Selçuk Tıp Dergisi

Selcuk Medical Journal

Yıl/Year: 2025 Cilt/Volume: 41 Sayı/Issue:2

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

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SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; **e-ISSN:** 2149-8059
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SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; **e-ISSN:** 2149-8059
Cilt/Volume:41 **Sayı/Issue:** 2 **Yıl/Year:2025**

Sahibi/ Owner

Necmettin Erbakan Üniversitesi Rektörlüğü
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NEU Press
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Kapak ve Logo Tasarım/Cover and Logo designer: **Bünyamin Biçer**

Selçuk Tıp Dergisi; ULAKBİM/TR ve EBSCO, Inter-national Citation Index ve Türkiye Atıf Dizini tarafından indekslenmektedir

This journal is a member of, and subscribes to the principles of, the Committee on Publication Ethics (COPE)
www.publicationethics.org

Yayın Türü / Publication Type: Ulusal/Uluslararası Süreli Yayın; National/International periodical

Yayın Periyodu / Publication Period:Yılda dört kez (Mart, Haziran, Eylül ve Aralık) yayınlanır; Published fourth-annual (March, June,September and December)

Baskı Tarihi / Print Date: Haziran (June), 2025

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YAZARLARA BİLGİ/YAZIM KURALLARI

Selçuk Tıp Dergisi (Selcuk Med J), Necmettin Erbakan Üniversitesi'nin bilimsel, bağımsız, hakemli, açık erişimli yayın organıdır. Tıp doktorları, araştırmacılar ve bilim adamlarından oluşan geniş bir kitleye hitap eden disiplinli bir dergidir. Temel amaç Tıp/Sağlık alanında, tanı ve tedavideki güncel gelişmelerin, cerrahi yenilikler ve bilim dünyasına katkıda bulunacak çalışmaların ulusal ve uluslararası literatürde paylaşımının sağlanmasıdır.

Selçuk Tıp Dergisi, tıp bilimine ve akademik çalışmalara katkısı olan, klinik ve deneysel çalışmaları, editöryal yazıları, klinik olgu bildirimlerini, teknik ve eğitici derlemeleri, orijinal görüntü raporlarını ve editöre mektupları yayınlar. Anket/mülakat çalışmaları; Editörün ilk değerlendirmesi sonucunda çok değerli bir katkı sunuyorsa değerlendirmeye alınabilir.

Dergi gönderim kurallarına ve dergi kapsamına uygun görülen, editöryal çalışmalar hariç tüm yazılar alanında uzman hakemlere bilimsel değerlendirme için gönderilir. En az iki hakem kararı aranır. Yayımlanan tüm makaleler çift taraflı kör akran değerlendirmesi sürecine tabidir. Uygunluğunu tartışılan çalışmalarda yardımcı editörler hakemlerin yorumlarını dikkate alarak kendi değerlendirmelerini eklerler. Gönderilen tüm yazılar için nihai karar Baş Editör'e aittir. Bütün makaleler için süreçlerin editör ve yayın kurulu tarafından en geç üç ay içerisinde sonuçlandırılması hedeflenir. Fakat elde olmayan gecikmelerden dolayı bu süre uzayabilir.

Yayın kurulu kararları ile belirlenen bazı konular hakkındaki yazılar, yayın kurulu üyelerinin tamamının incelemesine sunulur. İncelemeler sonucu oy çokluğuna ulaşan çalışmaların dergideki süreçleri devam edecektir. Yayın kurulu kararları dergi web sitesinde yayınlanmaktadır.

Yayına kabul edilen yazıların her türlü yayın hakkı yazarlara ve Selçuk Tıp Dergisine aittir. Selçuk Tıp Dergisi, ilave olarak websitesinde bulunan telif hakları bildirim belgesinin de yazarlar tarafından onaylanarak imzalanmasını ve ıslak imzalı formun sisteme eklenmesini talep etmektedir. Dergi her yıl mart, haziran, eylül ve aralık aylarında olmak üzere dört sayı olarak yayımlanmaktadır. Derginin yayın dili İngilizcedir.

Gönderilen yazıların daha önce herhangi bir yerde/dergide yayınlanmamış olması ve yayın için başka bir dergiye gönderilmemiş olması gerekmektedir [Bilimsel kongrelerde sunulan sözlü bildiri ve posterler (özet ya da tam metin olabilir) bildirilmek kaydı ile hariçtir]. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal vb.) yazarlara aittir. Dergide yayımlanan yazılarda ifade edilen ifadeler veya görüşler yazarların görüşleri olup, editörlerin, yayın kurulu ve yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı, bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmemektedir. Yazım kurallarına uygun olarak hazırlanmamış olan yazıların incelenmeye alınıp alınmaması Editör ve Editöryal Kurulun insiyatifindedir.

Tüm çalışmalarda etik kurul onayı ve bu onamın belgelendirilmesi gerekmektedir. Tüm çalışmalarda yazarların çalışmaya katkı düzeyi ve onayı bildirilmelidir. Çalışmada veri toplanması, deney aşaması, yazım ve dil düzenlemesi dahil olmak üzere herhangi bir aşamasında finansal çıkar çatışması olmadığı bildirilmelidir. Çalışmada varsa ticari sponsorluk bildirilmelidir. Selçuk Tıp Dergisi'nde intihal programı (iThendicate) kullanılmaktadır. Akademik atıf sınırını aşan benzerlik taşıyan makaleler ve yayın kurallarına uygun olarak hazırlanmamış makaleler değerlendirmeye alınmayacaktır. Dergi intihal tarama raporunu yazardan talep edeceği gibi kendisi de tarama yapabilir.

Derginin yayın politikası ve süreçleri Uluslararası Medikal Dergisi Editörleri Komitesi (International Committee of Medical Journal Editors-I**CMJE),** Dünya Tıbbi Editörler Derneği (World Association of Medical Editors-**WAME),** Bilim Editörleri Konseyi (Council of Science Editors-**CSE),** Avrupa Birliği Derneği Bilim Editörleri (European Association of Science Editors-**EASE)** ve Yayın Etiği Komitesi (Committee on Publication Ethics-**COPE)** ve Ulusal Bilgi Standartları Örgütü (National Information Standards Organization-**NISO)** yönergelerini takip eder. Dergimiz 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) **(doaj.org/bestpractice)** uygundur. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında **COPE** kurallarına uygun olarak hareket edecektir.

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

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

Selçuk Tıp Dergisi, ücretsiz, açık erişim politikası benimsemektedir. Bu bağlamda dergide yayınlanan tüm yazılar https://www. selcukmedj.org adresinden erişime açık olup yazarlardan hiçbir ek ücret talep edilmeyecektir.

Yazarlık

Selçuk Tıp Dergisi'ne gönderilen çalışmalarda yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık koşullarını karşılaması gerekmektedir. ICMJE, yazarların aşağıdaki 4 koşulu karşılamasını önermektedir:

- Çalışmanın konseptine/tasarımına; ya da çalışma için verilerin toplanmasına, analiz edilmesine ve yorumlanmasına önemli katkı sağlamış olmak;
- Yazı taslağını hazırlamış ya da önemli fikirsel içeriğin eleştirel incelemelerini yapmış olmak;
- Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak;
- Çalışmanın herhangi bir bölümünün geçerliliği ve doğruluğuna ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Yazar olarak belirtilen her kişi yazarlığın dört koşulunu karşılamalıdır ve bu dört koşulu karşılayan her kişi yazar olarak tanımlanmalıdır. Yazar olarak atanan tüm kişiler yazarlık için hak kazanmalı ve hak kazanan herkes listelenmelidir. Dört kriterin hepsini karşılamayan kişilere makalenin başlık sayfasında teşekkür edilmelidir. Finansman alımı, veri toplanması ya da araştırma grubunun genel gözetimi, kendi başlarına, yazarlığı haklı çıkarmaz. Bir ya da daha fazla yazar, çalışma başlangıcından yayınlanmış makaleye kadar, bütün olarak çalışmanın bütünlüğünün sorumluluğunu üstlenmelidir.Çok merkezli çalışmalarda yazarlık bir gruba atfedilir. Yazar olarak adlandırılan grubun tüm üyeleri, yukarıdaki yazarlık kriterlerini tam olarak karşılamalıdır. Bu kriterleri karşılamayan grup üyeleri, onayları ile birlikte listelenmelidir. Mali ve maddi destek de kabul edilmelidir.

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Yazar Değişikliği Talepleri
Yazar listesindeki yazar isimlerinin eklenmesi, silinmesi veya yeniden düzenlenmesi ancak makale kabul edilmeden önce ve ancak dergi Editörü tarafından onaylandığı takdirde yapılabilir.
Böyle bir değişikliği talebi olursa Editör, sorumlu yazardan (a) yazar listesindeki değişikliğin nedeni ve (b) tüm yazarlardan eklemeyi kabul ettiklerine dair yazılı onay (e-posta), talep eder. Editör, yalnızca istisnai durumlarda, makale kabul edildikten sonra yazarların eklenmesini, silinmesini veya yeniden düzenlenmesini dikkate alacaktır.

Makale Yazımı
Orijinal araştırma makalesi kaleme alanlar, konuyu özgün bir şekilde ve nesnel bir tartışma ile ele almalıdır. Makale, başkalarının çalışmayı tekrarlamasına izin vermek için yeterli ayrıntı ve referansları içermelidir. Hileli veya bilerek yanlış beyanlar etik dışı davranış teşkil eder ve kabul edilemez.

Özgünlük
Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat sağlamalıdır. Makale yazımının yapay zekâ sistemleri kullanılarak yapıldığı çalışmalar kabul edilmemektedir. Yapay zekâ sistemleri, sadece yazıların dil düzenlemeleri için kullanılabilir.

Orijinal Kaynak Kullanımı ve Atıf Yapma
Yazarlar, tamamen özgün eserler yazdıklarından ve başkalarının eserlerini veya sözlerini kullanmışlarsa, bunun uygun şekilde alıntılandığından emin olmalıdır. Üçüncü taraflarla konuşma, yazışma veya tartışmalarda olduğu gibi özel olarak elde edilen bilgiler, kaynağın açık ve yazılı izni olmadan kullanılmamalıdır.

Veri Erişimi ve Muhafazası
Yazarlardan, editör incelemesi için makalelerini destekleyen araştırma verilerini sağlamaları ve/veya derginin açık veri gereksinimlerine uymaları istenebilir. Yazarlar, mümkünse, bu tür verilere kamu erişimi sağlamaya ve bu tür verileri yayınlandıktan sonra makul bir süre boyunca saklamaya hazır olmalıdır. Dergimiz, araştırma verilerinin TUBITAK'ın Aperta Portalı'na yüklenmesini tavsiye etmektedir.

Çoklu ve Eşzamanlı Yayın
Bir yazar aynı araştırmayı içeren makalesini birden fazla dergisinde yayımlamamalıdır. Aynı makalenin aynı anda birden fazla dergiye gönderilmesi etik dışı davranıştır. Bir yazar, özet şeklinde yayınlanmış olması dışında, daha önce yayınlanmış bir makaleyi başka bir dergide değerlendirilmek üzere sunmamalıdır.

Anket ve Mülakata Dayanan Çalışmaların Yayını ve Etik Kurul Onamları
Etik kurul izni gerektiren, tüm bilim dallarında yapılan araştırmalar için (etik kurul onayı alınmış olmalı, bu onay makalede belirtilmeli ve belgelendirilmelidir. Etik kurul izni gerektiren araştırmalarda, izinle ilgili bilgilere (kurul adı, tarih ve sayı no) yöntem bölümünde, ayrıca makalenin ilk/son sayfalarından birinde; olgu sunumlarında, bilgilendirilmiş gönüllü olur/onam formunun imzalatıldığına dair bilgiye makalede yer verilmelidir. Anket çalışmaları ve mülakata dayanan çalışmaların etik kurul onam belgeleri alınmış olmalı ve makale yüklenirken dergi sistemine eklenmelidir.

Çıkar Çatışması
Kişinin yaptığı işte çelişkiye düşmesine yol açacak, objektifliğini önemli oranda bozabilecek veya herhangi bir kişi ya da kuruluş lehine adil olmayan avantaj sağlayabilecek herhangi finansal ya da diğer tür çıkarlardır. Araştırmanın yürütülmesi ve makalenin hazırlanması sürecinde alınan tüm mali destek kaynakları ve sponsorların çalışmadaki rolü açıklanmalıdır. Finansman kaynağı yoksa bu da belirtilmelidir. Açıklanması gereken olası çıkar çatışması örnekleri arasında danışmanlıklar, maaş alımı, hibeler yer alır. Potansiyel çıkar çatışmaları mümkün olan en erken aşamada açıklanmalıdır.

Hata Bildirimi
Bir yazar yayınlanmış çalışmasında önemli bir hata veya yanlışlık fark ettiğinde, derhal dergiye bildirimde bulunmalıdır. Editör tarafından gerekli görüldüğü takdirde makaleyi geri çekmek veya düzeltmek için iş birliği yapmak da yazarın yükümlülüğüdür. Editör veya yayıncı, yayınlanan bir çalışmanın hata içerdiğini üçüncü bir şahıstan öğrenirse, yazarın konu hakkında editöre bilgi vermek de dahil olmak üzere editörle iş birliği yapması yazarın yükümlülüğüdür.

Görüntü Bütünlüğü
Bir görüntüde belirli bir özelliği geliştirmek, karartmak, taşımak, kaldırmak veya eklemek kabul edilemez. Yazarlar, dergi tarafından uygulanan grafik görseller için belirlenen politikaya uymalıdır.

Düzeltme ve Yayından Geri Çekme Talepleri
Selçuk Tıp Dergisi tarafından yayımlanan makaleler nihai versiyondur. Bu nedenle yayımlandıktan sonra düzeltme talepleri, Yayın Kurulu tarafından **COPE** yönergelerine göre değerlendirilir. Yayından geri çekme talepleri, makale kabulünden önce yapılmalıdır ve Editör Kurulu onayına tabidir. Makale kabulü sonrasında henüz yayınlanmadan önce bir geri çekme talebi olursa, gerekçesi ile birlikte baş editöre mail yolu ile ulaştırılmalıdır. Gerekçeler editör kurulu toplantısında değerlendirilerek nihai karar verilecek ve yazara mail yolu ile bildirilecektir. **Yayın aşamasına alınmış bir makalenin geri çekme talep başvuruları dikkate alınmayacaktır.** Yayımlanmadan önce çalışmasını geri çekme talebinde bulunmak isteyen yazar (lar), Geri çekme formunu doldurarak her bir yazarın ıslak imzası ile imzalanmış ve taratılmış halini editor@selcukmedj.org.tr adresi üzerinden e-posta aracılığıyla Baş Editör ve Editör kuruluna iletmekle yükümlüdür. Geri çekme formuna web sitemizin indirmeler sayfasından ulaşabilirsiniz(https://www.selcukmedj.org/tr-tr/indirmeler/). Editör Kurulu geri çekme bildirimini inceleyerek en geç 15 gün içerisinde dönüş sağlar.
Yazar isimleri, bağlantıları, makale başlıkları, özetler, anahtar kelimeler, herhangi bir bilgi yanlışı ve dijital nesne anımlayıcılardaki [digital object identifier (DOI)] yazım hataları, bir "erratum" ile düzeltilebilir.

Makale Değerlendirme Süreci
Dergiye gönderilen makalelerin hızlı bir şekilde değerlendirilmesi ve yayınlanması hedeflenmiştir. Tüm makaleler çift kör hakem değerlendirme sürecine tabidir. Makaleler, içerik, özgünlük, alandaki önem, istatistiksel analizin uygunluğu ve sonuçların çıkarılması için alanında uzman hakemler tarafından gözden geçirilecektir. En az iki hakem kararı aranacaktır. Hakemler arasında tutarsızlıklar olması durumunda, makale üçüncü ya da dördüncü bir hakeme gönderilebilecektir. Hakem kararları yardımcı editörler tarafından değerlendirilerek değerlendirme sonuçları baş editöre gönderilecektir. Gönderilen makalelerin kabulüne ilişkin nihai karar, baş editöre aittir.

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Hakemler tarafından bildirilen ve yazarlar için faydalı oldukları değerlendirilen yorum ve değerlendirmeler yazarlara gönderilir. Hakemler tarafından yapılan talimat, itiraz ve talepler kesinlikle yerine getirilmelidir. Hakem(ler)e cevap dosyası ayrıca bir Word belgesi halinde oluşturulmalıdır. Yazının gözden geçirilmiş şekliyle yazarlar, bu dosyada, hakemlerin taleplerine uygun olarak atılan her adımı açık ve net bir şekilde belirtmelidir. Yazar açıklama notları, hakemlerin değerlendirme sırasına göre numaralandırılmış olarak listelenmelidir. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak), revize edilmiş makale ve hakem önerilerine verilmiş yanıtları içeren formlar https://www. selcukmedj.org adresinden titizlikle yüklenmelidir.

Yazıların Gönderilmesi

Yazarlar Yayın Hakları Bildirim Formunu sisteme yüklemelidir. Tüm yazışmalar sorumlu yazara gönderilecektir. İlgili sorumlu yazarın, tüm diğer yazışmalar için bir e-posta adresi bildirilmelidir. Yazarlar makalelerininin alındığından kendisine verilen numara ile haberdar edilirler. Bildirilen makale numarası yapılan tüm yazışmalarda kullanılmalıdır. Yazarlara beyan edilir ki; editör ofisinin ilk değerlendirmesi sonucu okuyucunun menfaatine dönük olarak makalelerin içeriği dolayısıyla makalesi geri iade edilebilir. Bu hızlı reddetme süreci, yazarın başka bir yerde makalesini yayınlanmasına olanak sağlar.
Selçuk Tıp Dergisi'ne makale gönderilmesi, tüm yazarların, derginin yayın politikalarını ve yayın etiğini okuduğu ve kabul ettiği anlamına gelir. Makale gönderimi ve ilgili diğer tüm işlemler https://www. selcukmedj.org adresinden online olarak yapılacaktır.

Yazıların Hazırlanması

Yazarların, materyallerini göndermeden önce aşağıdaki kuralları okumaları ve makalelerini bu kurallara uygun halde sisteme yüklemeleri gerekmektedir:

Genel yazı biçimi: Tüm makaleler, her tarafta 2,5 cm genişliğinde kenar boşlukları bulunan standart A4 boyutunda bir word dosyası kullanılarak yazılmalı, kaynaklar, resim şekil ya da tablolar metinde geçiş sırasına göre numaralandırılmalıdır. Metin, sol hizalı ve heceli satır sonları olmayan 12 puntolu bir fontta çift boşluk kullanılarak ve Times New Roman karakterinde yazılmalıdır. Kelimeler arasında ve cümle noktası sonrasında tek boşluk bırakmaya özen gösterilmelidir. Paragraf için sol girintiyi sekme tuşu ile bir kez tıklayarak ayarlanmalıdır. Ölçüm birimleri için Uluslararası Birimler Sistemi (SI) kullanılmalıdır. Makalenin tüm sayfaları sayfa sonunda numaralandırılmalıdır. Tüm yazılar yazım kurallarına uymalı, noktalama işaretlerine uygun olmalıdır.

Tüm makalelerde; Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Devir Formu, ve gerekli ise hasta onam formu ayrı dosyalar olarak yüklenmelidir.
Kaynaklar makale dosyasında, makale biter bitmez değil ayrı bir sayfada başlamalıdır. Tablolar, tablo açıklamaları, resim/şekiller ve resim/şekil açıklamaları ayrıca makale ana dosyasına kaynakların ardından ayrı bir sayfada eklenmelidir. Tablo/Resim/şekil açıklamaları; Tablo/Resim/şekillerin hemen altlarında olmalıdır.

Makale bölümleri hakkında

1-Kapak Sayfası: Makalenin İngilizce tam başlığı ve 50'den fazla karakter içermeyen kısa bir başlık, tüm yazarların açık şekilde adları ve soyadları, ORCID numaraları, kurumları, sorumlu yazar ismi iş veya cep telefonu, e-posta ve yazışma adresi belirtilmelidir.Makale daha önce tebliğ olarak sunulmuş ise tebliğ yeri ve tarihi belirtilmelidir. Yazarlar ve kurumları hakkındaki bilgiler başlık sayfası haricinde ana metinde (materyal metot bölümü dahil), tablolarda, şekillerde ve video dokümanlarında yer almamalıdır. Herhangi bir hibe ya da diğer destek kaynaklarının detayları, makalenin hazırlanmasına katkıda bulunan ancak yazarlık kriterlerini karşılamayan bireylere teşekkür bölümü de kapak sayfasına eklenmelidir.

2-Ana makale dosyası; Ana makale dosyası, yazar isimleri ve kurumları gibi bilgiler içermemelidir. Ana makale dosyası:
1. Başlık, 2. Özet ve Anahtar Kelimeler, 3. Makale ana metni, 4. Kaynaklar, 5. Tablolar ve açıklamaları, 6. Resim ve Şekil açıklamaları ile birlikte resim ve şekiller, 7. Alt yazılar şeklinde dizilmelidir.
Başlık: Makale Word dosyasında en baş kısımda makalenin yazım dilinde tek uzun başlığı yer almalıdır.
Özet: Editöre Mektup haricinde tüm yazılar özet içermelidir. Orijinal araştırma makalelerinin özetleri Amaç, Gereçler ve Yöntem, Bulgular ve Sonuç alt başlıklarını içermelidir. Özetler; kaynak, şekil veya tablo numarası içermemelidir. Sözcük sayısı ve özellikler için Tablo 1'deki veriler dikkate alınmalıdır.
Anahtar sözcükler:Özelerin sonunda en az üç ile en fazla beş anahtar sözcük bildirilmelidir. Anahtar sözcükler kısaltmalar olmaksızın tam olarak listelenmeli birbirinden virgül ya da noktalı virgül kullanılarak ayrılmalıdır. Anahtar kelimeler, "Tıbbi Konu Başlıklarına **(MESH)"** uygun olmalıdır (Bakınız: www.nlm.nih.gov/mesh/MBrowser.html).
Kısaltmalar:Özetlerde ve başlıklarda kısaltmalar kullanılmamalıdır. Makalede kullanılacak kısaltmalar, mümkünse ulusal veya uluslararası kabul görmüş olmalı, ilk kullanıldığında metin içinde tanımlanmalı ve parantez içinde yazılmalıdır. Daha sonra metin boyunca o kısaltma kullanılmalıdır. Yaygın olarak kabul edilen kısaltmalar ve kullanım için lütfen "Bilimsel Stil ve Biçim"e bakınız. (https://www.scientificstyleandformat.org/Home.html). Ana metinde Bir ticari markalı ilaç, ürün, donanım veya yazılım programı ana metinde yer aldığında, ürün bilgisi, ürünün adını, ürünün imalatçısını ve şirket ile şirket merkezinin bulunduğu ülkeyi aşağıdaki biçimde parantez içinde verilmelidir: "Discovery St PET / CT tarayıcı (General Electric, Milwaukee, WI, ABD).
Makale ana metni:
Giriş: Konuyu ve çalışmanın amacını açıklayacak spesifik bilgilere yer verilir.
Gereçler ve Yöntem: Çalışmanın gerçekleştirildiği yer, zaman ve çalışmanın planlanması ile kullanılan elemanlar ve yöntemler bildirilmelidir. Verilerin derlenmesi, hasta ve bireylerin özellikleri, deneysel çalışmanın özellikleri ve istatistiksel metotlar detaylı olarak açıklanmalıdır. Çalışmaya alınanlar ve çalışmayı yürütmek için kullanılan tüm yöntemler ayrıntılı olarak açıklanmalıdır. Kullanılan yeni veya modifiye yöntemler ayrıntılı olarak açıklanmalı kaynak belirtilmelidir. İlaçların ve kimyasal ajanların dozları, konsantrasyonları, verilme yolları ve süresi belirtilmelidir. Elde edilen verileri özetlemek ve önerilen hipotezi test etmek için kullanılan tüm istatistiksel yöntemlerin kısa bir raporu, istatistiksel olarak anlamlı farklılık için belirlenen p değeri ölçütleri de dahil olmak üzere bir alt başlık altında sunulmalıdır. Yapılan istatistiksel değerlendirme ayrıntılı olarak açıklanmalıdır. Olabildiğince standart istatistiksel yöntemler kullanılmalıdır. Nadiren kullanılmış veya yeni istatistiksel yöntemler kullanılmışsa konuya ilişkin ilgili referanslar belirtilmelidir. Gerekirse, olağandışı, karmaşık veya yeni istatistiksel yöntemlerle ilgili daha ayrıntılı açıklamalar, çevrimiçi ek veri olarak okuyucular için ayrı dosyalarda verilmelidir.
Bulgular: Elde edilen veriler istatistiksel sonuçları ile beraber ayrıntılı olarak verilmelidir. Bulgular şekiller ve tablolar ile desteklenmelidir. Rakam ve tablolarda verilen bilgilerin gerekli olmadıkça metinde tekrarlanmamasına özen gösterilmelidir.
Tartışma: Çalışmanın sonuçları literatür verileri ile karşılaştırılarak değerlendirilmeli, yerel ve/veya uluslararası kaynaklarla desteklenmelidir. Yazıyla alakasız veya gereksiz genel bilgiler eklenmemeli, yazının amacına uygun yeterli uzunlukta olmalıdır.
Kaynaklar: Kaynaklar ayrı bir sayfaya yazılmalıdır. Kaynaklar APA 7 sistemine uygun olarak belirtilmelidir. Buna göre, kaynak numaraları cümle sonuna nokta konmadan () içinde verilmeli, nokta daha sonra konulmalıdır. Kaynak yazar isimleri cümle içinde kullanılıyorsa ismin geçtiği ilk yerden sonra () içinde kaynak verilmelidir. Birden fazla kaynak numarası veriliyorsa arasına ",", ikiden daha fazla ardışık kaynak numarası veriliyor ise rakamları arasına "-" konmalıdır [ör. (1,2), (1-4) gibi. Yazar sayısı 3 ve daha azsa tüm yazarların ismi olmalı, 3'dan daha fazla ise ilk3 yazar yazılıp diğerleri için et al. kullanılmalıdır. Kaynaklar metindeki kullanılış sırasına göre numaralandırılıp listelenmelidir. Atıf doğruluğu, yazarın sorumluluğundadır. Kaynaklar orijinal yazım, aksan, noktalama vb. ile tam olarak uyumlu olmalıdır. Metin içindeki tüm kaynaklar belirtilmelidir. Kaynak listesinde mükerrer yazım yapılmamalıdır. Farklı yayın türleri için kaynak stilleri aşağıdaki örneklerde sunulmuştur:

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

Araştırma Makalesi:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

Tek Yazarlı Kitaplar:

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

Kitap Bölümü:

- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Mesengiocapillary glomerulonephritis In: Williams G, ed. Oxford Textbook of Clinical Nephrology.New York:Oxford University Press, 1998: 591- 613.

Baskıdan önce çevrim içi olarak yayımlanan dergi makalesi:

- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Toplantı Raporları:

- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Bilimsel veya Teknik Rapor:

- Cusick M, Chew EY, Hoogwerf B, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Tez:

- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Web sayfası ve Sosyal Medya araçları: Yazar. Başlık. Erişim linki: URL. Erişim tarihi ve yılı

3-Tablolar ve açıklamaları: Tablolar, ana makale metnine dahil edilmelidir, kaynak listesinden sonra sunulmalı ve ayrı bir sayfada olmalıdır. Ana metinde yer alan sıraya göre numaralandırılmalıdır. Her bir tablonun üzerine açıklayıcı bir başlık konulmalıdır. Tabloda kullanılan kısaltmalar, tablonun altında dipnotlarla tanımlanmalıdır (ana metin içerisinde tanımlanmış olsa bile). Tablolar kolay okunması için açık bir şekilde düzenlenmelidir. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir.

4-**Şekil ve Resimler:** Şekil, grafik ve resimler makale gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) halinde yüklenmeli ilaveten ana makale dosyasında ayrı bir sayfada tablolardan sonra ana metin içinde de gösterilmelidir. Sisteme ayrı olarak yüklenmeyen sadece makale içerisinde geçen resimler kabul edilmeyecektir. Şekil ve resimler mutlaka isimlendirilmeli ve numaralandırılmalı, metin içinde sıralamaya dikkat edilerek belirtilmelidir. Ana metine eklenecek resim, şekil ve grafik altına açıklamaları da eklenmelidir. Resimler minimum 300 dots per inch (dpi) çözünürlüğünde ve net olmalıdır. Şekil ve resim altlarında kısaltmalar kullanılmış ise, kısaltmaların açılımı alfabetik sıraya göre alt yazının altında belirtilmelidir. Mikroskobik resimlerde büyütme oranı ve tekniği açıklanmalıdır. Yayın kurulu, yazının özünü değiştirmeden gerekli gördüğü değişiklikleri yapabilir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturmak için birleştirilebilir. Şekiller, alt birimleri göstermek için işaretlenmeli ve her birinin açıklamaları (a, b, c, vb.) yazılmalıdır. Şekilleri desteklemek için kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzer işaretler kullanılabilir. Makale içeriği gibi şekiller de kör olmalıdır. Bir birey ya da kurumu tanımlayabilecek resimlerdeki olası bilgiler anonimleştirilmelidir. Hasta fotoğrafı paylaşımlarında kimliğin birebir tanınmamasına özen göstermeli, hastalığı belirlemeye yetecek yeterlilikte görüntü paylaşılmalıdır. Hastanın kimliğini açık eden resim paylaşımları için, hastanın resminin paylaşımına izin verdiği onam formu şarttır.

Tablo 1. Makale türlerine göre sınırlamalar

Makale türü	Sözcük sınırı	Özet sınırı	Kaynak sınırı	Tablo sınırı	Şekil sınırı
Araştırma makalesi	4000	300	50	6	6
Derleme	6000	300	85	6	10
Olgu sunumu	1500	200	15	3	5
Editöre mektup	1000	Özet yok	8	Tablo içermez	Şekil içermez
Editöryal	1000	Özet yok	20	3	3
Orijinal görüntü raporu	200	Özet yok	5	1	3

Makale Türleri

Selçuk Tıp Dergisi'nde aşağıda kısaca açıklanan makale türleri yayınlamaktadır:

Araştırma Makaleleri: Orijinal araştırmalara dayanan yeni sonuçlar sağlayan en önemli makale türüdür. Orijinal makalelerin ana metni Giriş, Yöntemler, Bulgular, Tartışma, Sonuç ve Kaynaklar alt başlıklarıyla yapılandırılmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız. İstatistiksel analiz genellikle sonuçları desteklemek için gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489–93). İstatistiksel analizler hakkında bilgi Materyaller ve Yöntemler bölümünde ayrı bir alt başlık ile sağlanmalı ve süreç boyunca kullanılan istatistiksel yazılım belirtilmelidir. Birimler Uluslararası Birimler Sistemine (SI) uygun olarak hazırlanmalıdır.
Makalenin kısıtlılıkları, sakıncalar ve eksik yönler, sonuç paragrafından önce Tartışma bölümünde belirtilmelidir.

Derleme Makaleleri: Yeterli sayıda bilimsel makaleyi tarayıp, konuyu bugünkü bilgi ve teknoloji düzeyinde özetleyen, değerlendirme yapan ve bulguları karşılaştırarak yorumlayan yazılar olmalıdır. Temel ve uygulamalı bilim alanlarında tüm gelişmeleri ile birlikte son bilimsel çalışmalardaki teknik ve uygulamalar değerlendirilir. Belirli bir alan hakkında kapsamlı bilgi sahibi olan ve bilimsel geçmişi yüksek atıf potansiyeli olan yazarlar tarafından hazırlanan derlemeler dergimiz tarafından kabul edilecektir. Bu yazarlardan makale kabul şekli davet yöntemiyle de olabilir. Ana metin Giriş, Klinik ve Araştırma Sonuçları ve Sonuç bölümlerini içermelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Olgu Sunumları: Tanı ve tedavide zorluk teşkil eden, yeni tedaviler sunan veya literatürde yer almayan bilgileri ortaya koyan nadir olgu veya durumlar hakkında eğitici olgu sunumları dergimizde yayınlanmak için kabul edilir. Olgu sunumu, Giriş, Olgu Sunumu ve Tartışma ve Sonuç alt başlıklarını içermelidir.

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

İlginç ve sıra dışı resimler değerlendirme sürecinde bir avantajdır. Hasta tanımlayıcı resimlerde hasta kimliği açık ediliyorsa resmin paylaşımına izin veren hasta onamı mutlaka olmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöre Mektuplar: Bu yazı türü, daha önce yayınlanmış bir makalenin önemli kısımlarını, gözden kaçan yönlerini veya eksik kısımlarını tartışır. Derginin dikkatini çekebilecek konular başta olmak üzere, okuyucuların dikkatini çekebilecek konular hakkında makaleler, özellikle eğitici konularda Editöre Mektup şeklinde sunulabilir. Okuyucular, yayınlanmış yazılar hakkındaki yorumlarını Editöre Mektup olarak da sunabilirler. Özet, Anahtar Sözcükler ve Tablolar, Şekiller, Görüntüler ve diğer medya eklenmemelidir. Metin alt başlıkları içermemelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöryal: Tıbbın herhangi bir alanında bir görüşün açıklandığı ya da başkalarının görüşlerinin yayınlandığı, kısa makalelerdir. Normal bir dergi makalesine göre daha yaratıcı yazabilme olanağı sağlar. Dergide yakın zamanda yayınlanmış bir makale tartışılabilir, Tarihi materyal, Halk sağlığına dair konular, Sağlık politikaları, Tıp Eğitimi ve Tıpta teknolojik gelişmeler hakkındaki yazılar bu bölümde değerlendirilebilir. Tam bir derleme olamayacak bir konuda kısa derleme bu başlık altında değerlendirilebilir. Dergi editörü; okuyuculara kişisel mesaj iletmek, aynı sayıdaki bir makale ile ilgili yorum yapmak, okuyucunun dikkatini yeni gelişmelere çekmek isterse bu bölüme yazabilir. Bilimsel makalelerin tipik yazım bölümlerini içermez. Temel mesaj bir cümlede özetlenebilmelidir. Bu cümleyi editoryali yazmaya başlamadan belirlemek yazımı kolaylaştırır. Bu mesaj konusunda okuyucuyu ikna etmek için mantıklı bir tartışma yürütmelidir. Şekiller, Görüntüler ve diğer medya eklenebilir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Orijinal Görüntü Raporu: Tıbbın her alanına ait ilgi çekici, tanımlayıcı veya eğitici görüntüler (ilustrasyon ya da Fotoğraf) birkaç satırlık açıklayıcı metin ve referanslarla birlikte bu bölümde değerlendirmeye sunulabilir. Makale uzunluğu 200 kelimeyi geçmemelidir. Özet, tartışma veya sonuca gerek yoktur ancak kısa bir başlık eklenmelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Hakem Raporu Sonrasında Değerlendirme

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

Son Kontrol

1. Yayın hakkı devir ve yazarlarla ilgili bildirilmesi gereken konular formu gereğince doldurulup imzalanmış,
2. Ana makale metni ve özetlerde gerekli kelime sayıları aşılmamış
3. Yeterli sayıda anahtar kelime eklenmiş,
4. Başlık uzun ve kısa başlık şeklinde yazılmış,
5. Kaynaklar kurallara uygun olarak yazılmış,
6. Tablo, resim ve şekillerde bütün kısaltmalar açıklanmış olmalıdır.

Online Yükleme Basamakları, https://www. selcukmedj.org sayfasında;

1. Makale türü *
2. Uzun Başlık *
3. Kısa başlık *
4. Özet*
5. Anahtar kelimeler *
6. Yüklenmesi gerekli bölümler (Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Bildirim Formu ve gerekli ise hasta onam formu şeklinde tamamlanmalıdır.

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Necmettin Erbakan Üniversitesi Rektörlüğü

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SELCUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
ISSN: 1017-6616; e-ISSN: 2149-8059

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- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

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

Book Chapter:
- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.
- **Journal article published online ahead of print:**
- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Meeting Reports:
- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:
- Cusick M, Chew EY, Hoogwerf B, A et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis:
- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

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When sharing patient photos, ensure that the identity is not recognized one-to-one, and images sufficient to identify the disease should be shared. For sharing images that reveal the patient's identity, a consent form in which the patient authorizes the sharing of the image is necessary.

Table 1. Limitations according to article types

	limitation of article	abstract	references	Tables	Figures
Research Article	4000	300	50	6	6
Review	6000	300	85	6	10
Case Presentations	1500	200	15	3	5
Letters to the Editor	1000	(-)	8	(-)	(-)
Editorial	1000	(-)	20	3	3
Original Image Report	200	(-)	5	1	3

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Review Articles: Review articles should be articles that review a sufficient number of scientific articles, summarize the subject at the current level of knowledge and technology, evaluate and interpret the findings by comparing them. Techniques and applications in the latest scientific studies with all the developments in basic and applied sciences are evaluated. Reviews prepared by authors who have extensive knowledge of a particular field and have a scientific background with high citation potential will be accepted by our journal. Acceptance of manuscripts from these authors can also be by invitation. The main text should include Introduction, Clinical and Research Results and Conclusion. Please see Table 1 for word count and specifications.

Case Presentations: Educational case reports on rare cases or conditions that pose difficulties in diagnosis and treatment, offer new treatments or reveal information not included in the literature are accepted for publication in our journal. The case report should include the subheadings Introduction, Case Presentation and Discussion and Coclusion. Interesting and unusual pictures are an advantage in the evaluation process.

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SELCUK MEDICAL JOURNAL

ISSN: 1017-6616; e-ISSN: 2149-8059
Cilt/Volume:41 Sayı/Issue: 2 Yıl/Year:2025

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DOI:http:/dx.doi.org/10.30733/std.2025.01807
Selcuk Med J 2025;41(2): 55-60

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Increased Neutrophil Count As a Marker of Systemic Inflammation in Patients with Seborrheic Dermatitis: A Retrospective Controlled Study

Seboreik Dermatitli Hastalarda Sistemik Inflamasyonun Bir Belirteci Olarak Artmış Nötrofil Sayısı: Retrospektif Kontrollü Bir Çalışma

Metin Ozaslan[1]

[1]Konya Numune Hospital, Dermatology, Konya, Türkiye

ÖZET

Amaç: Bu çalışmanın amacı, seboreik dermatit (SD) tanılı hastalarda ve sağlıklı bireylerden oluşan bir kontrol grubunda inflamatuar parametreleri araştırarak hastalığın şiddetiyle olası ilişkileri değerlendirmektir.

Gereçler ve Yöntemler: Şubat ve Ağustos 2023 tarihleri arasında SD tanısına sahip 107 hastanın elektronik tıbbi kayıtları taranmıştır. Hasta grubu ile yaş ve cinsiyet açısından uyumlu 73 sağlıklı birey kontrol grubunu oluşturmuştur. Hastalar ve kontroller tam kan sayımından elde edilen nötrofil sayısı (NEU), lenfosit sayısı (LYM), beyaz kan hücresi sayısı (WBC), trombosit sayısı (PLT), trombosit-lenfosit oranı (PLR) ve trombosit-krit (PCT) ile ortalama trombosit hacmi (MPV)nden oluşan trombosit indeksleri açısından karşılaştırıldı. Her hasta için Seboreik Dermatit Alan ve Şiddet İndeksi (SDAŞİ) skoru ve her hastanın inflamatuar belirteçlerinin yaş ve SDAŞİ skoru ile korelasyonu hesaplanmıştır.

Bulgular: Ortalama NEU hasta grubunda sağlıklı kontrol bireylerine kıyasla anlamlı derecede yüksekti, (4.51 ± 1.489 x10^3/mm^3'e karşı 4.09 ± 1.096 x10^3/mm^3, p=0.038). Tek değişkenli analiz sonuçlarına göre, SD tanısı konan hastalarda NEU, kontrol grubuna kıyasla anlamlı derecede farklıydı (odds oranı, 1.274; %95 güven aralığı, 1.010-1.607, p=0.041). SD'li bireylerin ortalama MPV, NLR, PLR, WBC, NEU, LYM, PLT, ve SII değerleri kontrollere kıyasla daha yüksek olmasına rağmen, bu farklılıklar istatistiksel olarak anlamlı değildi. Hastaların MPV, NLR, PLR, SII, WBC, NEU, LYM, veya PCT değerleri ile yaş veya SDAŞİ skorları arasında anlamlı bir korelasyon bulunmamıştır. Bununla birlikte, PLT ile yaş arasında istatistiksel olarak anlamlı negatif korelasyon saptanmıştır (p=0.008). SDAŞİ skorları yaşla birlikte anlamlı olarak artış göstermiştir (p=0.025).

Sonuç: NEU, SD'de inflamatuvar bir belirteç olarak kullanılabilir. Yaş ve PLT arasındaki negatif korelasyon, SD'deki inflamasyon seviyesinin yaşla birlikte azaldığını gösterebilir.

Anahtar Kelimeler: İmmunoloji, İnflamatuar parametreler, Nötrofiller, Seboreik dermatit.

ABSTRACT

Objective: This study aimed to investigate inflammatory parameters in individuals affected by seborrheic dermatitis (SD) and in a control group of healthy subjects to assess potential associations with the severity of the disease.

Material and Methods: The electronic health data of 107 patients with SD enrolled between February and August 2023 were scanned. We employed a control group comprising 73 age-and- sex-matched healthy subjects. The patients and controls were compared for neutrophil count (NEU), lymphocyte count (LYM), white blood cell count (WBC), platelet count (PLT) counts, platelet-lymphocyte ratio (PLR) along with thrombocyte indices including platelet-crit (PCT) and mean platelet volume (MPV) measured from CBC. The Seborrheic Dermatitis Area and Severity Index (SDASI) of each patient was determined, and the correlations between each patient's age and SDASI score, and inflammatory markers were calculated.

Results: The mean NEU was significantly elevated in the patient group compared with that of the healthy controls, (4.51 ± 1.489 x10^3/mm^3 versus 4.09 ± 1.096 x10^3/mm^3, p=0.038). Based on the univariate analysis results, NEU in patients diagnosed with SD was significantly different compared to the control group (odds ratio, 1.274; 95% confidence interval, 1.010-1.607, p=0.041). Although individuals with SD had higher mean MPV, NLR, PLR, WBC, NEU, LYM, PLT, and SII values in comparison to the controls, these differences were not statistically significant. There was no significant correlation between age or SDASI scores in the MPV, NLR, PLR, SII, WBC, NEU, LYM, or PCT of the patients. However, PLT and age had a significant negative correlation (p=0.008). SDASI scores increased significantly with age (p=0.025).

Conclusion: NEU can serve as an inflammatory marker in SD. The negative correlation between age and PLT may indicate that the level of inflammation in SD decreases with age.

Keywords: Immunology, Inflammatory parameters, Neutrophils, Seborrheic dermatitis.

Geliş Tarihi/Received: 10 November/Kasım 2024 **Kabul Tarihi/Accepted:** 28 May/Mayıs 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

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Atıf yapmak için/ Cite this article as: Ozaslan M. Increased Neutrophil Count As a Marker of Systemic Inflammation in Patients with Seborrheic Dermatitis: A Retrospective Controlled Study. Selcuk Med J 2025;41(2): 55-60

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Seborrheic dermatitis (SD) is a chronic disease accompanied by erythematous scaly lesions. Although documented in individuals of all ages, SD is most commonly observed among infants and young adults (1). SD's multifactorial etiopathogenesis includes Malassezia colonization, immunological factors, keratinocyte proliferation and differentiation, and deterioration of the cutaneous barrier. Individuals with this condition show elevated levels of many inflammatory cytokines, including IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, and interferon-γ (2).

A complete blood count (CBC) is an easy-to-access test used to measure a range of inflammatory markers. Neutrophil count (NEU), lymphocyte count (LYM), white blood cell count (WBC), platelet count (PLT) counts, platelet-lymphocyte ratio (PLR) along with thrombocyte indices including platelet-crit (PCT) and mean platelet volume (MPV) measured from CBC, and neutrophil-lymphocyte ratio (NLR) have been documented as inflammatory markers in various chronic inflammatory diseases, including cardiovascular disease, diabetes, psoriasis, and atopic dermatitis (3-5). The Systemic Immune-Inflammation Index (SII) has been useful in determining prognoses in various malignancies, including melanoma, gastrointestinal, and urinary cancers, and Behçet's disease (6,7). Specifically, the SII has recently been found to increase in individuals affected by psoriasis (8). In the current study, we sought to evaluate changes in inflammatory markers and their various correlations with disease severity in individuals affected by SD compared with healthy controls.

MATERIALS AND METHODS

This retrospective controlled study received approval from the Karatay University Clinical Research Ethical Board (Date: 26.09.2023; Decision no: 2023/004). To determine the number of participants of the groups, a power analysis was conducted. Based on the results, to test the statistical significance at 80%, a 5% (α:0.05) margin of error level, the minimum sample size was determined as n = 73 people in each group. The effect size (d) of the PLR difference between the groups was 0.467, and the standard deviation was 40.7. The sample size was determined utilizing the G*Power 3.0.10 software package (Franz Faul, Universität Kiel, Kiel, Germany).

The electronic health data of 107 patients with SD enrolled between February and August 2023 were scanned. SD cases documented as acute exacerbations in patient records were included in the study. We employed a control group comprising 73 age-and- sex-matched healthy subjects. Smokers and those with a history of chronic inflammation, drug, or alcohol abuse, or both were eliminated from the study. The following characteristics were examined in both the patients and the controls: age, sex, platelet indices (MPV and PCT); and SII from CBC, NLR, PLR, PLT, WBC, NEU, and LYM. NLR was obtained by dividing NEU by LYM (NLR = NEU / LYM), while PLR was obtained by dividing PLT by LYM (PLR = PLT / LYM). The same formula (platelets × neutrophils / lymphocytes) was utilized to create SII values. Finally, each patient's Seborrheic Dermatitis Area and Severity Index (SDASI) score was determined, and the correlations between each patient's age and SDASI score, and inflammatory markers were calculated.

Statistical analysis

SPSS 22.0 statistical software was employed for the statistical analysis (SPSS Inc., Chicago, IL, USA) (9). When comparing the qualitative data for both patients and controls, Pearson's chi-square test was employed. The compatibility of the parameters with normal distribution was analyzed based on the Kolmogorov-Smirnov test. Intergroup comparisons were performed using Student's t-test for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters. Spearman's or Pearson's rank correlation coefficients were employed to determine the correlations between the variables. An analysis of univariate logistic regression was employed. Level of significance was determined as $p < 0.05$.

RESULTS

The research sample consisted of 180 participants. Between 107 patients and 73 healthy controls, there was no statistically significant difference with respect to sex or age (p=0.240 and p=0.162 for sex and age, respectively) (Table 1).

The mean NEU was significantly elevated in the patient group compared with that of the healthy controls (Table 2). Individuals with SD had higher mean MPV, NLR, PLR, WBC, NEU, LYM, PLT, and SII in comparison to the controls, these differences were not statistically significant (Figure 1). The patients' mean SDASI score was 3.42 ± 1.37.

There was no significant correlation between age or SDASI scores in the MPV, NLR, PLR, SII, WBC, NEU, LYM, or PCT of the patients (Table 3). However, PLT and age had a significant negative correlation (p=0.008). Moreover, the SDASI scores increased significantly with age (p=0.025).

Based on the univariate analysis results, NEU in patients diagnosed with SD was significantly different compared

Table 1. Mean Ages and Sex of the Patients and Controls

		Patients (n = 107)	Controls (n = 73)	p	t/ χ^2
Age in years Mean±SD		39.04 ± 17.953	42.67 ± 15.632	0.162	−1.404
Sex n (%)					
	Female	49 (45.8%)	27 (37%)	0.240	1.380
	Male	58 (54.2%)	46 (63%)		

t: Student's t test, χ^2: Pearson's chi-square test

Table 2. Between-Group Comparisons of Inflammatory Blood Parameters

	Patients (n = 107)	Controls (n = 73)	p[b]	t/z
WBC (×10³/mm³) Mean±SD	7.69 ± 1.626	7.24 ± 1.406	0.054	1.937
MPV (fL) Mean±SD	10.44 ± 0.881	10.37 ± 0.774	0.576	0.560
PCT[a] (%) Median (IQR)	0.26 (0)	0.26 (0)	0.729[a]	−0.346[a]
NEU (×10³/mm³) Mean±SD	4.51 ± 1.489	4.09 ± 1.096	0.038	2.085
LYM (×10³/mm³) Mean±SD	2.39 ± 0.706	2.35 ± 0.560	0.676	0.418
PLT[a] (×10³/mm³) Median (IQR)	251 (75)	260 (75)	0.854[a]	−0.184[a]
NLR[a] Median (IQR)	1.92 (1)	1.65 (1)	0.235[a]	−1.189[a]
PLR Mean±SD	119.98 ± 43.502	118.12 ± 38.488	0.769	0.295
SIIa Median (IQR)	462.77 (394)	441.32 (257)	0.216[a]	−1.237[a]
SDASI score Mean±SD	3.42 ± 1.37	NA	NA	NA

Note. Data are presented as M ± SD. LYM: lymphocyte count, MPV: mean platelet volume, NEU: neutrophil count, NLR: neutrophil-to-lymphocyte ratio, PCT: platelet-crit count, PLR: platelet-to-lymphocyte ratio, SDASI: Seborrheic Dermatitis Area and Severity Index, SII: Systemic Immune-Inflammation Index, WBC: white blood cell count.
[a] Mann–Whitney U test.
[b] p < 0.05 indicates statistical significance.

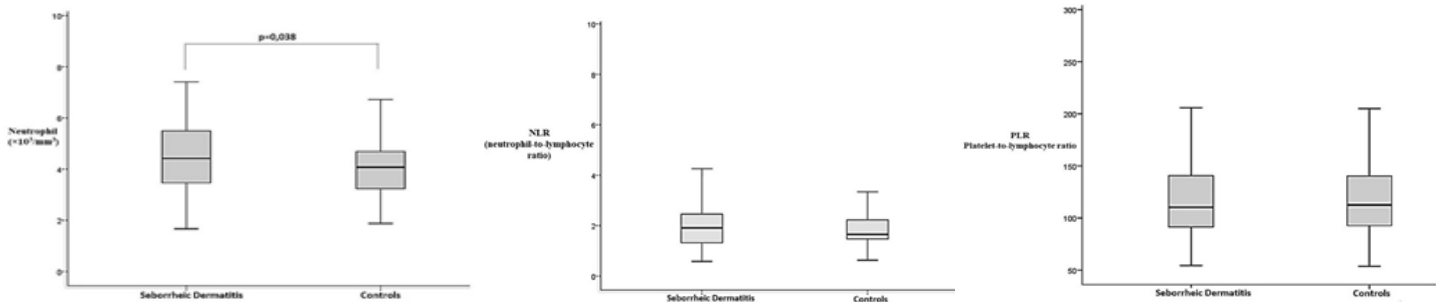

Figure 1. Comparison of NEU, NLR, and PLR measurements in patients with seborrheic dermatitis and the control group

Table 3. Correlation Coefficients between Age, SDASI Score, WBC, MPV, NEU, LYM, PLR, NLR, SII, PCT, and PLT in the Patient Group

	Age in years		SDASI score	
	r	p[b]	r	p[b]
WBC (×10³/mm³)	−0.039	0.691	−0.083	0.394
MPV (fL)	0.135	0.166	0.036	0.712
NEU (×10³/mm³)	−0.058	0.551	−0.043	0.663
LYM (×10³/mm³)	−0.038	0.700	0.001	0.992
PLR	−0.125	0.201	0.155	0.111
NLR[a]	0.001	0.991	0.010[a]	0.921[a]
SII[a]	−0.080	0.413	0.046[a]	0.635[a]
PCTa (%)	−0.176	0.069	0.157[a]	0.106[a]
PLTa (×10³/mm³)	−0.255	0.008	0.134[a]	0.168[a]
SDASI score	0.216	0.025	–	–

Note. LYM: lymphocyte count, MPV: mean platelet volume, NEU: neutrophil count, NLR: neutrophil-to-lymphocyte ratio, PCT: platelet-crit count, PLR: platelet-to-lymphocyte ratio, PLT: platelet count, SDASI: Seborrheic Dermatitis Area and Severity Index, SII: Systemic Immune-Inflammation Index, WBC: white blood cell count.
Pearson's correlation. [a] Spearman's correlation test was performed for the number sequence test.
[b] p < 0.05 indicates statistical significance.

Table 4. Logistic Regression Analysis of NEU Showing Significant Effect on Diagnosis of Seborrheic Dermatitis

		95% CI		
	OR	Lower	Upper	p
NEU	1.274	1.010	1.607	0.041
Constant	0.517			0.210

Note. CI: confidence interval, NEU: neutrophil count, OR: odds ratio.

Table 5. Inflammatory Blood Parameters in Seborrheic Dermatitis

	Metin et al. (n = 47)	Tosun et al. (n = 100)	Our study (n = 107)
Study design	Prospective case–control study	Retrospective case–control study	
Mean age, in years	35.7	35.2	39
Male-to-female ratio	23/24	56/44	58/49
Blood parameters compared with controls	Elevated NMR	Elevated PLR, MPV, and CRP	Elevated NEU
Correlation with SDASI score	LYM and LMR	RDW	-
Correlation with age	BMI	CRP	PLT and SDASI
Correlation with smoking	NEU	No data on smokers	Smokers excluded
Correlation with BMI	WBC, NEU, LYM, ESR, and CRP	Not evaluated	Not evaluated

Note. BMI: body mass index, CRP: C-reactive protein level, ESR: erythrocyte sedimentation rate, LMR: lymphocyte-to-monocyte ratio, LYM: lymphocyte count, MPV: mean platelet volume, NEU: neutrophil count, NMR: neutrophil-to-monocyte ratio, PLR: platelet-to-lymphocyte ratio, PLT: platelet count, RDW: red cell volume distribution width, SDASI: Seborrheic Dermatitis Area and Severity Index, WBC: white blood cell count.

to the control group. The results of the logistic regression analysis showed that the model was significant (p=0.036). The Nagelkerke R square value was 0.033, and the explanatory coefficient of the model was 55.6%. The effect of NEU on the model showed statistical significance (p=0.041). A one-unit increase in NEU increased the risk of seborrheic dermatitis by 1.274 times (Table 4).

DISCUSSION

In our study, compared to healthy controls, the mean NEU was significantly elevated in the patients with SD. Moreover, age was negatively correlated with PLT but positively correlated with SDASI scores in the patient group. Neutrophils, which determine immune response during chronic inflammation and can damage tissue, have an essential role in the pathogenesis of inflammatory diseases, including inflammatory bowel disease, atherosclerosis, diabetes, and systemic lupus erythematosus (SLE) (10). Neutrophils have a crucial role in the production of various inflammatory cytokines, including IL-1, IL-6, IL-12, and TNF-α, which are implicated in the development of SD (2,11). Considering that our study included cases of SD with acute exacerbations in which inflammatory activity increased, an elevated mean NEU was expected. Elevated NEU and other inflammatory markers have been documented in cases of inflammatory diseases, including psoriasis and cardiovascular disease. In a study with 2,041 patients, Pinto et al. (12) demonstrated that NEU and monocyte counts were significantly higher in individuals with cardiovascular disease than in controls. In another study (13), ESR, PLT, monocyte counts, and the levels of C-reactive protein (CRP) were also significantly elevated in rosacea cases compared to controls. In another study (14) involving 477 patients with psoriasis, WBC, NEU, PLT, NLR, and PLR were markedly elevated among the participants compared with the control population. Based on these results, the authors proposed that the NLR and PLR can be examined as systemic inflammation markers in psoriasis. However, the inflammatory markers examined in the study did not correlate with disease severity. Some studies suggest that SD may be associated with systemic inflammation and increased cardiometabolic risk (15-17). SD patients often have a higher prevalence of inflammatory markers (TNF-α, IL-6, CRP), dyslipidemia (low HDL, high triglycerides), and metabolic disorders such as insulin resistance and obesity. Additionally, Malassezia-induced inflammation and alterations in lipid metabolism may contribute to endothelial dysfunction, potentially increasing the risk of hypertension and cardiovascular risk. However, further research is needed to clarify these associations.

Only a few studies have investigated inflammatory markers in SD (see Table 5). In Metin et al.'s study (18), the NEU-to-monocyte ratio (NMR) was significantly elevated in SD patients compared to the controls, and both the LYM and lymphocyte-to-monocyte ratio were positively correlated with the SDASI score. The authors suggested that body mass index (BMI) and smoking may trigger SD by causing inflammation. Similarly, in our study, although we did not examine NMR, the significant increase in NEU among the patients compared with the controls indicates the role of chronic inflammation in SD. In Metin et al.'s study (18), patients with systemic disease or chronic medication use that might influence levels of chronic inflammatory markers were not excluded. However, in our study, we excluded patients with conditions that could affect the measurement of inflammatory blood parameters, and our patient sample was larger than in Metin et al.'s study (18) (n = 107 vs. n = 47).

In Tosun et al.'s study (19), PLR, MPV, and CRP were higher among patients with SD than controls, while red cell volume distribution width was positively correlated with SDASI score, and CRP was positively correlated with age. However, in Metin et al.'s study (18), CRP was not correlated with age. Although we did not examine CRP in our study, there was a negative correlation between PLT, a proinflammatory marker and age, which may indicate that the level of inflammation in SD decreases with age. With age, the activity of the sebaceous

glands decreases, which is the first step in SD pathogenesis and may reduce the formation of fatty acids and thus decrease inflammation (1,20). However, as far as we know, no previous research on SD has investigated changes in the inflammatory cytokine response in relation to age. In our study, the significant positive correlation between age and mean SDASI score may have been due to the relationship between age and Malassezia colonization. Previous research has shown that Malassezia colonization increases with age (21) and that Malassezia density and SD disease severity are directly correlated (22).

Platelet indices may vary over the course of chronic inflammatory diseases. For example, MPV increases in low-grade inflammatory diseases, such as psoriasis and Behçet's disease but decreases in high-grade inflammatory disorders, including RA and SLE (23). In our study, the finding that all inflammatory markers except PCT (i.e., NLR, PLR, SII, MPV, WBC, PLT, NEU, and LYM) were higher among patients than the controls, but not significantly so, may have been due to our small sample of patients.

Limitations of our study are as follows: This retrospective study included only patients with regular records in the patient registration system. Therefore, we could not analyze BMI or CRP. However, CRP is an essential indicator of systemic inflammation. In addition, the patients' BMIs may have affected their inflammatory blood parameters (24). The small number of patients was another limitation.

CONCLUSION

As far as we know, the current study is the first report showing that NEU can serve as an inflammatory marker in SD. Although our sample of patients was small, the negative correlation found between age and PLT may suggest that the level of inflammation in SD decreases with age. Therefore, in future research, prospective trials of large samples are required to elucidate the importance of inflammatory markers in SD.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01744
Selcuk Med J 2025;41(2): 61-65

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Molecular Characterization of Alpha Thalassemia via Multiplex Ligation Dependent Probe Amplification in Konya, Turkey: A Single Center Study

Konya Bölgesinde Multipleks Ligasyon Bağımlı Prob Amplifikasyonu Aracılığıyla Alfa Talaseminin Moleküler Karakterizasyonu: Tek Merkez Çalışması

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ÖZET

Amaç: Alfa talasemi, hipokrom mikrositer anemi ile karakterize, klinik fenotipi asemptomatikten lethal anemiye kadar değişkenlik gösteren, otozomal resesif kalıtılan bir hastalıktır. Alfa talasemi, %85 oranında HBA1 veya HBA2 genlerinin delesyonundan, %15 oranında ise nondelesyonel dizi değişimlerinden kaynaklanmaktadır. Biz de çalışmamızda alfa talasemi ön tanılı hastalarda Multipleks Ligasyon-bağımlı Prob Amplifikasyon (MLPA) yöntemiyle yaptığımız delesyon-duplikasyon analizi sonuçlarını sunmayı amaçladık.

Materyal and Metod: Çalışmamıza 2021-2023 yılları arasında alfa talasemi ön tanısıyla Çocuk Hematoloji bölümünde takip edilen ve Tıbbi Genetik polikliniğine yönlendirilen 29 hastanın (16 kız, 13 erkek) MLPA yöntemiyle belirlenen alfa globin kopya sayısı varyasyonları geriye dönük olarak incelendi ve MLPA'da delesyon saptanan hastaların hemogram parametreleri ve hemoglobin elektroforezi bulgularıyla genotip-fenotip korelasyonu yapıldı.

Bulgular: Alfa talasemi ön tanısı ile başvuran hastaların 15 (%51.7)'inde delesyon saptandı. Delesyon saptanan olguların 11'inde(7 kız, 4 erkek) bir α-globin gen kopyasında delesyon saptanırken; 4'ünde(3 kız, 1 erkek) ise iki α-globin gen kopyası delesyona uğramış olarak bulundu. Hastalarda en sık (%36.7) $-\alpha^{3.7}$ delesyonu gözlendi ve tespit edilen diğer delesyonlar arasında $-\alpha^{20.5}$ (%16.7), –αMED-1 (%6.6) delesyonları yer almaktaydı. İki olguda $-\alpha^{3.7}$ delesyonunun farklı formları [$-\alpha^{3,7(A)}/-\alpha^{3,7(D)}$, $-\alpha^{3,7(D)}/-\alpha^{3,7(F)}$] biallelik olarak gözlenirken, bir olguda $-\alpha^{3,7(D)}$ ile birlikte $(-\alpha)^{20,5}$ biallelik delesyonu ve diğer bir vakada ise $-\alpha^{3,7(D)}$ delesyonuna ek olarak dizi analizi ile HBA1 geninde p.Gly60Asp patojenik varyantı saptandı.

Sonuç: Alfa talasemi etiyolojisinden % 85 oranında α-globin genlerinin delesyonu sorumlu olduğundan; MLPA analizi ile moleküler genetik tanı oranı oldukça yüksektir. MLPA analizi normal olan veya saptanan α-globin gen kopya sayısının fenotipik bulguları açıklamadığı alfa talasemi olgularında HBA1 ve HBA2 genlerinin dizi analizi ile incelenmesi gerektiği akılda tutulmalıdır.

Anahtar Kelimeler: Alfa talasemi, delesyon, MLPA, amplifikasyon

ABSTRACT

Objective: Alpha thalassemia is an autosomal recessive hemoglobinopathy characterized by hypochromic microcytic anemia, exhibiting variable clinical phenotypes. Eighty-five percent of cases arise from deletions in the HBA1 or HBA2 genes. The objective of this study is to present the results of Multiplex Ligation Dependent Probe Amplification (MLPA) analysis of patients under the age of 18 with a preliminary diagnosis of alpha thalassemia.

Material and Methods: The present study examined alpha globin copy number variations determined by the MLPA method in patients who were followed up in the Pediatric Hematology department and referred to the Medical Genetics outpatient clinic with a preliminary diagnosis of alpha thalassemia between 2021-2023. We analyzed the hemogram parameters and hemoglobin electrophoresis results of the patients with deletions detected by MLPA and correlated them with their genotypes.

Results: A deletion was identified in 15 (51.7%) of 29 patients with a preliminary diagnosis of alpha thalassaemia. In eleven patients, one α-globin gene copy was deleted, while two α-globin gene copies were deleted in four patients. The most prevalent deletion was $-\alpha^{3.7}$ (36.7%), followed by $-\alpha^{20.5}$ (16.7%) and $-\alpha^{MED-1}$(6.6%). Biallelic observation of different forms of the $-\alpha^{3.7}$ deletion [$-\alpha^{3.7(A)}/-\alpha^{3.7(D)}$, $-\alpha^{3.7(D)}/-\alpha^{3.7(F)}$] was noted in two cases. Additionally, one case showed biallelic $-\alpha^{3.7(D)}$ deletion along with $(-\alpha)^{20.5}$ biallelic deletion, and in another case, besides $-\alpha^{3.7(D)}$ deletion, a pathogenic variant p.Gly60Asp was detected in the HBA1 gene through sequence analysis.

Conclusion: Since 85% of alpha thalassemia etiology is attributed to α-globin gene deletions, the molecular genetic diagnosis rate is considerably high with MLPA analysis. In alpha thalassemia cases where MLPA analysis is normal or identified α-globin gene copy numbers that do not explain the phenotypic findings, sequencing analysis of the HBA1 and HBA2 genes should be considered.

Keywords: Alpha thalassemia, deletion, MLPA, amplification

Geliş Tarihi/Received: 7 May/Mayıs 2024 **Kabul Tarihi/Accepted:** 22 October/Ekim 2024 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

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Atıf yapmak için/ Cite this article as: Goktas E, Sanal S, Tokgoz H, Zamani AG, Yildirim MS. Molecular Characterization of Alpha Thalassemia via Multiplex Ligation Dependent Probe Amplification in Konya, Turkey: A Single Center Study. Selcuk Med J 2025;41(2): 61-65

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Alpha thalassemia is an autosomal recessive hemoglobinopathy characterized by reduced synthesis of the alpha globulin chain, resulting in a disruption of the ratio of alpha to beta globulin chains (1). While the precise prevalence is uncertain, it is known that 5%-20% of the world's population carries one or more α-thalassemia variants and that it is the most common monogenic disease in African, South-East Asian and Middle Eastern countries, particularly in Mediterranean countries (2). The synthesis of human haemoglobin is mediated by an α-globin and β-globin gene cluster located on chromosome 16 and chromosome 11, respectively (3). Four functional α-globin genes (α2α1 / α2α1) are required for normal production of α-globin protein, however deletional (-) or non-deletional (α^T) variations in α-globin genes result in impaired production of this protein. Approximately 130 different molecular defects, mainly large fragment deletions, are known to cause α-thalassaemia (4). While the variation of one of the α-globin gene pairs (α2 α1) is called "heterozygous" (-α/αα) or "homozygous" (-α/-α) α^+-thalassemia; variations of both α-globin genes in a linked pair on the same chromosome 16 is called α^0-thalassemia (--/αα)(1). More than 40 variations of α^0 thalassemia have been identified, the most common being Southeast Asian ($-^{SEA}$/αα), Philippine ($-^{FIL}$/αα), and Mediterranean ($-^{MED}$/αα) (5).

While copy number changes in the α-globin genes and regulatory region sequences are responsible for the disease in 85% of alpha thalassaemia cases, non-deletional inactivations (point mutations) of the HBA1/HBA2 genes are responsible for the aetiology in 15% of cases. Copy number changes in the HBA1 and HBA2 genes can be detected with gene-targeted deletion/duplication analysis methods (Gap PCR, MLPA, chromosomal microarray, etc.), and the MLPA method is widely used for this purpose. Sequence analysis(Sanger or Next Generation Sequencing) of HBA1 and HBA2 can be performed if a common deletion was not identified with MLPA (6)

MLPA is a multiplex PCR technique that uses a single primer pair to amplify approximately 60 targeted probes. By comparing the signal patterns obtained from a sample with a set of reference samples, the number of genomic targets present in the sample of interest can be determined. MLPA can detect 50-70 nt sequence aberrations in a single gene that cannot be detected by fluorescent in situ hybridisation (FISH) (7). In alpha thalassaemia patients, most deletion variants, including common deletions such as the 3.7 kb deletion ($-\alpha^{3.7}$), the 4.2 kb deletion ($-\alpha^{4.2}$), and the Southeast Asian deletion ($--^{SEA}$), can be detected by MLPA (6).

The aim of this study is to detect variations in the HBA1 and/or HBA2 genes using the MLPA method in patients under the age of 18 who have presented to the Medical Genetics Polyclinic with a preliminary diagnosis of alpha thalassaemia, and to evaluate the influence of these variations on blood parameters.

MATERIALS AND METHODS

The study included 29 patients (16 girls, 13 boys, mean age 9±4.5 years) aged 0-18 years who were followed up at the Paediatric Haematology Department and were referred to the Medical Genetics Outpatient Clinic with a pre-diagnosis of alpha thalassemia between 2021-2023. Analyses of alpha globin copy number variation determined by the MLPA method were included. The study was approved by University Non-Drug and Medical Device Research Ethics Committee (number: 2024/4858). Written informed consent was obtained from the patients and their legal guardians. Genomic DNA was extracted from 2 ml of peripheral blood samples collected in EDTA tubes using an automated DNA isolation system (MaelstromTM 4800, Taiwan). Quality control and purity of isolated genomic DNA samples were identified spectrophotometrically using NanoDrop [NanoDrop 2000C; Thermo Fisher Scientific Inc., Wilmington, MA, USA]. Genomic deletions and duplications in the HBA1 and HBA2 genes were detected by MLPA analysis in high quality samples with A260/280 values between 1.8-2.0. The SALSA® MLPA® P140-C1 HBA probemix kit (MRC Holland, Amsterdam, The Netherlands) was tested according to the manufacturer's protocols. Fluorescent fragments obtained after ligation and amplification were separated on an ABI 3500 capillary electrophoresis system (Applied Biosystems™, California, USA) and the sizes of the fragments were determined using the GeneMapper program (Applied BioSystems, USA). The results were analysed using Coffalyser.Net data analysis software. HBA gene sequencing was performed with the next generation sequencing method (NGS, Illumina Miniseq System, San Diego, USA) in a patient whose clinical condition could not be explained by MLPA.

Statistical analysis of our study was performed using the SPSS package (SPSS for Windows, Version 25.0, SPSS Inc., USA). Descriptive statistics such as mean and standard deviation were used to characterise the haematological indices associated with each thalassemia genotype.

RESULTS

A deletion variant in the alpha globulin genes was found in 15 (51.7%) of 29 cases aged 3-18 years who presented with a preliminary diagnosis of alpha thalassaemia. Table 1 presents the distribution of globin deletions/mutations of the patients among the total number of allels. The most prevalent globin deletion was the $-\alpha^{3.7}$ deletion, observed in 36.7% of cases. The second most prevalent deletion was the $--^{20.5}$ deletion, which

Table 1. The distribution of globin deletions/mutations of the patients among the total number of allels.

Alpha globin variant	Affected allel count	%
αα (Normal)	11	36.7
-α3.7	11	36.7
--20.5	5	16.7
--MED	2	6.6
-αcd59	1	3.3
Toplam	**30**	**100**

Table 2. The age and hematological data of patients with alpha thalassemia associated with deletions.

Genotype	n	%	Gender	Age at diagnosis (years)	Hb (g/dL)	MCV (fL)	MCH (pg)	RBC (x1012/L)	RDW	Hb A2 (%)	Hb F (%)
$-\alpha^{3.7}/\alpha\alpha$	5	33.3	3M, 2F	13,4±4,16	12,32±2,54	69,48±8,3	21,52±3,15	5,72±0,81	18,32±3,56	1,6±0,14	0
$-\alpha^{3.7}/-\alpha^{3.7}$	2	13.3	2F	10±1,41	12,6±0,71	66,7±1,84	21,65±1,2	5,81±0,2	14,95±1,48	1,5±0,14	0
$--^{20.5}/\alpha\alpha$	4	26.7	3F, 1M	6,25±2,5	11,38±0,17	62,05±1,54	19,25±0,58	5,92±0,9	16,93±1,73	1,65±0,39	3±4,12
$--^{MED}/\alpha\alpha$	2	13.3	2F	3,5±0,71	9,3±0,42	59,95±1,06	18,35±1,06	5,07±0,4	19,65±4,03	1,6	0,4±0,57
$-\alpha^{3.7}/--^{20.5}$	1	6.7	1M	7	9,8	51,8	16	6,11	20,8	1,1	5,5
$-\alpha^{3.7}/\alpha\alpha^{cd59}$	1	6.7	1F	10	11,2	68,1	21,5	5,22	14,2	1,5	1,1
Total	15	100	---	9±4,5	11,4±1,7	64,5±6,8	20,1±2,4	5,6±0,5	17,5±3	1,5±0,2	1,3±2,6

was identified in 16.7% of cases. The most frequently detected genotype was $-\alpha^{3.7}/\alpha\alpha$ and its frequency was 33.3%. Two cases exhibited biallelic forms of the $-\alpha^{3.7}$ deletion, designated as [$-\alpha^{3.7(A)}/-\alpha^{3.7(D)}$, $-\alpha^{3.7(D)}/-\alpha^{3.7(F)}$]. In another case, $--^{20.5}$ biallelic deletion together with $-\alpha^{3.7(D)}$ was detected. Segregation analysis was performed on cases in which biallelic deletions were detected, and it was confirmed that the detected variants were in the trans position. $--^{MED}$ deletion, which includes 2 α globin genes, was detected in 13.3% of the cases. In another case, since the monoallelic $-\alpha^{3.7(D)}$ deletion did not explain the patient's clinic, HBA1/HBA2 genes were sequenced by next generation sequencing (Illumina Miniseq System, San Diego, USA) and a heterozygous c.179G>A G60D (Codon 59, Hb Adana) pathogenic variant was detected in the HBA1 gene. Other deletion patterns (e.g. $-\alpha^{4.2}$ $--^{SEA}$, $--^{FIL}$) and alpha triplications were not found in our paediatric patients. Figure 1 shows that MLPA images of patients with $--^{20.5}$ deletion, $--\alpha^{MED}$ deletion, biallelic $-\alpha^{3.7}/--^{20.5}$ deletion, and biallelic $-\alpha^{3.7(D)}/-\alpha^{3.7(F)}$ deletion. Table 2 presents the age and hematological data of patients with alpha thalassemia associated with deletions.

DISCUSSION

While the carrier frequency of alpha thalassaemia is between 3% and 4% in Turkey and Italy, countries around the Mediterranean, it is around 60% in eastern Saudi Arabia. Despite the existence of considerable gaps in our current understanding of the prevalence and health burden of alpha thalassaemia, the increasing speed and decreasing cost of genetic testing and other screening methods are facilitating the goal of treatment and future disease prevention (1). Understanding the genotype-phenotype relationships of different globin gene variants, as well as the interactions between multiple mutations when co-inherited, is essential for identifying mutations in carriers and affected patients (8). In

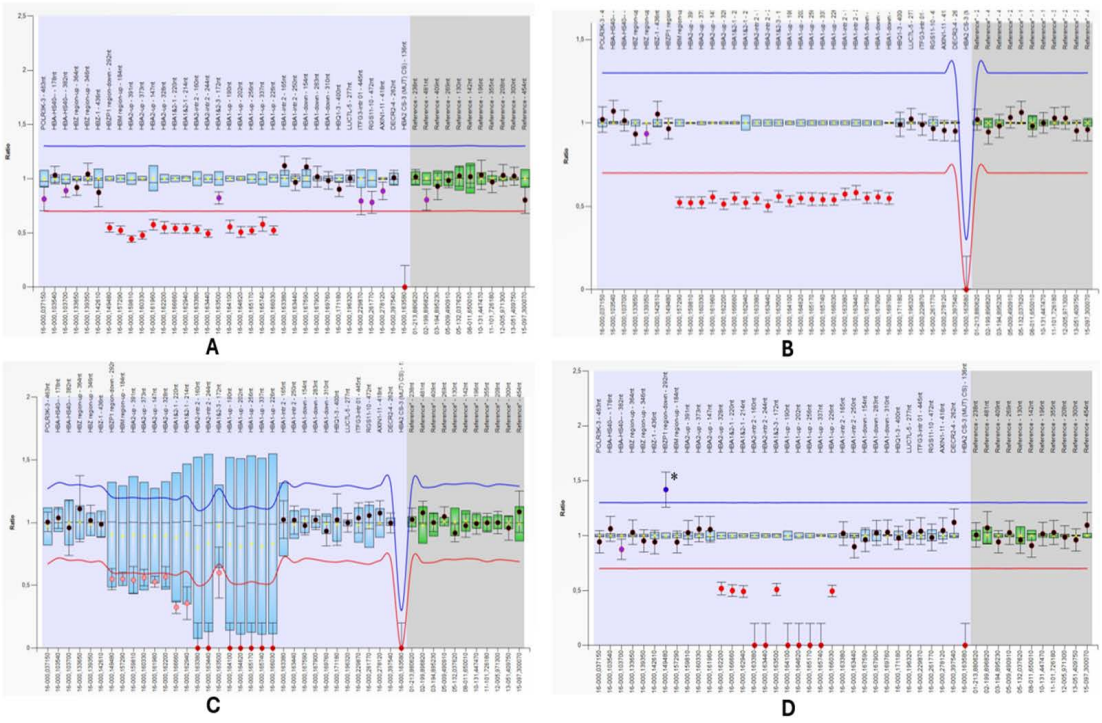

Figure 1. Coffalyser views of $--^{20.5}$ deletion (A); $--\alpha^{MED}$ deletion (B); biallelic $-\alpha^{3.7}/--^{20.5}$ deletion (C); and biallelic $-\alpha^{3.7(D)}/-\alpha^{3.7(F)}$ deletion (D). * In the patient who has biallelic $-\alpha^{3.7(D)}/-\alpha^{3.7(F)}$ deletion, additionally an Asian polymorphism indicating the duplication of the HBZ & HBZP1 locus was detected.

our study, four different alpha globin variants were determined. Three of them were deletions of varied sizes of the alpha globin gene cluster, the remaining one was co-occurrence of copy number variation type with the pathogenic sequence variant -α^{cd59}(c.179G>A, codon 59, G60D, Hb Adana, HbVar ID 87).

α^{+}-thalassemias are caused by deletions or inactivating mutations of one of the α-globin gene pairs (α2 α1) and the patient may be heterozygous or homozygous. -$\alpha^{3.7}$ or -$\alpha^{4.2}$ deletions, resulting from unequal crossing over in meiosis, causes deletional α^{+} thalassemias. According to Farashi at al., the most common α^{+} thalassemia deletion has been reported as the 3.7 kb deletion (-$\alpha^{3.7}$) (3,8). Former studies from at various times indicated that the frequency of -$\alpha^{3.7}$ deletions varies across different regions of Turkey: 52.28% in the Aegean Region, 43.2% in the southern region, 35.3% in the Trakya region among alpha thalassemia patients and also 39% of the hypochromic microcytic anemia patients in Istanbul (8–11). In our study, where data from the pediatric population aged 3-18 years were analyzed in Konya, located in the Central Anatolia region of Turkey, -$\alpha^{3.7}$ deletion was detected in 36.7% of the patients. And this rate is consistent with similar studies covering all age groups reported from Turkey.

It is reported that -$\alpha^{4.2}$, which is responsible for α^{+} thalassemias, occurs less frequently than the -$\alpha^{3.7}$ deletion (9). In two separate studies that shared data from different region of Turkey, the frequency of the -$\alpha^{4.2}$ deletion was reported as 0.95% and 4.2% (11,12) On the other hand, Onay et al (9) stated that they did not observe any -$\alpha^{4.2}$ deletion and similarly, in our study the -$\alpha^{4.2}$ deletion was not detected. The second most prevalent deletion detected in the present study was -$\alpha^{20.5}$, with a frequency of 16.7%. This variation consist of double gene deletion (α1 and α2) and is located in α0 thalassemias. This phenomenon has been rarely reported in Asia, the Middle East, and in Arab countries. However, it was reported to be the second most prevalant deletion in the studies performed by Demir (8) and Onay (9) et al. The --$^{20.5}$ deletion was followed by the --^{MED1} deletions with a frequency of 6.6%, in our study. --^{MED} deletions are a type of -α0 thalassemia. Demir (8) et al. stated the frequency of --^{MED} deletion as 2.6% and Onay (9) et al. indicated the frequency of --^{MED} deletion as 10.53%. One of the most prevalent copy number changes observed in the alpha globin gene cluster is triplication (8) However, we didn't find any triplications in our study.

The analysis of the molecular basis of alpha globin genes indicates that commonly observed variants of alpha thalassemia, previously attributed to the deletion of a single alpha globin gene copy, are in fact the result of unequal crossover and recombination occurrences. These events lead to the fusion of the two alpha globin genes into a single entity (13)

Although hematological parameters obtained from blood analyzers can serve as valuable predictive indicators of the number of deleted alpha genes, definitive diagnosis of α-thalassemia typically requires molecular studies. In previous studies, it has been widely reported that there is a considerable decrease in Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCH) when comparing patients with two functional alpha globin genes to those with one defective alpha globin gene (14, 15). Demir et al (8) and Barış et al (12) observed that the MCV value was lowest for the -$\alpha^{3.7}$/--^{SEA} genotype and the --^{MED}/αα genotype, respectively. Conversely, they found that the MCV value was highest for the -$\alpha^{3.7}$/αα genotype in their respective studies. While the patient population size is limited for conducting a statistical analysis, we revealed that MCV values were lower in patients with compound heterozygous -$\alpha^{3.7}$/--$^{20.5}$ and --^{MED} /αα deletions compared to those with -$\alpha^{3.7}$/αα genotypes. Additionally, Velasco-Rodríguez and colleagues have shown in their study, which included 129 alpha thalassemia cases with alpha globin gene deletions, that the MCH value is lower in α^{0} individuals compared to α^{+} individuals(14) In our study as well, the MCH concentration in cases with α^{0} alleles (--$^{20.5}$, --^{MED}) was found to be lower than in cases with α^{+} genotype.

The molecular complexity of alpha thalassemia renders diagnosis challenging. MLPA is a suitable method that can be used in the molecular diagnosis of alpha thalassemia. MLPA, a hybridization-based technique, has long been utilized for the detection of deletions and duplications. The MLPA method offers several advantages over alternative approaches, as highlighted in studies conducted by Colosimo et al. (15) However, sequencing methods like Sanger sequencing or NGS are necessary for identifying non-deletion mutations. While studies conducted both globally and within Turkey have primarily reported deletions as the predominant alpha globin mutations, instances of non-deletion mutations have also been documented. Our study demonstrated the effectiveness of the MLPA method in the diagnosis of alpha thalassemia in the pediatric age group and contributed to the literature on the frequency of HBA gene variants in the pediatric patient group.

A limitation of this research is the relatively small number of patients included. This was due to the fact that the study group consisted solely of paediatric patients. Secondly, sequence analysis was not applied to patients whose alpha-thalassemia MLPA was studied, despite the absence of a deletion being detected.

CONCLUSIONS

The molecular basis of alpha thalassemia is a complex phenomenon. Genetic counselling can be challenging in instances where thalassemia trait has been demonstrated clinically and haematologically, yet cannot be confirmed at the molecular level. In particular, molecular genetic diagnosis is of great value in cases of α^{+}-thalassemia and α^{0}-thalassemia. It enables the determination of the disease prognosis, the provision of accurate and effective genetic counselling, the assessment of the carrier risk of future pregnancies, and the dissemination of information about prenatal or preimplantation tests when necessary.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01789
Selcuk Med J 2025;41(2): 66-70

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

A Study on Changes in Retinal and Choroidal Structure in Children with Attention Deficit and Hyperactivity Disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğu Bulunan Çocuklarda Retina ve Koroid Yapısındaki Değişimler Üzerine Bir Araştırma

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ÖZET

Amaç: Bu çalışmada, Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) tanısı almış çocuklarda, retina sinir lifi tabakası (RSLT), ganglion hücre tabakası (GHT) ve makular koroid kalınlığının optik koherens tomografi (OKT) kullanılarak değerlendirilmesi amaçlanmıştır.
Gereçler ve Yöntem: 2019 yılında yürütülen çalışmada, K-SADS psikometrik testi ile DEHB tanısı almış 30 çocuk ile yaş ve cinsiyet açısından eşleştirilmiş 30 sağlıklı kontrol grubu karşılaştırılmıştır. Tüm katılımcılara kapsamlı bir göz muayenesi uygulanmış; en iyi düzeltilmiş görme keskinliği, biyomikroskopi ve fundus muayenesi yapılmıştır. RSLT, GHT ve makular koroid kalınlıkları OKT ile ölçülmüş, gruplar arası farklar istatistiksel olarak analiz edilmiştir.
Bulgular: DEHB grubundaki bireylerin yaş ortalaması 9,90 ± 2,15 yıl, kontrol grubunda ise 9,10 ± 2,80 yıl olarak bulunmuş; iki grup arasında yaş ve cinsiyet açısından anlamlı fark saptanmamıştır ($p > 0.05$). OKT ile yapılan ölçümlerde, RSLT, GHT ve koroid kalınlıkları yönünden gruplar arasında anlamlı bir fark bulunmamıştır ($p > 0.05$).
Sonuç: Bu çalışma, DEHB'li bireylerde retinal ve koroidal yapılarda anlamlı yapısal değişiklik olmadığını göstermektedir. Bulgular, bu anatomik yapıların DEHB ile ilişkili olmadığını düşündürmektedir. Gelecekte yapılacak daha geniş örneklemli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, retina, ganglion hücre tabakası, koroid, optik koherens tomografi

ABSTRACT

Objective: The aim of this study was to evaluate retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and macular choroidal thickness in children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) using optical coherence tomography (OCT).
Materials and Methods: Conducted in 2019, this study included 30 children diagnosed with ADHD using the K-SADS psychometric tool, along with 30 age and sex-matched healthy controls. All participants underwent full ophthalmologic examinations, including best corrected visual acuity, biomicroscopy, and fundus evaluation. OCT was used to measure RNFL, GCL, and macular choroidal thickness. Data were analyzed statistically to determine differences between the groups.
Results: The mean age was 9.90 ± 2.15 years in the ADHD group and 9.10 ± 2.80 years in the control group, with no significant difference ($p > 0.05$). Similarly, there were no statistically significant differences in terms of RNFL, GCL, or choroidal thickness between the two groups ($p > 0.05$).
Conclusion: The results indicate that structural changes in the retinal and choroidal layers are not prominent in children with ADHD. These findings suggest a lack of direct anatomical correlation. Further studies with larger populations are recommended to validate these results.

Keywords: Attention deficit hyperactivity disorder, retinal nerve fiber layer, ganglion cell layer, choroid, optical coherence tomography

Geliş Tarihi/Received: 3 September/Eylül 2024 **Kabul Tarihi/Accepted:** 20 May/Mayıs 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurocognitive disorder of childhood, with a reported prevalence ranging from 2% to 18% among children aged 6 to 17 years in developed countries (1–3). In a multicenter study conducted in Türkiye, the incidence of ADHD was reported to be 12.4% (4). ADHD is associated with difficulties in social, academic, cognitive, and emotional functioning (5). The core symptoms include inattention, hyperactivity, and impulsivity (6). The combined type of ADHD, which includes all three symptom domains, is considered the most common subtype (7). Neuroimaging studies have reported neuroanatomical and functional differences in individuals with ADHD compared to the normal population. Although the timing, specific regions, and characteristics of these morphological changes are not yet fully understood, ADHD is now classified as a neurodevelopmental disorder (8). During embryonic development, the optic nerve and retina differentiate from the diencephalon and are considered part of the central nervous system (9). Therefore, the retinal layer plays an important role in studies related to neurodevelopmental

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Atıf yapmak için/ Cite this article as: Tosun ZS, Vural Ozec A, Erdogan H. A Study on Changes in Retinal and Choroidal Structure in Children with Attention Deficit and Hyperactivity Disorder. Selcuk Med J 2025;41(2): 66-70

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

disorders.

Studies examining visual functions and ocular characteristics in children diagnosed with ADHD have addressed topics such as visual activity, strabismus, refractive errors, optic disc and retinal nerve fiber structure, and cognitive visual problems (10). The influence of the retina on the cognitive functions of individuals with ADHD has been observed. Histopathological studies have revealed a loss of retinal ganglion cells, while in vivo studies have reported thinning of the retinal nerve fiber layer (11).

Identifying and treating ocular problems in children diagnosed with ADHD may significantly improve their quality of life. Therefore, in this study, we aimed to compare retinal and choroidal changes in children diagnosed with ADHD to those in a control group.

MATERIALS AND METHODS

In 2019, two groups of participants were recruited from the Departments of Ophthalmology and Child and Adolescent Mental Health and Diseases of Sivas Cumhuriyet University Faculty of Medicine Hospital in Türkiye. The ADHD group consisted of patients diagnosed based on symptom history obtained from families presenting to the child and adolescent psychiatry outpatient clinic, observation of the child's current condition, and information gathered from schools and teachers, along with a supporting psychometric test. The psychometric assessment used was the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS). This test is a semi-structured interview designed to assess both current and past psychopathologies according to DSM-5 diagnostic criteria. Originally developed by Kaufman et al. in 1997 based on DSM-III and DSM-IV criteria, the interview schedule was updated in 2016 to align with DSM-5 diagnoses following the system's revision in 2013. The Turkish adaptation of the revised version, which includes both dimensional and categorical diagnostic evaluations, was validated and tested for reliability by Ünal et al. in 2018 (12).

The control group consisted of age- and sex-matched children who presented to the ophthalmology outpatient clinic for eye examinations, had no ocular disease history other than refractive errors, and did not have any psychiatric disorders. For each eye, patients with refractive errors greater than ± 3.0 diopters, axial eyeball length greater than 26 mm, cup-to-disc ratio greater than 0.3, cup-to-disc asymmetry between the two eyes greater than 0.2, history of eye surgery, glaucoma, uveitis, any eye with amblyopia, or children who had undergone treatment for retinopathy of prematurity were excluded from the study.

Ethical approval for the study was obtained. Additionally, written informed consent in accordance with the World Medical Association's Declaration of Helsinki was obtained from at least one parent or guardian of all children included in the study.

In the study, participants underwent detailed eye examinations, and optical coherence tomography (OCT) (OCT RS-3000 Advance, NIDEK CO. LTD., JAPAN) imaging was performed. The retinal nerve fiber layer (RNFL) thickness, ganglion cell layer (GCL) thickness, and macular choroidal thickness (MCT) were measured using OCT. The average RNFL thickness and the RNFL thickness in the four quadrants (nasal, temporal, superior, inferior) were recorded separately. RNFL thickness was measured in a 6×6 mm^2 area centered on the optic disc, while GCL thickness was measured in a 12×8 mm^2 area centered on the fovea. MCT was measured at five different points, in the region between the outer hyperreflective boundary of the retinal pigment epithelium and the inner scleral surface, subfoveal and 1 and 2 mm nasal and temporal to the fovea.

The data obtained from our study were entered into the SPSS 22.0 program. When the assumptions for parametric tests were met (Kolmogorov-Smirnov), the independent two-group comparisons were made using the t-test for the difference between two means. For the analysis of categorical data, the chi-square test was used, and the significance level was set at 0.05.

RESULTS

In the patient group, 9 (30%) were female and 21 (70%) were male, while in the control group, 10 (33.3%) were female and 20 (66.7%) were male. There was no significant difference between the groups in terms of gender ($p > 0.05$).

The mean age was 9.90 ± 2.15 years in the ADHD group and 9.10 ± 2.80 years in the control group. When comparing the individuals in both groups in terms of age, there was no statistically significant difference between the groups ($p > 0.05$).

The OCT measurements of 30 eyes from 30 children with ADHD were compared with 30 eyes from the control group. When comparing the individuals in both groups based on the RNFL thickness in the four quadrants, no statistically significant

Table 1. RNFL Thickness Values of Individuals

RNFL Thickness (Mean ± SD) (µm)	ADHD Group (n=30)	Control Group (n=30)	p value
Upper Quadrant	130.4±16.1	127.7±15.6	0.519
Nasal Quadrant	76.6±11.4	76.5±11.4	0.265
Lower Quadrant	137.8±17.1	137.9±16.3	0.221
Temporal Quadrant	70.5±9.8	71.7±10.9	0.587

Mean ± SD: Mean ± Standard deviation, µm = micrometer RNFL: Retinal Nerve Fiber Layer ADHD: Attention Deficit Hyperactivity Disorder

Table 2. GCL Thickness Values of Individuals

GCL Thickness (Mean±SD) (µm)	ADHD Group (n=30)	Control Group (n=30)	p value
Upper Quadrant	99.8±9.8	127.9±16.7	0.363
Lower Quadrant	100.5±10.1	97.9±9.8	0.324
Mean	100.2±9.6	97.7±8.2	0.302

Mean ± SD: Mean ± Standard deviation, µm = micrometer GCL: Ganglion Cell Layer ADHD: Attention Deficit Hyperactivity Disorder

Table 3. Choroid Thickness Values of Individuals

MCT (Mean±SD) (µm)	ADHD Group (n=30)	Control Group (n=30)	p value
Subfoveal choroidal thickness (µm)	390.6±66.8	379.6±61.3	0.510
Nasal 1 mm choroidal thickness (µm)	327.5±65.6	322.2±60.8	0.748
Nasal 2 mm choroidal thickness (µm)	293.3±66.8	290.5±59.0	0.861
Temporal 1 mm choroidal thickness (µm)	340.9±54.5	330.0±57.9	0.456
Temporal 2 mm choroidal thickness (µm)	321.0±51.1	311.0±58.2	0.483

MCT: Macular Choroidal Thickness Mean ± SD: Mean ± Standard deviation, µm = micrometer ADHD: Attention Deficit Hyperactivity Disorder

difference was observed ($p > 0.05$) (Table 1).

When comparing the GCL thickness in the upper, lower quadrants, and the average between the two groups, no statistically significant difference was observed ($p > 0.05$) (Table 2). When comparing the choroidal thickness in the subfoveal, nasal, and temporal regions between the two groups, no statistically significant difference was observed ($p > 0.05$) (Table 3).

DISCUSSION

ADHD is associated with various dysfunctions and abnormalities of the central nervous system. Numerous brain imaging studies have highlighted a cortical developmental delay in children with ADHD (13). In a long-term follow-up study, a maturation delay, especially in the prefrontal cortex and middle/upper temporal cortex, was observed in children with ADHD compared to the healthy group (13).

Both the retina and the brain areas responsible for cognitive functions originate embryonically from the prosencephalon. Considering this relationship, clinical studies have been planned, and results supporting the link between retinal-brain dysfunction and increased glaucoma prevalence in Alzheimer's patients have been obtained (14). Other supporting evidence comes from histopathological postmortem studies showing retinal ganglion cell loss in Alzheimer's patients (15) and in vivo studies (11,16). A reduced RNFL thickness has been reported in Alzheimer's patients (17).

In light of this information, we hypothesized that retinal area scanning, including retinal nerve fiber layer (RNFL) thickness, ganglion cell layer (GCL) thickness, and choroidal thickness, could be beneficial in ADHD patients. In our study, no significant difference was observed between the groups in terms of RNFL and GCL thickness. In a study by Bodur et al., involving 62 children, no significant difference in RNFL thickness was found between the ADHD and control groups, similar to our findings. However, in contrast, they found a thinner GCL thickness in the ADHD group compared to the control group (18). Hergüner et al. compared 45 ADHD patients with 45 controls in terms of RNFL thickness and found that the nasal quadrant was significantly thinner in the ADHD group compared to the control group. They also found a negative correlation between symptom severity and RNFL thickness (19). In the study by Işık et al., groups were formed as those receiving methylphenidate treatment, not receiving treatment, and healthy controls. When comparing the groups in terms of RNFL, GCL, and central macular thickness measurements, no statistically significant difference was found (20). Except for the study by Hergüner et al., no significant difference in RNFL thickness has been observed in clinical studies of children with ADHD, including our study. Işık et al. suggested that this might be due to ADHD being a neurodevelopmental rather than a neurodegenerative disorder (20).

Until now, a limited number of studies have been conducted on visual functions and ocular characteristics in patients with ADHD. In a study by Mezer et al., the frequency of ocular and visual function disorders was found to be higher (10). Additionally, it has been reported that the incidence of eye motility disorders and convergence insufficiency is also high in ADHD patients (21-23). Grönlund et al. detected abnormal ophthalmic symptoms in 76% of 42 children diagnosed with ADHD, including optic disc shrinkage and narrowing of the optic rim. Furthermore, the researchers pointed out morphological changes in the optic disc and retinal vasculature. They suggested that this may stem from the retinal ganglion neurons and extensions from the optic nerve, with the shrinkage in the neuroretinal area manifesting as a reduction in axons quantitatively or volumetrically in the optic nerve (24). In contrast to these findings, Mezer and Wygnanski-Jaffe, after detailed ophthalmic examinations of 32 children with ADHD and 9 children with other disorders, did

not observe any morphological changes in the optic nerve or retinal vasculature (10).

In this study, we compared the subfoveal and nasal and temporal choroidal thicknesses at 1 and 2 mm from the fovea between ADHD patients and the healthy control group. Similar to other studies, we found that the choroidal thickness was highest in the subfoveal area, decreasing as it moved away from the fovea, with thickness being greater in the temporal region.

In our study, children aged 5-16 years were included, and no significant difference was found between the patient and control groups in terms of age. Although no age stratification was performed, this suggests that the randomization of the cases included in the study was done appropriately.

Some studies have shown significant gender differences in choroidal thickness. Many studies have indicated that the choroid is thicker in men than in women. In a study by Barteselli et al., the choroidal thickness in men was found to be 7.4% greater than in women (25). This gender difference should be taken into account when performing EDI-OCT measurements. In this study, the groups were selected in such a way that there was no statistical difference in terms of gender. When comparing gender characteristics in the ADHD group, the proportion of males was found to be 70.0%, and females 30.0%. ADHD, which is more commonly seen in males, has been shown to have a male/female ratio ranging from 1/1 to 3/1 in population-based studies worldwide, while in clinical studies, this ratio can rise as high as 9/1 (26, 27). A large meta-analysis conducted in 2007 found the male/female ratio to be 4/1 (28). The findings regarding the gender-ADHD relationship in our study are consistent with those of other studies.

The limiting factors in our study include the relatively small sample size, the inclusion of children in the control group without excluding ADHD diagnosis, and the lack of analysis based on medication use in the ADHD group.

CONCLUSION

OCT, a modern measurement technique that allows for the comparison of pathologies with objective measurements, was difficult to use due to cooperation issues in the pediatric age group, but despite all the challenges with this age group, it was successfully utilized, allowing us to obtain valuable data. In light of these findings, despite various limitations, we believe our study will contribute to the literature.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01720
Selcuk Med J 2025;41(2): 71-77

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Evaluation of Electromyography Requests in a Tertiary Center

Üçüncü Basamak Bir Merkezde Elektromiyografi İstemlerinin Değerlendirilmesi

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ÖZET

Amaç: Elektrodiagnostik çalışmalar, sinir iletim çalışmaları ve iğne elektromiyografiyi kapsar. Artan sağlık maliyetleriyle birlikte, kliniklerden gelen ön tanı ve tanı uyumları önemli ölçüde ilgi çekmiş ve çalışmalara konu olmuştur. Çalışmamızın amacı, kliniğimizde sinir iletim çalışmaları ve iğne elektromiyografi istem nedenleri ile bu istemlerin sonuçlarının tutarlılığının karşılaştırılması ve bulguların elektromiyografi istem nedenlerini değerlendiren eski çalışmalarla karşılaştırılmasıdır.

Hastalar ve Yöntem: Bu çalışmada, laboratuvarımızda 2 yıllık süre içinde elektrodiagnostik incelemeler yapılan 590 kadın ve 549 erkekten oluşan toplam 1136 hasta verisi çalışmaya dahil edildi. Bu veriler geriye dönük incelenip bulgular demografik özellikler, istem nedenleri, sonuçlar, gönderen klinikler ve tanısal uyumları açısından sorgulanmıştır.

Bulgular: Elektromiyografik incelemeler ile yapılan istemlerin yaklaşık %60'ında patolojik sonuçlara ulaşıldığı görülmektedir. En çok istenen ön tanılar sırasıyla polinöropati ve tuzak nöropatilerdir. Tuzak nöropati istemlerinin çoğu Ortopedi kliniği (%60), polinöropati istemlerinin çoğu Nöroloji ve İç Hastalıkları klinikleri tarafından yapılmıştır. Olguların yarısından fazlasında sonuçlar patolojik raporlanmıştır. İstem nedenleri ve son tanı uyumu %44.8 olarak saptanmıştır. Ön tanı ve tanı uyumluluğuna bakıldığında, tuzak nöropati ön tanısıyla yapılan istemlerde Fizik Tedavi ve Rehabilitasyon kliniğinde bu uyum en yüksek olup, %42 oranında ön tanı-tanı uyumu izlenmiştir. İstem nedeni ve tanı uyumsuzluğu çoklu ön tanılarda önemli ölçüde yüksek bulunmuştur.

Sonuç: Elektromiyografinin teşhis ve tedavideki yararı, istenen ön tanı ve istem yapan klinikle yakından ilişkilidir. Elektromiyografi istem nedenleri ve son tanı uyumları öngörülebilir.

Anahtar Kelimeler: Nörolojik tanısal teknik, sinir iletim çalışması, elektromiyografi, üçüncü basamak merkez

ABSTRACT

Objective: Electrodiagnostic studies encompass nerve conduction studies and needle electromyography. The rationale behind the requests and diagnostic concordance according to referring clinic, coupled with escalating healthcare expenditures, have garnered considerable scholarly attention and been the focus of studies. Our study aims to compare the consistency of referred cases according to clinic and the interpretation of nerve conduction studies and needle electromyography studies, comparing the findings with previous studies evaluating electromyography requests.

Patients and Methods: In this study, data were included from 1136 patients, consisting of 590 women and 549 men who underwent electrodiagnostic examinations in our laboratory over a period of two years. These data were retrospectively analyzed, and the findings were evaluated in terms of demographic characteristics, reasons for referral, results, referring clinics, and diagnostic concordance.

Results: Electromyographic investigations were found to have a general pathology detection rate of approximately 60%. The preliminary diagnoses most requested were polyneuropathy and entrapment neuropathy, respectively. Most entrapment neuropathy referrals were from Orthopedics (60%), while the majority of polyneuropathy requests came from Neurology and Internal Medicine. Tests were reported as pathological in more than half of the cases. The overall concordance rate was found to be 44.8%. When examining the concordance between the referral diagnosis and the final diagnosis for entrapment neuropathies, the Physical Medicine and Rehabilitation clinic exhibited the highest rate at 42%. The rate of discrepancy between referral and outcome was significantly high in referrals with multiple indications.

Conclusion: The usefulness of electromyography for diagnosis and treatment is closely associated with pre-diagnostic considerations and the department responsible for the request. The concordance between referrals and outcomes can be predicted.

Keywords: Neurological diagnostic technique, nerve conduction study, electromyography, tertiary referral center

Geliş Tarihi/Received: 24 February/Şubat 2024 **Kabul Tarihi/Accepted:** 24 October/Ekim 2024 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

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Atıf yapmak için/ Cite this article as: Turkmen N, Kir HH, Guney F, Yuruten Corbacioglu B, Demir O, Uyar M. Evaluation of Electromyography Requests in a Tertiary Center. Selcuk Med J 2025;41(2): 71-77

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Nerve conduction studies (NCS) and electromyography (EMG) are important diagnostic tools for the evaluation of neuromuscular disorders, even with the advances in neuroradiology and imaging techniques. The reasons for requesting these tests and diagnostic concordance according to clinic, together with increasing health costs, have attracted attention and been the subject of many studies (1-3). The aim is to standardize clinical neurophysiology laboratories with the accumulation of experience that is increasing through the years. NCS and EMG allow objective assessments of neuromuscular physiology. While sensory and motor components of peripheral nerves are evaluated with nerve conduction studies, spontaneous and voluntary motor unit action potentials are analyzed with electromyography (4). Thus, the location of the pathology in the peripheral nerve or muscle, the type of injury and duration can be interpreted. Electromyography is a neurophysiological technique that requires expertise. It is a flexible procedure that is tailored to the individual patient.

Recent reports in the literature emphasized pathophysiology, evaluation, and natural history of radiculopathy, with a focus on the timing and efficacy of EMG (5). Recent articles emphasized that laboratory tests for neuropathies should be based on history, clinical presentation, and electrophysiological findings to target the suspected neuropathy type, avoiding unnecessary tests and expenses while considering the sensitivity and specificity of the tests applied (6). This study was deemed necessary for these reasons. We aimed to evaluate the appropriateness of EMG requests in a tertiary center, while also determining the areas of use of EMG, and to compare the reason for referrals and final diagnoses, taking into account previous studies.

PATIENTS AND METHODS

Patients admitted to the Electromyography Laboratory of Necmettin Erbakan University Medical Faculty, Department of Neurology and Clinical Neurophysiology were enrolled. Between 2018 and 2020, data from 1136 patients aged between 1 and 91 years, who were referred from external centers and departments within our hospital, were retrospectively reviewed. In this study, 1136 patients who underwent electrodiagnosis (EDX) testing in our laboratory between 2018 and 2020 were examined. A total of 1136 patients, consisting of 590 females and 546 males, were included in the study after excluding 64 patients due to repetitive requests. The findings were analyzed according to the demographic characteristics of the patients, consistency of referral reasons, and referring clinics after examining NCS and EMG according to standardized protocols. The study followed the Declaration of Helsinki, and ethical approval was obtained from the Necmettin Erbakan University Medical Faculty Ethics Committee on January 22, 2021 (Decision number 2021/3054). Electrodiagnostic tests were carried out in our laboratory using a Nihon Kohden Neuropack MEM-4104 K model device.

After gathering brief information about the patients, the referring clinic and the reason for referrals were obtained. A brief anamnesis was taken, neurological examination was performed, and the appropriate electrophysiological examination was initiated. If needed, the extremities were warmed up and appropriate conditions were provided beforehand. The procedures consisted of the appropriate protocol (nerve conduction studies and needle EMG) covering the extremities, facial muscles, and anal sphincter for the requested protocol, or repetitive nerve stimulation tests evaluating the neuromuscular junction. Anal sphincter EMG was performed transdermally in patients with fecal incontinence based on MUP analysis with needle EMG in four quadrants. As stated in the studies, MUP activity was evaluated subcutaneously in patients at the 3, 6, 9, and 12 o'clock positions and at an angle of 30-50 degrees on the anal canal axis, at the line level on the mucocutaneous junction, and anal orifice line (7).

All requests for radiculopathy, plexopathy, and unilateral entrapment neuropathy were studied by comparing them with the contralateral extremity. Three extremity nerve conduction studies were performed for polyneuropathy protocols, and needle EMG was performed in at least one muscle to exclude differential diagnoses. In the case of the detection of pathology with needle EMG, the study area was expanded to confirm the diagnosis. In the myopathy protocol, after motor and sensory nerve conduction study in the upper and lower extremities, needle EMG was performed to evaluate the proximal and distal muscles. Repetitive nerve stimulation (RNS) tests, such as 2, 3.5 Hz low-frequency, and 50 Hz high-frequency RNS, were performed when necessary for the evaluation of neuromuscular disorders. All of the examinations were performed by clinical neurophysiologists and were simultaneously reported and interpreted.

Referrals were categorized into referral reasons, including the most and least common suspected diagnoses. Reports were categorized as pathological or normal regarding the proportion of individual diagnoses. According to the referring physician's specialty, the frequency of referrals and final diagnoses, and the concordance and agreement of the referral diagnoses were reported. In conclusion, the data were analyzed in detail, including demographic characteristics such as age and sex, referral diagnoses, and their compatibility with final diagnoses after conducting the EDX tests, and the characteristics of the referral diagnoses and referring clinics.

Statistical Analysis

Descriptive statistics utilized mean and standard deviation for continuous numerical variables, and numbers, percentages, and rates for categorical variables and their relationships. Descriptive statistics were employed in this study. A significance level of $p<0.05$ was adopted for all comparisons. Research data were analyzed using IBM SPSS Statistics, version 24.0 (IBM Corp, Armonk, N.Y., USA).

Necmettin Erbakan University Medical Faculty, Neurology Department, Clinical Neurophysiology Electromyography Laboratory has been active since 1990. Readings are conducted by faculty members. Since 2012, subspecialists in Clinical

Table 1. Demographic characteristics of patients

	Female		Male	
	n	%	N	%
Under 18 years old	46	7.8	44	8.1
Ages 18-65	434	73.6	393	72.0
Over 65 years old	110	18.6	109	20.0
Total	590		546	

Neurophysiology have been trained in the department.

RESULTS

A total of 1136 patients, including 590 females and 546 males, had a mean age of 47.01 ± 18.95 years. Of the patients, 7.9% were under the age of 18, 72.8% were between the ages of 18-65, and 19.3% were over the age of 65. The demographic features of the patients are shown in Table 1. The findings were analyzed under three different headings: the referral request, findings, and characteristics of the referring clinics.

EMG Referrals

The most requested preliminary diagnoses were polyneuropathy (28%) and entrapment neuropathy (22%). Referrals for EMG requests and overall results are shown in Table 2. Entrapment neuropathy was requested mostly by the Orthopedic department (60%). Neurology and Internal Medicine clinics made the majority of referrals for polyneuropathy. Entrapment neuropathy is a commonly requested diagnosis by the Rheumatology department, which falls under the subspecialty of Internal Medicine. The most frequently requests by Neurology were for polyneuropathy and entrapment neuropathy. EMG requests referred by the Neurology clinic are shown in Table 2. The results revealed that the highest levels of concordance were observed for polyneuropathy, entrapment neuropathy, myopathy, and motor neuron disease within the requested referrals. A cohort of cases (5.4%) underwent EMG as "general screening" without any specific clinical indication, as demonstrated in Table 3.

EMG Findings

According to the data presented in Table 2, 40% of the requests resulted in normal findings. It was observed that 43% of the cases referred for a "general scan" were reported as normal. Less than 5% of the total cases were diagnosed with myopathy, neuromuscular junction disease, or motor neuron disease. Polyneuropathy and entrapment neuropathy were the most frequently detected pathological results, accounting for 16% and 13% of the cases, respectively. As shown in Table 4, the correlation between the initial and final diagnoses was influenced by the requesting clinic and protocol. The overall

Table 2. Distribution of EMG requests from the Neurology Clinic and all departments according to protocols and distribution of all results according to protocols

	Neurology Clinic EMG requests		All EMG requests		All EMG results	
Diagnosis	n	%	n	%	n	%
Polyneuropathy	215	43.9	318	28.0	178	15.7
Entrapment neuropathy	68	13.9	247	21.7	150	13.2
Radiculopathy/plexopathy	43	8.8	93	8.2	57	5.0
Myopathy	22	4.5	31	2.7	10	.9
Myasthenia gravis	19	3.9	21	1.8	4	.4
Motor neuron disease	21	4.3	27	2.4	13	1.1
M. sphincter ani denervation	2	0.4	147	12.9	128	11.3
Cranial neuropathy	9	1.8	87	7.7	69	6.1
Mononeuropathy/peripheral nerve injury	4	0.8	10	0.9	24	2.1
General scan	34	6.9	61	5.4	-	-
Normal	-	-	-	-	453	39.9
Polyneuropathy + entrapment neuropathy	18	3.7	24	2.1	35	3.1
Polyneuropathy + radiculopathy/plexopathy	10	2.0	18	1.6	4	0.4
Polyneuropathy + myopathy	3	0.6	17	1.5	1	0.1
Polyneuropathy + myasthenia gravis	1	0.2	1	0.1	0	0
Polyneuropathy + motor neuron disease	3	0.6	3	0.3	3	0.3
Entrapment neuropathy + radiculopathy/plexopathy	15	3.1	25	2.2	3	0.3
Entrapment neuropathy + motor neuron disease	1	0.2	1	0.1	1	0.1
Radiculopathy/plexopathy + myopathy	-	-	1	0.1	1	0.1
Radiculopathy/plexopathy + myasthenia gravis	-	-	1	0.1	0	0
Myopathy + motor neuron disease	2	0.4	3	0.3	0	0
Polyneuropathy + peripheral nerve injury	-	-	-	-	3	0.3
Radiculopathy + peripheral nerve injury	-	-	-	-	1	0.1
Tremor	-	-	-	-	1	0.1
Total	490	100.0	1136	100.0	1136	100.0

Table 3. Final diagnosis of cases with unclear referral diagnosis

Diagnosis	n	%
Polyneuropathy	9	14.8
Entrapment neuropathy	12	19.7
Radiculopathy/plexopathy	5	8.2
Myopathy	1	1.6
Normal	26	42.6
Mononeuropathy/peripheral nerve injury	4	6.6
Polyneuropathy + entrapment neuropathy	3	4.9
Total	61	100

Table 4. Concordance between electromyography referrals and outcomes (number of requests compatible with the final diagnosis/number of requests made in the relevant protocol)

	Neurology	Orthopedics	General Surgery	ENT	PMR	Neurosurgery	Pediatrics	IM	Oncology	Rh
Polyneuropathy	(92/215) 43%	(1/15) 7%	(1/1) 100%	(0/1) 0%	(10/21) 48%	(5/9) 56%	(5/26) 19%	(10/15) 67%	(4/4) 100%	(0/3) 0%
Entrapment neuropathy	(21/68) 31%	(30/86) 35%	-	-	(25/51) 49%	(12/30) 40%	-	(0/3) 0%	-	(2/7) 29%
Radiculopathy/ Plexopathy	(11/43) 26%	(1/13) 8%	-	-	(5/12) 42%	(4/8) 50%	(6/9) 67%	(1/2) 50%	-	(1/1) 100%
Myopathy	(7/22) 32%	(0/1) 0%	-	-	(0/1) 0%	-	(0/3) 0%	(1/1) 100%	-	(0/2) 0%
Myasthenia gravis	(3/19) 16%	(/)%	-	-	(3/4) 75%	-	(1/2) 50%	-	-	-
Motor neuron disease	(9/21) 43%	(0/4) 0%	-	-	-	-	(0/1) 0%	-	-	-
M. sphincter ani denervation	(1/2) 50%	(/)%	(124/145) 86%	-	-	-	-	-	-	-
Cranial neuropathy	(4/9) 44%	(0/1) 0%	-	(61/75) 81%	-	-	-	-	-	-
Mononeuropathy/ peripheral nerve injury	(2/4) 50%	(2/2) 100%	-	-	-	-	-	-	-	-
Polyneuropathy + ET	(4/18) 22%	(1/3) 33%	-	-	(0/1) 0%	(0/2) 0%	-	-	-	-
Polyneuropathy + radiculopathy/ Plexopathy	(1/10) 10%	(0/2) 0%	-	-	(0/3) 0%	(0/2) 0%	-	(1/1) 100%	-	-
Polyneuropathy + myopathy	(0/3) 0%	-	-	-	-	-	(0/14) 0%	-	-	-
ET + radiculopathy/ Plexopathy	(0/15) 0%	(0/2) 0%	-	-	(1/4) 25%	(0/3) 0%	-	-	-	(0/1) 0%
Concordance Rate	34%	27.1%	85.6%	80.3%	45.4%	38.9%	21.4%	54.2%	100%	21.4%

ET: Entrapment neuropathy, ENT: Ear, nose, throat, IM: Internal medicine, PMR: Physical medicine and rehabilitation, Rh: Rheumatology

Table 5. Concordance of preliminary and final diagnosis in patients with multiple preliminary diagnoses

EMG Requests	Concordant	Discordant	Total
Polyneuropathy + entrapment neuropathy	5 (21%)	19 (79%)	24
Polyneuropathy + radiculopathy/plexopathy	2 (11%)	16 (89%)	18
Polyneuropathy + myopathy	2 (12%)	15 (88%)	17
Polyneuropathy + Myasthenia Gravis	0 (0%)	1 (100%)	1
Polyneuropathy + motor neuron disease	0 (0%)	3 (100%)	3
Entrapment neuropathy + radiculopathy/plexopathy	1 (4%)	24 (96%)	25
Entrapment neuropathy + motor neuron disease	0 (0%)	1 (100%)	1
Radiculopathy/plexopathy + myopathy	0 (0%)	1 (100%)	1
Radiculopathy/plexopathy + myasthenia gravis	0 (0%)	1 (100%)	1
Myopathy + motor neuron disease	0 (0%)	3 (100%)	3
Total	10 (11%)	84 (89%)	94

concordance rate between the preliminary and definitive diagnoses for all requests was 44.8%. Considering the clinics that requested EMG the most, the rate of concordance was 34% for neurology, 27.1% for orthopedics, and 85.6% for general surgery. The concordance rate for each clinic is given in Table 4. Referrals with specific symptoms related to a single nerve, such as sphincter dysfunction and cranial neuropathy, had higher concordance rates. The rate of discrepancy between referral and outcome was significantly high at 89% for diseases with multiple indications, such as polyneuropathy plus entrapment neuropathy, while the concordance rate was only 11% (Table 5).

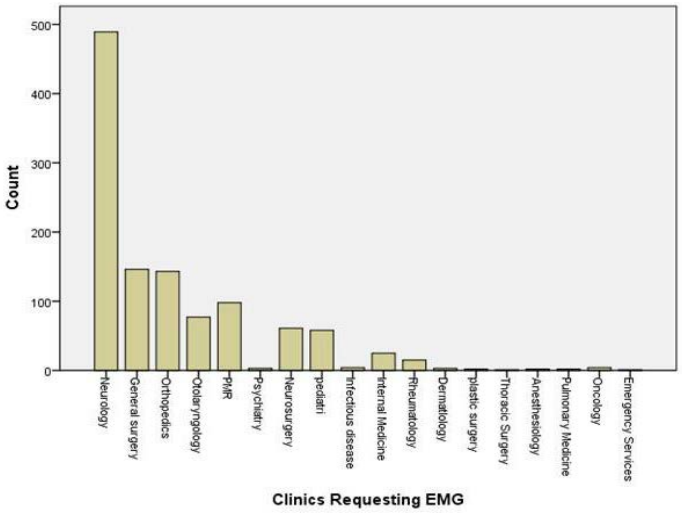

Figure 1. Referring Clinics for EMG
PMR: Physical medicine and rehabilitation, NCS: Nerve Conduction Studies, EMG: Electromyography, RNS: Repetitive Nerve Stimulation

Referring Clinics

EMG was mostly requested by Neurology (490), General Surgery (146), and Orthopedics (143) clinics, respectively. The clinics requesting EMG are summarized in Figure 1. When we examine the concordance between the referral diagnosis and the final diagnosis for entrapment neuropathies, physical medicine rehabilitation (PMR) had the highest rate at 42%. Entrapment neuropathies were confirmed by EMG at a rate of 40% when requested by Neurosurgery, 35% when requested by Orthopedic departments, and 31% when requested by Neurology. The highest diagnostic compatibility in the referrals made by Neurology was observed for polyneuropathies (43%). For polyneuropathies, this rate was 100% for requests by Oncology, and 56% for requests by Neurosurgery.

Polyneuropathy was the most common pre-diagnosis requested by Neurology, and 43% of these were confirmed by EMG. This rate was higher for Internal Medicine. Of all EMG requests, 40% were reported as "normal." Furthermore, the majority of requests from Orthopedics (58%) and Pediatrics (69%) were reported as "normal." The normal rate was significantly lower for more specifically requested cases by Ear, Nose, and Throat (ENT) (17%), Oncology (<1%), and General Surgery (12%) clinics. The general screening request was mostly used by Neurosurgery, with a rate of 12%. The compatibility of the diagnoses with the referral diagnosis according to the requesting clinics is shown in Table 4.

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DISCUSSION

The standardization of EMG processes relies on fundamental information gleaned from data collected since the 1940s (8). In 1999, Bischoff et al. published the first guidelines by the International Federation of Clinical Neurophysiology, although few clinics had the requisite equipment and infrastructure at that time (9). A new standardization statement was released in 2020 by Tankisi et al., which reflects the need for the ever-increasing use of EMG with the development and innovations of technology (10). For reliability, this interdisciplinary field necessitates a common terminology and approach, as referrals are made by different clinics. Recent studies demonstrate an approximately 10% increase in the number of EMG requests (11).

Research has indicated that relying solely on diagnostic procedures to replace comprehensive medical history and physical examination can lead to unfavorable implications concerning time and expenses. Moreover, the effective and efficient utilization of electrophysiological assessments necessitates a clear identification of the clinical indication (3). Clarifying the diagnosis through electrophysiological procedures is crucial, as is the exclusion of differential diagnoses, which are equally important in making an accurate diagnosis. The electrophysiology laboratory protocols should be followed after obtaining a detailed medical history and performing a thorough examination, taking into account the reason for referral of the case. It is imperative to recognize that the vulnerabilities of nerves to injuries exhibit variations beyond the scope of the existing literature (12); therefore, the appropriate technique and analysis should be selected based on the findings obtained (13).

Our study revealed that the three clinics with the highest frequency of EDX testing requests were Neurology, General Surgery, and Orthopedics clinics, respectively. Polyneuropathies were found to be the most common referral diagnosis, which is consistent with previous studies in the literature that focused on expert requests (1,11). The increase in EMG requests observed in our study aligns with the findings of Ohmori et al., highlighting the impact of technological advancements and growing clinician awareness on diagnostic practices (14). The most commonly requested preliminary diagnoses were polyneuropathy (28%) and entrapment neuropathy (22%), whereas disorders of the muscle and neuromuscular transmission were the least frequently cited causes for referral, consistent with recent studies (15).

Additionally, our finding that polyneuropathies are the most frequently referred diagnosis indicates a broad acknowledgment of the critical role of electrophysiological assessments in diagnosing and treating polyneuropathies. Nevertheless, the absence of long-term prospective studies has constrained the assessment of the accuracy and reliability of new morphometric and neurophysiological methods (16). Of the patients, 61 were referred without a clear working pre-diagnosis and "general screening" was requested in 5.4% of cases. While 43% of these cases were reported as normal, entrapment neuropathy was the most common pathological finding. Considering the findings obtained in a center with only neurologists, and that this rate is 3%, our rate of specifying a preliminary diagnosis is quite high (11). In 2004, Podnar found that only 50% of requests had a pre-diagnosis in their

laboratory (3). From this, it can be concluded that the rate of indicating a preliminary diagnosis has increased over the years. In our lab, electrodiagnostic testing requests were most frequently made with the pre-diagnosis of polyneuropathy. Neurology mostly referred for polyneuropathy, while other branches referred for entrapment neuropathy. Polyneuropathy and entrapment are common referral diagnoses in our lab, and their co-occurrence as dual diagnoses was seen in 3% of cases. Definitive myopathy, radiculopathy, plexopathy, motor neuron disease, and peripheral neuropathy diagnoses are based on electromyographic findings. It is accepted that nerve conduction studies are often normal in radiculopathies; therefore, the diagnosis is based on electromyography. Innervation of a muscle from two different roots, and preservation of compound muscle action potentials (CMAP) unless there is a significant loss of axons exceeding 50% or a reinnervation process develops, are the mechanisms that explain normal EMG findings. Although rare, in the case of pure demyelinating conduction block, EMG studies and motor unit potential (MUP) configurations will remain normal, even if a clinical loss of strength is observed in the relevant root (17).

AANEM emphasized the necessity for needle EMG in patients with normal nerve conduction studies to avoid unnecessary tests and exclude differential diagnoses in a statement published in 2015 (18). Although radiculopathy/plexopathy protocol requests constituted 8% of all requests, they account for only 5% of EMG diagnoses, which is consistent with similar recent studies(19). Focal demyelination can result in normal conduction studies distal to the lesion (20). In our study, 40% of patients with EMG requests had normal results, consistent with the literature (11). Proximal and distal lesions present with similar clinical findings, and definitive differential diagnosis is achieved through EMG. Needle EMG is essential in diagnosing carpal tunnel syndrome (CTS) as differential diagnoses such as radiculopathy or peripheral neuropathy must be excluded. Double crush syndrome, a rare partial nerve fiber lesion where axonal transport is interrupted both proximally and distally (21), was the referral diagnosis in 2% of cases in our study, but was detected by EMG in less than 1% of cases.

Clinical findings may indicate peripheral neuropathy, but normal electrodiagnostic results can occur due to misdiagnosis or mild nerve damage. Electrodiagnostic assessment evaluates large diameter myelinated nerves, and may not detect mild conduction block or axon degeneration (20). Some patients sent to the EMG laboratory have completely normal examination and EMG findings. Radiculopathy and focal demyelination may present as normal EMG results. In a study of CTS patients, only one-third with clinical complaints had electrodiagnostic abnormalities (22). In Turkey, the high density of outpatient clinics and patient requests often lead to unnecessary EMG referrals. The diagnostic concordance for electrodiagnostic procedures can vary. RNS has a high diagnostic concordance of 76% for generalized myasthenia but a relatively low diagnostic concordance of 48% for ocular myasthenia (23). A study of 300 patients, which evaluated the sensitivity of diagnostic hypotheses, found that the symptoms and clinical signs in patients can increase the diagnostic concordance of electrodiagnostic studies for CTS (3).

In our study, PMR clinics had the highest compatibility with the final diagnosis for entrapment neuropathies, General Surgery clinics had highest concordance for anal sphincter dysfunction, and the ENT clinic had highest concordance for facial paralysis. This can be explained by the high diagnostic concordance of the referring diagnosis when isolated to a single nerve, the low diversity of differential diagnoses, and the ease of recognizing clinical findings. Studies showed that concordance significantly increases in patients presenting with limited neurological findings such as isolated weakness (24).

When requests were examined according to the referring clinics, the highest confirmation rate for referrals from Neurology was for polyneuropathy, with a consistency of 43%. The higher rate of confirmation for Internal Medicine clinics may be related to the predominant presence of comorbid diseases such as malignancy, diabetes, and chronic renal failure. The differential diagnosis of CTS, which is the most common entrapment neuropathy, includes joint arthritis, cervical radiculopathy, flexor carpi radialis tenosynovitis, Raynaud's phenomenon, and cubital tunnel syndrome (25). Since these differential diagnoses are related to PMR departments, their high diagnostic concordance for the diagnosis of entrapment neuropathy is not surprising. To further investigate this difference, entrapment neuropathies should be classified according to severity or stage.

CONCLUSION

The utility of EMG in diagnosis and treatment is closely linked to several factors, including pre-diagnostic considerations and the department responsible for the request. Electrodiagnostic assessments represent an essential component of the neurological approach when considering differential diagnoses for neurological conditions, alongside the patient's clinical history and neurologic examinations. Nevertheless, factors such as the time-consuming and invasive nature of EMG, economic considerations involved, and variables that affect the reflection of neuromuscular pathology on the results, highlight the importance of establishing a thorough preliminary diagnosis before ordering these examinations. EDX studies are never a screening method, but they reveal pathology with high accuracy when performed with appropriate pre-diagnosis. EDX tests are not universally abnormal in all neuromuscular disorders, but should be considered for patients with clinical suspicion. Multiple pre-diagnoses decrease the diagnostic concordance and result in delays.

Electromyographic investigations were found to have a general pathology detection rate of approximately 60%. The findings of this study suggest that the diagnostic concordance of EMG increases when preliminary diagnoses are narrowed down based on clinical findings. Future studies should focus on developing more specific guidelines and standards to improve the clinical effectiveness of EMG referrals. Furthermore,

multidisciplinary approaches should be encouraged to improve concordance rates of different clinical specialties.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01839
Selcuk Med J 2025;41(2): 78-83

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Incidence of and Risk Factors For Postoperative Ileus in Patients Undergoing Gynecologic Cancer Surgery

Jinekolojik Kanser Cerrahisi Geçiren Hastalarda Postoperatif İleus İnsidansı ve Risk Faktörleri

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ÖZET

Giriş: Postoperatif dönemde görülen paralitik ileus, hastaların oral alıma geçişini geciktirerek taburculuk süresinin uzamasına, hasta memnuniyetinin azalmasına ve hastanede yatış maliyetlerinin artmasına neden olmaktadır. Bu çalışmada, jinekolojik kanser cerrahisi geçiren hasta grubunda postoperatif ileus insidansının belirlenmesi ve bu duruma etki eden temel risk faktörlerinin ortaya konması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif kohort çalışma, İzmir Şehir Hastanesi Jinekolojik Onkoloji Kliniğinde 15.10.2023–15.10.2024 tarihleri arasında opere edilen 240 jinekolojik onkoloji hastasının verilerine dayanmaktadır. Postoperatif ileus gelişen ve gelişmeyen hastalar demografik, operasyonel ve klinik değişkenler açısından karşılaştırılmıştır.

Bulgular: Postoperatif ileus insidansı %11,3 olarak saptanmıştır. Asit varlığı, ileus gelişen hastalarda %48,1 oranında izlenmiş ve gelişmeyen gruba kıyasla anlamlı şekilde yüksek bulunmuştur (p<0,001). Asit hacmi 500 ml'nin üzerinde olan olgularda ileus riski artmıştır (p=0,003). İnsizyon tipi ile ileus gelişimi arasında anlamlı ilişki gözlenmiş, supraumbilikal + subumbilikal insizyon yapılan hastalarda ileus oranı daha yüksek bulunmuştur (p<0,001). Transfüzyon uygulanan hastalarda ileus gelişme oranı %63,0 iken, transfüzyon yapılmayan grupta bu oran %12,2'dir (p<0,001). Ek analjezik kullanımı ileus gelişen hastalarda %59,3 oranında olup anlamlı düzeyde yüksektir (p<0,001). Diyabet ve hipertansiyon gibi komorbid hastalıklarla ileus gelişimi arasında anlamlı fark saptanmamıştır. Yeniden hastaneye yatış oranı, ileus gelişen grupta anlamlı şekilde yüksektir (p=0,024).

Sonuç: Jinekolojik onkolojik cerrahi geçiren hastalarda asit varlığı, insizyon tipi, transfüzyon gereksinimi ve ek analjezik kullanımı postoperatif ileus gelişimi ile anlamlı ilişkili bulunmuştur. Bu risk faktörlerinin ameliyat öncesi dönemde değerlendirilmesi, yüksek riskli hastaların tanımlanmasına ve bireyselleştirilmiş cerrahi planlamaya katkı sağlayabilir. Ayrıca, bu verilerin perioperatif yönetim protokollerine entegre edilmesiyle postoperatif komplikasyonların azaltılması ve hasta iyilik halinin artırılması mümkün olabilir.

Anahtar Kelimeler: Analjezi, Asit, İleus, Kanser Cerrahisi, Transfüzyon

ABSTRACT

Aim: Postoperative paralytic ileus delays the resumption of oral intake, prolongs hospital stays, reduces patient satisfaction, and increases hospitalization costs. This study aimed to determine the incidence of postoperative ileus and identify key associated risk factors in patients undergoing surgery for gynecologic malignancies.

Materials and Methods: This retrospective cohort study was conducted at the Gynecologic Oncology Clinic of Izmir City Hospital between October 15, 2023, and October 15, 2024. Clinical data from 240 patients who underwent surgery for gynecologic cancer were analyzed. Patients who developed postoperative ileus were compared with those who did not in terms of demographic, surgical, and clinical characteristics.

Results: The incidence of postoperative ileus was found to be 11.3%. Ascites was observed in 48.1% of patients with ileus, significantly higher than in those without (p<0.001). The risk of ileus increased significantly in cases with ascitic volume greater than 500 mL (p=0.003). A significant association was observed between the type of incision and ileus development; patients who underwent both supraumbilical and subumbilical incisions had a higher rate of ileus (p<0.001). The rate of ileus was 63.0% in patients who received blood transfusions, compared to only 12.2% in those who did not (p<0.001). Additional analgesic use was also significantly higher in patients with ileus (59.3%, p<0.001). No significant association was found between comorbidities such as diabetes or hypertension and ileus development. The hospital readmission rate was significantly higher among patients who developed ileus (p=0.024).

Conclusion: Ascites, incision type, transfusion requirement, and additional analgesic use were significantly associated with postoperative ileus in patients undergoing gynecologic oncology surgery. These findings may aid in the preoperative identification of high-risk patients, enabling individualized surgical planning and the development of targeted perioperative management strategies. Incorporating these findings into perioperative protocols may help reduce complications and enhance postoperative recovery.

Keywords: Analgesia, Ascites, Cancer Surgery, Ileus, Transfusion

Geliş Tarihi/Received: 28 February/Şubat 2025 **Kabul Tarihi/Accepted:** 20 May/Mayıs 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

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Atıf yapmak için/ Cite this article as: Akdemir C, Balci MF, Karaoglu S, Seker N, Ozen S, Ozuyar Simsek G, Bayramoglu D, Sanci M. Incidence of and Risk Factors For Postoperative Ileus in Patients Undergoing Gynecologic Cancer Surgery. Selcuk Med J 2025;41(2): 78-83

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Gastrointestinal dysfunction is one of the most common complications after abdominal gynecological oncology operations. It is characterised by nausea, vomiting and paralytic ileus in the postoperative period. Postoperative nausea and vomiting are prevalent among patients, with an estimated incidence of approximately 30% in the general surgical population (1). Paralytic ileus has been reported in 12.9% to 32% of cases following gynecological oncology surgery (2).

Postoperative paralytic ileus can result in a delay in transitioning patients to an oral regime, prolonged discharge times, reduced patient satisfaction, and elevated hospitalisation costs. Prolonged hospitalisation has been shown to result in a number of adverse outcomes, including hospital-acquired infections, deep vein thrombosis, wound infection and life-threatening complications such as pneumonia. Furthermore, prolonged recovery times and delayed discharge have been shown to hinder the timely initiation of adjuvant radiotherapy and/or chemotherapy in patients undergoing treatment for gynecologic cancers. This study was conducted to determine the possible risks and incidence of postoperative ileus after gynecological cancer surgery.

MATERAILS AND METHODS

This retrospective cohort study included patients who underwent surgery for gynecological cancer between October 15, 2023, and October 15, 2024, at the Gynecological Oncology Clinic of Izmir City Hospital. The present study was conducted in accordance with the Declaration of Helsinki. The data were retrieved from the archives of Izmir City Hospital, and the study was approved by its Ethics Committee (No: 2024/170, Date: 06/11/2024). The study was conducted by evaluating patient demographic characteristics, clinical parameters, operation details and postoperative complication data. Patients over the age of 18 who underwent surgery for gynecologic malignancies and had complete postoperative follow-up data were included in the study. Exclusion criteria were as follows: patients who underwent surgery for benign gynecologic conditions (such as fibroids, endometriosis, or benign ovarian cysts), those referred to another clinic during the postoperative period, patients who underwent HIPEC, those with incomplete follow-up data, inflammatory bowel disease, orthopedic problems affecting mobilization, a history of abdominal radiotherapy, neoadjuvant chemotherapy, or hyperthermic intraperitoneal chemotherapy, those who experienced intestinal injury during surgery, and those who underwent bowel resection. Data from 240 patients were analyzed, and the demographic and clinical characteristics of patients with and without ileus were compared.

All patients followed a standard clinical protocol prior to surgery. Low-molecular-weight heparin was administered based on body weight the evening before surgery, and intravenous prophylactic antibiotics were given 30 minutes prior to incision. Cefazolin was used for antibiotic prophylaxis, while clindamycin or metronidazole was administered in cases of penicillin allergy. All surgical procedures were performed by the same gynecologic oncology surgical team. Data were retrieved from the hospital's electronic medical records and surgical reports. Statistical analysis was conducted using licensed SPSS version 29 software.

In descriptive statistics, categorical variables were expressed as counts and percentages, while continuous variables were reported as medians (interquartile range) or means ± standard deviation. The chi-square test was used to compare categorical variables, while the Mann-Whitney U test or Student's t-test was applied for continuous variables, depending on data distribution. Logistic regression analysis was performed to identify risk factors associated with ileus development. A p-value of <0.05 was considered statistically significant. Results were presented in tables and figures, with odds ratios and 95% confidence intervals reported where appropriate.

RESULTS

A detailed analysis was conducted on the clinical and operative characteristics of 240 patients included in the study. The majority (62.5%) were diagnosed with endometrial cancer, followed by ovarian cancer (32.1%) and cervical cancer (5.4%). Postoperative ileus developed in 11.3% of patients and was noted as a significant clinical concern. Ascites was present in 16.3% of patients; of these, 76.9% had ascitic volumes below 500 mL, while 23.1% exceeded 500 mL. Regarding incision type, subumbilical incisions were used in 74.6% of cases, both subumbilical and supraumbilical in 17.9%, laparoscopic techniques in 5.4%, and Pfannenstiel incisions in 2.1%. Blood transfusion was required in 17.9% of patients; among these, 25.6% received transfusions preoperatively, 25.6% intraoperatively, and 48.8% postoperatively. Additional postoperative analgesic use was observed in 21.3% of patients. Prior abdominal surgery was reported in 47.5% of the cohort.

Comorbidities were present in 44.2% of patients, with diabetes and hypertension accounting for 25.0% and 25.4%, respectively. Drains were used in 68.3% of cases, omentectomy was performed in 32.5%, and lymphadenectomy in 53.3%. The readmission rate was 9.2%, and 34.2% of patients were smokers. Based on BMI, 45.8% were obese, 33.3% overweight, 20.0% normal weight, and 0.8% underweight, indicating a predominance of overweight and obese individuals (Table 1). Age, anthropometric data, laboratory values, and intraoperative variables were assessed in detail. The mean age was 57.4±12.7 years (median: 58, range: 21–87). The median height was 160 cm (143–175), and median weight 75 kg (50–115). These values reflect a predominantly overweight and obese cohort. The median preoperative hemoglobin level was 12.7 g/dL (8.4–15.9), dropping to 11.7 g/dL postoperatively. The median surgical time was 130 minutes (80–250), and anesthesia duration 160 minutes (110–300). Median length of hospital stay was 4 days (1–19), depending on the complexity and extent of surgery (Table 2). Patients who developed ileus showed significant clinical differences. Ascites was present in 48.1% of ileus cases, a significantly higher rate than in patients without ileus ($p<0.001$). The incidence of ileus was

Table 1. Distribution of surgery and patient characteristics

		N %
Indication for Surgery	Endometrial Cancer	150 (62.5)
	Ovarian Cancer	77 (32.1)
	Cervical Cancer	13 (5.4)
Ileus		27 (11.3)
Ascites		39 (16.3)
Ascites Volume	Under 500ml	30 (76.9)
	Above 500ml	9 (23.1)
Incision Type	Laparoscopic	13 (5.4)
	Supraumbilical + Subumblical	43 (17.9)
	Subumbilical	179 (74.6)
	Pfannenstiel	5 (2.1)
Transfusion		43 (17.9)
Transfusion Time	Preoperative	11 (25.6)
	Intraoperative	11 (25.6)
	Postoperative	21 (48.8)
Analgesic Use		51 (21.3)
Operation History		114 (47.5)
Additional Morbidity		106 (44.2)
Diabetes		60 (25.0)
Hypertension		61 (25.4)
Drain		164 (68.3)
Omentectomy		78 (32.5)
Lymph Node Dissection		128 (53.3)
Rehospitalisation		22 (9.2)
Cigarette		82 (34.2)
BMI	Underweight (<18.5)	2 (0.8)
	Normal (18.5-24.9)	48 (20.0)
	Overweight (25.0-29.9)	80 (33.3)
	Obese (29.9<)	110 (45.8)

BMI: Body Mass Index

Table 2. Detailed data on the age, body measurements, laboratory values and surgical procedure of 240 patients in the study.

	Median (IQR)	(Min-Mak)
Age*	58 (19.5) 57.4±12.7	(21-87)
Incision Length	13 (5)	(8-24)
Size	160 (8)	(143-175)
Weight	75 (16)	(50-115)
Preoperative Hemoglobin	12.7 (1.7)	(8.4-15.9)
Postoperative Hemoglobin*	11.7 (2.1) 11.6±1.4	(8-14.9)
Preoperative Potassium	4.2 (0.5)	(3-5.7)
Length of stay (Days)	4 (2)	(1-19)
Duration of Surgery (Min)	130 (80)	(80-250)
Duration of Anesthesia (Min)	160 (80)	(110-300)
Number of Lymph Nodes	6 (16)	(0-49)
BMI	29.4 (7.6)	(17.3-51.1)

• IQR: Interquartile Distribution , BMI: Body Mass Index
* Mean ± standard deviation was given in accordance with the normal distribution.

also significantly greater when ascitic volume exceeded 500 mL (p=0.003). Incision type was another significant factor; combined supraumbilical and subumbilical incisions were used in 59.3% of patients with ileus (p<0.001).

Blood transfusion was required in 63.0% of patients with ileus, compared to only 12.2% in those without (p<0.001), suggesting that transfusion or related factors may contribute to ileus development. Additional analgesic use was significantly higher in ileus patients (59.3%, p<0.001). No significant association was found between ileus and comorbidities such as diabetes or hypertension. However, the readmission rate was significantly elevated in ileus patients (22.2%, p=0.024) (Table 3). The median hospital stay was significantly longer in patients with ileus (7.5 days vs. 4 days, p<0.001). Surgery time (180 vs. 120 minutes, p<0.001), anesthesia duration (p=0.003), and postoperative hemoglobin levels (10.8±1.5 g/dL, p=0.004) were also significantly associated with ileus (Table 4). To identify independent risk factors, a logistic regression analysis included

Table 3. Comparison of operation and clinical features with development of ileus

		Ileus (+) N=27 N %	Ileus (-) N=213 N %	p
Operation Indication	Endometrial Cancer	17 (63.0)	133 (62.4)	0.869
	Ovarian Cancer	8 (29.6)	69 (32.4)	
	Cervical Cancer	2 (7.4)	11 (5.2)	
Ascites	Yes	13 (48.1)	26 (12.2)	<0.001
Ascites Volume	Under 500ml	6 (46.2)	24 (92.3)	0.003
	Above 500ml	7 (53.8)	2 (7.7)	
Incision Type	Laparoscopic	2 (7.4)	11 (5.2)	<0.001
	Supraumbilical+ Subumblical	16 (59.3)	27 (12.7)	
	Subumbilical	7 (25.9)	172 (80.8)	
	Pfannenstiel	2 (7.4)	3 (1.4)	
Transfusion	Yes	17 (63.0)	26 (12.2)	<0.001
Transfusion Time	Preoperative	2 (11.8)	9 (34.6)	0.199
	Intraoperative	6 (35.3)	5 (19.2)	
	Postoperative	9 (52.9)	12 (46.2)	
Analgesic Use	Yes	16 (59.3)	35 (16.4)	<0.001
Operation History	Yes	16 (59.3)	98 (46.0)	0.194
Additional Morbidity	Yes	12 (44.4)	94 (44.1)	0.975
Diabetes	Yes	9 (33.3)	51 (23.9)	0.288
Hypertension	Yes	3 (11.1)	58 (27.2)	0.07
Drain	Yes	19 (70.4)	145 (68.1)	0.809
Omentectomy	Yes	16 (59.3)	62 (29.1)	0.002
Lymph Node Dissection	Yes	19 (70.4)	109 (51.2)	0.06
Rehospitalisation	Yes	6 (22.2)	16 (7.5)	0.024
Cigarette	Yes	12 (44.4)	70 (32.9)	0.232

Chi-square test was applied.

Table 4. Comparison of ileus development and clinical parameters

	Ileus (+) N=27 Median (IQR)	Ileus (-) N=213 Median (IQR)	p
Age*	58(19.5)	58(19.5)	0.41
	59.3±12.4	57.4±12.7	
Incision Length	16(6)	13(4)	0.009
Height	160(8)	160(8)	0.769
Weight	77 (20)	75 (15)	0.978
Preoperative Hemoglobin	13.1 (2.2)	12.7 (1.6)	0.155
Postperative Hemoglobin*	10.5 (2.2)	11.7 (1.8)	0.004
	10.8±1.5	11.7±1.4	
Preoperative Potassium	4.2 (0.4)	4.2(0.5)	0.334
Length of stay (Days)	7.5 (3)	4(2)	<0.001
Duration of Surgery (Min)	180 (40)	120(80)	<0.001
Duration of Anesthesia (Min)	205 (60)	155(85)	0.003
Number of Lymph Nodes	11 (18)	4(16)	0.081
BMI	29.3 (8.3)	29.4(7.5)	0.928

Mann Whitney U test was used. BMI: Body Mass Index
* Student t test was performed in accordance with normal distribution and mean ±standard deviation was given.

Table 5. Logistic regression analysis of factors associated with ileus development

	Odds Ratio (OR)	OR 95% Confidence Interval	p
Postperative Hemoglobin	1.113	(0.655 – 1.888)	0.693
Transfusion	15.065	(2.401 – 94.524)	0.004
Analgesic Use	10.908	(2,586 – 46.015)	0.001
Hospitalisation Duration (Days)	1.510	(1.135- 2.008)	0.005
Rehospitalisation	21.065	(3.318- 133.721)	0.001
Duration of Surgery	1.018	(0.952- 1.089)	0.598
Omentectomy	3.020	(0.692- 13.184)	0.142
Ascites	8.421	(2.041 – 34.744)	0.003
Duration of Anesthesia	0.980	(0.918- 1.046)	0.540

Hosmer, Lemeshow Test: 0,733, Cox&Snell R Square :0,323, Nagelkerke R Square:0,638

all clinically and statistically relevant variables, regardless of individual significance. These included postoperative hemoglobin, length of stay, surgical and anesthesia duration, ascites, transfusion, analgesic use, omentectomy, and readmission. While variables like surgery time, anesthesia, and omentectomy were not statistically significant, they were retained to ensure a comprehensive model. Their inclusion did not affect the odds ratios or significance levels of the primary predictors.

Transfusion (OR: 15.065, 95% CI: 2.401–94.524), additional analgesic use (OR: 10.908, 95% CI: 2.586–46.015), and readmission (OR: 21.065, 95% CI: 3.318–133.721) were identified as the strongest independent predictors. The model demonstrated high diagnostic performance, with a sensitivity of 59.3% (95% CI: 40.5–76.3), specificity of 98.6% (95% CI: 96.4–99.6), positive predictive value of 84.2% (95% CI: 64.0–95.8), and negative predictive value of 95.0% (95% CI: 91.6–97.4). Overall accuracy was 94%, indicating robust discriminatory capacity (Table 5).

DISCUSION

Gastrointestinal dysfunction is a serious postoperative problem that may progress with complications frequently seen in the postoperative period and cause prolonged hospitalisation. Although postoperative gastrointestinal dysfunction may resolve spontaneously, slow return to normal bowel function is associated with increased costs, electrolyte disturbances, malnutrition, patient dissatisfaction, additional complications and delay in adjuvant therapy. The median length of hospitalisation was 7.5 days in patients with ileus (3) and 4 days in patients without ileus (2). The aetiology of postoperative ileus remains unclear; however, it is hypothesised to be the result of a complex interplay between systemic stress responses and local trauma. The pathophysiology of postoperative ileus can be classified as neurogenic, inflammatory and pharmacological (3). Postoperative ileus is a more probable occurrence in prolonged major surgical procedures due to excessive gastrointestinal manipulation and prolonged general anaesthesia. Postoperative pain medications, especially opioids, have been shown to promote the development and worsening of postoperative ileus due to their known inhibitory effects on intestinal motility. Patients undergoing surgery for malignancies are at high risk for postoperative ileus due to the complexity of the procedure, the extensive nature of the operations, and excessive gastrointestinal manipulation.

Numerous studies have shown that excessive manipulation of the intestinal tract during surgical procedures can trigger mast cell activation and subsequent intestinal inflammation, ultimately impairing gastrointestinal motility (4). The advent of minimally invasive techniques has led to a substantial decline in postoperative ileus, attributable to a reduction in tissue trauma and a diminished stimulation of the bowel (5). Although the use of minimally invasive techniques has increased in gynecologic oncology practice, most procedures are still performed via laparotomy, maintaining a persistent risk of postoperative ileus. Despite the occasional necessity for blood transfusion in major surgery, there is an increasing body of evidence indicating its association with a number of postoperative complications. Recent studies in the literature suggest that blood transfusion is associated with a variety of adverse clinical and postoperative complications (6,7). Bakkum-Gamze et al. conducted a study to ascertain the risk factors and incidence of postoperative ileus in women undergoing surgery for ovarian malignancy. The study demonstrated a higher incidence of postoperative ileus in patients who received blood transfusions compared to those who did not. Moreover, the incidence of ileus increased proportionally with the volume of transfused blood (7).

In our study, the need for transfusion was found to be 63.0% in patients who developed ileus, but only 12.2% in those who did not ($p<0.001$). The potential risks associated with the increased incidence of ileus following blood transfusion remain unclear. These risks are likely to arise from difficult surgical resection, prolonged surgery time, impaired fluid balance, contamination, reduced oxygen-carrying capacity and tissue oxygen delivery due to anaemia, and the dose-dependent immunomodulatory effects attributable to allogeneic transfusions (8,9). It has been demonstrated by preceding studies that extended operative times are associated with an increased inflammatory response to bowel manipulation and trauma. As demonstrated by research in the field of animal studies, there is a demonstrable correlation between the extent of bowel manipulation in both the small and large intestine, and the degree of leukocyte infiltration into the intestinal muscularis, as well as the degree of intestinal dysmotility (10). In our study, the median duration of surgery was 180 minutes (IQR: 40) in patients who developed ileus and 120 minutes (IQR: 80) in those who did not ($p<0.001$). In our study, the rate of ileus development in patients who underwent wide incision (supraumbilical+subumblical) was found to be 59.3% and this rate was significantly higher than other incision types.

In gynecological oncology, malignant ascites is most commonly seen in patients with advanced ovarian cancer (11). In the present study, the presence of ascites was observed in 48.1% of patients who developed ileus, a rate that was significantly higher than in patients who did not develop ileus. Furthermore, the development of ileus was found to be significantly increased in cases where the volume of ascites exceeded 500 ml. A review of the literature shows a close correlation between the frequency and volume of ascites and the stage of the disease (12,13). In a study conducted by Huang et al. on patients with epithelial ovarian cancer, it was reported that the incidence of ascites and mean ascites volume increased with disease stage. Moreover, the volume of ascitic fluid has been demonstrated to be associated with the number of tumour metastases (13). The incidence of ileus in patients with ascites may be attributed to the stage of the disease, the extent of surgical intervention, and the prolonged duration of surgery. We hypothesise that the presence of abdominal ascites amplifies the inflammatory response to intraoperative manipulation by increasing intestinal oedema and permeability. Further randomised controlled trials are

warranted to elucidate the relationship between ascites and the development of postoperative ileus in this patient population.

Opioids have been demonstrated to exert inhibitory effects on the gastrointestinal tract. These effects encompass a reduction in gastric motility and emptying, an increase in resting tone, an escalation in periodic spasms of the small intestine, and a diminution in propulsive colon movements (14). The use of opioids in perioperative pain management has been implicated in the development of postoperative ileus, and evidence suggests that minimising opioid use may reduce its incidence (15). In the present study, an additional analgesic prescription was observed in 59.3% of patients who developed ileus during the postoperative period, a rate that was found to be significantly high. In light of our findings, special attention should be paid to the selection and administration of analgesics in patients undergoing gynecologic cancer surgery. The adoption of multimodal analgesia strategies and minimisation of opioid use where feasible may significantly contribute to reducing the incidence of postoperative ileus. Individualising postoperative pain management strategies for high-risk patients may significantly enhance recovery outcomes.

The primary limitation of this study is its single-centre design, which focused exclusively on postoperative ileus following gynecologic surgeries. Consequently, the findings may not be generalisable beyond the specific patient demographics, surgical techniques, and postoperative care protocols of the institution. It is important to acknowledge that considerable variability exists in clinical practices and patient populations across different healthcare settings. Consequently, it may not be possible to extrapolate the results of this study to other institutions or to a generalised context. Since the study is specific to our clinic, it is recommended that caution be exercised when interpreting the results on a wider scale.

Consequently, postoperative ileus was observed in 11.3% of patients who underwent surgical treatment for gynecologic malignancies. The primary predictive factors identified were the presence of ascites, the requirement for blood transfusion, and the administration of additional postoperative analgesics. To mitigate the risk of postoperative ileus, analgesics should be administered judiciously, with particular caution regarding opioid use. Patients receiving transfusions or presenting with ascites should be closely monitored in the postoperative period, and early mobilisation should be actively encouraged.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2025.01822
Selcuk Med J 2025;41(2): 84-88

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Evaluation of Children with Chest Wall Deformities: Single Center Experience

Göğüs Duvarı Deformitesi Olan Çocukların Değerlendirilmesi: Tek Merkez Deneyimi

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ÖZET

Amaç: Göğüs duvarı deformiteleri göğüs duvarının anormal gelişimi ile ortaya çıkabilir. Bu çalışma ile göğüs duvarı deformitesi olan çocukların demografik ve klinik özelliklerini değerlendirmek ve deformitenin fark edildiği yaş ve deformite fark edildikten sonra hastaneye başvuruya kadar geçen süre ile göğüs duvarı deformitesinin tipi arasındaki ilişkiyi araştırmak amaçlanmıştır.

Gereçler ve Yöntem: 2023 - 2024 yılları arasında tek bir Çocuk Göğüs Hastalıkları merkezine başvuran göğüs duvarı deformitesi olan tüm çocukların verileri retrospektif olarak hastane kayıtlarından değerlendirildi. En sık görülen iki göğüs duvarı deformitesi alt grubu demografik ve klinik bulgular açısından karşılaştırıldı. Deformitenin fark edildiği yaş ve deformite fark edildikten sonra hastaneye başvuruya kadar geçen süre arasındaki ilişki deformite tipine göre incelendi.

Bulgular: Çalışmaya göğüs duvarı deformitesi olan 92 çocuk dahil edildi; bunların %47,8'inde pektus karinatum ve %46,7'sinde pektus ekskavatum vardı. Ortanca yaş 6 (0,2-17) yıl idi ve göğüs duvarı deformitesinin fark edildiği ortanca yaş 4,3 (0-17) yıl idi. Deformitenin fark edildiği andan hastaneye başvuruya kadar geçen ortanca süre 6 (0-144) ay olarak bulundu. Solunum fonksiyon testi sonuçları göğüs duvarı deformitesi alt gruplarında normal sınırların içinde saptandı. Göğüs duvarı deformitesinin fark edildiği yaş ile deformite fark edildikten sonra hastaneye başvuruya kadar geçen süre arasında istatistiksel olarak anlamlı bir korelasyon bulunmadı (p=0,420).

Sonuç: Göğüs duvarı deformitesi olan çocuklarda akciğer kapasitesi üzerinde bir etki tespit edilmedi çünkü deformitenin fark edildiği yaş gençti ve deformite fark edildikten sonra hastaneye başvuruya kadar geçen süre göğüs duvarı deformitesinin türünden bağımsız olarak kısaydı. Bununla birlikte, göğüs duvarı deformitesi olan çocuklar zamanla akciğer sistemi etkilenebileceğinden belirli aralıklarla takip edilmelidir.

Anahtar Kelimeler: Çocuk, göğüs duvarı, pektus, pulmoner

ABSTRACT

Aim: Chest wall deformities may occur with abnormal development of the chest wall. It was aimed to evaluate the demographic and clinical characteristics of the children with chest wall deformity, and to investigate the relationship between the age at which the deformity was noticed and the duration until hospital admission with the type of chest wall deformity.

Materials and Methods: Data of all children with chest wall deformity in a single pediatric pulmonology center between 2023 - 2024 were evaluated retrospectively. The two most common chest wall deformity subgroups were compared in terms of demographic and clinical findings. The relationship between the age at which the deformity was noticed and the duration until the hospital admission was examined according to the type of deformity.

Results: There were 92 children with chest wall deformity; 47.8% of whom had pectus carinatum and 46.7% had pectus excavatum. The median age was 6 (0.2-17) years, the median age at which deformity was noticed was 4.3 (0-17) years and the median duration from deformity was noticed until admission was 6 (0-144) months. Pulmonary function test results were within normal limits. No statistically significant correlation was found between the age at which the deformity was noticed and the duration until admission (p=0.420).

Conclusions: In children with chest wall deformities, no effect on lung capacity was detected, likely because the deformity was noticed at a young age and the duration from detection to admission was short, regardless of the type of deformity. Nevertheless, children should be monitored because pulmonary system may be affected over time.

Keywords: Chest wall, pectus, pediatrics, pulmonary

Geliş Tarihi/Received: 11 November/Kasım 2024 **Kabul Tarihi/Accepted:** 20 June/Haziran 2024 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

INTRODUCTION

Chest wall deformities occur with abnormal development of the chest wall, such as the absence, shortness, fusion or bifurcation of one or more ribs or cartilages (1,2). These deformities can be seen as pectus excavatum (PE), pectus carinatum (PC), Poland syndrome, sternal defects and isolated costa-cartilage anomalies (1). The most common congenital chest wall deformity is PE, followed by PC and other abnormalities (1,3).

Pectus excavatum is the most common chest wall deformity in which the anterior chest wall appears concave due to deep sternum depression (3,4). PE occurs in 0.1–0.3% of live births and is common in men (3,5). It is usually noticed within first year of life and usually worsens at the beginning of puberty (3). Monitoring the PE depth during control examinations by measuring the distance from the deepest depression of the sternum to the top of the rib cage can show the progression of the deformity over time

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Atıf yapmak için/ Cite this article as: Asfuroglu P. Evaluation of Children with Chest Wall Deformities: Single Center Experience. Selcuk Med J 2025;41(2): 84-88

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

(6). PC is the second most common chest wall deformity, which is characterized by convex anterior protrusion of the sternum and costochondral joints (4,7). PC occurs in approximately 1/1000 live births (4). Lung development can be usually normal in children with PC (3). Poland syndrome is characterized by partial/total absence of pectoral muscles, pectus arcuatum (PA) is a mixed deformity that involves both excavatum and carinatum (4,8). Other chest wall deformities are sternal defects, rib and cartilage disorders (1).

Chest wall deformities can reduce respiratory system compliance by inhibiting growth or restricting movement of the thorax, and the most common effect on the lung is a restrictive lung defect (3,9). Children with chest wall deformities may be asymptomatic, and although patients may have various symptoms, these are not specific to chest wall deformities (9,10). Shortness of breath, exercise intolerance, chest pain, tachypnea and abnormal auscultatory findings may be observed (9). Although lateral and antero-posterior chest radiographs can also be helpful in follow-up, a computed tomography (CT) scan provides more detailed information (6). The Haller index, which can be measured on CT and is considered the gold standard in determining the severity of chest wall deformity, is based on the ratio of the horizontal distance between the two sides of the rib cage to the anterior-posterior diameter (6,11). Lung involvement in children with chest wall deformity can be determined by pulmonary function tests (PFT) (6). Surgical repair and follow-up of chest wall deformities are important to prevent further deterioration of lung function and rarely provide significant improvement in lung function (9). The aim of this study was to evaluate the demographic and clinical characteristics of children with chest wall deformities and to investigate the relationship between the age at which the deformity was noticed and the duration until hospital admission with the type of chest wall deformity.

MATERIALS AND METHODS

The data of all children with chest wall deformity who applied to the pediatric pulmonology outpatient clinic between June 2023 and April 2024 were evaluated retrospectively. The age, gender, type of deformity, characteristics of the deformity (depth, asymmetrical/symmetrical), age when the deformity was noticed, duration after the deformity was noticed until admission, complaint at admission, presence of scoliosis and comorbid diseases, radiological findings (chest X-ray, thorax CT if available), PFT results, echocardiography results, thoracic surgery follow-up and reparative treatment were evaluated. PFT was performed on cooperative children aged 6 years and older in accordance with the American Thoracic Society and European Respiratory Society guidelines (12). PFT data included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), mid-expiratory flow between 25-75% of forced vital capacity (MEF_{25-75}) as the percentage of predicted, and FEV_1/FVC ratio. In PE, the depth of deformity was measured and recorded from the deepest point to the imaginary line passing through the areolas while the patient was in the supine position (13). Although CT can be considered the gold standard tool in the evaluation of thoracic morphology (14), the amount of radiation was kept in the foreground for the pediatric age group, and CT was not applied to every patient, and those who were requested to have thorax CT by the thoracic surgery department or those who had thorax CT for any other reason were recorded.

Demographic, clinical and radiological characteristics of children with PE and PC, the two most common chest wall deformity subgroups, were compared.

Ethics committee approval was obtained for this study, and all procedures in the study were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki. The study was designed retrospectively, and informed consent was not obtained because the data obtained during routine follow-up of the participants were used and no additional examinations, interventions, etc. were performed for the study.

Statistical Analysis

The IBM SPSS Statistics version 22.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analysis. The conformity of variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov Test). For descriptive statistics, categorical variables were expressed

Table 1. The demographic and clinical characteristics of all children with chest wall deformity

Gender	
Female (n / %)	22 / 23.9
Male (n / %)	70 / 76.1
Current age (years) [median (min-max)]	6 (0.2-17)
Age at which deformity was noticed (years) [median (min-max)]	4.3 (0-17)
Type of deformity (n / %)	
Pectus excavatum	43 / 46.7
Pectus carinatum	44 / 47.8
Other	
Pectus arcuatum	1 / 1.1
Costal arch dislocation	2 / 2.2
Costal collapse	1 / 1.1
Poland syndrome	1 / 1.1
Complaint at admission (n / %)	(n=18)
Dyspnea	8 / 44.4
Cough	6 / 33.3
Chest pain	3 / 16.7
Wheezing	1 / 5.6
Chronic diseases (n / %)	(n=30)
Respiratory*	11 / 36.7
Cardiovascular**	5 / 16.7
Neurological & Neuromuscular***	4 / 13.3
Diaphragm related problems****	3 / 10.0
Other*****	7 / 23.3

*Asthma, cystic fibrosis, primary ciliary dyskinesia
** Aortic dilatation, congenital heart disease, dextrocardia
*** Epilepsy, muscular dystrophies, cerebral palsy
**** Operated diaphragmatic hernia, diaphragm eventration
***** Autism, immunodeficiency, Down syndrome, metabolic storage disease, diabetes mellitus, operated esophageal atresia

as absolute numbers and percentages, and continuous variables were expressed as means ± standard deviations or medians (minimum-maximum). For comparisons between two independent variables, Mann-Whitney U test was used for data not normally distributed, and independent samples t test was used for normally distributed data. For correlations, Spearman's correlation test was used for data not normally distributed, and Pearson's correlation test was used for normally distributed data. Chi-square tests were used for comparisons of categorical variables between independent groups. The p value <0.05 was considered statistically significant.

RESULTS

A total of 92 children with chest wall deformity were included in the study, 70 (76.1%) of them were male. The median age was 6 (0.2-17) years. The median age at which deformity was noticed was 4.3 (0-17) years and the median duration after deformity was noticed until admission was 6 (0-144) months. 18 (19.6%) children had complaint at admission, 8 (44.4%) of them had dyspnea. Scoliosis was found in 12 (13.0%) children. Other chronic diseases was found in 30 (32.6%) children. The demographic and clinical characteristics of all children were presented in Table 1.

All of children had chest X-ray; 49 (53.3%) were normal, 36 (39.1%) had interstitial thickness and 7 (7.6%) had other findings such as linear atelectasis, elevated diaphragm, increase in aeration, chronic findings due to comorbid diseases. 11 (12.0%) had thorax CT and 5 (45.5%) were normal, in others peribronchial thickening, bilateral reticular densities and nodules were observed.

Pulmonary function test could be attempted in 40 (43.5%) children, 8 (20.0%) of whom could not cooperate and perform the test. The mean FEV_1, FVC, FEV_1/FVC and MEF_{25-75} were 108.1±18.5 %, 98.6±16.1 %, 115.5±14.9 and 124.2±29.0 %, respectively.

Echocardiography was found in 27 (29.3%) children; 17 (63.0%) of them were normal, 2 (7.4%) of them had mild pulmonary hypertension and were being followed without medication.

Although patients were directed to follow-up at the thoracic surgery clinic, there were 12 (13%) children who applied to the thoracic surgery clinic and were followed up at the time the study was conducted. Vacuum was recommended for 4 (66.7%) of the 6 children with PE who were followed up in the thoracic surgery department, and a chest belt was recommended for 1 (20.0%) of the 5 children with PC. There were no children who had a surgical plan.

Pectus excavatum was in 43 (46.7%), PC was in 44 (47.8%), PA was in 1 (1.1%) and other deformities (such as costa arch dislocation, costal collapse, Poland syndrome) was in 4 (4.3%) children. The deformity was symmetrical in 28 (62.2%) children with PC. The median depth of deformity in children with PE

Table 2. The demographic, clinical and radiological characteristics of children with pectus excavatum and pectus carinatum

	Pectus excavatum	Pectus carinatum
Gender		
Female (n / %)	9 / 20.9	11 / 25
Male (n / %)	34 / 79.1	33 / 75
Current age		
(years) [median (min-max)]	7 (0.2-17.0)	6 (0.5-17.0)
Age at which deformity was noticed		
(years) [median (min-max)]	5 (0-17.0)	4 (0-14.0)
Duration after deformity was noticed until admission		
(months) [median (min-max)]	6 (0-72)	6 (0-144)
Complaint at admission (n / %)	(n=10)	(n=6)
Dyspnea	3 / 30	4 / 66.7
Cough	5 / 50	1 / 16.7
Chest pain	1 / 10	1 / 16.7
Wheezing	1 / 10	-
Echocardiography (n / %)	(n=15)	(n=10)
Normal	8 / 53.3	8 / 80
Abnormal / other findings	7 / 46.7	2 / 20
Radiological examination		
Chest X-ray (n / %)	(n=43)	(n=44)
Normal	22 / 51.2	23 / 52.3
Interstitial thickness	18 / 41.9	17 / 38.6
Other findings*	3 / 7.0	4 / 9.1
Thorax CT (n / %)	(n=4)	(n=5)
Normal	2 / 50.0	2 / 40
Other findings#	2 / 50.0	3 / 60

* linear atelectasis, elevated diaphragm, increase in aeration, chronic findings due to comorbid disease
# peribronchial thickening, bilateral reticular densities, nodules

Table 3. The comparison of pulmonary function tests of children with pectus excavatum and pectus carinatum

	Pectus excavatum (n=14)	Pectus carinatum (n=17)	p
FEV_1[#] (%)			
median (min-max)	98.5 (75-119)	115 (82-148)	0.024*
FVC[+] (%)			
median (min-max)	89 (67-111)	101 (71-130)	0.009*
FEV_1/FVC			
median (min-max)	118 (101-188)	116 (93-118)	0.532
MEF_{25-75}[β] (%)			
median (min-max)	112 (76-154)	129 (80-191)	0.164

* statistically significant
[#] forced expiratory volume in one second
[+] forced vital capacity
[β] mid-expiratory flow between 25-75% of forced vital capacity

was 10 (5-31) mm. The demographic, clinical and radiological characteristics of children with PE and PC are shown in Table 2. There were 14 children with PE and 17 children with PC who could perform PFT. Although FEV_1 and FVC values in the PFTs were statistically significantly lower in children with PE compared to those with PC, median PFT values in both groups were within the normal range. The comparison of PFTs of children with PE and PC is shown in Table 3.

There were no significant differences between PE and PC in terms of current age, age at which deformity was noticed and duration after deformity was noticed until admission (p=0.554, p=0.541 and p=0.795, respectively).

There was no statistically significant correlation between the age at which deformity was noticed and the duration after deformity was noticed until admission (p=0.420). There was no statistically significant correlation between the age at which deformity was noticed and PFT results (p>0.005).

DISCUSSION

This study stated that although the age at which chest wall deformity was noticed was young and the duration between detection of deformity and hospital admission of children was short, these did not differ according to the type of deformity.

In a study conducted with 15,862 children aged 12-19, 1.6% of whom were found to have chest wall deformities, it was concluded that 30% of those with deformities were aware of their deformities and that awareness was higher in those with severe deformities (15). In this study, children were only asked whether they were aware or not of their chest wall deformities, and no questions were asked about the age at which they became aware (15). In our study, it was determined that the age at which chest wall deformity was noticed did not differ according to the type of deformity. This suggested that parents' awareness was high because the age at which the deformity was noticed was found to be young in our study.

Studies have shown male predominance in PE and PC (2-4). In our study, both PE and PC were detected more frequently in males, similar to the literature. In chest wall deformities, especially pectus excavatum, the deformity usually becomes clearer between the ages of 7-9 (1). However, although it can be easily noticed in childhood, it can sometimes be ignored (4). In our study, the age at which the deformity was noticed was relatively younger, and there was no statistical difference between the types of deformity.

As reported in some studies, children with chest wall deformities may be asymptomatic and may also have some signs and symptoms, although they are not specific to these deformities (9,10). Most of the children with chest wall deformity in our study were asymptomatic. Children with symptoms had symptoms such as dyspnea and cough, consistent with the literature. However, the symptoms of these children were not evaluated as being due to chest wall deformity but rather as being related to their additional chronic diseases.

Chest wall deformities may affect lung capacity due to the inability of the rib cage to fully expand. This effect may develop gradually and a decrease in total lung capacity may occur over time (9). In our study, it was observed that chest wall deformities did not impair PFTs in children who were able to perform the test. When PE and PC, the two major subgroups of chest wall deformity, were compared, although the FEV_1 and FVC values in PFT were significantly lower in those with PE compared to those with PC, the median was within the normal range in both groups. Children did not require further testing such as diffusing capacity of the lungs for carbon monoxide (DLCO); because the first step, PFT, was found to be not impaired.

In a study by Lawson ML et al. (16), it was observed that the preoperative FEV_1 and FEF_{25-75} of patients aged 11 years and older were at the lower limit of the normal range of predicted percentages, but were not considered impaired because they were still within normal limits. In the same study, it was discussed that other studies have also reported decreases in lung function in patients with chest wall deformities, but the results are often within the normal range (16). In an adult study, PFT values were found to be lower than predicted but were still interpreted as within the normal range (17). The authors noted in another study that patients with more severe deformities were much more likely to demonstrate a restrictive lung pattern on PFT (18). Since there were no children with severe deformities in our study, PFT values may have been found to be in the normal range. Patients should remain under follow-

up as their lung capacity may be affected by the progression of their chest deformities

The limitations of the study are that it is a single center and retrospective study. However, it was considered an important issue to draw attention to since chest wall deformity can be overlooked compared to other diseases.

CONCLUSION

In conclusion, in this study, regardless of the type of deformity, the age at which the deformity was noticed was found to be young and the time from detection to hospital admission was short. In addition, it was observed that there was no effect on lung capacity in children with chest wall deformity, but since lung capacity may be affected over time in children with chest wall deformity, it is important to follow up the child in all types of chest wall deformity, even if the child is asymptomatic.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that she did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01765
Selcuk Med J 2025;41(2): 89-93

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Effect of Lupus Nephritis on Cardiac Remodeling and Left Ventricular Relative Wall Thickness

Lupus Nefritinin Kardiyak Yeniden Yapılanma ve Sol Ventriküler Göreli Duvar Kalınlığı Üzerine Etkisi

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ÖZET

Amaç: Sistemik Lupus Eritematozus (SLE), yüksek kardiyovasküler komplikasyonlara yol açabilen otoimmün bir hastalıktır. Amacımız SLE'de böbrek tutulumunun sol ventrikül rölatif duvar kalınlığına (RWT) etkisini araştırmaktır.

Yöntem: Lupus nefriti olan ve olmayan SLE hastalarının ekokardiyografik özelliklerini karşılaştırmak için tek merkezli gözlemsel bir çalışma yapıldı. Çalışmaya toplam 125 hasta dahil edildi.

Bulgular: Lupus nefriti olan hastaların ortalama yaşı 31, lupus nefriti olmayanlarda ise 40 idi. Lupus nefriti olan hastalarda interventriküler septum kalınlığının daha ince olduğu görüldü. Lupus nefritli hastalarda Mitral A dalgası daha düşüktü (62,5±17 vs. 74,9±20,5, p<0,05). Lupus nefritli hastalarda sol ventrikül RWT daha düşük olduğu hesaplandı (0,38±0,06 vs. 0,43±0,07, p<0,05).

Sonuç: SLE yüksek kardiyovasküler komplikasyonlara yol açan ilerleyici bir hastalıktır. Lupus nefritinin gelişimi önemli miyokardiyal etkiye neden olur. Sol ventrikül RWT olumsuz kardiyovasküler sonuçları gösteren önemli bir parametredir.

Anahtar Kelimeler: Sistemik Lupus Eritematozus, lupus nefriti, sol ventrikül, rölatif duvar kalınlığı, diyastolik fonksiyon bozukluğu

ABSTRACT

Aim: Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with an increased risk of cardiovascular problems. Our objective is to investigate the effect of renal involvement in SLE on left ventricular relative wall thickness (RWT).

Methods: A single-center observational study was conducted to compare the echocardiographic characteristics of patients with SLE who had lupus nephritis and those without. A total of 125 patients were included in the study.

Results: The mean age was 31 years in patients with lupus nephritis and 40 years in those without. In patients with lupus nephritis, the interventricular septum thickness was found to be thinner. The Mitral A wave was lower in patients with lupus nephritis (62.5±17 vs. 74.9±20.5, p<0.05). Left ventricular relative wall thickness (RWT) was calculated to be lower in patients with lupus nephritis (0.38±0.06 vs. 0.43±0.07, p<0.05).

Conclusion: The development of lupus nephritis has a significant impact on myocardial function, and left ventricular RWT is an important parameter associated with adverse cardiovascular outcomes.

Keywords: Systemic Lupus Erythematosus, lupus nephritis, left ventricle, relative wall thickness, diastolic dysfunction

Geliş Tarihi/Received: 7 July/Temmuz 2024 **Kabul Tarihi/Accepted:** 10 November/Kasım 2024 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic progressive autoimmune disease associated with high cardiovascular risk, where the underlying pathophysiological mechanisms are not fully understood. In SLE patients, myocardial and pericardial diseases increase the risk of heart failure (1-4). Although SLE alone carries a high cardiovascular risk, the development of nephritis, medications, lupus anticoagulant, and antiphospholipid antibodies can further exacerbate cardiac damage (5). Over time, myocardial fibrosis occurs in SLE patients, providing a basis for the development of heart failure. Approximately 50% of SLE patients experience kidney involvement (6). The development of lupus nephritis typically presents as the initial organ manifestation and can lead to end-stage renal failure. The rate of cardiovascular

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Atıf yapmak için/ Cite this article as: Tatar S, Sahin AT, Yavuz YE, Ozer H, Nicolalde B, Moloshova N, Ergun MC. Effect of Lupus Nephritis on Cardiac Remodeling and Left Ventricular Relative Wall Thickness. Selcuk Med J 2025;41(2): 89-93

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

disease development in patients with lupus nephritis is twice as high as in those without (7).

Abnormalities in left ventricular relative wall thickness (RWT) have been identified as independent predictors in diseases affecting cardiovascular mortality and morbidity, such as heart failure, coronary artery disease, atrial fibrillation, and stroke (8). RWT is a parameter that reflects left ventricular geometry. Abnormal RWT is associated with cardiac remodeling. In hypertensive individuals with normal left ventricular mass, abnormal RWT is related to concentric remodeling, indicating early adaptation of the heart to hypertension (9). Pathological changes in left ventricular RWT may serve as an early indicator of systolic and diastolic dysfunction. Detecting these changes early is crucial for predicting cardiovascular complications and ensuring close monitoring of patients. In our study, we aimed to demonstrate the pathological alterations in left ventricular RWT in patients with lupus nephritis compared to those without nephritis.

METHODS

Participants

This is a single-center, retrospective, observational study performed at the Rheumatology Clinic. A total of 125 patients diagnosed with systemic lupus erythematosus who underwent routine echocardiography between 2020 and 2023 were included in the study. Patients with pathologically confirmed lupus nephritis were included in the study. Patients with other comorbidities or conditions that can confound SLE-associated echocardiography findings were excluded: History of coronary artery disease (n=6), heart failure (n=8), atrial fibrillation (n=4), ischemic stroke (n=1), hematological diseases (n=2), chronic kidney failure (n=2), malignancy (n=2), severe valvular disease (n=3), and pacemaker implantation (n=2). Patients with a direct impact on left ventricular function and dimensions and those with a history of active infection within the last month were also excluded. After excluding 30 patients, from the remaining 95 patients 22 had pathologically reported lupus nephritis and 73 without renal involvement. The flow chart in Figure 1 illustrates the inclusion and exclusion of patients. The present study followed the tenets of the Declaration of Helsinki. Ethics committee approval for the study was received with the ethics committee approval number 4901 of 2024.

Transthoracic echocardiography:

Comprehensive transthoracic echocardiography were performed by two experienced cardiologists. Philips Epiq 7c device was used. Echocardiographic measurements were performed according to the American Society of Echocardiography guidelines (10). The end-diastolic diameter of the left ventricle was measured. The posterior wall thickness of the left ventricle during diastole was also measured. RWT was calculated using the following formula RWT = 2 × PWT (posterior wall thickness)/LVDd (left ventricular diastolic diameter).

Data collection and data analysis

Patients' medical charts were reviewed to collect their demographic characteristics and clinical data, including laboratory tests. Data analysis was conducted using SPSS software (version 20.0; SPSS Inc, Chicago, IL) and presented as mean ± standard deviation or median (interquartile range [IQR]). Independent Student t-tests were used to compare differences between the two groups, while the Mann–Whitney U test was employed for non-normally distributed variables. Categorical variable differences were assessed using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Participants

The mean age of patients with lupus nephritis was 31.4 (SD=12.9), while the mean age of patients without lupus nephritis was 40.3 (SD=4.4) (p=0.009). The female sex was predominantly in both groups. There was no statistical difference in the duration of the disease, as well other comorbidities such as hypertension, diabetes mellitus, and obesity which showed homogenization in between groups. Most of laboratory findings did not show significant difference with the exception of complement and proteinuria which were higher in the lupus nephritis group (Table 1).

Transthoracic echocardiography

Echocardiographic features of the patients are shown in Table 2. No significant difference was found in left ventricular ejection fraction between the two groups (59±8.8 vs. 60.1±4.6, p>0.05), indicating the absence of systolic dysfunction. Patients with lupus nephritis had a thinner interventricular septum, and this difference was statistically significant (0.89±0.17 vs. 0.98±0.16, p=0.02). The Mitral A wave velocity, representing left ventricular diastolic pressure, was significantly different

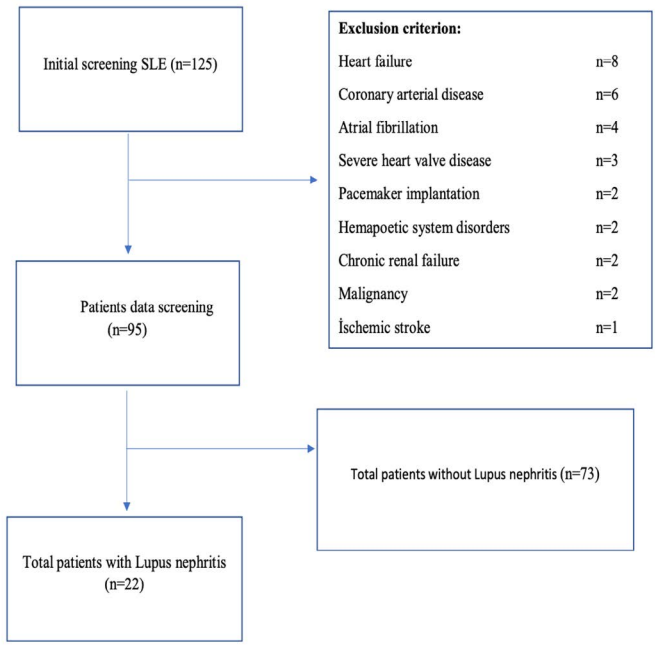

Figure 1. Study flow chart.

Table 1. Demographic and clinical characteristics of the patients

Variables	With Lupus nephritis (n=22)	Without Lupus nephritis (n=73)	P value
Age, years*	31.4±12.9	40.3±14.4	0.009
Sex, n, %			NS
Male	2(9.1)	6(8.2)	
Female	20(90.9)	67(91.8)	
ANA, n, %	20(23.8)	64(76.2)	NS
Anti-Ds DNA, n, %	21(25)	63(75)	NS
Disease duration, years*	5.6±4.3	7.4±4.9	NS
HT, n, %	9(20.5)	35(79.5)	NS
DM, n, %	1(14.3)	6(85.7)	NS
Obesity, n, %	2(25)	6(75)	NS
WBC, (µl/ml)*	7.5±2.4	6.5±2.8	NS
PLT, (103/L)*	233.7±86.3	251.7±89.4	NS
ESR, mg/h*	30±27.1	21.2±18.9	NS
CRP, mg/L*	4.0±5.3	5.5±6.9	NS
Proteinuria, mg/day*	3152.8±4056.7	841.9±1744.2	0.022
C3, mg/dl*	0.65±0.31	0.97±0.34	0.001
C4, mg/dl*	0.08±0.05	0.16±0.08	0.001

ANA: Antinuclear antibody, HT: Hypertension, DM: Diabetes mellitus, WBC: White blood cell, PLT: Platelet, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, C3: Complement 3, C4: Complement 4, NS: No significant
*Student t-test was used

Table 2. Echocardiographic parameters of the patients

Variables	With Lupus nephritis (n=22)	Without Lupus nephritis (n=73)	P value
EF, %	59±8.8	60.1±4.6	NS
IVS thickness, cm	0.89±0.17	0.98±0.16	0.02
Posterior wall thickness, cm	0.88±0.16	0.95±0.14	NS
End-diastolic diameter, cm	4.6±0.53	4.4±0.48	NS
End-systolic diameter, cm	2.8±0.51	2.65±0.44	NS
Mitral E, cm/sec	78.5±20.1	79.3±19.6	NS
Mitral A, cm/sec	62.5±17	74.9±20.5	0.014
E/A ratio	1.3±0.49	1.1±0.35	NS
Relative posterior wall thickness, cm	0.38±0.06	0.43±0.07	0.011

EF: Ejection Fraction, IVS: Interventricular septum, NS: No significant

in patients with lupus nephritis (p=0.014). Although the components of relative posterior wall thickness (RWT), including left ventricular posterior wall thickness and end-diastolic diameter, were similar between the groups and did not show statistically significant differences, the left ventricular RWT, was lower in patients with lupus nephritis, and the results were statistically significant (0.38±0.06 vs. 0.43±0.07, p=0.011). These findings suggest that despite normal systolic function, patients with lupus nephritis develop different cardiac remodeling than patients without nephritis, and changes could represent diastolic disfunction.

DISCUSSION

This study is one of the investigations focused on the ability of left ventricular relative wall thickness (RWT) to predict cardiac outcomes in patients with lupus nephritis.

SLE is a progressive disease that can lead to diastolic dysfunction and heart failure. Over time, SLE patients may develop dilation in the left ventricle and left atrium (11). Several echocardiographic parameters are used to assess diastolic dysfunction in SLE patients. Among these, the E/e' ratio, E/A ratio, left ventricular end-diastolic diameter, and left ventricular mass are commonly employed (12). However, there is no definitive data on which parameter is superior. RWT is a frequently used parameter in clinical practice and offers higher specificity compared to other diastolic parameters. While studies on diastolic dysfunction in SLE patients exist in the literature, limited data are available regarding the condition in patients with lupus nephritis. Our study demonstrated that RWT values were lower in patients with lupus nephritis compared to those without renal involvement. When examining the pathogenesis of lupus nephritis, inflammation and fibrosis are prominent factors that contribute to cardiovascular complications. These factors disrupt the structure and function of the left ventricle (LV), leading to adverse cardiovascular outcomes. Inflammatory markers such as HE4, along with changes in other biomarkers, have been linked to both renal and cardiovascular damage in patients with lupus nephritis (13). Systemic inflammation and the development of fibrosis further contribute to LV remodeling and dysfunction, potentially exacerbating cardiovascular risks. This suggests that if renal involvement develops in SLE patients, more severe

diastolic dysfunction may accompany the clinical picture. In a study by He et al., lupus nephritis patients were found to have more significant myocardial involvement based on global longitudinal strain (GLS) values (14). These findings are consistent with our study results. Although GLS is a parameter indicative of diastolic dysfunction and myocardial damage, it is not easily applicable or accessible in clinical practice. Especially in economically challenged countries, implementing such parameters can be challenging. Instead, as in our study, evaluating RWT is practical, cost-effective, and easy to use with high accuracy.

Gardin et al. demonstrated an association between RWT and ventricular arrhythmias. Specifically, each 0.01 decrease in RWT was associated with an approximately 10% increase in the risk of ventricular arrhythmia and death (15). Several mechanisms can explain this relationship. Decreased RWT is often associated with fibrosis. Fibrosis can lead to reentry circuits and early depolarizations, increasing the risk of malignant arrhythmias. In patients with fibrosis, oxidative stress and diastolic dysfunction in the left ventricle contribute to the likelihood of ventricular arrhythmias. While left ventricular end-diastolic diameter and left ventricular mass are important for predicting malignant arrhythmias, RWT can be considered a more sensitive echocardiographic indicator. Patients with lupus nephritis have higher rates of myocardial fibrosis. Based on these results, patients with lupus nephritis require closer monitoring for ventricular arrhythmias and heart failure.

Many studies on left ventricular function focus on the left ventricular mass index. However, an essential point to remember is that while these parameters are used for assessing cardiac remodeling, the left ventricular mass index may be normal while the RWT value is abnormal. Eguchi et al. conducted a study in hypertensive individuals with type 2 diabetes mellitus and found that RWT, unlike left ventricular mass index and other echocardiographic parameters, independently predicted cardiovascular events [8]. Similarly, Hashem et al. investigated patients with non-cardioembolic stroke and identified abnormal RWT values despite a normal left ventricular mass index, emphasizing the importance of RWT for accurately assessing left ventricular geometry (16). These findings align with the results of our study. In our research, although initial classic echocardiographic measurements indicated normal left ventricular systolic function in patients, pathological differences were detected at the diastolic level. Additionally, the Mitral A wave velocity, representing left ventricular diastolic pressure, was lower in patients with lupus nephritis, further supporting the presence of diastolic dysfunction in this group. The development of lupus nephritis may lead to earlier and more severe cardiac dysfunction compared to SLE patients without renal involvement.

Limitations

One of the limitations of our study is the absence of ProBNP measurements, which are typically used to evaluate heart failure status in patients. In our study, inflammatory markers such as ESR, CRP, and WBC were evaluated; however, more specific chronic inflammatory markers were not assessed. This can be considered one of the limitations of the study. MRI (magnetic resonance imaging) is used to show cardiac involvement in patients with lupus. The fact that we did not use MRI in our study can be considered among our limitations. As is known, kidney diseases cause an increased risk of diastolic heart disease. Adding non-lupus-related kidney disease to the groups and comparing this group with lupus nephritis could have made the study more meaningful. Comparison of patients without lupus nephritis with a healthy control group could also have increased the quality of the study.This situation can be counted among our limitations. Our study's single-center design and lack of assessment of strain echocardiography parameters, which are indicative of diastolic dysfunction, are among our limitations. Additionally, the follow-up duration for patients was not sufficiently long, and their outcomes related to cardiovascular complications during this period were not evaluated. In future studies, we hope to better understand the significance of RWT in predicting cardiovascular complications during long-term follow-up of patients with lupus nephritis.

CONCLUSION

Systemic Lupus Erythematosus (SLE) is a progressive disease that leads to high cardiovascular complications. The development of lupus nephritis results in significant myocardial impact. Relative wall thickness (RWT) is an important parameter indicating that patients with lupus nephritis should be closely monitored for ventricular arrhythmias, heart failure, and diastolic dysfunction.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01833
Selcuk Med J 2025;41(2): 94-98

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Is The Clock Position Method Practical and Accurate to Determine The Axis of The Fetal Heart? Comparison with The Bronshtein (Right-Hand Rule) Method

Saat Pozisyonu Yöntemi, Fetal Kalp Ekseni Belirlemede Pratik ve Doğru Bir Yöntem midir? Bronshtein (Sağ El Kuralı) Yöntemi ile Karşılaştırma

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ÖZET

Amaç: Bu çalışma, birinci yıl kadın doğum asistanları arasında Saat pozisyonu yöntemi ile Bronshtein yöntemi arasındaki fetal kalp aksı belirleme süresi ve doğruluğunu karşılaştırmayı amaçladı.

Gereçler ve Yöntemler: Bu prospektif çalışma, Ankara Etlik Şehir Hastanesi'nde Şubat 2024 - Haziran 2024 tarihleri arasında gerçekleştirildi. Çalışmaya birinci yıl kadın doğum asistanı olan 37 katılımcı dahil edildi. Katılımcılar baş, makat, transvers ve baş (situs inversuslu bir fetus) prezentasyon olmak üzere dört farklı fetal prezentasyon için fetal kalp aksını hem Saat pozisyonu yöntemi hem de Bronshtein yöntemi kullanarak değerlendirdi. Saat pozisyonu yönteminde fetal omurga her zaman saat 12 hizasında olacak şekilde bir saat olarak görüntülenir. Baş gelişte , fetal kalp saat 5 hizasındadır. Makat gelişte, fetal kalp saat 7 hizasındadır. Her iki yontemin değerlendirme süresi ve fetal kalp aksı belirleme doğruluğu kaydedildi.

Bulgular: Saat pozisyonu yöntemi, tüm fetal pozisyonlar için Bronshtein yöntemine kıyasla anlamlı derecede daha hızlıydı ($p < 0,001$). Saat pozisyonu yönteminde en kısa değerlendirme süresi baş prezentasyonda (medyan: 17 saniye, IQR: 11–22), en uzun süre ise situs inversus vakalarında (medyan: 22 saniye, IQR: 15–27) gözlendi. Bronshtein yöntemi, baş prezentasyonda en kısa (medyan: 28 saniye, IQR: 23–38) ve transvers prezentasyonda en uzun (medyan: 76 saniye, IQR: 40–90) süreyi gerektirdi. Saat pozisyonu yöntemi tüm fetal pozisyonlarda %100 doğruluk sağlarken, Bronshtein yöntemi situs inversus vakalarında daha düşük doğruluk oranına sahipti (%81,1).

Sonuç: Saat pozisyonu yöntemi, fetal kalp aksının belirlenmesinde daha hızlı ve daha doğru bir yöntem olup, Bronshtein yöntemine kıyasla daha pratik bir alternatif sunmaktadır. Basit uygulanabilirliği, fetal hareketlerden bağımsız olması ve bilişsel yükü azaltması, özellikle erken dönem kadın doğum asistanları için bu yöntemi değerli kılmaktadır.

Anahtar Kelimeler: Saat pozisyonu yöntemi, bronshtein (sağ el kuralı) yöntemi, fetal kalp, kardiyak aks

ABSTRACT

Objective: This study aimed to compare the evaluation time and accuracy of the Clock position method and the Bronshtein method for determining the fetal heart axis among first-year obstetrics and gynecology residents.

Materials and Methods: This prospective study was conducted at Ankara Etlik City Hospital between February 2024 and June 2024. Thirty-seven first-year obstetrics and gynecology residents evaluated four fetuses with the following presentations: vertex, breech, transverse, and vertex with situs inversus. Each participant determined the fetal heart axis using both the Clock position method and the Bronshtein method. In the Clock position method, the fetal thorax is visualized as a clock, with the fetal spine always positioned at 12 o'clock. In vertex presentation, the fetal heart is located at the 5 o'clock position, whereas in breech presentation, it is at the 7 o'clock position. The evaluation time and the accuracy of fetal heart axis assessment were recorded.

Results: The Clock position method was significantly faster than the Bronshtein method across all fetal positions ($p < 0.001$ for all comparisons). The shortest evaluation time using the Clock method was in the vertex position (17 seconds, 11–22), while the longest was in situs inversus cases (22 seconds, 15–27). In contrast, the Bronshtein method required significantly longer evaluation times, with the shortest duration in the vertex position (28 seconds, 23–38) and the longest in the transverse position (76 seconds, 40–90). The Clock method demonstrated 100% accuracy across all positions, whereas the Bronshtein method showed lower accuracy, particularly in situs inversus cases (81.1%).

Conclusion: The Clock position method is a faster and more accurate approach for fetal heart axis determination than the Bronshtein method. Its simplicity, independence from fetal movements, and reduced cognitive load make it a valuable technique for obstetrics and gynecology residents, particularly those in the early stages of training.

Keywords: Clock position method, bronshtein (right-hand rule) method, fetal heart, heart axis

Geliş Tarihi/Received: 10 February/Şubat 2025 **Kabul Tarihi/Accepted:** 29 May/Mayıs 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

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Atıf yapmak için/ Cite this article as: Bucak M, Seyhanli Z, Sucu S, Karabay G, Ulusoy CO, Aktemur G, Tokgoz Cakir B, Yilmaz Ergani S, Keskin HL, Celen S. Is The Clock Position Method Practical and Accurate to Determine The Axis of The Fetal Heart? Comparison with The Bronshtein (Right-Hand Rule) Method. Selcuk Med J 2025;41(2): 94-98

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Congenital heart defects (CHD) are the most common fetal anomaly, occurring in 8–9 per 1,000 live births (1). Fetal heart evaluation is an essential component of prenatal care, with the optimal timing for heart assessment occurring between 18 and 22 weeks of gestation (2).

Guidelines standardize the evaluation of fetal heart anatomy, emphasizing the importance of fetal heart axis assessment (2,3). During early development, the fetal heart axis is initially in the midline around 8 weeks of gestation and gradually rotates leftward by the end of the first trimester (4). In the second and third trimesters, the heart is positioned in the left thorax, with its long axis forming an angle of approximately 45° ± 20° to the anteroposterior thoracic axis (5). Deviations outside this range-whether leftward, midline, or rightward-are considered abnormal and may indicate congenital heart defects, diaphragmatic hernia, or thoracic mass lesions (6,7). When a four-chamber view of the heart is obtained, the fetal heart axis should be focused on, and the axis should be determined.

The Cordes method and the Bronshtein method are widely used techniques for determining fetal heart axis (8,9). Recently, Dursun et al. introduced the Clock position method, which provides a simpler approach for fetal heart axis evaluation (10). This method is particularly practical for obstetrics and gynecology clinicians due to its ease of use and independence from complex hand positioning.

We hypothesized that the Clock position method is faster and more accurate than the Bronshtein method, especially among first-year obstetrics and gynecology residents. The aim of this study was to compare the evaluation time and accuracy of the Clock position method and the Bronshtein method among first-year obstetrics and gynecology residents.

MATERIAL METHODS

This prospective study was conducted at Ankara Etlik City Hospital between February 2024 and June 2024 with ethical approval from the Institutional Ethical Committee (AESH-BADEK-2024-108). The study complied with the Helsinki Declaration of Ethical Principles.

Fetal Heart Axis Assessment Methods

Clock position method: This method involves the clinician sitting on the patient's right side, holding the ultrasound probe in the right hand, and using a transabdominal approach. The thoracic cavity is visualized as a clock, with the fetal spine always at 12 o'clock. In vertex presentation, the fetal heart is at 5 o'clock (Figure 1). In breech presentation, the fetal heart is at 7 o'clock (Figure 2). In transverse presentation, the probe is turned towards the mother's head and the axis is determined according to the fetal structure closest to the clinician (vertex or breech) (10).

Bronshtein method (right-hand rule): The clinician uses their right forearm and thumb as a model for fetal positioning. The dorsal forearm represents the fetal back, while the thumb always points toward the fetal left side, confirming heart orientation (9).

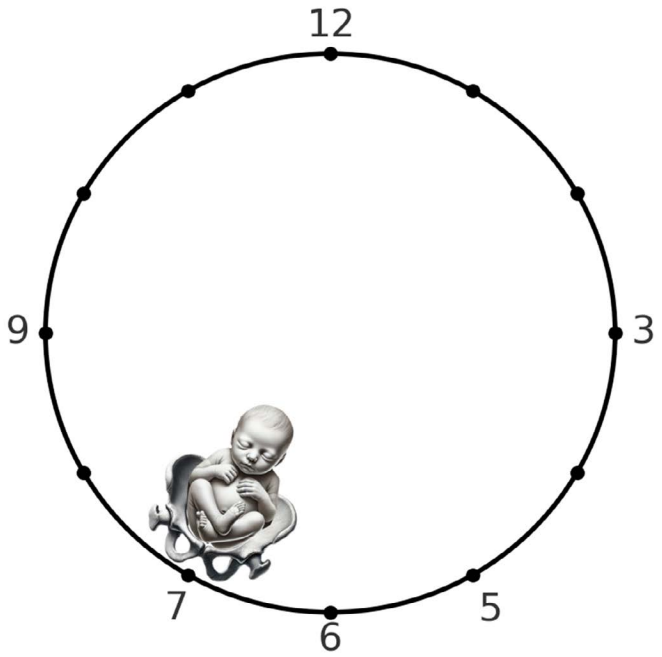

Figure 1. Illustration of the Clock position method for fetal heart axis evaluation in a fetus with vertex presentation. This image was generated using DALL·E, an artificial intelligence tool developed by OpenAI.

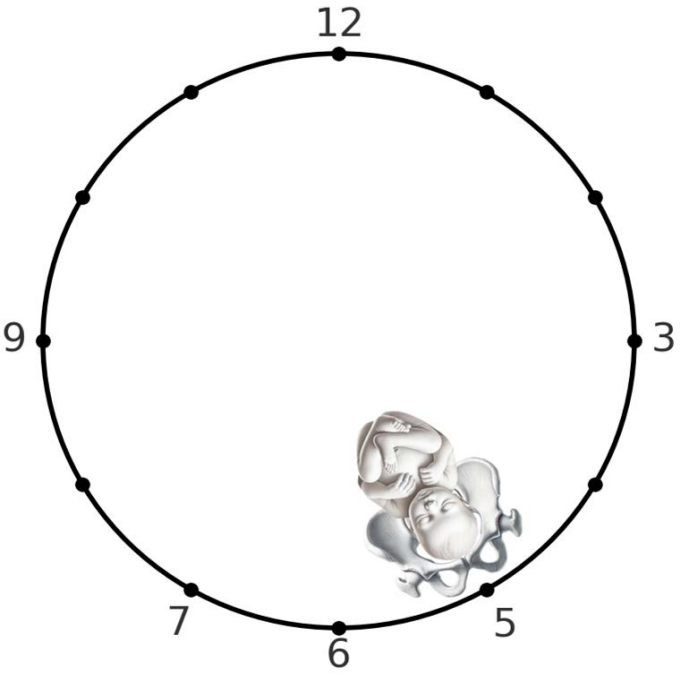

Figure 2. Illustration of the Clock position method for fetal heart axis evaluation in a fetus with breech presentation. This image was generated using DALL·E, an artificial intelligence tool developed by OpenAI.

Study Participants and Protocol

A total of 37 first-year obstetrics and gynecology residents and four pregnant women participated in this study. The residents were trained in both the Clock position method and the Bronshtein method by an experienced obstetrician (M.B.) before the study. Each resident evaluated the fetal heart axis of four different fetuses at 22 weeks of gestation without prior knowledge of the axis. All ultrasound examinations were performed transabdominally using a Voluson S10 ultrasound machine (GE Healthcare Ultrasound, Milwaukee, WI, USA). The four fetuses included three with normal heart axis representing vertex, breech, and transverse presentations and one fetus with vertex presentation and situs inversus totalis, with the heart axis positioned on the right side.(11) The residents were blinded to both the patients and the fetal axis. Each resident was brought into the ultrasound room one at a time and first assessed the fetal heart axis using the Clock position method, followed by the Bronshtein method. The time taken from the start of the evaluation to the final decision (in seconds) was recorded, and the accuracy of the fetal heart axis determination (true/false) was noted. The study included first-year obstetrics and gynecology residents who had no prior experience in fetal heart axis assessment and voluntarily participated. Residents with prior knowledge or experience in fetal heart axis evaluation were excluded. Pregnant women were informed about the study, and their participation was based on voluntary consent. Pregnant women who declined participation were excluded.

The primary outcome of this study was to measure the time required for each fetal heart axis assessment and the accuracy of fetal axis determination using both methods.

Statistical Analysis

All statistical analyses were performed using the SPSS software (version 29.0, IBM Corp., Armonk, NY, USA) to analyze the data. The Shapiro-Wilk test was performed to assess normality. Continuous variables were summarized as median and interquartile range (Q1-Q3), while categorical variables were presented as frequency and percentage. The Wilcoxon test was used to compare the time required for fetal heart axis evaluation between methods. Accuracy rates were analyzed descriptively. Since the Clock method demonstrated 100% accuracy across all cases, a statistical comparison of accuracy between methods was not feasible. A p-value of less than 0.05 was considered to show a statistically significant.

RESULTS

A total of 37 first-year obstetrics and gynecology residents were included in the study. The median age of the participants was 27 years (IQR: 26–29.5), and the median duration of residency training was 5 months (IQR: 4–6). The majority of the residents were female (n = 27, 73%), while male residents comprised 27% (n = 10) (Table 1).

Each resident evaluated four fetuses with the following presentations: vertex, breech, transverse, and vertex (situs inversus).The time required for fetal heart axis evaluation was significantly shorter with the Clock method compared to the

Table 1. Demographic Characteristics of First-Year Obstetrics and Gynecology Residents

		n=37
Age		27 (26-29.5)
Gender		
	Female	27 (73)
	Male	10 (27)
Duration of Residency Training (months)		5 (4-6)

Values are presented as median (Q1-Q3) and frequency (percentage).

Table 2. Comparison of Evaluation Time for Fetal Heart Axis Evaluation Between Methods

Fetal Position	**Clock Position Method (seconds)**	**Bronshtein Method (seconds)**	**p**
Vertex	17 (11 – 22)	28 (23 – 38)	<0.001
Breech	23 (18 – 38)	49 (40 – 55)	<0.001
Transverse	25 (23 – 34)	76 (40 – 90)	<0.001
Vertex (Situs inversus)	22 (15 – 27)	43 (30 – 48)	<0.001

Values are presented as median (Q1-Q3).

Table 3. Comparison of Accuracy Between Methods for Fetal Heart Axis Evaluation

Fetal Position	**Clock Position Method (Correct / Incorrect / Accuracy %)**	**Bronshtein Method (Correct / Incorrect / Accuracy %)**
Vertex	37 / 0 / 100%	35 / 2 / 94.6%
Breech	37 / 0 / 100%	33 / 4 / 89.2%
Transverse	37 / 0 / 100%	32 / 5 / 86.5%
Vertex (Situs inversus)	37 / 0 / 100%	30 / 7 / 81.1%

Bronshtein method across all fetal presentations ($p < 0.001$, for all comparisons). The Clock method had the shortest evaluation time in the vertex presentation (median: 17 seconds, IQR: 11–22) and the longest in the situs inversus presentation (median: 22 seconds, IQR: 15–27). In contrast, the Bronshtein method required longer evaluation times, with the shortest duration observed in the vertex position (median: 28 seconds, IQR: 23–38) and the longest in the transverse position (median: 76 seconds, IQR: 40–90) (Table 2).

The Clock method demonstrated 100% accuracy across all fetal positions. However, the Bronshtein method showed reduced accuracy, particularly in situs inversus cases (81.1%). Incorrect fetal heart axis assessments using the Bronshtein method were recorded in 2 vertex cases (accuracy: 94.6%), 4 breech cases (89.2%), 5 transverse cases (86.5%), and 7 situs inversus cases (81.1%) (Table 3).

DISCUSSION

This study evaluates the practicality and accuracy of the Clock position method in determining the fetal heart axis compared to the Bronshtein method. The findings demonstrate that the Clock position method is significantly faster and maintains a 100% accuracy rate across all fetal positions, making it a valuable technique for obstetrics and gynecology residents.

Lee et al. conducted a study on fetal ultrasound training among obstetrics and gynecology residents, concluding that only two-thirds of the participants believed they would achieve sufficient competency by the time of their graduation (12). This finding raises concerns about the adequacy of current ultrasound training programs in obstetrics and gynecology residency education.

Our findings align with those of Aktoz et al., who demonstrated that the Clock position method is faster and easier to learn compared to the Bronshtein and standard methods (13). Both studies highlight that the Clock position method eliminates the need for complex hand positioning, reducing cognitive load and making it more intuitive for inexperienced residents. While Aktoz et al. focused on general fetal heart axis evaluation, our study further supports its effectiveness across various fetal presentations, including situs inversus cases, where the Bronshtein method showed lower accuracy. These findings suggest that integrating the Clock position method into residency training could improve both efficiency and diagnostic precision in fetal heart assessment.

In clinical practice, obstetricians and gynecologists typically hold the ultrasound probe with their right hand during fetal assessment. The Bronshtein method also requires the use of the right hand to determine fetal situs (9). However, as the fetus moves or the heart assessment progresses, clinicians must repeatedly use their right hand for situs determination, which can lead to misinterpretation and confusion. Some clinicians attempt to mentally position themselves in place of the fetus to determine the heart axis and situs, further increasing cognitive load and the potential for errors. The Clock position method eliminates these challenges by offering a simplified and intuitive approach, making it easier to apply in clinical settings.

Liu et al. investigated the assessment of fetal heart axis in congenital heart disease using fetal heart magnetic resonance imaging (MRI) and reported a strong correlation between ultrasound and MRI findings (14). Their study highlights the importance of ultrasound in fetal heart assessment. Accurate determination of the heart axis is crucial for identifying potential congenital heart abnormalities. The Clock position method, particularly for novice obstetrics and gynecology residents, reduces the risk of errors and facilitates a more structured approach to fetal heart evaluation.

One of the strengths of this study is the direct comparison between the Clock position method and the Bronshtein method for fetal heart axis determination, contributing further evidence on the effectiveness and accuracy of these techniques. The inclusion of various fetal presentations, including situs inversus cases, enhances the study's clinical relevance. Additionally, by evaluating both time effectiveness and accuracy, this study provides a comprehensive assessment of these methods. However, this study has certain limitations. As a single-center study, its external validity and generalizability are limited. Furthermore, the sample size (37 participants, 4 fetal positions) may not be sufficient to draw broader conclusions. Future studies with larger, multi-center cohorts should validate these findings and further investigate the method's long-term benefits in clinical training and practice.

CONCLUSION

The Clock method provides a faster and more accurate approach for fetal heart axis determination than the Bronshtein method across all fetal positions. Its simple application, independence from fetal movements, and reduced cognitive load make it a valuable technique for obstetrics and gynecology residents, particularly those in the early stages of training.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01837
Selcuk Med J 2025;41(2): 99-109

OPEN DERLEME / REVIEW

Animal Models of Diabetes and Complications for Studying Disease Mechanisms

Diyabet ve Komplikasyonlarının Hastalık Mekanizmalarını İncelemek İçin Hayvan Modelleri

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ÖZET

Bu derleme, diyabetin patofizyolojisini ve komplikasyonlarını anlamak için hayvan modellerinin kullanımını ve etkinliğini incelemeyi amaçlamaktadır. Bu derleme, hayvan modellerinde diyabet kaynaklı komplikasyonları inceleyen güncel literatürün analizini içermektedir. Sadece İngilizce makaleler dahil edilmiştir ve çoğunluğu 2018 sonrası yayımlanmıştır. Alloksan ve Streptozotosin gibi kimyasal modellerin etkili bir şekilde diyabet oluşturabildiği, ancak toksisite ve sistemik yan etkilere yol açabileceği görülmektedir. Alloksan, β-hücre toksisitesi yoluyla Tip 1 diyabeti tetiklerken, STZ hem Tip 1 hem de Tip 2 diyabeti modellemek için tercih edilmektedir. Otoimmün diyabeti simüle eden NOD fareleri veya obezite kaynaklı diyabet geliştiren db/db fareleri gibi genetik modeller, hastalığın genetik yönlerini incelemek için avantajlıdır ancak yüksek maliyet ve karmaşıklık gibi dezavantajlar taşımaktadır. Cerrahi yaklaşımlar, insülin sekresyonu ve pankreas fonksiyonlarını değerlendirmede önemli bilgiler sunarken, bu yöntemlerin invaziv olması ve fizyolojik olarak bazı farklılıklara yol açması sınırlayıcı bir faktördür. Modellerin çoğu, diyabete bağlı oksidatif stres ve inflamasyonun, nefropati, retinopati, nöropati ve kardiyovasküler hastalıklar gibi komplikasyonlara yol açtığını göstermektedir. Özellikle diyabetik böbrek hastalığında podosit hasarı, proteinüri ve glomerüler filtrasyon değişiklikleri gözlemlenirken, diyabetik retinopati modelinde vasküler değişiklikler ve görme kaybı tespit edilmiştir. Diyabetik nöropati, duyusal ve motor fonksiyon kayıplarına yol açarken, kardiyovasküler komplikasyonlar damar sertliği, hipertansiyon ve kalp yetmezliği ile ilişkilendirilmiştir. Diyabetin ilerleyişi ve komplikasyonlarını değerlendirebilmek için model seçimi büyük önem taşımaktadır. Ancak her modelin kendine özgü avantajları ve sınırlamaları vardır. Kimyasal ajanlar hızlı ve düşük maliyetli bir seçenek sunarken, genetik modeller daha fizyolojik ancak maliyetli ve teknik olarak karmaşıktır. Bu derleme, diyabet araştırmalarında en uygun hayvan modelinin belirlenmesine rehberlik edebilir ve yeni terapötik stratejilerin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Diyabet, Komplikasyonlar, Hayvan Modeli, STZ, Alloksan

ABSTRACT

This review aims to examine the use and effectiveness of animal models in understanding the pathophysiology and complications of diabetes. This review includes an analysis of recent literature investigating diabetes-related complications in animal models. Only English-language articles were included, with the majority published after 2018. Chemical models such as Alloxan and Streptozotocin (STZ) effectively induce diabetes; however, they may cause toxicity and systemic side effects. While Alloxan triggers Type 1 diabetes through β-cell toxicity, STZ is preferred for modeling both Type 1 and Type 2 diabetes. Genetic models, such as NOD mice simulating autoimmune diabetes or db/db mice developing obesity-induced diabetes, provide advantages in studying the genetic aspects of the disease. However, these models have drawbacks, including high costs and complexity. Surgical approaches offer valuable insights into insulin secretion and pancreatic function, but their invasive nature and potential physiological differences pose limitations. Most models demonstrate that oxidative stress and inflammation associated with diabetes lead to complications such as nephropathy, retinopathy, neuropathy, and cardiovascular diseases. Specifically, diabetic nephropathy is characterized by podocyte damage, proteinuria, and changes in glomerular filtration, while diabetic retinopathy models show vascular alterations and vision loss. Diabetic neuropathy results in sensory and motor function loss, whereas cardiovascular complications are linked to arterial stiffness, hypertension, and heart failure. Selecting the appropriate model is crucial for evaluating diabetes progression and its complications. However, each model has its unique advantages and limitations. Chemical agents offer a fast and cost-effective approach, while genetic models provide a more physiologically relevant but expensive and technically complex alternative. This review may guide researchers in selecting the most suitable animal model for diabetes studies and contribute to the development of new therapeutic strategies.

Keywords: Diabetes, Complications, Animal Model, STZ, Alloxan

Geliş Tarihi/Received: 21 February/Şubat 2025 **Kabul Tarihi/Accepted:** 23 June/Haziran 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

INTRODUCTION

Diabetes, a chronic disease that is widely prevalent worldwide, can lead to serious health problems due to disruptions in the regulation of blood sugar in the body. Diabetes can manifest in different types based on the disorders in the body's blood sugar regulation. Type 1 diabetes develops as a result of the immune system attacking the beta cells of the pancreas, which produce insulin. On the other hand, type 2 diabetes represents a condition where the effective use of insulin is impaired. Understanding these types of the disease and developing effective treatment methods is crucial, and for this purpose, experimental diabetes models play a vital role. In the scientific research, animal models are frequently employed to gain deeper insights into the pathophysiology and treatment of diabetes. Through these models, valuable

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Atıf yapmak için/ Cite this article as: Dagli Gul AS, Arihan O. Animal Models of Diabetes and Complications for Studying Disease Mechanisms. Selcuk Med J 2025;41(2): 99-109

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

information is obtained regarding the interaction of genetic and some environmental factors in diabetes, the progression of the disease, and potential treatment strategies. This review discusses how experimental diabetes models are established in animals, how these models are evaluated in diabetes research, which models are more suitable for specific experiments, and their effects on complications.

MATERIALS AND METHODS

This review examines the investigation of complications induced by diabetes in animal models through a review of the scientific literature. Only English articles have been included in the review, with the majority of the articles being from after 2018.

What is Diabetes Mellitus?

Diabetes is a chronic disease characterized by the impairment of the body's ability to regulate blood sugar levels. Essentially, it arises when the pancreas is unable to generate sufficient insulin or when the body is ineffective in utilizing the insulin it produces. Diabetes can lead to various complications in the long term, such as neuropathy, retinopathy, nephropathy, cardiomyopathy, vascular damage, and others (1). In 2019, the World Health Organization updated the classification of diabetes. According to this classification, Type 1 Diabetes is considered as an autoimmune disease which affects beta cells of the pancreas. This condition leads to almost no insulin production. Type 2 Diabetes is a condition where insulin resistance develops, meaning the body's cells cannot effectively utilize insulin, and over time, there is a reduction in insulin production from the Langerhans islets. Gestational Diabetes is a type of diabetes that arises during pregnancy or is first detected during pregnancy, typically temporary, but sometimes can persist postpartum (2). In addition to these, there are various special types of diabetes that include genetic or other types of diabetes based on reasons such as infection, medications, and chemicals.

Pathophysiology of Diabetes

We encounter different molecules in the pathophysiology of diabetes such as insulin. Insulin is a polypeptide hormone produced as preproinsulin by the beta cells of the Langerhans islets in the pancreas. Its primary functions include increasing glucose uptake into cells, facilitating the storage of glucose as glycogen and fat, and regulating protein synthesis. This hormone initiates mechanisms by binding to receptors on cell membranes, making it easier for glucose to enter cells. This process is crucial for maintaining glucose metabolism and energy homeostasis.

Understanding the mechanism of intracellular insulin secretion and the cellular factors that regulate it is crucial in diabetes treatment strategies. Insulin release from beta cells of the pancreas' Langerhans islets occurs after a complex process. In beta cells, enzymes such as glucose transporters (GLUT) and glucokinase, which allow glucose to enter the cell, are present. When post-digestion blood glucose levels rise, and glucose levels inside beta cells increase, ATP production increases as a result of glucose metabolism. With the increase in ATP/ADP in the cytosol of beta cells, ATP-sensitive potassium channels (KATP) close. This causes cell depolarization, the opening of voltage-sensitive calcium channels, and, consequently, the entry of calcium into the cell. In addition, cyclic AMP further increases intracellular calcium levels by reducing the intake of Ca++ into intracellular organelles and modulating second messenger molecules independently or dependently on protein kinase A (3). Calcium is essential for the exocytosis process of insulin vesicles, allowing insulin to be released from the cell into the bloodstream (4).

The regulation of insulin secretion is associated with various factors, including cellular, hormonal, and neural, in addition to plasma glucose. Among cellular factors, gastrointestinal hormones (e.g., glucagon-like peptide-1), neurotransmitters, and intermediates in the glucose metabolic pathway play a role. For example, glucagon-like peptide-1 (GLP-1), which reaches beta cells through endocrine and paracrine pathways, can increase insulin production (5). Neural regulations have a significant impact, with the activity of the autonomic nervous system playing a major role. Sympathetic nervous system activity can regulate insulin secretion through neural stimulation or alpha and beta adrenergic receptors on the surface of beta cells (6). Various signaling pathways in beta cells that modulate intracellular calcium levels and second messenger molecules also influence insulin release (7).

After insulin is secreted, it reaches target cells through the circulation. Insulin receptors are specialized protein structures located on the surface of cells with tyrosine kinase enzyme activity (8). Insulin receptors are made up of four subunits, resulting from the repetition of two different types called alpha (α) and beta (β). The alpha subunits of the receptor assist in insulin binding and the insertion of the receptor into the cell surface, while the beta subunits transmit the insulin signal, initiating cellular responses (9). The binding of insulin results in the dimerization of the receptor's alpha subunits. This dimerization triggers the activation of intracellular signaling pathways by increasing the interaction of the beta subunits, leading to the opening of voltage-sensitive calcium channels. These signaling pathways regulate intracellular signal transduction and direct the effects of insulin in target tissues. In particular, signaling pathways such as the MAPK (mitogen-activated protein kinase) and the PI3K (phosphoinositide 3-kinase) pathways regulate a significant portion of insulin cellular effects (10).

Diabetic Complications

When predisposing factors for diabetes progress from prediabetes to diabetes, individuals face many complications of these pathophysiological conditions. Diabetes can lead to various complications due to long-term high blood sugar levels. These complications are generally classified as microvascular (related to small blood vessels) and macrovascular (related to large blood vessels) complications. Diabetes can lead to microvascular complications such as nephropathy, retinopathy, neuropathy and macrovascular complications such as diabetic foot syndrome, cardiovascular diseases and thrombotic events.

Retinopathy is one of the most common complications

of diabetes. Prolonged high blood glucose levels can lead to proliferative retinopathy or non-proliferative retinopathy, eventually resulting in vision loss. Diabetic nephropathy results from damage to the filtration system of the kidneys due to chronic uncontrolled glucose metabolism. Impaired kidney function can lead to an increased risk of kidney failure, proteinuria, and the loss of blood pressure control (11). Neuropathy often presents symmetrically in the extremities, resembling gloves and socks, in diabetic patients. It can also affect nerves responsible for autonomic functions in the digestive, cardiovascular, and urinary system (12). Cardiovascular diseases may develop due to impaired glucose metabolism in diabetes, due to the formation of Advanced Glycation End Products (AGES) and oxidative damage (13). Diabetic foot ulcers are observed in approximately 30% of diabetic patients. Poor circulation and sensory nerve damage make wound healing difficult and increase the risk of infection (14). Thrombotic events occur due to reasons such as reduced anti-thrombotic activity, platelet reactivation, increased concentration and activity of coagulation factors (15). These complications highlight the importance of effective diabetes management so we made a particular effort to focus on modelling of diabetic complications in animal experiments in this article.

Diabetes Models in Experimental Animals

Due to the complex pathophysiology and treatment requirements of diabetes, understanding this disease better and developing effective treatment strategies is of great importance. Before clinical research, it is necessary to conduct cell culture studies and test with experimental diabetes models in animals. Experimental diabetes models aim to mimic certain aspects of diabetes types such as Type 1 and 2 in a laboratory setting. These models are used as tools to understand how various factors contribute to the development of diabetes, investigate the effects of drug candidate chemicals or plant extracts in diabetes, and study complications. In diabetes research, experimental models created using genetic methods, chemical compounds, or dietary manipulations are quite common.

Various models are applied to create Type 1 and Type 2 diabetes in mice and rats. The main categories for triggering diabetes include chemical methods (Alloxan and STZ), spontaneous autoimmune and genetic methods (16). Surgical methods can also be added to these methods. One of the oldest and simplest ways to induce experimental diabetes in animals is the partial or complete removal of the pancreas (17). Towards the end of the 19th century, physicians discovered the association between diabetes and the pancreas and began research to understand the role of this organ. Although open abdominal surgery is generally preferred, laparoscopic methods have also been tested recently (18). Complete removal of the pancreas or Langerhans is compatible with Type 1 diabetes since it eliminates insulin production. In contrast, partial removal can be adapted to a Type 2 model (19). It is worth noting that rats and mice have significant anatomical and physiological differences in their pancreas compared to humans (20). The head of the rodent pancreas is located in the duodenal region and is scattered within the mesentery. The body part extends to the spleen, and the tail ends at the hilum of the spleen (21).

In addition to this difference, there are adverse effects of total pancreatectomy. Total pancreatectomy eliminates not only endocrine but also exocrine cells, resulting in a more severe condition than the true diabetic syndrome. Furthermore, this method destroys not only beta cells but also other critical cells that secrete hormones such as alpha, delta, pp, and epsilon cells (22). Since the aim of partial pancreatectomy is to remove over 90% of the pancreas, the disadvantages of this method are similar to total pancreatectomy (23). Despite the ease of this surgical method, its undesired side effects have led researchers towards practices where diabetes can be modeled more easily without causing significant harm to animals. Looking more closely at these methods, it can be seen that the most common applications are chemical or toxin applications. Although within this model framework, the ditizone model (24), ferric nitrilotriacetate injection (25), insulin antibody model (26), and diet modification with high-fat or high-glucose diets can be used to model conditions similar to type 2 diabetes in animals, the two most commonly used chemical substances are Alloxan and Streptozotocin (STZ) (27).

The advantages, disadvantages, mechanisms of action and complications of experimental diabetes models are given in table 1.

Alloxan

Alloxan is one of the molecules frequently used in modeling experimental diabetes in animals. It is a hydrophilic derivative of pyrimidine that is similar to glucose. Due to its resemblance to glucose, it can easily enter pancreatic beta cells and liver cells through the GLUT2 transporters (28). Its chemical structure contains five carbonyl groups, allowing it to react with thiol groups in cells. It inhibits the function of the thiol-based enzyme glucokinase, which acts as a glucose sensor in beta cells by forming disulfide bonds (29). Furthermore, it increases intracellular ROS production, leading to DNA damage and consequently, beta cell apoptosis (30). The increased production of hydroxyl radicals inside the beta cells is related to ascorbic acid, and this effect is pronounced in the mitochondria (31). A study investigating the effects of age-related alloxan administration in Wistar albino rats reported that the best induction of diabetes was observed in rats aged 7-9 weeks (32). Mostafavinia and colleagues reported that subcutaneous experiments with different doses of alloxan resulted in the most desirable outcome for Type 1 diabetes induction at a dose of 120mg/kg (33). However, there are limitations to the use of alloxan. It not only reduces glucokinase activity in beta cells but also in liver cells, which has led to the incompatibility of this model with human diabetes (34).

Streptozotocin

Streptozotocin is a broad-spectrum antibiotic that was initially isolated from *Streptomyces achromogenes* in the 1960s and was later reported to have diabetogenic effects (35, 36). In those years, it was used as a chemotherapeutic agent for

Table 1. Comparison of Common Experimental Diabetes Models and Complications

Model Type	Induction Method	Mechanism	Main Type of DM	Advantages	Disadvantages	Common Complications
Alloxan	Chemical	GLUT2-mediated entry, ROS production	Type 1	Simple, inexpensive, rapid induction	Affects liver cells, short half-life, inconsistent	Kidney damage, Retinopathy, Neuropathy
Streptozotocin (STZ)	Chemical	GLUT2-mediated entry, DNA alkylation, ROS	Type 1 & Type 2 (with high-fat diet)	More stable than Alloxan, high specificity for β-cells	Causes severe β-cell destruction, can induce early death	Kidney damage, Retinopathy, Neuropathy
Pancreatectomy	Surgical	Partial/total removal of pancreas	Type 1 or Type 2 (depending on extent)	Accurately mimics insulin deficiency	Invasive, affects both endocrine and exocrine function	Severe pancreatic damage, multi-organ dysfunction
NOD Mouse	Genetic	Spontaneous autoimmune diabetes	Type 1	Autoimmune resemblance to human T1DM	High cost, variability in diabetes onset	Retinopathy, Neuropathy
db/db Mouse	Genetic	Leptin receptor mutation, leading to obesity	Type 2	Obesity and insulin resistance model	Does not perfectly mimic human T2DM	Nephropathy, Cardiomyopathy
High-Fat Diet + STZ	Combined	Diet-induced insulin resistance, STZ-induced β-cell destruction	Type 2	Mimics human T2DM better than genetic models	Requires precise dosing, variability in response	Nephropathy, Retinopathy
Non-Human Primates	Genetic Surgical Chemical	Multiple pathways	Type 1 & Type 2	Close physiological resemblance to humans	High cost, ethical concerns	Kidney damage, Retinopathy, Neuropathy

metastatic pancreatic cancers. In fact, after a trial with 52 patients, reductions in tumor size were observed, but it was reported that five patients died due to organ damage (37). STZ is not suitable for oral administration because it is affected by stomach acid, so parenteral administration is preferred. It remains in the bloodstream at high levels for 15 minutes after injection and is then excreted through the kidneys and bile ducts (38). Similar to alloxan, STZ is a hydrophilic agent with a structure resembling glucose. STZ's specific effect on pancreatic beta cells is explained by its entry into the cells through GLUT2 receptors on the surface of pancreatic beta cells. In its chemical formula, it contains a nitrosourea group similar to adenosine, leading to DNA methylation in beta cells. Furthermore, it increases nitric oxide production and free radical formation, causing cell death (39). Surviving beta cells continue their existence with oxidative stress and mitochondrial dysfunction (40). Beta cell damage and hence insulin deficiency are typical features of type 1 diabetes, which is why STZ is considered more suitable for type 1 diabetes models. However, it is often added to models for type 2 diabetes, such as high-fat diets (41) or combined with agents like nicotinamide (42) to create these models. The nicotinamide model is based on the experiment conducted by Junod and colleagues in 1969 (43). In this combined model, approximately 60% loss of function is observed in pancreatic islets (44). The STZ-NA protocol's induction of hyperglycemia, reduction of insulin receptors in skeletal muscle, partial reversibility with metformin, development of a dyslipidemic profile, and especially histopathological changes in the liver indicate that it is a suitable model for T2DM (45).

In addition to the chemical and functional differences between alloxan and STZ, there are also differences in stability. Alloxan starts to degrade at approximately 1.5 minutes at 37°C and pH 7.4, whereas STZ can remain stable for up to about one hour at pH 7.4 and 37°C (38). Acidic environments extend the stability periods for both substances.

Dosages of STZ Application

The dosages of STZ can vary depending on the species, gender, age, and the purpose of the experiments with animals. Additionally, both repeated low-dose applications and single high-dose models are used. It is anticipated that diabetes created with multiple low doses leads to beta cell dysfunction through an inflammatory process rather than beta cell destruction, which is considered to be closer to reality (44). In mice, STZ dosages typically range from 100 to 200 mg/kg through intraperitoneal injection for creating type 1 diabetes. Dosages ranging from 40 to 60 mg/kg are used in combination with different models for type 2 diabetes (46). For generating type 1 diabetes in rats through intraperitoneal injection, dosages typically range from 40 to 65 mg/kg, although lower dosages can be used to model insulin resistance or type 2 diabetes. In a study conducted to determine the optimal dosage for inducing diabetes in rats with a single intraperitoneal dose, dosages of 30, 35, 40, and 50 mg/kg were compared. According to the results, it was reported that the likelihood of diabetes occurring was 0.764 with a dosage of 40 mg/kg, despite a low mortality rate (33). The development of diabetes begins in the days following STZ injection. In many protocols, the formation of a diabetes profile is accepted to occur with the increase in fasting blood glucose levels measured at 72 hours. Reference values for plasma glucose vary, but 200 mg/dL and above is commonly considered the lower limit. Hyperglycemia levels are often categorized as stage 1 for 200-450 mg/dL and stage 2 for 451 and above (47).

Untoward effects due to the use of STZ

Although it is widely used in rodent diabetes models, some researchers argue that it is not ideal for experimental diabetes models. Wszola et al. reported that since a single dose of STZ in small rodents caused more than 90% beta cell destruction in the pancreatic islets of Langerhans, it was not a suitable diabetes model for transplantation studies (48).

In the STZ diabetes model, different results are obtained depending on the age of the animal. WangFischer et al investigated age-related effects. In their study, it was observed that acute deaths within 1 week after STZ injection were 3% in rats aged 6-11 weeks, 83% in rats aged 12-17 weeks, and 91% in rats older than 18 weeks (49).

Finally, although there are fewer deaths in the STZ-induced diabetes model compared to alloxan, the resulting diabetes is longer-lasting and irreversible. STZ also shows greater selectivity to beta cells than alloxan (17).

Genetic Models

It is possible to create genetic diabetes models by modifying or silencing specific genes. Some common genetic type 1 diabetes models include: NOD Mouse Model (Non-Obese Diabetic): This model have a tendency to develop a disease similar to autoimmune type 1 diabetes.

Rat Insulin Promoter-LAK Mouse Model: This model involves the addition of a toxin gene (LAK) that halts insulin production. db/db Mouse Model: This model includes mutations in the leptin receptor, leading to obesity and diabetes,

Akt-Insulin Resistance Mouse Model: Mutations are made in the Akt gene, disrupting insulin signaling, Lipodystrophy Mouse Models: These models involve a lack or dysfunction of adipose tissue (16).

Different Experimental Animal Models

Another category to consider is the use of various animal species. Different animal models offer various advantages and disadvantages, providing different opportunities. Among these models: Non-Human Primate Models: These models have the closest physiological resemblance to humans but are often challenging to use due to cost and ethical concerns. Dog and Pig Models: These species pose similar problems in terms of cost and long-life cycles.

Non-Mammalian Models: Non-mammalian models may not be preferred due to their diverse physiological features, despite offering opportunities in terms of life cycle and cost. Rodent Models: Rodent models are the most commonly used models. Although pancreatic islet structures may not closely resemble those of humans, their cost-effectiveness, short life cycles, and demonstrated validity make them a top choice (50). Each of these animal models has its unique advantages and limitations, and the choice of model depends on specific research goals, budget, and ethical considerations. The ultimate goal with these models and species is to induce and study tissue and organ damage such as diabetic cardiomyopathy, nephropathy, neuropathy, and retinopathy, with the aim of advancing our scientific knowledge on the subject (16).

Effect of animal species and age on experimental success in different models In order to evaluate the validity and clinical implications of the data obtained in diabetes models, the age, sex, species and physiological characteristics of the animals used and the induction method of the model are of great importance. For example, while animal age affects the response to insulin secretion in streptozotocin application, alloxan sensitivity may also vary among species. In addition, environmental factors (e.g. diet, housing conditions and stress level) directly affect metabolic responses. Therefore, it is important for researchers to evaluate these variables comparatively when choosing a model. A comparative table summarizing some basic variables related to age and species in the most commonly used diabetes models is presented in Table.2.

Understanding pathophysiology of diabetic complications for model selection Diabetes is a multisystem disorder that leads to serious organ damage in the long term. Chronic hyperglycemia triggers oxidative stress, inflammation and glycation processes at the cellular level, forming the basis for both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, peripheral artery disease) complications. Hyperglycemia increases the production of reactive oxygen species (ROS) within the cell, leading to mitochondrial dysfunction (51). This triggers cellular damage and apoptosis processes. At the same time, the formation of advanced glycation end products (AGEs) disrupts the function of protein and lipid structures; AGE-RAGE (receptor for advanced glycation end products) interaction activates proinflammatory signaling pathways (52). Protein

Table 2. Effect of animal species and age on model success in the most commonly used experimental diabetes models.

Model	Animal Type	Age (weeks)	Administration Method	Age-Related Effects
STZ (Type 1 DM)	Rat, Mouse	4–6 wks (juvenile): High sensitivity 8–12 wks (young adult): Stable glucose response	i.p./i.v. single dose (45–65 mg/kg)	Severe β-cell destruction in 4–6 wk animals, but mortality may increase. 8–12 wk animals provide a more stable model.
Alloxan (Type 1 DM)	Rabbit, Rat	6–8 wks: Maximum oxidative stress response	i.v. or i.p. injection	Juvenile animals have lower antioxidant defense, increasing sensitivity to alloxan.
HFD + STZ (Type 2 DM)	Mouse, Rat	HFD started at 4 wks; STZ at 8–12 wks (30–35 mg/kg)	Diet + low-dose STZ	Starting HFD at 4 wks facilitates insulin resistance development; low-dose STZ in adults causes partial β-cell damage.

kinase C (PKC) activation contributes to processes such as endothelial dysfunction, increased vascular permeability, and angiogenesis (53). Activation of the polyol pathway causes osmotic stress within the cell, causing damage especially, to nerve and kidney cells (54). The hexosamine pathway also tries to process excess glucose through an alternative pathway, affecting transcription factors and increasing fibrosis and inflammation mechanisms (55).

In microvascular complications, these processes manifest themselves with pathologies specific to each organ systems. In retinopathy, thickening of the retinal capillaries, pericyte loss and neovascularization develop (56). Whereas in nephropathy, glomerular basement membrane thickening, mesangial expansion and podocyte damage are seen. In neuropathy, slowing of nerve conduction, axonal degeneration and microvascular perfusion disorders are prominent (57). Macrovascular complications are characterized by the acceleration of the atherosclerosis process (58). The combination of hyperglycemia, dyslipidemia, low-grade chronic inflammation and endothelial dysfunction results in deterioration of the arterial wall structure and accelerates plaque formation (59). Modeling these multifaceted pathophysiological processes is important to more accurately investigate complication-specific targets in experimental systems.

Experimental model selection according to complication

Understanding the mechanisms underlying complications such as nephropathy, retinopathy, neuropathy, and cardiovascular dysfunction is critical for disease management and development of treatment strategies. However, not every experimental diabetes model can accurately reflect the development of every complication. For example, the most commonly used method for diabetic nephropathy models is the application of manipulations that increase renal stress, such as puromycin aminonucleoside (PAN) or unilateral nephrectomy, in addition to STZ-induced hyperglycemia (60). In diabetic retinopathy studies, retinal microvascular changes are observed as a result of long-term hyperglycemia induced by STZ, while this process can be accelerated by agents that increase oxidative stress. For diabetic neuropathy, chronic STZ models or db/db mice with leptin receptor mutation are preferred in terms of slowing of peripheral nerve conduction, nerve fiber loss and development of thermal/mechanical hyperalgesia (61). Cardiovascular complications are studied through models that reveal both metabolic syndrome and cardiac dysfunction as a result of STZ administration combined with a high-fat diet (62). Each complication model shows variable sensitivity depending on the duration of hyperglycemia, age and species of the animal, and meticulous standardization of protocols is of great importance for translational validity. Therefore, suitable models for each complication are discussed separately below.

Studying Diabetes-Induced Complications in Animal Models

Kidney Damage Models

Diabetes affects various tissues, including the kidneys, due to the microvascular damage it causes. In an effort to prevent this damage, different natural substances are being tested in many research studies. One of these substances is quercetin. The effects of quercetin usage in animal models studying kidney damage have been evaluated in a meta-analysis. As inflammation and oxidative stress are known to increase under diabetes, quercetin's anti-inflammatory and antioxidant properties can be predicted as protective (63).

In addition to the approach of trying to prevent damage by providing natural or synthetic substances directly, there is a research approach that targets molecular pathways. Sirtuin-1 (SIRT-1) can be given as an example in this context. Overexpression of SIRT-1 has been reported in structures such as podocytes and renal tubular cells in animals with diabetes. The protective effects of SIRT-1 in diabetic nephropathy are among the research topics in the molecular field (64). Wenshen Jianpi Recipe (WSJPR), widely used in traditional Chinese medicine, is considered and used as beneficial for diabetic nephropathy. Cao and colleagues used this recipe in a diabetes model induced by STZ (60 mg/kg i.p.) in rats. WSJPR given at different doses for 8 weeks reduced urinary total protein, albumin, and urea nitrogen and led to improvements in glomerular hypertrophy and mesangial expansion. Additionally, the expression of nephrin and podocin mRNA was increased. The researchers suggested that WSJPR is beneficial in diabetes-induced kidney damage and could be considered

as an approach for the treatment of diabetic nephropathy (65).

Another study, based on traditional Chinese medicine, tested the Jiedu Tonlguo Baoshen formula (JTBF) for its protective effects against proteinuria and kidney damage induced by diabetes. In a rat diabetes model induced by a high-fat diet + STZ, blood and urine samples were provided with an automatic analysis device. JTBF was found to reduce 24-hour urinary protein excretion and increase the expression of podocin, nephrin, and WT-1 in podocytes. This suggests that podocyte damage was reduced with JTBF. Additionally, it was found that this formula changed the expression of proteins related to autophagy in podocytes and affected signaling pathways through proteins such as Akt and mTOR (66).

Retinopathy

One of the most significant complications of diabetes is diabetic retinopathy (DR). DR is one of the leading causes of non-trauma-related blindness worldwide. This condition can affect patients on a scale ranging from a decline in visual quality to total blindness, impacting millions of people. While rodents are most commonly used in modeling this pathological condition, other organisms like dogs and zebrafish can also be preferred. Each model has its advantages, and for directly modeling the pathophysiological development in humans, one model alone may not suffice (67). Animal models are crucial for understanding the pathogenesis of DR, providing insights into both proliferative and non-proliferative DR. Different DR models have been developed to examine these aspects. In animal models, these conditions can be induced by selecting genetically suitable animals or performing appropriate applications to trigger the disease (68).

In a study conducted on Wistar albino rats, animals that developed diabetes after a 55 mg/kg i.p. STZ application were subjected to experiments. Electroretinography, as well as Evans blue and dextran fluorescence retinal angiography, were performed at 1, 3, 6, and 9 months after this administration. Significant changes were observed in electroangiography in the diabetic groups. Furthermore, the observation of conditions such as vascularization, ischemic changes, increased vascular permeability, and vitreous neovascularization in diabetic rats suggests that this model may be a good one for modeling the pathology of diabetic retinopathy in humans and testing treatment options (69).

In another study related to DR, the effect of melatonin on VEGF, IL-6, TNF-alpha, and parameters related to apoptosis in rats was investigated. In a diabetes model triggered by STZ (60 mg/kg i.p.), melatonin was administered at a dose of 10 mg/kg for 20 days. The results showed that melatonin administration reduced the expression of VEGF, cytokines, and apoptosis. The authors evaluated this result as an indication that melatonin has the potential to improve adverse conditions related to DR (70).

Neuropathy

One of the significant long-term complications that diabetes can cause is neuropathy. This condition is the subject of various research studies that suggest that it can be attributed to not only the effects of elevated glucose but also different pathways involving insulin receptors on peripheral nerves and dyslipidemia (71). While different animal models successfully model various aspects of neuropathy observed in humans, they may not be sufficient in other aspects. For example, diabetes in cats is good for modeling advanced diabetic neuropathy in humans, but rodent models do not provide reliable results to reflect functional impairments observed in early stages in humans. However, it's worth noting that the use of STZ in inducing diabetes itself can be problematic as it has direct neurotoxic effects (72).

Depression

Similar to diabetes, depression is a disease that significantly affects the quality of life and should be taken into consideration. The increased prevalence of depression in individuals with diabetes necessitates the elucidation of the mechanisms linking these two conditions. In a model induced by STZ and accompanied by a high-fat diet, after 12 weeks, depression-like behaviors were observed in diabetic animals, as evidenced by their performance in a challenging swimming test. Researchers attributed these observations to the increased levels of cytokines such as IL-6 and TNF-alpha. The increase in these pro-inflammatory molecules, which is associated with the underlying inflammation in many diseases, appears to be linked to induced diabetes. In this model, researchers found that daily agmatine administration (10-20 mg/kg) reduced depression-like behaviors and inflammation markers examined in brain tissue (73).

Anxiety

Anxiety, like depression, is a topic frequently researched in experimental animals. Increases in anxiety-like behaviors, evaluated in setups such as the light-dark box, open field test, and elevated plus maze test, are used to assess whether animals develop anxiety following a pathology or administration. In STZ induced diabetes in rats, anxiety-like behaviors were increased in the elevated plus maze test, while melatonin reduced these behaviors (74).

Mice with diabetes induced by a single dose of STZ were treated with fluoxetine, a serotonin reuptake inhibitor. It was observed that anxiety-like behaviors decreased in different behavioral tests (elevated plus maze, open field, dark and light transition, Y maze). Additionally, it was noted that fluoxetine reduced the increased astrocyte activation associated with STZ. One possible reason for this effect is suggested to be the reduction of myelin basic protein loss in oligodendrocytes due to diabetes with fluoxetine (75).

Memory and Learning

Memory problems and Alzheimer's disease, which are among the most important health issues related to aging, significantly impact the quality of life and pose significant financial challenges in terms of caregiving. The higher prevalence of Alzheimer's disease in individuals with diabetes suggests that diabetes increases susceptibility to Alzheimer's disease in older individuals. There is growing evidence of similarities in the pathophysiology of both diseases in terms of cognitive impairment. Cognitive impairments triggered by diabetes also constitute a significant topic in behavioral

studies involving animals (76).

Accumulation of amyloid-beta (Aβ) and cerebrovascular inflammation, which are important changes in Alzheimer's disease, have been studied in an Alzheimer's mouse model. Researchers crossed transgenic Alzheimer's mice (APP23) with two different diabetic mice strains (ob/ob and NSY mice). The changes in metabolism and brain pathology provided insights into the role of vascular changes and insulin signaling function in the cognitive impairments observed in Alzheimer's disease (77).

The relationship between the brain and the gut is a research topic that has attracted increasing attention in recent years. In another study related to Alzheimer's disease, *Akkermansia muciniphila* (Akk) from the gut microbiota was administered via gavage to APP/PS1 mice for six months. The results showed that this intervention reduced diabetes-related parameters such as fasting blood sugar, improved intestinal barrier function, enhanced cognitive function as demonstrated in Y-maze tests, and reduced brain AB 40-42 levels. This approach represents an original way to address diabetes through microbiota intervention, beyond the direct application of a chemical substance, active ingredient, or extract (78).

Oxidative Stress

Oxidative stress is an important component in the pathogenesis of many diseases, is also important in diabetes. The effects of exercise or changes in diet towards healthier directions on reducing oxidative stress have been investigated in various studies. In a study that examined the effects of swimming exercise in C57BL/6 mice in which type 2 diabetes was induced, it was shown that diabetes increased oxidative stress in mice by elevating MDA and GSSG levels and that swimming exercise had a protective effect against this stress (79).

The nicotinamide-STZ model, which is a less common method of inducing diabetes, it was reported that crocin, one of the active ingredients of the saffron plant (*Crocus sativus*), restored the disrupted liver oxidant-antioxidant balance related to diabetes in rats and restored Total Antioxidant Capacity. Crocin also exhibited a similar protective effect in the kidneys (80).

Inflammation is often observed alongside oxidative stress, and it is also among the components of diabetes. In response to diabetes, proinflammatory cytokines such as IL-1B and IL-16 increase in tissues. One of these tissues is the brain tissue. Irisin molecules have been observed to reduce neuroinflammation in the mentioned mice and improve cognitive function based on behavioral test results (81).

Coagulation Disorders

In a study conducted to determine the potential protective effects of melatonin on hemostatic parameters in rats with diabetes induced by streptozotocin (40 mg/kg), 32 adult male healthy Wistar Albino rats were divided into four groups. After achieving the desired blood sugar levels for diabetes, melatonin (50 mg/kg i.p.) was administered for 8 weeks. Diabetic rats showed significantly increased platelet counts and fibrinogen levels. The administration of melatonin to diabetic rats partially improved these values, as well as PT and INR levels, indicating an improvement in the procoagulant state caused by diabetes (82).

Another study examining complications related to diabetes-induced coagulation used a leaf aqueous extract of *Terminalia catappa* (400 and 800 mg/kg - 28 days) in rats where diabetes was induced with STZ and a high-fat diet. The results suggested that the plant extract increased coagulation and bleeding time in diabetic rats and, due to its anticoagulant properties, it could be beneficial in reducing hematological problems related to diabetes (83).

Diabetic Foot Ulcer Model

Diabetes, when combined with neuropathic conditions, can lead to tissue damage ranging from ulcers to tissue necrosis. Innovative approaches such as 3D skin models, angiogenesis models, and skin bioprinting are being explored in research on this topic. However, traditional animal models are still being used (84).

Different parameters of this topic, from the development of tissue damage to the healing process, are also tested in animal studies. While rodents are more commonly used in these studies, larger animals like pigs can also be subjects of research. Although pigs have some model advantages in terms of nutrition and physiology, parameters such as cost, skin structure, and the long duration required for healing often lead to the preference for rats. Zucker Diabetic Sprague-Dawley rats are recommended models for investigating diabetic ulcers (85).

CONCLUSION

This review summarizes the pathophysiology of Diabetes Mellitus (DM), treatment strategies, and the link between experimental DM models and diabetic complications. Choosing appropriate animal models is essential for studying complications, as Type 1 DM results from autoimmune beta cell destruction, while Type 2 DM involves insulin resistance and beta cell dysfunction. Models must align with human disease features, though species differences limit full replication. Rodents are widely used due to cost and accessibility, while rabbits and primates serve specific roles. Diabetes can be induced by genetic manipulation, surgery, diets, or chemicals like STZ and Alloxan. NOD mice and chemically induced models are common for Type 1 DM; ob/ob mice and high-fat diets are used for Type 2 DM.

This review emphasizes complications such as nephropathy, retinopathy, neuropathy, and cognitive deficits. Natural compounds have shown benefits in reducing kidney damage, oxidative stress, and inflammation. Psychological and cognitive impairments are also addressed, with some treatments improving memory and anxiety. Antioxidants and anti-inflammatory agents appear effective in mitigating complications.

In conclusion, selecting the right animal model is critical for understanding DM and developing targeted, effective treatments to enhance patient outcomes.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01849
Selcuk Med J 2025;41(2): 110-114

OPEN OLGU SUNUMU / CASE REPORT

Full Facial Resurfacing Followed by Enucleation in a Patient with Xeroderma Pigmentosum: A Case Report

Xeroderma Pigmentosum Tanılı Bir Hastada Tam Yüz Cilt Yenilemesi ve Enükleasyon: Olgu Sunumu

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ÖZET

Kseroderma Pigmentosum, DNA onarım mekanizmalarının bozukluğu ile karakterize nadir görülen otozomal resesif geçişli bir genetik hastalıktır. Bu hastalık, ultraviyole (UV) ışınlarına karşı aşırı hassasiyetle kendini gösterir ve genellikle çocukluk çağında başlar. UV kaynaklı DNA hasarının onarılamaması sonucu, bu bireylerde ciltte erken yaşta malign lezyonlar gelişir. Özellikle güneşe maruz kalan bölgelerde skuamöz hücreli karsinom, bazal hücreli karsinom ve malign melanom gibi cilt kanserleri sıkça görülür. Bu yazıda, 26 yaşında, Orta Doğulu kadın bir hastada ortaya çıkan Kseroderma Pigmentosum olgusu sunulmaktadır. Hasta, yüz bölgesinde tekrarlayan cilt tümörleri ile başvurmuş olup, bu lezyonlar hem estetik açıdan deformitelere hem de genel sağlık açısından riskler oluşturmuştur. Hastanın yaşam kalitesini artırmak amacıyla, kısmi kalınlıkta deri grefti kullanılarak tam yüz yeniden yüzeylendirme (resurfacing) işlemi uygulanmıştır. Uygulanan cerrahi müdahale, yeniden yüzeylendirilen ciltte yeni tümörlerin gelişmesini engellemeyi başarmıştır. Ancak, takip sürecinde hastanın sol göz küresinden dışa doğru büyüyen bir kitle gözlemlenmiştir. Yapılan değerlendirmede, bu kitlenin Kseroderma Pigmentosum hastalarında sıklıkla karşılaşılan agresif ve hızlı ilerleyen cilt tümörlerinin bir sonucu olduğu anlaşılmıştır. Görme fonksiyonlarını tehdit etmesi ve çevre dokulara yayılma riski nedeniyle, enükleasyon (göz küresinin çıkarılması) önerilmiştir. Bu olgu, Kseroderma Pigmentosum hastalarında yüzey yenileme işlemlerinin olumlu etkilerini gösterirken, aynı zamanda tümör gelişiminin agresif seyrine de dikkat çekmektedir. Erken tanı ve düzenli takip tedavi başarısını artıran temel unsurlardır. Bildiğimiz kadarıyla, hem yüz yenileme (resurfacing) hem de enükleasyonun aynı hastada uygulandığı nadir bir vakadır.

Anahtar Kelimeler: Xeroderma Pigmentosum,Enükleasyon,Yeniden yüzeylendirme,Skuamöz Hücreli Karsinom,Malign Melanom

ABSTRACT

Xeroderma Pigmentosum is a rare autosomal recessive genetic disorder that marked by defective DNA repair mechanisms. We present a unique case of Xeroderma Pigmentosum in a 26-year-old Middle Eastern female who exhibited recurrent skin tumors, leading to substantial cosmetic and health-related challenges. The decision to perform a facial resurfacing operation with partial thickness skin graft was made to address the multiple lesions on the face and to improve the patient's quality of life. The procedure was successful in preventing the development of new tumors on the resurfaced skin during the follow-up period. However, one year following the resurfacing operation the subsequent development of a mass protruding from the patient's left globe highlights the aggressive nature of tumors in patients with Xeroderma Pigmentosum. Enucleation was recommended to prevent further complications. To our knowledge, this is a rare case in which both facial resurfacing and enucleation were performed concurrently in a single patient.

Keywords: Xeroderma Pigmentosum, Enucleation, resurfacing, Squamous Cell Carcinoma, Malignant Melanoma,

Geliş Tarihi/Received: 14 April/Nisan 2025 **Kabul Tarihi/Accepted:** 19 June/Haziran 2025 **Yayın Tarihi/Published Online:** 27 June/Haziran 2025

INTRODUCTION

Xeroderma Pigmentosum is a rare autosomal recessive genetic disorder that is characterized by defective DNA repair mechanisms (1). The condition was first described in 1874 by dermatologist Moriz Kaposi, who reported four patients presenting with dry, thin, and wrinkled skin, irregular pigmentation, and the development of skin tumors. Over time, further case studies revealed a broader spectrum of symptoms, including progressive neurological degeneration in some patients. The clinical presentation of XP can vary widely—from isolated UV sensitivity and cutaneous lesions to more severe forms that include neurological deficit, dwarfism, gonadal hypoplasia, and intellectual disability (2).

Currently, there is no definitive treatment for Xeroderma Pigmentosum. Medical and surgical approaches aim to alleviate the symptoms of the disease, improve the quality of life, and eventually increase the survival rate of these miserable patients. Multi-disciplinary collaboration with dermatologists, plastic surgeons, neurologists, psychiatrists and ophthalmologists is

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Atıf yapmak için/ Cite this article as: Halbony H, Ceviz M, Dincgözoglu A, Bekerecioglu M. Full Facial Resurfacing Followed by Enucleation in a Patient with Xeroderma Pigmentosum: A Case Report. Selcuk Med J 2025;41(2): 110-114

Disclosure: *The author has no financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

essential to provide comprehensive care for these patients and to prevent the development of potentially life-threatening complications.

CASE

This case report is to describe a rare case of Xeroderma Pigmentosum in 26-year-old female patient presenting with recurrent skin tumors to the Department of Plastic Reconstructive and Aesthetic Surgery.

The patient developed her initial lesion at the age of seven, when she got diagnosed after being on a summer vacation to the beach. Afterwards the patient developed several lesions which were excised locally. Over the years, and with the wars in the middle eastern region, the patient had limited access to sun

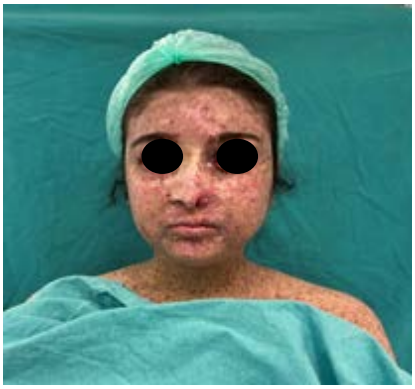

Figure 1. Shows the preoperative appearance of our patient

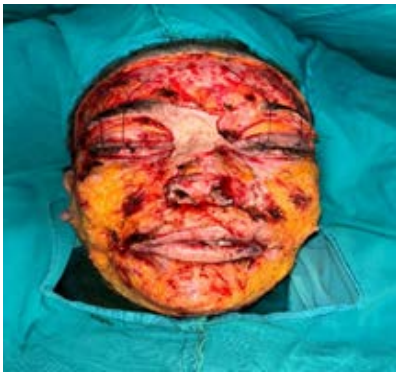

Figure 2. Shows the intraoperative appearance after skin excision

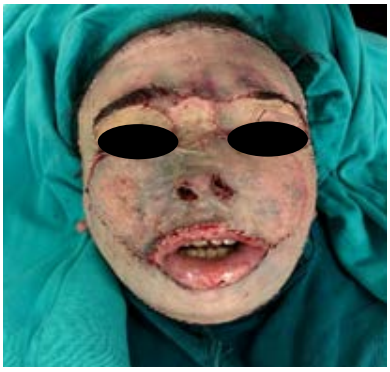

Figure 3. Shows the appearance after the graft was applied to the recipient area

Figure 4. Shows the excised skin

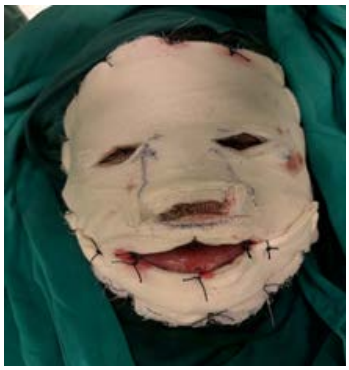

Figure 5. Shows the tie over dressing

Figure 6. Shows the preoperative appearance of the globe Squamous Cell Carcinoma

Figure 7. Shows the intraoperative appearance during the enucleation procedure

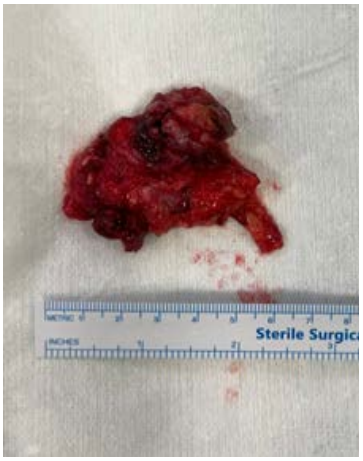

Figure 8. Shows the enucleated globe

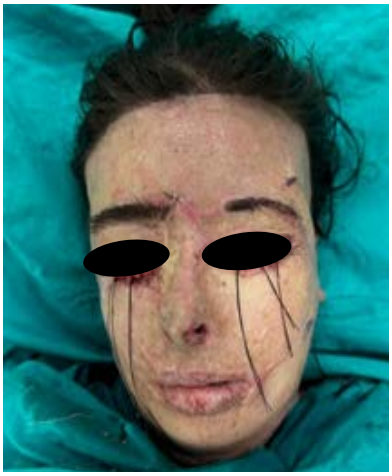

Figure 9. Shows the postoperative appearance after the enucleation procedure

Figure 10

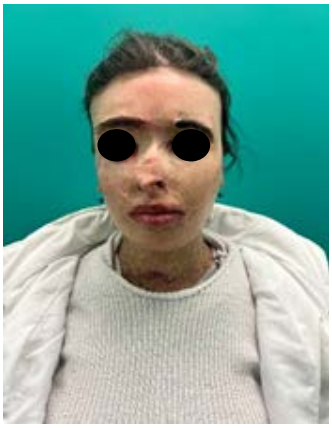

Figure 11

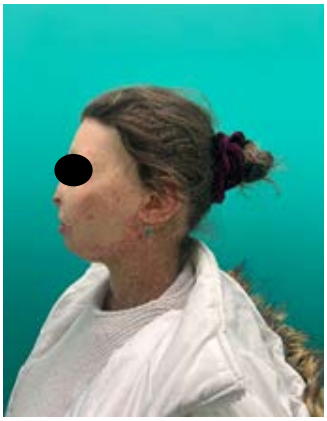

Figure 12

Figure 10,11,12. Shows the postoperative first month appearance after the enucleation procedure

Figure 13

Figure 14

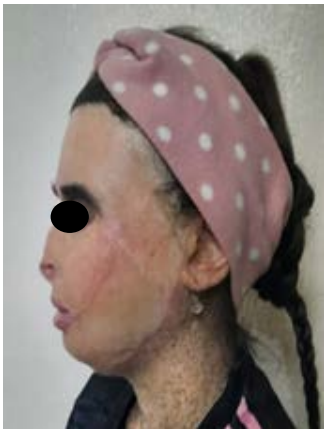

Figure 15

Figure 13,14,15. Show the postoperative second-year appearance after the resurfacing procedure

protection, the patient moved as a refugee to Kahramanmaras, Turkey, where she was followed up in our institution, later with the occurrence of the devastating 2023 earthquake in southeastern Turkey, the patient's condition even worsened.

The patient initially presented to our hospital eight years ago with a lesion on her dorsal nasal area which was locally excised by our team and the defect was closed by a full -thickness skin graft from her inguinal region. Afterward the patient presented 17 times for local excision of various tumors including Basal Cell Carcinoma, Squamous Cell Carcinoma, Malignant Melanoma, Keratoacanthoma,and Collagenoma, which were excised locally, and the defects were closed primarily. The patient's recurrent skin tumors posed significant cosmetic and health concerns. Due to the development of these recurrent lesions especially on the face of the patient except on the grafted area we applied 8 years ago, we decided to perform a facial resurfacing operation with split-thickness skin graft from the patient's abdominal area. As the patient dressed decently, her abdominal area was thought to be UV- protected Fig.1 shows the preoperative appearance of our patient. The patient and her family were notified about the advantages and possible complications of this procedure, and they accepted the procedure. Our operation was done with respect to the aesthetic facial subunits preserving the periorbital skin, the previously grafted area and the lips of the patient fig.2,3. The procedure was done, and the excised full-face skin was sent for pathological examination fig. 4. Postoperatively the patient was followed-up with tie-over dressing using paraffine mesh Fig.5, and after wounds healed uneventfully, the patient was advised to perform massage using silicone-based anti-scar jells to improve the cosmetic outcome fig.6 shows the postoperative 1- year result.

After performing the procedure, the patient did not develop any malignant tumors in her resurfaced skin. However, one year later she presented with a mass protruding from her left globe figure 6. Enucleation procedure was recommended to the patient, and she accepted the procedure with no hesitation. The globe along with the lacrimal gland were sent to pathological examination fig.8 which revealed minimal invasive Squamous Cell Carcinoma, and the lacrimal gland was tumor free. The postoperative period was uneventful, and the patient got discharged on the third postoperative day Fig.9. Fig.10 ,11 and 12 show the postoperative first month appearance of the patient. Fig,13,14 and 15 show the postoperative second year appearance after the initial resurfacing procedure.

DISCUSSION

Xeroderma Pigmentosum (XP) is a rare autosomal recessive genetic disorder caused by defects in the DNA nucleotide excision repair pathway, resulting in an impaired ability to repair UV-induced DNA damage. Clinical manifestations of Xeroderma Pigmentosum (XP) generally appear in early childhood, with key signs including freckling before the age of two and severe sunburn after even minimal exposure to sunlight. Individuals with XP face a markedly elevated risk of developing skin cancers at an unusually young age. Non-melanoma skin cancers often arise around the age of nine, while melanoma tends to appear by the early twenties. In our case the patient developed her first malignant melanoma at the age of 22 which was invasive type superficial spreading subtype of on the dorsal aspect of her right hand. In addition, individuals with Xeroderma Pigmentosum often experience premature skin aging, characterized by symptoms such as thinning, dryness, telangiectasia, and uneven pigmentation (2). In addition to the autosomal recessive version of XP a dominant version has also been reported in a Scottish female with a milder clinical course (3).

Currently there is no definitive treatment for Xeroderma Pigmentosum. Genetic counseling and prenatal diagnosis are essential for preventing the occurrence of the disease. In our case the patient was the only affected member of her family, and she did not have a family history of such condition. Several treatments have demonstrated a reduction in the severity of the course of the disease including less invasive treatments as , topical 5-fluorouracil, oral retinoids, chemical peeling, dermabrasion in addition to surgical treatment by simple excision, sub-total facial excision and resurfacing by composite tissue allotransplantation, full thickness and split thickness skin grafts(3,4,5,6) . Grafts are typically harvested from sun-protected areas of the body, such as the abdomen, thighs, and buttocks, which are presumed to be the least exposed to sunlight. Full-thickness skin grafts are considered cosmetically superior to split-thickness grafts due to their lower tendency for secondary contraction, as well as better-preserved pigmentation, sebaceous, and sweat glands in the recipient area. However, split-thickness grafts offer an advantage in terms of allowing easier surveillance for the recurrence of skin cancer in the grafted site. (7).

Ocular manifestations are present in approximately 40–100% of individuals with Xeroderma Pigmentosum (XP), ranging from benign degenerative changes to more severe ocular and periocular malignancies. The most observed malignant tumor affecting the ocular surface is ocular surface squamous neoplasia (OSSN). Risk factors for the development of OSSN include prolonged exposure to ultraviolet (UV) radiation, immunosuppression (such as in HIV infection or chronic corticosteroid use), XP, infection with Human Papillomavirus (HPV), heavy tobacco use, male gender, and advanced age. Diagnosis is usually clinically with definitive diagnosis made with a biopsy (8,9,10). In our case the patient carried two of the risk factors above where in addition to being a XP patient, she had a history of chronic use of ophthalmic steroids drops.

Conclusion

Xeroderma Pigmentosum (XP) is a rare autosomal recessive disorder characterized by defective DNA repair mechanisms, particularly in response to ultraviolet (UV) light-induced damage. Clinically, the condition manifests as severe hypersensitivity to UV radiation, with involvement of the ocular system and, in some cases, progressive neurological deterioration. Given the absence of a definitive cure, management is predominantly focused on conservative strategies, with strict UV protection being the cornerstone of

care to minimize the risk of skin and ocular complications (11). The case presented underscores the profound impact of Xeroderma Pigmentosum on both the physical and psychological well-being of patients, especially in the context of recurrent and potentially life-threatening skin malignancies and especially taking into consideration the gender of our patient. Despite the challenges posed by the disease, early intervention, rigorous UV protection, and advanced techniques such as skin resurfacing surgery can significantly improve both cosmetic outcomes and the patient's overall quality of life. The successful management of this patient highlights the necessity of a multidisciplinary approach, involving dermatological screening, surgical intervention, and psychological support, to address both the medical and emotional needs of individuals with XP. Continuous surveillance and preventive care are critical in reducing the risks associated with this disorder and improving patient outcomes.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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Patient consent permission: *We have a signed copy of the form of the patient consent permission in this case report.*

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