.2 - 2.6) | 1.3 (0.9 - 2.7) | 0.055 |
| AST (U/L) | 41.0 (26.0 - 78.0) | 34.0 (20.0 - 76.0) | 0.081 |
| ALT (U/L) | 30.0 (16.0 - 54.0) | 26.0 (18.0 - 46.0) | 0.485 |
| Sodium (mEq/L) | 137.0 (134.0 - 140.0) | 136.0 (134.0 - 139.0) | 0.207 |
| Potassium (mmol/L) | 4.3 (3.8 - 4.7) | 4.2 (3.8 - 4.6) | 0.433 |
| Albumin (g/dl) | 2.8 (2.2 - 3.1) | 3.1 (2.8 - 3.5) | **< 0.001** |
| Total Bilirubin (mg/dl) | 0.6 (0.4 - 1.1) | 0.5 (0.4 - 1.0) | 0.180 |
| CRP (mg/dl) | 108.0 (55.0 - 172.0) | 66.0 (19.5 - 179.5) | **0.001** |
| Troponin (ng/L) | 24.5 (11.5 - 120.0) | 58.0 (21.0 - 143.0) | **0.024** |
| Hemoglobin (g/dl) | 9.6 (8.2 - 11.6) | 10.1 (8.8 - 11.7) | 0.160 |
| Hematocrit (%) | 29.0 (24.0 - 33.5) | 30.0 (26.5 - 34.0) | 0.082 |
| WBC (×10$^9$/L) | 11.8 (8.2 - 16.8) | 10.1 (8.1 - 15.4) | 0.339 |
| Platelet (×10$^6$/L) | 221.0 (153.0 - 312.0) | 236.5 (166.5 - 299.5) | 0.414 |
| Infection, n (%) | 18 (16.1) | 28 (21.7) | 0.060 |
| Covid-19, n (%) | 14 (12.5) | 36 (27.9) | **0.018** |
| AKI, n (%) | 14 (12.5) | 16 (12.4) | 0.980 |
| GI bleeding, n (%) | 4 (3.6) | 5 (3.4) | 0.898 |
| Stroke, n (%) | 7 (4.7) | 7 (5.4) | 0.504 |
| Postoperative, n (%) | 12 (10.7) | 12 (9.3) | 0.466 |
| DKA/HHNC, n (%) | 3 (2.7) | 4 (3.1) | 0.920 |
| Duration of Hospitalization (day) | 8.3 (4.6 - 11.8) | 7.5 (4.5 - 10.5) | **0.008** |
| Amount of CM (ml) | | 32.5 (24.5 - 84.0) | |
| CA-AKI, n (%) | | 2 (1.5) | |
| Medications | | | |
| Antiplatelet | 22 (14.7) | 16 (12.4) | 0.541 |
| Oral Anticoagulant | 8 (5.3) | 5 (3.8) | 0.125 |

AKI; acute kidney injury, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BUN; blood urea nitrogen, CRP; C-reactive protein, DKA; diabetic ketoacidosis, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, hs; high-sensitive, SBP; systolic blood pressure, WBC; white blood cell

The Mann-Whitney U test was used to compare parameters that were not normally distributed. We performed binary logistic regression analysis to determine the independent predictors of in-hospital mortality after eliminating one of the parameters that showed a significant correlation with each other. Therefore, we performed two regression models in a stepwise fashion with a forward likelihood model;

one of them included the CAG status, and the other one included the intervention status as a categorical variable. Pairs such as urea-creatinine and hemoglobin-hematocrit, which were found to have a significant linear correlation, were also analyzed separately. We presented the results of the variables that were significantly related to in-hospital mortality. We conducted a prior power analysis based on the average results obtained from the in-hospital mortality data of randomized studies comparing conservative and invasive treatments in patients with acute coronary syndrome over the past decade. The calculated sample size, effect size, type I error probability, and power values we obtained are as follows: 242, 0.362, 0.05 and 0.80. When compared to our sample size calculation, one group had 9 fewer patients, while the other group had 8 more patients. Therefore, a post-hoc power analysis was also conducted based on the number of patients included in the study and the average of composite endpoint incidences. The calculated *Cohen's h* value found to be 0.118 and power value was found to be 0.974. All statistical testing was based on a 2-sided $\alpha = 0.05$ significance level.

**Table 2.** Comparison of baseline characteristics between patients who survived and those who died during the in-hospital period.

| Parameter | Survived (n = 199) | Exitus (n = 42) | p value |
|---|---|---|---|
| Age (years) | 68.5 (60.0 – 73.5) | 72.0 (62.5 – 81.5) | **0.030** |
| Gender (female), n (%) | 86 (43.2) | 18 (42.8) | 0.864 |
| Heart Rate (bpm) | 82 (59-118) | 85 (50 - 126) | 0.150 |
| SBP (mmHg) | 122 (94.0 – 135.0) | 118 (91.0 - 130.0) | 0.086 |
| BMI ($kg/m^2$) | 23.8 (18.9- 27.5) | 25.1 (19.3 - 29.7) | 0.258 |
| Smoking, n (%) | 60 (30.1) | 13 (30.9) | 0.820 |
| Hypertension, n (%) | 128 (64.3) | 27 (64.2) | 0.952 |
| Diabetes Mellitus, n (%) | 102 (51.2) | 22 (52.3) | 0.285 |
| Dyslipidemia, n (%) | 85 (42.7) | 18 (42.9) | 0.950 |
| History of CHD, n (%) | 27 (13.5) | 6 (14.2) | 0.290 |
| Ejection Fraction (%) | 51.0 (46.0 - 56.0) | 49.0 (44.5 - 55.5) | 0.098 |
| GRACE score | 111.0 (88.0 - 135.0) | 138.5 (105.5 - 172.3) | **0.001** |
| Glucose (mg/dL) | 129.0 (108.0 - 175.0) | 132.5 (97.0 - 218.0) | 0.110 |
| BUN (mg/dl) | 58.0 (42.0 - 96.0) | 78.50 (52.0 - 122.0) | **0.002** |
| Creatinine (mg/dl) | 1.19 (1.02 - 1.90) | 1.38 (1.10 - 2.22) | **0.035** |
| AST (U/L) | 41.0 (22.5 - 86.0) | 45.5 (23.5 - 78.5) | 0.060 |
| ALT (U/L) | 24.5 (18.5 – 54.0) | 27.5 (19.0 - 53.5) | 0.345 |
| Sodium (mEq/L) | 132.5 (128.5 - 136.0) | 134.0 (130.5 - 139.5) | 0.186 |
| Potassium (mmol/L) | 4.3 (3.7 - 4.9) | 4.2 (3.8 - 4.8) | 0.660 |
| Albumin (g/dL) | 3.8 (2.8 - 4.4) | 2.2 (1.9 - 3.0) | **< 0.001** |
| Total Bilirubin (mg/dL) | 0.42 (0.31 - 1.0) | 0.95 (0.55 - 1.80) | **0.002** |
| CRP (mg/dL) | 64.0 (42.0 - 105.5) | 72.5 (48.5 - 124.5) | **0.040** |
| Troponin (ng/L) | 42.0 (28.0 - 110.0) | 58.5 (35.0 - 139.5) | **0.003** |
| Hemoglobin (g/dL) | 10.9 (9.2 – 12.8) | 10.2 (8.4 - 11.6) | 0.550 |
| Hematocrit (%) | 29.4 (26.5 – 35.4) | 28.8 (25.1 - 33.2) | 0.332 |
| WBC ($\times 10^9$/L) | 10.2 (8.4 - 15.4) | 11.4 (8.9 - 18.5) | 0.184 |
| Platelet ($\times 10^6$/L) | 228.5 (161.0 - 315.0) | 230.0 (162.5 - 321.0) | 0.640 |
| Infection, n (%) | 38 (19.1) | 8 (19.0) | 0.896 |
| COVID-19, n (%) | 35 (17.6) | 15 (35.7) | **< 0.001** |
| AKI, n (%) | 25 (12.5) | 5 (11.9) | 0.285 |
| GI bleeding, n (%) | 8 (4.0) | 1 (2.4) | 0.089 |
| Stroke, n (%) | 11 (5.5) | 3 (4.8) | 0.072 |
| Postoperative, n (%) | 20 (10.0) | 4 (9.5) | 0.788 |
| DKA/HHNC, n (%) | 6 (3.0) | 1 (2.4) | 0.115 |
| PCI | 59 (29.6) | 10 (23.8) | **0.001** |

AKI; acute kidney injury, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, BUN; blood urea nitrogen, CHD; coronary heart disease, CRP; C-reactive protein, DKA; diabetic ketoacidosis, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, hs; high-sensitive, PCI; percutaneous coronary intervention, SBP; systolic blood pressure, WBC; white blood cell.

## Results

A total of 241 patients were included in this study. While 112 patients (46.4%) received medical therapy only (Group 1), 129 patients (53.6%) underwent CAG (Group 2). The median age (70 [61.5 - 73.5] vs 71 [64.5 - 81.0], p=0.052) and sex (female patients; n=46 [41.1] vs n=58 [44.9], p=0.058) distribution for Group 1 and 2 were similar. All parameters (laboratory findings including troponin level, primary diagnosis of patients, risk factors such as hypertension and diabetes mellitus, ejection fraction, amount of contrast media, and contrast-associated acute kidney injury percentages) in addition to the demographic characteristics of patients were presented in Tables 1 and 2.

Upon analyzing the results based on whether patients underwent coronary angiography (CAG), we found significant differences in ejection fraction (EF),

serum BUN, albumin, CRP, and troponin levels, as well as the prevalence of diabetes mellitus (DM) and COVID-19 infection between the two groups (Group 1 and Group 2) (Table 1). The number of patients who underwent PCI was significantly higher in the group of participants who survived compared to those who did not (59 of 199 patients [29.6%] vs 10 of 42 patients [23.8%], p=0.001) (Table 2). The subgroup analysis of in-hospital mortality indicated that patients receiving medical therapy from the onset and as a result of CAG had a significantly higher mortality rate (32 of 172 patients, 18.6%) compared to those who underwent PCI (10 of 69 patients, 14.4%), with a p-value of 0.040.

**Table 3.** The results of binary logistic regression analysis.

| | | 95% CI of OR's | | |
|---|---|---|---|---|
| **Parameters (reference category)** | **Odds Ratio** | **Lower** | **Upper** | **p value** |
| Age | 1,15 | 1,011 | 1,091 | **0.006** |
| Gender (female) | 0,89 | 0,375 | 2,113 | 0.791 |
| HT (-) | 0,863 | 0,346 | 2,156 | 0.752 |
| DM (-) | 0,952 | 0,408 | 2,226 | 0.910 |
| PCI (-) | 0,095 | 0,036 | 0,249 | **< 0.001** |
| Infection (-) | 1,435 | 0,413 | 4,985 | 0.570 |
| COVID-19 (-) | 2,01 | 1,425 | 4,615 | **0.012** |
| EF | 0,975 | 0,901 | 1,21 | 0.286 |
| BUN | 1,18 | 1,08 | 1,218 | **0.001** |
| Albumin | 0,16 | 0,063 | 0,407 | **< 0.001** |
| Bilirubin | 2,207 | 1,409 | 3,455 | **< 0.001** |
| CRP | 0,997 | 0,993 | 1,002 | 0.237 |
| Hemoglobin | 0,973 | 0,788 | 1,202 | 0.800 |
| WBC | 1,007 | 0,989 | 1,026 | 0.449 |
| AKI (-) | 0,783 | 0,245 | 2,504 | 0.680 |
| GI bleeding (-) | 0,303 | 0,036 | 2,534 | 0.270 |
| Stroke (-) | 0,168 | 0,021 | 1,365 | 0.095 |
| Postoperative (-) | 0,861 | 0,234 | 3,174 | 0.882 |
| DKA/HHNC (-) | 0,577 | 0,035 | 4,476 | 0.700 |
| Troponin | 1,641 | 1,18 | 2,282 | **< 0.001** |

*The p-value of the model's Hosmer-Lemeshow test was found to be 0.23", AKI; acute kidney injury, BUN; blood urea nitrogen, CRP; C-reactive protein, DKA; diabetic ketoacidosis, DM; diabetes mellitus, EF; ejection fraction, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, HT; hypertension, PCI; percutaneous coronary intervention, WBC; white blood cell., Dependent variable: In-hospital Mortality

The study population was also compared based on whether in-hospital mortality occurred. While age, GRACE score, the number of patients with Covid-19, BUN, creatinin, total bilirubin, and troponin levels were significantly higher in patints who died during in-hospital period; serum albumin level was significantly higher in patient who survived (Table 2). The number of patients who underwent PCI was significantly higher in the group of participants who survived compared to those who did not (Table 2).

All percutaneous interventions were successful, and no major complications were recorded. The incidence of contrast-associated acute kidney injury (CA-AKI) was 1.5% (n=2) in Group 2 and 17.3% (n=12) in patients who further underwent PCI; however, none of them required hemodialysis, and their renal functions returned to the normal range during the in-hospital period. We observed exitus in only 1 of the 14 cases with CA-AKI; therefore, we did not include this parameter in the regression analysis.

We also took possible confounders into account in terms of being predictors of in-hospital mortality. The binary logistic regression models revealed that advanced age, elevated total bilirubin, BUN, and troponin levels, decreased serum albumin, and the presence of COVID-19 infection were significant predictors of in-hospital mortality (Figure 1 and Table 3). After adjusting for all confounders, the analysis showed that PCI and elevated serum albumin levels were significantly associated with lower in-hospital mortality (Figure 1 and Table 3). Serum creatinine levels (data not shown due to a separate regression analysis correlating with BUN) and CRP levels (see Figure 1 and Table 3) were found to have no significant relationship with in-hospital mortality.

## Discussion

Predicting in-hospital mortality for high-risk patients with acute coronary syndrome (ACS) is crucial for improving patient outcomes. Comparing outcomes between patients who received medical therapy only and those who underwent PCI can provide valuable insights into the effectiveness of different treatment approaches. Several randomized controlled trials and meta-analyses of many randomized trials have evaluated conservative versus invasive approaches, and they supported an early invasive strategy for patients who are at moderate to high risk (5).

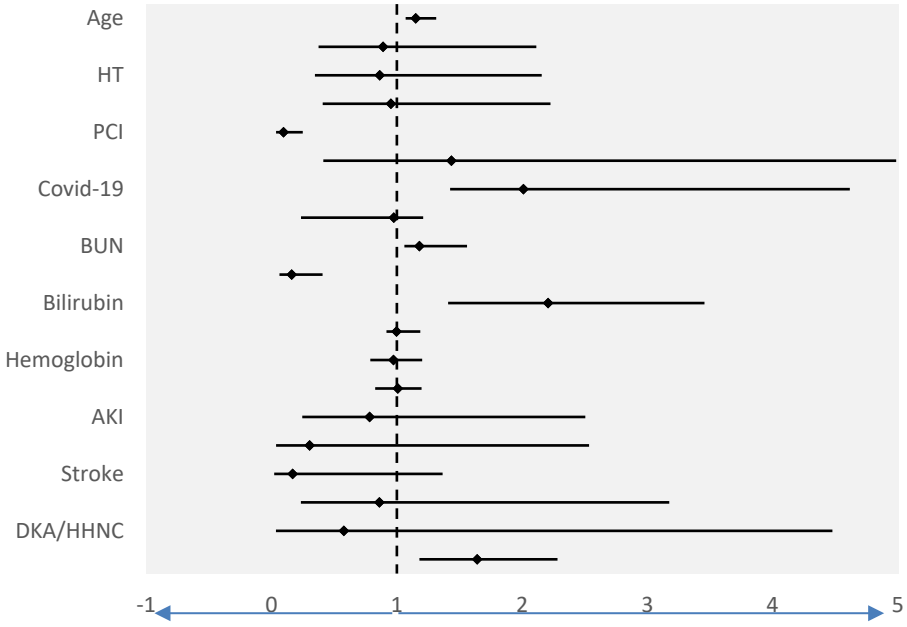



**Figure 1.** Forest plot graphic for possible predictors of in-hospital mortality.

We found that in-hospital mortality was significantly lower in the PCI group, although the number of patients managed conservatively was higher compared to the invasive management group due to the high-risk factors of our study patients (such as active infection, hemodynamic instability, frailty, recent stroke, etc.). The remaining patients who had no such risk factors and received only medical therapy were at relatively low risk according to the GRACE score. After adjusting for key covariates, we identified serum albumin levels as having a negative relationship with in-hospital mortality, while BUN, bilirubin, and troponin levels were positively associated with increased mortality.

A meta-analysis showed that serum albumin level is an independent predictor of all-cause mortality (risk ratio [RR] 2.15; 95% confidence interval [CI] 1.68 - 2.75) in patients with ACS (6). However, clinical trials could not demonstrate that correcting serum albumin level by intravenous infusion decreases the mortality rate in ACS patients. It was also shown in a study that serum albumin (< 3.65 mg/dL) at admission was an independent predictor of high SYNTAX score (odds ratio 4.329, 95% confidence interval 2.028 - 8.264; $p < 0.001$) and in-hospital all-cause mortality in patients with ACS (7). Another clinical trial demonstrated that serum albumin level ≤ 3.50 g/dl was an independent predictor of new-onset heart failure and in-hospital mortality in this patient group (8). The inflammatory state may be speculated as an underlying mechanism for hypoalbuminemia in this clinical setting. Hypoalbuminemia was linked with increased oxidative stress, platelet activation and aggregation, which triggered thrombotic events; moreover, low albumin level can result in decreased formation of lipoxins, resolvins and protectins, tilting the balance more toward pro-inflammatory events, leading to an increased risk of death for the critically ill (9,10).

Another marker we found to be linked with increased in-hospital mortality in our study population was BUN level. Kirtane et al. (11) found that among patients with ACS and normal to mildly reduced glomerular filtration rate (GFR), an elevated BUN was associated with increased mortality independent of other biomarkers. An elevated BUN may reflect a state of renal hypoperfusion due to hypovolemia, renovascular disease, or reduced cardiac output. In these states, BUN may rise independent of a change in GFR or serum creatinin due to enhanced urea reabsorption under activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (12). This may be of particular relevance in patients with milder reductions in glomerular filtration rate. Another prospective study showed that patients with BUN > 32.5mg/dl were almost 20 times more likely to be associated with mortality as compared to reference group (13).

The other marker which we found to be related to mortality was total bilirubin. In a meta-analysis it was shown that elevated serum total bilirubin level was significantly positively associated with in-hospital cardiovascular death and MACE in patients with ACS (14). Bilirubin is an endogenous antioxidant, which resists the oxidative modification of low-density lipoprotein cholesterol, participates in scavenging oxygen-free radicals, and increases

heme oxygenase activity and the ability of serum cholesterol to dissolve. The level of bilirubin increased transiently in the acute phase of AMI and returned to the normal instantly, and initial serum bilirubin levels may reflect the severity of acute myocardial damage (15). In our study serum bilirubin levels were measured at the time of the diagnosis of ACS; therefore, this might be a coincidental finding.

Lastly, and not surprisingly, elevated serum troponin level was an independent predictor of mortality in our study, which is a well-known fact in the literature.

We also included primary diagnoses of the study population into the binary logistic regression analysis to see whether a specific comorbidity was related to in-hospital mortality or not. None of the diagnoses were significantly related to in-hospital mortality, except Covid-19 infection. In a recent trial, it was shown that gastrointestinal bleeding was not related to in-hospital mortality in patients with acute cardiovascular diseases; however, it was an independent risk factor for subsequent cardiovascular events (16). Another study revealed that PCI is safe in patients with recent ischemic stroke, and showed that the primary endpoints (composite of death, recurrent MI, coronary re-intervention, recurrent stroke, or bleeding during 1-year follow-up) were not enhanced in the PCI arm compared to the medical therapy arm (17). In a recent trial, it was shown that in-hospital mortality and follow-up events were not significantly increased in patients with ACS and concomitant chronic kidney disease (eGFR < 60 mL/kg/m2) for whom an early invasive approach was preferred (18). Patel et al. (19) had also found that the incidence of acute kidney injury requiring dialysis and in-hospital mortality among patients with chronic kidney disease and ACS were not significantly related to the timing of PCI. Recent studies showed that 7 - 36% of patients with COVID-19 infection develop myocardial injury (20,21). The results of a meta-analysis by Santoso A. et al. (22) demostrated that acute myocardial injury concomitant with COVID-19 infection was associated with a more severe clinical picture (RR 13.81, $p < 0.001$; I2: 0%), more frequent hospitalizations in intensive care units (RR 7.94, $p = 0.01$; I2: 79%), and higher mortality rates (RR 7.95, $p < 0.001$; I2: 65%). The results of an observational cohort study also revealed that patients with COVID-19 and ACS had higher in-hospital (OR: 3.27; 95% (CI): 2.41 - 4.42) and thirty-day (OR: 6.53, 95% CI: 5.1 - 8.36) mortality, compared to patients with ACS without a diagnosis of COVID-19 infection (23). The SARS-CoV-2 virus can directly cause myocardial injury by entering cardiomyocytes through the angiotensin-converting enzyme 2 (ACE-2) receptors. Upon binding to the ACE-2 receptors, the virus leads to the downregulation of these receptors, resulting in decreased synthesis of angiotensin (1-7) and increased activity of angiotensin II. The predominance of angiotensin II then triggers a cascade of pathological processes, including systemic vasoconstriction, apoptosis, inflammation, and proliferation, ultimately leading to de novo cardiomyocyte damage or worsening of pre-existing cardiovascular disease. In addition to the direct viral effects, COVID-19-associated myocardial injury can also be mediated by indirect mechanisms, such as cytokine release, microvascular dysfunction (due to intravascular coagulation and thrombosis), hypoxemia, and inflammation. These factors can contribute to myocardial injury by destabilizing existing atherosclerotic plaques and causing an increase in cardiac troponin levels (21,24). We found in our study that COVID-19 infection was an independent predictor of in-hospital mortality in patients with ACS (OR: 2.01, 95% CI [1.425 - 4.615], $p = 0.012$).

*Limitations of the study*

First of all, this study was a retrospective, single-center study with a relatively small sample size, which limits the ability to make definitive conclusions about the underlying pathophysiological mechanisms and generalizability. Another limitation of our study is that the decision for intervention was based on the operator's clinical experience rather than fractional flow reserve measurements.

## Conclusion

We found that advanced age, low serum albumin, elevated bilirubin, BUN, cardiac troponin levels, and COVID-19 infection were linked to increased in-hospital mortality in patients with acute coronary syndrome referred from other clinics. Notably, percutaneous intervention was associated with a reduction in in-hospital mortality for this patient population.

## Acknowledgements

Special thanks to Professor Dr. Öner ÖZDOĞAN for his invaluable contributions to our study

## Conflict of interest statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

**Ethics Committee Approval:** Ethical Committee of Tepecik Training and Research Hospital (13.07.2023; 2023/ 06-36)

**Funding:** None declared.

## References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction. Circulation. 2018;138(20):e618-e651.
2. Boulanger M, Béjot Y, Rothwell PM, et al. Long-term risk of myocardial infarction compared to recurrent stroke after transient ischemic attack and ischemic stroke: systematic review and meta-analysis. J Am Heart Assoc. 2018;7(2):e007267.
3. Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-367.
4. Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study (GRACE). Br. Med. J. 2006;333(7578):1091–4.
5. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol. 2006;48(7):1319-25.
6. Zhu L, Chen M, Lin X. Serum albumin level for prediction of all-cause mortality in acute coronary syndrome patients: a meta-analysis. Biosci Rep. 2020;40(1):BSR20190881.
7. Kurtul A, Murat SN, Yarlioglues M, et al. Usefulness of Serum Albumin Concentration to Predict High Coronary SYNTAX Score and In-Hospital Mortality in Patients With Acute Coronary Syndrome. Angiology. 2016;67(1):34-40.
8. González-Pacheco H, Amezcua-Guerra LM, Sandoval J, et al. Prognostic Implications of Serum Albumin Levels in Patients With Acute Coronary Syndromes. Am J Cardiol. 2017;119(7):951-8.
9. Plakht Y, Gilutz H, Shiyovich A. Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II) project. Int J Cardiol. 2016;219:20-4.
10. Das UN. Albumin infusion for the critically ill–is it beneficial and, if so, why and how? Crit Care. 2015;19(1):156.
11. Kirtane AJ, Leder DM, Waikar SS, et al. TIMI Study Group. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. J Am Coll Cardiol. 2005;45(11):1781-6.
12. Usberti M, Federico S, Di Minno G, et al. Effects of angiotensin II on plasma ADH, prostaglandin synthesis, and water excretion in normal humans. Am J Physiol. 1985;248(2):254-9.
13. Adam AM, Nasir SAR, Merchant AZ, et al. Efficacy of serum blood urea nitrogen, creatinine and electrolytes in the diagnosis and mortality risk assessment of patients with acute coronary syndrome. Indian Heart J. 2018;70(3):353-9.
14. Shen H, Zeng C, Wu X, et al. Prognostic value of total bilirubin in patients with acute myocardial infarction: A meta-analysis. Medicine (Baltimore). 2019;98(3):e13920.
15. Okuhara K, Kisaka T, Ozono R, et al. Change in bilirubin level following acute myocardial infarction is an index for heme oxygenase activation. South Med J. 2010;103(9):876-81.
16. Sakai S, Tara S, Yamamoto T, et al. Gastrointestinal bleeding increases the risk of subsequent cardiovascular events in patients with acute cardiovascular diseases requiring intensive care. Heart Vessels. 2021;36(9):1327-35.
17. Zeus T, Ketterer U, Leuf D, et al. Safety of percutaneous coronary intervention in patients with acute ischemic stroke/transient ischemic attack and acute coronary syndrome. Clin Res Cardiol. 2016;105(4):356-63.
18. Sacco A, Montalto C, Bravi F, et al. Non-ST-elevation acute coronary syndrome in chronic kidney disease: prognostic implication of an early invasive strategy. Minerva Cardiol Angiol. 2023;71(1):44-50.
19. Patel B, Carson P, Shah M, et al. Acute kidney injury requiring dialysis and in-hospital mortality in patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome undergoing early vs delayed percutaneous coronary intervention: A nationwide analysis. Clin Cardiol. 2017;40(12):1303-8.
20. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
21. Lala A, Johnson KW, Januzzi JL, et al. Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. J Am Coll Cardiol. 2020;76(5):533-46.
22. Santoso A, Pranata R, Wibowo A, et al. Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: A meta-analysis. Am J Emerg Med. 2021;44:352-7.
23. Rashid M, Wu J, Timmis A, et al. Outcomes of COVID-19-positive acute coronary syndrome patients: A multisource electronic healthcare records study from England. J Intern Med. 2021;290(1):88-100.
24. Chilazi M, Duffy EY, Thakkar A, et al. COVID and Cardiovascular Disease: What We Know in 2021. Curratheroscler Rep. 2021;23(7):37.

*Doi: 10.47572/muskutd.1484687*

# Percutaneous Pinning Method and Our Results in Unstable Distal Radius Fractures

# Stabil Olmayan Radius Distal Uç Kırıklarında Perkütan Çivileme Yöntemi ve Sonuçlarımız

**Burak ŞENER[1], Mustafa Faik SEÇKİN[2], Şenol AKMAN[3], Adnan KARA[4], İrfan ÖZTÜRK[2]**

[1]Mugla Sıtkı Kocman University. Orthopedics and Traumatology. Muğla. Turkey
[2]Istanbul Science University. Orthopedics and Traumatology. Istanbul. Turkey
[3]Orthopedics and Traumatology. Istanbul. Turkey
[4]Istanbul Medipol University. Orthopedics and Traumatology. Istanbul. Turkey

**Öz**

Distal radius kırıkları tüm vücut kırıkları arasında en sık görülen kırık tipidir. Bu kırıkların tedavisinde çeşitli cerrahi yöntemler tanımlanmış olmasına rağmen standart tedavi yöntemi tartışmalıdır. Stabil olmayan distal radius kırık tedavisinde kapalı redüksiyon ve perkütan çivileme yöntemi önerilmesine rağmen bu yöntemin tedavideki rolü belirsizdir. Bu çalışmanın amacı; kapalı redüksiyon ve perkütan çivileme yönteminin sonuçlarını prospektif olarak değerlendirmektir. Bu prospektif çalışmaya stabil olmayan distal radius kırığı bulunan 30 hastanın 30 el bileği dahil edildi. Hastaların 16'sı kadın, 14'ü erkekti. Ortalama takip süresi 13,1 ± 3,2 ay (aralık: 6-24 ay) dı . Ortalama hasta yaşı 49,63 ± 18,66 yıl (aralık: 20-85 yıl) idi. Kırıklar Frykman sınıflamasına göre değerlendirildi. Hastaların kontrol grafileri Steward kriterlerine göre değerlendirildi. Steward radyolojik kriterlerine göre; olgularımızın 6'sında mükemmel, 17'sinde iyi, 6'sında orta, 1'inde kötü sonuç alınmıştır. Gartland-Werley klinik değerlendirme kriterlerine göre; 30 hastanın 6'sında mükemmel, 17'sinde iyi, 6'sında orta, 1'inde kötü sonuç alınmıştır. Distal Radius kırıklarında kapalı redüksiyon ve perkütan çivileme yönteminin uygun redüksiyon sağlanabilen her hastaya uygulanabileceği, klinik ve radyolojik sonuçların diğer yöntemlere göre kabul edilebilir olduğu düşünülebilir.

**Anahtar Kelimeler:** Perkütan, Radius, Stabilizasyon

**Abstract**

Distal radius fractures are the most common type of fracture among all body fractures. Although various surgical methods have been described for the treatment of these fractures, the standard treatment method is controversial. Despite the recommendation of closed reduction and percutaneous pinning for the treatment of unstable distal radius fractures, the role of this method in treatment is uncertain. The aim of this study is to evaluate the results of closed reduction and percutaneous pinning method prospectively. Unstable distal radius fractures were included in this prospective study, involving 30 wrists. Sixteen patients were female and 14 were male. The mean follow-up time was 13.1 ± 3.2 months (range: 6-24 months). The mean patient age was 49.63 ± 18.66 years (range: 20-85 years). The fractures were evaluated according to Frykman classification. Patients follow-up X-rays were evaluated according to Steward criteria. According to Steward radiological criteria; in our cases, 6 were excellent, 17 were good, 6 were fair, and 1 was poor. According to Gartland-Werley clinical evaluation criteria; 6 of the 30 patients were excellent, 17 were good, 6 were fair, and 1 was poor.

**Keywords:** Percutaneous, Radius, Stabilization

## Introduction

Distal radius fractures are the most common type of fractures among all body bone fractures. They make up about 8-15% of all fractures (1). 75-80% of these are stable non-articular fractures and are treated conservatively in the emergency department (2).

In selecting treatment methods, factors such as the type of fracture, age of the patient, lifestyle, associated health issues, compliance with treatment, and physical and mental capacity should be taken into consideration(3). The majority of these fractures can be treated conservatively. However, the clinical and functional unsuccessful results observed in the conservative treatment of complex type unstable fractures seen in young individuals with high-energy trauma have led to new approaches in treatment.

Various surgical intervention methods and fixation materials have been described for the treatment of unstable fractures, but a standard treatment method has not been established. Surgical treatment alternatives include percutaneous pinning or external fixation after closed reduction, limited open or open reduction followed by pinning, internal fixation, some combinations of these procedures, and additional procedures such as grafting, arthroscopy-assisted reduction and stabilization (2).

In this study, patients with distal radius fractures treated prospectively with closed reduction and fixation with a plaster splint were followed up and the treatment outcomes were evaluated radiologically, clinically, and functionally.

| | ORCID No |
|---|---|
| Burak ŞENER | 0000-0002-5998-5807 |
| Mustafa Faik SEÇKİN | 0000-0002-5037-2772 |
| Şenol AKMAN | 0009-0001-5599-1476 |
| Adnan KARA | 0000-0001-8437-5405 |
| İrfan ÖZTÜRK | 0009-0000-9883-6786 |

Başvuru Tarihi / Received: 11.06.2024
Kabul Tarihi / Accepted : 08.01.2025

Adres / Correspondence : Mehmet Ferdi KINCI
Mugla Sıtkı Kocman University. Orthopedics and Traumatology. Muğla. Turkey
e-posta / e-mail : b.sener@yahoo.com.tr

## Material and Method

Between September 2002 and June 2004, a total of 30 patients with unstable distal radius fractures who presented to the emergency department of the Orthopedics and Traumatology Clinic at Istanbul

University Health Sciences Şişli Etfal Training and Research Hospital were included in our study. Of these patients, 16 were female (54%) and 14 were male (46%), with a female-to-male ratio of 1.14. The average age was found to be 43.8 years (ranging from 14 to 79).

Among the cases, 16 were aged between 20-44 (52%), 10 were aged between 45-60 (33%), and 4 were above 60 years old (15%). There were 11 fractures on the right side (36%) and 19 on the left side (64%). According to the mechanism of injury, 4 fractures (13%) were caused by non-traffic accidents, 4 (13%) by falls from height, and 22 (74%) by falls while walking. . The mean follow-up time was 13.1 ± 3.2 months (range: 6-24 months). The mean patient age was 49.63 ± 18.66 years (range: 20-85 years). The fractures were evaluated according to Frykman classification. Patients follow-up X-rays were evaluated according to Steward criteria. According to Steward radiological criteria; in our cases, 6 were excellent, 17 were good, 6 were fair, and 1 was poor. According to Gartland-Werley clinical evaluation criteria; 6 of the 30 patients were excellent, 17 were good, 6 were fair, and 1 was poor. In this study, a cross-tabulation (Crosstabs) analysis was conducted to evaluate the relationship between clinical and radiological findings. Pearson Chi-Square test was applied to assess statistical significance. All analyses were performed using SPSS (IBM SPSS Statistics, version X). A p-value of <0.05 was considered statistically significant.

Patients who presented to the emergency clinic with wrist trauma underwent physical examination, followed by routine wrist AP and lateral X-rays. Using a purposive sampling method fractures of the distal radius up to 2.5 cm proximal to the wrist joint were classified as distal radius fractures based on the X-ray findings. Cases that were determined to be unstable according to LaFontaine et al.s criteria formed our study group. Fractures were evaluated using Frykmans classification, with 10 cases being Frykman type 1, 6 cases type 2, 2 cases type 3, 1 case type 4, 2 cases type 6, 2 cases type 7, and 7 cases type 8. (Table 1).

**Table 1.** Fracture types according to Frykman Classification

| Tip | 1 | 2 | 3 | 4 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| | 10 | 6 | 2 | 1 | 2 | 2 | 7 |

*Surgical Procedure:*

Except for two patients, all patients were operated on as outpatient cases. The patients we couldnt treat as outpatients were those with hip fractures. Eight of our patients (26%) were operated on on the first day after the trauma, while 22 (74%) were operated on on the second day or later. The average time between the date of application and the date of operation was 4.56 (0-16) days. Following anesthesia consultations, general anesthesia was administered to 5 patients in good condition, while regional anesthesia was applied to 25 patients. Patients were placed in a supine position in the operating room. Following anesthesia administration, 2 grams of intravenous Sodium Cefazolin was prophylactically administered. After necessary cleaning and draping, traction was applied from the proximal fingers and forearm while the elbow was flexed at 90 degrees. After approximately half a minute of straight traction, the distal part was brought into flexion to reduce the fracture. The adequacy of reduction was checked with fluoroscopy. In patients where reduction was not adequate, the reduction maneuver was repeated. In patients where the desired reduction was achieved, two cross K wires were sent from the radial styloid proximally under fluoroscopy control, and if the fractures were considered unstable, one or more K wires were sent from the ulnar side. The ends of the wires were bent and a short arm circular cast was applied in neutral position. Patients who had post-operative wrist AP and lateral radiographs taken, were explained in detail about circulation monitoring, discharged on the same day, and called for circulation control the next day. Patients called for film and exercise control in the 1st, 2nd, 3rd week after the operation were called for radiographic control six weeks later. Patients with sufficient healing had their casts removed, and the K wires were removed. Early wrist and forearm pronation-supination exercises were started. Patients follow-up radiographs were evaluated according to Steward and colleagues radiological evaluation criteria (6). The Gardland-Werley clinical evaluation system was used for examining clinical outcomes (7).

## Results

According to the evaluation criteria of Gardland Werley Clinic, excellent results were obtained in 6 out of 30 patients (20%), good results in 17 patients (57%), moderate results in 6 patients (20%), and poor results in 1 patient (3%) (Table 2).

**Table 2.** Clinical results according to Gartland-Werley Classification

| RESULTS | Number of Fractures |
|---|---|
| Excellent | 6 |
| Good | 17 |
| Fair | 6 |
| Bad | 1 |

According to the radiological evaluation criteria of Steward and colleagues, excellent results were obtained in 6 of our cases (20%), good results in 17 (57%), moderate results in 6 (20%), and poor results in 1 (3%) (Table 3). A significant association was found between clinical and radiological findings (Pearson Chi-Square: 90.000, p<0.001). Given the sample size (n=30), the cross-tabulation analysis provided meaningful results.

We identified tendon adhesion, a complication that can be seen during the treatment of distal radius fractures, in 1 case (3%). In this case where we believe that tendon adhesion occurred as a result, the K wires were removed in the 3rd week, intensive finger movements were applied, and a response to treatment was achieved. Reflex sympathetic dystrophy developed in 10 of our cases (34%). These patients, who responded well to physiotherapy, had a reduction in their complaints. In one case (3%) where sufficient reduction was not achieved due to a late application, malunion occurred. The functional results of this patient were also determined to be poor. The rate of complications leaving no disability in our cases was determined to be 40%.

**Table 3.** Radiological Evaluation Results

| RESULTS | Number of Fractures |
|---|---|
| Excellent | 6 |
| Good | 17 |
| Fair | 6 |
| Bad | 1 |

## Discussion

The treatment of distal radius fractures, along with the increased life expectancy and quality of life, has become of great importance. These fractures, usually treated conservatively, are now more commonly treated surgically to improve functional outcomes after a fracture (8). In particular, intra-articular fractures affecting the wrist joint are mostly seen in young and active individuals who are more exposed to high-energy trauma, often in young and middle-aged individuals (8). In our study, the average age of our patients was determined to be 43.1, supporting the literature. These fractures, more commonly affecting the dominant extremity, resulted in significant loss of workforce (9,10). In our study, different from other case series, fractures were more commonly found in the non-dominant side. It can be thought that the reason for this is related to the low number of patients in our study. Additional injuries such as shoulder dislocation, elbow fractures, or wrist and metacarpal fractures can occur as a result of high-energy trauma along with fragmentary intra-articular fractures of the distal radius (11). In our study, additional lesions were present in 3 of our patients at the time of referral. An ipsilateral femur intertrochanteric fracture was detected in two patients, and an ipsilateral medial malleolus fracture detected in one patient. In the treatment of distal radius fractures, the most important factors affecting the outcome are the inability to provide appropriate radial inclination and palmar inclination, the presence of radial shortening, or intra-articular fracture. Depalma et al. reported poor results when there was dorsal angulation of more than 5 degrees or more than 3 mm shortening in the radius after reduction (12). Biomechanical studies on cadaver forearms have reported that a 2.5 mm shortening in the distal radius or an increase in dorsal angulation after reduction significantly increases axial load on the ulna (13). An increase in ulnar loading can lead to post-traumatic arthritis and chronic pain on the ulnar side of the wrist. Post-traumatic arthritis following distal radius fractures is one of the most important complications. Frykman et al. reported that this condition is not only valid for the radiocarpal joint but also for the radioulnar joint (5). Knirk et al. showed that in cases where there is more than 1 mm step-off on the joint surface, post-traumatic arthritis can occur in 90% of cases (9). As a result of our study, we did not encounter posttraumatic arthritis in any of our patients with follow-up periods ranging from 6 months to 24 months. Consequently, there is a close relationship between the quality of reduction in distal radius fractures and functional outcomes. The findings we obtained in our study also showed that there is a significant relationship between reduction quality and our clinical outcomes. According to the radiographic evaluation criteria of Steward et al., the results of our 6 patients who scored 0 points were excellent according to the Gardland-Werley functional evaluation criteria, the functional results of our 17 patients who scored 1 point were good, the functional results of our 6 patients who scored 2 points were fair, and the functional result of our 1 patient who scored 3 points was determined to be poor. According to Steward et al.s radiographic evaluation criteria, the best result is 0 points and the worst result is 3 points. The only case with a poor functional result was a patient with a Frykman type 1 distal radius fracture who underwent closed reduction due to general condition deterioration 16 days after the fracture.

The most important criterion determining the prognosis in distal radius fractures is controversial. According to the study by Gartland et al., the average palmar tilt should be 11 degrees, and the average radial deviation should be 23 degrees (7). On the other hand, Aro et al. reported that radial shortening is the most important factor affecting the outcome in distal radius fractures. More than 3 mm of shortening negatively affects the results regardless of angulation or step-off on the joint surface (14). In our cases, it was found that the prognosis depends on multiple factors. These factors include intra-articular step-off along with radial shortening. It was observed that the deterioration of palmar inclination did not affect the prognosis as negatively as intra-articular step-off or radial shortening. Another factor that negatively affects the prognosis of patients is the presence of an ulna styloid fracture along with a radius fracture. According to Knirk et al., a non-union styloid fracture has a negative impact on the prognosis(9). However, according to Pogue et al.s experimental study, the presence of an ulna styloid fracture along with a distal radius fracture does not cause a significant change in the total contact surface

of the joint and therefore generally does not show clinical symptoms (15). According to our cases, based on the clinical results of Gardland-Werley, it was determined that patients with Frykman type 1 fractures (those without ulna styloid fractures) had one excellent, seven good, one fair, and one poor result, while patients with Frykman type 2 fractures had three excellent, two good, and one fair result. Although the number of cases is small, in our opinion, the presence of a styloid fracture did not cause a significant change in functional outcomes.

Treatment of distal radius fractures today should be planned according to the stability of the fracture. LaFontaine and colleagues have identified criteria that determine the stability of the fracture. An unstable fracture must have at least three of the following criteria: 1) Dorsal angulation of more than 20 degrees when the fracture occurs, 2) Dorsal metaphyseal fragmentation, 3) Intra-articular extension into the radiocarpal joint, 4) Associated ulnar styloid fracture, 5) Patient age over 60 years (16). Percutaneous pinning and casting for unstable distal radius fractures is a widely used method with good functional outcomes in appropriate cases. DePalma and colleagues reported excellent results in 52.7%, good results in 25%, and fair to poor results in 17.8% of intra-articular fractures treated with percutaneous pinning and casting (12).

One of the other treatment methods applied to unstable distal radius fractures is closed reduction and external fixation. Similar results are obtained when comparing the closed reduction and casting method with the external fixation treatment method. Jenkins et al. compared the external fixation method with the casting method and observed reduction loss in all cases treated with the casting method. However, no reduction loss was detected in the patient group treated with the external fixation method (17). When comparing closed reduction and percutaneous pinning with closed reduction and external fixation method, according to Clancey et al., percutaneous pinning is the most suitable treatment method for minimally displaced intra-articular fractures, but they recommend the external fixation method for intra-articular fractures with more than two pieces (18). According to DePalma et al., the superiority of the percutaneous pinning method over the external fixation method is that nail route infections are less common and complications such as hand dysfunction due to fixation in the metacarpal region are not observed (12). Additionally, in our countrys conditions, percutaneous pinning and casting method is relatively more cost-effective and better in terms of patient comfort compared to closed reduction and external fixation method. Due to these advantages, in our study, patients were treated with percutaneous pinning and casting method. Knirk et al. recommended closed reduction and external fixation method in the treatment of intra-articular distal radius fractures due to the possibility of reduction loss with percutaneous pinning method (9). In the cases we followed in our study, reduction loss was not observed with the percutaneous pinning method.

## Conclusion

Between September 2002 and June 2004, in patients treated with closed reduction and percutaneous pinning method at the Şişli Etfal Training and Research Hospital of Health Sciences University; it is considered an effective treatment method due to the short surgical time of the method we used and its applicability to all distal radius fractures that can be reduced closed. For this technique to be successful, the fracture should be operated on as early as possible. This study demonstrated a significant relationship between clinical and radiological findings, suggesting that these assessments are consistent and can be used together in patient management. Future studies with larger patient cohorts are recommended to confirm these findings.

## Conflict of interest statement

None

**Ethics Committee Approval:** This study had local ethical committee approval of the Bakırcay University (2024/1592) and was conducted in accordance with the Helsinki Declaration of 2013

## References

1. Ekin A, Yaldiz K, Boya H, et al. Distal radius kırıklarında açık redüksiyon, plak ve / veya eksternal fiksatör uygulamaları. XV Milli Türk Ortopedi ve Travmatoloji Kongre Kitabı. 1997;117-21.
2. Seitz WH, Froimson Al, Brooks DB, et al. External fixator pin insertion techniques: Biomechanical analysis and clinical relevance. J Hand Surg Am. 1991;16(3):560-3.
3. Cooney WP, Linsheid RL, Dobyns JH. External pin fixation for unstable Colles fractures. J Bone Joint Surg. 1979;61-A:840-5.
4. Y, Doi K, Kuwata N, et al. Surgical options for distal radius fractures: indications and limitations. Arch Orthop Traum Surg. 1998;117: 188-92.
5. Frykman G. Fracture of the distal radius including sequelae-Shoulder-handfinger syndrome, disturbance in the distal radioulnar joint and impairment of nerve function. Acta Orthop Scand(Suppl). 1967;108:1-153.
6. Steward H.D, Innes A.R, Burke F.D. The hand complications of Colles fractures. J Hand Surg. 1985;10B:103-6.
7. Gardland JJ Jr, Werley WC. Evaluation of healed Colles fractures. J Bone Joint Surg. 1951;33-A:895-907.
8. Ark J, Jupiter JB. The rationale for precise management of distal radius fractures. Clin. Orthop North Am. 1993;24(2):205-10.
9. Knirk JL, Jupiter JB. Intra-articular fractures of the distal end of the radius in young adults. J Bone Joint Surg. 1986;68-A (5):647-59.
10. Cooney WP. External fixation of the distal radius fractures. Clin.Orthop. 1983;180:44-9.
11. Jones KG. Colles fracture. J. Arkansas Med Soc. 1976;3:244-7.

12. De Palma A.F. Comminuted fractures of the distal radius treated by ulnar pinning. J. Bone Joint Surg. 1952;34A: 651-62.
13. Palmer A, Werner F. The triangular fibrocartilage complex of the wrist. Anatomy and function. J. Hand Surg 1981;6:153-61.
14. Aro H, Koivunen T. Minor axiel shortening of the radius affects outcome of the Colles fractures treatment. J. Hand Surg. 1991;16:392-8.
15. Pague DJ, Viegas SF, Patterson RM. Effects of distal radius fracture malunion on wrist mechanism. J. Hand Surg 1990;15(A):721.
16. Lafontaine M, Hardy D, Delience P.H. Stability assesment of distal radius fractures. Injury 1989;20:208-10.
17. Jenkins NH, Jones DG. External fixation of colles fractures an anatomical study. J. Bone Joint Surg. 1987;69(B):207-11.
18. Clancey G.J. Percutaneous kirschner-wire fixation of colles fractures. J. Bone Joint Surg. 1984;66A:1008-14.

*Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi 2025;12(1):47-49* *Olgu Sunumu/Case Report*
*Medical Journal of Mugla Sitki Kocman University 2025;12(1):47-49* *Karayer Ozgul et al.*
*Doi: 10.47572/muskutd.1511518*

# Brucella Spondylodiscitis Complicated with Abscess: Case Report

## Abse ile Komplike Olan Brusella Spondilodiskiti: Olgu Sunumu

**Nihal KARAYER ÖZGÜL[1], Sami ÖZGÜL [2], Gönen MENGİ[3]**

[1]Mugla Sıtkı Kocman University, Faculty of Medicine, Physical Medicine and Rehabilitation, Mugla, Turkey
[2]Mugla Sıtkı Kocman University, Faculty of Medicine, Radiology, Mugla, Turkey
[3]Mugla Sıtkı Kocman University, Faculty of Medicine, Physical Medicine and Rehabilitation, Rheumatology, Mugla, Turkey

**Öz**

Romatoloji poliklinik başvurularının önemli bir kısmını bel ağrısı oluşturmaktadır. Spondilodiskit nadiren bel ağrılı olguların etiyolojileri arasında yer almaktadır. Spondilodiskit, disk ve vertebral korpusun inflamatuar süreçle birlikte etkilendiği bir durumdur. Spondilodiskite Staphylococcus aureus, Escherichia coli, Mycobacterium tuberculosis, Brucella neden olabilir. Ayırıcı tanıda; vertebral kolonun tümöre bağlı harabiyeti, kırıklar, spondiloartropatiler düşünülebilir. Brusella, farklı ülkelerde farklı prevalanslarda bildirilmesine rağmen spondilodiskitin önemli nedenlerinden biridir. Brusella Türkiye'de endemiktir. Brusella vertebral yapıları tutmasına rağmen apse ile komplike olması çok nadirdir. Olgu sunumumuzda romatoloji polikliniğine ağrı şikayeti ile başvuran bir hastada tespit edilen ve apse ile komplike olan brusella spondilodiskiti tartışılacaktır.

**Anahtar Kelimeler:** Abse, Bel ağrısı, Brusella, İnflamasyon, Spondilodiskit

**Abstract**

Rheumatology outpatient clinic referrals low back pain accounts for a significant proportion. Spondylodiscitis is rarely among the etiologies of pain cases of low back pain. Spondylodiscitis is a condition which disc and vertebral corpus are affected together with inflammatory process. Spondylodiscitis may be caused by Staphylococcus aureus, Escherichia coli, Mycobacterium tuberculosis, Brucella. In the differential diagnosis; destruction of the vertebral column due to tumor, fractures, spondyloarthropathies can be considered. Brucella is one of the notable causes of spondylodiscitis, although it is reported with different prevalence in different countries. Brucella is endemic in Turkey. Although Brucella involves vertebral structures, it is very rare for it to be complicated with abscess. In our case report, brucella spondylodiscitis complicated with abscess and detected in a patient presenting to the rheumatology outpatient clinic with pain will be discussed.

**Keywords:** Abscess, Low Back Pain, Brucella, Inflammation, Spondylodiscitis

### Introduction

Brucellosis is a systemic infectious disease, caused by a nonencapsulated, nonmotile, gram-negative bacilli belonging to the genus Brucella (1). This disease is a zoonosis transmitted to humans from infected animals such as goats, sheep, cows and dogs. The prevalence is higher in Mediterranean area, the Arabian Peninsula, Mexico, and Central and South America. Brucellosis is endemic in Turkey (2). Brucellosis is a systemic disease that affects many tissues and organs, especially the reticuloendothelial and musculoskeletal systems (3). Spinal involvement is the most important cause of the debilitating and disabling complications which can be either focal or diffuse (4). The focal form is usually restricted to the anterior part of an end-plate. The diffuse type tends to involve the entire vertebral body and it can be extended to adjacent structures such as intervertebral disk, epidural space and paravertebral muscles.

Disc space infection and paravertebral and epidural extension of the inflammatory process can be clearly documented on magnetic resonance imaging (MRI) up to 50% of cases with brucellosis may have spinal involvement that is mostly seen as spondylitis whereas abscess formation is very rare (2,5). In our case report, brucella spondylodiscitis complicated with abscess and detected in a patient presenting to the rheumatology outpatient clinic with back pain will be discussed.

| | ORCID No |
|---|---|
| Nihal KARAYER ÖZGÜL | 0000-0002-9618-2835 |
| Sami ÖZGÜL | 0009-0008-7398-780X |
| Gönen MENGİ | 0000-0001-5804-5680 |

Başvuru Tarihi / Received: 29.07.2024
Kabul Tarihi / Accepted : 10.02.2025

Adres / Correspondence : Nihal KARAYER ÖZGÜL
Mugla Sıtkı Kocman University, Faculty of Medicine, Physical Medicine and Rehabilitation, Mugla, Turkey
e-posta / e-mail : nihalkarayer505@gmail.com

### Case

A 64-year-old woman presented to our rheumatology outpatient clinic with complaints of low back pain that increasing at night. On systemic questioning, it was learnt that she had undulating fever, weight loss and weakness. On examination, the patient was found to be in a decreased general condition and musculoskeletal examination was normal. Routine blood tests and lumbar Magnetic Resonance Imaging (MRI) were performed in the patient in whom differential diagnoses of malignancy and infection were considered in the first plan. Laboratory results revealed sedimentation: 80 mm/h, CRP: 72 mg/L (N: 0-5 mg/L). On MRI, signal increase was found in STIR (short tau inversion recovery) sequence series in the L4 - L5 vertebral corpus and disc spaces and was evaluated as compatible with spondylodiscitis (Figure 1).

It was learnt that the patient obtained milk and dairy products from her own animals. Brucella tube agglutination test was performed. And the result was found to be positive at 1/1280 titration. The patient was referred to infectious diseases department and

rifampicin and doxycycline treatments were commenced. In the follow-up, streptomycin was added due to an increase in the brucella titre. Lumbar MRI with contrast was repeated due to aggravation of low back pain in the follow-up. Contrast uptake at the level of L4 - L5 vertebrae and disc, a 24x23 mm mass lesion with predominantly peripheral contrast between the psoas muscle and vertebrae on the right, which was evaluated as paravertebral abscess in the first plan (Figure 2). Paravertebral abscess was surgically drained and rifampicin and ciprofloxacin treatments were continued. Antibiotherapy was maintained during 1-year, general condition improved and low back pain regressed.

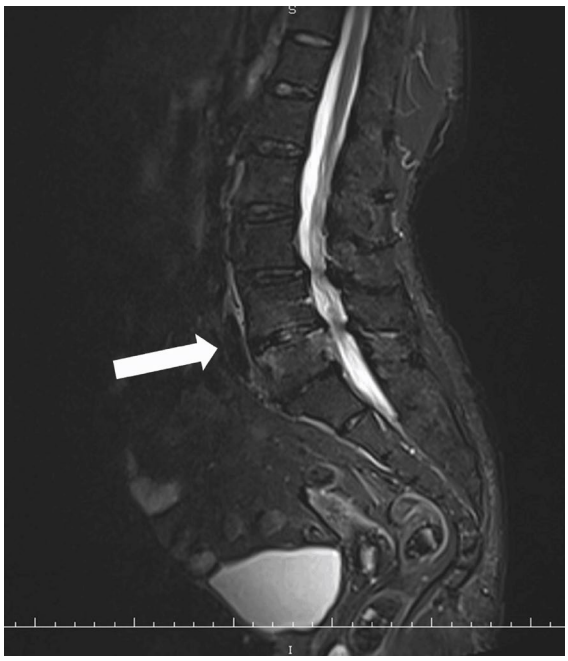


**Figure 1.** Signal increase in STIR sequence series in L4 – L5 vertebral body and disc distances.

## Discussion

Low back pain accounts for a significant proportion of Rheumatology outpatient clinic referrals. (6). Low back rarely among the etiologies of pain cases of spondylodiscitis are included (7).

Spondilodiscitis may be caused by Staphylococcus aureus, Escherichia coli, Mycobacterium tuberculosis, Brucella (8). In the differential diagnosis, destruction of the vertebral column due to tumor, fractures, spondyloarthropathies should be considered.

Brucella may effects vertebral structures however it is very rare for it to be complicated with abscess (9). The endemicity of brucellosis in Turkey, which is reported at different prevalences in different countries, is of value in terms of being included among our differential diagnosis. The etiology of low back pain, which is one of the common causes of referral to rheumatology outpatient clinics dealing with many pain conditions, ranges from muscle pain to malignancies (10). Cases of spondylodiscitis are important causes of low back pain. Brucella, which is endemic in Turkey, is one of the causes of spondylodiscitis. As in our case, there is a risk of progression with many complications. Brucella is an important differential diagnosis that every physician should keep in mind.

## Conclusions

In our rheumatology outpatient clinics where low back pain is a common reason for admission, we wanted to report our case to emphasise that the presence of infectious conditions such as Brucella among the possible differential diagnoses is important in terms of diagnosing the patient in a short time and starting treatment.

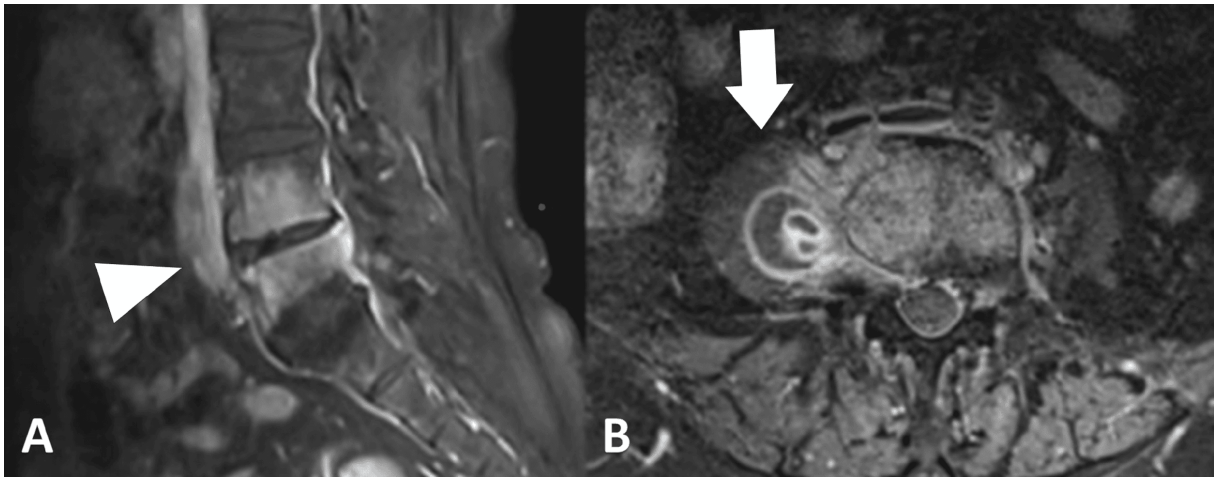



**Figure 2. A.** (Arrowhead) Contrast enhancement at the L4 – L5 vertebra and disc level; **B.** (arrow) a mass lesion of 24x23 mm, which is evaluated as a paravertebral abscess in the first plane, with predominantly peripheral contrast enhancement between the psoas muscle and the vertebrae on the right, and occasionally containing semisolid areas.

## Conflict of interest statement

There is no conflict of interest in this case report.

**Written consent:** Consent to the writing of the article was given by the patient on 25 March 2023.

**Funding:** No Funding

## References

1. Głowacka P, Zakowska D, Naylor K, et al. Brucella-virulence factors, pathogenesis and treatment. Pol J Microbiol. 2018;67(2):151-61.
2. Görgülü A, Albayrak BS, Görgülü E, et al. Spinal epidural abscess due to Brucella. Surg Neurol. 2006;66(2):141-6.
3. Boyaci A, Boyaci N, Tutoglu A, et al. Spinal epidural abscess in brucellosis. BMJ Case Rep. 2013;2013:bcr2013200946.
4. Adam AA, Hassan MS, Osman AA. Spinal brucellosis causing spondylodiscitis. Ann Med Surg (Lond). 2022;82:104782.
5. Farrokhi MR, Mousavi SR. Spinal brucellosis with large circumscribed paraspinal and epidural abscess formation: a case report. Br J Neurosurg. 2021;1-5.
6. Speed C. Low back pain. BMJ. 2004;328(7448):1119-21.
7. Amin MH, Salzman GA. Infectious spondylodiscitis diagnosis and treatment. Mo Med. 2013;110(1):80-4.
8. Fonseca del Pozo FJ, Valle Alonso J, Caracuel Ruiz MÁ. Community acquired spondylodiscitis caused by Escherichia Coli; Case report and literature review. Bull Emerg Trauma. 2016;4(3):174-9.
9. Shafizad M, Ehteshami S, Shojaei H, et al. Cervical spine epidural abscess caused by brucellosis: A case report and literature review. Clin Case Rep. 2022;10(3):e5644.
10. Casiano VE, Sarwan G, Dydyk AM. Back Pain. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK538173.

*Doi: 10.47572/muskutd.1572906*

# Poroid Hidradenoma: Succesfully Treated with Excision A Case Report

## Poroid Hidradenom: Eksizyon ile Başarılı Tedavi Edilen Olgu Sunumu

**Öyküm ÖZALP[1], Alp Eren KÖROĞLU[1], Emine Tuğba ALATAŞ[1], Suzan Demir PEKTAŞ[1], Havva ÖZŞEKER[2]**

[1]Mugla Sıtkı Kocman University, Faculty of Medicine, Department of Dermatology and Venereal Diseases, Mugla, Turkey
[2]Mugla Sıtkı KocmanUniversity, Faculty of Medicine, Department ofPathology, Mugla, Turkey

**Öz**

Poroid hidradenom (PH), ekrin ter bezinin farklılaşmasını gösteren nadir görülen iyi huylu bir tümördür. Çoğunlukla yetişkinlerde görülür ve 0,5 ila 2 cm boyutlarında, çoğunlukla baş, boyun ve gövdede intradermal nodül olarak bulunur. Literatürde alt ekstremitede bildirilen PH sayısı yaklaşık 17'dir, bu da alt ekstremitenin nadir bir tutulum bölgesi olduğunu göstermektedir. Bu olgu sunumunda, alt ekstremitede soliter lezyonu olan ve total eksizyonla başarılıyla tedavi edilen ve iki yıl boyunca takip edilen hastamızın herhangi bir nüks göstermeyen nadir PH vakasını sunarakliterature katkıda bulunmayı amaçladık.

**Anahtar Kelimeler:** Adneksiyal tümörler, Ekrin bezler, Poroid, Eksizyon

**Abstract**

Poroid hidradenoma (PH) is a rare benign tumor that shows the differentiation of the eccrine sweat gland. It is usually seen in adults and is seen as an intradermal nodule measuring 0.5 to 2 cm, most commonly located on the head, neck, and trunk. The literature describes approximately 17 cases of PH in the lower extremity, indicating that it is an uncommon site of involvement. In this case report, we aim to contribute to the literature by presenting a rare case of PH with a solitary lesion in the lower extremity, which was successfully treated with total excision, with no recurrence observed during a two-year follow-up.

**Keywords:** Adnexal Tumors, Eccrine glands, Poroid, Excision

### Introduction

Poroid hidradenoma is a rare benign neoplasm with eccrine differentiation (1). Since its initial description in 1990, fewer than 20 cases have been reported in the literature (2). PH typically, is a solitary tender nodule with a diameter ranging from 0.5 to 2 cm It appears skin-colored or slightly reddish and consists of both solid and cystic components, confined within the dermis (3). The most common sites of involvement are the head and neck regions, with a predilection for the centrofacial area (approximately 85% of cases). Less frequently, it occurs in the axilla, trunk, and extremities (4).

Surgical treatment of PH involves radical excision of the lesion with a 4-mm margin to minimize the risk of recurrence or malignant transformation. Similar to other skin malignancies, excision should extend to the fascia layer (5). We present this case because PH is a rare benign tumor. Our case demonstrates that wide local excision with a 4-mm margin is the definitive treatment, with no recurrence observed during a two-year follow-up.

| | ORCID No |
|---|---|
| Öyküm ÖZALP | 0009-0006-5463-115X |
| Alp Eren KÖROĞLU | 0009-0009-9334-5043 |
| Emine Tuğba ALATAŞ | 0000-0002-5727-9474 |
| Suzan Demir PEKTAŞ | 0000-0001-5074-986X |
| Havva ÖZŞEKER | 0000-0001-5615-5923 |

Başvuru Tarihi / Received: 25.10.2024
Kabul Tarihi / Accepted : 01.04.2025

Adres / Correspondence : Öyküm ÖZALP
Mugla Sıtkı Kocman University, Faculty of Medicine, Department of Dermatology and Venereal Diseases, Mugla, Turkey
e-posta / e-mail : oykum-ozalp@hotmail.com

### Case

A 42-year-old male presented with a painless, non-itchy cyst in the inferior left patella region that had been present for approximately three to four years. He was initially diagnosed with a soft tissue infection at an external center, where he was prescribed oral antibiotic therapy. However, the lesion continued to enlarge despite treatment.

Upon presentation at our clinic, physical examination revealed a nodular cystic lesion in the left leg, which was elastic in consistency and mobile, resembling a gelatinous fluid-filled structure (Figure 1).

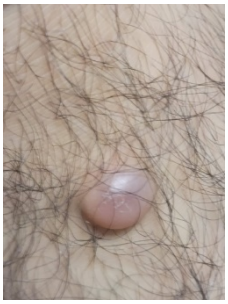


**Figure 1.** The nodular cystic structure in the leg area was palpable with anelastic consistency and mobile as if it contained gelatinous fluid.

A cyst puncture was attempted, yielding a small amount of serosanguineous fluid, but the lesion size remained unchanged (Figure 2). The patient was subsequently referred to plastic surgery for total excision.

The differential diagnosis included dermatofibroma, eccrine poroma, Kaposi sarcoma,

*Doi: 10.47572/muskutd.1572906*

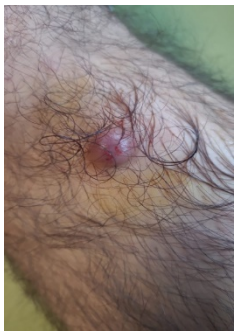
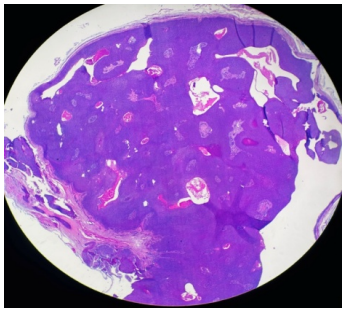


**Figure 2.** An attempt was made to perform a cyst puncture on the nodular lesion, but no material was removed.

hemangioma, angiokeratoma, and poroid hidradenoma. A wide local excision with a 4-mm margin extending to the fascia layer was performed by the surgical team.

Histopathological examination of the excised lesion confirmed poroid hidradenoma, revealing a dermal tumor composed of solid and cystic components. Tumor nests contained small, dark poroid cells and larger, pale cuticular cells with clear cytoplasm (Figure 3).

The patient recovered uneventfully, and no recurrence was observed during a two-year follow-up period.

**(A).** 

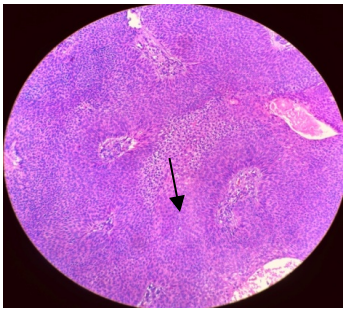
**(B).** 

**Figure 3. (A)** Tumor composed of solid and cystic components in the mid dermis (H&E, x40), **(B)** Solid tumor cells nest composed of small dark poroid cells (White arrow) and larger pale cuticular cells (black arrow) with clear cytoplasm (H&E, x20).

## Discussion

PH has a wide age distribution, with peak incidence in the seventh decade of life (1). No gender or ethnic predilection has been reported (1). Our patient was 42 years old, younger than the typical age range. The most commonly affected site is the head and neck, followed by the axilla, trunk, and extremities (2). Involvement of the lower extremity, as seen in our case, is exceedingly rare.

Histopathological examination of PH typically reveals solid and cystic components, confined to the dermis (6). The tumor consists of two distinct cell types: poroid cells, which are small, uniform cuboidal cells with oval-round nuclei, and cuticular cells, which have abundant eosinophilic cytoplasm with larger, sometimes multinucleated nuclei. Cystic spaces contain eccrine secretory fluid and are lined by flattened epithelial cells (4). Our case exhibited these classic histopathological features.

The differential diagnosis of PH includes other poromas (hidroacanthoma simplex, dermal duct tumor, eccrine poroma) and apocrine hidradenoma. While hidroacanthoma simplex contains nests of round cells within normal epidermal cells, dermal duct tumors are located entirely within the dermis. Eccrine poroma, on the other hand, features a distinct border between normal epidermal keratinocytes and dark cuboidal cells. Apocrine hidradenomas secrete mucoid material and exhibit decapitation secretion, characteristic of apocrine differentiation (7).

Although PH is typically covered by intact skin, approximately 15% of cases exhibit ulceration, often due to trauma or lesion erosion (8). Our case showed no ulceration. Some PHs exhibit a bluish hue due to the Tyndall effect of cystic components, similar to angiomas, melanomas, and nevi, necessitating careful differential diagnosis (8).

Wide local excision with a 4-mm margin extending to the fascia layer remains the gold standard for treatment, as PH originates from dermal tissue. Although the prognosis of PH is excellent, one case of recurrence has been reported in the literature (9). In our case, the patient remained recurrence-free at the two-year follow-up.

## Conclusions

PH is effectively treated with total excision, and its malignant transformation risk is minimal (<1%). The prognosis is favorable, and recurrence is rarely reported. This case highlights the diagnostic challenges associated with PH, particularly when it occurs in uncommon locations such as the lower extremity. Histopathological evaluation is essential for differentiation from other adnexal neoplasms, and wide local excision remains the definitive treatment.

## Acknowledgements

None

## Conflict of interest statement

There are no conflicts of interest.

**Written consent:** A written consent statement was obtained (10.11.2024).

**Funding:** No funding

## References

1. Q Brooks A, Morris M, Cuda J, et al. Poroid Hidradenoma: Case Report and Comprehensive Review of the Literature. Case Rep Dermatol. 2023;15(1):202-16.
2. Mlika M, Chelly B, Boudaya S, Ayadi-Kaddour A, Kilani T, El Mezni F. Poroid hidradenoma: a case report. Our Dermatol Online 2012; 3(1): 43-5.
3. Lim JS, Kwon ES, Myung KB, et al. Poroid Hidradenoma: A Two-Case Report and Literature Review. Ann Dermatol. 2021;33(3):289-92.
4. Yamamoto O, Hisaoka M, Yasuda H, Kasai T, Hashimoto H. Cytokeratin expression of apocrine and eccrine poromas with special reference to its expression in cuticular cells. J Cutan Pathol. 2000;27:367-73.
5. R M Whitmore 1, C J Anderson, T Piper. Poroid hidradenoma. A case presentation. J Am Podiatr Med Assoc. 1998;88(10):510-3.
6. Arwyn-Jones J, O'Hara N, De Leo A, et al. Poroid Hidradenoma: Case Report and Excision Rationale. J Cancer Ther, 2016;7:270-4.
7. Chiu HH, Lan CCE, Wu CS, et al. A single lesion showing features of pigmented eccrine poroma and poroid hidradenoma. *J Cutan Pathol*. 2008;35:861-5.
8. Battistella M, Langbein L, Peltre B, Cribier B. From hidroacanthoma simplex to poroid hidradenoma: clinicopathologic and immunohistochemic study of poroid neoplasms and reappraisal of their histogenesis. Am J Dermatopathol. 2010;32:459–68.
9. Hoshida Y, Hanai J, Matsushita N, Yonekawa M, Kobayashi Y, Kawakami H, et al: Poroid hidradenoma: Report of a case with cytologic findings on fine needle aspiration. Acta Cytol 1999; 43: 471-4.

*Doi: 10.47572/muskutd.1622746*

# Aortic Dissection Presenting as Paraplegia Complicated with Pulmonary Embolism

# Pulmoner Emboli ile Komplike Parapleji Olarak Başvuran Aort Diseksiyonu

**Nuri KÖSE[1], Tamer KIRAT[2], Gökhan ERGÜN[3], Fatih AKIN[1], İbrahim ALTUN[1]**

[1]Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Türkiye
[2]Department of Cardiology, Private Yücelen Hospital, Muğla, Türkiye
[3]Kayseri City Hospital, Clinic of Cardiology, Kayseri, Türkiye

**Öz**

Aort diseksiyonu ve pulmoner emboli ciddi ve potansiyel olarak yaşamı tehdit eden kardiyovasküler hastalıklardır. Akut aort diseksiyonu sonucu gelişen parapleji en ciddi komplikasyonlardan biridir. Venöz tromboembolizm riski paraplejili hastalarda artar. Aort diseksiyonu, parapleji, derin ven trombozu ve pulmoner embolinin birlikteliği çok nadirdir. Bu yazıda, akut tip I aort diseksiyonu sonucu spinal kord iskemisine bağlı parapleji gelişen, subakut fazda derin ven trombozu ve pulmoner emboli ile komplike olan 81 yaşında bir erkek hastayı sunduk.

**Anahtar Kelimeler:** Aort Diseksiyonu, Derin Ven Trombozu, Parapleji, Pulmoner Emboli

**Abstract**

Aortic dissection and pulmonary embolism are serious and potentially life-threatening cardiovascular diseases. Paraplegia is one of the most life-threatening complication of aortic dissection. The risk of venous thromboembolism increases in patients with paraplegia. The coexistence of aortic dissection, paraplegia, deep vein thrombosis and pulmonary embolism are very rare. This paper reports a case of an 81-year-old male patient, developing paraplegia related to spinal cord ischemia due to acute type I aortic dissection, in the subacute phase, complicated with deep vein thrombosis and pulmonary embolism.

**Keywords:** Aortic dissection, Deep Vein Thrombosis, Paraplegia, Pulmonary Embolism

## Introduction

The incidence of acute aortic disection (AD) is 2.6–3.5 cases per 100 000 person-years, and it is characterized by the presence of an intimal flap separating the true from the false lumen. Acute AD occurs most commonly in males and typically presents with sudden, severe chest and back pain (1). There are several classifications of AD, but the most commonly used are DeBakey and Stanford. DeBakey's classification distinguishes 3 types: type I the most common type, dissection involves the entire aorta, type II; it involves only the ascending aorta and type III; dissection involves only the descending aorta. Stanford type A correspond to DeBakey types I and II, and Stanford type Bto type III (1,2). Paraplegia due to spinal cord injury in patients with AD is a rare complication that occurs in about 2-8 % (3).

Venous thromboembolism encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT can be determined in approximately two-thirds of PE patients. AD and PE are common and life-threatening cardiovascular disease. Early diagnosis and appropriate treatment are important due to the high mortality rates of both diseases. The combination of these two conditions are exceptional and forms a therapeutic dilemma, between the anticoagulant treatment for pulmonary embolism that would negatively affect the dissection and the harmful therapeutic abstention due to the embolism (2).

| | ORCID No |
|---|---|
| Nuri KÖSE | 0000-0001-8658-2598 |
| Tamer KIRAT | 0000-0002-7746-0844 |
| Gökhan ERGÜN | 0000-0002-1863-4605 |
| Fatih AKIN | 0000-0003-4865-8947 |
| İbrahim ALTUN | 0000-0002-5916-614X |

Başvuru Tarihi / Received: 18.01.2025
Kabul Tarihi / Accepted : 25.03.2025

Adres / Correspondence : Nuri KÖSE
Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Türkiye
e-posta / e-mail : drnurikose@hotmail.com

## Case

An 81-year-old male patient admitted emergency unit with complaints of shortness of breath, weakness and inactivity in the legs, inability to stand and walk. Chest pain, which began 21 day ago, lasted half day, hit the back of patients and descendingly stopped, was reported. Moreover, inactivity of the legs began on the same day. The swelling initiated in the patient's left leg a week earlier than the admittance. Another complaint was sudden onset of shortness of breath in the last 2 days. The family did not have a history of hypertension and AD. The patient did not have any history of coagulation disorders, previous PE or DVT.

In physical examination, fever was 36.9 °C, blood pressure was 100/60 in the right arm and 90/60 mmHg in the left arm, radial pulse was 103/min, oxygen saturation was 89% at room air and respiratory rate was 24/min. In blood gas evaluations, pH was determined as 7.37, PaCO2 was 42 mmHg, and PaO2 was 82 mmHg. His height was 172 cm and his weight was 86 kg. 1/4 diastolic murmur was heard in the aortic focus. All peripheral arterial pulses could be measured. There was a significant increase in diameter in the left lower extremity and Homan's test result was positive.

*Doi: 10.47572/muskutd.1622746*

Simplified version of Geneva clinical prediction score for pulmonary embolism was 5 (PE-likely≥3).

Patient could not stand with or without support. There was hypoesthesia starting from the bottom of the nine (9) thoracic vertebrae. Bilateral Babinski reflexes were positive. Paralysis was observed in both lower limbs, more apparently in the left lower limb. Muscle strength in right lower extremity was 3/5 in proximal and distal, in left lower extremity was 2/5 in distal and 3/5 in proximal.

The patient had no significant abnormalities in the cervical and lumbar spinal magnetic resonance imaging (MRI) examinations. De Bakey type I AD that started from the ascending aorta to the descending aorta was detected in the thoracic spine MRI (Figure 1). Moreover, the primary pathological image was not identified in vertebrae except spondylarthrosis. The sinus tachycardia (127/min), S1Q3T3 pattern, V1-3 T wave negativity and DII, III, aVF, V4-6 ST segment depression were observed in electrocardiography (Figure 2).

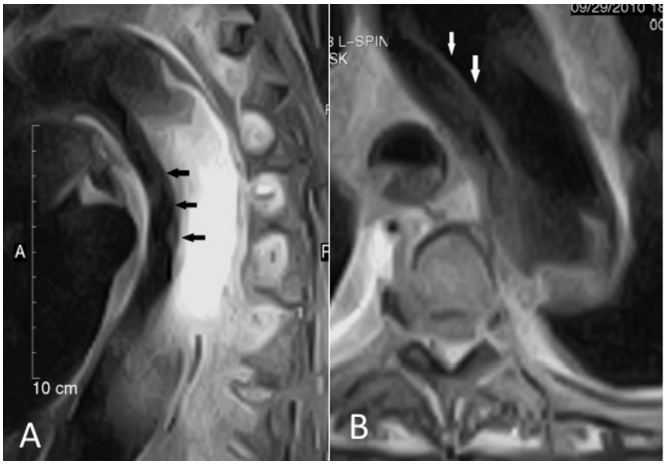



**Figure 1. (A)** Dissecting flap was observed in the aortic arch and descending aorta in axial MRI *(black arrows)*; **(B)** sagittal FSE T2 sequences MRI *(white arrows).*

In posteroanterior chest radiography, both hilar and mediastinal was found to be wide, oligemic areas in the middle zone of the right lung, thoracic aortic aneurysm and cardiothoracic index were found to be increased (Figure 3A). In transthoracic echocardiography, right heart dilatation, flattening of the interventricular septum and with depressed contractility of the right ventricular free wall compared to the echocardiographic right ventricular apex (McConnell sign) was observed. Pulmonary artery pressure was measured as 50 mmHg in the patient with moderate tricuspid valve insufficiency (Figure 3B). Moreover, the diameter of ascending aorta was observed as 5.8 cm, and dissection flap that started from the descending aorta lying abdominal aorta was seen (Figure 3C). In addition, moderate regurgitation was observed in aortic valve. Any pathological finding other than the image of the dissection extending beyond abdominal aorta was revealed in abdominal ultrasonography. Thrombus that was in distal part of the left superficial femoral vein and in popliteal vein in subacute period was observed in lower extremity venous Doppler ultrasound.

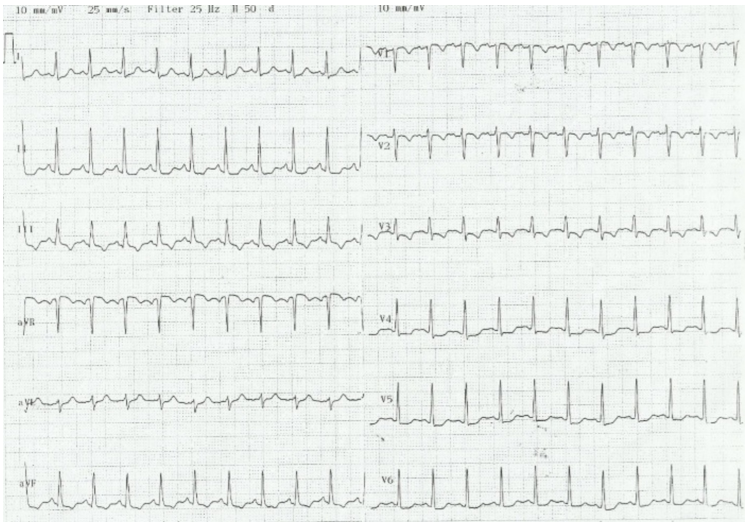


**Figure 2.** 12-lead electrocardiogram during admission.

*Doi: 10.47572/muskutd.1622746*

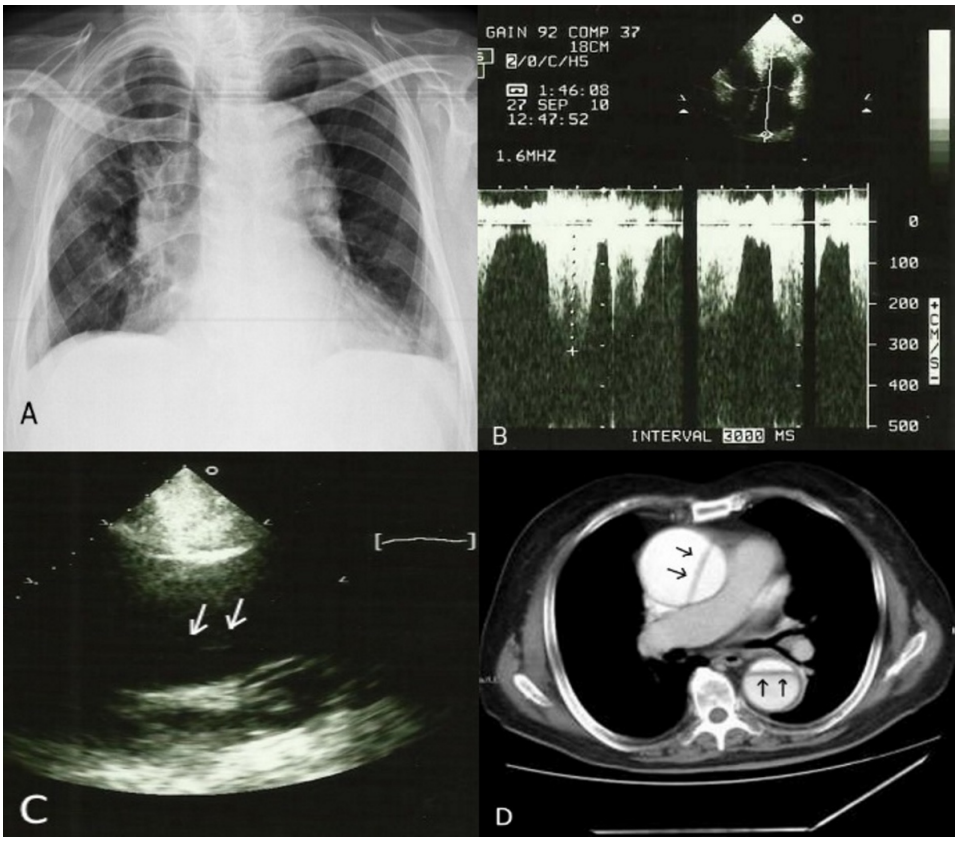



**Figure 3. (A)** Cardiomegaly and broad view in mediast were monitored on posteroanterior chest radiograph; **(B)** Transthoracic echocardiography revealed right heart dilatation and moderate pulmonary artery hypertension (50 mmHg); **(C)** 5.8 mm diameter of the ascending aorta with aneurysm view in the parasternal long-axis and dissection flap were observed in transthoracic echocardiography *(white arrows)*; **(D)** Flap of chronic type I dissection in both ascending and descending aorta and true and false lumen images were observed in the thoracic CT *(black arrows)*.

The results of blood biochemical examination were as follows; D-dimer >5.00 ug/ml (0.063-0.704), Troponin T 0.062 ng/ml (<0.014), proBNP 984 ng/mL (0-125), White Blood Counts 10.0 103/uL (4-11), Hb 11.6 gr/dL (11-18.8), Thrombocyte Counts 189 103/uL (150-400), Blood Urea Nitrogen 74 mg/dL, Creatinine 1.48 mg/dL (0.4-1.4), Glomerular Filtration Rate 48.4 mL/min/1.73 m2, Alanine Aminotransaminase 24 UL (0-50), Lactate Dehidrogenase 442 IU/L (0-450), Erythrocyte Sedimentation Rate 80 mm/s (0-20).

Contrast-enhanced pulmonary computed tomography (CT) angiography was not performed decreased glomerular filtration rate. Acute pulmonary embolism was diagnosed based on clinical findings, presence of deep venous thrombosis, electrocardiography and transthoracic echocardiography findings. Simplified pulmonary embolism severity index (sPESI) score was 3 (≥1). The patient was evaluated in intermediate-high risk cathegory. Cardiovasvascular surgery was consulted for an opinion. Medical management and close monitoring were continued for the patient. The intravenous unfractionated heparin was applied to the patient and this lasted for seven days. The warfarin sodium was initiated on the second day and treatment was continued for six months through keeping the international normalized ratio (INR) values between 2-3. Metoprolol succinate tablets 50 mg/day was subsequently started. In echocardiographical examination that was performed fifteen days later, the right heart chambers were measured as normal width, right ventricular wall motion as normal, and pulmonary artery systolic pressure was measured as 25 mmHg. Medical follow-up was decided for AD considering the patient's age, stage of subacute AD accompanying the complications and the patient's preference. Physical therapy rehabilitation program was started after fifteen days of hospital admission; a total of 30 physical therapy sessions was applied to the patient. He began to walk with only a cane 2 months later, and normally walked six months later. The physical examination findings were normal after sixth month and there was no neurological sequela. Lower extremity venous Doppler ultrasound performed at 6 months after discharge did not detect any residual thrombi in the left superficial femoral vein or popliteal vein. The diameter of ascending aorta was observed as 6.0 cm, and chronic type I dissection with aneurysm that started from the ascending aorta lying abdominal aorta was seen in

thoracic CT for control purpose two years later (Figure 3D). In the seven year of follow-up, ascending aortic diameter was 6.2 cm in transthoracic echocardiography and event-free survival continued. However, the patient was died due to urinary tract infection and progressive sepsis 10 years after suffering acute aortic dissection.

## Discussion

AD is characterized with an intimal tear that suddenly occurs and separates the false lumen from true lumen of the aorta. Dissection can involve the side branches by spreading as the antegrade or retrograde, and it may cause the complications such as Malperfusion syndrome depending dynamic or static obstruction (3). AD is mostly seen in fifty or sixty years of age and often seen in males as twice than in females. Most cases have hypertension and the most common symptom is a sudden onset of severe chest or back pain. Some patients may not have pain. The mortality and morbidity rate of ascending AD is about 75% including especially in the first 24-48 hours at first two weeks. The prognosis of chronic dissection is better. The therapeutic approach towards AD depends on the location of involvement. Emergency surgery should be required in ascending AD while uncomplicated descending AD can be medically monitored at the beginning. Neurological sequelae after AD occur in approximately one fifth of patients. Paraplegia showing the spinal cord ischemia is mostly seen in descending ADs and may also occur in the ascending and abdominal ADs. The paraplegia can be also seen as a complication of thoracic and abdominal aortic surgery or in patients undergoing endovascular aortic graft (4). Paraplegia developed after dissection may be temporary or permanent. In acute phase of therapy, patients who had paraplegia receive the treatments such as cerebrospinal fluid drainage, anti-edema therapy, ensuring the volume balance and fluid-electrolyte, and prevention of hypotension (4,5). Following this, the patient may benefit from rehabilitation programs. In our case, paraplegia was completely resolved only after physical therapy and rehabilitation programs.

The anterior spinal artery that forms by the merger of the two branches of the vertebral artery nourishes the two third of anterior segment, two posterior spinal artery that is separated from the vertebral artery branch nourishes the one third of posterior segment of spinal cord. Other arteries that nourish the spinal cord through supplying it are the radicular arteries and primarily arise from the spinal branches of the lateral sacral, ascending cervical, deep cervical, vertebral, posterior intercostal arteries. Large anterior radicular artery, also known as the artery of Adamkiewicz, provides a large amount of blood to the two third of inferior part of spinal cord in low thoracal and lumbar region, and this artery is the most important artery of thoracolumbar region. This artery most commonly originates from the left side, between T9-12, inferior intercostal or superior lumbar arteries. Anterior spinal artery especially provides the blood supply to radicular arteries in the T10-12 level. Spinal cord blood flow is lower than other regions in T10-12 level. The nutrition of spinal cord in this region largely depends on anterior spinal artery blood stream and it is very sensitive to a decrease in blood stream. Therefore, the serious symptoms of spinal ischemia such as paraplegia may easily develop (6).

It may be difficult to distinguish spinal cord injury developing as a result of AD from acute transverse myelitis, the vascular diseases of the spinal cord, and other spinal cord diseases such as spinal cord malformations. Paraplegia in AD can suddenly develop or within minutes or hours. Acute transverse myelitis is a relatively indolent and there is no involvement of other organs. There are sudden onset of paraplegia, severe chest and abdominal pain in hemorrhage caused by spinal cord vascular disease. However, there is no other symptoms of AD in hemorrhage and be made distinct by imaging techniques such as magnetic resonance imaging. Intermittent claudication that suddenly starts and affects the legs is the main finding in patients with spinal vascular malformations. In this case, magnetic resonance imaging is useful in the differential diagnosis and spinal angiography confirms diagnosis (6).

The underlying mechanism simultaneous development of AD and PE remains unclear. Various factors may contribute to such comorbidity. Firstly, the likely cause of this simultaneous occurrence may be the close anatomical relationship between them, where compression of the right pulmonary artery induced by AD can cause the stagnation of blood flow that may lead to PE. Secondly, another possible cause may be DVT occurring in the lower extremities which travels up to the pulmonary artery and cause PE. Thirdly, AD can trigger a widespread coagulation response leading to venous thromboembolism (7).

It remains controversial how to treat PE patients concomitant with AD whether to choose fibrinolytic therapy, surgical embolectomy, percutaneous catheter directed treatment, pharmaco-mechanical approach, or inferor vena cava filter (7-10). Acute aortic dissection is a contraindication for thrombolytic and anticoagulant therapy.

Chen et al (7), successfully treated patients with descending AD combined with low-risk PE with a nonsurgical, non-anticoagulant treatment regimen. Nakamura et al (8), successfully treated a patient with aortic dissection who developed massive pulmonary embolism in the second postoperative week with anticoagulant therapy and urokinase. Tudaron et al (9), treated a patient with acute pulmonary embolism and dissected ascending aortic

aneurysm with unfractionated heparin and acenocoumarol and performed a successful operation after postponing surgical treatment for dissection for one month. Kagawa et al (10), detected a Stanford type A dissection, DVT, and PE in a 71-year-old woman. They successfully treated the PE in this patient with low-dose heparin, retrievable inferior vena cava filter, and warfarin-based anticoagulation.

In the moderate-high-risk group, thrombolytic therapy should be considered in case of clinical deterioration. Thrombolytic therapy was not considered for our patient because of the rapid improvement in his clinical condition within a few days after treatment, improvement in electrocardiographic findings, and complete normalization of right ventricular loading on echocardiography. In addition, the patient's excellent response to medical treatment and significant improvement in clinical and laboratory findings supported our diagnosis of pulmonary embolism.

Our case was a DeBakey type I AD in the subacute phase on the 21th day, who was admitted with acute PE. We started treatment of unfractionated heparin and continued warfarin-based anticoagulation for six months. We successfully treated venous thromboembolism and paraplegia without developing any adverse event in this case. We followed up the AD in this patient medically because the patient was older, the dissection was stable in the subacute phase, AD was complicated by paraplegia and PE and the patient did not want surgical treatment.

## Conclusions

Consequently, the paraplegia may occur as a rare complication of AD. AD should be also considered in patients with paraplegia in the etiology. On the other hand, it should be taken into consideration that the risk of venous thromboembolism significantly increases in patients with paraplegia. The treatment of PE in patients with AD complicated with paraplegia is controversial. The treatment options should be considered based on clinical characteristics of each patient for following up such incidents.

## Acknowledgements

None

## Conflict of interest statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

**Written consent:** Written consents of the patients were obtained on 29.05.2017.

**Funding:** None

## References

1. Bossone E, Eagle KA. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes. Nat Rev Cardiol 2021;18:331–48.
2. Tiemtoré-Kambou BM, Koama A, Kontogom S, et al. Aortic dissection-Pulmonary embolism association: A therapeutic dilemma. Radiol Case Rep. 2022;17(8):2779-83.
3. Geirsson A, Szeto WY, Pochettino A, et al. Significance of malperfusion syndromes prior to contemporary surgical repair for acute type A dissection: outcomes and need for additional revascularizations. Eur J Cardiothorac Surg. 2007;32:255-62.
4. Tuygun AK, Şahin S, Yurtseven N, et al. Late paraplegia after repair of a type I aortic dissection: an uncommon complication. Turkish J Thorac Cardiovasc Surg. 2005;13:263-6.
5. Shimura S, Cho Y, Aki A, et al. Successful reversal of immediate paraplegia associated with repair of acute Type A aortic dissection using cerebrospinal fluid drainage. Interact Cardiovasc Thorac Surg. 2013;17:1051-3.
6. Sui RB, Zhang L, Liu K. Aortic dissection presenting primarily as acute spinal cord damage: a case report and literature review. J Int Med Res. 2012;40:2014-20.
7. Chen XG, Shi SY, Ye YY, et al. Successful treatment of aortic dissection with pulmonary embolism: A case report. World J Clin Cases. 2022;10(16):5394-9.
8. Nakamura K, Orii K, Hanai M, et al. Management of acute pulmonary embolism after acute aortic dissection surgery. J Cardiol Cases. 2020;22(4):195-7.
9. Tudoran M, Tudoran C. High-risk pulmonary embolism in a patient with acute dissecting aortic aneurysm. Niger J Clin Pract. 2016;19(6):831-3.
10. Kagawa Y, Ota S, Hoshino K, et al. Acute Pulmonary Thromboembolism and Deep Vein Thrombosis during the Medical Treatment of Acute Aortic Dissection was Successfully Treated by the Combination of Inferior Vena Cava Filter Installation and Anti-Coagulant Therapy: A Case Report. Ann Vasc Dis. 2015;8(1):36-9.

*Doi: 10.47572/muskutd.1424743*

# Successful Surgical Repair of Semilunar Valves in an Adult Female with Congenital Ventricular Septal Defect

# Doğumsal Ventriküler Septal Defektli Erişkin Kadın Hastada Semilunar Kapakların Başarılı Cerrahi Onarımı

**Hande İŞTAR, Buğra HARMANDAR**

Mugla Sitki Kocman University Medical Faculty, Department of Cardiovascular Surgery, Muğla, Turkey

**Öz**

Ventriküler septal defect (VSD), sağ kalbi ve pulmoner vasküler sistemi, pulmoner vasküler rezistansı arttırarak etkileyen en sık asiyanotik hastalıktır. Tanı almamış subaortik VSD, zaman içinde, ciddi pulmoner arter hipertansiyon yanı sıra aort kapak yetmezliğine de neden olabilir. Ek olarak, VSD yoluyla oluşan soldan sağa şant ile, sağ kalp dilatasyonu gelişebilir. İlerleyen dönemde geri dönüşsüz pulmoner arter hipertansiyonu (PAH) (Eisenmenger Sendromu) gelişebilir. Olgu sunumumuzda, efor dispnesinden yakınan 45 yaşında kadın hastamızı sunmaktayız. Hastada geç tanı almış VSD nedeniyle gelişmiş aort ve pulmoner kapak yetmezliği mevcuttu. Başarılı semilunar kapak onarımı ve eş zamanlı doğumsal kalp defekti onarımı yapıldı. Her 2 kapak otolog perikard dokusu kullanılarak onarıldı. Hastamızda çift mekanik kapak replasmanı yapmak yerine, ömür boyu antikoagülasyona bağlı komplikasyonlardan kaçınmak için kapak onarımı tercih ettik. Olgu sunumumuz erişkin hastadaki kapak patolojisine doğumsal kalp cerrahı yorumunu sunmayı amaçlamaktadır. Olgumuzun VSD'nin hem aort hem pulmoner kapağı komplike etmesi bakımından ve semilunar kapakların yetmezliği yanısıra bu kapakların prolapsusu ile pulmoner overflowun engellenmesi bakımından tek örnek olduğuna inanıyoruz.

**Anahtar Kelimeler:** Aort Kapak Yetmezliği, Erişkin, Pulmoner Kapak Yetmezliği, Ventriküler Septal Defekt

**Abstract**

Ventricular septal defect (VSD) is the most common acyanotic congenital heart disease that affects the right heart and pulmonary vascular system by increasing pulmonary vascular resistance. Undiagnosed subaortic VSD may over time cause aortic valve insufficiency as well as severe pulmonary arterial hypertension. Moreover, right heart dilatation can be seen due to the left-to-right shunt through the VSD. The final stages may include irreversible pulmonary artery hypertension (PAH) (Eisenmenger's syndrome) and right-to-left shunting. In our case report, we present a 45-year-old female patient suffering from exertional dyspnea. She was diagnosed with severe aortic and pulmonary valve insufficiency caused by late-diagnosed VSD. Successful surgical repair of degenerated semilunar valves with concomitant heart defect was performed. Both valves were repaired using autologous pericardium tissue. Instead of performing double mechanical valve replacement in our patient, we preferred valve repair to avoid complications related to lifelong anti-coagulation. This case report aims to present the congenital heart surgeon's interpretation of valvular pathology in the adult patients. We believe that our case is unique in that VSD complicated both the semilunar valves insufficiency, limited the pulmonary overflow due to the prolapsus of these valves until adult ages.

**Keywords:** Aortic Valve Insufficiency, Adult, Pulmonary Valve Insufficiency, Ventricular Septal Defect

## Introduction

Ventricular septal defect (VSD) accounts for 20% in congenital heart diseases in childhood and 10% in adult congenital heart malformations (1). It is usually diagnosed in pediatric ages due to incidentally detected cardiac murmur in routine physical examination, in routine examination of fetal echocardiography or further evalution of severe symptoms of congestive heart insufficiency. It is well known that in case of subaortic VSD, the aortic valve leaflet tends to prolapse into the VSD due to the Venturi pulling effect, and aortic insufficiency occurs. In some of cases, tricuspit septal leaflet may produce a pouch to limit the shunt flow through the defect. Therefore, pulmonary overflow can be reduced by this effect. For this reason, VSD can be occult until adult ages. In literature, there are a few cases about adult VSD patients and their outcomes (2,3). In the present study, we introduce an adult female patient diagnosed with VSD, aortic and pulmonary valve insufficiency and her preoperative and postoperative management.

| | ORCID No |
|---|---|
| Hande ISTAR | 0000-0002-7150-0171 |
| Buğra HARMANDAR | 0000-0002-7487-1779 |

Başvuru Tarihi / Received: 23.01.2024
Kabul Tarihi / Accepted : 06.12.2024

Adres / Correspondence : Hande ISTAR
Mugla Sitki Kocman University Faculty of Medicine, Department of Cardiovascular Surgery, Mugla, Turkey
e-posta / e-mail : handeistar@yahoo.com

## Case

A 45-year-old female patient was admitted to our clinic due to acute onset severe dyspnea. She had not been diagnosed with any cardiac disease previously. Physical examination showed systolic murmur in pulmonary and aortic valves. Transthoracic echocardiography revealed severe pulmonary and aortic valve insufficiency and a subarterial VSD 20 mm in diameter. After cardiac catheterization, no coronary artery disease was observed and mean pulmonary artery pressure was 60 mmHg, pulmonary vascular resistance (PVR) value was 5 Wood Unit (WU); Qp/Qs was >1.5. Reversibility test was performed at the same time and results were in favour of reversible state. Due to severe dyspnea, diuretic medical treatment was given following the diagnosis. Written informed consent was provided by the patient. Through median sternotomy and under cardiopulmonary bypass (CPB), right atriotomy,

*Doi: 10.47572/muskutd.1424743*

transverse pulmonary arteriotomy, and transverse aortotomy were performed to obtain an adequate exposure. A pouch made by the tricuspid septal leaflet had covered the perimembranous VSD. Additionally, the right coronary cusp of the aortic valve and adjacent cusp of pulmonary valve were prolapsed due to the Venturi effect of chronic jet flow through the VSD (Figure 1A,1B). Moreover both cusps were adherent to this pouch. The pouch, prolapsed aortic right coronary cusp and adjacent prolapsed pulmonary valve cusp were explored and they were excised carefully (Figure 1A, 1B). The VSD was repaired using a polytetrafluoroethylene patch with a continuous 5/0 propylene suture (Figure 2).

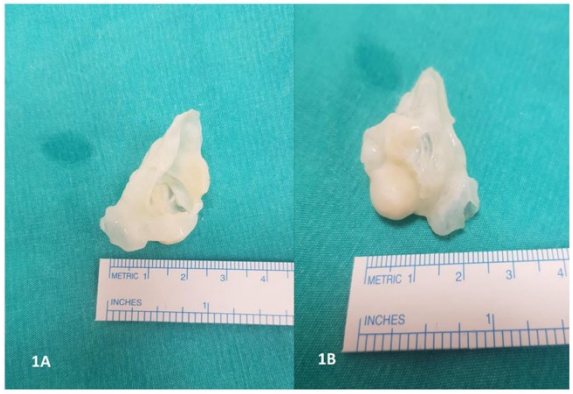



**Figure 1.** Resected parts of degenerated pulmonary valve and right coronary cusp of aortic valve.

Afterward, the defect of the pulmonary valve cusp was repaired with glutaraldehyde-treated autologous pericardium with a 6/0 propylene suture. A similar repair was performed for the right coronary cusp of the aortic valve in addition to aortic resuspension of three commissures. CPB was terminated with a low dose of inotropic agent. The postoperative course was standard except she required sildenafil 25 mg three times a day. Postoperative transthoracic echocardiogram showed minimal aortic and pulmonary valve insufficiency and no residual VSD, with a pulmonary artery systolic pressure of 25 mmHg. On the 10th postoperative day, she was discharged without any complication. Sildenafil treatment was continued until the 3rd month postoperatively. Postoperative mid-term outcome was reasonable.

## Discussion

A VSD is generally diagnosed in childhood due to cardiac murmur during routine physical examination, except for a large VSD which results congestive heart failure in the neonatal period. Depending on its size, location in the heart, PAH value, and PVR value symptoms can occur at different ages. The most common VSD in adults is a small VSD and it remains asymptomatic (4). Rarely, VSD causes valvular infective endocarditis over time (5). Other complications of unrepaired VSD in adult are aortic regurgitation, aortic right coronary cusp prolapsus, pulmonary stenosis, pulmonary regurgitation, mitral valve prolapsus and (1,2). VSD repair in adults is rare in literature (1,4).

On behalf of European Society of Cardiology (ESC) guide in 2020, in patients with evidence of left ventricle volume overload and no PAH (PVR <3 WU in case of such signs), VSD closure is recommended regardless of symptoms (Class I). In patients with no significant left to right (LR) shunt, but a history of repeated episodes of infective endocarditis, VSD closure should be considered (Class IIa), in patients with VSD-associated prolapse of an aortic valve cusp causing progressive aortic regugitation, surgery should be considered (Classs IIa). In patients who have developed PAH with PVR 35 WU, VSD closure should be considered when there is still significant LR shunt (Qp:Qs >1.5) (Class IIa). In patients who have developed PAH with PVR >5 WU, VSD closure may be considered when there is still significant LR shunt (Qp:Qs >1.5), but careful individual decision in expert centres is required (Class IIb). It should be considered that in adults, coronary artery disease might be concomitant with VSD (3).

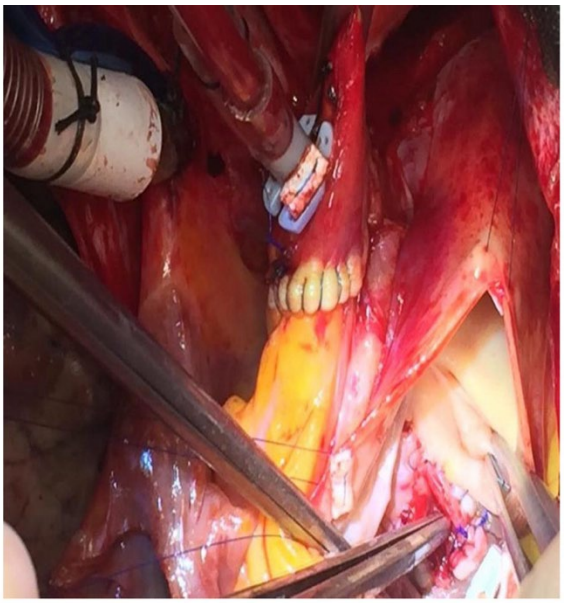


**Figure 2.** Intraoperative view of patch closure of VSD.

In this case, a pouch limited the PAH by covering the VSD. Additionally, the pulling effect of the pouch and the jet flow, degenerated and enlarged the right coronary aortic valve and adjacent cusp of pulmonary valve. Therefore, this effect probably diminished the flow through the VSD. Thus, the patient tolerated the left to right shunt until the 4th decade. Despite this limitation, our patient had significant pulmonary hypertension at the time of diagnosis and she required sildenafil treatment postoperatively. Prolapsus of cusps and severe valvular insufficiency can be repaired using mechanical valves in general.

However, in our case, removing the excess tissue of prolapsed aortic and pulmonary cusps, and repair the missing part using glutaraldehyde treated autologous pericardium provided adequate coaptation for both damaged semilunar valves.

## Conclusions

It is important to conduct a further examination in the case of pulmonary hypertension, to eliminate undiagnosed VSD in adult people. The damaged cusps of aortic and pulmonary valves can be repaired using autologous pericardium in adult patients safely instead of mechanical valve replacement to protect the patient from complications of lifelong anticoagulation in appropriate cases.

**Conflict of interest statement:** The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

**Written consent:** Written informed consent was provided by the patient (23.02.2022).

**Funding:** The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

## References

1. Kim MG, Chung W-J, Choi CH, et al. Right coronary cusp prolapse resembling subpulmonic stenosis in an old adult patient with ventricular septal defect. J Cardiovasc Ultrasound. 2011;19(4):216-20.
2. Chen Z, Chen W, Chen H, et al. Outcomes of closure of doubly committed subarterial ventricular septal defects in adults. Cardiol Young. 2020;30(5):599–606.
3. Tayama E, Fujita S, Ueda T, et al. Ventricular septal defect in an octogenarian: A case report of VSD surgical repair concomitant with coronary artery bypass and valvular surgery. Case Rep Cardiol. 2012;2012:1–4.
4. Dallarosa J, Aneja A, Shimizu S, et al. Lightning strikes twice. A. defectiva causing tri-valvular infective endocarditis (IE) in a patient with ventricular septal defect. Am J Respir Crit Care Med. 2023;207:A1807.
5. Hartman B, Dwyer A, DeJoy R. There's a hole in my heart: A case of an unrepaired VSD. Vis J Emerg Med. 2023;30:101581.

*Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi 2025;12(1):61-66* *Derleme/Review*
*Medical Journal of Mugla Sitki Kocman University 2025;12(1):61-66* *Çakıcı and Gökdoğan*
*Doi: 10.47572/muskutd.1554390*

# Otitis Media İn Immunodeficient Children

# İmmün Yetmezlikli Çocuklarda Otitis Media

**Kerimcan ÇAKICI[1], Ozan GÖKDOĞAN [2]**

[1]Erciş Şehit Rıdvan Çevik Devlet Hastanesi, Department of Otorhinolaryngology, Van, Turkey
[2]Muğla Sıtkı Koçman University, Faculty of Medicine, Department of Otorhinolaryngology, Muğla, Turkey

**Öz**
İmmün yetmezlik, bağışıklık sistemini oluşturan elemanlarda gözlenen eksiklik veya fonksiyon bozukluğu ve buna bağlı gelişen klinik bulguları tanımlamaktadır. İmmün yetmezlik yaratan durumlar oldukça heterojen bir yapıda olup başlıca primer ve sekonder immün yetmezlikler olarak sınıflandırılmaktadır. Akut otitis media normal bağışıklık sistemine sahip çocuklarda en sık karşılaşılan enfeksiyonlardan biridir. İmmün yetmezliği olmayan çocuklarda da otitis medianın sıkça görülmesi immün yetmezlikli çocukların tanı almasını zorlaştırmaktadır. Pediatrik çağdaki rekürren ve şiddetli enfeksiyonların tedavilerinde zorluklar yaşanmaktadır. Otitis media geçiren bir çocukta bazı uyarıcı semptomlar altta yatan immünolojik bir eksikliği düşündürebilir. Bu derlemede immün yetmezliği olan çocuklarda görülen orta kulak hastalıkları, bu hastalıkların yönetimi ve tedavileri tartışılmıştır.
**Anahtar Kelimeler:** İmmün Yetmezlik, İmmün Yetmezlikli Çocuklar, Otitis Media

**Abstract**
Immunodeficiency refers to deficiencies or dysfunctions in the components of the immune system and the associated clinical manifestations. The conditions leading to immunodeficiency are highly heterogeneous and are primarily classified into primary and secondary immunodeficiencies. Acute otitis media is one of the most common infections in children with a normal immune system. However, the frequent occurrence of otitis media in children without immunodeficiency can complicate the diagnosis of immunodeficiency in affected children. Managing recurrent and severe infections in the pediatric population poses significant challenges. In a child with otitis media, certain indicative symptoms may suggest an underlying immunological deficiency. In this review, the middle ear diseases observed in children with immunodeficiency, as well as their management and treatments, are discussed.
**Keywords:** Immunodeficiency, Immunodeficient Children, Otitis Media

## Introduction

Otitis media is an infectious process characterized by inflammation of the middle ear and associated cavities. Clinically, it generally presents in three forms. Among the most common clinical forms of otitis media are acute otitis media (AOM), otitis media with effusion (OME), and chronic suppurative otitis media (CSOM). Acute otitis media is usually a condition that develops secondary to self-limiting viral upper respiratory tract infections. While bacterial agents can lead to the development of infection in conjunction with viral agents, they can also occur as secondary infections following the initial viral infection (1,2).

In terms of prevalence, up to 50% of children will experience at least one episode of otitis media by the age of 1, and by age 3, up to 80% will have had at least one episode. Otitis media is more frequently observed in boys compared to girls and is a leading indication for antibiotic prescriptions in children. In particular, viral acute otitis media (AOM) in young children can quickly progress to secondary bacterial infections (3,4).

| | ORCID No |
|---|---|
| Kerimcan ÇAKICI | 0000-0002-9676-152X |
| Ozan GÖKDOĞAN | 0000-0002-1338-7254 |

Başvuru Tarihi / Received: 23.09.2024
Kabul Tarihi / Accepted : 12.12.2024

Adres / Correspondence : Kerimcan ÇAKICI
Erciş Şehit Rıdvan Çevik Devlet Hastanesi, Department of Otorhinolaryngology, Van, Turkey
e-posta / e-mail : kerim_cak@hotmail.com

Otitis media is more prevalent in children than in adults. Contributing factors include the incomplete structural and functional development of the Eustachian tube, increased incidence of adenoid hypertrophy, supine feeding practices in infants, passive smoke exposure, and allergies. Additionally, diseases associated with immunodeficiencies can further heighten susceptibility to AOM. Although immunodeficiencies are relatively rare risk factors for AOM, conditions that lead to local or systemic immunodeficiencies can contribute to recurrent otitis media and its complications.

Among the bacterial agents leading to the development of acute otitis media (AOM), *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common. Although less frequent, other agents that can cause AOM include *Moraxella catarrhalis* and *Mycoplasma spp* (5).

*Middle Ear Immunity*

In a healthy host, the natural immune system is adept at rapidly identifying and clearing pathogens from the middle ear. Histological analyses of the middle ear and associated structures, including the Eustachian tube and mastoid cells, reveal that upper respiratory epithelial cells, dendritic cells, and mast cells possess surface recognition receptors. These receptors facilitate the detection of bacterial surface molecules and the subsequent activation of various effector mechanisms. A decline in these immunological identification and protective functions can result in recurrent, persistent, or complicated inflammatory processes within the middle ear.

The middle ear mucosa employs a complex immune response mechanism to combat pathogenic microorganisms. Mast cells are the predominant immunological cells present in the middle ear mucosa. In response to infection, T and B lymphocytes are recruited. During otitis media with effusion, there is a predominant secretion of secretory IgA, accompanied by smaller quantities of IgG and IgM.

Given the frequent occurrence of otitis media in children with an otherwise normal immune system, the diagnosis of immunodeficiencies in such children may be delayed. It is crucial not to overlook specific triggering conditions in a child with otitis media. When these findings are present, a thorough evaluation for primary immunodeficiencies should be conducted.

*Immunodeficiencies and Acute Otitis Media*

Certain primary and secondary immunodeficiencies are notably associated with an increased frequency and severity of middle ear infections. Children with humoral immunodeficiencies often present with recurrent acute otitis media (AOM) as a primary complaint. The severity of ear pathology tends to correlate with the extent of impairment in producing antibody responses to polysaccharide antigens. Chronic suppurative otitis media in children should raise concern for potential underlying immunodeficiencies. Moreover, any complications arising from AOM in children should prompt a thorough evaluation for possible immunodeficiencies.

A study by Haddad et al. investigated 75 hospitalized patients with diagnosed immunodeficiency and found that 80% of these patients had an upper respiratory tract infection. Microbiological analysis of these infections identified the pathogens as community-acquired microorganisms, consistent with those typically found in healthy individuals (6).

*Primary Immunodeficiency Disorders*

Primary immunodeficiency disorders (PIDs) encompass a diverse group of over 130 conditions resulting from defects in the development and/or function of the immune system. Although PIDs are relatively rare, early diagnosis is essential to mitigate the associated morbidity and mortality. Delays in identifying and treating PIDs can lead to unnecessary antibiotic use and the performance of ineffective and often low-success-rate surgical interventions. Surgical procedures in these patients frequently exhibit low success rates and high complication rates (7).

Certain symptoms and clinical conditions should raise suspicion for a primary immunodeficiency. It is imperative that these indicative conditions are not overlooked.

*Warning Symptoms for PID Diagnosis*

The following symptoms should prompt consideration of primary immunodeficiency disorders (PIDs):

1. Eight or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Minimal response to antibiotics despite two or more months of treatment
4. Two or more episodes of pneumonia within one year
5. Failure to achieve normal weight gain or growth in an infant
6. Recurrent deep skin or organ abscesses
7. Persistent oral or cutaneous thrush beyond age one
8. Requirement for intravenous antibiotics
9. Two or more deep tissue infections
10. Family history of primary immunodeficiency (8).

*AOM Characteristics Indicative of PID*

Certain features of acute otitis media (AOM) may also suggest an underlying primary immunodeficiency. Clinicians should be particularly alert to:

- Onset of otitis media before 3-4 months of age
- Recurrence of AOM following antibiotic treatment
- Complications such as mastoiditis
- Invasive infections
- Recurrence despite the presence of ventilation tubes
- Need for recurrent tube insertions (9).

This section will review the most common primary immunodeficiency disorders that predispose individuals to otitis media. A summary of the diseases, their types, pathophysiology and treatments is presented in Table 1.

*X-linked (Bruton's) Agammaglobulinemia (XLA)*

X-linked (Bruton's) agammaglobulinemia is characterized by the complete absence of B lymphocytes and plasma cells. During the first six months of life, affected children may appear asymptomatic due to maternal antibodies. Post this period, they typically present with recurrent pyogenic upper respiratory tract infections, including those caused by *Pseudomonas aeruginosa*, *Haemophilus influenzae*, pneumococci, and other streptococci (10).

Clinically, significant indicators may include the absence or marked reduction of tonsils and cervical lymph nodes. For patients presenting with frequent otitis media and/or sinusitis, the assessment of serum immunoglobulin (Ig) concentrations is warranted if tonsils and cervical lymph nodes are notably small or absent.Further evaluations should involve

**Table 1.** Primary immunodeficiencies that frequently cause otitis media

| Disease Name | Subtype | Pathophysiology | Age of Diagnosis | Primary ENT Findings and Infections | Potential Pathogens | Treatment |
|---|---|---|---|---|---|---|
| **1. X-linked (Bruton's) Agammaglobulinemia (XLA)** | Humoral Immunodeficiency | Mutation in Bruton's tyrosine kinase (Btk) leading to impaired B cell differentiation | After 6 months | Absence or significant reduction of tonsils, absence of cervical lymph nodes, recurrent pyogenic upper respiratory tract infections | *Pseudomonas aeruginosa*, *H. influenzae*, pneumococcus, and other streptococci | IVIG therapy, Antibiotic therapy |
| **2. Common Variable Immunodeficiency (CVID)** | Humoral Immunodeficiency | Low serum immunoglobulin concentration, defective specific antibody production, possibly polygenic | Variable based on symptom severity (diagnosis can occur in adulthood) | Chronic respiratory infections, sinusitis, otitis media, intestinal system infections | Encapsulated bacteria, Herpesvirus family | IVIG therapy and Antibiotic prophylaxis |
| **3. IgG Subclass Deficiency** | Humoral Immunodeficiency | Not clearly defined; may involve B cell differentiation disorders | Typically in childhood | Recurrent ear infections, sinusitis, bronchitis, and pneumonia | Particularly encapsulated bacteria | IVIG therapy, Antibiotic therapy |
| **4. Selective IgA Deficiency (IgAD)** | Humoral Immunodeficiency | Not clearly defined; potentially defects in class switching | After age 4 | Rhinosinusitis, otitis media, mastoiditis, adenotonsillitis, and recurrent parotitis | *Streptococcus pneumoniae*, *Haemophilus influenzae* (encapsulated bacteria) | Antibiotic therapy during infections or prophylactically; IgA replacement is not recommended due to anaphylaxis risk |
| **5. Hyper-IgM Syndrome (HIGMS)** | Humoral Immunodeficiency | CD40 Ligand defect leading to IgM production due to impaired B cell differentiation | 6 months - 2 years | Peritonsillar and other soft tissue infections, adenotonsillar hypertrophy, pneumonia | *Pneumocystis carinii* pneumonia | IVIG therapy, Antibiotic therapy, G-CSF if necessary |
| **6. Wiskott-Aldrich Syndrome** | Combined Immunodeficiency | Mutations in WASP (Wiskott-Aldrich Syndrome Protein) | Within the first year | Pneumonia, sepsis, meningitis, otitis media | Encapsulated bacteria, *P. carinii*, Herpesvirus | IVIG, splenectomy, Bone marrow transplantation |

measuring the percentage of peripheral circulating B cells if at least two of the three primary serum Ig classes (IgM, IgG, and IgA) are below normal levels (11).

Clinical outcomes are generally favorable with gammaglobulin replacement therapy and aggressive antibiotic use. Boys with XLA experience improved quality of life with appropriate treatment, and life-threatening infections are rare among those receiving intravenous gammaglobulin (12).

*Common Variable Immunodeficiency (CVID)*

Common Variable Immunodeficiency is characterized by low serum immunoglobulin levels, defective specific antibody production, and increased susceptibility to bacterial infections. Patients with CVID often present with autoimmune cytopenias, lymphoproliferative disorders, and granulomas, coupled with frequent respiratory tract infections. Accumulated mucus in the airways may lead to obstruction, bacterial colonization, and recurrent infections. Due to anatomical factors, the middle ear and upper respiratory tract are particularly affected in children (13).

The most common infections in CVID include acute bronchitis, pneumonia, acute otitis media, chronic bronchitis, and chronic sinusitis. Diagnosis is often delayed, typically occurring 5.8 to 8.9 years after symptom onset. The high incidence of recurrent minor infections and significant overlap with atopic conditions complicates the diagnostic process (14,15).

Literature reports on otitis media prevalence in CVID patients vary between 25% and 98% (15–19). Advances in diagnostic and therapeutic approaches, including timely intravenous immunoglobulin (IVIG) treatment, have significantly reduced CVID-related mortality. B cell abnormalities continue to play a critical role in the chronic disease trajectory and prognosis (20–22).

*IgG Subclass Deficiency*

The four IgG subclasses (IgG1, IgG2, IgG3, and IgG4) account for approximately 70%, 20%, 7%, and 3% of total IgG levels, respectively. Each subclass has unique structural, antigenic, and biological properties. Notably, IgG2 is crucial for antibody responses against polysaccharide antigens. IgG subclass deficiency is defined by normal or near-normal total IgG levels but with one or more subclasses below age-appropriate norms by less than 2 standard deviations (23).

Clinically, both children and adults with IgG subclass deficiency often experience recurrent respiratory infections, including otitis media, sinusitis, and bronchitis, due to common respiratory pathogens. In children under ten, a deficiency in a single subclass may resolve spontaneously if there is no complete absence of the subclass. Symptomatic adults may progress to Common Variable Immunodeficiency (CVID). Regular subclass assessments are recommended for both children and adults (23).

*Selective IgA Deficiency (IgAD)*

IgA plays a critical role in mucosal immunity in the gastrointestinal and respiratory systems (24). The pathophysiology of selective IgA deficiency is not entirely understood but may involve impaired differentiation of B lymphocytes into IgA-secreting plasma cells and defective class switching (25). Diagnosis is confirmed in individuals aged 4 years and older when serum IgA levels are less than 0.07 g/L (26). This deficiency, which can range from partial to complete absence, impairs mucosal immunological barriers and increases susceptibility to infections, autoimmunity, and allergies (24).

Most patients with IgA deficiency are asymptomatic; however, approximately one-third may experience recurrent infections, including frequent sinopulmonary and gastrointestinal infections. Heterologous IgA treatment poses risks of anaphylaxis in many patients due to anti-IgA antibodies (27).

*Hyper-IgM Syndrome (HIgM)*

Patients with Hyper-IgM syndrome typically exhibit normal or elevated levels of IgM. Recurrent bacterial sinopulmonary infections generally begin after the sixth month of life due to the protective effect of maternal immunoglobulins. In children under two years, recurrent otitis media, respiratory infections, and Pneumocystis carinii pneumonia are commonly observed.

*Wiskott-Aldrich Syndrome*

Wiskott-Aldrich Syndrome, inherited in an X-linked recessive pattern due to mutations in the Wiskott-Aldrich Syndrome Protein (WASP), is characterized by impaired cellular immunity and reduced antibody responses to polysaccharide and protein antigens (IgM and sometimes IgG) (28).

Infections such as pneumonia, sepsis, meningitis, and otitis media often occur within the first year of life, primarily caused by pneumococci, encapsulated bacteria, P. carinii, and herpesviruses. AOM, atopic asthma, and eczema are frequent in these patients. Survivors beyond infancy are at risk for autoimmune vasculitis and malignancy (29,30). Bone marrow transplantation can be considered if a matched sibling donor is available; otherwise, mortality rates are high in the second decade of life (31).

*Secondary Immunodeficiencies*

*Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)*

Upper respiratory tract infections are common in HIV-infected individuals, occurring in about 40% of patients. Children with HIV frequently experience recurrent AOM, with pathogens including *Staphylococcus epidermidis*, *Pneumococcus*, *Enterococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Treatment typically involves broad-spectrum antibiotics, and surgical interventions, such as mastoidectomy, may be necessary in cases where medical management is inadequate. HIV patients face an elevated risk of unilateral and bilateral facial nerve paralysis (32).

Other causes of secondary immunodeficiency include chemotherapy, autoimmune diseases, malignancies, nephrotic syndrome, splenectomy, long-term corticosteroid use, and diabetes mellitus.

*Management of Acute Otitis Media in Children with Immunodeficiency*

In managing AOM in children with known immunodeficiencies, treatment should be tailored according to the specific type of underlying immunodeficiency. Antibiotic therapy should target possible etiological agents, and complications are more prevalent in these patients, necessitating more aggressive antibiotic treatment. Miringotomy can assist in identifying infecting organisms and determining their antibiotic sensitivities, guiding effective treatment choices. Early initiation of antibiotic therapy, and in some cases, parenteral treatment with intravenous antibiotics, can help control the disease. Treatment should involve collaboration between infectious disease specialists and otolaryngologists, with preparedness for potential complications.

For children with immunodeficiency who frequently develop ear infections, long-term prophylactic antibiotics may reduce the frequency of AOM episodes by up to 50% (33). Continuous or intermittent antibiotics are used in various immunodeficiencies associated with frequent otitis media, such as Wiskott-Aldrich Syndrome, Common Variable Immunodeficiency, specific antibody deficiency, IgA deficiency, chronic

granulomatous disease, and C2 deficiency (34,35). While prophylactic antibiotics do not replace immunoglobulin and antibody replacement therapy, they are commonly used in immunodeficient patients despite limited clinical research on their efficacy. For patients with recurrent and complicated infections despite the use of prophylactic antibiotics, and those with hypogammaglobulinemia, immunoglobulin replacement therapy should be prioritized (36).

In secondary immunodeficiencies, addressing the underlying condition is essential, and treatment should be tailored accordingly.

## Conclusions

Otitis media is one of the most prevalent conditions in childhood, with its frequency and severity influenced by developmental and environmental factors. Recurrent otitis media is commonly encountered in clinical practice and can present significant treatment challenges. Although immunodeficiencies are rare, they can be overlooked in intensive clinical settings, leading to issues with disease progression, complication development, and increased treatment costs. Aggressive treatment of immunodeficiencies and a multidisciplinary approach are crucial for effective management.

## Conflict of interest statement

There is no conflict of interest.

**Ethics Committee Approval:** No ethics committee approval is needed.

**Funding:** No funding is received.

## References

1. Subcommittee on Management of Acute Otitis Media. Diagnosis and Management of Acute Otitis Media. Pediatrics. 2004;113(5):1451-65.
2. Heikkinen T, Chonmaitree T. Viral-bacterial synergy in otitis media: Implications for management. Curr Infect Dis Rep. 2000;2(2):154-9.
3. Howie VM. Otitis Media. Pediatr Rev. 1993;14(8):320.
4. Berman S, Byrns PJ, Bondy J, et al. Expenditures in a pediatric medicaid population. Pediatrics. 1997;100(4):585-92.
5. Bulut Y, Güven M, Otlu B, et al. Acute otitis media and respiratory viruses. Eur J Pediatr. 2007;166(3):223-8.
6. Haddad J, Brager R, Bluestone CD. Infections of the ears, nose, and throat in children with primary ımmunodeficiencies. Arch Otolaryngol Neck Surg. 1992;118(2):138-41.
7. Manning SC, Wasserman RL, Leach J, et al. Chronic sinusitis as a manifestation of primary ımmunodeficiency in adults. Am J Rhinol. 1994;8(1):29-36.
8. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2014;136(5):1186-205.e78.
9. Costa-Carvalho BT, Grumach AS, Franco JL, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol. 2014;34(1):10-22.
10. De Vincentiis GC, Sitzia E, Bottero S, et al. Otolaryngologic manifestations of pediatric immunodeficiency. Int J Pediatr Otorhinolaryngol. 2009;73(SUPPL.1):S42-8.
11. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr. 2002;141(4):566-71.
12. Quartier P, Debré M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: A retrospective survey of 31 patients. J Pediatr. 1999;134(5):589-96.
13. Magliulo G, Iannella G, Granata G, et al. Otologic evaluation of patients with primary antibody deficiency. Eur Arch Oto-Rhino-Laryngology. 2016;273(11):3537-46.
14. Cunningham-Rundles C. Common variable immunodeficiency. Curr Allergy Asthma Rep. 2001;1(5):421-9.
15. Quinti I, Soresina A, Spadaro G, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007;27(3):308-16.
16. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34-48.
17. Ramírez-Vargas N, Arablin-Oropeza SE, Mojica-Martínez D, et al. Clinical and immunological features of common variable immunodeficiency in Mexican patients. Allergol Immunopathol (Madr). 2014;42(3):235-40.
18. Urschel S, Kayikci L, Wintergerst U, et al. Common variable ımmunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr. 2009;154(6):888-94.
19. Tabolli S, Giannantoni P, Pulvirenti F, et al. Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies. Front Immunol. 2014;5(11):1-9.
20. Carsetti R, Rosado MM, Donnanno S, et al. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. J Allergy Clin Immunol. 2005;115(2):412-7.
21. Warnatz K, Denz A, Dräger R, et al. Severe deficiency of switched memory B cells (CD27+IgM-IgD-) in subgroups of patients with common variable immunodeficiency: A new approach to classify a heterogeneous disease. Blood. 2002;99(5):1544-51.
22. Ko J, Radigan L, Cunningham-Rundles C. Immune competence and switched memory B cells in common variable immunodeficiency. Clin Immunol. 2005;116(1):37-41.
23. Stiehm ER. The four most common pediatric immunodeficiencies. J Immunotoxicol. 2008;5(2):227-34.
24. Latiff AHA, Kerr MA. The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem. 2007;44(2):131-9.
25. Abolhassani H, Aghamohammadi A, Hammarström L. Monogenic mutations associated with IgA deficiency. Expert Rev Clin Immunol. 2016;12(12):1321-35.
26. Singh K, Chang C, Gershwin ME. IgA deficiency and autoimmunity. Autoimmun Rev. 2014;13(2):163-77.
27. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. N Engl J Med. 1986;314(9):560-4.

28. Ochs HD. The Wiskott-Aldrich syndrome. Semin Hematol. 1998;35(4):332-45.
29. Sullivan KE, Mullen CA, Blaese RM, et al. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125(6 PART 1):876-85.
30. Akman IO, Ostrov BE, Neudorf S. Autoimmune manifestations of the Wiskott-Aldrich syndrome. Semin Arthritis Rheum. 1998;27(4):218-25.
31. Ozsahin H, Le Deist F, Benkerrou M, et al. Bone marrow transplantation in 26 patients with Wiskott-Aldrich syndrome from a single center. J Pediatr. 1996;129(2):238-44.
32. Iacovou E, Vlastarakos PV, Papacharalampous G, et al. Diagnosis and treatment of HIV-associated manifestations in otolaryngology. Infect Dis Rep. 2012;4(1):9.
33. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database Syst Rev. 2006;2006(4):CD004401.
34. Fasano MB, Hamosh A, Winkelstein JA. Recurrent systemic bacterial infections in homozygous C2 deficiency. Pediatr Allergy Immunol. 1990;1(1):46-9.
35. Weening RS, Kabel P, Pijman P, et al. Continuous therapy with sulfamethoxazole-trimethoprim in patients with chronic granulomatous disease. J Pediatr. 1983;103(1):127-30.
36. Wilson NW, Hogan MB. Otitis media as a presenting complaint in childhood immunodeficiency diseases. Curr Allergy Asthma Rep. 2008;8(6):519-24.

# YAYIN HAKKI DEVİR FORMU
# *COPYRIGHT TRANSFER AGREEMENT*

**Makale Başlığı / *Manuscript Title***

**.....**

**.....**

Yazarları arasında olduğum makale başka bir yerde sunulmamış ve yayımlanmamıştır. Makalenin içinde yer alan yazı, şekil veya diğer malzeme üzerinde başka bir kişinin veya kuruluşun yayın hakkı bulunmamaktadır. Aşağıdaki isimleri belirtilen kişiler makalede sunulan çalışmaya katkıda bulunmuşlardır. Yazarlar bu makalenin Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi / Medical Journal of Mugla Sitki Kocman University adlı dergide belirtilen isim sıralaması ile yayınlanmasını onaylamaktadırlar. Katkıda bulunan bu kişi(ler) varsa işveren(ler)i yayın hakkı dışında aşağıda belirtilen telif haklarına sahiptirler: a) Patent hakkı b) Yazar(lar)ın ileride yazacakları kitap, verecekleri konferans, ders veya sözlü sunumlarda ücretsiz olarak makalede yer alan tüm bölümleri kullanma hakkı, c) Kendi kullanım amaçları dışında kopyalayarak çoğaltma hakları olup bu kopyaları satma hakları yoktur. Ancak, çoğaltma, sergileme, başkalarına verme ve diğer dağıtım durumlarında işbu makalenin tümüyle veya kısmen bir ortamda kullanımında Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'ne atıf yapmaları gereklidir.

The manuscript titled above is not published or presented for publication elsewhere. Text, illustrations, and any other materials included in the manuscript do not infringe upon any existing copyright or other rights of anyone. The authors whose names appear below have contributed to the work presented and unanimously approve the publication of the manuscript in Medical Journal of Mugla Sitki Kocman University / Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi with the names in the order indicated below. The Contributor(s) or, if applicable the Contributor's Employer, retain(s) all proprietary rights other than copyright, such as a) patent rights; b) to use, free of charge, all parts of this article for the authors' future works in books, lectures, classroom teaching or oral presentations; c) the right to reproduce the article for their own purposes provided that the copies are not offered for sale. However, reproduction, posting, transmission or other distribution or use of the article or any material contained therein, in any medium as permitted here under, requires a citation to Medical Journal of Mugla Sitki Kocman University.

**Yazışmadan Sorumlu Yazar / *Corresponding Author*** **İmza / *Signature***

| | | |
|---|---|---|
| **Adı Soyadı / *Full Name*** | | |
| **Adres / *Address*** | | |
| **Telefon / *Telephone*** | | |
| **e-posta / *e-mail*** | | |

| | **Adı Soyadı / *Full Name*** | **Tarih / *Date*** | **İmza / *Signature*** |
|---|---|---|---|
| **1.** | | | |
| **2.** | | | |
| **3.** | | | |
| **4.** | | | |
| **5.** | | | |
| **6.** | | | |
| **7.** | | | |

**Lütfen yazarların tüm isimlerini yazınız / Please write the full names of the authors**