



Harran Üniversitesi Tıp Fakültesi Dergisi

Journal of Harran University Medical Faculty

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Journal of Harran University Medical Faculty

YAZARLARA AÇIKLAMA

Dergi Harran Üniversitesi Tıp Fakültesi'nin yayın organıdır. Dergimize yazı hazırlarken lütfen aşağıdaki açıklamaları okuyunuz. Harran Üniversitesi Tıp Fakültesi Dergisi tıp bilimine ve akademik çalışmalara katkısı olan, klinik ve deneysel çalışmaları, editöre mektuplar, klinik olgu bildirimlerini, teknik ve eğitici davetli derlemeleri, tıp konusundaki son gelişmeler ile orijinal görüntüleri, görüntülü hastalık tanımlama sorularını ve editöre mektupları yayınlar. Makale değerlendirme ve yayın sürecinde yazarlardan herhangi bir ücret talep edilmemektedir.

Yayına kabul edilme, en az iki hakem ve editöryal komite kararı ile alınır. Yayına kabul edilen yazıların her türlü yayın hakkı dergiye aittir. Bu hak özel düzenlenmiş yayın hakkı devir formu ile bütün yazarların imzası ile tespit edilir. Dergi yılda 3 kez yayınlanır. Derginin yayın dili Türkçe veya İngilizcedir. Türkçe yazılarda İngilizce özet, İngilizce yazılarda Türkçe özet zorunludur. Gönderilen yazılar daha önce herhangi bir dergide yayınlanmamış ve orijinal olmalıdır (Bilimsel kongrelerde sunulan sözlü bildiri ve posterler bildirme kaydı ile hariçtir). Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal vb.) yazarlara aittir. **Yazım Kurallarına uymayan ve intihal programıyla yapılan incelemede benzerlik oranı %25 üzerinde olan makaleler değerlendirmeye alınmamaktadır.**

YAZIM KURALLARI

Yayına gönderilen yazılar Microsoft Word programında yazılmalıdır. Yazı, şekil ve grafiklerin tamamı elektronik ortamda gönderilmelidir. **Kapak sayfası hariç yazının hiçbir yerinde çalışmanın yapıldığı kurum ve yazarların ismi geçmemelidir.**

Tüm yazılar aşağıdaki şekilde dizilmelidir.

1. Kapak Sayfası
2. Türkçe Özet
3. İngilizce Özet
4. Makale Metni
5. Açıklamalar
6. Kaynaklar
7. Tablolar
8. Şekiller ve resimler
9. Alt yazılar

Araştırma inceleme yazılarının makale kısmı (özet, referanslar, tablo, şekil ve alt yazılar hariç) toplam 4000 kelimeyi, özet kısmı 400 kelimeyi, referanslar 40'ı, tablo ve şekil sayısı 10'u geçmemelidir. Limitler aşağıdaki tabloda özetlenmiştir. Olgu bildirileri şu bölümlerden oluşmalıdır: Başlık, İngilizce başlık, Türkçe ve İngilizce özet, giriş, olgunun/olguların sunumu, tartışma ve kaynaklar. Olgu sunumları toplam 8 sayfayı geçmemelidir. Teknik ve tıp alanındaki gelişmelere ait yazılar ve orijinal konulara ait görüntü sunumları 2 sayfayı geçmemelidir.

Tip	Kelime limiti	Özet kelime limiti	Tablo ve şekil sayısı limiti	Referans limiti
Orijinal makale	4000*	400	10	40
Vaka sunumu	2000*	200	2	10
Editöre mektup	500		2	5
Görüntü sunumları	300		2	3
Derleme**	-	-	-	-

*Özet, referanslar, tablo, şekil ve alt yazılar hariç

**Herhangi bir limit uygulanmamaktadır.

YAZILARIN HAZIRLANMASI

Metinde sade ve anlaşılır bir yazım dili kullanılmalı, bilimsel yazım tarzı benimsenmeli ve gereksiz tekrarlardan kaçınılmalıdır. Yazı; iki satır aralıklı olarak, Times New Roman 12 punto ile yazılmalıdır. Sayfalar sağ alt köşesinde numaralandırılmalıdır.

Yazılar sisteme 2 dosya halinde yüklenmelidir.

1 –KAPAK SAYFASI

Yazının başlığı ve kısa başlığı kapak sayfasında yer almalıdır. Her iki başlık Türkçe ve İngilizce olarak yazılmalıdır. Yazının başlığı 100 karakteri, kısa başlığı ise 50 karakteri geçmemelidir. Yazıda çalışmaya katkısı olan tüm yazarların adları, soyadları, çalıştıkları kurumlar, e-posta adresleri ve [ORCID ID](#) numaraları açık olarak yazılmalıdır.

Çalışma daha önce herhangi bir kongrede sunulmuş ise kongre adı, zamanı (gün-ay-yıl ve kongre yeri) belirtilmelidir.

Çalışma lisansüstü tezlerden üretilmiş ise tarihi ve tez numarası (Ulusal Tez Merkezi) belirtilmelidir.

Başlık sayfasının en altına iletişim kurulacak yazarın adı, soyadı, açık adresi, posta kodu, telefon ve e-posta adresi yazılmalıdır.

2-TAM METİN

Değerlendirme sürecinde hakemler tarafından incelenecek olan tam metinler tek bir dosya olarak sisteme yüklenmelidir. Tam metin dosyası aşağıda belirtilen kısımlardan oluşturulmalı ve bu sıraya göre düzenlenmelidir.

a) Özetler

Yazının Başlığı; kısa, kolay anlaşılır ve yazının içeriğini tanımlar özellikte olmalıdır. Türkçe (Öz) ve İngilizce (Abstract) özetlerin başında Türkçe ve İngilizce başlık bulunmalıdır. Özet makaleyi yansıtacak nitelikte olmalı, önemli sonuçlar verilmeli ve bunların kısaca yorumu yapılmalıdır. Özetle açıklanmayan kısaltmalar kullanılmamalıdır. Özet, araştırma inceleme yazılarında 400, olgu sunumlarında 200 kelimeyi geçmemelidir.

Özet;

- Amaç/Background,
 - Materyal ve Metod/Materials and Methods,
 - Bulgular/Results ve
 - Sonuç/Conclusions bölümlerinden oluşmalıdır.
- Derleme ve olgu sunumu yazılarında bu bölümlere gerek yoktur.

Anahtar Kelimeler: Türkçe ve İngilizce özetlerin altında listelenmelidir. En az üç en fazla beş anahtar kelime yazılmalıdır. Kelimeler birbirlerinden virgül (,) ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)"e uygun olarak verilmelidir (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler Türkiye Bilim Terimleri'ne uygun olarak verilmelidir. (www.bilimterimleri.com).

Tüm Ölçümler metrik sisteme (Uluslararası Birimler Sistemi, SI) göre yazılmalıdır. Örnek: mg/kg, µg/kg, mL, mL/kg, mL/kg/h, mL/kg/min, L/min/, mmHg, vb. Ölçümler ve istatistiksel veriler, cümle başında olmadıkları sürece rakamla belirtilmelidir. Herhangi bir birimi ifade etmeyen dokuzdan küçük sayılar yazı ile yazılmalıdır. Metin içindeki kısaltmalar, ilk kullanıldıkları yerde parantez içinde açıklanmalıdır.

b) Ana Metin

Araştırma makalelerinde ana metin;

- Giriş,
- Materyal ve Metod,
- Bulgular ve
- Tartışma bölümlerinden oluşmalıdır.

Giriş: Konuyu ve çalışmanın amacını açıklayacak bilgilere yer verilir.

Materyal ve Metod: 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.

Bulgular: Elde edilen veriler istatistiksel sonuçları ile beraber verilmelidir.

Tartışma: Çalışmanın sonuçları literatür verileri ile karşılaştırılarak değerlendirilmelidir.

Tüm yazımlar Türkçe yazım kurallarına uymalı, noktalama işaretlerine uygun olmalıdır. Kısaltmalardan mümkün olduğunca kaçınılmalı, eğer kısaltma kullanılacaksa ilk geçtiği yerde parantez içerisinde açıklanmalıdır. Kaynaklar, şekil, tablo ve resimler yazı içerisinde geçiş sırasına göre numaralandırılmalıdır.

c) Kaynaklar

Kaynaklar iki satır aralıklı olarak yazılmalıdır. Kaynak numaraları cümle sonunda noktadan önce () içinde verilmelidir. Birden fazla kaynak numarası veriliyorsa arasına “,” ikiden daha fazla ardışık kaynak numarası

veriliyor ise rakamları arasına “-” konmalıdır [ör. (1,2), (1-3) gibi]. Kaynak olarak dergi kullanılıyorsa: yıl, cilt, sayı, başlangıç ve bitiş sayfaları verilir. Kaynak olarak kitap kullanılıyorsa: sadece yıl, başlangıç ve bitiş sayfaları verilir. Kaynaklarda yazarların soyadları ile adlarının baş harfleri yazılmalıdır. Kaynaklarda yazar sayısı 6’dan fazla ise ilk 6 yazarın ismi yazılır ve sonrasındaki yazarların isimleri yerine İngilizce kaynaklarda “et al.”, Türkçe kaynaklarda “ve ark.” yazılır. Dergi isimleri Index Medicus’a göre kısaltılmalıdır. Kaynak yazılma şekli aşağıdaki örnekler gibi olmalıdır. Kişisel görüşler ve yayınlanmamış yazılar kaynak olarak gösterilmemelidir.

Metin içi ve metin sonu kaynak gösterimi için National Library of Medicine (NLM) stili (https://www.nlm.nih.gov/bsd/uniform_requirements.html) kullanılmalıdır.

Kaynaklar, yazının alındığı dilde ve aşağıdaki örneklerde görüldüğü şekilde düzenlenmelidir.

Dergilerdeki yazılar

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Türkiye’de yayımlanan ulusal dergilerin adları (indekslenenler hariç) tam olarak yazılmalıdır.

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Kitaplar;

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d) Açıklamalar

Yazar katkıları, çıkar çatışması, etik onam, varsa finansal kaynaklar, katkı sağlayan kurum, kuruluş ve kişiler bu bölümde belirtilmelidir.

Çıkar ilişkisi: Yazarların herhangi bir çıkar dayalı bir ilişkisi varsa bu açıklanmalıdır.

Teşekkür: Bu bölümde yazar olarak ismi geçmeyen ancak teşekkür edilmesi gereken kişiler veya kurumlar yer almalıdır.

e) Tablo, Şekil, Resim ve Grafikler

Tablolar ve şekiller (çizim, resim, grafik, mikrograf ve radiograf vb.) mutlaka isimlendirilmeli, metinde geçiş sırasına göre numaralandırılmalı ve metin içinde geçtiği yerlerde ilgili cümlelerin sonunda belirtilmelidir. Tablolar (Tablo 1., Tablo 2., ...) ve şekiller (Şekil 1., Şekil 2., ...) ardışık numara ile gösterilmeli ve Roma rakamları kullanılmamalıdır. Tablolar ve şekiller ana metin içinde kaynaklardan sonra ayrı bir sayfada verilmelidir. Tablo başlıkları tablonun üstünde, şekil başlıkları ise şeklin altında yer almalıdır. Tablo ve şekillerin açıklamaları ve alfabetik sıraya göre kısaltmaları altta yer almalıdır. Mikroskopik resimlerde büyütme oranı ve tekniği açıklanmalıdır. Resimler minimum 300 dots per inch (dpi) çözünürlüğünde ve net olmalıdır.

Yayın kurulu, yazının özünü değiştirmeden gerekli gördüğü değişiklikleri yapabilir.

YAYIN ETİĞİNE UYUM

Çalışmalar Helsinki Bildirgesi'ne (<https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/>) uygun olmalıdır. Yazıların araştırma ve yayın etiğine uygun olarak hazırlanması bir zorunluluktur. Yazarlar, insan ile ilgili tüm klinik araştırmalarda etik ilkeleri kabul ettiklerini, araştırmayı bu ilkelere uygun olarak yaptıklarını belirtmelidirler. Bunların ilgili olarak Gereç ve Yöntem bölümünde: klinik araştırmanın yapıldığı kurumdaki etik kuruldan prospektif ve retrospektif her çalışma için onay aldıklarını ve çalışmaya katılmış kişilerden veya bu kişilerin vasilerinden bilgilendirilmiş onam aldıklarını; hayvanlar ile ilgili deneysel çalışmalarda ise hayvan haklarını koruduklarını, ilgili deney hayvanları etik kurulundan onay aldıklarını belirtmek zorundadırlar. İnsan veya deney hayvanı üzerinde yapılan deneysel çalışmaların sonuçları ile ilgili olarak, dergiye yapılan başvuru esnasında, etik kurul onay belgesinin sunulması zorunludur. Yazar(lar), ticari bağlantı veya çalışma için maddi destek veren kurum varlığında; kullanılan ticari ürün, ilaç, firma vb. ile nasıl bir ilişkisi olduğunu sunum sayfasında Editöre bildirmelidir. Böyle bir durumun yokluğu da yine ayrı bir sayfada belirtilmelidir.

Etik kurul izni gerektiren çalışmalarda **Etik Kurul Onay Belgesinin** makale gönderim sürecinde sisteme yüklenmeli ve izinle ilgili bilgiler (kurul adı, tarih ve sayı no) Materyal ve Metod bölümünde ve ayrıca makalenin tartışma kısmından sonra açıklamalar bölümünde belirtilmelidir.

Etik Kurul izni gerektiren araştırmalar aşağıdaki gibidir.

- Anket, mülakat, odak grup çalışması, gözlem, deney, görüşme teknikleri kullanılarak katılımcılardan veri toplanmasını gerektiren nitel ya da nicel yaklaşımlarla yürütülen her türlü araştırmalar,
- İnsan ve hayvanların (materyal/veriler dahil) deneysel ya da diğer bilimsel amaçlarla kullanılması,
- İnsanlar üzerinde yapılan klinik araştırmalar,
- Hayvanlar üzerinde yapılan araştırmalar,
- Kişisel verilerin korunması kanunu gereğince retrospektif çalışmalar, (Arşiv taraması yapılan çalışmalarda istenildiğinde çalışmanın yapıldığı kurumdaki alınan izin belgesi de ayrıca sisteme yüklenmelidir).
- Olgu Sunumu- Serisinde hastanın açık kimliği paylaşılmamalı ve hastadan yayına izin verildiğine dair "Aydınlatılmış onam formu"nın alındığının belirtilmesi gerekmektedir.

HAKEM RAPORU SONRASINDA DEĞERLENDİRME

Yazarlar hakem raporunda belirtilen düzeltmede istenen konuları maddeler halinde bir cevap olarak kendilerine ayrılan cevap bölümüne yazmalıdırlar. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak) online olarak tekrar göndermelidirler.

SON KONTROL

1. Yayın Hakkı Devir Formu doldurulup imzalanmış,
2. Yazar Katkı Formu doldurulup imzalanmış,
3. Başlık ve Kısa Başlık Türkçe ve İngilizce olarak yazılmış,
4. Özet makalede 400, olgu sunumunda 200 kelimeyi aşmamış,
5. Türkçe ve İngilizce Anahtar Kelimeler (3-5 arası),
6. Kaynaklar National Library of Medicine (NLM) stili kurallarına uygun olarak yazılmış,
7. Tablo ve şekiller ana metnin sonunda numaralandırılarak verilmiş,
8. Etik kurul onayı ve "bilgilendirilmiş onam (rıza) formu" bilgisi eklenmiş,
9. Başka bir dergiye gönderilmemiş olduğu bilgisi verilmiş (editöre mektup),
10. İki satır aralıklı olarak, Times New Roman 12 punto ile yazılmış, sayfalar sağ alt köşesinde numaralandırılmış.

Instructions to Authors

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3. English Abstract
4. Main Text (Manuscript)
5. Explanations
6. References
7. Tables
8. Figures and pictures
9. Subtitles

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Type	Word limit	Abstract word limit	Limit on the number of tables and figures	Reference limit
Original article	4000*	400	10	40
Case report	2000*		2	10
Letter to the editor	500		2	5
Image presentations	300		2	3
Review **	-		-	-

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**No limit is applied.

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- Results
- Conclusions

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Introduction: Information to explain the subject and the purpose of the study is included.

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Supplement

Solca M. Acute pain management: Unmet needs and new advances in pain management. *Eur J Anaesthesiol* 2002;19 Suppl 25: S3-10.

Unpublished online article

Das RR, Singh M, Naik SS. Vitamin D as an adjunct to antibiotics for the treatment of acute childhood pneumonia. *Cochrane Database Syst Rev*. 2018 Jul 19;7:CD011597. doi: 10.1002/14651858.CD011597.pub2. [Epub ahead of print] Review.

Books

1) Krogman WM, Iscan MY. *The Human Skeleton in Forensic Medicine*. Second ed. Springfield Illinois: Charles Thomas Publisher, 1986:189-243.

2) Beard SD, Gaines PA, eds. *Vascular and Endovascular Surgery*. London: WB Saunders, 1998:319-29.

Chapter from a Book

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2) Friedman WF. The intrinsic properties of the developing heart. In: Sonneblick E, Leschi M, Friedman WF, eds. *Neonatal Heart Disease*. New York: Grunestratton, 1999:21-50.

Internet article

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. *Am J Nurs* [serial on the Internet] 2002 [cited 12 Aug 2002]. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Thesis

Gezer R: *Morphological Characteristics of Rugae Palatina and Individual Differences*. Master's Thesis, Şanlıurfa: Harran University Institute of Health Sciences, 2016.

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Author contributions, conflict of interest, ethical approval, financial resources (if any), contributing institutions, organizations and individuals should be indicated in this section.

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[A Bibliometric Analysis of 4269 Articles Published on Laparoscopic Sleeve Gastrectomy in Journals Indexed in Scientific Citation Index-Expanded Between 2000-2023](#)

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Sayfa: 415-417.

Inflammatory Markers, Impulsivity and Aggression in Fibromyalgia Patients

Fibromiyalji Hastalarında İnflamatuvar Belirteçler, Dürtüsellik ve Saldırganlık

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Abstract

Background: Fibromyalgia syndrome (FMS) is a chronic pain disorder associated with psychological symptoms, especially impulsivity and aggression. Although inflammation has recently been suggested to play a role in the etiopathogenesis of FMS, the relationship between this mechanism and psychological factors is unclear. The aim of this study was to examine the relationship between inflammatory markers and impulsivity and aggression in FMS patients.

Materials and Methods: This study included 73 FMS patients and 73 healthy controls matched for age, gender and body mass index (BMI). Impulsivity was assessed with the Barratt Impulsivity Scale-11 Short Form (BIS-11-SF) and aggression was assessed with the Buss-Perry Aggression Questionnaire (BPAQ). The BIS-11-SF measures motor, cognitive and planning impulsivity, while the BPAQ assesses physical aggression, verbal aggression, anger and hostile attitudes. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII) and aggregate systemic inflammation index (AISII) were analyzed and the relationship between inflammatory markers and psychological parameters was examined with Pearson correlation test.

Results: BIS-11-SF (58.6 ± 16.8 vs. 48 ± 15.4 , $p < 0.001$) and BPAQ (71.9 ± 18.4 vs. 55.9 ± 16.8 , $p < 0.001$) scores of FMS patients were significantly higher than the control group. However, no significant difference was found between the groups in terms of NLR, PLR, MLR, SII, SIRI and AISII levels ($p > 0.05$). In addition, no significant correlation was found between inflammatory markers and impulsivity and aggression scores.

Conclusions: The high levels of impulsivity and aggression in FMS patients suggest that these psychological factors may play an important role in the symptomatology of the disease. However, the fact that inflammatory markers are not associated with these psychological parameters suggests that hematologic indices may be insufficient to predict impulsivity and aggression. Further studies with larger patient groups may contribute to a more detailed evaluation of these relationships.

Keywords: Fibromyalgia, Inflammatory markers, Impulsivity, Aggression

Öz

Amaç: Fibromiyalji sendromu (FMS), psikolojik semptomlar, özellikle dürtüsellik ve agresyon ile ilişkili kronik bir ağrı bozukluğudur. Son yıllarda inflamasyonun FMS'nin etiopatogenezinde rol oynayabileceği öne sürülse de, bu mekanizmanın psikolojik faktörlerle ilişkisi belirsizdir. Bu çalışmanın amacı, FMS hastalarında inflamatuvar belirteçler ile dürtüsellik ve agresyon arasındaki ilişkiyi incelemektir.

Materyal ve Metod: Bu çalışmaya 73 FMS hastası ve yaş, cinsiyet ve vücut kitle indeksi (VKİ) açısından eşleştirilmiş 73 sağlıklı kontrol dahil edilmiştir. Dürtüsellik düzeyi Barratt Dürtüsellik Ölçeği-11 Kısa Formu (BIS-11-SF) ile; agresyon düzeyi ise Buss-Perry Agresyon Anketi (BPAQ) ile değerlendirilmiştir. BIS-11-SF, motor, bilişsel ve planlama dürtüsellikliğini ölçerken; BPAQ, fiziksel agresyon, sözel agresyon, öfke ve düşmanca tutumları değerlendirmektedir. Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), monosit-lenfosit oranı (MLR), sistemik inflamatuvar yanıt indeksi (SIRI), sistemik immün-inflamasyon indeksi (SII) ve agregat sistemik inflamasyon indeksi (AISII) analiz edilmiş ve inflamatuvar belirteçler ile psikolojik parametreler arasındaki ilişki Pearson korelasyon testi ile incelenmiştir.

Bulgular: FMS hastalarının BIS-11-SF ($58,6 \pm 16,8$ vs. $48 \pm 15,4$, $p < 0,001$) ve BPAQ ($71,9 \pm 18,4$ vs. $55,9 \pm 16,8$, $p < 0,001$) skorları kontrol grubuna göre anlamlı derecede yüksek bulunmuştur. Ancak, NLR, PLR, MLR, SII, SIRI ve AISII düzeyleri açısından gruplar arasında anlamlı bir fark saptanmamıştır ($p > 0,05$). Ayrıca, inflamatuvar belirteçler ile dürtüsellik ve agresyon skorları arasında anlamlı bir korelasyon bulunmamıştır.

Sonuç: FMS hastalarında dürtüsellik ve agresyon düzeylerinin yüksek bulunması, bu psikolojik faktörlerin hastalığın semptomatolojisinde önemli bir rol oynayabileceğini göstermektedir. Ancak, inflamatuvar belirteçlerin bu psikolojik parametrelerle ilişkili olmaması, hematolojik indekslerin dürtüsellik ve agresyonu öngörmede yetersiz kalabileceğini düşündürmektedir. Daha geniş hasta grupları ile yapılacak ileri çalışmalar, bu ilişkilerin daha ayrıntılı bir şekilde değerlendirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Fibromiyalji, İnflamatuvar belirteçler, Dürtüsellik, Saldırganlık

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Introduction

Fibromyalgia Syndrome (FMS) is a chronic, widespread pain condition characterized by diverse clinical symptoms, including diffuse musculoskeletal pain of unknown origin, fatigue, cognitive impairments, psychiatric symptoms, and sleep disturbances (1). Classified as one of the central sensitization syndromes, FMS lacks clear evidence of tissue damage or inflammation, yet findings of altered nociception are consistently reported (2). It is the third most common musculoskeletal disorder, following lumbar pain and osteoarthritis, predominantly affecting women, with a peak prevalence of 2–4% in the 50–60 age group (3).

FMS represents a significant public health concern. It has a significant impact on patients' quality of life and daily functioning (1). The etiology of FMS is multifactorial. It involves complex interactions of epigenetic, genetic, and environmental factors. Although abnormalities in the peripheral and central nervous systems and neuroendocrine dysfunctions have been linked to fibromyalgia symptoms, the underlying mechanisms remain incompletely understood (4). Research suggests that inflammation and neuroinflammation play roles in the etiopathogenesis of FMS (5,6), with studies showing elevated inflammatory marker levels in FMS patients compared to control groups (7).

Inflammatory markers, increasingly utilized in clinical practice, are derived from ratios and indices calculated based on complete blood count parameters. An elevated inflammatory response is characterized by increased neutrophil production and lymphocyte apoptosis, resulting in a higher neutrophil count and a reduced lymphocyte count. Consequently, the neutrophil-to-lymphocyte ratio (NLR) is considered an indicator of inflammation severity (8). Similarly, the platelet-to-lymphocyte ratio (PLR) and the monocyte-to-lymphocyte ratio (MLR), calculated using platelet, monocyte, and lymphocyte counts, have been reported as markers of inflammation severity (9). Additionally, composite indices such as the systemic inflammatory response index (SIRI), which incorporates neutrophils, monocytes, lymphocytes, and platelets; the systemic immune-inflammation index (SII); and aggregate index of systemic inflammation (AISI) are also recognized as valuable markers of systemic inflammation (10,11). Samanci R. et al., one of the studies examining the relationship between inflammation and FMS in the literature, found no difference in NLR between FMS patients and healthy controls (12). Akturk S. et al. found that NLR was significantly higher in FM patients (13). Al-Nimer MSM. et al. also reported increased NLR, PLR and FIQ scores in FM patients (14). Sariyildiz A. et al. found high SII, SIRI and AISI values in patients with FM compared to the control group (7).

Psychological and psychosomatic mechanisms are known to play a significant role in the development of FMS (3,15). Patients with FMS often experience various psychological challenges, such as maladaptive thought patterns and ineffective coping strategies, which are thought to contribute to an increased perception of pain (16).

The prevalence of psychiatric comorbidities in FMS patients is higher than in the general population and is commonly associated with conditions such as depression, anxiety, and posttraumatic stress disorder (17,18). Studies have also identified elevated levels of impulsivity and aggression in individuals with FMS (19). Impulsivity is defined as the inability to inhibit a voluntary response to a stimulus (20) and is characterized by behavioral tendencies such as attention deficits, superficial thinking, and a shortened response threshold. Impairments in working memory and deficits in executive functions have been implicated in its etiology (21). Aggression, defined as behavior intended to cause physical or psychological harm, has been linked to decreased serotonergic activity and increased dopaminergic activity (22). Despite these findings, there is a limited number of studies exploring the relationship between impulsivity, aggression, and fibromyalgia. A study conducted by Montoro et al (23) found that the neuroticism-psychoticism dimension was higher in the FMS group. Shelley-Tremblay et al (24) observed that FMS patients exhibited higher levels of depression, anger, and aggression compared to healthy participants. Baykara et al (25) found a correlation between disease severity and impulsivity in their study examining the relationship between FMS severity and impulsivity. It is known that inflammation in fibromyalgia is associated with psychological states (26). This raises the question of whether these psychogenic factors influence hematological and inflammatory parameters in FMS patients. Thus, this study aims to investigate the relationship between impulsivity and aggression levels, disease severity, and inflammatory markers in FMS.

Materials and Methods

This study was approved by the Firat University Faculty of Medicine Ethics Committee (date: March 21, 2024; no: 2024/05-43) and carried out in compliance with the Declaration of Helsinki's principles. All participants signed an informed consent form prior to participation in the study. The study initially included 80 female patients aged 18–60 years, with no known comorbidities, who were diagnosed with FMS based on the 2016 diagnostic criteria of the American College of Rheumatology (27). These patients were recruited from the Internal Medicine and Physical Medicine and Rehabilitation outpatient clinics at Elazığ Fethi Sekin City Hospital. Additionally, 75 healthy female volunteers with no known comorbidities, who visited the hospital for routine check-ups and were confirmed to have no pathologies based on the tests performed, served as the control group. However, 7 patients from the FMS group and 2 participants from the control group voluntarily withdrew from the study, leaving a total of 73 participants in the patient and control groups.

The severity of FMS was assessed using the Fibromyalgia Impact Questionnaire (FIQ) (28). Impulsivity levels were evaluated with the Barratt Impulsivity Scale (BIS-11) (29), while

aggression levels were measured using the Buss-Perry Aggression Questionnaire (BPAQ) (30).

Scales used in the study:

1) Sociodemographic and Clinical Data Form: This form, prepared by us, includes data such as demographic characteristics of individuals, disease duration, and blood values.

2) Fibromyalgia Impact Questionnaire (FIQ): It was developed by Burckhardt et al. (28). It is a 10-item scale that evaluates FM patients. Item 1 consists of 10 questions, each question is scored between 0-3. In items 2 and 3, the respondent is asked to mark a day for the determination of "being affected by disease" and "not being able to go to work". In the remaining 7 questions, the appropriate place on the Visual Equivalence Scale is marked. The score range is 0-100. The validity study was conducted by Sarmer et al. (31). Higher scores mean more impairment. The mean value is 50. Scores of 70 and above are considered as "severely affected patients".

3) Barratt Impulsivity Scale Short Form (BIS-11-SF): It consists of 30 items. It is divided into 3 subscales: attention, motor impulsivity and lack of planning. When it is evaluated; four different sub-scores are obtained as total score, non-planning, attention and motor impulsivity. Turkish validity study was conducted by Güleç et al. (32).

4) Buss-Perry Aggression Questionnaire (BPAQ): It is a 5-point scale and has a scoring between "Strongly Disagree" (1) and "Strongly Agree" (5). It consists of 29 items aiming to measure 4 different dimensions of aggression: physical aggression, verbal aggression, anger and hostility. There are 5 questions related to verbal aggression subscale, 9 questions related to physical aggression subscale, 8 questions related to hostility subscale and 7 questions related to anger subscale. Buss and Perry determined internal consistency coefficients for the subscales in their original study (33).

Blood Sampling and Inflammatory Marker Analysis: After at least eight hours of fasting, blood samples were taken from each participant between 8:00 and 9:00 AM. Hemograms were obtained from both the patient and control groups. 3 cc of EDTA-anticoagulated whole blood (Beckman Coulter DXH 800 automated hematology analyzer) were used for standard hemogram assays. The following parameters were recorded for all participants: hemoglobin (Hgb), white blood cell (WBC) count, neutrophil, lymphocyte, monocyte, and platelet values.

Additionally, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and aggregate index of systemic inflammation (AISI) were calculated. Neutrophils were divided by the number of lymphocytes to determine NLR, platelets by the number of lymphocytes to determine PLR, and monocytes by the number of lymphocytes to determine MLR. The formulas for SII, SIRI, and AISI were as follows:

$$SII = [(platelet \times neutrophil) / lymphocyte]$$

$$SIRI = [(neutrophil \times monocyte) / lymphocyte]$$

$$AISI = [(neutrophil \times platelet \times monocyte) / lymphocyte] (10,34).$$

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 22.0). The normal distribution of data was assessed using the Shapiro-Wilk test, kurtosis-skewness values, and histogram plots. Age, hemogram values, inflammation indices, and scale scores were compared using the Student's t-test. The hemogram values, inflammation indices, and scale scores of participants taking different medications were analyzed using the Kruskal-Wallis test. Scale scores of FMS patients on different medications and controls were evaluated by Kruskal-Wallis test. Bonferroni correction test was used as a post-hoc test. Pearson's correlation test was employed to examine relationships between variables. A *p*-value of less than 0.05 was considered statistically significant.

Results

The study included 73 female participants in case group and 73 female participants in the control group. The mean age of the case group was 42.4 ± 9.9 years, while the mean age of the control group was 44.8 ± 10.2 years ($p > 0.05$). There were no significant differences between groups in terms of body mass index (BMI), WBC, hemoglobin, platelet, lymphocyte, neutrophil, or monocyte counts ($p > 0.05$). Additionally, the groups were similar in terms of NLR, PLR, and MLR ratios ($p > 0.05$). There was no significant difference in SII, SIRI and AISI index.

The BIS-11-SF scale score for the case group was 58.6 ± 16.8 , while the score for the control group was 48 ± 15.4 ($p < 0.001$). Similarly, the BPAQ score for the case group was 71.9 ± 18.4 , compared to 55.9 ± 16.8 in the control group ($p < 0.001$). The FIQ scale score, administered only to the case group, was 59.2 ± 13.4 . A comparison of blood parameters, inflammation indices, and scale scores between the groups is presented in Table 1.

In the case group, 26 participants (35.6%) were drug-free, 26 (35.6%) were taking duloxetine, 12 (16.4%) were on gabapentin, and 9 (12.3%) were on pregabalin. When the blood values, inflammation indices, and scale scores of participants using different medications in the case group were compared, no significant differences were found ($p > 0.05$). While the BPAQ scores of the control group were significantly lower than all other FMS subgroups, no difference was observed in pairwise comparisons of FMS subgroups. The BIS-11-SF scale score of the control group was found to be significantly lower than that of the patients who did not use medication and who used duloxetine and gabapentin, while it was similar to that of the patients who used pregabalin. No difference was found between the BIS-11-SF scores of patients using medication. Test values for the comparisons are summarized in Table 2.

Table 1. Comparison of blood parameters, inflammation indices and scale scores of the groups

	Case group (n=73) Meas±Sd	Control group (n=73) Meas±Sd	p* value
Age (years)	42.44±9.99	44.85±10.21	0.161
BMI (kg/m ²)	24.66±2.63	24.76±2.45	0.821
WBC (10 ⁹ /L)	6.96±1.31	6.98±1.80	0.943
Hemoglobin (g/dL)	13.44±1.14	13.70±1.12	0.175
Platelets (10 ⁹ /L)	270.55±59.42	275.97±62.17	0.599
Lymphocyte (10 ⁹ /L)	2.37±0.59	2.50±0.91	0.342
Neutrophil (10 ⁹ /L)	3.90±0.99	3.70±1.14	0.286
Monocyte (10 ⁹ /L)	0.67±0.16	0.71±0.23	0.247
SII	455.81±143.29	431.84±165.14	0.362
SIRI	1.14±0.37	1.12±0.47	0.810
AISI	307.16±109.24	311.52±146.29	0.843
Neutrophil/Lymphocyte ratio	1.71±0.51	1.59±0.59	0.220
Platelet / Lymphocyte ratio	117.98±28.25	118.09±34.25	0.983
Monocyte / Lymphocyte ratio	0.295±0.074	0.299±0.076	0.699
BIS-11-SF	58.67±16.83	48.07±15.43	<0.001
BPAQ	71.95±18.45	55.91±16.86	<0.001

*Student t-testi

Sd: Standard deviation, BMI: Body mass index, WBC: White Blood Cell, SII: Systemic immune inflammation index, SIRI: Systemic inflammatory response index, AISI: aggregate index of systemic inflammation, BIS-11: Barrat impulsivity scale short form, Buss-Perry Aggression Questionnaire (BPAQ)

Table 2. Comparison of scale scores according to participants' medication use

		Median (Min – Max values)	p value
BPAQ	Control – medication-free FMS	62 (29 – 100) – 72.50 (35 – 100)	0.001
	Control - Duloxetine	62 (29 – 100) – 73 (36 – 24)	0.001
	Control - Gabapentin	62 (29 – 100) – 81.50 (42 – 112)	<0.001
	Control - Pregabalin	62 (29 – 100) – 74 (35 – 125)	0.019
	Control – medication-free FMS	50 (30 – 100) – 55.50 (30 – 102)	0.043
BIS-11-SF	Control - Duloxetine	50 (30 – 100) – 60 (30 – 100)	0.006
	Control - Gabapentin	50 (30 – 100) – 65 (40 – 105)	0.001
	Control - Pregabalin	50 (30 – 100) – 54 (30 – 100)	0.443

Kruskal-Wallis test

BIS-11-SF: Barrat impulsivity scale short form; BPAQ: Buss-Perry Aggression Questionnaire

The relationship between hemogram values, inflammation indices, and scale scores was assessed using Pearson's correlation test for all participants. A significant negative correlation was observed between BMI and SII ($r = -0.246$, $p = 0.003$), SIRI ($r = -0.176$, $p = 0.038$) and NLR ($r = -0.276$, $p = 0.001$). No significant correlation was found between age, BIS-11, BPAQ, and the indices. The correlations between

the variables are presented in Table 3.

In the case group, the relationship between hemogram values, inflammation indices, and scale scores was evaluated using Pearson's correlation test. No significant correlations were found between the variables. The data related to these test values are presented in Table 4.

Table 3. Correlation between variables

		SII	SIRI	AISI	NLR	PLR	MLR
Age	r	-0.095	-0.011	0.000	-0.106	0.001	0.121
	p	0.262	0.893	1.000	0.213	0.994	0.153
BMI	r	-0.246	-0.176	-0.144	-0.276	-0.147	-0.086
	p	0.003	0.038	0.090	0.001	0.083	0.314
BIS-11-SF	r	0.033	0.049	0.040	0.034	0.015	0.044
	p	0.701	0.569	0.639	0.693	0.860	0.608
BPAQ	r	0.045	0.076	0.016	0.094	-0.015	0.016
	p	0.595	0.373	0.855	0.267	0.857	0.848

Pearson correlation test

BMI: Body mass index, BIS-11-SF: Barrat impulsivity scale short form, BPAQ: Buss-Perry Aggression Questionnaire

Table 4. Correlations between the parameters of the case group

		SII	SIRI	AISI	NLR	PLR	MLR
Age	r	-0.125	-0.168	-0.148	-0.155	0.130	0.045
	p	0.293	0.155	0.213	0.190	0.274	0.708
BMI	r	-0.200	-0.111	-0.187	-0.043	0.053	0.045
	p	0.090	0.351	0.113	0.718	0.657	0.702
BIS-11 SF	r	-0.073	0.016	-0.076	-0.024	-0.176	-0.042
	p	0.538	0.891	0.522	0.841	0.137	0.725
BPAQ	r	-0.063	0.078	0.002	-0.056	-0.122	0.042
	p	0.597	0.513	0.988	0.638	0.302	0.722
FIQ	r	0.094	-0.053	0.090	-0.078	0.084	-0.038
	p	0.430	0.654	0.449	0.514	0.481	0.748

Pearson correlation test

BMI: Body mass index, BIS-11-SF: Barrat impulsivity scale short form, BPAQ: Buss-Perry Aggression Questionnaire, FIQ: Fibromyalgia Impact Questionnaire

Discussion

In this study, in which we evaluated impulsivity, aggression levels, and inflammatory parameters in women with fibromyalgia syndrome, inflammatory markers were found to be similar between fibromyalgia patients and the control group. However, impulsivity and aggression levels were significantly higher in fibromyalgia patients compared to healthy controls. When analyzing the degree to which inflammatory marker levels predicted impulsivity and aggression levels, no statistically significant relationship was found. To the best of our knowledge, this is the first study to investigate the relationship between inflammatory markers and impulsivity and aggression in FMS.

The role of increased inflammation in the etiopathogenesis of fibromyalgia is frequently discussed. Inflammatory substances are thought to contribute to pain formation by disrupting nociceptive transmission (35). Several studies have investigated the role of interleukins (ILs), important regulators of the inflammatory response, in FMS, yielding conflicting results. It has been suggested that proinflammatory ILs contribute to central and peripheral sensitization and cause pain from normally painless stimuli through N-methyl-D-aspartate (NMDA) receptor activation. In contrast, ILs with anti-inflammatory properties, such as IL-10, have been suggested to be decreased in FM patients (36-37). However, other studies have found no significant difference in IL levels between FM patients and healthy controls, and some have observed higher levels of IL-1 β , an anti-inflammatory cytokine (38). In a study investigating C-reactive protein (CRP), IL-6, and IL-8, erythrocyte sedimentation rate (ESR) levels in FM patients, CRP levels were found to be higher than in healthy controls, whereas IL-6, IL-8 and ESR levels were similar (39). Ratios and indices derived from complete blood count parameters, which have recently been examined for their diagnostic and prognostic value in various systemic diseases, have been studied to a limited extent in FMS. In a study by Samancı et al. (12), NLR levels were found to be similar between FM patients and healthy controls. Additionally, other studies have reported higher NLR and PLR levels in FM patients compared to controls (14). In our study, however, SII, SIRI, AISI, NLR, PLR and MLR levels

were similar between the patient and control groups. This finding supports the hypothesis that the role of inflammation in FM may be limited.

It has been determined that neurotic personality traits are common in patients diagnosed with FMS and are also associated with disease severity (40). Bucourt et al. (41) demonstrated in their study that increases in neuroticism and impulsivity were associated with higher levels of chronic pain. Margari F. et al. (41) found that impulsivity and neuroticism were linked to pain catastrophizing in FMS patients. In our study, FM patients exhibited significantly higher levels of impulsivity and aggression compared to the control group. These findings are consistent with the literature (18). This suggests that psychiatric symptoms such as impulsivity and aggression may play a significant role in the clinical presentation and symptomatology of FM. The increased impulsivity and aggression observed in FM patients may be related to altered neurotransmitter systems and limbic system dysfunction, which are implicated in the pathogenesis of FM. In particular, it has been reported that impulsivity, aggression, and pain may be linked through serotonergic and adrenergic systems in patients with chronic pain (42). When analyzing the correlation between the severity of FIQ and impulsivity and aggression levels in our study, no correlation was found, which is contrary to previous findings (41). This result may be related to the smaller size of our sample group. Furthermore, no relationship was observed between impulsivity and aggression levels and the NLR, PLR, MLR, SII, SIRI, and AISI levels in our patients. Yıldız et al. (43) found no relationship between impulsivity levels and NLR and PLR in patients with gambling disorder. The present results suggest that hematological parameters are inadequate in predicting impulsivity and aggression. To our knowledge, no other studies have investigated the relationship between impulsivity, aggression, and these parameters in FMS.

Conclusion

Impulsivity and aggression are higher in FM patients compared to the general population and may be related to the

etiopathogenesis and clinical course of the disease. Therefore, in addition to traditional diagnostic and therapeutic approaches, it is important to evaluate patients for impulsivity and aggression, and to consider appropriate therapeutic interventions. Inflammatory markers, which can be obtained through inexpensive and feasible complete blood count parameters, appear to be insufficient in predicting impulsivity and aggression. Future studies with larger patient populations are needed to clarify this issue. Understanding this relationship could enhance the foundation for both medical and psychiatric treatments for FMS patients, ultimately improving their quality of life.

Limitations

The limitations of the study include the cross-sectional design and the small sample size, which limited the participants to the female gender.

Ethical Approval: This study was approved by the Firat University Faculty of Medicine Ethics Committee (date: March 21, 2024; no: 2024/05-43) and carried out in compliance with the Declaration of Helsinki's principles.

Author Contributions:

Concept: M.F.U., E.Y.U.

Literature Review: M.F.U., E.Y.U.

Design : M.F.U., E.Y.U., S.Y.

Data acquisition: M.F.U., E.Y.U., S.Y.

Analysis and interpretation: M.F.U., E.Y.U., M.F.T.

Writing manuscript: M.F.U., E.Y.U., S.Y.

Critical revision of manuscript: M.F.U., E.Y.U., M.F.T.

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Gender Prediction Using Machine Learning Algorithms with Parameters Obtained from Calcaneus

Calcaneus'tan Elde Edilen Parametrelerle Makine Öğrenme Algoritmaları Kullanılarak Cinsiyet Tahmini

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Abstract

Background: Partial or total disruption of body integrity may occur in cases such as war, natural disasters and accidents. In such cases, the importance of the calcaneus bone, which has a hard and minimal structure, increases for identification. With this hypothesis, the aim of this study is to estimate gender from the calcaneus by utilising the current approach of machine learning (ML) algorithm.

Materials and Methods: The study was performed on X-Ray images of 200 female and 200 male subjects aged 18-65 years. Maximum length, facies articularis cuboidea height, maximum width, body width, minimum length, anteroposterior length of the calcaneus, posterior facet angle, anterior angle of the cuboid facet of the calcaneus, facet height, posterior facet length, anterior process length, calcaneus inclination angle, talocalcaneal angle, Böhler angle, Gissane angle and calcaneus tuber angle were measured. Then the obtained data were used in the input of ML algorithms.

Results: As a result, a highly accurate and reliable sex prediction rate between 0.86-0.91 was obtained with ML algorithms. In addition, it was found that the maximum width of the calcaneus parameter made the highest contribution to sex prediction among the parameters with SHapley Additive exPlanations.

Conclusions: As a result of our study, it was found that calcaneus with minimal and rigid structure provided high accuracy in terms of gender prediction using ML algorithms. In this respect, we think that this study will be a reference for forensic and morphometric studies.

Keywords: Calcaneus, X-Ray, Machine learning algorithms, Gender prediction

Öz

Amaç: Savaş, doğal afetler ve kazalar gibi durumlarda vücut bütünlüğünün kısmen veya tamamen bozulması söz konusu olabilir. Bu gibi durumlarda sert ve minimal bir yapıya sahip olan kalkaneus kemiğinin kimlik tespiti için önemi artmaktadır. Bu hipotezle, bu çalışmanın amacı makine öğrenmesi (ML) algoritmasının güncel yaklaşımını kullanarak calcaneus'tan cinsiyet tahmini yapmaktır.

Materyal ve Metod: Çalışma 18-65 yaş arası 200 kadın ve 200 erkek bireyin X-Ray görüntüleri üzerinde gerçekleştirildi. Maksimum uzunluk, facies articularis cuboidea yüksekliği, maksimum genişlik, gövde genişliği, minimum uzunluk, calcaneus'un ön-arka uzunluğu, arka faset açısı, calcaneus'un küboid fasetinin ön açısı, faset yüksekliği, arka faset uzunluğu, ön proses uzunluğu, calcaneus inklinasyon açısı, talokalkaneal açısı, Böhler açısı, Gissane açısı ve kalkaneus tuber açısı ölçüldü. Daha sonra elde edilen veriler ML algoritmalarının girişinde kullanıldı.

Bulgular: Sonuç olarak, ML algoritmaları ile 0,86-0,91 arasında oldukça doğru ve güvenilir bir cinsiyet tahmin oranı elde edilmiştir. Ayrıca SHapley Additive exPlanations ile parametreler arasında cinsiyet tahminine en yüksek katkıyı calcaneus'un maksimum genişliği parametresinin yaptığı tespit edildi.

Sonuç: Çalışmamız sonucunda minimal ve rijit yapıya sahip calcaneus'un ML algoritmaları kullanılarak cinsiyet tahmini açısından yüksek doğruluk sağladığı tespit edilmiştir. Bu açıdan bu çalışmanın adli ve morfometrik çalışmalar için referans olacağını düşünmekteyiz.

Anahtar Kelimeler: Calcaneus, X-Ray, Makine öğrenmesi algoritmaları, Cinsiyet tahmini

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Introduction

Identity is a term that refers to the totality of personal knowledge and characteristics that allow an individual to distinguish themselves from other individuals. It defines a person's uniqueness, social status, cultural context and self-expression. At the same time, it reflects the relationships and ties of an individual with the groups and communities to which he/she belongs. In forensic anthropology case studies, gender estimation is one of the basic parameters and should be given priority in the examination of skeletal remains (1).

Forensic anthropologists frequently use morphological and metric methods for sex estimation of skeletal remains. It has been demonstrated that measurements taken directly from bones show higher reliability and reproducibility, and therefore sex estimation in this way is more reliable than other methods. The determination of sex using skeletal remains poses a major challenge for forensic experts, especially when a human body part is present. In forensic cases where decomposed corpses and human remains are brought for examination by forensic investigation authorities, identification is of great importance. The examination of bones and their anatomical measurements not only provides information on their origin, but also on ancestry, sex, height and age at death. It therefore helps to establish the identity of an individual (1-3).

In the literature, sex prediction studies have been performed using many bones and different methods. Although long bones, pelvis and cranium are the most frequently used bones in sex prediction, sexual dimorphism studies have also been performed on well-preserved bones such as calcaneus because bone integrity is deformed too much

and good results have been obtained. When we look at the literature studies, calcaneus is seen as an important bone used in sex prediction (4-9).

Deoxyribonucleic acid (DNA) technologies, which are considered to be the most reliable method today, have many disadvantages due to accessibility and cost. For this reason, osteometry, which has a lower cost and easy access, is preferred for sex prediction. Machine learning (ML) is a specialised data analysis method that automates model building with machines that learn to use specific algorithms. In order to create a gender prediction model, classification is required and ML algorithms are one of the most commonly used methods for this classification. ML helps forensic experts, anatomists and anthropologists in many areas (10-14).

The aim of our study is to predict gender with high accuracy using ML algorithms with parameters obtained from calcaneus.

Materials and Methods

Population and Ethical Approvals

The study was performed with the decision of İzmir Bakırçay University Non-Interventional Local Ethics Committee dated 31.05.2023 and numbered 1064. Images were obtained randomly and retrospectively from the archive system of the Department of Radiology, İzmir Bakırçay University Çili Training and Research Hospital. The study was performed on direct radiographs (X-Rays) of 200 female and 200 male individuals aged 18-65 years. Verbal or written constant was not obtained from the patients to use the X-Ray. Exclusion criteria were pathology and/or surgical intervention in the calcaneus.

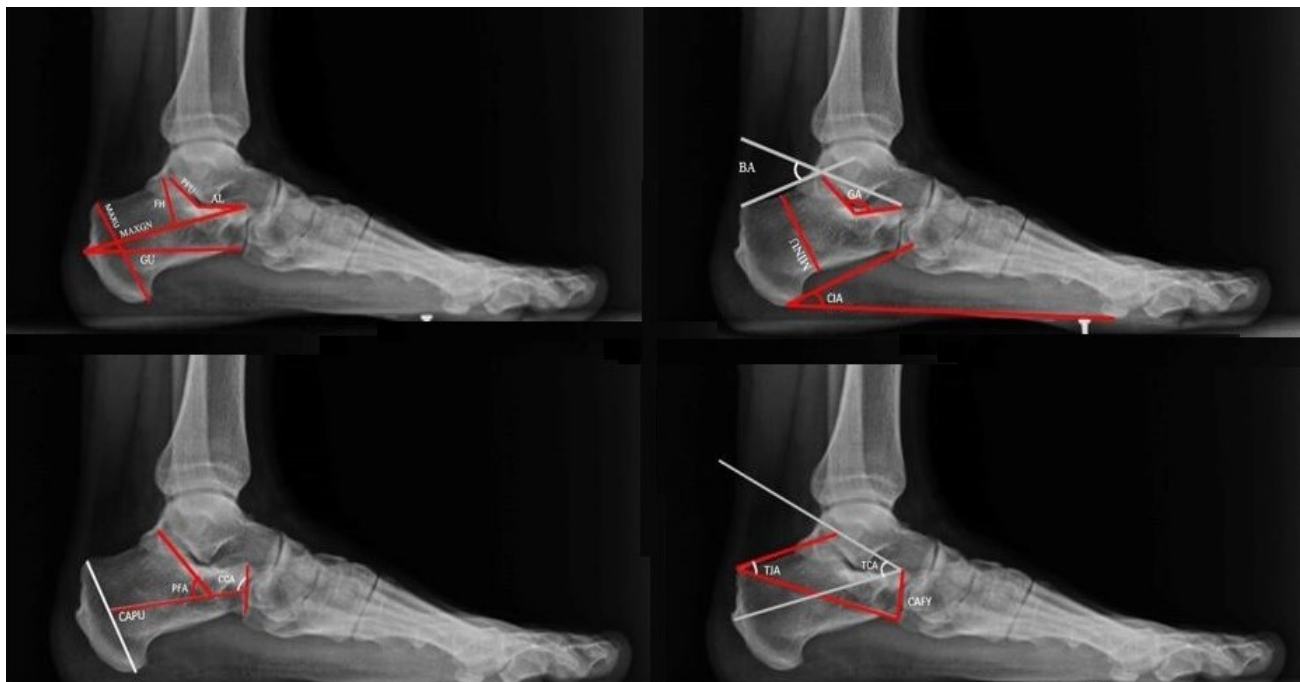


Figure 1. Demonstration of parameters

Measurement and Analysis Methodology

Images in Digital Imaging and Communications in Medicine (DICOM) format were transferred to Radiant DICOM Wiewer (64-bit version) and 16 parameters were measured using the measurement console of the programme. Parameters;

- 1) Maximum width (MAXGN),
- 2) Body length (GU),
- 3) Minimum calcaneus length (MINU),
- 4) Maximum calcaneus length (MAXU),
- 5) Calcaneus anterior facet height (CAFY),
- 6) Talocalcaneal angle (TCA),
- 7) Böhler angle (BA),
- 8) Gissane angle (GA),
- 9) Posterior facet angle (PFA),
- 10) Anteroposterior length of the calcaneus (CAPU),
- 11) Anterior angle of the cuboid facet of the calcaneus (CCA),
- 12) Facet height (FH),
- 13) Posterior facet length (PFU),
- 14) Processus anterior length (AL),
- 15) Calcaneus inclination angle (CIA),
- 16) Talo-tuber angle (TJA) (Figure 1) (7, 9, 15-17).

The obtained numerical data were analysed using ML algorithms. ML algorithms were performed using a personal computer with Monster Abra i5 operating system. Python 3.9 programming language and scikit-learn 1.1.1 framework were used for modelling. Modelling was performed with 20% of the data as test and 80% as training. Logistic regression (LR), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), decision tree (DT), random forest (RF), extra tree classifier (ETC), Gaussian Naïve Bayes (GaussianNB), k-nearest neighbours (k-NN) algorithms were used as ML models. Accuracy (Acc), Specificity (Spe), Sensitivity (Sen), F1 score (F1) values were used for the performance of the models. In addition, the contribution of the parameters to the overall result was revealed with the SHapley Additive exPlanations (SHAP) analyser of the RF algorithm.

$$Acc = \frac{TP}{TP + FN + FP + TN}$$

$$Sen = \frac{TP}{TP + FN}$$

$$Spe = \frac{TN}{TN + FP}$$

$$F1 = 2 \frac{Precision \times Recall}{Precision + Recall}$$

Equation 1. Performance Criteria (TP; True positive, TN; True negative, FP; False positive, FN; False negative).

Statistical Analysis

Statistical analysis of the data was performed using Minitab 17 and SPSS 21 package programs and $p < 0.05$ was considered statistically significant. Anderson Darling test was used as normality test. Mean $\pm$ standard deviation was used for descriptive statistics of normally distributed data and median (min-max) values were used for non-normally distributed data. For comparison in terms of gender, Two Sample T test was used for normally distributed data and Mann Whitney-U test was used for non-normally distributed data. The relationship between the parameters and the degree of relationship were determined by Pearson correlation test for normally distributed data and Spearman rho correlation test for non-normally distributed data. Basic statistical analyses and ROC analysis were used to evaluate the contribution of parameters in terms of gender.

Results

In this study performed on foot X-Ray images of 200 female and 200 male subjects, it was found that all parameters except MAXGN, CAFY, PFA, TJA and age were not normally distributed. Descriptive statistics and gender comparisons of the normally distributed parameters are shown in Table 1. All parameters had higher values in males than females. Two Simple T test showed that MAXGN and CAFY parameters were significant in terms of gender ($p < .005$).

Table 1. Statistical analysis of normally distributed parameters by Two Simple T test

Parameters	Gender	Mean $\pm$ standard deviation	p*
MAXGN	Male	83.94 $\pm$ 5.00	.000
	Female	74.58 $\pm$ 4.51	
CAFY	Male	26.90 $\pm$ 2.06	.000
	Female	24.16 $\pm$ 2.04	
PFA	Male	47.506 $\pm$ 3.961	.256
	Female	47.011 $\pm$ 4.707	
TJA	Male	39.342 $\pm$ 3.354	.064
	Female	38.699 $\pm$ 3.570	

(MAXGN: Maximum width, CAFY: Calcaneus anterior facet height, PFA: Posterior facet angle, TJA: Talo-tuber angle)

Descriptive statistics of non-normally distributed parameters are shown in Table 2. Mann Whitney U test showed that all non-normally distributed parameters except the CIA parameter were significant in terms of gender ($p < .005$).

According to Pearson correlation analysis, a moderate correlation was found between MAXGN and CAFY parameter ($p < .005$) (Table 3).

According to Spearman rho correlation analysis, a high correlation was found between MAXU and MINU and CAPU

and GU parameters ($p < .005$) (Table 4).

Table 2. Statistical analysis of non-normally distributed data by Mann Whitney U test

Parameters	Gender	Median (minimum-maximum)	p**
GU	Male	79.35 (68.10-93.60)	.000
	Female	70.50 (60.00-85.40)	
MINU	Male	41.25 (32.10-49.40)	.000
	Female	36.00 (29.80-44.70)	
MAXU	Male	48.25 (39.00-60.00)	.000
	Female	42.70 (33.80-52.10)	
TCA	Male	38.660 (26.000-50.200)	.028
	Female	37.850 (29.000-51.600)	
BA	Male	35.300 (25.000-47.700)	.000
	Female	39.300 (26.000-45.199)	
GA	Male	119.000 (109.500-132.400)	.030
	Female	118.050 (105.300-136.900)	
CAPU	Male	63.80 (50.70-78.40)	.000
	Female	58.30 (45.20-75.90)	
CCA	Male	100.000 (87.800-107.200)	.000
	Female	98.300 (86.200-114.200)	
FH	Male	28.30 (22.10-33.80)	.000
	Female	25.05 (20.70-31.40)	
PFU	Male	25.30 (18.10-32.20)	.000
	Female	22.70 (17.30-29.10)	
AL	Male	19.40 (14.80-26.30)	.000
	Female	17.85 (14.20-22.50)	
CIA	Male	45.043 (19.700-45.198)	.184
	Female	45.044 (22.000-45.198)	

(GU: Body length, MINU: Minimum calcaneus length, MAXU: Maximum calcaneus length, TCA: Talocalcaneal angle, BA: Böhler angle, GA: Gissane angle, CAPU: Calcaneus anteroposterior length, CCA: Anterior angle of the cuboid facet of the calcaneus, FH: Facet height, PFU: Posterior facet length, AL: Processus anterior length, CIA: Calcaneus inclination angle)

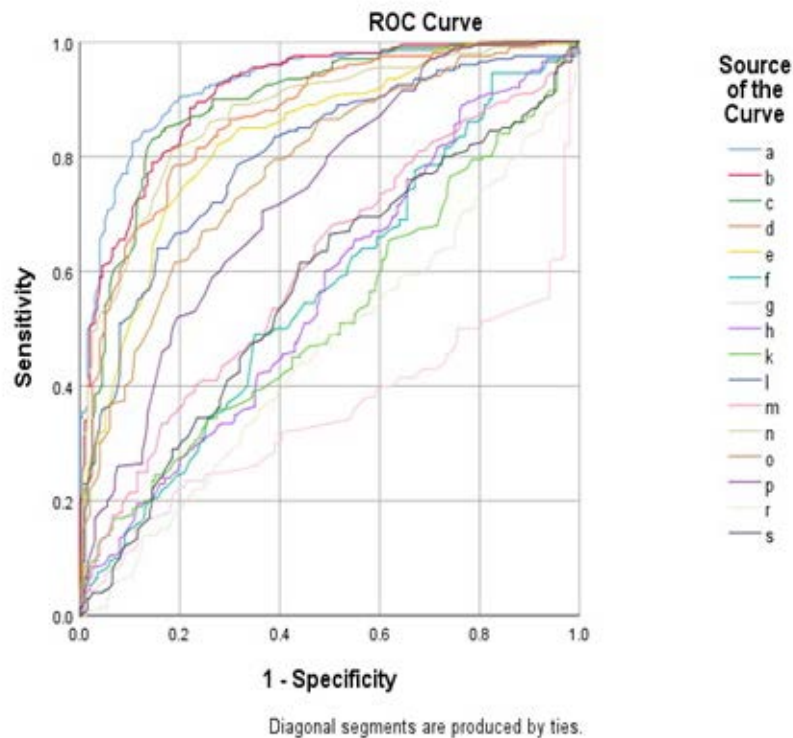


Figure 2. ROC curve (a: MAXGN, b: GU, c: MINU, d: MAXU, e: CAFY, f: TCA, g: BA, h: GA, k: PFA, l: CAPU, m: CCA, n: FH, o: PFU, p: AL, r: CIA, s: TJA)

Table 3. Pearson correlation test

Parameters	MAXGN	CAFY	PFA
CAFY	0.624 0.000		
PFA	0.031 0.541	-0.007 0.896	
TJA	-0.086 0.085	0.093 0.063	

(CAFY: Calcaneus anterior facet height, PFA: Posterior facet angle, TJA: Talo-tuber angle, MAXGN: Maximum width)

The effect of the parameters on the overall outcome was evaluated by ROC analysis and it was found that the MAXGN parameter made the highest contribution in terms of gender prediction (Figure 2, Table 5).

As a result of ML algorithms, the highest accuracy rate was 0.91 with QDA and GaussianNB algorithm (Table 6).

As a result of the ML algorithms, the highest accuracy rate was obtained in the QDA algorithm, which correctly

predicted all 44 male individuals and 29 of 36 female individuals in the test set, and in the GaussianNB algorithm, which correctly predicted 39 of 44 male individuals and 34 of 36 female individuals (Figure 3).

We evaluated the contribution of the parameters for gender prediction with the SHAP solver of the RF algorithm and found that the MAXGN parameter provided the highest contribution (Figure 4).

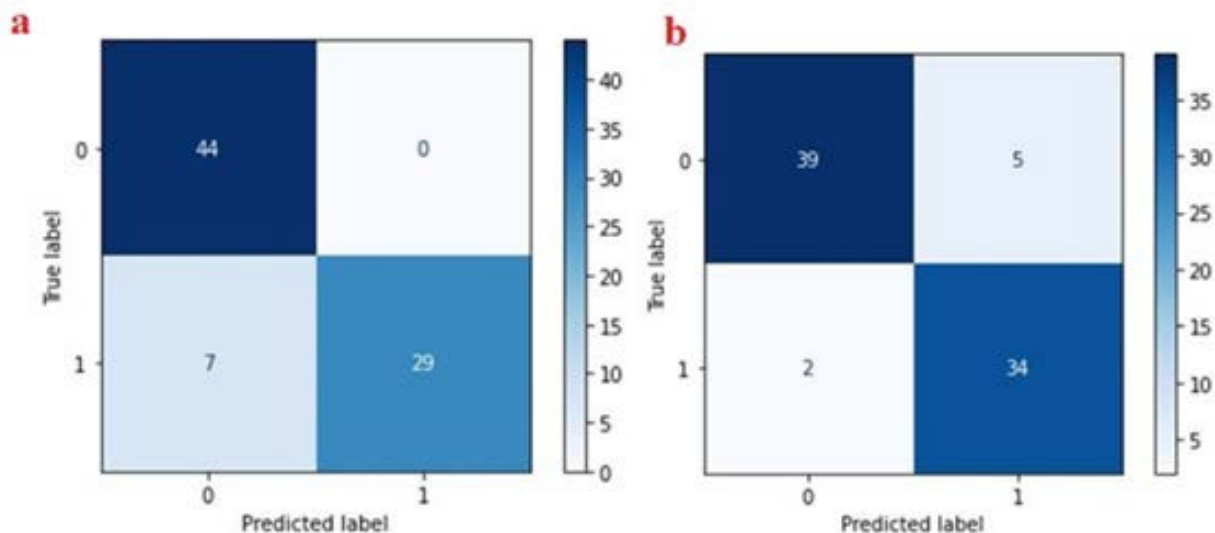
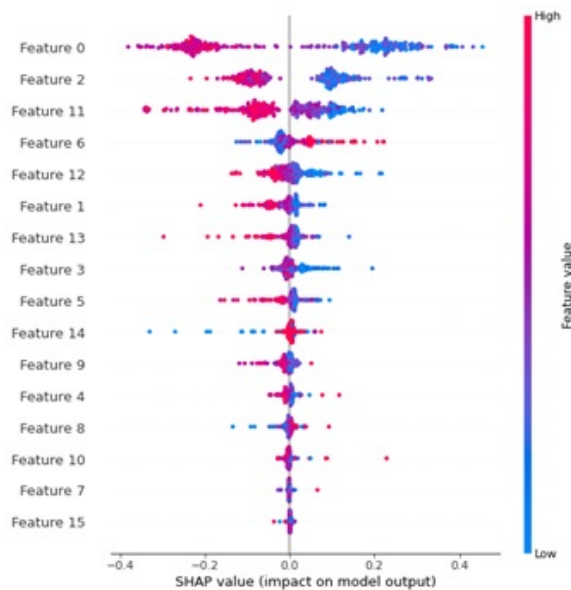
**Figure 3.** Confusion matrix table of the algorithms with the highest performance (a: QDA, b: GaussianNB)

Table 4. Spearman rho correlation analysis

Parameters		GU	MINU	MAXU	TCA	BA	GA	CAPU	CCA	FH	PFU	AL
CIA	MINU	0.662 0.000										
	MAXU	0.677 0.000	0.869 0.000									
	TCA	0.021 0.676	0.087 0.083	0.097 0.052								
	BA	-0.176 0.000	-0.194 0.000	-0.176 0.000	-0.003 0.953							
	GA	0.137 0.006	0.129 0.010	0.085 0.091	0.033 0.514	-0.031 0.532						
	CAPU	0.774 0.000	0.457 0.000	0.436 0.000	-0.015 0.766	-0.094 0.061	0.067 0.181					
	CCA	0.051 0.310	0.154 0.002	0.156 0.002	0.026 0.599	-0.071 0.158	0.080 0.110	0.058 0.246				
	FH	0.616 0.000	0.642 0.000	0.626 0.000	0.126 0.012	-0.202 0.000	0.084 0.093	0.478 0.000	0.155 0.002			
	PFU	0.457 0.000	0.446 0.000	0.434 0.000	0.028 0.573	-0.094 0.060	0.017 0.729	0.429 0.000	0.155 0.021	0.507 0.000		
	AL	0.481 0.000	0.336 0.000	0.367 0.000	0.065 0.198	-0.120 0.017	0.024 0.631	0.439 0.000	0.176 0.000	0.324 0.000	0.254 0.000	
	CIA	-0.029 0.559	-0.006 0.907	-0.008 0.869	-0.048 0.336	0.015 0.770	0.008 0.871	0.007 0.893	-0.002 0.970	-0.025 0.616	-0.063 0.210	-0.021 0.681

(MINU: Minimum calcaneus length, MAXU: Maximum calcaneus length, TCA: Talocalcaneal angle, BA: Böhler angle, GA: Gissane angle, CAPU: Anteroposterior length of calcaneus, CCA: Anterior angle of the cuboid facet of the calcaneus, FH: Facet height, PFU: Posterior facet length, AL: Processus anterior length, CIA: Calcaneus inclination angle, GU: Body length)

**Figure 4.** SHAP decoder of the RF algorithm

(Feature 0: MAXGN: Maximum width, 1: GU: Body length, 2: MINU: Minimum calcaneus length, 3: MAXU: Maximum calcaneus length, 4: CAFY: Calcaneus anterior facet height, 5: TCA: Talocalcaneal angle, 6: BA: Böhler angle, 7: GA: Gissane angle, 8: PFA: Posterior facet angle, 9: CAPU: Anteroposterior length of the calcaneus, 10: CCA: Anterior angle of the cuboid facet of the calcaneus, 11: FH: Facet height, 12: PFU: Posterior facet length, 13: AL: Processus anterior length, 14: CIA: Calcaneus inclination angle)

Table 5. ROC analysis performance values

(MAXGN: Maximum body length, GU: Body length, MINU: Minimum calcaneus length, MAXU: Maximum calcaneus length, CAFY: Calcaneus ante-

Parameters	AUC (95%)	Cutt off	p	Sen	Spe
MAXGN	0.927 (0.902-0.952)	7.895	0.000	85	85
GU	0.910 (0.882-0.938)	7.465	0.000	81.5	81.5
MINU	0.893 (0.861-0.924)	3.805	0.000	83.5	84
MAXU	0.870 (0.836-0.904)	4.535	0.000	78.5	79
CAFY	0.832 (0.792-0.871)	2.555	0.000	76.5	77
TCA	0.563 (0.507-0.619)	38.25	0.028	54.5	55
BA	0.352 (0.296-0.408)	36.55	0.000	40	39.5
GA	0.563 (0.507-0.619)	118.35	0.030	52.5	52.5
PFA	0.522 (0.465-0.579)	47.45	0.441	49	48
CAPU	0.801 (0.758-0.844)	6.095	0.000	72	72
CCA	0.608 (0.553-0.663)	98.85	0.000	57	58
FH	0.875 (0.841-0.909)	2.685	0.000	81	81.5
PFU	0.780 (0.735-0.824)	2.395	0.000	70.5	70.5
AL	0.728 (0.680-0.777)	1.865	0.000	64.5	67
CIA	0.462 (0.405-0.518)	45.04	0.185	49	49
TJA	0.570 (0.513-0.626)	38.95	0.016	58	57

rior facet height, TCA: Talocalcaneal angle, BA: Böhler angle, GA: Gissane angle, PFA: Posterior facet angle, CAPU: Anteroposterior length of the calcaneus, CCA: Anterior angle of the cuboid facet of the calcaneus, FH: Facet height, PFU: Posterior facet length, AL: Processus anterior length, CIA: Calcaneus inclination angle, TJA: Talo-tuber angle, Sen: Sensitivity, Spe: Specificity)

Table 6. Performance results of machine learning algorithms

Algorithms	Acc	Spe	Sen	F1
QDA	91	93	90	91
GaussianNB	91	91	92	91
RF	90	90	90	90
ETC	90	90	90	90
DT	89	89	89	89
LR	89	89	89	89
k-NN (k=5)	86	86	86	86

(QDA: Quadratic discriminant analysis, GaussianNB: Gaussian Naive Bayes classification, RF: Random forest, ETC: Extra-tree classification, DT: Decision tree, LR: Logistic regression, k-NN: K-Nearest neighbors regression, Acc: Accuracy, Spe: Specificity, Sen: Sensitivity)

Discussion

As a result of our study, an accuracy of up to 0.91 was obtained in gender estimation from calcaneus with ML algorithms, which is a current methodology. In addition, the MAXGN parameter was found to have the highest contribution to gender estimation.

When mass deaths occur in events such as accidents, natural disasters and war, identification is important for forensic medicine. In these cases, factors such as disruption of body integrity and decomposition make identification difficult. Another beneficial effect of identification in mass deaths is the importance of returning them to their families. The morphometry of bones provides information about the origin of individuals, as well as the cause of death, gender, height and age. In identification, gender must first be determined. Establishing gender reduces the likelihood of biological elements of identity. Sex estimation is vital in forensic anthropology applications to obtain critical information such as identification, age and ethnicity estimates (3, 18, 19).

To date, sexual dimorphism of the calcaneus has been studied in various populations such as Italy, Greece, South Africa and Colombia. In these studies, no sex difference was observed between races (20-23). In the literature, it was seen that there were studies conducted on X-Ray in the Turkish population. Torun and Çay found that calcaneal inclination angle was associated with foot morphology in both sexes in their study (15). In another evaluation in terms of gender, it was shown that there were significant differences in medial arch angle, lateral arch angle and foot length measurements in adults (16). As a result of our study, we obtained the highest accuracy rate of 0.91 among ML algorithms in terms of gender prediction from QDA and GaussianNB algorithms.

BA is an angle used as an important parameter in medicine performed on the calcaneus. This angle plays an important role in the evaluation of calcaneus fractures. BA was introduced by Dr. Lorenz Bohler in 1931 and he gave its value between 30°-35° in his paper (24). Seyahi et al. In their study for the Turkish population, they found BA to be 20°-46° ($p=0.198$), but they did not find any difference between genders in BA (25). In our study, BA was found between 25°-47° and was 35±10 in males and 39±7 in females. We found that this parameter ranked 4th in determining gender among the parameters we used.

GA is as important as BA in healing after surgical procedure applied to calcaneus fractures (26). Seyahi et al. 2009, they did not find a significant result between genders ($p=0.177$) (25). In this study, it was found between 105°-136° in both male and female gender. This value was 118±13° in women and 119±10° in men. In the SHAP analysis, this parameter ranked 14th in determining gender. When the studies conducted for sex prediction of the MAXGN parameter were examined, it was observed that this length was evaluated too much. Çekdemir et al. 2021,

which aimed to estimate gender from calcaneus, measured the MAXGN value as 85.65±5.16 mm in males and 76.74±4.21 mm in females. They found statistically significant differences between both sexes with these values ($p<0.001$) (17). Riepert et al. In their 1995 study on sex estimation from calcaneus in a Central European population, they measured the MAXGN value and found no significant difference between males and females (27). In our study, a value of 74.58±4.51 mm was found in women and 83.94±5 mm in men. The highest usefulness and accuracy in terms of both ML and cross-gender algorithms was achieved with the MAXGN measure. Çekdemir et al. 2021, in their study on gender estimation from calcaneus of 489 individuals, found the CAFY parameter as 28.83±2.13 mm in males and 25.45±1.99 mm in females and reported a significant difference between genders ($p<0.001$) (17). In our study, the results were 26.90±2.06 mm for males and 24.16±0.204 mm for females. In our study, an accuracy of 86-91% was found according to the ML algorithm, and this parameter ranks 12th in determining gender.

Riepert et al. reported the MINU parameter as 42.3±3.1 mm in men and 37.8±2.9 mm in women in their gender study on radiography (27). These data are similar to our data. Agoada conducted a study on X-Ray and cadaver in 2018 and measured the MAXU parameter as 50.50±5.68 mm on X-Ray and 49.75±4.31 mm on cadaver (28). This parameter ranked 9th in determining gender in our study. Kumar et al. found a value of 47.38±5.07 mm in men and 47.15±5.54 mm in women in their study and the findings were found to be insignificant similar to our study ($p=0.882$) (29).

In this retrospective study, it can be considered as a limitation that the body mass index of the patients, the type of footwear used, the calcaneus was not evaluated in three dimensions, and pediatric and octogenarian individuals were not included in the study.

When the literature is examined, to our knowledge, there is no study on gender estimation from calcaneus using ML algorithms. In this respect, we believe that our study will make great contributions to the literature.

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Ethical Approval: The study was performed with the decision of İzmir Bakırçay University Non-Interventional Local Ethics Committee dated 31.05.2023 and numbered 1064. The study was a retrospective study, conducted through the image archive and personal confidentiality was observed.

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Evaluation of Violence Against Women: A Retrospective Study

Kadınlara Yönelik Şiddet Vakalarının Değerlendirilmesi: Retrospektif Çalışma

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Abstract

Background: In this study, it was aimed to evaluate adult female cases admitted to the forensic medicine clinic and reported for violence against women.**Materials and Methods:** All female cases over the age of 18 years for whom a forensic report was issued in the forensic medicine clinic between 01.01.2011 and 31.12.2020 due to violence against women were included in the study. Groups were compared with parametric and non-parametric tests. A "p" value above 0.05 was accepted for statistical significance.**Results:** The mean age of the patients was 35.26±14.43 years; 56.9% (n:281) of the cases were married. Most of the cases (n:136, 31.6%) were exposed to violence by their spouses and 43.1% (n:213) were exposed to violence by intimate partners. The overwhelming proportion of the cases (93.9%) were exposed to blunt trauma and 40.9% of the cases (n:225) had multiple injuries. Only 2.2% (n:11) of the cases were reported as life-threatening. The mean injury severity score (ISS) was 1.16±0.54 and the mean new-injury severity score (NISS) was 2.26±3.26 in 444 patients with traumatic lesions. ISS and NISS scores were markedly higher in women who were exposed to violence by their intimate partners (p<0.01). Males with sharps or gunshot wounds had statistically higher ISS and NISS scores than those with blunt trauma (p<0.001).**Conclusions:** We believe that violence against women can be reduced by ensuring legal regulations against domestic violence, educating women about their rights in the face of violence and what to do for protection before and after violence, and increasing and supporting spouse therapy between spouses.**Keywords:** Women, Violence, Injury, Trauma Scores, Forensic medicine

Öz

Amaç: Bu çalışmada, adli tıp kliniğine başvuran ve kadına yönelik şiddet nedeniyle rapor düzenlenen erişkin kadın olguların değerlendirilmesi amaçlanmıştır.**Materyal ve Metod:** Adli tıp kliniğinde 01.01.2011 – 31.12.2020 yıllarında kadına yönelik şiddet nedeniyle adli rapor düzenlenen erişkin tüm kadın olgular çalışmaya dahil edildi. Gruplar parametrik ve non-parametrik testler ile karşılaştırılmıştır. İstatistiksel anlamlılık için p'nin 0,05 üzeri değer kabul edildi.**Bulgular:** Olguların yaş ortalaması 35,26±14,43'tür. Olguların %56,9'u (n:281) evliydi. Olguların en sık (n:136, %31,6) eşi tarafından şiddete maruz kalmış olup %43,1'i (n:213) yakın partner tarafından şiddete maruz kalmıştı. Olguların büyük çoğunluğu (%93,9) künt travmaya maruz kalmıştı. Olguların %40,9'u (n:225) birden fazla bölgeden yaralanmıştı. Olguların sadece %2,2'sinde ise (n:11) hayati tehlikeye neden olacağı yönünde rapor düzenlenmiştir. Travmatik lezyon tespit edilen 444 olgunun ortalama injury severity score (ISS) 1.16±0,54 ve new-injury severity score (NISS) ortalaması ise 2,26±3,26'dır. Yakın partneri tarafından şiddete maruz kalan kadınlarda da ISS ve NISS skorları anlamlı derecede daha yüksekti (p<0,01). Kesici delici alet veya ateşli silah ile yaralanan kadınların künt travmaya maruz kalan kadınlara göre ISS ve NISS skoru istatistiki olarak daha yüksekti (p<0,001).**Sonuç:** Kadına yönelik şiddetin engellenmesinde aile içi şiddete karşı yasal düzenlemelerin sağlanması, kadınların şiddet karşısında ne gibi hakları olduğu ve şiddet öncesi ve sonrasında korunmak için nelerin yapılması konusunda eğitilmesi ve eşler arasında eş terapisinin artırılması ve desteklenmesi ile kadına yönelik şiddetin azaltılabileceğini düşünüyoruz.**Anahtar Kelimeler:** Kadın, Şiddet, Yaralanma, Travma skorları, Adli tıp

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Introduction

Violence against women is not only a major public health problem but also a human rights issue (1). While violence against women can cause simple injuries, disabilities and even death in the acute phase, it can also cause serious mental illnesses in survivors in the long term (2). According to World Health Organization data, 30% of women all over the world are exposed to physical or sexual violence during their whole lives (3).

Violence against women is one of the most prevalent public health problems that occupy the agenda in our country as well as all over the world. According to the Violence against Women in Turkey Survey 2014 report, 36% of women are subjected to physical violence, 12% to sexual violence and 44% to emotional violence by their husbands or intimate partners (4). In a study from Manisa, 23.9% of the female cases admitted to the forensic medicine outpatient clinic were admitted due to domestic violence or partner violence (5). In a study conducted in Elazığ, 51.5% of females experienced to physical violence (6). In another study conducted in central Manisa, 14.8% of the women had been subjected to physical abuse (7). This situation shows that regional cases of violence against women in Turkey may be above the world average.

Injury severity score (ISS) is a widely used scoring system to indicate trauma severity (8). The ISS is a trauma scoring system using the AIS as the basis and dividing the body into six sites. The ISS is the sum of the square of the AIS score of the three most seriously affected body areas (9). NISS is a scoring system that takes the sum of the squares of the three most severe wounds, no matter which part of the body is injured. The NISS can therefore be equal to or higher than the ISS. NISS is a beneficial trauma scoring system to indicate the gravity of injury and predict mortality (8).

This study aimed to evaluate adult female cases admitted to the forensic medicine clinic and reported for violence against women.

Materials and Methods

This study was conducted at Bolu Abant İzzet Baysal University Forensic Medicine Clinic. Ethics committee approval for the study was obtained from Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (dated 05.10.2021 and numbered 2021/241).

In this retrospective cohort study, 494 cases over 18 years, for whom a forensic report was requested for alleged battery between 01.01.2011 and 31 December 2020 were included. The study excluded cases under 18 years of age, male and with missing data. Hospital automation systems, forensic documents and patient charts of the cases were analysed retrospectively.

The cases were evaluated per the following parameters: 'age, marital status, accused, sex of the accused, type of injury, site of injury and forensic degree of injury, trauma score [ISS and NISS]'. ISS and NISS were measured using the AIS 2008 update.

Statistical Package For Social Science (SPSS), version 21.0 (IBM SPSS Statistics for Window, Version 20.0, Armonk, NY: IBM Corp.) statistical program was utilized for statistical analyzes. Whether the distributions were normally ranged was analysed using graphical (histogram plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Descriptive statistics were presented as frequency, percentage, mean, median and standard deviation values.

Non-parametric tests were performed for non-normally distributed variables: paired groups by the Mann-Whitney U Test and groups of more than two by the Kruskal-Wallis Test (Post-Hoc: Dunn-Bonferroni test). Continuous variables are expressed as median (interquartile range [IQR]) and categorical variables are given as frequency and percentage. P-value less than 0.05 was accepted as a statistically significant result.

Results

The mean age of the 494 cases was 35.26 ± 14.43 years (min: 18, max: 92) and more than half of the cases (59.3%) were in their 20s and 30s. (Table 1). 56.9% (n:281) were married, 33.4% (n:165) were single, 6.1% (n:30) were divorced and 3.6% (n:18) were widowed. In this study, 83.8% of the accused were male (n:414) and 16.2% (n:80) were female. The cases were often (n:136, 31.6%) subjected to violence from their spouses and second from strangers (n:76, 15.4%). On the other hand, 43.1% (n:213) of the women had been subjected to violence by intimate partners (Table 1).

The overwhelming proportion of the cases (93.9%) were exposed to blunt trauma and 40.9% of the cases (n:225) had multiple injuries (Table 1). No traumatic lesion was detected in 50 cases of alleged assault. In 13.4% (n:66) of the cases, a report was issued stating that the injury could not be treated with a simple medical intervention, and in 2.2% (n:11) of the cases, a report was issued stating that the injury would cause life-threatening.

ISS and NISS

The mean ISS of the 444 patients with traumatic lesions was 1.16 ± 0.54 and the mean NISS was 2.26 ± 3.26 . No statistically significant relationship was detected between the marital status of the victims and the severity of injury ($p > 0.05$) (Table 2 and 3). ISS and NISS scores of female victims of violence by male defendants were significantly higher ($p < 0.01$) (Table 2 and 3). ISS and NISS scores were significantly higher in women who had experienced violence by an intimate partner ($p < 0.01$) (Table 2 and 3). Women injured with sharps or firearms had significantly higher ISS and NISS scores than women exposed to blunt trauma ($p < 0.001$) (Table 2 and 3). Although no statistically significant correlation was found between the site of injury and trauma severity in terms of ISS score ($p > 0.05$) (Table 2), the NISS score was found to be significantly higher in multiple site injuries ($p < 0.001$) (Table 3).

Discussion

In a study from Mersin, the mean age of women who were subjected to violence was 35.8 ± 10.7 years and the most

common age range was 26-35 years (37.1%) (10). In another study conducted at Çukurova University, the average age was reported to be 35.9 years (11). In the study of Çelebi et al., the average age was 35.72±10.84 years (6). The study included 494 patients. The mean age of the patients was 35.26±14.43 years (min: 18, max: 92) and more than half of the patients (59.3%) were in their 20s and 30s (Table 1).

In studies from Turkey, the majority of victims of violence against women (47.2%-91%) are married (7,12-14). In this study, over half of the cases were married (n:281, 56.9%) in accordance with the literature. Ünal et al. reported that the defendants of violence against women in Istanbul were males (95.6%) predominantly, while only 4.4% were females (15). This study's defendants were predominantly male (n:414, 83.8%). In studies conducted in Turkey, the perpetrators of violence were mostly spouses (75.6%-89.2%) in cases of violence against women (14,16). In this study, most of the cases (n:136, 31.6%) were exposed to violence by their spouses, while 43.1% (n:213) were exposed to violence by

intimate partners (Table 1). The higher number of spouses as accused seems to be closely related to the fact that the majority of the victims are married.

In Tunisia, 78% of women victims of violence were injured by blunt trauma (17). Koca Yavuz et al. reported that victims of violence against women admitted to Çukurova University Faculty of Medicine Forensic Medicine Clinic were most frequently (74.4%) injured with blunt trauma (11). Most of the cases (93.9%) in this study had experienced blunt trauma (Table 1). However, the incidence of the type of trauma is strongly correlated with the seriousness of the damage. In studies involving cases of femicide, firearm injuries and sharps injuries are more common (12,18,19).

In a study conducted in Tunisia, the most common (76%) site of injury was the face (17). According to Toprak et al., the most common injuries sustained by female homicide victims were to the head (29.9%) and thorax (19.3%) (12). In this study, 40.9% (n:225) of the patients were injured in more than one region (Table 1).

Table 1. Distribution of age, marital status, accused, accused gender, type, site and degree of injury

		n	%
Age	18-19 years	51	10.3
	20-29 years	171	34.6
	30-39 years	122	24.7
	40-49 years	66	13.4
	50-59 years	48	9.7
	60-69 years	24	4.9
	70-79 years	6	1.2
	80-89 years	5	1.0
	90-99 years	1	0.2
Marital status	Single	165	33.4
	Married	281	56.9
	Divorced	30	6.1
	Widow	18	3.6
Accused gender	Male	414	83.8
	Female	80	16.2
Accused	Spouse	156	31.6
	Foreigner	76	15.4
	Friends	60	12.1
	Neighbour	46	9.3
	Boyfriend	39	7.9
	Distant relative	18	3.6
	Sibling	12	2.4
	Father	11	2.2
	Child	9	1.8
	Ex-spouse	9	1.8
	Brother	9	1.8
	Sister-in-law	8	1.6
	Ex-boyfriend	7	1.4
	Others	34	6.9
Injury type	Blunt trauma	464	93.9
	Sharp object	18	3.6
	Gunshot	10	2.2
	Burning	2	0.4
Injury site	Head-neck	141	28.5
	Body	23	5.1
	Extremities	78	15.8
	Multiple	202	45.5
Degree of forensic injuries	No lesions	50	10.1
	Cured by simple medical intervention	367	74.3
	Not cured by simple medical intervention	66	13.4
	Life-threatening	11	2.2

In their study conducted in Manisa, Karabağ et al. reported that 59.8% of the victims of violence against women had injuries that could be treated with a simple medical intervention (SMI), 34.8% had injuries that could not be treated with SMI and only 11.2% had life-threatening injuries (5). Koca Yavuz et al. reported that 87.6% of the cases were injured at a level that could be treated with SMI, 6.4% were injured at a level that could not be treated with SMI and only 2.8% had life-threatening injuries in Adana province (11).

In this study, in accordance with the literature, the most common injury was reported to be at a degree that could be treated with SMI. In 13.4% (n:66) of the cases, the injury could not be treated with SMI, and in 2.2% (n:11) of the cases, a report was issued that the injury would cause life-threatening. In general, although simple injuries are more common in cases of violence against women, regional differences can be observed in the frequency of life-threatening injuries.

ISS (Injury Severity Score) – NISS (New – Injury Severity Score)

In this study, the mean ISS of the 444 patients with traumatic lesions was 1.16 ± 0.54 and the mean NISS was 2.26 ± 3.26 .

In this study, no statistical correlation appeared between marital status and injury severity ($p > 0.05$) (Table 2 and 3). In general, the majority of cases of violence against women are perpetrated by males (15). Considering the difference in physical strength between males and females, it is expected that the severity of injury will be higher in cases where the accused is a male. In our study, ISS and NISS scores of female victims of violence by male perpetrators were significantly higher ($p < 0.01$) (Table 2 and 3).

Toprak and Ersoy reported that 49.4% of femicide cases were killed by intimate partner between 2000-2010 (12). Koç reported that 88% of the defendants died due to intimate partner violence in a study involving cases of violence against women in Turkey between 2010 and 2017 (19). The reason why the accused in femicide cases is often an intimate partner may be that in intimate partner homicides, separation, jealousy, infidelity and honour killings are more common and the violence related to them is more frequently shown (12). In this study, ISS and NISS scores were found to be considerably greater in females who experienced violence by their intimate partners ($p < 0.01$) (Table 2).

Table 2. ISS distribution by accused, accused gender, victim marital status, type and site of injury

		Injury severity score (ISS)					p ¹
		Mean	S.D.	Median	25th per	75th per	
Accused gender	Male	1.19	± 0.58	1.00	1.00	1.00	0.007
	Female	1.01	± 0.12	1.00	1.00	1.00	
Accused	Intimate partner	1.24	± 0.68	1.00	1.00	1.00	0.006
	Others	1.09	± 0.38	1.00	1.00	1.00	
Accused	Foreigner	1.07	± 0.30	1.00	1.00	1.00	0.122
	Acquaintance	1.17	± 0.57	1.00	1.00	1.00	
Marital status	Single	1.16	± 0.51	1.00	1.00	1.00	0.636 ²
	Married	1.14	± 0.57	1.00	1.00	1.00	
	Divorced	1.14	± 0.45	1.00	1.00	1.00	
	Widow	1.31	± 0.79	1.00	1.00	1.00	
Injury type	Blunt trauma	1.09	± 0.35	1.00	1.00	1.00	<0.001 ²
	Sharp object	1.77	± 1.21	1.00	1.00	2.25	
	Gunshot	2.90	± 1.28	3.00	2.00	3.50	
	Burning	1.00	± 0.00	1.00	1.00	1.00	
Injury site	Head-neck	1.11	± 0.31	1.00	1.00	1.00	0.510 ²
	Body	1.08	± 0.41	1.00	1.00	1.00	
	Extremities	1.11	± 0.42	1.00	1.00	1.00	
	Multiple	1.22	± 0.69	1.00	1.00	1.00	

¹Mann-Whitney U test ²Kruskal-wallis test

When this study and the literature data are evaluated together, we can say that violence perpetrated by intimate partners is more serious and is more likely to result in death if necessary measures are not taken in these cases.

In general, the most common method used in cases of violence against women is blunt trauma, while the most common methods used in cases of femicide are gunshot wounds (37.2%-84.1%) and sharps injuries (34.6%-49.3%) (12,18–20). This is due to the higher severity of injury to the victim caused by these two methods. In this study, ISS and NISS scores of women injured with sharps or firearms were significantly higher than those of women exposed to blunt trauma ($p < 0.001$).

Morbidity and mortality rates are higher in multiple trauma injuries compared to single site injuries (21). The NISS score was demonstrated to be considerably greater in multiple site injuries in this study ($p < 0.001$) (Table 3), even though there was no statistically significant link between the site of injury and trauma severity in terms of ISS score ($p > 0.05$) (Table 2). Injury severity is expected to be higher with multiple site injuries. Although ISS is frequently used in trauma injury, it has some limitations. For example, while it scores highest on a single part of the body, it does not measure other milder injuries on the same body part. The NISS takes into account the three

most serious injuries in the body, regardless of the affected body parts. Accordingly, the NISS may significantly exceed the ISS score in patients with multiple trauma (9).

Therefore, the NISS is considered more reliable than the ISS in assessing trauma severity in patients with multiple trauma (21,22).

Table 3. NISS distribution by accused, accused gender, victim marital status, type and site of injury

		New-Injury severity score (NISS)					p ¹
		Mean	S.D.	Median	25th per	75th per	
Accused gender	Male	2.42	±3.50	2.00	1.00	2.00	<0.001
	Female	1.35	±0.68	1.00	1.00	1.75	
Accused	Intimate partner	2.73	±4.39	2.00	1.00	3.00	0.005
	Others	1.89	±1.88	1.00	1.00	16.00	
Accused	Foreigner	1.87	±1.65	1.00	1.00	2.00	0.405
	Acquaintance	2.33	±3.48	1.00	1.00	2.00	
Marital status	Single	2.25	±3.23	1.00	1.00	2.00	0.924 ²
	Married	2.23	±3.42	1.00	1.00	2.00	
	Divorced	2.11	±2.00	1.00	1.00	2.00	
	Widow	2.81	±3.97	1.00	1.00	2.75	
Injury type	Blunt trauma	1.83	±1.52	1.00	1.00	2.00	<0.001 ²
	Sharp object	5.11	±7.07	1.00	1.00	5.75	
	Gunshot	14.9	±10.94	9.00	7.25	27.00	
	Burning	1.00	±0.00	1.00	1.00	1.00	
Injury site	Head-neck	1.41	±1.15	1.00	1.00	1.00	<0.001 ²
	Body	1.39	±1.87	1.00	1.00	1.00	
	Extremities	1.48	±1.71	1.00	1.00	1.00	
	Multiple	3.24	±4.38	2.00	2.00	3.00	

¹ Mann-Whitney U test ² Kruskal-wallis test

Our study has some limitations. Firstly, our study was designed retrospectively. Therefore, due to lack of data, parameters such as occupation, educational status, socioeconomic status, smoking and alcohol use of victims and defendants could not be included. Since the study covers a single clinic and does not include fatal cases, it cannot be said that it fully represents all cases of violence against women.

Conclusion

In this study, we showed that more than half of the victims of violence against women in Bolu province were married and the crimes were mostly perpetrated by spouses and intimate partners. We also found that the severity of violence perpetrated by intimate partners was significantly higher. The majority of the victims were injured with blunt trauma and injuries occurred in more than one region. We think that violence against women can be reduced by providing legal regulations against domestic violence, educating women about what rights they have against violence and what to do for protection before and after violence, and increasing and supporting partner therapy between spouses to prevent violence against women.

Ethical Approval: Ethics committee approval dated 05.10.2021 and numbered 2021/241 was obtained from Bolu Abant İzzet Baysal University Clinical Research Ethics Committee for the study.

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Changes in Sexual Functions and Effects on Partner Sexual Functions in Obese Men after Bariatric Surgery

Obez Erkeklerde Bariatrik Cerrahi Sonrası Cinsel Fonksiyonlardaki Değişiklikler ve Partner Cinsel Fonksiyonları Üzerine Etkileri

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Abstract

Background: The aim of this study was to evaluate the efficacy of bariatric surgery (BS) by evaluating preoperative and postoperative sexual functions in obese men undergoing BS.

Materials and Methods: Male patients who underwent BS due to obesity between January 2013 and September 2021 were included in this observational study. Patients underwent standardized laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. For sexual function, the International Index of Erectile Function (IIEF) inquiry form was filled in before, and one year after BS. In addition, the age, Body Mass Index (BMI) and Female Sexual Function Index (FSFI) scores of the female partners were recorded before and after the operation. Follow-up weight, waist circumference, serum biochemistry and hormone values of the patients were re-evaluated in the 6-12 month period after the operation.

Results: A total of 1027 patients were included in the study. The mean age of the male patients was 37.33±12.40 years, and the mean preoperative BMI was 38.51±3.98kg/m² (35.20-49.80). The postoperative follow-up period of the patients was 9.72±2.98 months. There was a significant increase in the IIEF (all sub-dimensions) scores of the patients after the operation (p<0.001 for each). An increase in FSFI scores was found in female partners after surgery (21.67±6.78 vs. 27.55±5.48; p<0.001). The change in IIEF-EF scores was moderately inversely correlated with partner BMI, moderately correlated with vitamin D levels, and linearly correlated with testosterone levels (p=0.034, r=-0.434; p=0.012, r=0.537 and p=0.027, r=0.476, respectively).

Conclusions: BS provides a significant increase in the sexual functions of obese men. This increase shows a significant relationship with partner BMI and vitamin D levels.

Keywords: Bariatric surgery, Erectile function, Sexual function, Partner satisfaction, Vitamin D

Öz

Amaç: Bu çalışmanın amacı, bariatrik cerrahi (BC) geçiren obez erkeklerde ameliyat öncesi ve sonrası cinsel işlevleri değerlendirilerek BC'nin etkinliğini incelemektir.

Materyal ve Metod: Bu gözlemsel çalışmaya Ocak 2013 ile Eylül 2021 arasında obezite nedeniyle BC geçiren erkek hastalar dahil edildi. Hastalara standardize laparoskopik Roux-en-Y gastrik bypass veya laparoskopik sleeve gastrektomi uygulandı. Cinsel işlev için, BC'den önce ve bir yıl sonra Uluslararası Ereksiyon Fonksiyonu İndeksi (IIEF) sorgulama formu dolduruldu. Ayrıca, kadın partnerlerin yaşı, Vücut Kitle İndeksi (BMI) ve Kadın Cinsel İşlev İndeksi (FSFI) skorları operasyon öncesi ve sonrası kaydedildi. Hastaların takip kilosu, bel çevresi, serum biyokimyası ve hormon değerleri operasyondan sonraki 6-12 aylık dönemde yeniden değerlendirildi.

Bulgular: Çalışmaya toplam 1027 hasta dahil edildi. Erkek hastaların yaş ortalaması 37.33±12.4 yıl, ameliyat öncesi ortalama BMI 38.51±3.98 kg/m² (35.20-49.80) idi. Ameliyat sonrası takip süresi 9.72±2.98 ay idi. Hastaların IIEF (tüm alanlarda) skorlarında ameliyattan sonra anlamlı artış vardı (her biri için p<0.001). Ameliyat sonrası kadın partnerlerin FSFI skorlarında artış olduğu saptandı (21.67±6.78'e karşı 27.55±5.48; p<0.001). IIEF-EF skorlarındaki değişimin partner BMI ile orta düzeyde ters korelasyon gösterdiği, D vitamini düzeyleri ile orta düzeyde korelasyon gösterdiği ve testosteron düzeyleri ile doğrusal korelasyon gösterdiği bulundu (sırasıyla p=0.034, r=-0.434; p=0.012, r=0.537 ve p=0.027, r=0.476).

Sonuç: BC obez erkeklerin cinsel fonksiyonlarında önemli bir artış sağlar. Bu artış partner BMI ve D vitamini seviyeleri ile önemli bir ilişki göstermektedir.

Anahtar Kelimeler: Bariatrik cerrahi, Erektile fonksiyon, Cinsel fonksiyon, Partner memnuniyeti, D vitamini

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Introduction

Obesity is a worldwide public health problem and has serious psychological and social effects. According to a 2013 study worldwide, 2.1 billion people sweat in the overweight or obese class (1). Obesity is associated with diabetes mellitus, cardiovascular diseases, depression and other chronic diseases (2). It both threatens life and reduces the quality of life with accompanying chronic diseases (3). Coexistence of chronic diseases, depression, sleep apnea syndrome and sexual dysfunction are common in obese men (4).

Obesity is associated with significant disturbances in endocrine function. Hyperinsulinemia and insulin resistance are the best-known changes in obesity. Leptin secretion is increased in obesity. Testosterone and gonadotropin levels are low, especially in men with morbid obesity. Cortisol production and clearance are increased in these patients. Ghrelin, an orexigenic factor, has been found to be reduced in obese individuals. There is also a tendency for TSH and free T3 levels to increase in obesity (5).

Candidates for bariatric surgery are more likely to have mood disorders, anxiety, alcohol use, or personality disorders compared to controls (6,7). In terms of psychological characteristics, obese patients report higher levels of depression, anxiety, stress, and lower self-esteem and quality of life scores compared to those with normal body weight. Obese patients also have higher rates of eating behavior disorders, such as binge eating episodes and eating anxiety (8,9).

Erectile function has been associated with obesity in studies. One study found that 79% of men with erectile dysfunction (ED) were obese or overweight (10). Abdominal obesity and the loss of self-confidence caused by obesity also contribute to the formation of ED (11). The association of obesity with low testosterone levels also causes a decrease in sexual desire. In addition, high reactive oxygen production and antioxidant reduction lead to endothelial damage that can cause ED (12,13).

Bariatric surgery (BS) is operations performed to treat morbidly obese patients, complications of type 2 diabetes mellitus, sleep apnea syndrome, and to improve renal and cardiovascular functions. Recent studies have shown that BS not only improves weight loss, but also improves sexual functions. However, the reasons such as the small sample size and heterogeneity in the studies cannot show the relationship exactly.

The aim of this study is to evaluate pre- and post-surgical sexual functions in obese men undergoing BS and to examine the effectiveness of BS.

Materials and Methods

Male patients who underwent BS due to obesity between January 2013 and September 2021 were included in this observational study. Ethics committee approval was obtained for the study. Written informed consent was obtained from each patient participating in the study. The study was designed and implemented in accordance with the Declaration of Helsinki.

Patients with a previous diagnosis of hypogonadism, diabetes-related complications (such as neuropathy, retinopathy, nephropathy), patients with GFR<60, patients who had previous pelvic surgery, and patients with psychiatric problems were excluded from the study.

Detailed medical and sexual histories of all patients were taken before BS. Height, weight, abdomen and arm region measurements of the patients were made, fasting blood glucose, urea, creatinine, AST, ALT, total testosterone values were examined.

Weight was measured using an electronic balance while the patient was barefoot and wearing light clothing, and was recorded as closest to 0,1 kg. Length was measured to the nearest 0,5 cm using a fixed wall. Waist circumference was measured with a standard flexible tape measure. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m). In addition, the age, BMI and Female sexual Function Index (FSFI) scores of the female partners were recorded before and after the operation.

For sexual function, the International Erectile Function Index (IIEF) inquiry form was filled in before and 1 year after BS. IIEF is a 15-question test on sexual function during the previous 4 weeks. IIEF, erectile function (EF; maximum score 30 points), orgasmic function (OR; maximum score 10 points), sexual desire (SD, maximum score 10 points), intercourse satisfaction (IS; maximum score 15 points), and overall satisfaction (OS has ratings that include a maximum score of 10 points).

The Turkish validated form of the FSFI was used to assess partner sexual functions (14). This form, consisting of 19 questions, evaluated six areas: sexual desire (questions 1,2), arousal (questions 3-6), lubrication (questions 7-10), orgasm (questions 11-13), satisfaction (questions 14-16) and pain (questions 17-19) in the last 4 weeks. Each question was scored between 0-5 (total score 2-36). Those with a total score of >26.55 were considered as having sexual dysfunction.

Venous blood samples of the patients before the operation were taken between 08.00 and 11.00 in the morning after 8 hours of fasting. LDL, HDL, triglyceride, urea, creatinine, AST, ALT, total testosterone, FSH, LH and prolactin levels were examined from the patients.

Patients underwent standardized laparoscopic Roux-en-Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (LSG) (15). After surgery, nutritional and medical counseling was provided according to guidelines published by our obesity unit multidisciplinary staff (16).

Follow-up weight, waist circumference, serum biochemistry and hormone values of the patients were re-evaluated in the 6-12 month period after the operation. The IIEF questionnaire was used once again to assess sexual functions. The parameters in the group with and without improvement in sexual functions were examined.

Statistical analysis

SPSS 25.0 (IBM, USA) program was used for statistics. Distribution of cases was evaluated with Kolmogorov-Smirnov test. Dependent sample t-test, fisher exact test were used. Multivariate logistic regression analysis was performed. Significant p value was determined as <0.05.

Results

A total of 1027 patients were included in the study. The mean age of the male patients was 37.33 ± 12.40 years, and the mean preoperative BMI was $38.51 \pm 3.98 \text{ kg/m}^2$ (35.20-49.80). The mean age of their partners was 39.35 ± 8.42 . The mean preoperative total testosterone levels of the patients were $272.55 \pm 110.42 \text{ ng/ml}$. Testosterone level was below 400 ng/ml in 78.09% (802/1027) of the patients. Demographic data of the patients are given in Table 1.

The postoperative follow-up period of the patients was 9.72 ± 2.98 months. The BMI levels of the patients had decreased to 23.25 ± 2.18 . The preoperative IIEF-EF score of the patients was 14.65 ± 6.10 . The IIEF-OF score was 7.58 ± 1.33 , the IIEF-SD score was 6.54 ± 2.81 , the IIEF-IS score was 7.76 ± 2.21 and the IIEF-OS score was 6.72 ± 1.97 . There was a significant

increase in the IIEF-EF, OF, SD, IS and OS scores of the patients after the operation ($p < 0.001$ for each). While the mean FSFI score of the female partners of the patients was 21.67 ± 6.78 before the operation, the mean FSFI score of the women after the operation increased to 27.55 ± 5.48 ($p < 0.001$). There was a significant increase in vitamin B12 and vitamin D levels in the postoperative period ($p = 0.010$ for vitamin B12; $p = 0.012$ for vitamin D) (Table 2).

Table 1. Demographic characteristics

	Mean $\pm$ SD
Age	37.33 $\pm$ 12.40
BMI	38.51 $\pm$ 3.98
Partner Age	39.35 $\pm$ 8.42
Total Testosterone	272.55 $\pm$ 110.42
Vitamin B12	341.42 $\pm$ 134.43
Vitamine D	15.55 $\pm$ 5.52
Preoperative IIEF-EF	14.65 $\pm$ 6.1
Preop. Partner FSFI	21.67 $\pm$ 6.78

BMI: Body Mass Index, IIEF-EF: International Index of Erectile Function-Erectile Function, FSFI: Female Sexual Function Index

Table 2. Comparison between preoperative and postoperative values of patients

	Preoperative	Postoperative	p value
Total Testosterone	272.55 $\pm$ 110.42	356.78 $\pm$ 115.91	<0.001
Vitamin B12	341.42 $\pm$ 134.43	410.92 $\pm$ 135.45	0.010
Vitamine D	15.55 $\pm$ 5.52	17.08 $\pm$ 4.01	0.012
IIEF-EF	14.65 $\pm$ 6.1	20.91 $\pm$ 3.45	<0.001
IIEF-OF	7.58 $\pm$ 1.33	8.97 $\pm$ 1.03	<0.001
IIEF-SD	6.54 $\pm$ 2.81	8.78 $\pm$ 1.33	<0.001
IIEF-IS	7.76 $\pm$ 2.21	8.95 $\pm$ 1.73	<0.001
IIEF-OS	6.72 $\pm$ 1.97	8.03 $\pm$ 1.89	<0.001
Partner FSFI	21.67 $\pm$ 6.78	27.55 $\pm$ 5.48	<0.001

IIEF: International Index of Erectile Function, EF: Erectile Function, OF: Orgasmic Function, SD: Sexual Desire, IS: Intercourse Satisfaction, OS: Overall Satisfaction, FSFI: Female Sexual Function Index

In the univariate and multivariate regression analysis, the improvement of postoperative sexual functions was associated with a decrease of more than 10 units in BMI (OR: 2.012), high preoperative vitamin D levels (OR: 2.365), and low partner BMI value (OR: 0.774) (Table 3).

The change in IIEF-EF scores was moderately inversely correlated with partner BMI ($p = 0.034$, $r = -0.434$), moderately

correlated with vitamin D levels ($p = 0.012$, $r = 0.537$), and linearly correlated with testosterone levels ($p = 0.027$, $r = 0.476$). No statistically significant correlation was found between patient age and partner FSFI scores ($p = 0.413$, $r = 0.155$ and $p = 0.521$, $r = 0.289$ respectively). (Table 4).

Table 3. Univariate and multivariate regression analysis of factors affecting postoperative sexual functions.

	Univariate Analysis			Multivariate Analysis		
	OR	p	CI	OR	p	CI
Age	0.358	0.511	0.256-0.456			
Post-operative BMI reduction	1.789	0.001	1.112-1.987	2.012	<0.001	1.582-2.231
Partner Age	1.315	0.568	0.871-1.512			
Partner BMI	0.892	0.001	0.595-1.001	0.774	<0.001	0.601-0.912
Total Testosterone	1.012	0.135	0.998-1.025			
Vitamin B12	1.345	0.341	1.001-1.701			
Vitamine D	2.561	0.001	1.801-4.056	2.365	<0.001	2.035-2.714
Preoperative IIEF-EF	1.511	0.056	1.034-1.988			
Preop. Partner FSFI	1.341	0.109	0.788-2.561			

BMI: Body Mass Index, IIEF-EF: International Index of Erectile Function-Erectile Function, FSFI: Female Sexual Function Index

Table 4. Univariate analysis of the change in IIEF-EF scores

	Δ IIEF-EF	
	r	p
Age	-0.155	0.413
Partner FSFI	0.289	0.521
Partner BMI	-0.434	0.034
Vitamin D	0.537	0.012
Total testosterone	0.476	0.027

FSFI: Female Sexual Function Index, IIEF-EF: International Index of Erectile Function-Erectile Function, BMI: Body Mass Index.

Discussion

As a result of our study, significant improvements in sexual function were observed in obese men after BS. This improvement was found to be associated with preoperative vitamin D and testosterone levels, postoperative BMI reduction, and partner BMI.

Obesity is a very common health problem. This condition, which affects the quality of life and can be fatal, can also affect sexual functions. Due to many factors, individuals experience sexual function problems. Especially in studies conducted with men, symptoms such as erectile function, ejaculation dysfunction, decreased desire and desire can be seen.

In obese men, erectile function may be affected due to organic and psychological causes. These patients may have erectile dysfunction due to hypoandrogenism secondary to obesity, the presence of metabolic syndrome, and mechanical difficulty in retracting the foreskin and achieving penetration (17). The increased risk of oxidative stress due to obesity can damage arteries and veins, leading to impaired blood flow to the penis (18). Postoperative follow-up of patients who underwent BS showed improvement in their sexual functions (19). Due to both changes in body structure and decrease in adipose tissue, the individual increases his/her self-esteem (20). The decrease in symptoms related to comorbidities (hypertension, diabetes) after BS also contributes to the improvement in erectile functions (21). A recent review found an increase of 19% more in IIEF scores after BS (22). In our study, significant improvement was found in all sub-dimensions of IIEF. This situation was found to be related to the literature.

Changes in sex hormones after BS have been demonstrated in previous studies. A recent meta-analysis found a significant increase in total testosterone levels in male patients (23). It is argued that there is an increase in testosterone levels with the decrease of aromatase enzyme in adipose tissue after BS (24). In addition, the leptin hormone has been shown to affect testosterone synthesis and levels in obese patients (25). In our study, a significant relationship was found between testosterone levels and BMI decrease and erectile function in the post-surgical period.

Vitamin D has effects on many mechanisms such as nitric oxide release and endogenous androgen receptor in the endothelial system (26). Previous studies have shown the negative effects of vitamin D deficiency on sexual functions (27,28). Vitamin D plays an important role in steroidogenesis by regulating the expression of the CYP19A1 gene (29).

It has been shown that the vitamin D levels of obese individuals in the society are lower than those of normal weight (30). In our study, it was found that patients with high vitamin D levels had better effects on sexual functions after BS and there was a significant difference. Since vitamin D indirectly affects the synthesis of testosterone, we think that this benefit is related to the synthesis of testosterone.

LSG is one of the most frequently preferred methods in BS. In addition, LRYGP, laparoscopic adjustable gastric band and biliopancreatic diversion with duodenal switch are also used (31). The most important advantage of LSG compared to other methods is the low mortality, morbidity, and cost, and the higher patient satisfaction and weight loss. However, Calderón et al., found that all methods were equally effective in achieving normal testosterone levels after BS (32). Sarwer et al., in their prospective study of 32 men undergoing LRYGB, found no significant change in sexual function at 3 years (33). A meta-analysis found that the rate of improvement in sexual function was lower with gastric bypass surgery than with other surgical methods (34).

The study has some limitations. Studies generally report an average follow-up of one year after bariatric surgery (22,34). The most important limitation of this study is that the follow-up period was shorter than one year. Psychological and social factors were not evaluated in the study. In addition, aromatase, leptin, etc., which can affect secondary hormone synthesis not being evaluated is another limitation.

Conclusion

At the end of the study, BS provides a significant increase in the sexual functions of obese men. This increase shows a significant relationship with partner BMI and vitamin D levels. A large number of studies with participation are needed to evaluate the effects of BS on male sexual health.

Ethical Approval: In accordance with the 1964 Helsinki Declaration and its layer amendments, our study was approved by the Clinical Research Ethics Committee of the Health Sciences University, Adana City Training and Research Hospital (Ethical Committee approval number: 106/1963 Date: 30.05.2022). Written informed consent was obtained from each patient participating in the study.

Author Contributions:

Concept: G.G., M.A., C.G., K.K.

Literature Review: M.A., E.V., B.A., A.A.

Design : G.G., M.A., C.G., K.K.

Data acquisition: E.V., B.A.

Analysis and interpretation: C.G., A.A., K.K.

Writing manuscript: G.G., M.A., C.G., B.A.

Critical revision of manuscript: E.V., A.A., K.K.

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Are NMDA Antagonists or Venlafaxine More Effective in the Forced Swimming Test?

NMDA Antagonistleri mi Venlafaksin mi Zorlu Yüzme Testinde Daha Etkili?

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Abstract

Background: The aim of this study is to compare the antidepressant-like effects of NMDA antagonists (zinc sulfate, amantadine, and folic acid) with venlafaxine.

Materials and Methods: Ninety-six male Swiss Albino mice were used in the experiments and divided into experimental groups. To assess depression-like behaviors in the animals, the forced swim test was performed. The effects of the drugs on locomotor activity were measured using the open field test.

Results: No differences were found between venlafaxine, folic acid, or zinc sulfate when administered alone in the experimental depression model. When administered in combination, the highest antidepressant-like effect was observed in the zinc-amantadine combination and the zinc sulfate-amantadine-folic acid combination. When venlafaxine and folic acid were administered together, the antidepressant-like effect was greater compared to other venlafaxine combinations.

Conclusions: The use of these combinations in the treatment of depression is important for the enhancement of antidepressant efficacy.

Keywords: Amantadine, folic acid, depression, NMDA, zinc sulfate, venlafaxine

Öz

Amaç: Bu çalışmada NMDA antagonistlerinin (çinko sülfat, amantadin ve folik asit) antidepresan benzeri etkilerinin venlafaksin ile karşılaştırılması amaçlanmıştır.

Materyal ve Metod: Deneylerde doksan altı Swiss Albino erkek fare kullanıldı ve deney gruplarına ayrıldı. Hayvanların depresyon benzeri davranışlarını test etmek amacıyla zorlu yüzme testi yapıldı. İlaçların lokomotor aktivite üzerindeki etkileri açık alan testi kullanılarak ölçüldü.

Bulgular: Venlafaksin, folik asit veya çinko sülfat tek başına uygulandığında aralarında deneysel depresyon modelinde fark bulunmadı. Kombinasyon halinde uygulandığında en yüksek antidepresan benzeri etki çinko sülfat-amantadin kombinasyonunda ve çinko sülfat-amantadin-folik asit kombinasyonunda gözlemlendi. Venlafaksin ve folik asit birlikte uygulandığında antidepresan benzeri etki diğer venlafaksin kombinasyonlarına göre daha fazlaydı.

Sonuç: Bu kombinasyonların depresyon tedavisinde kullanılması antidepresan etkinliğin artışı açısından önemlidir.

Anahtar Kelimeler: Amantadin, Folik asit, Depresyon, NMDA, Çinko sülfat, Venlafaksin

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Introduction

Depression, a significant health issue, negatively affects patients' daily lives, reduces work productivity, and can lead to hospitalization in severe cases. Despite the availability of various treatments, the success rate in treating depression is often unsatisfactory (1). Depression, being a psychiatric disorder, carries significant morbidity and mortality rates (2). It is estimated that depression is responsible for 50-70% of suicides, making it a crucial public health concern (3). Currently prescribed antidepressant medications mostly target monoamines, such as serotonin, noradrenaline, or dopamine, by inhibiting their reuptake or metabolism (4). Recent preclinical research indicates that the glutamate N-methyl-D-aspartate (NMDA) receptor might play a role in the mechanism of action of antidepressant medications (5,6). Studies have shown that functional antagonists targeting the NMDA receptor complex exhibit antidepressant like effects in animal models of depression (7-8).

Zinc sulfate is essential for various enzymatic processes, including DNA replication, transcription, and protein synthesis and it regulates cell division and differentiation (9). Zinc sulfate is also essential for a number of metabolic activities and is a strong inhibitor of the NMDA receptor complex (10). Research has indicated that individuals with depression exhibit reduced levels of zinc sulfate in their blood, which return to normal following therapy (11,12).

Serum and red blood cell folic acid concentrations in patients with major depressive disorder were considerably lower than those in healthy controls. Depression severity is associated with lower serum folic acid concentrations (13). It has been previously shown that folic acid has an antidepressant effect via NMDA antagonism. (14).

Glutamatergic system research, and NMDA receptor antagonists have garnered more attention in recent years owing to their possible antidepressant benefits. Amantadine, a non-competitive NMDA receptor antagonist, has been shown to reduce the immobility time in rats during forced swimming tests. Amantadine has already been approved for clinical trials in conditions such as Parkinson's disease (15).

Venlafaxine is a potent inhibitor of the reuptake of both norepinephrine and serotonin. The drug is used in the treatment of major depression, as well as in anxiety disorders and panic disorder. While all currently available antidepressants, including venlafaxine, demonstrate therapeutic effectiveness in about 60-70% of patients with depression, they often fall short in cases of treatment-resistant depression. As a result, ongoing research continues to explore new approaches and treatments for depression (16).

This study aimed to compare the effectiveness of zinc sulfate, folic acid, and amantadine, either separately or in combination, as NMDA receptor antagonists in treating depression, with venlafaxine, a commonly used antidepressant.

Materials and Methods

This study was conducted with the required authorization and consent from the Erciyes University Faculty of Medicine Ethics Committee (No: 01/175, dated 02.05.2006). The Scientific Research Projects Unit of Erciyes University provided funding for the study's supplies and the laboratory animals under project code TT-06-35. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

In the experiments, ninety-six male Swiss Albino mice weighing 25-30 g were used. The mice were kept in 40×28×17cm cages at a constant temperature of 23–24°C. They had full access to water and a normal laboratory diet, and their cages were light- and dark-cycled every 12 hours. The experiments were carried out at the Erciyes University Experimental Clinical Research Center (DEKAM).

Drugs

All the medications were dissolved in physiological saline. The drugs were administered to the mice via intraperitoneal injection at the same volume (0.5 ml/Mouse), 24 hours, 1 hour, and 15 minutes before the experiment. The solutions were freshly prepared daily. The drugs used are listed shown in Table 1.

Table 1. Study drugs

Drugs	Company	Dose
Folic acid	Sigma-Aldrich, Stenheim, Switzerland	5 mg/kg
Amantadine HCL	Sigma-Aldrich, St. Louis, MO, USA	20 mg/kg
Zinc sulfate	Merck KGaA, Darmstadt, Germany	30 mg/kg
Venlafaxine	Wyeth, Pearl River, NY, USA	30 mg/kg

The forced swimming test

The glass pool used was cylindrical and measured 25 cm in height and 10 cm in diameter. The water in the glass pool was maintained at 22-23°C and was added to a depth of 10 cm. Mice were placed in a water-filled glass pool, and their immobility times during the last 4 min of the 6 min duration they spent in the glass pool were recorded (very slight movements made by the mice to keep their heads above the water and their immobility on the water surface were considered as immobility) (17).

Locomotor activity test

For the test, a transparent white non-transparent plexiglass box measuring 30×30×25 cm in size and in a square shape was used. The floor is divided into four equal parts with black lines (18). The experimental animals were gently introduced into the open field test apparatus, consistently in the same direction. During the thirty-minute test period, the frequency of line crossings by the animals was assessed. Line crossing was defined as the number of times the experimental animal moved from one square to another using all four limbs. An increase in locomotor activity was determined if the number of line crossings in the medication group exceeded that in the control group. Conversely, a

decrease in locomotor activity was inferred if the number of line crossings was lower than that of the control group.

Statistics

The Shapiro-Wilk test was used to determine if the data obtained from the groups had a normal distribution. One-way analysis of variance (ANOVA) was used to determine the significance of the differences between groups. When a significant difference was found, Tukey's test was used for multiple comparisons under the assumption that variances were homogeneous. For all tests, a significance level of $p < 0.05$ was considered statistically significant.

Results

Table 2 illustrates the impact of venlafaxine, amantadine, zinc sulfate, and folic acid treatment on the immobility scores of mice. Venlafaxine and zinc sulfate, administered at dose of 30 mg/kg, resulted in a significant reduction in immobility time, by approximately 50%. Similarly, amantadine at a dose of 20 mg/kg and folic acid at a dose of 5 mg/kg decreased in immobility time.

No significant difference ($p > 0.05$) was observed between the groups that received venlafaxine and those receiving zinc sulfate and folic acid. Immobility time in the amantadine-treated group was significantly shorter than that in the control group ($p < 0.01$). Conversely, the mean immobility time of the zinc sulfate + folic acid group was significantly longer than that of the folic acid + amantadine group ($p < 0.01$). Similarly, the mean immobility time of the zinc sulfate + amantadine and zinc sulfate + folic acid + amantadine groups was significantly shorter than that of the folic acid + amantadine group ($p < 0.05$). There was no noticeable difference in the mean immobility time between the zinc sulfate + amantadine and zinc sulfate + amantadine + folic acid groups ($p > 0.05$). Additionally, the mean immobility time of the amantadine group alone was significantly shorter than that of the zinc sulfate + folic acid group ($p < 0.05$) (Table 2).

Table 3 shows the effects of zinc sulfate, folic acid, and amantadine alone or in combination on spontaneous locomotor activity in mice. Compared to the control and other groups, the group that received venlafaxine had a considerably reduced mean number of line crossings ($p < 0.01$). There was no significant difference in the mean number of line crossings among the zinc sulfate, folic acid, and zinc sulfate + folic acid groups ($p > 0.05$). However, the mean number of line crossings in these groups was notably lower than that in the control group and all other groups except for the venlafaxine group ($p < 0.01$).

When comparing the amantadine, folic acid + amantadine, zinc sulfate + amantadine, and zinc sulfate + folic acid + amantadine groups with the control group, the mean number of line crossings didn't significantly change ($p > 0.05$). However, the mean number of line crossings in these groups was significantly higher than in the venlafaxine group ($p < 0.01$) (Table 3).

Table 2. Mean $\pm$ SD values of immobility times obtained in the forced swimming test for each group

Groups	n	Mean $\pm$ SD (sec)
Control	8	167.3 $\pm$ 5.86*
Venlafaxine 30 mg/kg	8	91.49 $\pm$ 2.51
Zinc sulfate 30 mg/kg	8	93.99 $\pm$ 2.8*
Folic acid 5 mg/kg	8	93.20 $\pm$ 1.72
Amantadine 20 mg/kg	8	72.91 $\pm$ 3.38*
Zinc sulfate 30 mg/kg + Folic acid 5 mg/kg	8	85.24 $\pm$ 3.88****
Folic acid 5 mg/kg with Amantadine 20 mg/kg	8	67.54 $\pm$ 3.88**,***
Zinc sulfate 30 mg/kg with Amantadine 20 mg/kg	8	62.12 $\pm$ 2.29
Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg + Amantadine 20 mg/kg	8	62.05 $\pm$ 0.95

* : The comparison of the venlafaxine, zinc sulfate and folic acid groups than that of the control group ($p < 0.01$)

** : The comparison of the zinc sulfate + folic acid group than that of the folic acid + amantadine group ($p < 0.01$).

*** : The comparison of the zinc sulfate + amantadine and zinc sulfate + folic acid + amantadine groups than that of the folic acid + amantadine group ($p < 0.05$)

**** : The comparison of the amantadine group alone than that of the zinc sulfate + folic acid group ($p < 0.05$)

The effects of venlafaxine alone or in when combination with zinc sulfate, folic acid, and amantadine on immobility scores in mice are illustrated in Table 4. The mean immobility times of all groups (except control group) were significantly shorter than those of the venlafaxine group ($p < 0.01$). The mean immobility time, the venlafaxine + folic acid group was significantly shorter than that of the other groups ($p < 0.01$). The mean immobility time of the venlafaxine + amantadine group was significantly shorter than that of the venlafaxine + zinc sulfate group ($p < 0.01$). The mean immobility time of the venlafaxine group was significantly shorter than that of the control group ($p < 0.01$) (Table 4). The effects of venlafaxine administration, both independently and in conjunction with other medications, on the spontaneous locomotor activity in mice are illustrated in Table 5. The mean number of line crossings in the venlafaxine group is significantly lower than in all other groups ($p < 0.05$). There is no significant difference in the mean number of line crossings between the folic acid + venlafaxine group and the venlafaxine + zinc sulfate group ($p > 0.05$). However, the mean number of line crossings in both of these groups is significantly lower than that in the venlafaxine + amantadine group ($p < 0.01$). Except for the venlafaxine + amantadine group, the mean number of line crossings in all groups is significantly lower than that of the control group ($p < 0.01$). There is no significant difference in the mean number of line crossings between the venlafaxine + amantadine group and the control group ($p > 0.05$) (Table 5).

Table 3. Values of line crossing numbers obtained in the open field test for each group

Groups	n	Mean $\pm$ SD (sec)
Control	8	78.25 $\pm$ 2.25 *, **
Venlafaxine 30 mg/kg	8	60.50 $\pm$ 1.60 ***
Zinc sulfate 30 mg/kg	8	69.37 $\pm$ 2.50
Folic acid 5 mg/kg	8	73.00 $\pm$ 2.72
Amantadine 20 mg/kg	8	78.00 $\pm$ 2.00
Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg	8	72.25 $\pm$ 2.76
Folic acid 5 mg/kg with Amantadine 20 mg/kg	8	77.37 $\pm$ 3.24
Zinc sulfate 30 mg/kg with Amantadine 20 mg/kg	8	80.00 $\pm$ 2.00
Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg + Amantadine 20 mg/kg (Group 8)	8	78.50 $\pm$ 1.41

*: The comparison of the venlafaxine than that of the control group ($p < 0.01$)

**: The comparison of the zinc sulfate, folic acid, and zinc sulfate + folic acid groups than that of the control group ($p < 0.01$)

***: The comparison of the amantadine, folic acid + amantadine, zinc sulfate + amantadine, and zinc sulfate + folic acid + amantadine groups than that of the venlafaxine group ($p < 0.01$)

Table 4. Values of immobility times in the forced swimming test for venlafaxine combined with other drugs and the venlafaxine group

Groups	n	Mean $\pm$ SD (sec)
Control	8	167.29 $\pm$ 5.86****
Venlafaxine 30 mg/kg	8	91.49 $\pm$ 2.51*
Venlafaxine 30 mg/kg + Folic acid 5 mg/kg	8	62.76 $\pm$ 1.74**
Venlafaxine 30 mg/kg + Zinc sulfate 30 mg/kg	8	82.25 $\pm$ 2.58***
Venlafaxine 30 mg/kg + Amantadine 20 mg/kg	8	70.64 $\pm$ 1.98

*: The comparison of the all groups(except control group) than of the venlafaxine group ($p < 0.01$)

**: The comparison of the all groups than that of the venlafaxine + folic acid group ($p < 0.01$)

***: The comparison of the venlafaxine + amantadine group than that of the venlafaxine + zinc sulfate group ($p < 0.01$)

****: The comparison of the venlafaxine than that of the control group ($p < 0.01$)

Table 5. Values of line crossing numbers obtained in the open field test for venlafaxine combined with other drugs and the venlafaxine group

Groups	n	Mean $\pm$ SD (sec)
Control	8	78,25 $\pm$ 2,25***
Venlafaxine 30 mg/kg	8	60,50 $\pm$ 1,60*
Venlafaxine 30 mg/kg + Folic acid 5 mg/kg	8	64,12 $\pm$ 2,53
Venlafaxine 30 mg/kg + Zinc sulfate 30 mg/kg	8	63,87 $\pm$ 2,53
Venlafaxine 30 mg/kg + Amantadine 20 mg/kg	8	77,62 $\pm$ 2,66**

*: The comparison of the all groups than that of the venlafaxine group ($p < 0.05$)

**: The comparison of the venlafaxine+folic acid and venlafaxine + zinc sulfate groups than that of the venlafaxine + amantadine group ($p < 0.01$).

***: The comparison of the venlafaxine, venlafaxine+folic acid and venlafaxine+zinc sulfate groups than that of the control group ($p < 0.01$).

Discussion

Clinically effective antidepressant treatment includes pharmacological and non-pharmacological methods such as electroconvulsive therapy, encompassing a notable structural diversity of drugs, primarily targeting monoamine reuptake or metabolism. Only about 60-70% of patients respond to these treatments, and they have a range of undesirable side effects (19). Consequently, research has been ongoing for years in the quest for "better" antidepressants. Recently, functional glutamatergic-NMDA receptor antagonists have been shown to possess antidepressant-like properties (20).

Our findings revealed that non-competitive NMDA receptor antagonists, such as zinc sulfate, folic acid, and amantadine, reduced immobility time in the forced swimming test in mice to a degree comparable to that of venlafaxine. This is consistent with previous research indicating a dose-dependent decrease in the immobility duration in rats following treatment with amantadine and memantine (21). The antidepressant effects of the NMDA receptor antagonist ketamine and MK-801 were demonstrated in a study using the forced swimming test as a model of depression. (22). In the forced swimming test in mice, it was observed that the antidepressant like effects of both zinc sulfate hydroaspartate and citalopram were enhanced when administered in combination, and the locomotor activity of the animals decreased compared to the control group (23). Ketamine is an anesthetic drug used in dissociative anesthesia. The antidepressant effect of ketamine has been investigated for a long time. In addition clinical research has demonstrated the antidepressant benefits of ketamine, a potent NMDA antagonist, in depressive patients (24, 25). In the present study, the antidepressant like effects of venlafaxine were compared when administered alone and in combination with zinc sulfate, folic acid, and amantadine, as well as when these three drugs were administered separately.

Zinc sulfate has an antidepressant like effect that has been shown in the literature in prior research as well as in our study. NMDA receptor antagonism has been shown to play a role in the antidepressant like effect of zinc sulfate (26). This study also compared the antidepressant like effects of zinc sulfate with those of amantadine and folic acid. Similar to previous studies, zinc sulfate did not enhance locomotor activity in the present study. When zinc sulfate was administered alone, it showed a similar effect to venlafaxine and folic acid, but was found to be less effective than amantadine. However, when zinc sulfate was combined with amantadine, the resulting antidepressant like effect was greater than that of the combination with folic acid. The effect of the zinc sulfate + amantadine combination was similar to that of the zinc sulfate + amantadine + folic acid combination. In terms of locomotor activity, zinc sulfate did not increase locomotor activity when administered alone or in combination with other drugs. When administered with

venlafaxine, the combination of zinc sulfate showed a greater antidepressant like effect than venlafaxine alone, but showed less antidepressant like effects than the combinations of venlafaxine + folic acid and venlafaxine + amantadine. The zinc sulfate + venlafaxine combination reduced locomotor activity compared to that in the control group. Imipramine, citalopram, tianeptine and zinc sulfate hydro-aspartate were administered repeatedly for 7, 14 and 21 days in rats. In most rats, treatments resulted in a decrease in the amplitude of pharmacologically isolated NMDA and AMPA/kainate receptor-mediated field potential components. The effects of zinc sulfate and tianeptine were evident even after 7 days of treatment (27). Folic acid has been shown to contribute to the recovery and improvement of individuals with depression. According to studies conducted on patients with depression, there is a relationship between depressive conditions (especially severe depression) and low levels of folic acid (28). When combined with zinc sulfate, folic acid exhibit a higher antidepressant like effect than venlafaxine alone. In our study, we observed that when amantadine was administered, the antidepressant like effect increased when combined with zinc sulfate. When applied in a triple combination of folic acid, zinc sulfate, and amantadine, the antidepressant like effect was higher than when administered in binary combinations or alone. Folic acid enhanced the effect of venlafaxine and was found to be more effective than the venlafaxine-zinc sulfate and venlafaxine-amantadine combinations. Patients who did not respond adequately to antidepressant treatment had low levels of folic acid in their blood. It was observed that the effectiveness of the treatment increased when patients were given folic acid treatment before the treatment (29). In a study involving 110 outpatient patients with severe depression during an 8-week fluoxetine treatment period, serum folic acid, B12 vitamin, and homocysteine levels were monitored. The clinical response to improvement initially showed a 30% reduction in the Hamilton Depression Rating Scale (HDRS) score and subsequently a 50% reduction after eight weeks. Low serum folic acid levels were observed at the beginning of clinical improvement. Serum folic acid levels increased over time (30). Similar to our study, when venlafaxine was combined with folic acid and administered for 14 and 21 days, an increase in antidepressant like effect was observed in both the forced swim test and the tail suspension test (31). In this study, amantadine alone exhibited a higher antidepressant like effect than venlafaxine, zinc sulfate, and folic acid. When venlafaxine and amantadine were administered together, they showed a lower antidepressant like effect than venlafaxine alone and venlafaxine + folic acid, but a higher antidepressant like effect than venlafaxine + zinc sulfate. In another study, imipramine, venlafaxine, fluoxetine, and non-competitive NMDA antagonists, amantadine, memantine, and nalmefexane were used in a forced swimming test in mice to demonstrate synergistic interactions (32). In our study, it was observed that the antidepressant like

effect increased when folic acid and zinc sulfate were administered. Similarly, magnesium and copper deficiencies have been thought to contribute to depression. It is suggested that both minerals exert antidepressant like effects through NMDA antagonism (33).

Conclusion

When comparing the antidepressant like effects of zinc sulfate, folic acid, and amantadine, the highest antidepressant like effect was observed with amantadine. If these drugs are administered in binary combination form, the highest antidepressant like effect is observed with the zinc sulfate + amantadine combination. When these drugs were combined with venlafaxine, the highest antidepressant like effect was observed with the combination of venlafaxine and folic acid. The use of these combinations in the treatment of depression is important in terms of efficacy. Further research is needed on the use of these combinations for the treatment of depression.

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Hazır Kardiyopleji Seti ve Sıvı Seti Yolu ile Verilen Kardiyoplejilerin, Veriliş Süresi Yönünden Karşılaştırılması

Comparison of Cardioplegia Given by Ready Cardioplegia Set and Liquid Set in Terms of Administration Time

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Öz

Amaç: Kardiyopulmoner Bypass eşliğinde açık kalp cerrahisi uygulanan hastalarda hazır setler ile verilen kardiyoplejik solüsyonların, sıvı setler ile verilenlere göre veriliş sürelerine etkisi incelenerek postoperatif morbidite ve mortalite yönünden araştırılmasını amaçladık.

Materyal ve metod: Kardiyopulmoner baypas ile açık kalp ameliyatı geçiren 18 yaş üstü toplam 88 hasta (59 erkek ve 29 kadın) retrospektif olarak çalışmaya dahil edildi. Bu hastalara ait ilk 24 saatlik postoperatif bilgiler incelendi. Hastalar kardiyopleji verilme setlerine göre iki gruba ayrıldı. Grup 1 (n= 44): hazır set ile kardiyopleji verilen grup, grup 2 (n=44): sıvı sette hazırlanarak kardiyopleji verilen grup. Gruplar arasında kardiyopleji veriliş sürelerinin toplam kros klemp sürelerine etkisi ve postoperatif laktat, üre, kreatinin, potasyum, CRP, WBC, idrar seviyeleri ile ekstübasyon, yoğun bakım, hastanede yatış süreleri ve mortalitenin istatistiksel analizi ve karşılaştırmaları yapıldı.

Bulgular: Gruplar arasında tanımlayıcı istatistik verileri incelendiğinde sıvı set kullanılan grup ile karşılaştırıldığında; hazır set kullanılan grupta postoperatif laktat düzeyinin anlamlı olarak daha düşük (p=0,002), ekstübasyon süresi (p<0,001), yoğun bakım ünitesinde kalış süresi (p=0,043), kros klemp süresi (p<0,001) ve total bypass süresinin de (p<0,001) anlamlı olarak daha kısa olduğu tespit edildi. Ancak, gruplar arasında mortalite açısından anlamlı bir farklılık olmadığı saptandı (p=0,246).

Sonuç: Hazır set ile kardiyopleji verilen grupta ekstübasyon süresi, yoğun bakım ünitesinde kalış süresi, kros klemp süresi ve total bypass süresi daha kısa olsa da hazır setler ile sıvı setlerin mortalite açısından benzer sonuçlara sahip olduğu saptandı.

Anahtar Kelimeler: Kardiyopleji, Kardiyopulmoner Bypass, Miyokardiyal Koruma

Abstract

Background: We aimed to investigate the effect of cardioplegic solutions given with ready-made sets on the duration of administration compared to those given with liquid sets in patients undergoing open heart surgery with Cardiopulmonary Bypass in terms of postoperative morbidity and mortality.

Materials and Methods: A total of 88 patients (59 males and 29 females) over 18 years of age who underwent open heart surgery with cardiopulmonary bypass were retrospectively included in the study. The first 24 hours postoperative data of these patients were analyzed. Patients were divided into two groups according to cardioplegia administration sets. Group 1 (n=44): cardioplegia was administered with a prepared set, group 2 (n=44): cardioplegia was administered with a liquid set. Statistical analysis and comparison of the effect of cardioplegia administration times on total cross-clamp times and postoperative lactate, urea, creatinine, potassium, CRP, WBC, urine levels, extubation, intensive care unit, hospitalization times and mortality were performed between the groups.

Results: When the descriptive statistical data between the groups were analyzed, it was found that the postoperative lactate level was significantly lower (p=0.002), extubation time (p<0.001), intensive care unit stay (p=0.043), cross-clamp time (p<0.001) and total bypass time (p<0.001) were significantly shorter in the group using the ready-made set compared to the group using the liquid set. However, there was no significant difference in mortality between the groups (p=0.246).

Conclusions: Although extubation time, intensive care unit stay, cross-clamping time and total bypass time were shorter in the group given cardioplegia with ready-made sets, it was found that ready-made and liquid sets had similar outcomes in terms of mortality.

Keywords: Cardioplegia, Cardiopulmonary Bypass, Myocardial Protection

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Giriş

Kardiyopulmoner bypass (KPB), kalp ve akciğerlerin yerini pompa ve oksijenatörden oluşan bir sistemin alması ile bu organların işlev dışı bırakılarak kardiyovasküler cerrahinin gerçekleştirilmesini sağlayan tekniktir (1). Kalp akciğer makinesi ve masa arasındaki bağlantı tüp setleri ve kanüller aracılığıyla yapılmaktadır. Bu bağlantı sayesinde kan, cerrahi alandan rezervuara aktarılmakta buradan da pompa vasıtasıyla oksijenatöre gönderilerek oksijenlenmesi sağlandıktan sonra arteriyel hat yoluyla sistemik dolaşıma geri kazandırılmaktadır. Bu teknik ile gerçekleştirilen dolaşıma ekstrakorporeal dolaşım veya vücut dışı dolaşım denilmektedir (2). KPB sırasında kansız bir alan oluşturabilmek için elektif kalp durması gerçekleştirilmektedir. Fakat, bu aşamada farklı seviyelerde oluşabilecek miyokardiyal hasarın engellenebilmesi için çeşitli kardiyoplejik solüsyonlar kullanılmaktadır. Genelde tercih edilen kardiyoplejik solüsyonlar arasında St. Thomas kardiyoplejisi (STK) ve kan kardiyoplejisi (KK) solüsyonu bulunmaktadır (3). Ayrıca son dönem de kullanılmaya başlanan bir diğer kardiyopleji solüsyonu ise del Nido'dur (DNK). En önemli özelliği tek doz uygulama yönteminin olmasıdır (4). Bu solüsyonlar, retrograd veya anterograd yolla ya da her iki yolun kombinasyonu ile birlikte uygulanabilir (5).

Kardiyopleji solüsyonlarının verilmesinde de farklı yöntemler ve setlerde kullanılmaktadır. Bu yöntemler arasında doğrudan kalp-akciğer makinesinden hastaya kapalı devre ile kardiyoplejinin verilmesi, anestezi tarafından farklı setler kullanılarak basınç torbası ile verilmesi ve son dönemde daha pratik olan hazır kardiyopleji setleri (kapalı devre) ile kardiyoplejinin verilmesi yer almaktadır.

Bu retrospektif çalışmada, hazır kardiyopleji setleri (kapalı devre) ile verilen kardiyoplejik solüsyonların, sıvı setler (kliniklerde bulunan standart serum setleri) ile verilen kardiyoplejik solüsyonlara göre kros klempe sürelerine (kalbin çalışmadığı süre) etkisi incelenerek; postoperatif morbidite ve mortalite yönünden araştırılmasını amaçladık.

Materyal ve Metod

Etik Karar

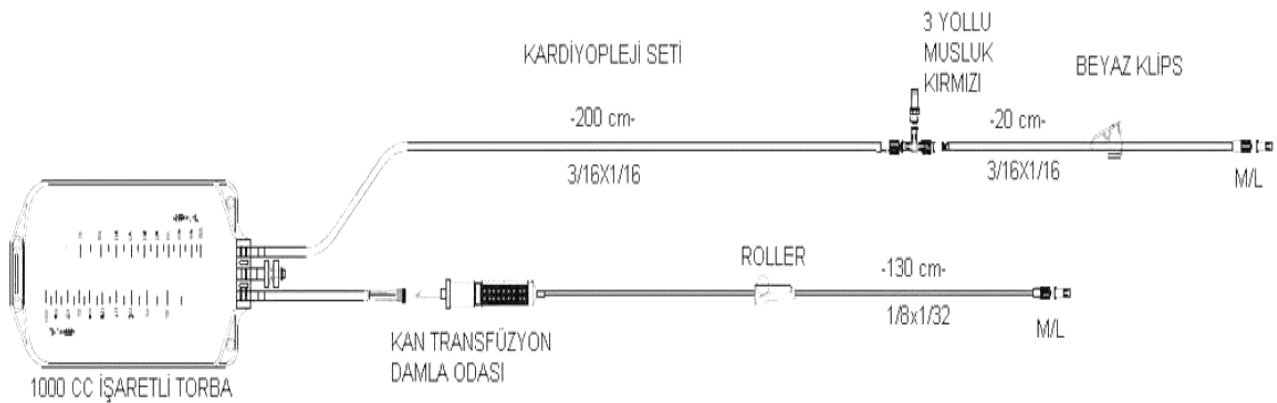
Çalışma verilerinin toplanacağı Harran Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesinden izin alındı. Etik kurul onayı, Harran Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan alındı (Tarih: 07.10.2024, karar: 24/15/23). Ayrıca çalışma Helsinki Bildirgesi prensiplerine uygun olarak yapıldı.

Çalışma Grupları

Bu çalışma için 18 yaş üzeri KPB desteği ile açık kalp cerrahisi yapılan 59 erkek, 29 kadın olmak üzere toplam 88 hasta retrospektif olarak araştırmaya dahil edildi. Bu hastalara ait ilk 24 saatlik postoperatif bilgiler incelendi. Hastalar kardiyopleji verilme setlerine göre iki gruba ayrıldı. Grup 1 (n=44): hazır kardiyopleji seti (kapalı devre) ile kardiyopleji verilen grup, grup 2 (n=44): sıvı sette hazırlanarak kardiyopleji verilen grup. Bu gruplar arasında kardiyopleji verilme sürelerinin toplam kros klempe sürelerine etkisi istatistiksel olarak incelendi. Ayrıca postoperatif laktat, üre, kreatinin, potasyum (K), CRP (C-reaktif protein), WBC (Beyaz Kan Hücreleri), idrar seviyeleri ile ekstübasyon, yoğun bakım ve hastanede yatış sürelerinin istatistiksel analizi ve karşılaştırmaları yapıldı.

Hazır kardiyopleji seti: Hazır setler ile pompa arasında bağlantı kurularak anesteziye oradan da hastaya kardiyopleji verilir (kapalı devre) (Şekil 1).

Standart sıvı seti: Perfüzyonist tarafından sıvı seti içerisinde hazırlanarak anesteziye teslim edilir ve yine kalbi durdurup kansız bir alan sağlamak için anestezi tarafından hastaya gönderilir.



Şekil 1. Hazır kapalı devre kardiyopleji set çizimi

Çalışmaya Dahil Edilme ve Dışlanma Kriterleri

Çalışmaya, KPB desteği ile açık kalp cerrahisi gerçekleştiren 18 yaş üstü hastalar dahil edildi. 18 yaş altı hastalar, KPB tekniği kullanılmadan yapılan ameliyatlara ve ameliyat sırasında meydana gelen ölüm gibi durumlar ek cerrahi planlanan hastalar, bilinen sistemik inflamatuvar hastalığı olanlar, yeniden kardiyak cerrahi ameliyatı geçirenler hastalar, kronik hemodiyaliz hastaları, hematolojik hastalığı olanlar dışlanma kriteri olarak kabul edildi.

İstatistiksel Analiz

Verilerin normal dağılıma uygunluğu Kolmogorow-Smirnov testi ile kontrol edilmiştir. Sayısal değişkenlerin normal dağılım gösterenler için Independent Samples t Test normal dağılım göstermeyenler için bağımsız iki grup karşılaştırmalarında Mann-Whitney U testi kullanıldı ve ikiden fazla bağımsız grupta karşılaştırılmasında normal dağılım gösteren özellikler için Tek yönlü varyans analizi (ANOVA) ve LSD çoklu karşılaştırma testleri, normal dağılmayan özellikler için ise Kruskal Wallis testi ve All pairwise çoklu karşılaştırma testi kullanılmıştır. Tanımlayıcı istatistik olarak sayısal değişkenler için ortalama±standart sapma, kategorik değişkenler için ise sayı ve % değerleri verilmiştir. İstatistiksel analizler için SPSS Windows version 25.0 paket programı kullanılmış ve P<0.05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

KPB desteği ile yapılan 88 ameliyat türünün sayısı ve yüzdesi tablo 1’de verilmiştir. Buna göre; tekli koroner arter bypass greft (KABGX1) sayısı 7 (%7,95), KABGX2: 4 (%4,55), KABGX3: 21 (%23,86), KABGX4: 29 (%32,95), KABGX5 ise 8’dir (%9,09). Ayrıca aort kapak replasman ameliyatı (AVR) sayısı 3 (%3,41), mitral kapak replasman ameliyatı (MVR) 6 (%6,82), atriyal septal defekt ameliyatı (ASD) 2 (%2,27), ventriküler septal defekt ameliyatı (VSD) 1 (%1,14), anevrizma ameliyatı 2 (%2,27), çift kapak ameliyatı (AVR+MVR) 2 (%2,27), aort diseksiyon ameliyatı 1 (%1,14), benthall ameliyatı 1 (%1,14) ve subaortik rezüksiyon ameliyatı sayısı 1 (%1,14)’dir.

Yapılan toplam 88 ameliyatın cinsiyet dağılımı tablo 2’de verilmiştir. Bu dağılıma göre; 88 ameliyatın 60’ını erkek (%68,18), 28’ini kadın (%31,82) hastalar oluşturmaktadır. Yapılan 88 ameliyatın 87’si 32 °C’de gerçekleştirilirken sadece 1 ameliyat 31 °C’de yapılmıştır.

Hazır setler ve sıvı setler ile verilen kardiyoplejilerin miktarı ve sayısı tablo 3’de verilmiştir. Bu verilere göre; 800 ml’lik birinci kardiyopleji solüsyonu 88 (%100) vakanın hepsinde uygulanırken, ikinci kardiyopleji 78 (%88,64), üçüncü kardiyopleji 24 (%27,27) ve dördüncü kardiyopleji solüsyonu ise sadece 4 vakada (%4,55) verildi.

Hastaların yaşam durumunu belirten veriler tablo 4’te gösterilmiştir. Tablo 4’e göre; hazır set ile kardiyopleji verilen

grupta 44 hastanın 5’inde ex durumu gözlemlendi ve ölüm yüzdesi %11,4’idi. Sıvı set ile kardiyopleji verilen grupta 44 hastanın 8’inin ex olduğu görüldü ve ölüm yüzdesi ise %18,18 olarak hesaplandı. Gruplar arası yapılan analize göre istatistiksel olarak anlamlı bir fark görülmedi (p=0,246).

Tablo 1. Ameliyat Frekans Analizi

Ameliyat Türü	Sayı	Yüzde
KABGX1	7	7,95
KABGX2	4	4,55
KABGX3	21	23,86
KABGX4	29	32,95
KABGX5	8	9,09
AVR	3	3,41
MVR	6	6,82
ASD	2	2,27
VSD	1	1,14
Anevrizma	2	2,27
AVR+MVR	2	2,27
Aort Dis.	1	1,14
Benthall	1	1,14
Subaortik Rezuksiyon	1	1,14
Total	88	100

ASD: Atrial septal defekt, AVR: Aort kapak replasman ameliyatı, KABG: Koroner arter bypass greft, MVR: Mitral kapak replasman ameliyatı

Tablo 5’de gruplar arasında tanımlayıcı istatistik verileri incelendiğinde hazır set kullanılan grupta; ekstübasyon süresi (saat) ($4,76 \pm 0,42$; $p<0,001$), yoğun bakım kalış süresi (gün) ($1,98 \pm 1,6$; $p=0,043$), kros klemp süreleri (dak) ($46,18 \pm 11,86$; $p<0,001$) ve total bypass süreleri (dak) ($79,8 \pm 19,79$; $p<0,001$) daha kısa olduğu, postoperatif laktat düzeyinin de ($3,04 \pm 2,56$; $p=0,002$) daha düşük olduğu görüldü. İstatistiksel olarak anlamlı bulundu ($p<0,05$). Ancak her iki grup arasında diğer parametreler bakımından (Hastane yatış süresi, Üre, kreatinin, K, CRP, idrar, WBC, flow, yaş [hazır set: $57,15 \pm 11,81$, sıvı set: $60,06 \pm 9,51$]) istatistiksel olarak anlamlı bir fark görülmedi ($p>0,05$).

Tablo 2. Cinsiyet Frekans Analizi

Cinsiyet	Sayı	Yüzde
Erkek	60	68,18
Kadın	28	31,82
Total	88	100

Tablo 3. Kardiyopleji Solüsyon Durumu Frekans Analizi

Kardiyopleji Solüsyon Durumu			
Solüsyon	Durum/Süre	Sayı	Yüzde
1. kardiyopleji (800ml)	Verilmedi	0	0
	Verildi	88	100
2. kardiyopleji (400ml)	Verilmedi	10	11,36
	Verildi	78	88,64
3. kardiyopleji (400ml)	Verilmedi	64	72,73
	Verildi	24	27,27
4. kardiyopleji (400ml)	Verilmedi	84	95,45
	Verildi	4	4,55
Hazır set toplam (dak)	0 dk	44	50,00
	2,40 dk	3	3,41
	3,60 dk	25	28,41
	4,80 dk	16	18,18
Sıvı set kardiyopleji toplam (dak)	0 dk	44	50,00
	4,00 dk	9	10,23
	6,00 dk	20	22,73
	7,00 dk	2	2,27
	8,00 dk	10	11,36
	10,00 dk	3	3,41
	Total	88	100

Tablo 4. Hastaların Yaşam Durumu

	Hazır set (n=44)	Sıvı set (n=44)	P-değer
Hastane içi ölüm (%)	5 (11,4)	8 (18,8)	0,246

N: sayı, %: yüzde

Tablo 5. Gruplar Arası Tanımlayıcı İstatistik

	Hazır Set ile Verilen Kardiyopleji			Sıvı Set ile Verilen Kardiyopleji			P-değer
	Min	Max	Ort±SS	Min	Max	Ort±SS	
ES (Saat)	4	5,5	4,76 ± 0,42	5	7	5,48 ± 0,59	0,001**
YBKS (Gün)	1	8	1,98 ± 1,6	1	12	2,86 ± 2,68	0,043*
HYS (Gün)	0	17	5,57 ± 3,32	0	24	6,09 ± 4,09	0,539
Laktat (Post)	0,9	14,4	3,04 ± 2,56	1,3	23	4,74 ± 4,09	0,002*
Üre (Post)	17,12	109,14	43,63 ± 21,77	23,54	115,56	42,66 ± 18,17	0,708
Kreatinin (Post)	0,27	6,24	1,03 ± 0,88	0,48	2,69	1,04 ± 0,45	0,119
K (Post)	3	5,6	4,27 ± 0,54	3,3	5,6	4,45 ± 0,5	0,181
CRP (Post)	1,88	27,48	8,34 ± 5,93	0,31	31,77	7,44 ± 5,66	0,602
İdrar (cc) (Post)	0	2800	738,41 ± 526,46	0	3500	955,58 ± 796,74	0,372
WBC (Post)	7,489	22,06	12,71 ± 3,76	4,68	21,07	12,67 ± 3,32	0,561
Flow (Akış hızı)	3730	5310	4386,82 ± 390,55	3660	5340	4477,95 ± 386,99	0,230
Kros klemp (dak)	25	64	46,18 ± 11,86	44	208	77 ± 38,56	0,001**
Total bypass(dak)	45	123	79,8 ± 19,79	61	279	113,12 ± 48,78	0,001**
Yaş (yıl)	22	76	57,15 ± 11,81	29	77	60,06 ± 9,51	0,205

Mann-Whitney U Testi p<0,05, **p<0,001. CRP: C-reaktif protein, ES: Ekstübasyon Süresi, HYS: Hastane Yatış Süresi, K: Potasyum, Post.: Postoperatif, WBC: Beyaz Kan Hücreleri, YBKS.: Yoğun Bakım Kalış Süresi

Tartışma

KPB'de aortik kros klemp süresi, KPB süresi, cinsiyet, yaş, aynı hastada gerçekleştirilen ameliyat sayısı, hastanelerdeki ameliyat yoğunluğu, postoperatif mortalite ve morbidite perioperatif sonuçlar ile ilişkili faktörler arasında bulunmaktadır (6). Ayrıca miyokardiyal hasarın engellenebilmesi için kullanılan kardiyoplejik solüsyonlarında verilirken arada oluşan zaman kaybı total bypass (Total perfüzyon) ve kros klemp sürelerini etkilemektedir. Bu durum postoperatif biyokimyasal parametreler ile yoğun bakım yatış süresi, hastanede yatış süresi, morbidite ve mortalite üzerine nasıl bir

etkisi olduğu konusunda literatürde değişken sonuçlar bulunmaktadır.

Kardiyak cerrahi sonrası elde edilen sonuçlar KPB süreleri (total perfüzyon, kros klemp, kardiyopleji verilmiş süreleri vb.) ile ilişkili olduğu gibi ilişkili olmaya da bilmektedir. Konvansiyonel tam sternotomi ile minimal invaziv yaklaşımları karşılaştıran bir çalışmada; kros klemp ve total perfüzyon süreleri, hastanede kalış süresi, morbidite ve mortaliteyi de kapsayan klinik sonuçlar değerlendirilmiştir. Konvansiyonel tam sternotomi yaklaşımında total perfüzyon ve kros klemp

sürelerinin daha kısa olmasına rağmen, elde edilen sonuçların gruplar arasında komplikasyon ve mortalite bakımından benzer olduğudur. Total perfüzyon ve kros klemp sürelerinin bağımsız bir risk faktörü olmadığını açıklamışlardır (7). Mehmood ve arkadaşları çalışmalarında, kros klemp ve total perfüzyon sürelerinin kardiyak cerrahi sonrası hastane yatış süresinin uzaması ile bağlantılı olmadığını kanıtlamışlardır ve klinik sonuçları tespit etmede KPB süresi ile kros klemp süresi haricinde klinik faktörlerin daha büyük etkisi olabileceğini ileri sürmüşlerdir (6). Bu çalışmaların aksine Madhavan ve arkadaşları KPB desteği ile gerçekleştirdikleri koroner arter bypass cerrahisi ameliyatlarında total bypass ve kros klemp sürelerinin uzamasının yoğun bakım yatış süresinin de uzamasına neden olduğunu bildirmişlerdir (8). Amaç ve arkadaşları, uzamış kros klemp ve uzamış KPB sürelerinin hastane yatış süresinin de artmasına neden olduğunu rapor etmişlerdir. Buna ilaveten, bazı biyokimyasal belirteçlerde de olumsuz sonuçların oluştuğunu saptamışlardır (9). Konjenital kalp hastalığı (ağırlıklı olarak ASD) cerrahisinin yapıldığı bir çalışmada, KPB süresinin uzaması yoğun bakım yatış süresinin ve hastane yatış süresinin de paralel olarak uzaması ile ilişkilendirilmiştir (10). Yapılan bir meta-analiz çalışmada, kardiyak cerrahi operasyonu olan hastalarda KPB süresinin postoperatif olumsuz klinik sonuçlara neden olduğunu açıklamışlardır (11). Pagowska-Klimek ve arkadaşları çalışma sonucunda elde ettikleri bulgulara göre, cerrahi yöntemlerin geliştirilerek KPB süresinin kısa tutulması yoğun bakım ünitesinde ve hastanede kalışı kısaltmada kritik rol oynayabileceği gibi postoperatif sürecinde komplikasyonsuz olabileceğini bildirmişlerdir (12). KPB'nin her on dakikalık uzayışı, akut solunum sıkıntısı sendromu bulunan hastalarda hastanedeki mortaliteyi %9,3 arttırırken; yoğun bakımdaki mortalitenin de %13,3 artmasına neden olduğu kanıtlanmıştır (13). Kapadinhos ve arkadaşları, kros klemp ve KPB sürelerinin uzaması yoğun bakımda kalış süresini de uzattığı sonucuna varmışlardır (14).

Çalışmamızda elde ettiğimiz sonuçlara göre, hazır set ile kardiyopleji verilen grupta total bypass ve kros klemp ile ekstübasyon sürelerinin daha kısa, yoğun bakım yatış ve hastane yatış sürelerinin daha az ve postoperatif laktat düzeylerinin de daha düşük olduğu görüldü. Ancak sıvı set ile kardiyopleji verilen grupta ise tam tersi sonuçlar elde edildi. Ek olarak; postoperatif idrar seviyeleri, morbidite ve mortalite ile biyokimyasal parametrelerden üre, kreatinin, K, CRP ve WBC'de her iki grup arasında anlamlı bir farklılık görülmedi. Bu durum, kros klemp ve total bypass sürelerini kısa tutmanın postoperatif komplikasyonlar üzerine direkt olarak etkili olmadığını göstermiştir.

Sınırlamalar

Çalışmanın sınırlılıkları arasında çalışmanın tek merkezli olması, retrospektif olması ve sınırlı sayıda hasta verisi içermesi yer almaktadır. Daha çok merkezli, daha fazla hasta popülasyonlarında ve prospektif çalışmaların yapılmasının daha kapsamlı sonuçlar vereceğini düşünmekteyiz.

Sonuç

Çalışmamızda hazır set ile kardiyopleji verilen grupta total bypass, kros klemp ve ekstübasyon süreleri kısa, postoperatif laktat düzeyleri, yoğun bakım ve hastanede yatış süreleri daha düşük bulundu. Ancak elde edilen veriler, gruplar arasında morbidite ve mortalitenin benzer olduğunu gösterdi.

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Nötrofil-Lenfosit Oranı ve LENT Skorunun Malign Plevral Efüzyonlarda Prognosta Etkisi

The Impact of Neutrophil-Lymphocyte Ratio and LENT Score on Prognosis in Malignant Pleural Effusions

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Öz

Amaç: Bu çalışmanın amacı; malign plevral efüzyon ile izlenen hastaların serum nötrofil/lenfosit oranı, Doğu Kooperatif Onkoloji (ECOG) performans skoru ve LENT (serum laktat dehidrogenaz (LDH), ECOG performans skoru, Kan Nötrofil/Lenfosit Oranı (NLO), Tümör tipi (T)) risk skorunun mortalite ve prognoz üzerindeki klinik etkisini araştırmaktır.

Materyal ve metod: Retrospektif, gözlemsel ve tek merkezli olan bu çalışmada Ekim 2022 ile Temmuz 2024 tarihleri arasında malign plevral efüzyon (MPE) ve paramalign plevral efüzyon (PMPE) nedeniyle takip edilen 73 hastanın sonuçları değerlendirilmiştir.

Bulgular: Çalışmaya dahil edilen hastaların yaş ortalamasının 66.493 ± 13.988 yıl olduğu tespit edildi. Eşlik eden komorbiditeler ($p=0.017$), metastatik hastalık varlığı ($p=0.045$) ve plevral mayinin görüldüğü taraf ($p=0.032$) ile sağkalım süresi arasında istatistiksel olarak anlamlı bir ilişki bulundu. Uygulanan tedavi yöntemleri açısından yapılan değerlendirmede, torasentez uygulanan hastalar ile sağkalım süresi arasında istatistiksel açıdan anlamlı ilişki tespit edildi ($p=0.033$).

NLO sonuçları değerlendirildiğinde, yoğun bakım takibi yapılan hastalarda ($p=0.006$) ve mortalite grubunda ($p=0.014$) istatistiksel olarak anlamlı derecede yüksek olduğu görüldü.

ECOG performans skoru analizinde, yoğun bakımda izlenen olgularda ($p<0.001$) istatistiksel olarak anlamlı bir ilişki bulunurken, mortalite analizi ($p=0.203$) açısından değerlendirildiğinde anlamlı bir ilişki saptanmadı.

LENT risk skor sonuçlarına göre, yoğun bakımda takip edilen olgularda ($p<0.001$) ve mortalite analizinde ($p=0.003$) istatistiksel olarak anlamlı ilişki olduğu görüldü.

Sonuç: Çalışmamızda; minimal invaziv girişimlerden biri olan torasentez uygulanan hastalar ile sağkalım süresi arasındaki istatistiksel olarak anlamlı ilişki, hastaya yönelik tedavi yönteminin seçiminde prognozun belirlenmesinin önemli olduğunu ortaya koymaktadır.

Malignite nedeniyle takip edilen hastalarda plevral mayi tespit edildiğinde, LENT skorlamasının uygun olmadığı durumlarda prognoz hızla değerlendirilmesi açısından NLO değerinin kullanılabileceği düşünülmektedir. NLO'nun düşük maliyetli ve kolay hesaplanabilir olması, klinik karar sürecinde avantaj sağlayabilecek bir parametre olduğunu göstermektedir.

Anahtar Kelimeler: ECOG Performans Skalası, LENT Skoru, Malign Plevral Efüzyon, Nötrofil-Lenfosit Oranı, Paramalign Plevral Efüzyon

Abstract

Background: This study aims to investigate the clinical impact of serum neutrophil-to-lymphocyte ratio (NLR), Eastern Cooperative Oncology Group (ECOG) performance status, and LENT risk score (which includes serum lactate dehydrogenase (LDH), ECOG performance status, blood neutrophil-to-lymphocyte ratio (NLR), and tumor type (T)) on mortality and prognosis in patients with malignant pleural effusion.

Materials and Methods: This retrospective, observational, single-center study evaluated the outcomes of 73 patients who were followed between October 2022 and July 2024 due to malignant pleural effusion (MPE) and paramalignant pleural effusion (PMPE).

Results: The mean age of the included patients was 66.493 ± 13.988 years. A statistically significant relationship was found between survival time and the presence of comorbidities ($p=0.017$), metastatic disease ($p=0.045$), and the side of pleural effusion ($p=0.032$). In the analysis of treatment modalities, a statistically significant correlation was observed between survival time and patients who underwent thoracentesis ($p=0.033$).

Evaluating NLR results revealed significantly higher values in patients requiring intensive care monitoring ($p=0.006$) and in the mortality group ($p=0.014$). In the ECOG performance status analysis, a statistically significant association was found in patients monitored in the intensive care unit ($p<0.001$), while no significant relationship was observed in mortality analysis ($p=0.203$). According to the LENT risk score results, a statistically significant correlation was found in patients requiring intensive care follow-up ($p<0.001$) and in the mortality analysis ($p=0.003$).

Conclusions: Observing a statistically significant relationship between thoracentesis, as the least invasive method, and the number of survival days in patients suggests the importance of determining the prognosis when selecting a treatment approach. In cases of pleural effusion observed in patients with malignancy, whether or not they have a diagnosis of MPE, it can be suggested that the NLR may be used for rapid prognosis assessment when calculating the LENT score is deemed unsuitable. Its affordability and ease of calculation present significant advantages.

Keywords: ECOG Performance Status, LENT Score, Malignant Pleural Effusion, Neutrophil-to-Lymphocyte Ratio, Paramalignant Pleural Effusion

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Giriş

Plevral efüzyon yaygın olarak karşılaşılan bir klinik tablodur ve en sık nedenleri konjestif kalp yetmezliği, pulmoner hipertansiyon, pankreatit, siroz, pnömoni, malignite, tüberküloz ve romatolojik hastalıklar olarak bilinmektedir (1-3). İki bin yirmi bir yılında yapılan çalışmada; her yıl yaklaşık olarak 1,5 milyon yeni efüzyon vakasının tanımlandığı ve bu olguların % 15'inin malign efüzyon tanısı aldığı bildirilmiştir (4).

Plevral sıvının sitolojik değerlendirilmesinde veya plevral biyopside malign hücrelerin saptanması; malign plevral efüzyon (MPE) olarak tanımlanmaktadır (5). Malignite tanısı almış hastalarda; plevrada invazyon ya da sitolojide tümör hücreleri saptanmadığı durumlarda, tümörün dolaylı etkileri sonucu gelişen sıvı birikimi paramalign plevral efüzyon (PMPE) olarak değerlendirilmektedir. Bu durum; tümöral yapının plevrayı invaze etmeksizin postobstrüktif pnömoni, atelektazi, basıya bağlı venöz obstrüksiyon veya mediastinal lenf nodlarına bası sonucu lenf drenajının bozulması gibi sekonder nedenlere bağlı olarak da gelişebilir (5,6).

Torasentez, plevral kateter yerleştirilmesi, tüp torakostomi, plöredez uygulanması, torakoskopik cerrahi tedavi seçenekleri arasında yer almaktadır. Ayrıca, plöroperitoneal şant uygulanması, radyoterapi ve kemoterapi de seçenekler arasındadır. Tedavideki asıl amaç; mayinin direnajiyla akciğerin yeniden genişlemesinin sağlanması, semptomların azaltılması, yaşam kalitesinin düzeltilmesi ve tekrar sıvı birikiminin önlenmesidir.

Malignite tanısı olan olgularda plevral efüzyon gelişmesinin; yaygın veya ileri hastalığı gösterdiği bilinmektedir (7). Hatta MPE gelişiminin kötü prognoza işaret ettiği ve bu hastalarda beklenen yaşam süresinin 3 ila 12 ay arasında değiştiği gösterilmiştir (8). Takip sürecinde plevral efüzyon gelişen hastalarda tedavi yöntemi morbiditeyi etkileyebilir. Olguların klinik durumu ve prognozunun değerlendirilmesi, yaşam kalitesini korumak ya da iyileştirecek şekilde tedavilerinin planlanması açısından önem taşımaktadır.

MPE ile takip edilen vakaların sağkalımını incelemek amacıyla; plevral mayide serum laktat dehidrogenaz (LDH) sonucu, Doğu Kooperatif Onkoloji Grubu (ECOG) performans skoru, kan nötrofil/lenfosit oranı (NLO), tümörün tipi (T) parametrelerini kullanarak LENT risk skoru geliştirilmiştir (9). Bu çalışmada, malignite ile takipli; MPE veya PMPE gelişen olgular NLO, LENT risk skoru ve ECOG performans skoru değerlendirilmiştir. Elde edilen veriler analiz edilerek, bu skorların ve oranların mortalite ve prognoz tahmini üzerindeki klinik etkisinin incelenmesi amaçlanmıştır.

Materyal ve Metod

Retrospektif tanımlayıcı türde olan bu çalışma için Kayseri Şehir Hastanesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan onay alındı (Tarih: 30.07.2024, Karar No:145). Tüm çalışma Dünya Tıp Birliği Helsinki Bildirgesi'ne uygun olarak yürütüldü. Ekim 2022 ile Temmuz 2024 tarihleri arasında plevral efüzyon nedeniyle takip edilen malignite tanısı olan 176 hasta değerlendirildi. Çalışmaya; dahil edilme ve dışlama kriterlerini karşılayan 73 hasta alındı.

Hastalar; demografik özellikleri, komorbid hastalıkları, plevral mayi ile ilgili verileri, tedavi yaklaşımları, hastanede yatış süresi, yoğun bakım yatış varlığı, kan sonuçları, ECOG performans skoru, NLO, LENT skoru sonuçları ve mortalite ile değerlendirildi. Vefat eden hastaların sağ kalım süreleri mayiye müdahale edildiği gün not edilerek hesaplandı.

Hastaların çalışmaya dahil edilme kriterleri; 18 yaş ve üzeri MPE ve PMPE ile değerlendirilen hastalar çalışmaya alındı.

Çalışmadan dışlanma kriterleri; 18 yaşının altındaki olgular, laboratuvar verileri ve radyolojik görüntülemeleri elde edilemeyen hastalar değerlendirilmeye alınmadı.

İstatistiksel Analiz

Verilerin istatistiksel analizleri IBM SPSS (versiyon 26.0), TURCOSA (www.turcosa.com.tr) ve R programlama dili (versiyon 4.3.0, www.r-project.org) kullanılarak yürütüldü. Uygulanan analiz türü ve gereksinimlere göre ilgili yazılımlar bir arada kullanıldı.

Ölçek puanlarının gruplar arası karşılaştırmalarında student t-testi ve tek yönlü varyans analizi (ANOVA) testlerinden yararlanıldı. Normallik dağılımının sağlanmadığı durumlarda ise Mann-Whitney U testi ve Kruskal-Wallis testleri tercih edildi. Kategorik değişkenler bakımından gruplar arası karşılaştırmalarda ise Ki-Kare testlerinden (Pearson, Fisher, vb.) yararlanıldı.

Karşılaştırma yapılan gruplar bakımından sağkalım sürelerinin farklılık gösterip göstermediği Kaplan-Meier analizleri ile değerlendirildi. Yapılan tüm analizler için istatistiksel anlamlılık düzeyi $p < 0.05$ olarak kabul edilmiştir.

Bulgular

Çalışmada değerlendirilen 73 hastanın 45'i kadın, 28'i erkekti. Yaş ortalaması 66.493 ± 13.988 yıl (23-86 yaş) olarak hesaplandı. Yaş, komorbiditenin varlığı, metastatik hastalığın varlığı ve vefat eden olguların sayısı açısından incelendiğinde cinsiyetler arasında istatistiksel olarak anlamlı farklılık gözlemlenmedi (Tablo 1).

Malignite grupları arasında yapılan değerlendirmede, primer akciğer malignitesi olan 22, larinks kökenli 3, intestinal sistem kaynaklı 8, renal kökenli 2, pankreas kaynaklı 5, mesane kökenli 2, jinekolojik maligniteye sahip 4, primer meme malignitesi olan 3, hematolojik kökenli 10, ürogenital sistemden kaynaklanan 3, tiroid kökenli 1 ve iki primeri bulunan (akciğer ve intestinal kökenli) 1 hasta tespit edilmiştir. Gruplar içerisindeki hasta sayılarının düşük olması nedeniyle NLO, ECOG performans skoru genel olarak değerlendirilmiştir. LENT skorlaması içinde tümör tipine göre puanlandırılması yapılarak analiz edilmiştir.

Hastaların 39 (% 53,42) tanesinin yoğun bakımda takip edildiği, 58'inin (% 79,45) vefat ettiği belirlendi. Vefat eden hastaların sağkalım süreleri incelendiğinde; cinsiyetler arasında anlamlı bir farklılık tespit edilmedi ($p=0.759$). Komorbiditenin eşlik etmesi ($p=0.017$), metastatik hastalığın oluşu ($p=0.045$) ve plevral mayinin görüldüğü taraf ($p=0.032$) ile sağ kalım süresi kıyaslandığında aralarında istatistiksel açıdan anlamlı ilişki görüldü.

Uygulanan tedavi yönetimi açısından değerlendirildiğinde; torasentez yapılan olgularda hesaplanan sağ kalım süresi arasında istatistiksel açıdan anlamlı ilişki tespit edildi ($p=0.033$). Heimlich valf ile takip edilen hastalar ve sağ kalım süresi kıyaslandığında aralarında anlamlı ilişki olduğu bulundu ($p=0.011$). Bir hastaya tanınal amaçlı torakoskopik müdahale edilmiştir. Komplikasyon gelişen tüm hastaların yoğun bakım yatışı olduğu ve bu durumun istatistiksel olarak anlamlı olduğu tespit edilmiştir ($p<0.001$) (Tablo 2).

NLO ($p=0.136$), ECOG performans skoru ($p=0.512$) ve LENT risk skalası ($p=0.395$); cinsiyetler arasında kıyaslandığında istatistiksel açıdan anlamlı farklılık görülmedi. NLO ($p=0.014$) ve LENT risk skor ($p=0.003$) sonuçları mortalite analizi açısından değerlendirildiğinde aralarında anlamlı ilişki bulundu (Tablo 3).

Plevral sıvı sitoloji raporu sonuçları iki gruba ayrılarak değerlendirildi. Malign plevral efüzyon grubunda, sitoloji sonucu Class III, Class IV ve Class V olarak raporlanan olgular yer aldı.

Paramalign plevral efüzyon grubuna ise Class I ve Class II sitolojik sonuçları olan hastalar dâhil edildi. Malign ve paramalign plevral mayi grupları NLO, ECOG performans skoru, LENT risk skoru açısından kıyaslandığında aralarında anlamlı ilişki tespit edilmedi (Tablo 3).

NLO değeri, yoğun bakım yatışı olan olgularda 13.541 ± 8.411 ($p=0.006$), yoğun bakımda takibi yapılırken vefat eden hastalarda 14.054 ± 8.584 ($p=0.025$) ve tüm mortalite olgularında 12.023 ± 8.591 ($p=0.014$) olarak ölçülmüş olup, istatistiksel olarak anlamlı şekilde yüksek olduğu görüldü. ECOG performans skalası sonuçları değerlendirildiğinde; yoğun bakımdaki olgularda ($p<0.001$), yoğun bakımda vefat eden hastalarda ($p<0.001$) sonuçların ilişkili olduğu, mortalite açısından değerlendirildiğinde ($p=0.203$) anlamlı ilişki olmadığı görüldü. LENT risk skor sonuçları incelendiğinde; yoğun bakımda ($p<0.001$), mortalitede ($p=0.003$), yoğun bakımdayken vefat eden hastalar arasında ($p<0.001$) istatistiksel olarak anlamlı ilişki olduğu görüldü (Tablo 3).

Tablo 1. Hastaların demografik özellikleri

	Toplam (n=73)	Kadın (n=45)	Erkek (n=28)	p
Yaş	66.493 ± 13.988	65.533 ± 15	68.035 ± 12.291	0.461
Komorbid hastalık varlığı	52 % 71.23	35 % 47.94	17 % 23.28	0.117
Komorbid hastalık yokluğu	21 % 28.76	10 % 13.69	11 % 15.06	
Metastatik hastalık	58 % 79.45	39 % 53.42	19 % 26.02	0.053
Vefat eden hastalar	58 % 79.45	37 % 50.68	21 % 28.76	0.458

Tablo 2. Yoğun bakım takibi yapılan hastalar, vefat eden hastalar ve plevral mayiye müdahale edildikten sonra vefat eden olguların sağ kalım süreleri ile ilgili veriler verilmiştir. Mayinin tarafı, mayinin özelliği, müdahale yöntemleri ve takiplerine göre özellikleri değerlendirilmiştir.

		Toplam (n)	Yoğun bakım da takip edilen hastaların sayısı	P	Vefat eden Hastaların sayısı	p	*Mayi tespit edildikten sonra vefat eden hastaların sağ kalım süresi	p
Cinsiyet	Kadın	45 % 61.64	22 % 30.13	0.325	37 % 50.68	0.458	25 [12.5, 119.5]	0.759
	Erkek	28 % 38.35	17 % 23.28		21 % 28.76		35 [16.5, 84]	
Komorbid hastalığın eşlik ettiği olgular		52 % 71.23	25 % 34.24	0.149	42 % 57.53	0.661	60 [14.5, 158.5]	0.017
Metastatik hastalık varlığı		58 % 79.45	31 % 42.46	0.994	49 % 67.12	0.036	34 [14, 92]	0.045
Mayinin görüldüğü taraf								
Sol		29 % 39.72	15 % 20.54	0.813	21 % 28.76	0.227	35 [16, 61.5]	0.032
Sağ		44 % 60.27	24 % 32.87		37 % 50.68		31 [15.5, 189]	
Mayinin özelliği								
Eksuda		50 % 68.49	25 % 34.24	0.387	40 % 54.79	0.864	46.5 [19.5, 111]	0.610
Transuda		23 % 31.5	14 % 19.17		18 % 24.65		20.5 [10, 72.25]	
Tedavi yönetimi								
Gözlem ile takip edilen		7 % 9.58	4 % 5.47	0.836	7 % 9.58	0.157	25 [16, 385]	0.374
Torasentez yapılan		13 % 17.80	5 % 6.84	0.233	11 % 15.06	0.611	25 [16, 385]	0.033
Kateter torakostomi		46 % 63.01	27 % 36.98	0.239	35 % 47.94	0.353	34 [11, 85]	0.350
Tüp torakostomi		18 % 24.65	8 % 10.95	0.379	13 % 17.80	0.382	46 [24.5, 99]	0.166
Plörodez		18 % 24.65	10 % 13.69	0.835	15 % 20.54	0.639	34 [20, 85]	0.226
Hemlick valf ile takip edilen		4 % 5.47	3 % 4.10	0.374	4 % 5.47	0.575	36,5 [25, 60]	0.011
Cerrahi		1 % 1.36	1 % 1.36	1	1 % 1.36	1	34	0.976
Komplikasyon gelişmesi		12 % 16.43	12 % 16.43	<0.001	12 % 16.43	0.061	22.5 [8.5, 52.75]	<0.001

* Tanımlayıcı istatistikler Ortalama ± SS ya da Ortanca [Ç1, Ç3] olarak raporlanmıştır.

Tablo 3. NLO, ECOG performans skoru ve LENT risk skorunun analiz sonuçları gösterilmektedir.

	Nötrofil-lenfosit oranı (NLO)	p	ECOG Performans skalası				p	LENT SKORU			P
			1	2	3	4		Düşük risk grubu (skor 0-1)	Orta risk grubu (skor 2-4)	Yüksek risk grubu (skor 5-7)	
Kadın (n=45)	12.27 ± 8.758	0.136	1 % 1.36	19 % 26.02	18 % 24.65	7 % 9.58	0.512	7 % 9.58	11 % 15.06	27 % 36.98	0.395
Erkek (n=28)	9.352 ± 6.682		1 % 1.36	16 % 21.91	7 % 9.58	4 % 5.47		4 % 5.47	11 % 15.06	13 % 17.80	
Yoğun bakım takibi yapılan hastalarda (n=39)	13.541 ± 8.411	0.006	2 % 2.73	8 % 10.95	18 % 24.65	11 % 15.06	<0.001	3 % 4.10	4 % 5.47	32 % 43.83	<0.001
Serviste takip edilen hastalarda (n=34)	8.410 ± 6.877		0	27 % 36.98	7 % 9.58	0		8 % 10.95	18 % 24.65	8 % 10.95	
Takiplerine devam edilen hastalar (n=15)	7.782 ± 4.676	0.014	1 % 1.36	10 % 13.69	3 % 4.10	1 % 1.36	0.203	1 % 1.36	10 % 13.69	4 % 5.47	0.003
Vefat eden hastalar (n=58)	12.023 ± 8.591		1 % 1.36	25 % 34.24	22 % 30.13	10 % 13.69		10 % 13.69	12 % 16.43	36 % 49.31	
Yoğun bakım takibi yapılan ve vefat eden hastalarda (n=35)	14.054 ± 8.584	0.025	1 % 1.36	6 % 8.21	18 % 24.65	10 % 13.69	<0.001	2 % 2.73	2 % 2.73	31 % 42.46	<0.001
Plevral Mayi Sitolojisi											
* Paramalign plevral efüzyon grubu (n=33)	13.175 ± 8.556	0.052	2 % 2.73	14 % 19.17	14 % 19.17	3 % 4.10	0.144	4 % 5.47	9 % 12.32	20 % 27.39	0.643
* Malign plevral efüzyon grubu (n=40)	9.482 ± 7.404		0	21 % 28.76	11 % 15.06	8 % 10.95		7 % 9.58	13 % 17.80	20 % 27.39	

* Paramalign plevral efüzyon grubu; Class I ve Class II sitolojiyi içeren grup

* Malign plevral efüzyon grubu; Class III, Class IV ve Class V sitolojiyi içeren grup

Tartışma

Kanser insidansındaki artış ve tedavi yöntemlerindeki ilerlemeler sonucunda, MPE olgularında artış yaşanmasının beklenildiği ileri sürülmüştür (10). Kanser nedeniyle hayatını kaybeden olgular arasında yapılan postmortem çalışmalarda; hastaların %15'inde MPE bulunduğu rapor edilmiştir (11). Çalışmamızda PMPE ve MPE sonuçları kıyaslanarak değerlendirildi. MPE ile izlenen hastaların yaş aralığı incelendiğinde, %83'ünün 50 yaşın üzerinde olduğu bildirilmiştir (12). Çalışmamızda yaş ortalamasının 66.493±13.988 yıl olduğu hesaplandı. Deniz et al. akciğer kanseri ile takip edilen olgularda yaptıkları çalışmada, MPE'nin kadın hastalarda daha sık olduğu gösterilmiştir (13). 2020 yılında yayınlan başka bir çalışmada MPE nedeniyle takip edilen hastalarda erkek olguların sayısının daha yüksek olduğu gösterilmiştir (14). PMPE'lu hastaların değerlendirildiği iki çalışmada cinsiyetler arasında farklılık tespit edilmediği yayınlanmıştır (14, 15). Bu çalışmada kadın, erkek cinsiyet arasında istatistiksel olarak anlamlı bir farklılık saptanmadı.

İngiliz Toraks Derneği tarafından yayımlanan kılavuzlar, beklenen yaşam süresinin bir aydan kısa olduğu olgularda terapötik torasentez yapılmasını önermektedir (9, 16). Çalışmamızda; tedavi, takip yöntemleri arasından sadece torasentez yapılan ve Heimlich valfi ile takip edilen hastaların

sağkalım süresi istatistiksel açıdan değerlendirildiğinde, anlamlı ilişki olduğu görüldü.

Nötrofil-lenfosit oranı kolorektal, pankreas, hepatosellüler ve küçük hücreli dışı akciğer kanseri gibi birçok kanser türünde risk faktörü olarak kabul edilen sistemik bir inflamatuvar belirteçtir (17, 18). Lee ve ark. serum NLO skorlarının, MPE'li akciğer kanseri hastalarında genel sağkalım açısından önemli bir prognostik faktör olduğunu yayınlamışlardır (19). Otoshi ve ark. serum NLO ile malign plevral mezotelyomalı hastaların sağkalımı arasında bir ilişki saptamadıklarını bildirmişlerdir (20). Bununla birlikte, serum NLO değerindeki yüksekliğin MPE, malign mezotelyoma ve küçük hücreli olmayan akciğer kanseri de dahil olmak üzere malignite vakalarında zayıf sağkalımla ilişkili olduğu birçok çalışmada gösterilmiştir (9, 21-28).

Templeton ve ark. tarafından solid tümörlerde yapılan sistematik incelemede, NLO için medyan sınır değerinin 4 olduğu bildirilmiştir (21). Yapılan çalışmalarda, MPE' de serum NLO değerinin 3 ila 9 arasındaki kesme değerlerinde düşük sağkalım ile ilişkilendirilmiştir (21, 23-28). 2021 yılında yapılan bir çalışma, MPE'de kan NLO>5 olan olgularda genel sağkalımın önemli ölçüde daha kötü olduğunu gösterdi (29). Bizim çalışmamızda vefat eden olgulardaki NLO değeri 12.023±8.591 olarak kaydedilirken, takibi devam

eden diğer olgularda NLO değeri 7.782 ± 4.676 olarak tespit edildi. PMPE ve MPE olgularında NLO değeri ortalaması yüksek olmakla birlikte; aralarında istatistiksel olarak anlamlı farklılık görülmedi. Eksüda vafında plevral efüzyon nedeniyle 465 hastanın incelendiği çalışmada; MPE ve PMPE olgularının NLO medyan değerleri kıyaslandığında istatistiksel olarak anlamlı bir farklılık görülmediği yayınlanmıştır (30). ECOG performans skorunun, kanser hastalarında prognostik bir faktör olarak kullanıldığını raporlayan çalışmalar mevcuttur (22, 31-33).

Anevlavis ve ark. MPE olgularında ECOG performans skorunun derecesinin, primer tümör tipinin ve NLO'nun sağkalımı etkileyen prognostik faktörler olduğunu bildirmiştir (22). Yayınlanan başka bir çalışmada MPE ile takip edilen hastalar arasında ECOG performans skoru 1 olanların, skor değeri 4 olanlara kıyasla daha uzun sağkalım süresine sahip olduğu bildirilmiştir (31).

Bizim analizimizde; ECOG performans skoru, MPE ve PMPE nedeniyle yoğun bakımda takip edilen ve yoğun bakımda vefat eden hastalar arasında prognostik açıdan ilişkili olduğu görüşü çıkarılmaktadır.

LENT risk skorunun ECOG ile kıyaslandığı bir yayında; LENT skorunun sağkalımı öngörmede daha iyi performans gösterdiği bildirilmiştir (9). LENT risk skorlama sistemi değerlendirildiğinde; riskin yüksek olduğu hastalarda yoğun bakım yatışı ($p < 0.001$), mortalite ($p = 0.003$) ve yoğun bakım-da takipliyken vefat eden hastalar ($p < 0.001$) arasında istatistiksel olarak ilişki olduğu hesaplanmıştır.

MPE'lerde üç yıl süren bir çalışmada, LENT risk skoruna göre orta risk grubunda mortalitenin yüksek olduğu, düşük risk grubunda ise mortalite görülmediği bildirilmiştir (34).

MPE'da kalıcı plevral kateter yerleştirilmesi sonrası vakaların LENT skoru değerlendirildiğinde; Clive ve ark. yüksek risk grubunda ortalama sağkalım süresini 44 gün, Abisheganaden ve ark. 190,5 gün, Akram ve ark. ise 35 gün olarak hesaplamıştır (9,35,36).

Gayaf ve ark. 'un yaptığı çalışmada MPE'de 1 aylık ve 12 aylık mortalite değerlendirildiğinde LENT risk skorunun kesme değeri >4 olarak tespit edilmiş ve istatistiksel olarak anlamlı görülmüştür (37). Çalışmamızda; yoğun bakımda takip edilen, yoğun bakım sürecinde vefat eden hastalar ve genel mortalite açısından değerlendirildiğinde, LENT risk skorunun 5-7 arasında olduğu ve bu hastaların yüksek risk grubunda yer aldığı tespit edilmiştir. Bu durum istatistiksel olarak anlamlı bulunmuştur.

Yapılan farklı bir çalışmada, sitolojik ya da histolojik değerlendirme sonucuna göre malign efüzyon tanısının konulmadığı durumlarda, plevral efüzyonun kanser hastaları için kötü prognozla ilişkili olduğu vurgulanmıştır (38). Grendelmeier ve ark. ise MPE'li olgularda LENT skorunun sağkalımı tahmin etmede güçlü olduğunu ancak klinik olarak şüpheli MPE veya paramalign efüzyon grupları için genelleme yapamadığını belirtmişlerdir (39). Benzer olarak bizim çalışmamızda da MPE ve PMPE efüzyonlu hastalarda karşılaştırılan NLO, ECOG performans skoru ve LENT risk skalası açısından anlamlı farklılık yoktu.

Sonuç

MPE gelişen hastalarda prognozun genellikle kötü olduğu bilinmektedir. Çalışmamızda, metastatik hastalık varlığı ve plevral sıvının sağ tarafta yer almasının sağkalım süresi ile ilişkili olabileceği ve prognozun değerlendirilmesinde önemli bir faktör olarak dikkate alınabileceği görülmüştür. NLO ve LENT risk skoru prognozu öngörmede önemli parametreler olup, yoğun bakım yatışı, mortalite ve yoğun bakımda takip edilen hastaların ölüm oranları ile istatistiksel olarak anlamlı bir ilişki göstermiştir. Prognostik değerlendirme sonucunda klinik gerekliliklere göre tekrarlayan drenaj işlemleri hastaların semptomatik rahatlamasına ve sağkalım süresinin uzamasına katkı sağlayabilir.

MPE tanısı kesinleşmemiş ya da malignite nedeniyle takip edilen ancak plevral efüzyonu yeni gelişen hastalarda, LENT skoru hesaplamasının mümkün olmadığı durumlarda, prognozun hızlı bir şekilde belirlenmesine yardımcı olabilecek ucuz ve kolay bir yöntem ile fikir edinebilmek için NLO'nun kullanılabileceği düşünülmektedir. Sonuçların genellenebilmesi için çok merkezli, prospektif daha çok çalışmaya ihtiyaç duyulmakla birlikte; elde edilen bulguların, uygun tedavi yaklaşımının belirlenmesinde yol gösterici olacağı düşünülmektedir.

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Nadir Hastalıklar Gerçekten Nadir Mi? Nedeni Bilinmeyen Hepatosplenomegalili Hastalarda Gaucher Hastalığı Taraması

Are Rare Diseases Really Rare? Gaucher Disease Screening in Patients with Hepatosplenomegaly of Unknown Origin

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Öz

Amaç: Gaucher hastalığı (GH) nadir görülen, otozomal resesif (OR) geçişli, lizozomal depo hastalığıdır. En sık tip 1 GH görülmekte olup, yaklaşık %80'inde hepatomegali, %90'ında splenomegali saptanır. Bu çalışmada hepatosplenomegali saptanan ve nedeni bulunamayan hastalarda GH sıklığı araştırılmıştır.

Materyal ve metod: Eylül 2016- Mayıs 2019 tarihleri arasında polikliniğine başvuran, gastroenteroloji, hematoloji ve enfeksiyon tetkikleri sonrası hepatomegali ve/veya splenomegalinin etiyolojik nedeni saptanamayan hastalar çalışmaya alındı. Hastalardan kuru kan testi için hazırlanmış hazır formlara, parmak ucundan bir damla kan alındı ve tetkik için Viyana (Avusturya)'da bulunan Archimed laboratuvarına gönderildi. Beta-glukoserebrosidaz için cut-off>2,5, asid-sfingomyelidaz için >0,9 mikromol/L alındı.

Bulgular: Tarama yapılan 22 hastadan 11 tanesi (% 50) kadın, yaş ortalaması 38,86 ± 13,78 (yaş dağılımı 20-76) idi. GH düşünülen dört hastanın ikisi (%50 kadın), yaş ortalaması 43,2 ± 16,7 (yaş dağılımı 20-60) idi. Beta-glukoserebrosidaz düzeyi cut-off değerinin altında altı hasta (%26) saptandı. Mutasyon saptanan, ikisinde asid-sfingomyelidaz düzeyi de düşük ve ikisinde aile hikayesi olan dört hastanın (%18,0), tip1 GH olduğu görüldü.

Sonuç: Sık görülen hastalıklar ekarte edildikten sonra nedeni halen saptanamayan hepatomegali ve/veya splenomegalisi olan hastaların taramasında, hastaların dörtte birinde beta-glukoserebrosidaz enzim düşüklüğü saptanmış, 22 hastadan dört tanesine tip 1 GH tanısı konulmuştur. İyi araştırılmış bu hastalarda tarama yapıldığında nadir görülen bir hastalık olarak bilinen GH'nın bu grup için nadir olmadığı gösterilmiştir.

Anahtar Kelimeler: Hepatomegali, Splenomegali, Gaucher hastalığı

Abstract

Background: Gaucher disease (GD) is a rare, autosomal recessive lysosomal storage disorder. Type 1 GD is the most common type, with hepatomegaly observed in approximately 80% of patients and splenomegaly in about 90%. This study investigated the frequency of GD in patients presenting with hepatosplenomegaly of unknown etiology. This study aimed to determine the frequency of GD in patients with hepatosplenomegaly of unknown etiology.

Materials and Methods: Patients who presented to the outpatient clinic between September 2016 and May 2019 and had no detectable cause for hepatomegaly and/or splenomegaly following comprehensive gastroenterological, hematological, and infectious disease assessments were enrolled in the study. Capillary blood samples were collected via finger prick and applied to standardized dried blood spot cards. The samples were subsequently analyzed at Archimed Laboratory (Vienna, Austria). Enzymatic activity cut-off values were defined as >2.5 µmol/L for β-glucocerebrosidase and >0.9 µmol/L for acid sphingomyelinase.

Results: Of the 22 patients screened, 11 (50%) were female, with a mean age of 38.86 ± 13.78 years (range: 20–76). Among the four patients evaluated for Gaucher disease (50% female), the mean age was 43.2 ± 16.7 years (range: 20–60). Beta-glucocerebrosidase activity was below the cut-off value in six patients (26%). Four patients (18%) were found to carry pathogenic mutations; among them, two had reduced acid sphingomyelinase activity, and two had a positive family history. Based on these findings, type 1 Gaucher disease was considered in these four patients.

Conclusions: Following the exclusion of common causes, screening of patients with hepatomegaly and/or splenomegaly of unknown etiology revealed low beta-glucocerebrosidase activity in approximately one-fourth of the cases, and type 1 Gaucher disease was diagnosed in 4 out of 22 patients. These findings suggest that in a well-characterized cohort, Gaucher disease, although typically considered a rare disorder, may be more frequent than previously thought.

Keywords: Hepatomegaly, Splenomegaly, Gaucher Disease

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Giriş

Gaucher hastalığı, glukoserebrosidaz (GBA1) genindeki mutasyonların neden olduğu, otozomal resesif, doğuştan gelen ve lizozomal depo hastalıklarının en sık görülen formudur (1). Bu hastalık geleneksel olarak klinik bulgulara, seyrine ve hastanın etnik kökenine göre alt tiplere ayrılmıştır. Tip 1 GH (GH1, yetişkin tipi) en yaygın biçimdir. Tip 2 GH (GH2, infantil) en şiddetli formdur ve 2 yıldan az yaşam beklentisi ile yaşamın ilk 6 ayında başlar. Tip 3 GH'de (GH3, juvenil), hastalarda hem visseral tutulum hem de nörolojik bulgular bulunur ve daha uzun sağ kalım vardır (2).

Tip 1 GH esas olarak visseral tutulumla ait belirtilerle karakterizedir. Belirti ve semptomlar arasında splenomegali, hepatomegali, trombositopeni, anemi, kemik hastalığı ve yorgunluk bulunur. Tip 2 GH ve tip 3 GH'ında nörolojik tutulum vardır. Tip 2 GH'ında hızlı ilerleyen, yaşamın ilk yıllarında ölüme yol açan, Tip 3 GH'da ise daha hafif nörolojik bulgular vardır (3). Tip 1 GH'ında klinik prezentasyon çocukluk çağında erken başlangıçlı formlardan yaşam boyu semptomsuza kadar değişmektedir (4).

GH'nin teşhisinde, daha az invaziv ve sağlam enzimatik testin mevcut olması ve kemik iliği muayenesinin, trombositopeni ve koagülopatiyeye bağlı kanama komplikasyonlarına neden olabileceği nedeniyle rutin kemik iliği muayenesi önerilmemektedir (5).

Tip 1 GH için enzim replasman tedavisi (ERT) ve substrat azaltma tedavisi (SRT) olmak üzere iki farklı tedavi yaklaşımı mevcuttur. İntravenöz olarak uygulanan ERT'nin, makrofajlara yöneliktir ve biriken glikolipidlerin parçalanmasını artırır, hastalığın iç organ ve hematolojik komplikasyonlarının tedavisinde çok etkili olduğu kanıtlanmıştır (6-10).

Bu çalışmada hepatosplenomegalisi tespit edilerek tetkik edilen ve nedeni bulunamayan hastalarda GH sıklığının araştırılması; nadir görüldüğü bilinen bu hastalığın gerçekten nadir görülüp görülmediğinin tespit edilmesi amaçlanmıştır.

Materyal ve Metod

Eylül 2016- Mayıs 2019 tarihleri arasında Harran Üniversitesi Tıp Fakültesi Gastroenteroloji Polikliniğine başvuran, gastroenteroloji, hematoloji ve enfeksiyon tetkikleri sonrası hepatomegali ve/veya splenomegalinin etiyolojik nedeni saptanamayan hastalar çalışmaya alındı. Harran Üniversitesi Etik Kurulu'ndan etik kurul onayı (Karar no: HRÜ/2022/25/28)

alındı. Hastalardan kuru kan testi için hazırlanmış hazır formlara, parmak ucundan bir damla kan alındı ve tetkik için Viyana (Avusturya)'da bulunan Archimed laboratuvarına gönderildi. Beta-glukoserebrosidaz için cut-off>2.5, asid-sfingomyelidaz için >0,9 mikromol/L alındı (11). Etiyolojik nedeni bilinen, test yaptırmak istemeyen hastalar ve 18 yaş altı hastalar çalışmaya alınmadı.

İstatistiksel analiz

İşlenmiş (sınıflandırılmış veya grafiklendirilmiş) verilerin temel özelliklerinin belirlenmesi için tanımlayıcı istatistiklerden faydalanılmış bu analizler SPSS 20 programında yapılmıştır. Veriler ortalama $\pm$ standart sapma olarak belirtilmiştir. Tüm veriler tanımlayıcı olarak özetlenerek istatistiksel testlere yer verilmemiştir. Kategorik değişkenler için tanımlayıcı istatistikler grubundan olan ortalama ve standart sapma (SD) kullanılmış, sürekli değişkenler için ise yüzde (%) ve aralıklar olarak ele alarak değerlendirilmiştir.

Bulgular

Yapılan tanımlayıcı istatistik sonuçlarında tarama yapılan 22 hastanın 11 tanesinin (%50) kadın, yaş ortalamasının $38,86 \pm 13,78$ (dağılım 20-76) yıl arasında değişiklik gösterdiği gözlemlenmiştir. Hastaların tamamında beta-glukoserebrosidaz düzeyi, 15 tanesinde asid-sfingomyelidaz düzeyi çalışılmıştır. Asid-sfingomyelidaz düzeyi bakılan on beş hastadan iki tanesinde (%13,3) enzim düzeyi düşük bulundu, bu hastaların eş zamanlı olarak beta-glukoserebrosidazının da düşük olduğu görüldü.

Beta-glukoserebrosidaz düzeyi cut-off değerinin altında yirmi iki hastadan altı hasta (%27,2) saptandı ve bu hastalarda gen mutasyonu çalışıldı. Bu hastaların yirmi ikisinin dördünde (%18,1) mutasyon saptandı, aynı zamanda bu dört hastanın ikisinde asid-sfingomyelidaz düzeyi de düşüktü ve yine bu dört hastanın ikisinde aile hikayesi vardı. Bu hastaların Tip1 GH olduğu düşünüldü.

GH düşünülen bu 4 hastanın ikisi (%50 kadın), yaş ortalaması $43,2 \pm 16,7$ (yaş dağılım 20-60 yıl) idi. Hastalar yaş sırasıyla 20 yaş kadın, 46 yaş kadın, 47 yaş kadın, 60 yaş erkek idi.

Hastalardan 2 tanesinde beta-glukoserebrosidaz cut-off değerine göre sınırdışı düşüktü, asid-sfingomyelidaz düzeyleri normal saptandı, bakılan glukoserebrosidaz (GBA) gen analizlerinde de mutasyon saptanmadığı için GH düşünülmedi ve takibe alındı. Bu bulgular Tablo 1'de özetlenmiştir.

Tablo 1. Gaucher Hastalığı İçin Taranan Hastalar

Demografik ve Tarama Özellikleri	Taranan hastalar (n=22)	Tip 1 GH (n=4)
Taranan hasta sayısı, n (%)	22	4 (%18,1)
Yaş ortalaması (Yıl $\pm$ SS)	$38,86 \pm 13,78$	$43,2 \pm 16,7$
Cinsiyet dağılımı, n (%)	11 (% 50)	2 (% 18,1)
Kadın	11 (% 50)	2 (% 18,1)
Erkek	22	4 (% 18,1)
Beta-glukoserebrosidaz, n (%)	15	2 (% 13,3)
Asid-sfingomyelidaz, n (%)	6	4 (% 66,6)
GBA gen taraması, n (%)		

GH: Gaucher hastalığı, K: kadın, E: erkek

Tartışma

GH tanısı genellikle ilk klinik ve laboratuvar bulguların başlamasından birkaç yıl sonra konulabilir. Bu durum ilerleyici semptomların başlangıcı ile karakterize nadir hastalıklarda görülen tipik bir sorundur. Tip 1 GH'nın, klinik prezentasyonu çocukluk çağında erken başlangıçlı formlardan yaşam boyu semptomsuza kadar değişmektedir. İlk semptomlar oldukça değişkendir ve hastalara her yaşta tanı konabilir. Hepatomegali, hastaların % 60-80'inde görülür. Splenomegali, hastaların % 90'ından fazlasında görülür ve bazen masiftir (4,12,13). Aslında, hepatosplenomegali tek klinik işaret olabilir ve GH düşünülmezse gereksiz testlere yol açabilir (14).

Biz de çalışmamızda hepatosplenomegali ile başvurmış gastroenterolojik, hematolojik ve enfeksiyöz açıdan tetkik edilmiş ancak nedeni bulunamamış 22 hastada GH sıklığını araştırmayı amaçladık.

2017'de 11 ülkeyi içeren toplam 1209 hastada yapılan bir çalışmada tip 1 GH için yaş ortalaması 40,4 yıl olarak saptanmıştır (15). Bizim çalışmamızda taradığımız hastaların yaş ortalaması 38,8 yıl olup, GH saptanan hastaların yaş ortalaması literatürle uyumlu olarak 43,2 idi.

GH asit glukoserebrosidazı kodlayan GBA1 genindeki mutasyonlardan kaynaklanır. Bu enzimin azaltılmış aktivitesi, özellikle makrofajların lizozomal bölmesinde ortaya çıkan glukozilseramid birikimine neden olur ve bu hücreler "Gaucher hücreleri" olarak adlandırılır (3). GH için tanısıl test periferik kan lökositlerinde düşük asit beta-glukozidaz aktivitesinin gösterilmesidir (normal aralık 2,1-5,3 µmol/l/saat). GH teşhisi için altın standart olan enzim aktivitesi, genellikle florometrik bir analizde substrat 4-metilumbelliferil-β-D-glikopirranranid kullanılarak periferik kan lökositlerinde ölçülür (16). Biz de tanıda aynı yöntemlerden yararlandık.

Klinik değişkenlik kısmen spesifik GBA mutasyonları ile açıklanabilir. P.N370S aleli, homozigot veya bileşik heterozigot olduğunda, her zaman Tip 1 GH'a neden olur (17). Çalışmamızda dört hastada gen mutasyonu saptandı, bu hastalardan bir tanesinde bileşik heterozigot gen mutasyonu vardı.

GH tanısında klinik şüphe önemli bir parametredir. Hepatosplenomegali, trombositopeni, anemi, karakteristik kemik lezyonları ve özellikle Tip 2 ve Tip 3 için nörolojik tutulum varlığında GH akla gelmelidir. Sonuç olarak iyi araştırılmış, nedeni bilinmeyen hepatosplenomegalili hastalarda tarama yapıldığında nadir görülen bir hastalık olarak bilinen GH bu grup hastalar için nadir değildir.

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The Role of Inflammatory Indices in Predicting Pancreatic Fistula After Distal Pancreatectomy

Distal Pankreatektomi Sonrası Pankreatik Fistül Gelişimini Tahmin Etmede İnflamatuar İndekslerin Rolü

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Abstract

Background: The significance of inflammatory markers in forecasting pancreatic fistula development has not been thoroughly investigated in patients who have undergone distal pancreatectomy. This study seeks to assess the predictive value of postoperative inflammatory indices, particularly SII (systemic immune inflammation index), NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio), concerning the onset of pancreatic fistula in these patients.

Materials and Methods: This retrospective study analyzed patients who underwent distal pancreatectomy for pancreatic cancer between January 2020 and December 2023. Statistical analyses were performed by retrospectively examining the data obtained from the prospectively filled clinical notes of patients who developed pancreatic fistula (Grade B and C) using the SII, NLR and PLR calculated based on the laboratory results obtained on the third postoperative day.

Results: The study included 72 patients who fulfilled the established criteria. Pancreatic fistulas were observed in 25 (34.7%) of the patients. In this study, BMI and soft pancreatic tissue were statistically significant risk factors for pancreatic fistula development ($p=0.02$ for both). SII and NLR from the third postoperative day were statistically significant predictors of pancreatic fistula development, while postoperative PLR did not provide statistically significant results. SII was a more significant predictor of pancreatic fistula than NLR.

Conclusions: This study conveys that monitoring the increase in SII and NLR, which are inflammation-related indices, is an effective method for predicting the development of pancreatic fistula after distal pancreatectomy, whereas PLR is not effective in predicting the development of pancreatic fistula.

Keywords: Distal pancreatectomy, Pancreatic fistula, SII, NLR, PLR

Öz

Amaç: İnflamatuar belirteçlerin, distal pankreatektomi sonrası pankreatik fistül gelişimini tahmin etmedeki önemi, bu konuda yapılan çalışmalarla yeterince derinlemesine incelenmemiştir. Bu çalışma, distal pankreatektomi yapılan hastalarda postoperatif inflammatuar indekslerin, özellikle SII (sistemik immün inflamasyon indeksi), NLR (nötrofil-lenfosit oranı) ve PLR (trombosit-lenfosit oranı), pankreatik fistül gelişimi ile ilişkisini değerlendirmeyi amaçlamaktadır.

Materyal ve Metod: Bu retrospektif çalışmada, Ocak 2020 ile Aralık 2023 arasında pankreatik kanser nedeniyle distal pankreatektomi uygulanan hastalar analiz edilmiştir. İstatistiksel analizler, pankreatik fistül (B ve C dereceleri) gelişen hastaların, üçüncü postoperatif günde elde edilen laboratuvar sonuçlarına dayalı olarak hesaplanan SII, NLR ve PLR verileri retrospektif olarak incelenerek yapılmıştır.

Bulgular: Çalışmaya, belirlenen kriterlere uyan 72 hasta dahil edildi. Bu hastaların 25'inde (% 34.7) pankreatik fistül gözlemlendi. Bu çalışmada, BMI ve yumuşak pankreatik doku pankreatik fistül gelişimi için istatistiksel olarak anlamlı risk faktörleri olarak bulundu (her ikisi için $p=0.02$). Postoperatif üçüncü günde ölçülen SII ve NLR, pankreatik fistül gelişiminin istatistiksel olarak anlamlı prediktörleri olurken, postoperatif PLR'nin pankreatik fistül gelişimini tahmin etmede istatistiksel anlamlı sonuç vermediği görüldü. SII'nin pankreatik fistül gelişiminin tahmin edilmesinde NLR'den daha güçlü bir prediktör olduğu görüldü.

Sonuç: Bu çalışma, inflamasyonla ilişkili indeksler olan SII ve NLR'deki artışın, distal pankreatektomi sonrası pankreatik fistül gelişiminin tahmin edilmesinde etkili bir yöntem olduğunu göstermektedir. Buna karşılık, PLR'nin pankreatik fistül gelişimini tahmin etmede etkili olmadığı görüldü.

Anahtar Kelimeler: Distal pankreatektomi, Pankreatik fistül, SII, NLR, PLR

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Introduction

Regardless of the surgical technique employed for pancreatic cancer, morbidity and mortality rates remain high. Complication rates following distal pancreatectomy vary between 9% and 30%, with pancreatic fistula being the most significant complication. Other general complications are bleeding, intra-abdominal abscesses, and delayed gastric emptying (1,2).

Pancreatic Fistula definition was revised in 2016. According to this new definition, drain amylase levels that indicate a grade A fistula are considered biochemical leaks rather than true pancreatic fistulas (3).

In the literature, it is stated that deaths after distal pancreatectomy are 3% and morbidity varies between 22% and 47%. The rate of pancreatic fistula development after surgery are between 15% and 31%. Since there is no anastomosis in distal pancreatectomy, pancreatic fistulas that arise after the procedure typically close on their own and seldom necessitate reoperation (2-4).

Methods like closing the pancreatic stump with staples or stitches, using tissue adhesives, administering prophylactic octreotide and using cautery or scalpel techniques for cutting the pancreas, have not proven effective in preventing pancreatic fistula formation after distal pancreatectomy. Fistula development rate may be affected by patient-related factors rather than the surgical approach itself. Reasons such as advanced age, obesity, intraoperative bleeding, high ASA score, concurrent splenectomy, vascular resection, and hypoalbuminemia have been associated with an increased risk of developing pancreatic fistula (1,4,5).

In last years, a broader array of biological markers has been increasingly utilized in clinical practice due to their cost-effectiveness and easy accessibility. One such markers are the complete blood count (CBC), that is a straightforward, widely available, and economical test. This test provides detailed counts of various blood cell types, including neutrophils, platelets, and lymphocytes. From these counts, several inflammation-related indices can be derived, such as the systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). Many researchs have shown significant associations between these inflammation-related indices and a wide range of diseases, including infectious, neoplastic, metabolic, autoimmune, and cardiovascular diseases (6,7).

The role of inflammatory markers in predicting the development of pancreatic fistulas hasn't been extensively studied in patients who have had distal pancreatectomy. This research aims to evaluate the predictive significance of postoperative inflammatory indices, specifically SII, NLR, and PLR, in relation to the occurrence of pancreatic fistulas in these individuals.

Materials and Methods

Study design

Postoperative pancreatic fistula (POPF) was categorized according to the criteria established by the International Study Group on Pancreatic Fistula (ISGPF) (3). Data regarding laboratory results for patients who experienced pancreatic fistula (Grades B and C) were collected through a retrospective review of prospectively maintained clinical records.

The study included patients aged 18 to 75 who underwent distal pancreatectomy for pancreatic ductal adenocarcinoma between January 2020 and December 2023 in Atılım University Faculty of Medicine-affiliated Medicana International Ankara Hospital. Those with benign conditions, other malignancies aside from adenocarcinoma, individuals who received palliative surgery, patients with distant metastases (M1), concurrent malignancies, different surgical procedures apart from distal pancreatectomy, autoimmune diseases, a history of previous malignancy, and those who had neoadjuvant chemotherapy or radiotherapy were excluded.

Parameters such as age, sex, BMI, stump closure technique, tumor diameter, number of metastatic lymph nodes, and pancreatic texture were evaluated. The consistency of the pancreatic tissue, whether firm or soft, was subjectively assessed by the operating surgeon through palpation based on their experience, after resection and immediately before the pancreaticojejunostomy.

A drain was routinely inserted intraperitoneally to monitor patients during the postoperative period. Antibiotics (ceftriaxone 1gr and metronidazole 500mg) were administered to all patients for five days postoperatively. Octreotide was not routinely used in the postoperative period. Blood cell counts were obtained on postoperative day (POD) 3. All blood cell counts will be represented as $\text{count} \times 10^3/\mu\text{L}$.

$\text{SII} = [\text{platelet count (PLT)} \times \text{neutrophil count (NC)}] / \text{lymphocyte count (LC)}$

$\text{NLR} = \text{neutrophil count} / \text{lymphocyte count}$

$\text{PLR} = \text{platelet count} / \text{lymphocyte count}$

Statistical Methods

Statistical analysis was performed using SPSS v27, with a significance threshold set at $p < 0.05$. The normality of continuous variables was assessed using Skewness and Kurtosis tests. Data that conformed to a normal distribution are presented as mean $\pm$ standard deviation (SD). For data that did not follow a normal distribution, results are shown as median (25th–75th percentile). Categorical variables are reported as counts and percentages. The Independent-samples t-test, Mann–Whitney U test and chi-squared test were used to compare the groups.

The predictive value of variables was assessed using a receiver operating characteristic (ROC) curve, with the occurrence of Grade B and C pancreatic fistula defined as the primary endpoint for this analysis. Areas under the ROC curve (AUROC) were calculated for postoperative SII, NLR, and PLR. The results of the ROC analysis, including sensitivity and specificity, were examined, and the highest values were determined as cut-off points. Consequently, AUROC, confidence intervals (CI), and p-values were compared.

Results

Between January 2020 and December 2023, 121 patients who underwent distal pancreatectomy in our clinic were evaluated. The study included a total of 72 patients who fulfilled the established criteria. An open surgery including splenectomy was performed on all patients. Pancreatic fistulas were observed in 25 (34.7%) of the patients. Patient information, including age, gender, body mass index (BMI),

pathological results, pancreatic stump closure, and the condition of pancreatic tissue in the presence of pancreatic fistula, is presented in Table 1.

In this study, BMI and the presence of soft pancreatic tissue were identified as statistically significant risk factors for the development of postoperative pancreatic fistula (POPF). In this study, the cut-off values for the postoperative inflammatory indices were established as follows: the SII was set at 1881, resulting in 92% sensitivity and 51% specificity; the NLR at 8.4, which also achieved 92% sensitivity and 51% specificity; and the PLR at 170, which yielded a sensitivity of 55% and specificity of 68%. Postoperative SII and NLR were found to be statistically significant predictors of POPF development, with SII showing a stronger predictive capability than NLR. In contrast, postoperative PLR did not yield statistically significant results for predicting POPF. The comparisons of AUROC, CI, and p-values for postoperative SII, NLR, and PLR are illustrated in Table 2 and Figure 1.

Table 1. Patient Characteristics, Pathological Findings and Pancreatic Fistula Outcomes

	Pancreatic Fistula (+)	Pancreatic Fistula (-)	p
Age	61.8 (±6.1)	58.7 (±8.9)	0.08
Gender			
Male	10 (13.9%)	20 (27.8%)	0.8
Female	15 (20.8%)	27 (37.5%)	
Body Mass Index (BMI)	30.4 (±3.8)	28.3 (±2.6)	0.02
Stump Closure Technique			
Stapler	24 (33.3%)	41 (56.9%)	0.4
Suture	1 (1.4%)	6 (8.4%)	
Pancreatic Tissue			
Soft	14 (19.4%)	13 (18.1%)	0.02
Firm	11 (15.3%)	34 (47.2%)	
Tumor Size (mm)	45.4 (±21.8)	39.8 (±23.6)	0.3
Metastatic lymph node	0 (0-2)	0 (0-1)	0.33

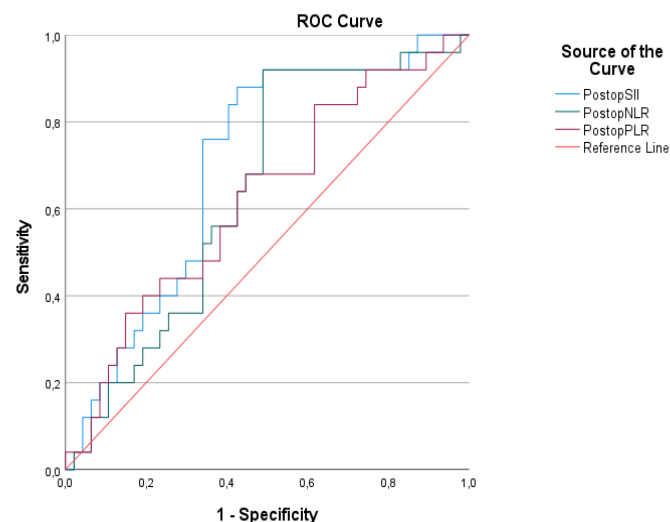


Figure 1. Comparison of postoperative SII, NLR and PLR with ROC analysis to predict pancreatic fistula development of patients

Table 2. Comparison of postoperative SII, NLR and PLR with ROC analysis to predict pancreatic fistula development of patients

	AUROC	Confidence Interval (CI)	Std. Error	p value
Postoperative SII	0.70	0.57-0.82	0.63	0.006
Postoperative NLR	0.64	0.51-0.77	0.66	0.05
Postoperative PLR	0.62	0.48-0.76	0.69	0.08

Discussion

The mortality rate following pancreatic resection has declined in recent years to less than 4% in high-volume centers; however, morbidity remains significantly high. Among the complications that arise after distal pancreatectomy, pancreatic fistula is the most prevalent and is a major contributor to morbidity (4,5). Predicting the onset of pancreatic fistula is challenging, yet early detection is crucial for improving patient prognosis. In examining the dynamics of circulating immune cells in cancer patients, neutrophilia serves as an indicator of systemic inflammatory response, while lymphopenia reflects host immunosuppression. Additionally, the role of thrombocytosis in cancer progression underlies the significance of SII, NLR, and PLR scores. Schlanger et al. demonstrated that significant changes occur in the populations of circulating immune cells following tumor resection, noting that total counts of neutrophils, monocytes, and platelets, as well as NLR, PLR, and SII, increase significantly after surgery (8).

In scenarios involving strong triggers of systemic inflammatory response, such as sepsis, malignancy, and trauma, platelet proliferation is stimulated by pro-inflammatory cytokines in addition to the presence of neutrophilia and lymphopenia. The potential significance of SII arises from the specific interplay between neutrophils, lymphocytes, and platelets, all of which play critical roles in various inflammatory processes. The Systemic Immune-Inflammation Index (SII), introduced into the literature in 2014, is a novel biomarker that was initially utilized to predict prognosis in various types of cancer (9). It has also proven to be a valuable marker for examining the interaction between thrombocytosis and immune inflammation in the context of sepsis, postoperative complications, and cerebrovascular diseases (10). In this retrospective study, we identified a cut-off value for SII of 1881, which was shown to predict the development of pancreatic fistula with a sensitivity of 92% and specificity of 51%, achieving statistical significance ($p = 0.006$).

NLR was defined by Zahorec in 2001 and has been proposed as a simple, reliable, and cost-effective parameter for assessing various conditions, including sepsis and trauma, in critically ill patients (11,12). In this study, the cut-off value for NLR was determined to be 8.4. This ratio was found to effectively predict the occurrence of pancreatic fistula in patients who underwent distal pancreatectomy, showing a sensitivity of 92% and a specificity of 51%, with statistical significance ($p = 0.05$).

PLR was first introduced by Smith et al. (13). In this study, a cut-off value of 170 was identified for PLR, which exhibited 68% specificity and 55% sensitivity; however, this result was not statistically significant in predicting fistula development ($p = 0.08$).

Qi et al. conducted a study evaluating the relationship between inflammatory markers and postoperative complications, finding a significant correlation between postoperative SII and NLR values and the occurrence of anastomotic leakage in patients who underwent low anterior resection

for rectal cancer. Notably, preoperative values were not significant for predicting anastomotic leakage (14). In this article, we focus on evaluating postoperative blood results in relation to the development of pancreatic fistula.

Ma et al. showed that SII, NLR, and PLR are significant predictors of pancreatic fistula development in patients undergoing pancreaticoduodenectomy (7). In this retrospective study, a statistically significant association was found between SII and NLR with the occurrence of pancreatic fistula, while PLR did not demonstrate a significant relationship. The lack of significance for PLR may be attributed to the inclusion of patients with fever in the study. Conversely, complications such as bile leakage and anastomotic leakage are not typically encountered following distal pancreatectomy. Thus, we propose that inflammatory markers may be more effective in predicting pancreatic fistula development in distal pancreatectomy than in pancreaticoduodenectomy. The statistically significant findings related to PLR in patients undergoing pancreaticoduodenectomy may also be influenced by the presence of additional complications beyond pancreatic fistula.

Various studies have explored both preoperative and postoperative inflammatory markers, yielding mixed results regarding their significance (7,14-16). Surgical trauma may trigger an exaggerated inflammatory response or suppress cell-mediated immunity, as evidenced by research indicating that surgical trauma significantly impacts the immune system (17,18). The challenge lies in determining whether complications stem from preoperative tumor immunology, are a consequence of surgical stress post-tumor removal, or arise from blood count changes after complications occur. In this study, we analyzed SII, NLR, and PLR derived from postoperative blood results.

Limitations

A key limitation of this study is the small patient cohort, underscoring the need for further research with larger sample sizes to validate these findings.

Conclusions

This study revealed that increases in the SII and NLR, both of which are inflammation-related indices, are associated with a heightened risk of complications. Furthermore, SII was found to be a statistically more significant predictor of pancreatic fistula compared to NLR. The affordability and straightforward calculation of these markers may facilitate the early prediction of pancreatic fistula in the postoperative period.

Ethical Approval: Ethics committee approval number '45' dated 18.12.2023 was received from Atılım University Faculty of Medicine-affiliated Medicana International Ankara Hospital for this study. This manuscript adheres to the principles outlined in the Declaration of Helsinki (2013).

Author Contributions:

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Design : M.K.

Data acquisition: G.Ç., A.C.E.

Analysis and interpretation: M.K.

Writing manuscript: G.Ç., A.C.E.

Critical revision of manuscript: M.K.

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Acil Tıpta Ultrasonografi: Doktorların Yetkinliklerinin Değerlendirilmesi

Point-of-Care Ultrasound in Emergency Medicine: Assessing Physicians' Competency Levels

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Öz

Amaç: Acil tıp hastalara hızlı ve doğru tanıları koymayı gerektiren yüksek riskli bir alandır. Son yıllarda ultrasonografi acil tıpta teşhis ve tedavi süreçlerini hızlandıran kritik bir araç haline gelmiştir. Bu çalışma, acil tıp doktorlarının yatak başı ultrasonografi (YBU) yetkinliklerini değerlendirmeyi, eğitim geçmişlerini, cihaz erişimlerini ve Türkiye'deki acil servislerde karşılaştıkları zorlukları incelemeyi amaçlamıştır.

Materyal ve metod: Türkiye'deki çeşitli hastanelerden 430 acil tıp doktoru ile kesitsel bir anket çalışması gerçekleştirildi. Veriler; demografik bilgileri, YBU eğitimini, cihaz kullanım alışkanlıklarını, altı alanda (FAST, kardiyak, abdominal, torasik, vasküler, kas-iskelet) kendi yetkinlik düzeyi değerlendirmelerini (1-5 Likert ölçeği) ve karşılaşılan engelleri içermektedir. SPSS 26.0 kullanılarak istatistiksel analizler (Mann-Whitney U, Kruskal-Wallis, Spearman korelasyonu, Ki-kare, çoklu regresyon) yapıldı ve anlamlılık düzeyi $p < 0,05$ olarak belirlendi.

Bulgular: Katılımcıların %58,1'i (n=250) YBU eğitimi almış olup, en yaygın eğitimler FAST (Focused Assessment with Sonography for Trauma) (%62,8) ve kardiyak odaklı ultrasonografi (FOCUS) (%51,2) alanlarında idi. FAST alanındaki yetkinlik ortalaması en yüksekti (M=3,62, SD=1,22). Eğitim alan doktorlar, kardiyak ($p=0,012$) ve FAST ($p=0,033$) alanlarında eğitimlilere göre daha üstün yetkinlik gösterdi. Hekimin deneyimi, aylık YBU uyguladığı hasta sayısı güçlü bir şekilde ilişkiliydi ($r=0,71$, $p<0,001$) ve FAST alanındaki yetkinlik puanlarını etkiledi ($r=0,59$, $p<0,001$). Cihaz sık kullanımı abdominal alanda yetkinliği artırdı ($p=0,008$). Çoklu regresyon, FAST uygulama yetkinliğinde eğitimi ($\beta=0,42$, $p=0,015$) ve deneyimi ($\beta=0,38$, $p=0,022$) ana belirleyiciler olarak gösterdi ($R^2=0,51$). Cihaz yetersizliği (%51,2) ve teknik bilgi eksikliği (%41,9) ise başlıca engellerdi.

Sonuç: YBU yetkinliği, eğitim ve deneyimle önemli ölçüde artarken, ekipman ve bilgi eksiklikleri tarafından kısıtlanmaktadır. Yapılandırılmış eğitim ve altyapı iyileştirmeleri, acil bakımda YBU'yu optimize etmek ve kullanımını arttırmak için gereklidir.

Anahtar Kelimeler: Yatak başı ultrasonografi, Acil tıp, FAST, FOCUS

Abstract

Background: Emergency medicine is a high-risk field that requires rapid and accurate diagnoses of patients. In recent years, ultrasonography has become a critical tool that accelerates the diagnostic and treatment processes in emergency medicine. This study aimed to evaluate the competency of emergency physicians in point-of-care ultrasound (POCUS), examining their training backgrounds, device accessibility, and challenges encountered in emergency departments (EDs) across Turkey.

Materials and Methods: A cross-sectional survey was conducted with 430 emergency physicians from various hospitals in Turkey. The collected data included demographic information, POCUS training, device usage habits, self-assessment of competency level (on a 1–5 Likert scale) in six domains (FAST, cardiac, abdominal, thoracic, vascular, musculoskeletal), and encountered barriers. Statistical analyses were performed using SPSS 26.0 (Mann-Whitney U, Kruskal-Wallis, Spearman correlation, Chi-square, and multiple regression), with a significance level set at $p < 0.05$.

Results: 58.1% of participants (n=250) had received training in Point-of-Care Ultrasound (POCUS), with the most common areas of training being FAST (Focused Assessment with Sonography for Trauma) (62.8%) and cardiac-focused ultrasound (FOCUS) (51.2%). The average competency in the FAST area was the highest (M=3.62, SD=1.22). Physicians who received training demonstrated superior competency in cardiac ($p=0.012$) and FAST ($p=0.033$) assessments compared to those without training. The physician's experience was strongly correlated with the number of patients undergoing POCUS per month ($r=0.71$, $p<0.001$) and affected competency scores in the FAST area ($r=0.59$, $p<0.001$). Frequent use of the device increased competency in the abdominal area ($p=0.008$). Multiple regression analysis indicated that training ($\beta=0.42$, $p=0.015$) and experience ($\beta=0.38$, $p=0.022$) were the main determinants of competency in the FAST area ($R^2=0.51$). Device inadequacy (51.2%) and lack of technical knowledge (41.9%) were identified as major barriers.

Conclusions: POCUS competency significantly improves with training and experience but is constrained by equipment shortages and knowledge deficits. Structured training programs and infrastructure enhancements are essential to optimize POCUS utilization and improve emergency care delivery.

Keywords: Point-of-care ultrasound, Emergency medicine, FAST, FOCUS

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Giriş

Acil tıp, hastaların hayatta kalma şansını belirleyen hızlı ve doğru tanıları gerektiren yüksek riskli bir alandır. Yatak başı ultrasonografi (YBU), acil servislere (AS) gerçek zamanlı, invaziv olmayan bir görüntüleme sunarak teşhis süreçlerini hızlandıran devrim niteliğinde bir araçtır (1). Travma, kardiyak arrest ve akut solunum yetmezliği gibi durumlarda FAST (Focused Assessment with Sonography for Trauma), kardiyak odaklı ultrasonografi (FOCUS) ve torasik görüntüleme gibi protokoller, geleneksel radyolojiye bağımlılığı azaltarak hasta sonuçlarını iyileştirmiştir (2,3). Ancak, YBU'nun etkinliği, doktorların teknik yetkinliğine bağlıdır ve bu yetkinlik, eğitim, deneyim ve işlevsel ultrason cihazlarına erişim gibi faktörlere göre büyük ölçüde değişir (4).

Uluslararası düzeyde, YBU'nun acil tıbbi entegrasyonu, Amerikan Acil Tıp Doktorları Koleji gibi kuruluşlar tarafından desteklenmekte ve asistanlık eğitimlerinde zorunlu bir bileşen olarak önerilmektedir (5). Çalışmalar, yapılandırılmış YBU eğitiminin tanısal doğruluğu artırabildiğini göstermektedir (6). YBU yalnızca teşhis hızını artırmakla sınırlı kalmaz; aynı zamanda maliyet etkinliği ve hasta güvenliği açısından da avantaj sağlar (7).

Ancak, cihaz eksikliği, tutarsız eğitim programları ve zaman kısıtlamaları gibi engeller, YBU'nun yaygın kullanımını zorlaştırmaktadır (8). Türkiye gibi acil servislerin yüksek hasta hacmiyle karşı karşıya olduğu ve altyapının değişkenlik gösterdiği bir ortamda, YBU yetkinliklerine dair sistematik değerlendirmeler ise yetersizdir. Türkiye'deki acil servislere ultrasonografi kullanımının yeterli düzeyde olmaması bu araştırmanın yapmamızı tetiklemiştir. Türkiye'de yapılan çalışmalarda acil servislere YBU kullanımının sınırlı olduğu ve altyapı eksikliklerinin yaygın olduğu bildirilmiştir (9,10). Çalışmamız, Türkiye'deki acil tıp doktorlarının YBU yetkinliklerini değerlendirmeyi, eğitim geçmişlerini, deneyim yıllarını, cihaz kullanım alışkanlıklarını ve karşılaşılan zorlukları incelemeyi amaçlamaktadır.

Materyal ve Metod

Çalışma Tasarımı ve Katılımcılar

Çalışmamız prospektif kesitsel bir anket çalışması olup hastane etik kurul onayı alınmıştır (Sağlık Bilimleri Üniversitesi Gazi Yaşargil Eğitim ve Araştırma Hastanesi Etik Kurulu Tarih: 17.01.2025, Karar No: 311). Türkiye'deki farklı hastanelerde çalışan acil tıp doktorları, Google Forms yazılımı kullanılarak hazırlanan bir çevrimiçi ankete katılmaya davet edildi. Tüm katılımcılardan anketin ilk sayfasında bireysel onamı istenmiş olup, onam vermeyen ve eksik verisi olan katılımcılar çalışma dışı bırakıldı. Çalışmamız Türkiye'deki devlet hastaneleri (%48,8, n=210), eğitim ve araştırma hastaneleri (%32,6, n=140) ve üniversite hastanelerinden (%18,6, n=80) toplamda 430 acil tıp doktorunu kapsayacak şekilde gerçekleştirildi.

Katılımcılar, uzman hekimler (%62,8, n=270), asistan hekimler (%27,9, n=120) ve akademik personel (%9,3, n=40) olarak dağıldı.

Veri Toplama Aracı

Anket beş bölümden oluşuyordu:

- 1. Demografik Bilgiler:** Yaş, cinsiyet, hastane tipi, akademik unvan ve acil serviste deneyim yılları (pratisyen hekimlik hariç).
- 2. YBU Geçmişi:** Asistanlıkta YBU kullanımı (hiç, nadiren, ara sıra, sık sık, her zaman), eğitim durumu (evet/hayır), eğitim kaynakları (hastane temelli, dış kuruluşlar/üniversiteler, kendi kendine) ve eğitimin içeriği (örneğin, FAST, kardiyak ultrason).
- 3. Kullanım Ölçütleri:** Acil servisteki ultrason cihaz sayısı, kullanım sıklığı (çok nadir, ara sıra, sık sık), aylık YBU yapılan hasta sayısı ve birincil uygulama alanı (örneğin, kırımızı alan).
- 4. Yetkinlik Değerlendirmesi:** FAST, kardiyak, abdominal, torasik, vasküler ve kas-iskelet alanlarında 1-5 Likert ölçeğiyle kendi kendine değerlendirilen yeterlilik (1=çok düşük, 5=çok yüksek).
- 5. Zorluklar ve İhtiyaçlar:** Karşılaşılan engeller (örneğin, cihaz yetersizliği, teknik bilgi eksiklikleri) ve ihtiyaç duyulan eğitim türleri (örneğin, uygulamalı, simülasyon).

İstatistiksel Analiz

Veriler, SPSS 26.0 ve R Studio ile analiz edildi. Mann-Whitney U, Kruskal-Wallis, Spearman korelasyonu, Ki-kare, çoklu regresyon testleri kullanıldı. Normallik, Shapiro-Wilk testiyle değerlendirildi; çoğu alanda normal dağılım ihlali ($p < 0,05$) nedeniyle non-parametrik testler (Mann-Whitney U, Kruskal-Wallis, Spearman korelasyonu, Ki-kare) tercih edildi. Mann-Whitney U ve Kruskal-Wallis testleri normal dağılıma uymayan sürekli verilerin karşılaştırılmasında, Ki-kare testi kategorik veriler için, Spearman korelasyon katsayısı korelasyon analizinde kullanıldı. Non-parametrik testler, veri dağılımının asimetrik olması ve aykırı değerlerin varlığı nedeniyle seçildi. FAST yetkinliğini öngörmek için çoklu regresyon analizi yapıldı; modele eğitim (evet/hayır), deneyim (yıl) ve cihaz sayısı (0-2) dahil edildi. Anlamlılık düzeyi $p < 0,05$ olarak belirlendi ve etki büyüklükleri (r , ϕ , η^2) hesaplandı. Ana karşılaştırmalar için post-hoc güç analizi > 80 güç doğruladı. Eksik veriler ($< 5\%$) çift bazında hariç tutuldu.

Etik Hususlar

Çalışma, Helsinki Deklarasyonu'na uygun olarak yürütüldü. Katılımcı anonimliği korundu ve veriler yalnızca araştırma amacıyla güvenli bir şekilde saklandı.

Bulgular

Katılımcı Özellikleri

430 katılımcının %81,4'ü ($n=350$) erkek, %18,6'sı ($n=80$) kadın; yaş ortalaması 34,8 yıl ($SD=7,1$), acil servis deneyim ortalaması 7,4 yıl ($SD=5,6$). Hastane tipi dağılımı: devlet hastaneleri (%48,8, $n=210$), eğitim ve araştırma hastaneleri (%32,6, $n=140$), üniversite hastaneleri (%18,6, $n=80$). Akademik unvanlar: uzman hekim (%62,8, $n=270$), asistan hekim (%27,9, $n=120$), öğretim üyesi (%9,3, $n=40$).

YBU Eğitimi ve Hekim Deneyimi

Katılımcıların %58,1'i (n=250) bir veya birden fazla YBU eğitimi aldığını bildirdi; eğitim kaynakları arasında dış kuruluşlar/üniversiteler (%64,0, n=160), bireysel çabalar (%48,0, n=120) ve hastane temelli programlar (%32,0, n=80) yer aldı (birden fazla yanıt mümkün). Eğitim içerikleri: FAST (%62,8, n=270), kardiyak ultrason (%51,2, n=220), torasik görüntüleme (%46,5, n=200) ve vasküler görüntüleme (%39,5, n=170) idi. YBU deneyimi: 0-1 yıl (%20,9, n=90), 2-5 yıl (%27,9, n=120), ≥6 yıl (%7,0, n=30); %44,2'si (n=190) eğitim almadığı için deneyim bildirmedi.

Cihaz Erişimi ve Kullanımı

Ultrason cihaz durumu: yok (%9,3, n=40), bir cihaz (%58,1,

n=250), iki cihaz (%23,3, n=100). Kullanım sıklığı: çok nadir (%37,2, n=160), ara sıra (%25,6, n=110), sık sık (%11,6, n=50); %25,6'sı (n=110) kullanım verisi eksik (eğitimsiz/kullanıcı olmayan). Aylık YBU yapılan hasta sayısı: 0-5 hasta (%55,8, n=240), 6-10 hasta (%7,0, n=30), 11-20 hasta (%4,7, n=20), 21-50 hasta (%7,0, n=30). En sık cihaz kullanımı kırımızı alanda saptandı (%60,5, n=260).

Yetkinlik Puanları

Altı alandaki kendi kendine değerlendirilen yetkinlik puanları (1-5 Likert ölçeği) Tablo 1'de sunulmuştur. Normal dağılım ihlali (Shapiro-Wilk $p<0,05$) nedeniyle medyanlar da raporlanmıştır (Tablo 1).

Tablo 1. YBU Uygulama Alanları ve Yetkinlik Puanları

Alan	Ortalama	SD	Medyan (Q1-Q3)	Shapiro-Wilk p
FAST	3,62	1,22	4,0 (3,0-4,5)	0,032
Kardiyak	3,26	1,31	3,0 (2,5-4,0)	0,048
Abdominal	2,81	1,18	2,0 (2,0-3,0)	0,067
Torasik	2,95	1,46	3,0 (2,0-3,5)	0,029
Vasküler	2,86	1,53	3,0 (2,0-3,5)	0,015
Kas-İskelet	2,26	1,55	2,0 (1,5-2,5)	0,008

*Kısaltmalar: YBU=Yatak Başı Ultrasonografi, FAST=Focused Assessment with Sonography for Trauma, SD=Standart Sapma, Q1=Birinci Çeyrek (alt %25), Q3=Üçüncü Çeyrek (üst %25). Not: Q1, Q3 ve medyan, veri setinin çeyrekler arası dağılımını gösterir. İstatistiksel anlamlılık düzeyi $p<0,05$.

Eğitimin Etkisi

Eğitim alanlar (n=250), eğitimsizlere (n=180) göre kardiyak ultrasonografi (Medyan=4,0 vs. 2,5, U=152,5, $p=0,012$, $r=0,38$) ve FAST alanlarında (Medyan=4,0 vs. 3,0, U=165,0, $p=0,033$, $r=0,32$) anlamlı derecede daha yüksek puan aldı. Abdominal alan yetkinliğinde fark anlamlı değildi (Medyan=3,0 vs. 2,0, U=190,5, $p=0,208$) (Tablo 2).

Hekim Deneyimi, Aylık YBU uygulanan hasta sayısı ve YBU Uygulama Alanları Yetkinlik Korelasyonları

Spearman korelasyonu, hekim deneyimi ile aylık YBU uygulanan hasta sayısı ($r=0,71$, $p<0,001$), hekim deneyimi ile FAST uygulama yetkinliği ($r=0,59$, $p<0,001$) ve aylık YBU uygulanan hasta sayısı ile abdominal alan yetkinliği ($r=0,48$, $p=0,001$) arasında güçlü pozitif ilişkiler gösterdi. Kardiyak alandaki yetkinlik de deneyimle ilişkiliydi ($r=0,52$, $p<0,001$)

(Tablo 3).

Hastane Tipi ve Akademik Unvan

Kruskal-Wallis testi, hastane tipleri ($H=1,82$, $p=0,402$) ve akademik unvanlar ($H=2,15$, $p=0,341$) arasında FAST uygulama yetkinliğinde anlamlı fark bulmadı (Tablo 4 ve Tablo 5). Devlet hastanelerinde cihaz yetersizliği daha sık raporlanırken (%55, n=115), üniversite hastanelerinde ise teknik bilgi eksikliği ön plandaydı (%50, n=40).

Kullanım Sıklığı

Ki-kare analizi, kullanım sıklığı ile abdominal alan yetkinliği arasında anlamlı bir ilişki gösterdi ($\chi^2=11,89$, $p=0,008$, $\phi=0,43$); sık kullananlar daha yüksek puan aldı (Medyan=4,0) (Tablo 6).

Tablo 2. Eğitim Durumuna Göre YBU Uygulama Alanları Yetkinlik Puanları

Alan	Eğitim Alan N=250 Medyan (Q1-Q3)	Eğitimsiz N=180 Medyan (Q1-Q3)	U Değeri	p Değeri	Etki Büyüklüğü (r)
FAST	4,0 (3,0-4,5)	3,0 (2,5-3,5)	165,0	0,033	0,32
Kardiyak	4,0 (3,0-4,5)	2,5 (2,0-3,0)	152,5	0,012	0,38
Abdominal	3,0 (2,0-3,5)	2,0 (1,5-2,5)	190,5	0,208	0,18
Torasik	3,0 (2,0-3,5)	2,0 (1,5-2,5)	182,0	0,154	0,22
Vasküler	3,0 (2,0-3,5)	2,0 (1,5-2,5)	198,5	0,276	0,16

*Kısaltmalar: N=Örneklem büyüklüğü U=Mann-Whitney U istatistiği, r=Spearman korelasyon katsayısı. Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Tablo 3. Hekim Deneyimi, Aylık YBU uygulanan hasta sayısı ve YBU Uygulama Alanları Yetkinlikleri: Korelasyon Analizi

Değişken Çifti	r	p Değeri
Hekim deneyimi vs. Aylık YBU uygulanan hasta sayısı	0,71	<0,001
Hekim deneyimi vs. FAST uygulama yetkinliği	0,59	<0,001
Aylık YBU uygulanan hasta sayısı vs. Abdominal alan yetkinliği	0,48	0,001
Hekim deneyimi vs. Kardiyak alan yetkinliği	0,52	<0,001
Aylık YBU uygulanan hasta sayısı vs. Torasik alan yetkinliği	0,41	0,006

*Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Tablo 4. Hastane Tipine Göre FAST Uygulama Yetkinlik Puanları

Hastane Tipi	N	Medyan (Q1-Q3)	H Değeri	p Değeri
Devlet	210	4,0 (3,0-4,5)	1,82	0,402
Eğitim/Araştırma	140	4,0 (3,0-4,5)		
Üniversite	80	3,5 (2,5-4,0)		

*Kısaltmalar: H=Kruskal-Wallis H istatistiği. Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Tablo 5. Akademik Unvana Göre FAST Uygulama Yetkinlik Puanları

Unvan	N	Medyan (Q1-Q3)	H Değeri	p Değeri
Uzman Hekim	270	4,0 (3,0-4,5)	2,15	0,341
Asistan Hekim	120	3,0 (2,5-3,5)		
Öğretim Üyesi	40	3,5 (2,5-4,0)		

*Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Tablo 6. Kullanım Sıklığına Göre Abdominal Alan Yetkinlik puanları

Kullanım Sıklığı	N	Medyan (Q1-Q3)	χ^2	p Değeri	Phi
Çok Nadir	160	2,0 (1,5-2,5)	11,89	0,008	0,43
Ara Sıra	110	3,0 (2,0-3,5)			
Sık Sık	50	4,0 (3,0-4,5)			

*Kısaltmalar: χ^2 =Ki-kare istatistiği, Phi=Phi katsayısı. Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Çoklu Regresyon Analizi

FAST uygulama yetkinliğini öngörmek için çoklu regresyon analizi yapıldı. Modele eğitim (evet/hayır), deneyim (yıl), cihaz sayısı (0-2) dahil edildi. Model anlamlıydı ($R^2=0,51$, $F(3,39)=13,52$, $p<0,001$); FAST uygulama yetkinliğinde eğitim ($\beta=0,42$, $p=0,015$) ve deneyim ($\beta=0,38$, $p=0,022$) ana belirleyicilerdi (Tablo 7).

Zorluklar ve Eğitim İhtiyaçları

Başlıca engeller: cihaz yetersizliği (%51,2, $n=220$), cihaz kalitesi sorunları (%46,5, $n=200$), teknik bilgi eksikliği (%41,9, $n=180$) (Tablo 8). Tercih edilen eğitim türleri: uygulamalı oturumlar (%67,4, $n=290$), simülasyon (%37,2, $n=160$), uzun vadeli sertifikalı programlar (%30,2, $n=130$). Katılım isteği yüksekti: kesinlikle katılırim (%51,2, $n=220$), katılırim (%30,2, $n=130$).

Tablo 7. FAST Uygulama Yetkinliği için Çoklu Regresyon

Tahmin Edici	β	SE	t Değeri	p Değeri	%95 GA
Eğitim	0,42	0,18	2,33	0,015	[0,06, 0,78]
Deneyim	0,38	0,02	2,41	0,022	[0,01, 0,06]
Cihaz Sayısı	0,25	0,15	1,67	0,089	[-0,04, 0,54]

*Kısaltmalar: β =Regresyon katsayısı, SE=Standart hata, t=t-test istatistiği, GA=Güven Aralığı. Not: İstatistiksel anlamlılık düzeyi $p<0,05$.

Tablo 8. Yaygın Zorluklar ve Engeller

Zorluk	Frekans (n=)	%
Cihaz Yetersizliği	220	51,2
Cihaz Kalitesi Sorunları	200	46,5
Teknik Bilgi Eksikliği	180	41,9
Görüntü Yorumlama	140	32,6
Zaman Kısıtlamaları	110	25,6

* Kısaltmalar: n=Frekans, %=Yüzde

Tartışma

Bu çalışma, Türkiye'deki acil tıp doktorlarının YBU yetkinliklerini kapsamlı bir şekilde değerlendirerek, eğitimin etkinliği, deneyim ve operasyonel zorluklar hakkında bilgiler sunmaktadır. Bulgularımız, uluslararası literatürle paralellik göstermektedir. Eğitim alan doktorların kardiyak ($p=0,012$) ve FAST ($p=0,033$) alanlarındaki üstünlüğü, Amini ve ark. (4) çalışmasıyla uyumludur; eğitim, becerileri anlamlı şekilde artırabilir. Bu sonuç eğitimin önemini vurgulamakta ve yapılandırılmış eğitimin YBU yeterliliği için temel bir unsur olduğunu açıkça göstermektedir. Ayrıca Sanders ve ark. (8), YBU'nun acil serviste kullanımının, eğitimle doğrudan ilişkili olduğunu ve cihaz erişiminin kritik bir faktör olduğunu bildirmiştir.

Deneyim ile aylık YBU uygulanan hasta sayısı ($r=0,71$, $p<0,001$) ve FAST uygulama yetkinliği ($r=0,59$, $p<0,001$) ara

sındaki güçlü ilişki, Gaspari ve ark. (11) tekrarlanan uygulamaların ustalığı arttırdığına dair bulgularını desteklemektedir. Çalışmamızda Regresyon modeli ($R^2=0,51$) ile FAST uygulama yetkinliğinde eğitim ($\beta=0,42$) ve deneyim ($\beta=0,38$) ana faktörler olarak tanımlanmış; cihaz sayısının sınırdaki etkisi ($p=0,089$) ise altyapının ikincil rolünü öne çıkarmıştır. Ultrasonografinin sık kullanımının abdominal yetkinliği artırması ($p=0,008$, $\phi=0,43$) Atkinson ve ark. (6) simülasyon ve düzenli uygulama önerilerini doğrular niteliktedir. Tespit ettiğimiz cihaz yetersizliği (%51,2) ve teknik bilgi eksiklikleri (%41,9) gibi durumlar yoğun acil servislerde kritik tanıları geciktirebilir. Bu da Nagaraj ve ark. (12) ile Sanders ve ark. (8) kaynak sınırlı ortamlardaki raporlarını yansıtır niteliktedir. Ayrıca çalışmamızda Devlet hastanelerinde cihaz yetersizliğinin daha belirgin olduğu saptanmış olup, altyapının hastane tipine göre farklılık gösterdiği ortaya konmuştur.

Hastane tipi ($p=0,402$) veya unvan temelli farkların olmaması ($p=0,341$), sorunların sistematik olduğunu ve ulusal düzeyde çözümler üretilmesi gerektiğini göstermektedir. Çalışmamız, Kokulu ve ark. (9) ile Gülünay ve ark. (10) tarafından bildirilen Türkiye'deki YBU kullanımındaki sınırlılıkları ve altyapı eksikliklerini doğrulamaktadır. Ancak, bizim çalışmamızda eğitim ve deneyimin FAST uygulama yetkinliğini artırmadaki rolü daha ayrıntılı bir şekilde ortaya konmuştur. Girişgin ve ark. (13) da acil tıp alanında ultrasonografinin eğitim kalitesini arttırabileceğini ve hasta bakımını iyileştirebileceğini vurgulamış olup, Değirmenci ve ark. (14) teorik eğitim sonrası verilecek pratik eğitimle uygulama yetkinliğinin arttırılabileceğini göstermiştir. Çalışmamızda YBU'nun kırmızı alanda yoğun kullanımının tespit edilmiş olması, klinik uygulamalarda kritik hastalarda hızlı tanı ihtiyacını yansıtır niteliktedir. Ancak, abdominal ve kas-iskelet alanlarında düşük yetkinlikler bu alanlarda ek eğitim gerekliliğini vurgulamaktadır. Tüm bu bulgular, cihaz eksikliklerini giderme ve teknik eğitimi güçlendirme ihtiyacını ortaya koymaktadır. Türkiye'de acil tıp doktorlarının YBU yetkinliği, eğitim ve klinik deneyimle önemli ölçüde artmakta, ancak cihaz eksiklikleri ve teknik bilgi yetersizlikleri tarafından sınırlandırılmaktadır. Eğitim ve deneyimin FAST uygulama yetkinliğindeki ana belirleyiciler olması, yapılandırılmış eğitim ve pratiğin önemini ortaya koymaktadır.

YBU acil servislere hızlı tanı ve müdahale süreçlerinde kritik bir araç olup Türkiye'de kullanımının artırılması için eğitim, deneyim ve altyapı gibi faktörlerin iyileştirilmesi gerekmektedir. Teorik ve pratik eğitim programlarını teşvik etmenin, altyapı yatırımlarını arttırmanın ve kapsamlı stratejiler geliştirmenin acil bakımda YBU'nun rolünü yükseltebileceğine ve hasta sonuçlarını iyileştirebileceğine inanmaktayız.

Kısıtlılıklar

Çalışmanın kısıtlılıkları arasında örneklem büyüklüğünün ($n=430$) genellenebilirliği sınırlaması ve kendi kendine raporlanan yetkinliklerin öznel doğası yer alır. Gelecekteki nesnel değerlendirmeler (örneğin, yapılandırılmış klinik muayene gözlemi, yetkinlik düzeyini ölçmek için gözlemsel ve uygulamalı verilere dayanarak hazırlanmış formlar), daha büyük çok merkezli kohort çalışmalar, eğitim sonrası beceri gelişimini izleyen uzun süreli çalışmalar YBU öğrenme eğrisini daha iyi açıklayabilir.

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Homeobox A1 Expression in Diabetic Pregnancy: Immunohistochemical and Computational Perspectives

Dişabetik Gebelikte Homeobox A1 Ekspresyonu: İmmünohistokimyasal ve Kompütasyonel Perspektifler

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Abstract

Background: This study aimed to evaluate the expression of Homeobox A Cluster 1 (HOXA1) protein in placentas from patients with gestational diabetes mellitus (GDM) using immunohistochemical techniques and to investigate the role of HOXA1 in GDM-associated biological mechanisms through computational analyses.

Materials and Methods: A total of 80 participants, including 40 healthy pregnant women and 40 women diagnosed with GDM, were enrolled. Placental tissues were examined histologically using hematoxylin-eosin and HOXA1 immunostaining. Additionally, HOXA1 and GDM-related proteins were retrieved from the STRING database and analyzed using Cytoscape software to identify shared interaction networks, determine node centrality (degree, closeness, betweenness), and perform Gene Ontology (GO) molecular function analyses.

Results: Histopathological analysis revealed significant increases in villous degeneration, fibrin deposition, hemorrhage, syncytial knot formation, and leukocyte infiltration in the GDM group. Immunohistochemical analysis demonstrated a marked upregulation of HOXA1 protein expression in the GDM group compared to controls. Computational analyses identified 15 shared proteins within the HOXA1 and GDM networks, with H3C12, H3-3B, H3C13, and ESR1 emerging as central regulatory proteins. GO analysis indicated that these proteins are primarily involved in chromatin organization, DNA binding, epigenetic regulation, and protein-protein interactions.

Conclusions: GDM induces significant histopathological and molecular changes in placental tissues, associated with increased HOXA1 protein expression. HOXA1 may play a critical role in the molecular mechanisms underlying GDM-related placental dysfunction and could serve as a potential biomarker and therapeutic target.

Keywords: HOXA1, gestational diabetes mellitus, placenta, topological analysis, bioinformatic analysis

Öz

Amaç: Bu çalışmada, gestasyonel diyabet mellitus (GDM) hastalarına ait plasentalarda Homeobox A Cluster 1 (HOXA1) proteininin ekspresyonu immünohistokimyasal yöntemlerle değerlendirilmiş ve HOXA1'in GDM ile ilişkili biyolojik mekanizmalardaki rolü hesaplamalı analizlerle araştırılmıştır.

Materyal ve Metod: Çalışmaya 40 sağlıklı gebe ve 40 GDM tanılı gebe olmak üzere toplam 80 kadın dahil edilmiştir. Plasentalar, hematoxilen-eozin ve HOXA1 immün boyama yöntemleriyle histolojik olarak incelenmiştir. Ayrıca, HOXA1 ve GDM ile ilişkili proteinler STRING veri tabanından elde edilerek Cytoscape programı kullanılarak ortak etkileşim ağları analiz edilmiş, düğüm merkeziliği (degree, closeness, betweenness) belirlenmiş ve gen ontolojisi (GO) moleküler fonksiyon analizleri yapılmıştır.

Bulgular: Histopatolojik analizde GDM grubunda villöz dejenerasyon, fibrin birikimi, hemoraji, sinsityal düğüm oluşumu ve lökosit infiltrasyonunda anlamlı artış saptanmıştır. İmmünohistokimyasal analizde, HOXA1 ekspresyonu GDM grubunda kontrol grubuna kıyasla belirgin şekilde artmıştır. Hesaplamalı analizlerde, HOXA1 ve GDM ağlarının kesişiminde 15 ortak protein belirlenmiş, H3C12, H3-3B, H3C13 ve ESR1 proteinleri ağın en merkezi düzenleyici proteinleri olarak tanımlanmıştır. GO analizi, bu proteinlerin kromatin organizasyonu, DNA bağlanması, epigenetik düzenleme ve protein-protein etkileşimleri gibi temel moleküler süreçlerle ilişkili olduğunu göstermiştir.

Sonuç: GDM, plasental dokularda önemli histopatolojik ve moleküler değişikliklere yol açmakta, HOXA1 proteininin ekspresyonunda artış ile ilişkilendirilmektedir. HOXA1, GDM'ye bağlı plasental disfonksiyonun moleküler mekanizmalarında rol oynayabilecek potansiyel bir biyobelirteç ve hedef molekül olarak öne çıkmaktadır.

Anahtar Kelimeler: HOXA1, gestasyonel diyabetes mellitus, plasenta, topolojik analiz, biyoinformatik analiz.

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Introduction

Gestational diabetes mellitus (GDM) is a form of glucose intolerance that develops during pregnancy and typically resolves after childbirth. It arises due to hormonal alterations that impair pancreatic insulin production, leading to maternal hyperglycemia. Risk factors for GDM include obesity, advanced maternal age, family history of diabetes, and a previous history of GDM (1). The pathophysiology of GDM is multifactorial, encompassing β -cell dysfunction, chronic insulin resistance, oxidative stress, and neurohormonal imbalances (2, 3). Elevated levels of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), produced by monocytes and macrophages, are known to impair insulin sensitivity, thereby promoting hyperglycemia and contributing to the development of GDM (4). If not properly managed, GDM can result in both maternal and fetal complications, including preeclampsia, macrosomia, neonatal hypoglycemia, and increased risk of type 2 diabetes in later life (5).

The placenta is a key organ mediating nutrient and oxygen exchange between the mother and fetus, and its structural and functional integrity is critical for normal fetal development. In GDM pregnancies, placental histopathology frequently exhibits abnormalities such as villous edema, excessive fibrin deposition, hemorrhage, thickening of trophoblastic membranes, increased syncytial knot formation, and leukocyte infiltration (6-8). These structural alterations are thought to arise from impaired vascularization, abnormal angiogenesis, and inflammation induced by maternal hyperglycemia. Furthermore, studies have shown that GDM is associated with altered expression of genes and proteins involved in cell proliferation, apoptosis, immune signaling, and extracellular matrix remodeling (9, 10). Despite these findings, the molecular mechanisms linking GDM to altered placental development remain incompletely defined.

HOX genes are a highly conserved family of transcription factors that regulate embryonic patterning, segmentation, and organogenesis. Originally characterized in *Drosophila melanogaster*, their mammalian counterparts play essential roles in cell fate determination, tissue differentiation, and spatial development during early embryogenesis (11, 12). Disruption of HOX gene expression has been implicated in various pathological conditions, including congenital malformations and cancers. Among these, HOXA1 is known to be a critical regulator of cell proliferation, differentiation, and migration. Recent studies have identified aberrant HOXA1 expression in malignancies and suggested its involvement in abnormal tissue remodeling (13, 14). Although some HOX family members have been implicated in trophoblast differentiation and membrane formation, HOXA1 has not been comprehensively studied in the context of gestational diabetes.

Given its functional roles, dysregulated HOXA1 expression may contribute to impaired placental development observed in GDM (7-9, 15, 16).

Therefore, the objective of this study was to investigate the expression and immunolocalization of HOXA1 protein in pla-

cental tissues from GDM and healthy pregnancies. In addition, we aimed to explore HOXA1-associated molecular mechanisms through computational protein-protein interaction and gene ontology analyses.

Materials and Methods

Patient selection and study design

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Non-Interventional Research of Dicle University Faculty of Medicine (Approval Date: 14/02/2024, No: 78). The study population included two groups: 40 pregnant women diagnosed with GDM and 40 healthy pregnant women as controls.

GDM was diagnosed based on the oral glucose tolerance test (OGTT) with 75 g of glucose performed between the 24th and 28th weeks of gestation. Inclusion criteria for the GDM group were fasting plasma glucose ≥ 92 mg/dL (5.1 mmol/L), ≥ 180 mg/dL (10.0 mmol/L) at 1 hour, and ≥ 153 mg/dL (8.5 mmol/L) at 2 hours post-glucose load, in accordance with established guidelines (10).

Only singleton pregnancies resulting in delivery between 37 and 41 gestational weeks were included. Placental samples were collected immediately after delivery for histological analysis. The control group consisted of women without metabolic disorders who also delivered at term and had healthy placentas.

Exclusion criteria included pregestational diabetes, chronic hypertension, history of preeclampsia, autoimmune or chronic inflammatory disease, fetal anomalies, intrauterine growth restriction (IUGR), multiple pregnancies, placental insufficiency, or placental abruption. Participants with a history of alcohol consumption were also excluded. Additionally, samples with inadequate or excessive fixation compromising immunohistochemical analysis were not included.

Histological Tissue Processing

Placental samples were collected from the Department of Gynecology and Obstetrics and immediately fixed in zinc-formalin solution. After 24 hours of fixation, tissues were rinsed in tap water and dehydrated through a graded ethanol series (50%, 70%, 80%, 90%, 96%, and absolute alcohol). Following xylene clearing, the tissues were embedded in paraffin blocks.

Hematoxylin and Eosin (H&E) Staining

Paraffin-embedded sections were incubated at 37°C, and residual paraffin was removed by placing the slides in an oven at 58–62°C for six hours. After mounting on slides, sections were rehydrated through descending ethanol concentrations and rinsed in distilled water. H&E staining was performed using standard protocols. After staining, sections were dehydrated, cover-slipped with mounting medium, and examined under a Zeiss Imager A2 photomicroscope. Representative images were captured for analysis.

Immunohistochemical Staining

Sections mounted on poly-lysine-coated slides were incubated at 58–62°C for six hours to remove residual paraffin. Following deparaffinization in xylene and rehydration through decreasing ethanol concentrations, the sections were rinsed in distilled water. Endogenous peroxidase activity was blocked using hydrogen peroxide for 20 minutes. After PBS washing, Ultra V Block solution was applied for seven minutes to minimize non-specific binding.

Tissue sections were then incubated overnight at 4°C with primary antibody against HOXA1 (sc-293257, Santa Cruz, USA). The following day, sections were treated with a biotinylated secondary antibody and then exposed to streptavidin–peroxidase. The immune reaction was visualized using diaminobenzidine (DAB), and counterstaining was performed with hematoxylin. Slides were cover-slipped and examined using a Zeiss Imager A2 photomicroscope. Image analysis and quantification were performed using ImageJ software.

Semi-Quantitative Histological Scoring

Staining intensity for HOXA1 was evaluated using ImageJ (version 1.53, <http://imagej.nih.gov/ij>) according to the protocol described by Crowe et al. (11). Five randomly selected fields per sample were analyzed. Brown staining indicated positive immunoreactivity, while blue staining indicated negative areas. For each field, the ratio of HOXA1-positive area to total tissue area was calculated. The mean value across five fields was recorded as the semi-quantitative immunohistochemical score for each sample.

Network Topology and Gene Ontology (GO) Analysis

To explore the potential mechanisms associated with increased HOXA1 protein expression in GDM placentas, in silico analyses were conducted. Interactors of HOXA1 were retrieved from the STRING database, expanded to include 500 additional proteins (confidence score ≥ 0.4), and visualized in Cytoscape (v3.10.2). A similar procedure was applied to extract 500 GDM-related interactors. These two proteins–protein interaction (PPI) networks were intersected to identify shared proteins. Topological analysis of intersected nodes was performed using the CentiScaPe 2.2 plugin in Cytoscape to calculate degree, closeness, and betweenness centrality values. Degree centrality reflects the number of direct connections to other proteins, closeness indicates a protein's overall proximity to all others in the network, and betweenness measures its bridging potential between nodes (12). GO Molecular Function (MF) annotation was performed for the shared interactors using the DAVID database (13). Annotations with a p-value < 0.05 were considered statistically significant. A polar bar plot graph of enriched GO MF terms was generated using SRplot based on $-\log(p\text{-value})$ scores (14).

Statistical Analysis

All statistical analyses were performed using GraphPad Prism software (version 9.2.0; GraphPad Software, San Diego, CA). Data normality was assessed using the Shapiro–

Wilk test. Non-normally distributed data were expressed as median (interquartile range). Comparisons between groups were made using the Mann–Whitney U test. Statistical significance was indicated as follows: * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, **** $P \leq 0.0001$.

Results

Properties of patients

The demographic and laboratory characteristics of the study groups are presented in Table 1. There were no significant differences between the GDM and control groups in terms of age, gestational age, or HOMA-IR scores. However, body mass index (BMI) was significantly higher in the GDM group ($P = 0.016$). As expected, glucose values obtained from the OGTT were significantly elevated in the GDM group at all three time points (0 min, 1 hour, and 2 hours) compared to controls ($P = 0.001$ for all comparisons).

Histopathological findings

Figure 1 illustrates the histological features of placental sections stained with hematoxylin and eosin. In the control group (Figure 1A), placentas displayed well-organized floating chorionic villi with intact trophoblastic layers, villous stroma, and clearly defined chorionic capillaries. Fibrin accumulation was minimal, and no significant pathological alterations were observed. In contrast, placentas from the GDM group (Figure 1B) exhibited marked histopathological changes. These included widespread hemorrhage, leukocyte infiltration between villi, villous degeneration, and loss of structural integrity. Additionally, increased fibrin deposition, dilated and congested chorionic capillaries, and thickened syncytial knots were frequently observed. Histopathological scoring (Figure 1C) revealed that the GDM group had significantly elevated scores for villous degeneration, fibrin accumulation, hemorrhage, syncytial knot formation, and leukocyte infiltration compared to controls ($P < 0.05$ for all parameters). These findings indicate that GDM induces prominent structural disruptions in placental architecture.

HOXA1 Immunoexpression

Immunohistochemical analysis of HOXA1 protein expression is shown in Figure 2. In the control group (Figure 2A), HOXA1 immunoreactivity was observed in cytotrophoblasts, syncytiotrophoblasts, syncytial knots, and villous stromal cells. The staining was generally weak to moderate and distributed uniformly. In the GDM group (Figure 2B), HOXA1 protein expression was markedly increased. Strong and diffuse positive staining was noted in cytotrophoblasts, syncytiotrophoblasts, syncytial knots, villous stromal cells, and in various cells within the intervillous space. Semi-quantitative scoring of immunoreactivity (Figure 2C) confirmed a statistically significant increase in HOXA1 protein expression in placentas from the GDM group compared to controls ($P < 0.001$). These findings suggest that GDM is associated with upregulated HOXA1 protein expression in multiple placental compartments.

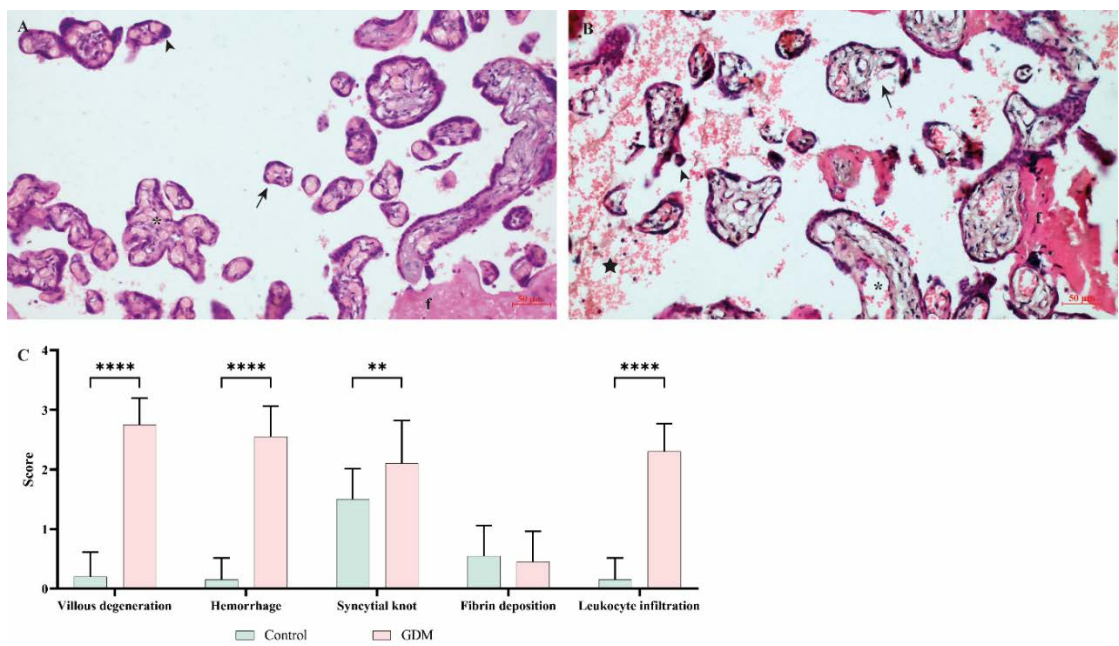


Figure 1. Cross sections of placental samples from pregnant women and histological scores. A) Control group; B) GDM group, C) Histopathological scoring, arrow: chorionic villus, arrowhead: syncytial knots, f: fibrin deposition, asterisk: villous stroma, star: hemorrhage, Bar: 50 μ m, Magnification: 20X

Table 1. Demographic and laboratory parameters of patients.

Parameters	Control (n: 40)	GDM (n: 40)	P value
Age (year)	28.0 $\pm$ 5.8	29.4 $\pm$ 4.8	0.703
Gestation (week)	26.9 $\pm$ 1.8	26.1 $\pm$ 1.7	0.390
BMI (kg/m ²)	28.5 $\pm$ 5.7	32.4 $\pm$ 4.9	0.016
HOMA-IR score	1.57 $\pm$ 1.18	1.94 $\pm$ 1.04	0.061
OGTT (75 gr)	80.2 $\pm$ 6.6	94.0 $\pm$ 8.1	0.001
0. scale glucose (mg/dl)			
OGTT (75 gr)	152.5 $\pm$ 11.2	210.2 $\pm$ 21.0	0.001
1. scale glucose (mg/dl)			
OGTT (75 gr)	139.0 $\pm$ 10.3	173.5 $\pm$ 20.3	0.001
2. scale glucose (mg/dl)			

BMI: Body mass index, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, OGTT: Oral Glucose Tolerance Test

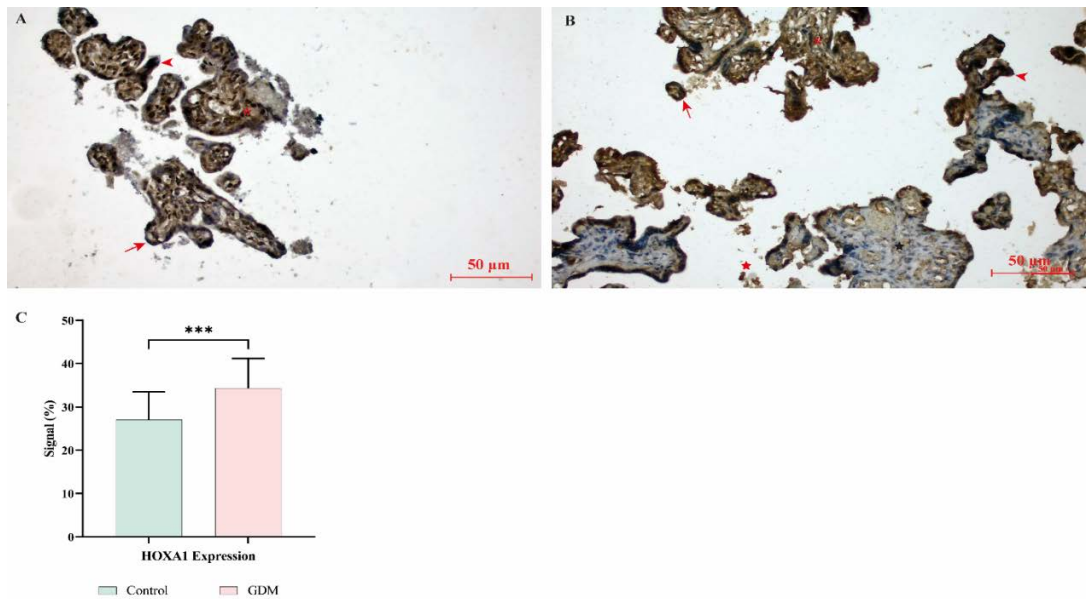


Figure 2. HOXA1 immune staining and semiquantitative scoring of placental sections per group. A) Control group; B) GDM group, C) Semi-quantitative scoring, arrow: chorionic villus, arrowhead: syncytial knots, f: fibrin deposition, asterisk: villous stroma, star: hemorrhage, Bar: 50 μ m, Magnification: 20X

Table 2. Node centrality values of GDM associated HOXA1 interactors

Gene	Description	Uniprot ID	Degree	Closeness	Betweenness
H3C12	H3 Clustered Histone 1	P68431	14.0	0.0714	5.873
H3-3B	H3 Histone, Family 3B	P84243	14.0	0.0714	5.873
H3C13	H3 Clustered Histone 13	Q71DI3	14.0	0.0714	5.873
ESR1	Estrogen Receptor 1	P03372	14.0	0.0714	5.873
CEBPA	CCAAT Enhancer Binding Protein Alpha	P49715	13.0	0.0666	4.858
H3-4	H3.4 Histone, Cluster Member	Q16695	13.0	0.0666	2.173
SIRT1	Sirtuin 1	Q96EB6	12.0	0.0625	0.363
DNMT1	DNA Methyltransferase 1	P26358	12.0	0.0625	0.363
JUN	Jun Proto-Oncogene, AP-1 Transcription Factor Subunit	P05412	12.0	0.0625	1.658
H3-5	H3.5 Histone	Q6NXT2	12.0	0.0625	0.363
H3-2	H3.7 Histone (Putative)	Q5TEC6	12.0	0.0625	0.363
DNMT3B	DNA Methyltransferase 3 Beta	Q9UBC3	11.0	0.0588	0.181
DNMT3A	DNA Methyltransferase 3 Alpha	Q9Y6K1	11.0	0.0588	0.181
TCF7L2	Transcription Factor 7 Like 2	Q9NQB0	7.0	0.0476	0.0
RXRA	Retinoid X Receptor Alpha	P19793	5.0	0.0434	0.0

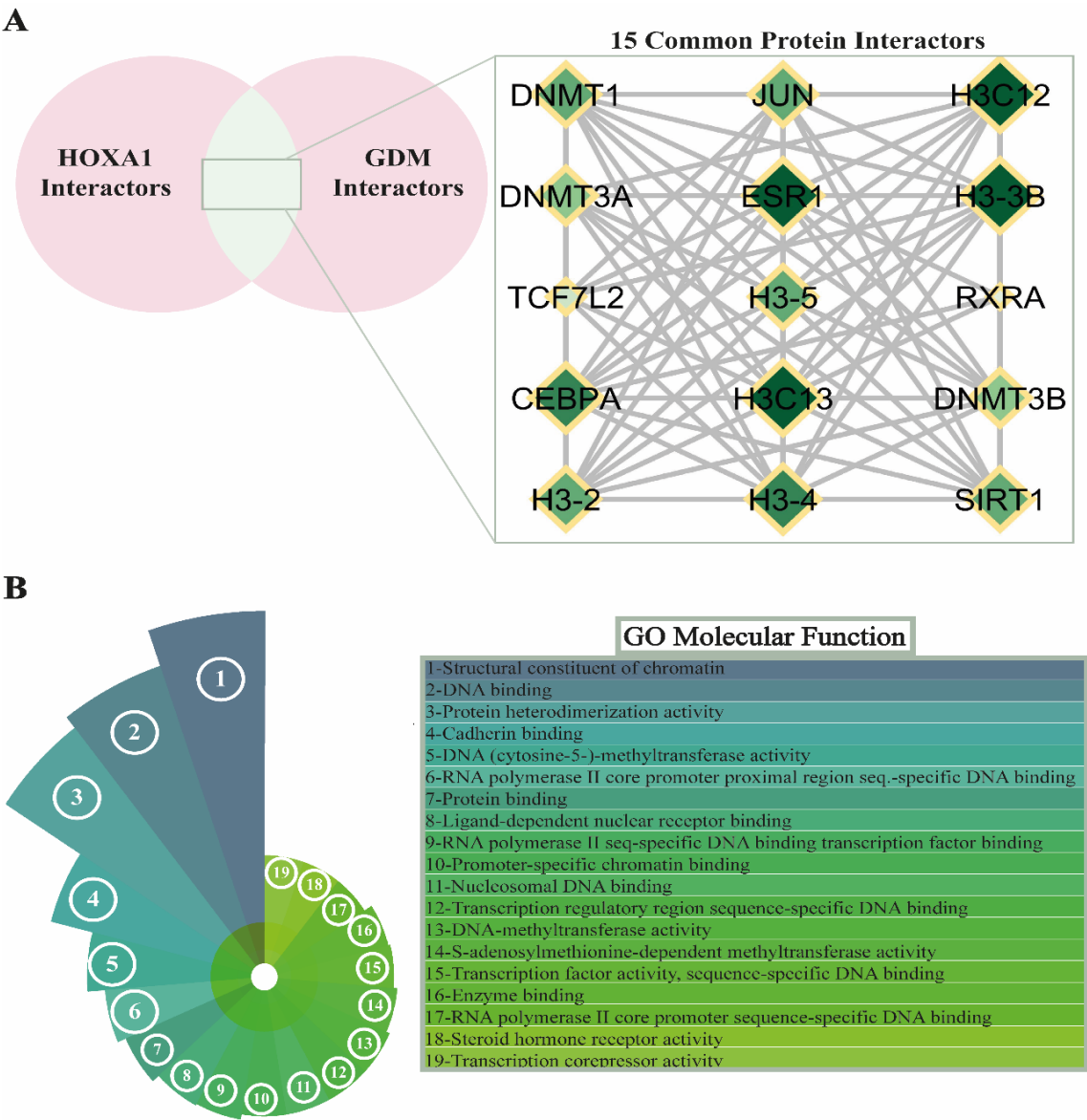


Figure 3. Node centrality and functional annotation analysis of common targets of HOXA1 and GDM. A. Node centrality analysis of 15 intersected proteins using the Centiscape. Larger nodes represent higher degree scores, while darker green color indicates higher closeness scores. B. Polar bar plot represents the significant GO Molecular Function terms of GDM-associated HOXA1 targets. The size of bars is proportional to “-log10(p-value)” values. Terms with a p-value less than 0.05 are considered statistically significant.

Node Centrality and GO Molecular Function Analysis of GDM associated HOXA1 interactors

The intersection of HOXA1 and GDM protein–protein interaction (PPI) networks yielded 15 common protein interactors, as listed in Table 2. The original HOXA1 and GDM networks contained 29,391 and 16,015 edges, respectively, prior to intersection. Node centrality analysis using degree, closeness, and betweenness metrics identified H3C12, H3-3B, H3C13, and ESR1 as the most central nodes within the intersected network (Figure 3A). These proteins exhibited the highest scores across all three centrality measures, indicating their potential regulatory importance within the HOXA1-GDM network. Gene Ontology Molecular Function (GO MF) enrichment analysis of the 15 shared proteins revealed significant associations with chromatin organization, DNA binding, epigenetic regulation, and protein–protein interactions (Figure 3B). These functions may underlie the mechanistic link between increased HOXA1 protein expression and placental pathology in GDM.

Discussion

Gestational diabetes mellitus (GDM) is a transient but significant metabolic disorder that can adversely impact both maternal and fetal health. While it is often limited to pregnancy, women with GDM are at elevated risk of developing type 2 diabetes mellitus (T2DM) later in life (17). Furthermore, GDM may unmask an underlying predisposition to metabolic dysregulation or autoimmune β -cell dysfunction, reinforcing the importance of early diagnosis and intervention.

Consistent with previous studies, our findings revealed notable structural abnormalities in placentas from GDM-affected pregnancies. These included villous degeneration, syncytial knot proliferation, fibrin deposition, leukocyte infiltration, and hemorrhagic areas, all of which are indicative of placental dysfunction(18-20). These histopathological features likely reflect impaired vascular remodeling, increased oxidative stress, and inflammatory responses driven by maternal hyperglycemia. The structural disorganization may compromise placental efficiency, thereby increasing the risk of adverse perinatal outcomes.

At the molecular level, our immunohistochemical analysis showed significantly elevated HOXA1 protein expression in multiple placental compartments from the GDM group. Increased immunoreactivity was observed in cytotrophoblasts, syncytiotrophoblasts, stromal cells, and intervillous cells, suggesting a widespread upregulation of this transcription factor. As a member of the highly conserved HOX gene family, HOXA1 plays critical roles in cell proliferation, differentiation, and developmental patterning, but its role in placental development under hyperglycemic conditions has remained unexplored (21, 22).

Our in silico analysis provides additional insights into the molecular context of HOXA1 in GDM. The intersected HOXA1-GDM network identified 15 shared interactors, with

H3C12, H3-3B, H3C13, and ESR1 emerging as central regulatory proteins. These proteins are involved in chromatin remodeling, DNA binding, and epigenetic regulation—processes that are essential for trophoblast invasion, differentiation, and maternal-fetal interface integrity. Dysregulation of these pathways may contribute to the altered placental phenotype observed in GDM. Prior studies have also reported epigenetic abnormalities in GDM placentas, including DNA methylation changes and miRNA dysregulation, which may influence gene expression relevant to fetal growth and metabolism (23-26).

Importantly, the increased expression of HOXA1 protein in GDM placentas, supported by both histological and bioinformatic data, raises the possibility that HOXA1 could serve as a biomarker of placental dysfunction in diabetic pregnancies. If further validated, HOXA1 expression levels could potentially aid in identifying pregnancies at higher risk for adverse outcomes. Moreover, given its role in regulating transcriptional programs involved in cell fate and vascular remodeling, HOXA1 may represent a therapeutic target for modulating placental function in GDM.

Limitations

This study has several limitations that should be acknowledged. First, it was observational in nature and based on tissue-level analysis, limiting the ability to infer causality. Second, although immunohistochemistry provides spatial information, it does not capture the functional consequences of altered HOXA1 protein expression. The lack of in vitro or in vivo mechanistic studies limits our understanding of how HOXA1 modulates placental cell behavior under diabetic conditions. Future studies incorporating gene knockdown or overexpression models will be necessary to clarify these pathways.

Conclusion

In conclusion, this study demonstrates that GDM induces significant histopathological and molecular alterations in placental tissues. Increased HOXA1 protein expression was observed in multiple placental cell types in the GDM group, suggesting that this transcription factor may be involved in the pathophysiology of diabetic pregnancies. Our in silico analysis further revealed that HOXA1 is functionally connected to key proteins involved in chromatin organization, DNA binding, and epigenetic regulation—processes that are critical for placental development and fetal health. Among the identified interactors, H3C12, H3-3B, H3C13, and ESR1 emerged as central regulatory nodes in the GDM-associated HOXA1 network. Taken together, these findings suggest that HOXA1 may play an important role in the molecular mechanisms underlying placental dysfunction in GDM. HOXA1 also holds potential as a biomarker for placental pathology and may serve as a target for therapeutic modulation in future interventions aimed at mitigating GDM-related complications.

Further research—including functional studies—is warranted to validate the mechanistic roles of HOXA1 and to explore its potential utility in clinical applications.

Ethical Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Non-Interventional Research of Dicle University Faculty of Medicine (Approval Date: 14/02/2024, No: 78).

Author Contributions:

Concept: A.S.A

Literature Review: A.S.A., G.E.A.A., Z.T.

Design : A.S.A, F.A.

Data acquisition: A.S.A, E.A, A.A.

Analysis and interpretation: T.K., F.A.

Writing manuscript: A.S.A., O.A., A.A., G.E.A.A.

Critical revision of manuscript: Z.T., F.A.

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Management of Incidentally Diagnosed Endometrial Cancer: A Single-Center Experience

Tesadüfen Tanı Konulan Endometrium Kanserinin Yönetimi: Tek Merkez Bir Deneyimi

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Abstract

Background: This study aimed to evaluate the clinical characteristics and treatment strategies of patients who were incidentally diagnosed with endometrial cancer following hysterectomy performed for benign indications.

Materials and Methods: In this retrospective study, data of patients who were referred to our gynecologic oncology clinic between October 15, 2023, and October 15, 2024, after being incidentally diagnosed with endometrial cancer following hysterectomy for benign reasons were reviewed. Clinical, pathological, and surgical data were obtained from hospital records, and descriptive statistics and comparative analyses were conducted using SPSS version 29.

Results: A total of 57 patients were included in the study. The mean age was 53.9 ± 8.2 years, and 57.9% of the patients were postmenopausal. The most common histological subtype was endometrioid (94.7%), and superficial myometrial invasion was present in 86.0% of the cases. Preoperative endometrial sampling had not been performed in 28.1% of the patients. While 28.1% of the patients underwent completion surgery, 71.9% were managed conservatively with close follow-up. Block revision of pathology slides was performed in 15 patients whose initial diagnoses were made at centers lacking experience in gynecologic oncology, to ensure diagnostic accuracy. Following expert pathological re-evaluation, diagnostic changes were identified in 8 of these cases (53.3%). In patients with grade 2–3 tumors, deep myometrial invasion, lymphovascular space invasion, and the need for further surgical intervention were found to be significantly more frequent ($p < 0.05$).

Conclusions: Incidentally diagnosed endometrial cancer requires a multidisciplinary and risk-adapted approach. This study highlights the value of pathology slide revision, particularly in cases initially reported by centers lacking gynecologic oncology expertise, in guiding postoperative management decisions. While conservative follow-up is safe for selected low-risk patients, timely completion surgery and adjuvant therapy are essential in high-risk cases.

Keywords: Hysterectomy, Endometrial Cancer, Incidental, Follow-Up, Management

Öz

Amaç: Bu çalışma, benign nedenlerle histerektomi uygulanan hastalarda tesadüfi olarak tanı alan endometrium kanserli olguların klinik özelliklerini ve tedavi yöntemlerini değerlendirmeyi amaçlamaktadır.

Materyal ve Metod: Bu retrospektif çalışmada, 15 Ekim 2023 – 15 Ekim 2024 tarihleri arasında benign endikasyonlarla histerektomi sonrası tesadüfen endometrium kanseri tanısı alarak jinekolojik onkoloji kliniğimize yönlendirilen hastaların verileri incelenmiştir. Klinik, patolojik ve cerrahi veriler hastane kayıtlarından elde edilmiş; tanımlayıcı istatistikler ile karşılaştırmalı analizler SPSS 29 programı kullanılarak gerçekleştirilmiştir.

Bulgular: Çalışmaya toplam 57 hasta dâhil edildi. Ortalama yaş $53,9 \pm 8,2$ yıl olup, hastaların %57,9'u postmenopozal dönemdeydi. En sık rastlanan histolojik alt tip %94,7 oranıyla endometrioid tip idi ve olguların %86,0'ında yüzeysel myometriyal invazyon mevcuttu. Preoperatif endometrial örnekleme hastaların %28,1'inde yapılmamıştı. Hastaların %28,1'ine tamamlamayı cerrahi müdahale planlanırken, %71,9'u konservatif olarak yakın takip ile yönetildi. Patoloji blok revizyonu, jinekolojik onkoloji alanında deneyimi olmayan merkezlerde değerlendirilen 15 hastada, tanısız doğruluğu sağlamak amacıyla gerçekleştirilmiştir. Uzman patoloji incelemesi sonucunda bu hastaların 8'inde (%53,3) tanıda değişiklik saptanmıştır. Grade 2–3 tümörlerde derin invazyon, lenfovasküler alan invazyonu ve cerrahi gereksinimi anlamlı olarak daha yüksek bulundu ($p < 0,05$).

Sonuç: Tesadüfen tanı konulan endometrium kanseri olgularında multidisipliner ve risk temelli bir yaklaşım gereklidir. Bu çalışma, özellikle jinekolojik onkoloji deneyimi olmayan merkezlerde raporlanan olgular için yapılan patoloji blok revizyonunun, tedavi kararlarını yönlendirmede önemli katkı sağladığını göstermektedir. Düşük riskli hastalarda konservatif takip güvenli bir seçenek olabilirken, yüksek riskli olgularda zamanında tamamlamayı cerrahi ve adjuvan tedavi uygulamaları hayati önemdedir.

Anahtar Kelimeler: Histerektomi, Endometrial Kanser, İnsidental, Takip, Yönetim

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Introduction

Endometrial cancer (EC) is the most frequently diagnosed gynecological malignancy in developed countries, and its incidence continues to rise. This upward trend has been attributed to lifestyle-related factors such as obesity, changes in dietary habits, diabetes mellitus, late-onset menopause, and an aging population. In 2024, approximately 67,000 new cases and nearly 13,000 deaths associated with uterine corpus cancers were reported globally (1).

Hysterectomy is one of the most commonly performed gynecological procedures worldwide, typically indicated for benign conditions such as abnormal uterine bleeding and uterine fibroids. Incidentally diagnosed endometrial cancer refers to malignancy that is unexpectedly identified during or after a surgical procedure performed for non-malignant reasons. A review of the literature reveals a divergence in the incidence of incidentally detected endometrial cancer, which is reported to range between 0.19% and 3%. In a 2017 study, Thomas et al. (2) reported an incidence of 0.3% to 3% among cases where hysterectomy was performed for benign indications. Similarly, Mahnert et al. (3), in a large-scale study involving over 370,000 patients, reported an incidence rate of 1.02%. In a cohort of 6,981 patients, Parsons et al. found an even lower rate of 0.19% (4).

Incidentally diagnosed endometrial cancer is often attributed to inadequate preoperative evaluation, the absence of endometrial biopsy prior to surgery, emergency surgeries performed without intraoperative frozen section analysis, errors in frozen section interpretation, or insufficient sampling techniques in the presence of focal lesions.

The absence of a preoperative diagnosis of malignancy may result in incomplete surgical staging and uncertainty in postoperative treatment decisions. Despite increasing clinical awareness, data regarding the incidence, risk factors, and optimal management strategies for incidentally diagnosed endometrial cancer remain limited in the current literature. Nonetheless, in most cases, the cancer is detected at an early stage. Management should be planned through a multidisciplinary approach, considering the stage of disease, histological subtype, depth of myometrial invasion, overall health status, age, and individual preferences of the patient.

This study aims to evaluate the clinical characteristics and management approaches of patients who were referred to our clinic with a postoperative diagnosis of endometrial cancer.

Materials and Methods

This retrospective cohort study was conducted by reviewing the medical records of patients referred to our gynecologic oncology clinic between October 15, 2023, and October 15, 2024, following an incidental diagnosis of endometrial cancer after undergoing hysterectomy for non-malignant indications. Data were retrieved from the institutional patient record system. No direct contact was made with the patients, and only existing clinical data were used. Maximum attention was paid to ensuring patient confidentiality throughout the study. Ethical approval was obtained from the Ethics Committee of İzmir city Hospital on 06/11/2024 (decision number: 2024/194).

In addition, block revision of pathology slides was performed in 15 patients whose initial diagnoses had been reported by centers lacking experience in gynecologic oncology and where diagnostic uncertainty was present. In these cases, histological subtype, tumor grade, depth of myometrial invasion, and the presence of lymphovascular space invasion (LVSI) were re-evaluated by a pathologist specialized in gynecologic pathology.

Descriptive statistics, including mean, standard deviation, minimum and maximum values, as well as frequencies and percentages, were used for data analysis. Pearson’s Chi-square test was employed to compare categorical variables. Statistical analyses were performed using licensed SPSS version 29 software.

Results

The mean age of the patients was 53.9 ± 8.2 years, ranging from 34 to 70. The mean gravida was 3.0 ± 1.9 , and the mean parity was 2.3 ± 1.6 . The mean preoperative Ca125 level was 38.1 ± 84.2 , and the mean preoperative endometrial thickness was 12.6 ± 6.9 mm (Table 1).

Among the patients with incidentally diagnosed endometrial malignancy, 57.9% were postmenopausal. Comorbid conditions were identified in 47.4% of cases, with hypertension (31.6%) and diabetes mellitus (29.8%) being the most common. Among the 9 patients with a history of previous surgery, 2 had a prior myomectomy, and of the 4 patients with a known cancer history, 3 had breast cancer and 1 had thyroid cancer. The most frequent preoperative clinical presentations were postmenopausal bleeding (54.4%) and abnormal uterine bleeding (22.8%). Additionally, menometrorrhagia was reported in 15.8% of patients, uterine prolapse in 3.5%, chronic pelvic pain in 1.8%, and a combination of pelvic pain and menometrorrhagia in 1.8%.

Table 1. Descriptive characteristics of patients with incidental endometrial cancer after hysterectomy.

	Average	Sd	Min	Max
Age	53.9	8.2	34	70
Gravida	3.0	1.9	0	8
Parity	2.3	1.6	0	7
Preoperative Ca125	38.1	84.2	3.9	479.0
Preoperative Endometrial Thickness	12.6	6.9	1.0	34.0

Sd: Standard Deviation, Min: Minimum, Max: Maximum

Table 2. Descriptive characteristics of patients with incidental endometrial cancer after hysterectomy.

	Number	(%)
Postmenopause	33	57.9
Additional Disease	27	47.4
Hypertension	18	31.6
Diabet	17	29.8
Past Operation History	9	15.8
Past Cancer History	4	7.0
Clinical Presentation		
Chronic Pelvic Pain and Menometrorrhagia	1	1.8
Chronic Pelvic Pain	1	1.8
Uterine descent	2	3.5
Menometrorrhagia	9	15.8
Postmenopausal Bleeding	31	54.4
Abnormal Uterine Bleeding	13	22.8
Preoperative Pathology		
None	16	28.1
Endometrial Intraepithelial Neoplasia	24	42.1
Endometrial Hyperplasia	13	22.8
Endometritis	2	3.5
Endometrium in the Proliferation Phase	2	3.5
Preoperative Myoma	30	52.6
Preoperative Ovarian Pathology	12	21.1
Operation Type		
TAH+BSO	29	50.9
TLH+BSO	24	42.1
VH	4	7.0
Frozen		
Benign	14	24.6
EN	15	26.3
Malign	13	22.8
Not wanted	15	26.3
Histological Subtype		
Endometrioid	54	94.7
Serous	2	3.5
Clear Cell	1	1.8
Invasion		
Superficial Invasion	49	86.0
Deep Invasion	8	14.0
LVSI	12	21.1
Grade		
Grade 1	41	71.9
Grade 2	14	24.6
Grade 3	2	3.5
Block Revision Request	15	26.3
Decision		
Follow-up	41	71.9
Surgical	16	28.1

TAH+BSO: Total Abdominal Hysterectomy+Bilateral Salpingo-Oophorectomy; TLH+BSO: Total Laparoscopic Hysterectomy+Bilateral Salpingo-Oophorectomy; VH: Vaginal Hysterectomy; EIN: Endometrial Intraepithelial Neoplasia; LVSI: Lymphovascular Space Invasion

Regarding preoperative endometrial histopathological findings, 28.1% of patients underwent surgery without endometrial sampling, while endometrial intraepithelial neoplasia (EIN) was identified in 42.1%, and endometrial hyperplasia in 22.8%. Leiomyoma were detected in 52.6% of patients preoperatively, and adnexal pathology in 21.1% (Table 2).

When analyzing the type of surgery performed, 50.9% underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, 42.1% underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, and 7.0% underwent vaginal hysterectomy.

Intraoperative frozen section results revealed EIN in 26.3% of patients, benign findings in 24.6%, and malignancy in 22.8%. In 26.3% of cases, frozen section analysis was not requested.

Endometrioid histology was the most frequent subtype, seen in 94.7% of cases. Serous carcinoma was identified in 3.5%, and clear cell carcinoma in 1.8%. Superficial myometrial invasion was observed in 86.0% of patients, while deep invasion was noted in 14.0%. Lymphovascular space invasion (LVSI) was present in 21.1% of cases. While 71.9% of incidentally diagnosed patients referred to our centre were given the decision for follow-up, 28.1% were given the decision for additional surgical intervention (Table 2).

Among patients with Grade 1 tumors, 63.4% were postmenopausal, compared to 43.8% in Grade 2–3 cases. Although not statistically significant, the presence of preoperative leiomyoma was higher in Grade 1 patients (61%) than in those with Grade 2–3 (31.3%) ($p = 0.043$). Adnexal pathology was found in 24.4% of Grade 1 cases and in 12.5% of Grade 2–3

($p = 0.477$). Endometrioid histology constituted 97.6% of Grade 1 and 87.5% of Grade 2–3 cases ($p = 0.187$). Superficial invasion was significantly more common in Grade 1 cases (97.6%) compared to 56.3% in Grade 2–3. Deep invasion was significantly more frequent in Grade 2–3 (43.8%) ($p < 0.001$). LVSI was present in 12.2% of Grade 1 cases and in 43.8% of Grade 2–3 cases ($p = 0.025$). The need for surgical intervention was higher in Grade 2–3 (68.8%), while 87.8% of Grade 1 cases were managed with observation ($p < 0.001$)

(Table 3).

Although intraoperative frozen section was reported in favor of malignancy in 13 patients, staging surgery could not be performed because there was no surgeon in the center to perform gynecologic oncologic staging. Block revision was performed in 15 cases, and pathological changes were noted in 53.3% ($n = 8$). Following revision, Grade 3 tumors were identified in 5 cases, serous carcinoma in 2, and clear cell carcinoma in 1.

Table 3. Descriptive characteristics of patients with incidental endometrial cancer after hysterectomy.

		Grade 1		Grade 2/3		p
		Number	(%)	Number	(%)	
Menopause	+	26	63.4	7	43.8	0.177
	-	15	36.6	9	56.3	
Preoperative Leiomyoma	+	25	61.0	5	31.3	0.043
	-	16	39.0	11	68.8	
Preoperative Ovarian Pathology	+	10	24.4	2	12.5	0.477
	-	31	75.6	14	87.5	
Histological Subtype	Endometrioid	40	97.6	14	87.5	0.187
	Nonendometrioid	1	2.4	2	12.5	
Invasion	Superficial	40	97.6	9	56.3	<0.001
	Deep	1	2.4	7	43.8	
LVSI	+	5	12.2	7	43.8	0.025
	-	36	87.8	9	56.3	
Decision	Follow-up	36	87.8	5	31.3	<0.001
	Surgical	5	12.2	11	68.8	

LVSI: Lymphovascular Space Invasion.

Discussion

The management of incidentally diagnosed endometrial cancer is multifaceted and depends on numerous variables. One of the most critical clinical dilemmas following diagnosis is determining whether a second surgery is necessary for complete surgical staging and how the need for adjuvant therapy should be assessed. Treatment strategies should be planned by considering not only the extent of disease, histological subtype, and prognostic characteristics of the tumor but also the patient's age, comorbidities, general performance status, and individual preferences. Therefore, each case should be carefully evaluated and managed through a personalized, multidisciplinary approach.

Preoperative endometrial assessment is a key step in the early detection of endometrial cancer. In our study, 28.1% of patients diagnosed with incidental endometrial cancer had not undergone endometrial sampling prior to surgery. Despite the fact that the pipelle method was the preferred technique in all 41 patients in this study, it is possible that this method may be inadequate for the detection of focal lesions. In the literature, the false-negative rate for pipelle biopsy has been reported to reach up to 10% (5). These findings suggest that either the absence of preoperative sampling or reliance on blind techniques such as pipelle may increase the risk of incidental diagnosis. Particularly in elderly patients presenting with abnormal uterine bleeding and ultrasonographic evidence of focal endometrial lesions, comprehensive evaluation including hysteroscopy-guided biopsy

is recommended when pipelle sampling is inconclusive. Hysteroscopy has been shown to offer more accurate diagnosis of histologic type and tumor grade in the presence of malignancy compared to blind endometrial biopsy (5,6).

Endometrial hyperplasia and EIN are recognized as precursor lesions of endometrial carcinoma and may coexist with malignancy. According to previous studies, approximately 40% of patients with atypical endometrial hyperplasia are diagnosed with concurrent endometrial carcinoma (7,8). Clinical and radiological factors that increase the risk of concurrent malignancy include advanced age, obesity, diabetes mellitus, and endometrial thickness ≥ 20 mm on transvaginal ultrasonography (8). In our study, 24 patients had a preoperative diagnosis of EIN and 13 had EH, underscoring the strong association of these lesions with underlying malignancy. These findings emphasize the need for meticulous preoperative endometrial evaluation and support the recommendation for surgical procedures to be performed in centers with expertise in gynecologic oncology staging.

Another crucial step in the management of patients with incidentally diagnosed endometrial cancer is the reevaluation of surgical specimens. When such a diagnosis is established, it is strongly recommended that the hysterectomy $\pm$ salpingo-oophorectomy specimens be re-examined at a center with expertise in gynecologic oncology pathology. During this process, a detailed pathological report should be requested, including confirmation of the diagnosis, histologic subtype, tumor grade, localization, depth of myometrial invasion, cervical involvement, tumor size, lymphovascular

space invasion (LVSI), and adnexal involvement.

In our study, pathological slide revision was performed in 15 patients, and significant changes were observed in 53.3% ($n = 8$). Following a thorough review of the relevant data, the tumour grade was re-evaluated and re-classified as Grade 3 in five patients. In addition, the serous carcinoma subtype was defined in two patients, and the clear cell carcinoma subtype was identified in one patient. These findings highlight the diagnostic and therapeutic importance of reviewing surgical specimens in patients with incidentally diagnosed endometrial cancer.

When surgery is performed at an external center, obtaining detailed intraoperative findings from the primary surgeon is essential for treatment planning. For example, in cases where supracervical hysterectomy has been performed or bilateral salpingo-oophorectomy was not carried out, the risk of cervical or synchronous ovarian involvement may pose significant clinical uncertainties. Completion staging surgery in such cases may help prevent unnecessary pelvic radiation. However, it is also associated with increased surgical morbidity. Therefore, individualized patient management through a multidisciplinary approach is of utmost importance.

For low-risk patients (Grade 1, endometrioid subtype, <50% myometrial invasion, LVSI-negative, tumor diameter <2 cm), current guidelines suggest that follow-up without staging surgery may be a safe alternative. Indeed, in this patient group, the risk of extrauterine disease is reported to be below 1%, with 5-year disease-free survival rates ranging between 95% and 99% (3,10). Especially in elderly or comorbid patients with high surgical risk, the morbidity of staging procedures may outweigh the potential survival benefit.

In contrast, for patients with Grade 2–3 tumors, serous or clear cell histological subtypes, positive LVSI, or deep myometrial invasion, it may be challenging to plan adjuvant treatment without comprehensive surgical staging. In such cases, lymph node evaluation, omentectomy, and peritoneal cytology are important not only for prognostic assessment but also for guiding further treatment.

The management of ovaries should be tailored based on the patient's age, histologic subtype, disease stage, presence of LVSI, and fertility expectations. In premenopausal patients who desire fertility preservation and have low-stage (Stage IA), low-grade (Grade 1–2), endometrioid-type tumors with <50% myometrial invasion and negative LVSI, ovarian preservation may be considered a safe option. However, in cases involving non-endometrioid histologic subtypes such as serous or clear cell carcinoma, high-grade tumors, positive LVSI, or suspected Lynch syndrome, bilateral salpingo-oophorectomy is generally recommended (10). In postmenopausal women, the risk of synchronous ovarian malignancy or metastatic involvement is higher; thus, oophorectomy is accepted as the standard approach.

In our study, three patients who underwent vaginal hysterectomy due to uterine prolapse did not undergo oophorectomy. All of these patients were premenopausal. Their final

pathology revealed endometrioid histology, superficial myometrial invasion, and negative LVSI. After thorough counseling and obtaining written informed consent, the patients opted to preserve their ovaries based on oncologic suitability and personal preference. These patients were monitored with a follow-up schedule similar to that recommended for high-risk cases.

In patients diagnosed with incidental endometrial cancer, postoperative imaging plays a critical role in assessing disease spread, evaluating the need for adjuvant therapy, and determining whether completion surgery is necessary. This is particularly important when preoperative staging has not been performed or when the initial surgery was conducted at an external facility, warranting a systematic imaging approach.

As a first step, contrast-enhanced thoracoabdominal-pelvic computed tomography (CT) is preferred for evaluating distant metastases (particularly pulmonary) and assessing pelvic and para-aortic lymph node size (9). Pelvic magnetic resonance imaging (MRI) offers higher sensitivity than CT in detecting local disease extension, including cervical and parametrial involvement (11). Additionally, in the presence of suspicious postoperative findings such as vaginal bleeding, pelvic mass, or elevated tumor markers, MRI can aid in assessing residual disease or recurrence (12).

Positron emission tomography/computed tomography (PET/CT) may be useful in identifying metabolically active lymph nodes and distant metastases. However, its routine use is not recommended in early-stage cases and is instead reserved for high-risk patients (e.g., those with positive LVSI, high tumor grade, or radiologically suspicious lesions) (12). The sensitivity and specificity of PET/CT for detecting lymph node metastases have been reported as %63 and %94.7 respectively. Due to the risk of false negatives, direct surgical staging may be a more reliable approach for guiding adjuvant treatment in high-risk cases (13).

One of the most important clinical dilemmas in the management of incidentally diagnosed endometrial cancer is determining the optimal timing for completion staging surgery. When reoperation is indicated following oncologic surgery, the timing should consider both oncologic factors and the biological phases of wound healing. During the proliferative phase of wound healing, particularly between day 21 and week 6 postoperatively, collagen breakdown and remodeling predominate (14). During this period, collagen fibrils are disorganized, and the surgical site remains mechanically vulnerable. Therefore, early reintervention carries increased risks of wound dehiscence, herniation, and infection.

In our study, 16 patients underwent completion surgery, which included bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, and omentectomy. For patients managed conservatively in the low-risk group, follow-up was planned every 6 months for the first 2 years, consisting of physical examination and symptom review. For those whose ovaries were preserved, follow-up also included abdominal

CT every 6 months for 2 years, in line with protocols for higher-stage disease.

Decision-making in these patients must be individualized and discussed within a multidisciplinary tumor board. Moreover, in cases where complete staging cannot be performed but adjuvant therapy is considered, treatment protocols must be structured with acknowledgment of this staging uncertainty.

Surgical morbidity increases significantly in elderly patients. The literature highlights the adverse effects of pelvic lymphadenectomy and complete staging surgery on quality of life and functional status, particularly in individuals aged 75 years and older (15,16). Therefore, for low-risk elderly patients, close follow-up without surgical staging may be a preferable and safer approach.

In patients with significant comorbidities, such as diabetes mellitus, heart failure or chronic obstructive pulmonary disease, the potential risks of additional morbidity from further surgical procedures should be meticulously evaluated. In this particular subgroup, the administration of adjuvant therapy may be considered with greater frequency. In particular, when high-risk features such as deep myometrial invasion, LVSI, or high-grade tumors are present, radiation-based treatment strategies may serve as appropriate alternatives to surgery (10).

The diagnosis of incidental endometrial cancer, often discovered following surgery performed for presumed benign conditions, carries significant psychological implications. Patients who receive an unexpected cancer diagnosis after hysterectomy frequently experience anxiety, loss of trust, anger, and guilt. Furthermore, they are often left with emotionally distressing questions such as, "Was the surgery incomplete?" or "Has the cancer already spread?", which can intensify uncertainty and distress about subsequent treatment decisions.

In particular, for patients who require additional surgery or adjuvant treatment, the process of conveying information must be managed with great sensitivity, and shared decision-making should be actively supported. Providing psychosocial support in the postoperative period can positively influence both treatment compliance and overall quality of life. A psycho-oncology specialist or clinical psychologist, integrated within the multidisciplinary team, should be available to offer timely and ongoing support during the post-diagnosis period (17).

From the moment of diagnosis, patients should receive clear and structured communication, both verbally and in writing. Topics such as the necessity for completion surgery, the rationale for adjuvant therapy, and potential follow-up plans should be explained transparently and comprehensively. This approach not only strengthens the patient and physician relationship but also helps to reduce anxiety (18).

Incidentally diagnosed endometrial cancer presents unique diagnostic and therapeutic challenges that require a multidisciplinary and risk-adapted approach. Our findings indicate that conservative follow-up is safe in selected low-risk

patients, whereas completion staging and individualized adjuvant therapy are essential in high-risk cases. The study underscores the importance of pathology slide revision and expert imaging in enhancing postoperative decision-making. By presenting real-world data on surgical reconsideration, pathological reassessment, and adjuvant strategies, our study offers valuable insight into the management of these patients. Despite its retrospective and single-center nature, the findings carry practical relevance for optimizing personalized care.

Ethical Approval: This study was designed in accordance with the Helsinki Declaration and approved by Ethics Committee of İzmir City Hospital. (Study ethics committee number: 2024/194; date 06/11/2024). Purpose and methods of the study were explained to patients, and they provided written informed consent.

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Design : C.A.

Data acquisition: M.F.B., G.Ö.Ş.

Analysis and interpretation: M.F.B., S.K.

Writing manuscript: C.A., D.B.

Critical revision of manuscript: M.S., D.B., E.Ş

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Sedation in Pediatric Patients Undergoing Magnetic Resonance Imaging: An Observational Comparison

Manyetik Rezonans Görüntülemesi Geçiren Pediatrik Hastalarda Sedasyon: Gözlemsel Bir Karşılaştırma

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Abstract

Background: This study aimed to compare sedation methods in pediatric patients undergoing magnetic resonance imaging (MRI) using three different anesthetic agents (sevoflurane, thiopental, and propofol) regarding safety, efficacy, time management, and side effects.

Materials and Methods: An observational study was conducted with 126 pediatric patients divided into three groups, each receiving one of the three sedative agents: Group S (n = 43), Group T (n = 41), and Group P (n = 42). Patients in Group S received induction with 8% sevoflurane, Group T received 5 mg kg⁻¹ of thiopental intravenously, and Group P received 2 mg kg⁻¹ of propofol intravenously, followed by maintenance via infusion.

Results: The mean age was 37.3 ± 2 months. Cranial MRI was most frequently requested (64.5%). Group P had higher desaturation (p = 0.029) and respiratory depression (p = 0.008) rates. Group T had the shortest induction time (p < 0.001), while Group S showed the fastest wake-up times (p = 0.002; p = 0.001).

Conclusions: Sevoflurane is distinguished by its rapid emergence from sedation and low incidence of side effects. Thiopental has a quick induction time, whereas propofol is associated with minimal agitation but higher respiratory complications. These findings can guide clinicians in selecting the most appropriate sedation method for pediatric MRI.

Keywords: Deep sedation, Magnetic resonance imaging, Propofol, Sevoflurane, Thiopental

Öz

Amaç: Bu çalışma, manyetik rezonans görüntüleme (MRG) geçiren pediatrik hastalarda üç farklı anestezi ajanı (sevofluran, tiyopental ve propofol) kullanılarak yapılan sedasyon yöntemlerini güvenlik, etkinlik, zaman yönetimi ve yan etkiler açısından karşılaştırmayı amaçladı.

Materyal ve Metod: Gözlemsel bir çalışma 126 pediatrik hasta ile gerçekleştirildi ve hastalar üç gruba ayrıldı; her grup üç sedatif ajanından birini aldı: Grup S (n = 43), Grup T (n = 41) ve Grup P (n = 42). Grup S'deki hastalara %8 sevofluran ile indüksiyon, Grup T'deki hastalara 5 mg kg⁻¹ tiyopental intravenöz yolla, Grup P'deki hastalara ise 2 mg kg⁻¹ propofol intravenöz yolla indüksiyon yapıldı ve ardından infüzyon yoluyla idame sağlandı.

Bulgular: Ortalama yaş 37,3 ± 2 ay olarak belirlendi. En sık istenen MRG türü kranial MRG idi (%64,5). Grup P'de desatürasyon (p = 0,029) ve solunum depresyonu (p = 0,008) oranları daha yüksekti. Grup T en kısa indüksiyon süresine sahipti (p < 0,001), Grup S ise en hızlı uyanma sürelerini gösterdi (p = 0,002; p = 0,001).

Sonuç: Sevofluran, sedasyondan hızlı derlenme ve düşük yan etki insidansı ile öne çıkmaktadır. Tiyopental, hızlı bir indüksiyon süresine sahipken, propofol minimal ajitasyon ancak daha yüksek solunum komplikasyonları ile ilişkilidir. Bu bulgular, pediatrik MRG için en uygun sedasyon yöntemini seçmede klinisyenlere rehberlik edebilir.

Anahtar Kelimeler: Derin sedasyon, Manyetik rezonans görüntüleme, Propofol, Sevofluran, Tiyopental

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Introduction

Magnetic resonance imaging (MRI) is a commonly used imaging technique due to its safety and non-ionizing radiation properties (1). In pediatric patients, ensuring immobility is crucial for obtaining clear images. Since MRI procedures often last 10 min or more, sedation is frequently required, particularly in children aged 1 to 8 years. The sedation used during MRI is generally at the "deep sedation" level, which is similar to general anesthesia (2). Deep sedation suppresses consciousness and protective reflexes, and patients may only respond to painful or repeated stimuli. The primary risks associated with deep sedation include respiratory depression and aspiration, which may necessitate airway management. Cardiovascular function, however, is generally preserved. Proper monitoring of vital signs is critical when determining the sedative agents or anesthetics to use (3).

During MRI sedation, oxygen saturation can decrease, so capnography is essential to detect early signs of apnea by measuring end-tidal carbon dioxide levels. Chest plethysmography belts are also used to monitor chest movement, ensuring regular respiratory monitoring (5). These MRI-compatible devices provide continuous respiratory data and help detect apnea in real-time (6).

Dexmedetomidine is commonly used for pediatric MRI in patients without cardiac risk, whereas propofol is more effective when administered by anesthesiologists or pediatric critical care specialists (5,7). Small doses of ketamine or nalbuphine, given toward the end of sedation with sevoflurane, have been shown to reduce emergence agitation without delaying recovery (8). Buccal dexmedetomidine, with or without oral midazolam, has been found to provide adequate sedation for MRI with few side effects, though the failure rate suggests dose adjustments may be necessary (9). Deep sedation is frequently required to ensure immobility during MRI in pediatric patients; however, the safety and efficacy profiles of the sedative agents used for this purpose vary. Therefore, the primary objective of this study was to compare the safety of sevoflurane, thiopental, and propofol in terms of respiratory depression and oxygen desaturation ($\text{SpO}_2 < 92\%$) in pediatric patients undergoing MRI. Secondary objectives included the evaluation of induction and recovery times, hemodynamic and airway safety, sedation success rates, agitation scores, requirement for additional dosing, and incidence of adverse events.

Materials and Methods

This cross-sectional observational study was conducted between September 2021 and December 2022 at university hospital, in accordance with the Declaration of Helsinki, and was approved by the local ethics committee (decision number: 2021/30-02, 14.09.2021). Pediatric MRI sedation was performed biweekly, with different sedative agents administered on alternating days. Blinding was not implemented to allow the anesthesia team and patients to be aware of the medications and potential side effects.

Patient Selection

The sample size of 75 patients was calculated with a 0.47 effect size, 80% power, and a 5% error margin using G-Power 3.1 software (Heinrich-Heine-Universität Düsseldorf, Germany), based on peripheral oxygen saturation values from the study by Oğurlu et al., which investigated sevoflurane concentrations for MRI sedation in pediatric patients (10). While the Oğurlu et al. study utilized a baseline SpO_2 value of 95%, our study employed a 92% threshold for defining desaturation, in accordance with clinical observations in our patient population. This distinction was considered during the sample size calculation. The sample size calculation was based on a one-way ANOVA comparing the three sedation groups (sevoflurane, thiopental, and propofol), using the incidence of desaturation as the primary endpoint. However, to increase the reliability of the results, the sample size was increased to 126 patients with the approval of the institutional ethics committee. This adjustment was made to reduce heterogeneity and enhance the robustness of subgroup analyses. The study was approved as an observational, cross-sectional study. Patients were recruited over 12 months based on predefined inclusion and exclusion criteria. Patients were by administering a different sedative drug each MRI day. The 126 patients were divided into three groups: Group S (sevoflurane, $n = 43$), Group T (thiopental, $n = 41$), and Group P (propofol, $n = 42$).

Children aged 1 month to 12 years with American Society of Anesthesiologists (ASA) scores of I–III undergoing elective MRI under sedation were included. Exclusion criteria included patients < 1 month or > 12 years, ASA score IV, Mallampati class IV, respiratory infections, craniofacial anomalies, non-fasting status, intensive care unit (ICU) admission, trauma-related imaging, severe cardiopulmonary disease, sleep apnea, imaging > 60 min, sedation with non-study drugs, and those undergoing general anesthesia with intubation or LMA insertion.

Anesthesia Procedures

Informed consent was obtained from the parents, and the patients were escorted to the MRI unit (Philips Ingenia 1.5 Tesla 2015, Netherlands). To standardize the procedures and practices prior to drug administration in the MRI room, all patients underwent a uniform preparation protocol. All steps were performed in the same sequence and by the same anesthesia team for all patients to maintain consistency. Upon arrival at the MRI unit, patients were monitored using pulse oximetry, noninvasive blood pressure cuffs, and spirometry belts for chest movements. To minimize the potential discomfort caused by MRI-related noise, all patients were provided with noise-canceling headphones. These measures were implemented in accordance with routine institutional practice to reduce auditory stimulation and prevent noise-induced arousal, which can interfere with sedation levels. Preoxygenation with 100% oxygen at 5 L/min was per-

formed for all patients for 3 minutes. Additionally, intravenous access was secured, and atropine ($10 \mu\text{g}/\text{kg}$) was administered to reduce secretions and prevent bradycardia. The induction time (seconds) was recorded as the time elapsed from the patient's entry into the MRI room, including these standardized preparation steps, until the start of imaging. Patients were randomly assigned to sedation groups, with the same drug used for all procedures on a given day. The sedation drug doses were determined based on our institutional clinical protocols, supported by a comprehensive literature review and a pilot study conducted to achieve a target Ramsey sedation score of 5–6. This approach ensured consistent sedation levels while optimizing imaging quality during MRI.

Patients in Group S were induced with 8% sevoflurane (Sevorane®, AbbVie, Türkiye) at a fresh gas flow of 5 L min^{-1} of oxygen, targeting a deep sedation level of Ramsey 5–6. Once the desired sedation was achieved, the sevoflurane dose was reduced to 1.5% minimum alveolar concentration (MAC), and if movement occurred during MRI, the concentration was increased to 2% MAC. Sevoflurane was discontinued 3 min before the procedure ended.

In Group T, thiopental sodium (Pentothal Sodium®, IE, Türkiye) was administered intravenously at a dose of 5 mg kg^{-1} . If movement was observed, an additional 1 mg kg^{-1} was given, with oxygen support at 5 L min^{-1} via nasal cannula. After 15 min, further doses of 3 mg kg^{-1} were administered every 10 min as required.

In Group P, patients were induced with 2 mg kg^{-1} propofol (Propofol-PF® 1%, Polifarma, Türkiye) followed by a maintenance infusion at a rate of $150 \mu\text{g kg}^{-1} \text{ min}^{-1}$ using an infusion pump (Medbar, İzmir). If movement occurred, 0.5 mg kg^{-1} propofol was added or the infusion rate was increased to $200 \mu\text{g kg}^{-1} \text{ min}^{-1}$. Oxygen support was provided at 5 L min^{-1} via nasal cannula, and propofol was discontinued 3 min before the procedure ended.

Baseline peripheral oxygen saturation values were recorded after the completion of anesthesia induction, rather than during the awake state. This approach was chosen to assess the effects of different sedation methods on the initial and final saturation values. During MRI, end-tidal carbondioxide, heart rate, oxygen saturation, chest movements (monitored via belt plethysmography), and respiratory rate were recorded every 5 min. If spontaneous breathing did not resume, options such as laryngeal mask airway (LMA) insertion or endotracheal intubation were considered. Time metrics, including "induction time" (entry into MRI room until imaging start), "wake-up time" (time to spontaneous response), and "total procedure time", were recorded. The total amount and dose of anesthetic agents administered, the type of MRI and use of contrast, were noted. Airway-related events during induction and MRI were scored (Figure 1 and 2). Sedation was deemed 'successful' if imaging was acceptable to the radiologist and adequate airway safety and sedation were achieved. In the recovery room, airway safety scores (Figure

3), 'recovery status (modified Aldrete score)' (Figure 4), 'recovery time (s)', and the 'patient calmness/agitation status at 5-10 min (Weldon agitation scale)' were recorded (Figure 5) (11). Recovery was considered complete when the modified Aldrete score reached 9 or higher. The Weldon agitation scale used in this study is an observer-rated scale commonly applied in pediatric anesthesia recovery. Any adverse events from induction to discharge were documented, including stridor, snoring, hiccup, cough, dizziness, desaturation, need for jaw thrust, prolonged desaturation, oropharyngeal tube placement, procedure failure, inadequate induction, severe agitation (agitation score average of 3 or 4), movement during MRI and sequence repetition (each movement counted as an adverse event), vomiting, micturition/defecation, prolonged sedation, unexpected hospital admission or ICU need, severe hypotension, bradycardia, and nystagmus.

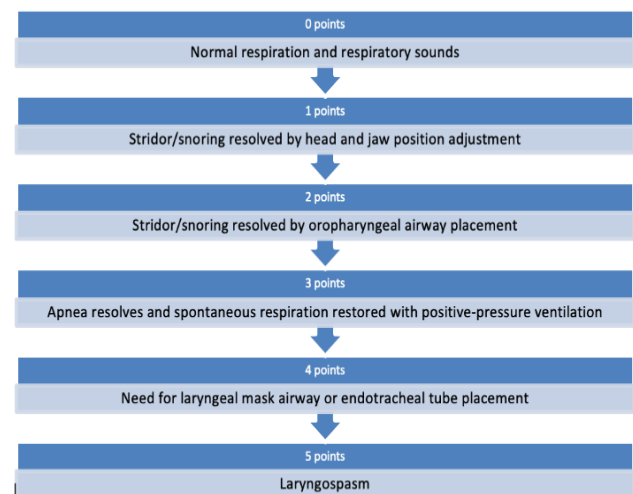


Figure 1. Post-Induction Airway Safety

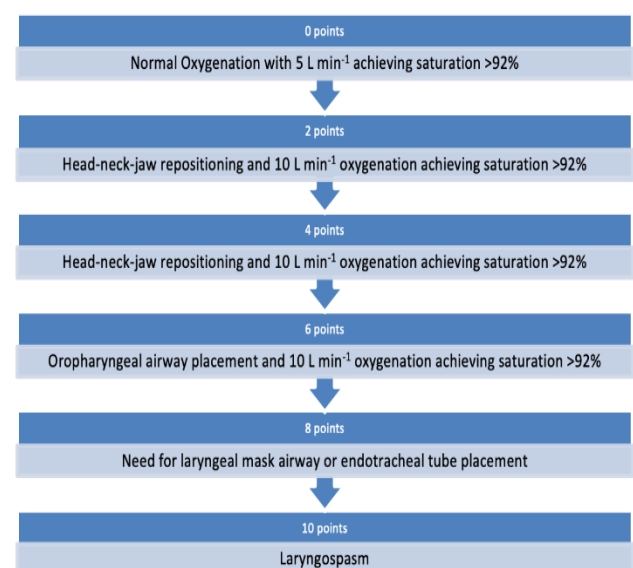


Figure 2. Airway safety during the MRI procedure

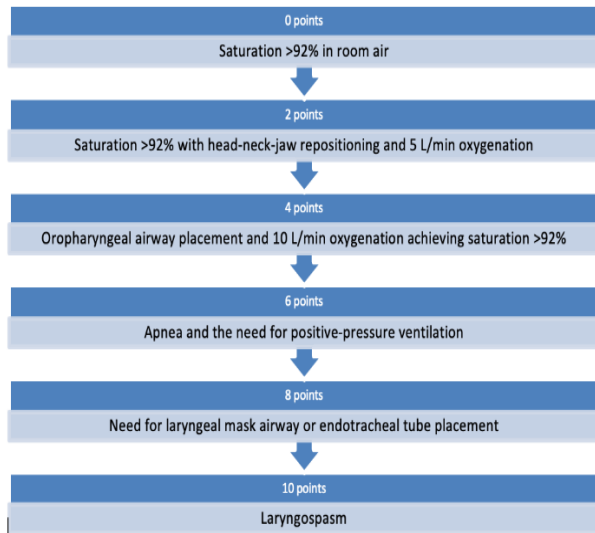


Figure 3. Airway Safety in the Recovery Room

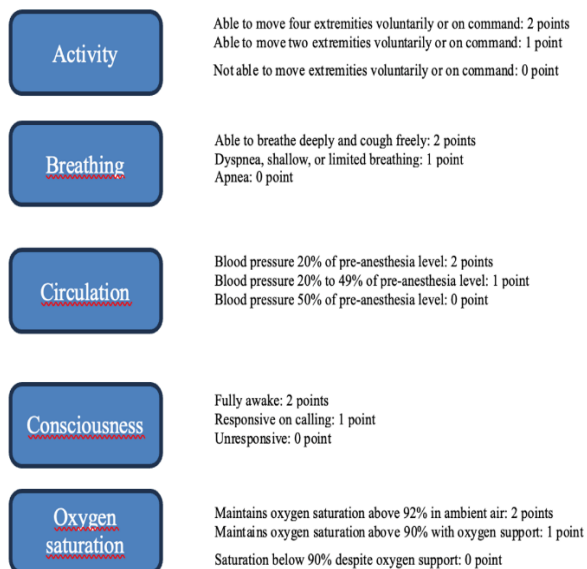


Figure 4. Modified Aldrete Score System

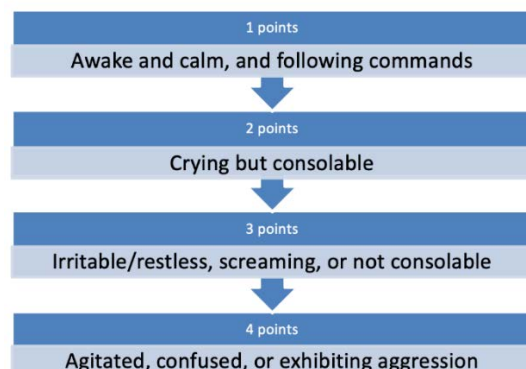


Figure 5. Weldon Agitation Score After Anesthesia

Statistical Analysis

The required sample size was calculated using G-Power 3.1 software (Heinrich-Heine-Universität Düsseldorf, Germany) based on the primary outcome—incidence of desaturation ($\text{SpO}_2 < 92\%$)—across three sedation groups using one-way ANOVA. An effect size (f) of 0.47, $\alpha = 0.05$, and power of 80% were used, yielding a minimum sample size of 75. To allow for subgroup analyses and improve statistical power, this was increased to 126 with ethics approval. Normality of distribution was assessed using the Shapiro–Wilk test due to the small sample sizes in each group ($n < 50$). To further support normality, we also evaluated mean-median closeness, skewness, kurtosis, and used histograms and Q–Q plots.

For categorical variables with expected cell frequencies < 5 , Fisher’s Exact Test was applied; otherwise, Pearson’s Chi-square test was used. Continuous variables were compared using ANOVA (normal distribution) or Kruskal–Wallis test (non-normal). Tukey’s HSD test was used as a post-hoc method. Statistical significance was set at $p < 0.05$. SPSS version 22 was used for all analyses.

Results

This study included 126 patients who were randomly assigned to three groups: Group S (sevoflurane, $n = 43$), Group T (thiopental, $n = 41$), and Group P (propofol, $n = 42$). Of the participants, 58.7% were male, and 41.3% were female. The mean age was 37.3 ± 2 months, and the average weight was 14.0 ± 8 kg. There were no significant differences among the groups in terms of age, gender, or ASA scores. MRI requests were predominantly for neurological indications and cranial imaging (Table 1).

Significant differences were noted in the desaturation status among the groups. Group P exhibited significantly higher desaturation rates than the other groups ($p = 0.029$). Group P also had lower oxygen saturation levels, both initially and after completing the MRI, with statistically significant differences compared to Groups S and T ($p = 0.001$, $p = 0.004$, $p = 0.002$) (Table 2). Agitation scores, as measured post-anesthesia, were significantly higher in Group S compared to Group P ($p = 0.037$).

No significant differences in heart rate, respiratory rate, or blood pressure changes were found between the groups during the imaging procedure ($p = 0.677$, $p = 0.38$, respectively). However, hypotension was significantly more common in Group T compared to Group S ($p = 0.018$, $p = 0.041$) (Table 2).

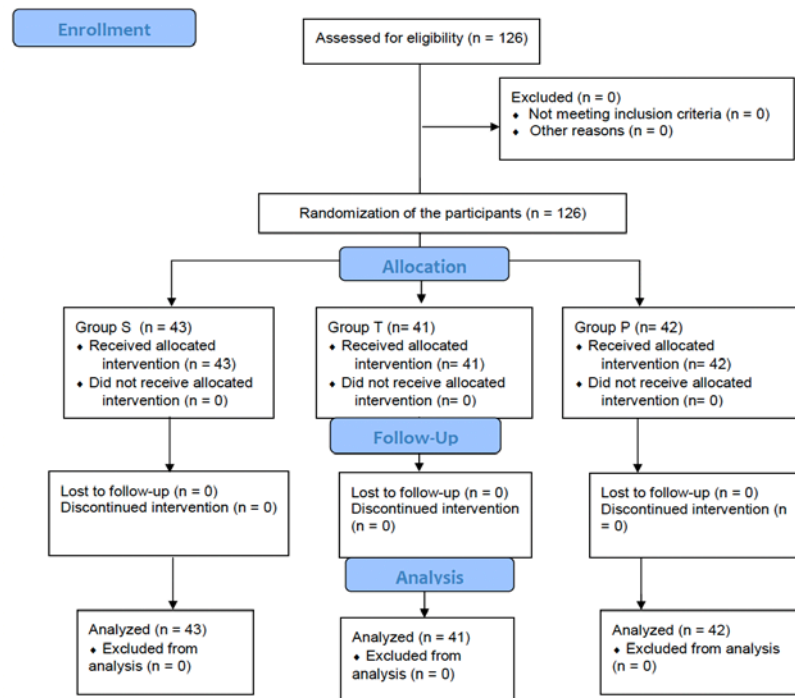


Figure 6. Consort diagram showing patient recruitment

Table 1. Distribution of age, age category, and ASA scores across the groups

		Sevoflurane		Thiopental		Propofol		p
Age (month), (n, %)		31.29 ± 20.63		43.85 ± 29.32		36.93 ± 32.18		0.152 ^x
Age category, (n, %)	≤12 months	10	23.3	5	12.2	9	21.4	0.387 ^y
	>12 months	33	76.7	36	87.8	33	78.6	
ASA scores, (n, %)	ASA 1	26	60.5	22	53.7	23	54.8	0.950 ^y
	ASA 2	15	34.9	16	39.0	17	40.5	
	ASA 3	2	4.7	3	7.3	2	4.8	

^x Kruskal–Wallis analysis, ^y Chi-square/Fisher's Exact Test analysis. **p* < 0.05 indicates significant difference. ASA: American Society of Anesthesiologists.

Table 2. Changes in vital signs and agitation scores across groups

		Sevoflurane		Thiopental		Propofol		p
Desaturation; (n, %)	Yes	2	4.7 ^{a,b}	1	2.4 ^a	8	19.0 ^b	0.029 ^{x*}
	No	41	95.3	40	97.6	34	81.0	
Baseline saturation, (Mean±SD)		97.02 ± 2.02 ^a		97.61 ± 1.76 ^a		95.60 ± 2.80 ^b		0.001 ^{y*}
Final saturation, (Mean±SD)		96.35 ± 2.25 ^{a,b}		97.34 ± 2.31 ^a		95.40 ± 3.34 ^b		0.004 ^{y*}
Average mean saturation, (Mean±SD)		96.69 ± 1.99 ^{a,b}		97.48 ± 1.77 ^a		95.50 ± 2.84 ^b		0.002 ^{y*}
Change in pulse rate, (Mean±SD)		0.30 ± 17.99		-4.34 ± 18.10		0.45 ± 16.33		0.677 ^x
Change in respiratory rate, (Mean±SD)		-0.30 ± 4.27		-1.46 ± 4.01		-0.55 ± 3.40		0.638 ^y
Change in systolic BP (mmHg), (Mean±SD)		-2.33 ± 16.38 ^a		-9.27 ± 10.87 ^b		-7.00 ± 12.01 ^{a,b}		0.018 ^{y*}
Change in diastolic BP (mmHg), (Mean±SD)		-3.33 ± 11.13 ^a		-9.56 ± 9.66 ^b		-4.69 ± 9.87 ^{a,b}		0.041 ^{y*}
Agitation score, (Mean±SD)		1.45 ± 0.63 ^a		1.28 ± 0.51 ^{a,b}		1.18 ± 0.45 ^b		0.037 ^{y*}

^x Chi-square /Fisher's Exact Test analysis, ^y Kruskal–Wallis analysis. **p* < 0.05, ^a statistically significant difference. ^{a,b} The group responsible for the difference. BP: Blood Pressure, SD: Standard Deviation.

When evaluating airway safety scores post-induction, no significant difference was found among the groups ($p = 0.935$). However, during MRI, Group P showed significantly more frequent respiratory depression compared to Groups S and T ($p = 0.008$). Airway safety scores in the recovery room revealed no statistically significant differences among the groups ($p = 0.368$). Overall, Group P had more respiratory depression incidents than Group T, showing a significant difference between these two groups ($p = 0.042$) (Table 3). Induction times were significantly shorter in Group T ($p < 0.001$), and Group S demonstrated shorter wake-up and recovery times compared to the other groups ($p = 0.002$, $p = 0.001$, respectively). There were no significant differences between the groups in terms of the total duration of the procedure ($p = 0.067$) (Table 3).

The overall success rate of the sedation procedures was

96.04%, with Group S achieving the highest success rate (97.7%). Group T and Group P had similar success rates (95.1% and 95.2%, respectively), with no significant differences between the groups ($p = 0.742$). Group P required significantly more additional doses during the procedure compared to Groups S and T ($p < 0.001$). Group S did not require any additional doses during induction, while 12.2% of patients in Group T and 45.2% of patients in Group P required extra dosing (Table 3).

In terms of adverse events, there were no significant differences in the overall number of events among the three groups ($p = 0.376$). Group P had the highest number of respiratory-related adverse events (26 out of 32), and Group T had more movement-related adverse events (8 out of 25) compared to the other groups (Table 3).

Table 3. Comparison of sedation process and its success among groups

		Sevoflurane		Thiopental		Propofol		p
Airway safety, (Mean±SD)	Post-induction	0.30±0.60		0.24±0.49		0.33±0.65		0.935 ^x
	During MRI	0.19 ±.73 ^a		0.15±.53 ^a		0.76±1.46 ^b		0.008 ^{y*}
	In the recovery room	0.00±0.00		0.00±0.00		0.05±0.31		0.368 ^x
	Total	0.49 ±1.16 ^{a,b}		0.39 ±0.74 ^a		1.14 ±2.14 ^b		0.042 ^y
Duration of MRI procedure (s), (Mean±SD)	Duration of MRI	778.26±314.78		1,019.63±543.04		930.95±531.64		0.067 ^x
	Induction time	324.00±57.53 ^a		221.71±77.88 ^b		301.83±128.70 ^a		<0.001 ^{x*}
	Emergence time	99.47±99.35 ^a		222.78±203.96 ^b		195.12±149.77 ^b		0.002 [*]
	Recovery time	226.74±101.27 ^a		396.10±287.06 ^b		367.33±217.83 ^b		0.001 [*]
Sedation success (n; %)	Successful	42	97.7	39	95.1	40	95.2	0.742 ^z
	Unsuccessful	1	2.3	2	4.9	2	4.8	
Need for additional doses (n; %)	Yes	0	0.0 ^a	5	12.2 ^a	19	45.2 ^b	<0.001 [*]
	No	43	100.0	36	87.8	23	54.8	
Movement during the MRI procedure	Yes	3	7.0	4	9.8	2	4.8	0.635 ^z
	No	40	93.0	37	90.2	40	95.2	
Number of movements (Mean±SD)		1.00±0.00		1.75±0.96		1.50±0.71		0.456 ^y
Number of sequences (Mean±SD)		1.33±0.58		3.00±1.63		2.00±-		0.330 ^y
Adverse events/Number of patients (Mean±SD)		0.44±0.80		0.61±0.98		0.76±1.32		0.376 ^y

^xKruskal–Wallis analysis, ^yOne-Way ANOVA, ^zChi-square or Fisher's Exact Test analysis. * $p < 0.05$ indicates significant difference. ^{a,b}Group responsible for the difference. MRI; magnetic resonance imaging, SD; Standard Deviation.

Discussion

This study compared the safety, efficacy, time management, and side effects of sevoflurane, thiopental, and propofol for MRI sedation in pediatric patients. Sevoflurane stands out with a high success rate, low incidence of side effects, shorter wake-up times, minimal respiratory complications, and hemodynamic stability. Therefore, it may be preferred in centers with the appropriate equipment for neonates and

patients with compromised general condition. Thiopental is advantageous due to its low rate of respiratory complications, airway safety, and fast induction time. However, attention is needed for patients with compromised general condition due to the risks of hypotension and bradycardia. Propofol is beneficial for its anxiolytic effect, low incidence of agitation, and ability to ensure patient immobility, but has a

higher risk of respiratory complications.

Kol et al. reported 22.7% movement in the propofol group, while no movement was observed in the sevoflurane group (12). Malviya et al. found a 15% incidence of movement due to inadequate sedation in a study with 922 patients (13). Dalal et al. reported a 1.4% movement rate in the propofol group, 12.2% in the pentobarbital group, and 22.5% in the chloral hydrate group among infants aged 0–12 months (14). Machata et al. detected 2.2% movement in a propofol-based MRI sedation study and administered additional doses accordingly (15). The movement rates in our study were similar to those reported in the literature, with no significant differences between the three anesthetic agents. Propofol rapidly distributes into brain tissue due to its high lipophilicity and undergoes hepatic metabolism. This pharmacokinetic property can lead to an increased need for additional doses during prolonged MRI procedures, as observed in our study, where 45.2% of patients in the propofol group required supplemental doses (16).

In this study, propofol resulted in the lowest average saturation (95.5%), while thiopental provided the highest (97.4%). Machata et al. found an average saturation of 98% using low dose propofol for MRI sedation in 500 patients (15). Atalay et al. reported an average saturation of 98.8% with thiopental in 300 MRI patients (17). Bloomfield et al. found an average saturation of 96.7% with propofol, noting that initial saturations tend to be lower, followed by an increase (18). Briggs reported an average saturation of 97.9% with sevoflurane in 640 newborns and infants undergoing MRI (19). Our findings align with the literature, except for the lower average saturation with propofol, which may be due to the higher propofol dose used in our study.

This study did not find any significant difference in prolonged desaturation rates between propofol and other anesthetic agents. Machata et al. administered propofol sedation to 500 patients and reported that only 0.4% required mask ventilation (15). Dalal et al. encountered respiratory events requiring mask ventilation and LMA placement in 2.9% of patients sedated with propofol for MRI (14). Atalay et al. sedated 300 patients with thiopental for MRI and did not report any cases requiring advanced airway management (17). Briggs found severe respiratory depression in 0.3% of newborns and infants sedated with sevoflurane for MRI (19). In this study, no patient required mask ventilation, LMA placement, or intubation. However, prolonged desaturation can be considered a significant airway event. All serious airway events in our study were associated with propofol. We believe that using propofol without the supervision of anesthesiologists is a risk factor for MRI procedures requiring sedation.

In this study, induction time refers to the duration from the start of induction to the beginning of the imaging procedure. Thiopental had the fastest induction time (around 3.6 min) in our study. Üstün et al. found an induction time of 2.3 min in the ketamine-propofol group and 0.9 min in the thiopental group (20). Thiopental is known for its rapid onset, being highly soluble in blood and quickly crossing the blood-brain

barrier (21). Our results are consistent with the literature, where numerous studies show that thiopental induces anesthesia rapidly. However, in contrast to our findings, another study comparing only propofol and thiopental reported significantly shorter induction and recovery times in the propofol group (22). This difference may be related to variations in dosing, sedation protocols, or study design.

Based on the findings of this study, it can be concluded that sevoflurane resulted in a shorter discharge time compared to the other two agents, considering wake-up and recovery periods. In previous studies, the sum of awakening and recovery times is referred to as total recovery or discharge time. In this study, the total recovery time with sevoflurane was approximately 5.3 minutes, which is notably shorter than previously reported values in the literature. For instance, earlier studies reported average recovery durations of around 11.5 to 15 minutes following sevoflurane sedation in pediatric MRI patients (23,24). This difference may be explained by the shorter imaging durations and the use of a lower maintenance dose of sevoflurane in our protocol compared to those studies.

Post-anesthesia delirium and agitation are important concerns. Trapani et al. reported that low dose propofol (1.2 mg kg⁻¹) has anxiolytic effects (25). Michel and Constantin found that sevoflurane can cause agitation and delirium (26). In Machata et al.'s study, 500 pediatric patients underwent propofol-based sedation for MRI, with no cases of agitation reported (15). In our study, none of the patients experienced post-sedation delirium or agitation requiring medication. When comparing agitation scores across drug groups for all imaging procedures, sevoflurane had the highest incidence of agitation, while propofol had the lowest. This difference was significant. Although the effect of age on agitation scores was not analyzed separately, the age distribution was similar among the groups; therefore, we believe the potential influence of age on agitation outcomes is minimal.

In large-scale studies on pediatric MRI sedation, the incidence of bradycardia was reported to be low across different agents. For instance, with sevoflurane, bradycardia was observed in only 0.3% of cases (23), and no cases were reported in a 300-patient cohort receiving thiopental (17). In contrast, rectal administration of thiopental was associated with a 6.6% bradycardia rate, whereas none occurred with rectal midazolam (27). In our study, none of the patients experienced bradycardia, bradypnea, hypertension, or hypotension requiring intervention. The routine use of low-dose atropine may have prevented bradycardia. Additionally, atropine's anticholinergic effects may have reduced airway secretions, enhancing sedation safety.

Mongodi et al. reported a 6.2% overall complication rate with sevoflurane sedation, including airway obstruction, laryngospasm, central respiratory depression, bronchospasm, coughing fits, hypersalivation, inadequate sedation, hiccups, severe agitation, seizures, bradycardia, and prolonged sedation (23). In our study, propofol had the highest number of adverse events, with respiratory-related problems being the

most common across all three groups. These events reduced patient satisfaction and increased the complexity of sedation.

One of the limitations of our study was the necessity to use a drip set for propofol infusion due to the absence of an MRI-compatible infusion pump. It was challenging to accurately adjust the infusion rate using drip sets, especially considering the typically small veins in children.

Conclusion

In conclusion, sevoflurane, thiopental, and propofol are widely used anesthetic agents for pediatric MRI sedation, each with distinct advantages. Sevoflurane demonstrates a high success rate, fewer adverse events, and faster recovery times, making it ideal for situations where efficient patient turnover is critical. Thiopental provides excellent airway security with the lowest rate of respiratory complications, particularly beneficial in vulnerable patient populations. Propofol, while effective in reducing post-anesthetic agitation, poses a higher risk of respiratory-related issues. This study provides clinicians with practical insights into selecting the most appropriate anesthetic agent, emphasizing the need for tailored sedation strategies based on individual patient profiles and clinical settings.

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Ethical Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University (Decision No: 2021/30-02, Date: 14.09.2021).

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Design : A.Ş.K., Ö.F.B.

Data acquisition: A.Ş.K., Ö.F.B., F.Ç.

Analysis and interpretation: Ö.F.B., F.Ç.

Writing manuscript: A.Ş.K., Ö.F.B., F.Ç.

Critical revision of manuscript: A.Ş.K., Ö.F.B., F.Ç.

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Interarm Blood Pressure Difference as a Predictor of Contrast-Induced Acute Kidney Injury in Patients Undergoing Peripheral Vascular Interventions

Periferik Vasküler Girişim Uygulanan Hastalarda Kontrast Nefropatisinin Bir Prediktörü Olarak Kollar Arası Kan Basıncı Farkı

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Abstract

Background: Contrast-induced acute kidney injury (CI-AKI) can be a serious complication for patients with peripheral artery disease (PAD) undergoing peripheral vascular interventions (PVI). An interarm blood pressure difference (IABPD) ≥ 10 mmHg has been identified as an independent risk factor for cardiovascular disease and mortality. This study aimed to evaluate the predictive value of IABPD for the risk of CI-AKI in PAD patients undergoing PVI.

Materials and Methods: This prospective study included 171 consecutive patients who underwent PVI. IABPD was defined as the difference in systolic blood pressure between the two arms and was considered significant if it was ≥ 10 mmHg. Patients were categorized into two groups based on the occurrence of CI-AKI.

Results: The incidence of CI-AKI after PVI was 21 %. The CI-AKI(+) group had a significantly higher incidence of IABPD > 10 mmHg (28% vs. 8%, $p < 0.001$). Multivariable logistic regression analysis identified IABPD (OR: 1.135, 95% CI: 1.037-1.243, $p = 0.006$) as an independent predictor of CI-AKI. Additionally, hypertension (OR: 2.308, 95% CI: 1.091-4.885, $p = 0.03$), higher mean blood pressure (OR: 1.055, 95% CI: 1.001-1.111, $p = 0.04$), lower eGFR (OR: 0.963, 95% CI: 0.948-0.978, $p < 0.001$), higher CRP levels (OR: 1.028, 95% CI: 1.006-1.050, $p = 0.01$), and lower LVEF (OR: 0.969, 95% CI: 0.938-0.998, $p = 0.04$) were significant predictors of CI-AKI. Furthermore, having TASC C-D lesions compared to TASC A-B was associated with a higher risk of CI-AKI (OR: 3.304, 95% CI: 1.197-9.117, $p = 0.02$).

Conclusions: This study demonstrated that IABPD is significantly associated with the development of CI-AKI in patients undergoing PVI for PAD. Assessing IABPD in patients before PVI could help clinicians identify those at an elevated risk for developing CI-AKI.

Keywords: Contrast-induced acute kidney injury, Interarm blood pressure difference, Peripheral artery disease, Peripheral vascular intervention

Öz

Amaç: Kontrast nefropatisi (KN), periferik arter hastalığı (PAH) nedeniyle periferik vasküler girişim (PVI) uygulanan hastalarda ciddi bir komplikasyon olabilir. İki kol arasındaki kan basıncı farkı (IABPD) ≥ 10 mmHg, kardiyovasküler hastalık ve mortalite için bağımsız bir risk faktörü olarak tanımlanmıştır. Bu çalışma, PAH nedeniyle PVI uygulanan hastalarda CI-AKI riskini öngörmeye IABPD'nin prediktif değerini değerlendirmeyi amaçladı.

Materyal ve Metod: Bu prospektif çalışmaya, PVI uygulanan 171 ardışık hasta dahil edildi. IABPD, iki kol arasındaki sistolik kan basıncı farkı olarak tanımlandı ve ≥ 10 mmHg olduğu durumlarda anlamlı kabul edildi. Hastalar, KN gelişimine göre iki gruba ayrıldı.

Bulgular: PVI sonrası CI-AKI insidansı %21 olarak bulundu. KN (+) grubunda, IABPD ≥ 10 mmHg oranı anlamlı derecede daha yüksekti (%28 vs. %8, $p < 0.001$). Multivaryant lojistik regresyon analizi, IABPD'yi (OR: 1.135, %95 CI: 1.037-1.243, $p = 0.006$) KN için bağımsız bir prediktör olarak tanımladı. Ayrıca, hipertansiyon (OR: 2.308, %95 CI: 1.091-4.885, $p = 0.03$), daha yüksek ortalama kan basıncı (OR: 1.055, %95 CI: 1.001-1.111, $p = 0.04$), daha düşük eGFR (OR: 0.963, %95 CI: 0.948-0.978, $p < 0.001$), daha yüksek CRP seviyeleri (OR: 1.028, %95 CI: 1.006-1.050, $p = 0.01$) ve daha düşük LVEF (OR: 0.969, %95 CI: 0.938-0.998, $p = 0.04$) de KN için anlamlı prediktörler olarak bulundu. Ek olarak, TASC C-D lezyonlarına sahip olmak, TASC A-B'ye kıyasla daha yüksek KN riski ile ilişkilendirildi (OR: 3.304, %95 CI: 1.197-9.117, $p = 0.02$).

Sonuç: Bu çalışma, IABPD'nin, PAH nedeniyle PVI uygulanan hastalarda KN gelişimi ile anlamlı bir şekilde ilişkili olduğunu göstermiştir. PVI öncesinde IABPD değerlendirilmesi, KN gelişim riski yüksek olan hastaların belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: Kontrast nefropatisi, İki kol arasındaki kan basıncı farkı, Periferik arter hastalığı, Periferik vasküler girişim

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Introduction

Contrast-induced acute kidney injury (CI-AKI) is one of the more well-known threats following cardiac, vascular, and radiologic procedures that demand the application of contrast agents(1-3). Although CI-AKI is typically transient and resolves within two weeks in most cases, it has been linked to increased risks of adverse events, mortality, and higher hospital costs(4,5). Consequently, CI-AKI is often utilized as a quality outcome measurement following these interventions. During peripheral vascular interventions (PVI) for peripheral arterial disease(PAD), iodinated contrast media (ICM) is commonly employed to visualize vascular anatomy, assess lesions, and guide endovascular treatments. However, ICM is believed to CI-AKI in approximately 10% of PVI cases, a condition with ties to significant mortality and morbidity(6). Early detection of CI-AKI in patients undergoing PVI is vital for halting its progression and ensuring a preferred outcome.

Interarm blood pressure differences (IABPDs) of less than 10 mmHg are generally considered normal. Typically, an IABPD of 10 mmHg or greater is classified as elevated(7). A meta-analysis of four cross-sectional studies among low-risk populations found a pooled prevalence of 19.6% for IABPDs of 10 mmHg or more(8). Several studies have established that IABPDs are correlated with cardiovascular mortality and morbidity(9,10). Additionally, many studies have demonstrated that increased IABPDs linked to a higher risk of aortic dissection and aneurysms, subclinical atherosclerosis, left ventricular hypertrophy, and asymptomatic intracranial and extracranial arterial stenosis(11-14). Previous research also indicates that the risk of PAD in patients possessing higher IABPD is increased(15). However, despite its quick and easy application at the bedside, this clinical tool is not commonly utilized in modern medical fields. The goal of this research was to analyze the predictive value of IABDP regarding the threat of CI-AKI in PAD patients undergoing PVI.

Materials and Methods

Study population

A total of 208 consecutive patients with suspected PAD who were referred for PVI between October 2024 and January 2025 were initially screened. Sixty-five of the potential participants were excluded from the study due to: active infection (n=11), malignancy (n=6), vasculitis (n=5), severe kidney disease ($GFR < 15 \text{ mL/min/1.73m}^2$) (n=13), aortic coarctation (n=1), or thoracic aortic dissection (n=1). Ultimately, data from 171 patients were analyzed in this study, which was conducted based upon the doctrines and ethics set out by the Declaration of Helsinki. It also received approval from the institutional review board. Each of the participants provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Laboratory data and definitions

Patient medical records provided laboratory data having to do with hemoglobin, troponin, creatinine, serum glucose, total cholesterol (Total-C), LDL-C, HDL-C, triglycerides, high-sensitivity C-reactive protein (hsCRP), albumin, and counts of white blood cells, neutrophils, and lymphocytes. To measure serum hsCRP levels, the nephelometric method was implemented using an IMMAGE 800 analyzer (Beckman Coulter, CA, USA). Kidney function was gauged through estimating the glomerular filtration rate (eGFR) determined through application of the Modification of Diet in Kidney Disease (MDRD) equation. This method involves the following formula: $eGFR (\text{mL/min/1.73 m}^2) = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$. Hypertension (HT) was classified as originating from diastolic blood pressure $\geq 90 \text{ mmHg}$, systolic blood pressure $\geq 140 \text{ mmHg}$, or a history with anti-hypertensive medication. Diabetes mellitus (DM) was identified as fasting serum glucose $\geq 126 \text{ mg/dL}$, glycated hemoglobin $\geq 6.5\%$, or a history of hypoglycemic medication use. Hyperlipidemia was classified by Total-C $> 200 \text{ mg/dL}$ and/or LDL-C $> 140 \text{ mg/dL}$. Qualifications for being categorized as a cigarette smokers were a history of smoking at least ten cigarettes per day for a year or more without making any attempt to break the habit. Patients did not receive any preventive treatment such as pre- or intra-procedural intravenous hydration for CI-AKI. Following angiography, all patients received continuous intravenous isotonic saline hydration (0.9% NaCl) at a standard rate (typically 1–1.5 mL/kg/h) for at least 12 hours, as part of the routine post-procedural care. All patients were given a non-ionic iso-osmolar contrast agent.

Measurement of Blood Pressure and Interarm Blood Pressure Difference

IABPD was calculated through the implementation of various blood pressure devices that had been authorized by the European Society of Hypertension (Omron HEM-7001-E; Omron Corp., Tokyo, Japan). The research made use of a standard cuff (12–13 cm x 35 cm) in accordance with the parameters of the European Society of Hypertension, with two additional cuffs available for arms that were either thicker or thinner. Patients were able to rest for five minutes before blood pressure (BP) was taken, and their arms remained parallel to their heart during this time. BP was measured simultaneously in both arms three different times at five-minute intervals, with the average BP for both left and right being calculated from these measurements. The discrepancy in systolic BP between the two arms IABPD was considered significant if it was calculated to be $\geq 10 \text{ mmHg}$. This cutoff value aligns with the guidelines laid out by The National Institute for Health and Clinical Excellence, with most previous research choosing to abide by them. Consequently, it provided the basis for participant classification (9,10). mean blood pressure (MBP) was estimated

from Systolic Blood Pressure (SBP) and diastolic blood pressure (DBP) as $DBP + (SBP-DBP)/3$

Diagnosis of Contrast-induced acute kidney injury

Patients were monitored for 72 hours following the angiographic procedure. Serum creatinine levels were measured at baseline and then once daily for three consecutive days to detect the development of CI-AKI. The diagnosis of CI-AKI was established based on criteria requiring either a minimum 25% rise in creatinine or an absolute increase of 0.5 mg/dL within 72 hours following the administration of CM. The patients were split into two separate groupings: those without confirmed CI-AKI (CI-AKI-) and those with confirmed CI-AKI (CI-AKI+).

Peripheral angiographic evaluation

Two interventional cardiologists analyzed the peripheral angiography images, categorizing occlusions of 70% or greater as indicative of severe peripheral vascular disease. The aortoiliac, femoropopliteal, and infrapopliteal arteries were assessed and stratified based on the severity of the conditions identified, following the classification system outlined in the Trans-Atlantic Inter-Society Consensus II (TASC-II) document. Lesion characteristics were determined from the angiographic findings. Treatment for these lesions included procedures such as balloon angioplasty and stent placement. Failing to navigate the guidewire through the occluded lesion during the percutaneous intervention or to achieve distal perfusion after the PVI resulted in a designation of procedural failure.

Statistical analysis

The way by which CI-AKI developed became the basis for categorizing the features of the study population. To test normality, the Kolmogorov-Smirnov test was employed. Continuous research data were conveyed as mean and standard deviation values or median and interquartile range (IQR) according to their normality. Categorical data, on the other hand, were represented by values that were either absolute and percentage-based. Mann-Whitney U test and Independent samples t-test were utilized to compare independent continuous data groups, while Fisher's exact test and Pearson's chi-squared were applied to compare categorical data groups. Univariate and multivariable logistic regression analyses were helpful in determining the independent predictors of the development of CI-AKI. Sensitivity analyses were conducted to ensure the robustness of the findings. Key predictors of CI-AKI identified in the multivariable logistic regression model were re-evaluated by excluding outliers or extreme values in variables such as eGFR and CRP. Odds ratio (OR) was used for Model's coefficients, and 95% was the chosen confidence interval (CI). For each of these analyses, 2-tailed probability (p) values less than .05 were indicative of statistical significance. A

post hoc power analysis was conducted based on the proportion of patients with IABPD >10 mmHg in the CI-AKI (+) and (-) groups (28% vs. 8%). Using these values and a total sample size of 171, the calculated power was 99.99% ($\alpha=0.05$), indicating sufficient statistical power to detect a significant difference. Jamovi and R 4.01 software (Vienna, Austria) was the vehicle by which all statistical analyses were conducted with "Hmisc", "ggplot", "rms" packages.

Results

The study included 171 patients who underwent PVI for PAD. The incidence of CI-AKI was 21% (n=36) (Figure 1). Patients were categorized into two groups: CI-AKI (+) (n=36) and CI-AKI (-) (n=135). Basic demographic and clinical information of these patients can be reviewed in Table 1. Those belonging to the CI-AKI (+) grouping were, on average, older than those that belonged to the CI-AKI (-) grouping (67.2 ± 7.2 years vs. 59.7 ± 10.2 years, $p<0.001$). HT and chronic heart failure were more prevalent in the CI-AKI (+) group (69% vs. 40%, $p<0.001$ and 28% vs. 5%, $p<0.001$, respectively). LVEF was significantly lower in the CI-AKI (+) group compared to the CI-AKI (-) group (55% [35–65] vs. 65% [60–65], $p<0.001$).

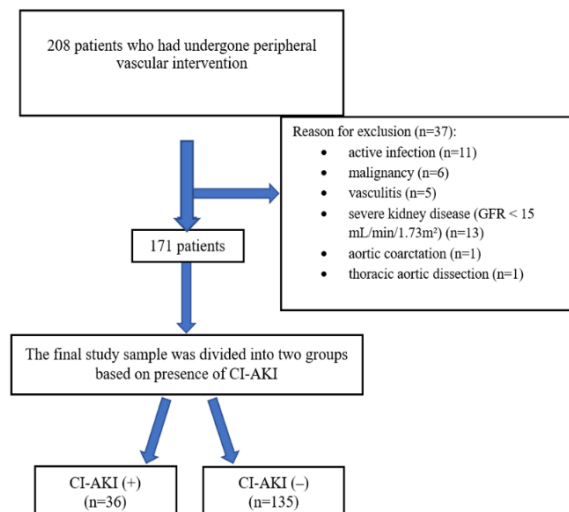


Figure 1. Consort flow diagram for inclusion in the study

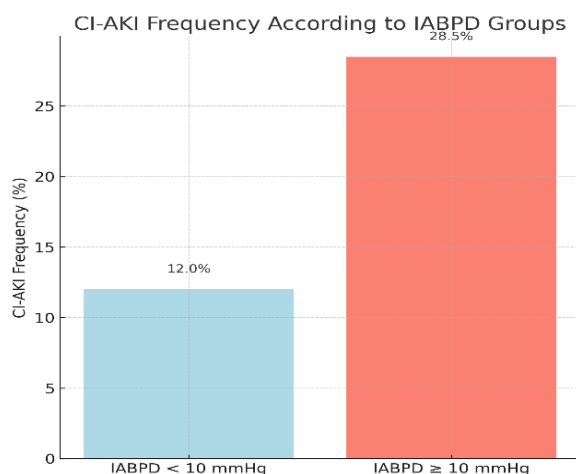
The CI-AKI (+) group had a higher prevalence of severe PAD, as indicated by the higher proportion of TASC C-D lesions (89% vs. 63%, $p<0.001$). The incidence of IABPD >10 mmHg was also significantly higher in the CI-AKI (+) group (28% vs. 8%, $p<0.001$) (Figures 2, 3). MBP was significantly higher in the CI-AKI (+) group for both the right and left brachial arteries (right brachial: 99.33 [94.66–101.66] mmHg vs. 97.35 [92.78–99.97] mmHg, $p=0.009$; left brachial: 96.90 [93.25–99.31] mmHg vs. 95.46 [91.20–97.44] mmHg, $p=0.004$). Patients in the CI-AKI (+) group had a significantly longer hospital stay compared to the CI-AKI (-) group (8 [7–10] days vs. 3 [2–6] days, $p<0.001$).

Table 1. Demographic and clinical characteristics of study patients based on development CI-AKI

Variables	CI-AKI (+) n= 36 (%21)	CI-AKI (-) n= 135 (%79)	p
Age (years)	67.2±7.2	59.7±10.2	<0.001
Gender (male), n (%)	33 (92)	115 (85)	0.083
BMI, kg/m ²	25.6±3.6	25.9±3.2	0.584
BSA, m ²	1.85±0.1	1.84±0.1	0.690
HT, n (%)	25 (69)	54 (40)	<0.001
DM, n (%)	20(55)	60 (44)	0.122
CAD, n (%)	21 (58)	72 (53)	0.357
CHF, n (%)	10 (28)	7 (5)	<0.001
Cerebrovascular Disease, n (%)	1 (2)	3 (2)	0.848
Smoking, n (%)	25 (69)	82 (60.7)	0.057
EF (%)	55(35-65)	65(60-65)	<0.001
Location of disease, n (%)			
Aortailiac	9 (25)	40 (30)	0.204
Femoro-popliteal	21 (58)	82 (61)	
infra-popliteal	5 (14)	22 (8)	
Balloon size	5 (5-6)	5 (5-6)	0.165
TASC C-D vs A-B	32 (89)	86 (63)	<0.001
IABPD>10 mmHg	10 (28)	12 (8)	<0.001
Stent usage, n (%)	17 (47)	54 (40)	0.261
RRT, n (%)	3 (8)	0 (0)	<0.001
In-hospital mortality, n (%)	2 (6)	0 (0)	<0.001
Amputation, n (%)	5 (14)	4 (3)	<0.001
Right brachial SBP (mmHg)	134(130-138)	132.2(127.4-137.2)	0.056
Left brachial SBP (mmHg)	126 (122-132)	128.8(124.2-132.6)	0.052
Right brachial DBP (mmHg)	81 (76-85)	79.2(74.2-83.3)	0.054
Left brachial DBP (mmHg)	79.2 (74.2-82.1)	80.8(75.7-83.8)	0.058
Right brachial MBP (mmHg)	99.33 (94.66-101.66)	97.35 (92.78-99.97)	0.009
Left brachial MBP (mmHg)	96.90 (93.25-99.31)	95.46 (91.20-97.44)	0.004
Length of hospital stay	8 (7-10)	3(2-6)	<0.001

BMI: Body Mass Index; BSA: Body Surface Area; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; CI-AKI: Contrast-induced acute kidney injury; CRP: C-reactive protein; DM: Diabetes Mellitus; EF: Ejection Fraction; Hb: Hemoglobin; HT: Hypertension; IABPD: Interarm Blood Pressure Difference; LDL: Low-Density Lipoprotein; MBP: mean blood pressure RRT: Renal Replacement Therapy; SBP: Systolic Blood Pressure; TASC: Transatlantic Intercommunal Consensus Document

Rates of renal replacement therapy (RRT), in-hospital mortality, and amputation were also significantly higher in the CI-AKI (+) group (8% vs. 0%, $p<0.001$; 6% vs. 0%, $p<0.001$; and 14% vs. 3%, $p<0.001$, respectively).

**Figure 2.** Bar Chart showing the rate of CI-AKI development patients according to the presence of IABPD

Laboratory findings indicated that those within the CI-AKI (+) grouping had significantly lower hemoglobin levels (12.3 [11.4-14.2] vs. 14.2 [12.3-15], $p<0.001$), lower eGFR (61.3 ± 27 vs. 94.1 ± 24.8, $p<0.001$), higher creatinine levels (1.28 [1-1.56] vs. 0.82 [0.7-0.97], $p<0.001$), and higher CRP levels (11.1 [4.16-34.6] vs. 3.8 [3.1-11.4], $p<0.001$) than the CI-AKI (-) grouping (Table 2).

Multivariable logistic regression analysis identified IABPD >10 mmHg (OR 1.135, 95% CI 1.037-1.243, $p=0.006$) as an independent predictor of CI-AKI. Additionally, hypertension (OR 2.308, 95% CI 1.091-4.885, $p=0.029$), higher MBP (OR 1.055, 95% CI 1.001-1.111, $p=0.045$), lower eGFR (OR 0.963, 95% CI 0.948-0.978, $p<0.001$), higher CRP levels (OR 1.028, 95% CI 1.006-1.050, $p=0.014$), and lower LVEF (OR 0.969, 95% CI 0.938-0.998, $p=0.043$) were significant predictors of CI-AKI. Furthermore, having TASC C-D lesions compared to TASC A-B was associated with a higher risk of CI-AKI (OR 3.304, 95% CI 1.197-9.117, $p=0.021$) (Table 3) ROC curve analysis showed that an IABPD cutoff of >5 mmHg predicted CI-AKI with an AUC of 0.678 (95% CI: 0.613–0.743; $p<0.001$), 83.6% sensitivity, and 55.0% specificity (Figure 4).

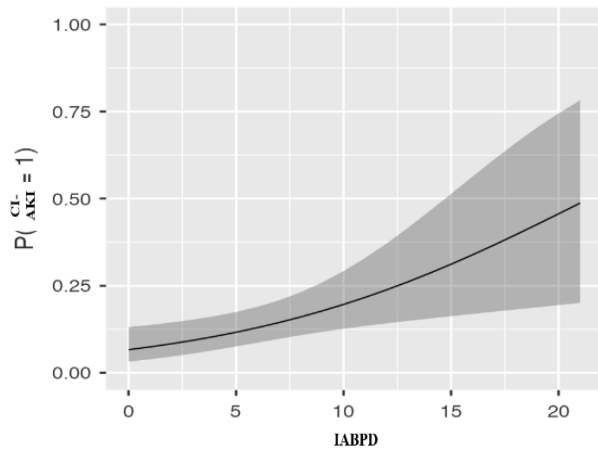


Figure 3. Marginal means plot showing the relationship between the probability of CI-AKI and IABPD

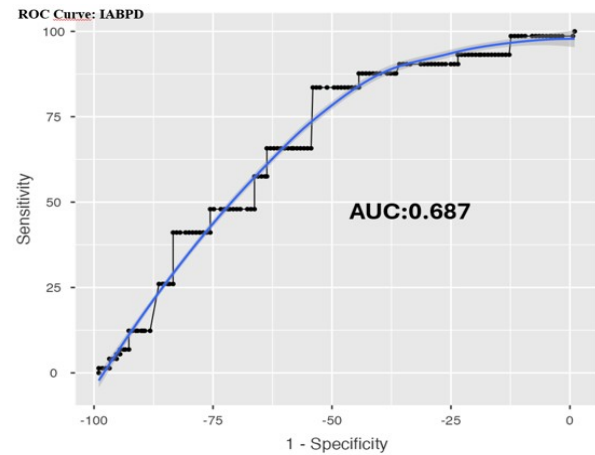


Figure 4. ROC curve analysis showed that an IABPD predicted CI-AKI with an AUC of 0.678 , 83.6% sensitivity, and 55.0% specificity.

Table 2. Laboratory finding comparisons between the groups based on development of CI-AKI.

Variables	CI-AKI (+) n= 36 (%21)	CI-AKI (-) n= 135 (%79)	p
WBC (10 ³ /μL)	9.2 (7.3-10.7)	8.7 (7.5-10.4)	0.310
Hemoglobin (g/dL)	12.3 (11.4-14.2)	14.2 (12.3-15)	<0.001
AST (IU/L)	20 (17-28.1)	19 (17.5-23.5)	0.427
ALT (IU/L)	17.5 (12.2-27)	16.6 (12-22.6)	0.243
Total Cholesterol (mg/dL)	189.2±43.2	201.5±48.7	0.094
Triglyceride (mg/dL)	142 (114-210)	129 (96-195)	0.274
HDL-C (mg/dL)	40.7±7.8	43±9.5	0.117
LDL-C (mg/dL)	118.3±36.5	126.3±38.9	0.177
eGFR (ml/min/1.73 m ²)	61.3±27.4	94.1±24.8	<0.001
Creatinine (mg/dL)	1.28 (1-1.56)	0.82 (0.7-0.97)	<0.001
Na (mEq/L)	138 (136-140)	138 (135-140)	0.458
K (mmol/L)	4.33±0.6	4.30±0.39	0.503
CRP (mg/L)	11.1 (4.16-34.6)	3.8 (3.1-11.4)	<0.001
Albumin (g/dL)	3.7 (3.3-3.9)	3.9 (3.7-4.3)	<0.001
Glucose (mg/dL)	128 (100-159)	106 (89-166)	0.027

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CI-AKI: Contrast-induced acute kidney injury CRP: C reactive protein; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; K: Potassium; LDL-C: low-density lipoprotein; Na: Sodium; WBC: white blood cell

Table 3. Multivariable analysis for prediction of CI-AKI.

Variables	Multivariable analysis			
	p	OR	95% Confidence Interval (CI)	
			Lower	Upper
Age	0.068	1.044	0.997	1.094
Sex (male)	0.057	4.294	0.956	19.293
Hypertension	0.029	2.308	1.091	4.885
IABPD>10 mmHg	0.006	1.135	1.037	1.243
MBP (mmHg)	0.045	1.055	1.001	1.111
eGFR (ml/min/1.73 m ²)	<0.001	0.963	0.948	0.978
Albumin (g/dL)	0.150	0.554	0.248	1.237
CRP (mg/L)	0.014	1.028	1.006	1.050
Hemoglobin (g/dL)	0.754	1.042	0.804	1.352
EF (%)	0.043	0.969	0.938	0.998
TASC CD vs AB	0.021	3.304	1.197	9.117

CRP: C-reactive protein; CI-AKI: Contrast-induced acute kidney injury EF: ejection fraction; IABPD: Interarm Blood Pressure Difference; MBP: mean blood pressure OR: odds ratio; TASC: Transatlantic Intercommunal Consensus Document

Discussion

This study investigated the relationship between IABPD and CI-AKI in patients undergoing PVI. Our findings demonstrated that IABPD ≥ 10 mmHg was significantly associated with CI-AKI and remained an independent predictor after adjusting for other known risk factors. Additionally, our study demonstrated LVEF, pre-intervention TASC score, preprocedural eGFR, presence of CKD, HT, MBP and CRP levels can also independently predict CI-AKI following PVI.

CI-AKI is a serious complication of PVIs, with complex and multifactorial pathophysiology. Contributing factors include contrast dose, cholesterol embolization, bleeding-related anemia, and infection (16–18). CI-AKI primarily results from tubular epithelial and endothelial injury, oxidative stress, and impaired renal microcirculation (19). Contrast agents may exacerbate these effects by increasing reactive oxygen species and reducing nitric oxide availability, leading to vasoconstriction (20). Numerous risk factors, such as chronic kidney disease, heart failure, older age, and the use of nephrotoxic agents, have been associated with increased CI-AKI risk (21). Our findings are consistent with this literature: lower baseline eGFR and reduced LVEF were both independently associated with CI-AKI in our cohort (3, 22). Inflammation also affects the pathogenesis of CI-AKI. Accumulating evidence is revealing that oxidative stress and a heightened inflammatory response are significant contributors to the growth and advancement of CI-AKI (23).

Inflammatory cells infiltrating tissue that has been damaged exacerbates renal injury. Multiple inflammatory cytokines, including tumor necrosis factor- α and interleukins-1 and -6 lead to impairment of tubular and endothelial cells, renal medullary hypoxia, and eventually impair renal function (24). Furthermore, inflammatory mediators' secretion induces vasoconstriction of intrarenal vessels, resulting in decreased pressure from glomerular filtration (25). The study also noted that CRP levels, indicating the level of inflammation in patients, were connected to the development of CI-AKI after PVI. Previous studies have also emphasized the role of baseline hydration status in the development of CI-AKI. Notably, inferior vena cava (IVC) diameter has been proposed as a reliable echocardiographic parameter to estimate volume status. Gungoren et al. demonstrated that reduced IVC diameter was associated with an increased risk of CI-AKI in patients undergoing cardiac catheterization (26). Although IVC assessment was not part of our protocol, this parameter could be considered in future studies for more comprehensive risk stratification.

We found that patients with TASC C-D lesions had a significantly higher risk of developing CI-AKI. This may be attributed to the increased complexity of interventions in these patients, which often require longer procedures and higher volumes of contrast media. Moreover, the presence of more advanced and diffuse atherosclerotic disease may exacerbate endothelial dysfunction and inflammation, contributing to renal injury. Previous studies have also shown that TASC C-D lesions are associated with poorer outcomes

and greater procedural difficulty (27,28).

MBP, reflecting systemic hemodynamic load, emerged as another independent predictor of CI-AKI in our study. Previous research has shown that MBP plays a key role in maintaining renal perfusion and preventing AKI, particularly in settings involving hemodynamic instability or increased venous congestion (29). Although MBP and IABPD are distinct parameters, both may reflect underlying vascular stiffness, asymmetric atherosclerosis, or impaired autoregulation factors that contribute to renal hypoperfusion and injury. Therefore, combining MBP with IABPD in pre-procedural assessment may offer a more nuanced and practical approach to identifying patients at high risk for CI-AKI in the clinical setting (30). IABPD is a non-invasive parameter that is easy to measure, though its clinical significance is not yet fully understood. The European Society of Hypertension has long recommended the assessment of IABPD as part of the physical examination for patients with arterial hypertension, suggesting that high IABPD findings ought to initiate a more thorough evaluation in search of vascular abnormalities (31). However, the American College of Cardiology and the American Heart Association do not currently address interarm blood pressure differences in their guidelines (32). If IABPD exceeds the physiological differences due to anatomical variations between the arms, it is counted as an indicator of atherosclerosis. It is also worth noting that a significant association exists between IABPD and the ankle-brachial index (11). Previous research has also indicated that patients with elevated IABPD have an increased risk of developing PAD (15). An IABPD > 10 mmHg is widely recognized as clinically significant. In our study, 44 patients (12.8%) had an IABPD exceeding 10 mmHg, a percentage notably higher than those of other studies (33). This difference may be due to our specific patient population, which was comprised of individuals undergoing PVI for PAD. IABPD serves not only as an indicator of atherosclerotic diseases, but it also affects prognosis. A cohort study conducted by Clark and colleagues noted that individuals possessing an IABPD of 10 mmHg or greater, or 15 mmHg or greater, were at a greater risk of all-cause mortality over a ten-year period (34). In line with these findings, a meta-analysis composed of nine separate cohort studies showed that the collective hazard ratio for cardiovascular and total mortality saw a jump to 2.98 in individuals with a higher IABPD (31). Durmus et al. examined the relationship between the SYNTAX score and IABPD in their retrospective study, which revealed that those with a high IABPD (≥ 10 mmHg) had significantly higher SYNTAX scores than those with a low IABPD (< 10 mmHg) (35). Additionally Park et al. demonstrated that among patients treated with PCI, the incidence of major adverse cardiovascular events was significantly higher in those with an IABPD of 10 mmHg or greater compared to those with an IABPD of less than 10 mmHg (36). Furthermore, in their recently-published work on 2120 patients with ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention, Simsek et al demonstrated

that an IABPD ≥ 10 mmHg serves to independently predict the development of CI-AKI in this patient population (37). Our results support this notion that a strong correlation exists between IABPD and the development of CI-AKI following PVI. Thus, IABPD may serve as a clinically important, simple, quick, and easy-to-measure tool for predicting the risk of CI-AKI in PAD patients undergoing PVI. The underlying pathophysiological process detected by IABPD could be related to increased inflammation, similar to that which was observed in atherosclerosis.

Limitations

There were a few noteworthy limitations in this research. Firstly, as a prospective, single-center, and observational study, there remains a risk of selection bias due to the specialized nature of our center and the patient population it serves. The small sample size no doubt negatively affects the generalizability of the findings. In addition, several studies have shown that the white coat effect could influence higher systolic IABPD. The use of antihypertensive therapy in some patients may have also influenced IABPD levels. Furthermore, our patient population consisted of individuals with peripheral arterial disease, which may explain the higher incidence of IABPD compared to other studies. The delay in detecting serum creatinine changes beyond the 72-hour post-contrast administration window could have led to an underestimation of CI-AKI incidence, particularly in cases where renal function deteriorated after discharge. The volume of CM used during angiography is critical in the genesis of CI-AKI. However, our study lacks data on the amount of CM administered to patients. An additional of our study is the imbalance in baseline renal function between the two groups, with the CI-AKI (+) group having significantly higher baseline serum creatinine levels. Although we excluded patients with severe renal impairment ($\text{eGFR} < 15 \text{ mL/min/1.73 m}^2$), higher baseline creatinine levels could still contribute to an increased risk of CI-AKI. We addressed this potential confounder by including eGFR in our multivariable logistic regression analysis and conducting sensitivity analyses. Nevertheless, this factor should be considered when interpreting our results. Moreover, our study did not evaluate baseline hydration status using echocardiographic parameters such as inferior vena cava diameter, which has been shown to predict the development of CI-AKI in prior studies. Lastly, more studies will help elucidate the pathophysiological roles of IABPD.

Conclusion

This study demonstrates that IABPD is significantly linked to the development of CI-AKI in PAD patients undergoing PVI. Predicting the threat of acquiring CI-AKI enables the optimization of procedures by shortening their duration, reducing the volume of CM administered, and implementing preventive measures to avoid CI-AKI. These findings underscore the need for further prospective research to validate the use of IABPD in clinical practice and to explore the underlying mechanisms linking IABPD to adverse renal outcomes.

Ethical Approval: This study adhered to the principles of the Declaration of Helsinki and received ethical approval from the Kartal Kaşuyolu Training and Research Hospital (Approval no: 2024/19/927).

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Analysis and interpretation: M.Ç., C.Y., M.M.T.

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Association of Sleep Duration with Chronic Diseases and Geriatric Syndromes

Uyku Süresinin Kronik Hastalıklar ve Geriatrik Sendromlar ile İlişkisi

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Abstract

Background: It was aimed to investigate the relationship between sleep duration and chronic diseases and geriatric syndromes in geriatric patients.**Materials and Methods:** Our cross-sectional study included 174 patients admitted to the geriatric outpatient clinic for the first time between January 2024 and June 2024. Patients under 65 years of age, with active infection, terminal illness, diagnosis of malignancy, and history of trauma and infection in the last month were excluded from the study. In our study, in accordance with the recommendations of the 'National Sleep Foundation' and the 'American Academy of Sleep Medicine (AASM)', we considered sleep duration over 8 hours/day as long sleep in geriatric patients.**Results:** In our study, 107 geriatric patients with no long sleep duration (≤ 8 hours) and 67 geriatric patients with long sleep duration (> 8 hours) were included. There was no significant difference between the two groups in terms of age and gender ($p=0.174$, $p=0.739$). There was no significant difference between the two groups in terms of chronic diseases, number of chronic diseases and number of medications. Sarcopenia (%49 vs %33, $p=0.046$) and malnutrition (%35 vs %21, $p=0.041$) were found to be significantly higher in patients with longer sleep duration. There was no statistically significant difference between the two groups in terms of frailty, depression, cognitive status, basic and instrumental activities of daily living ($p=0.208$, $p=0.062$, $p=0.097$, $p=0.110$, $p=0.117$).**Conclusions:** Sarcopenia and malnutrition were observed at a higher rate in patients with long sleep duration. Based on this, sarcopenia and malnutrition screening should be emphasised in geriatric patients with long sleep duration.**Keywords:** Geriatric Syndrome, Malnutrition, Sarcopenia, Sleep

Öz

Amaç: Geriatrik hastalarda uyku süresinin kronik hastalıklar ve geriatrik sendromlar ile ilişkisini araştırmak hedeflenmiştir.**Materyal ve Metod:** Çalışmamız kesitsel olarak Ocak 2024-Haziran 2024 tarihleri arasında geriatri polikliniğe ilk kez kabul edilen 174 hastayı içermektedir. 65 yaş altı, aktif enfeksiyonu, terminal dönem hastalığı, malignite tanısı, son bir ay içinde travma ve enfeksiyon öyküsü olan hastalar çalışma dışında bırakıldı. Çalışmamızda 'National Sleep Foundation' ve 'American Academy of Sleep Medicine (AASM)' önerileri doğrultusunda geriatrik hastalarda 8 saat/gün üzerindeki uyku sürelerini uzun uyku olarak aldık.**Bulgular:** Çalışmamıza uyku süresi uzun olmayan (≤ 8 saat) 107 ve uyku süresi uzun olan (> 8 saat) 67 geriatrik hasta alındı. İki grup arasında yaş ve cinsiyet açısından anlamlı farklılık yoktu ($p=0.174$, $p=0.739$). İki grup arasında kronik hastalıklar, kronik hastalık sayısı ve ilaç sayısı açısından anlamlı farklılık yoktu. Uyku süresi uzun olanlarda sarkopeni (%49'a karşı %33, $p=0.046$) ve malnütrisyon (%35'e karşı %21, $p=0.041$) istatistiksel olarak anlamlı daha yüksek saptandı. İki grup arasında kırılabilirlik, depresyon, bilişsel durum, temel ve enstrümental günlük yaşam aktiviteleri açısından istatistiksel anlamlı farklılık yoktu ($p=0.208$, $p=0.062$, $p=0.097$, $p=0.110$, $p=0.117$).**Sonuç:** Uyku süresi uzun olanlarda sarkopeni ve malnütrisyon daha yüksek oranda görülmüştür. Bundan yola çıkarak uyku süresi uzun olan geriatrik hastalarda sarkopeni ve malnütrisyon taramasına önem verilmelidir.**Anahtar Kelimeler:** Geriatrik sendrom, Malnütrisyon, Sarkopeni, Uyku

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Introduction

Sleep is one of the basic elements of life. The National Sleep Foundation (NSF) and the American Academy of Sleep Medicine (AASM) recommend the upper limit of sleep duration for young adults (18-25 years) and adults (26-64 years) as 9 hours (1,2). There are changes in sleep duration and quality with aging. In geriatric individuals (>65), the upper limit of sleep duration is accepted as 8 hours (1,2). Sleep duration in geriatric patients has a critical importance in terms of physical function, independence and quality of life. There are studies drawing attention to the fact that sleep duration may lead to sarcopenia, malnutrition, impaired cognitive functions and depression in geriatric patients (1-3).

Geriatric syndromes are considered to be clinical conditions with common risk factors in older adult patients (4). Although geriatric syndromes appear complex, they have common features. Geriatric syndromes such as sarcopenia, malnutrition, frailty, cognitive impairment and depression lead to increased mortality, morbidity and health care costs (5). Chen et al. found that sarcopenia was significantly increased in individuals who slept for more than 8 hours (6). There are studies supporting that long sleep duration may adversely affect sarcopenia, malnutrition, frailty, basic and instrumental activities of daily living among geriatric syndromes (7,8).

The aim of this study was to investigate the relationship between long sleep duration and geriatric syndromes such as sarcopenia, malnutrition, frailty, cognitive impairment, depression, basic and instrumental activities of daily living in geriatric patients. In addition, the relationship of sleep duration with chronic diseases and laboratory values was analysed.

Materials and Methods

Our cross-sectional study included 174 patients admitted to the geriatric outpatient clinic for the first time between January 2024 and June 2024. Ethical approval was obtained from the local ethics committee (Date 22.12.2023-Number 352).

Patients over 65 years of age were included in our study. Exclusion criteria included active infection, terminal illness, diagnosis of malignancy, trauma and infection in the last month. In addition, patients with implants that prevented the assessment of muscle mass for the diagnosis of sarcopenia from geriatric syndromes were excluded from the study. In our study, we considered sleep duration over 8 hours/day as long sleep in geriatric patients in accordance with the recommendations of the NSF and AASM (1,2). The 6-question Mini Nutritional Assessment Short- Form (MNA-SF) was used as a screening tool for malnutrition among geriatric syndromes. 12-14 points are considered normal nutritional status (9).

European Working Group on Sarcopenia in Older People 2 (EWGSOP2) diagnostic criteria were used in the evaluation of sarcopenia (10). The 5-question strength, assistance with walking, rising from a chair, climbing stairs, falls (SARC-F) test was used to screen for sarcopenia, and patients with low

muscle strength and low muscle mass were accepted for the diagnosis of sarcopenia (10). The 5-question fatigue, resistance, ambulation, illness, loss of weight fatigue, resistance, ambulation, illness, loss of weight (FRAIL) test was used to assess frailty status (11). A six-question activities of daily living questionnaire (washing, dressing, toileting, eating, bed and chair transfer, continence) and an 8-question instrumental activities of daily living test (telephone use, shopping, food preparation, housework, laundry, transport, medication use, financial management) were performed (12,13). The number of medications and chronic diseases of the patients were noted. C-reactive protein (CRP), erythrocyte sedimentation rate, haemoglobin, ferritin, haemoglobin A1c, thyroid-stimulating hormone (TSH), 25-OH vitamin-D, vitamin B12, folic acid, creatinine and notrophil/lymphocyte ratio at the date of geriatric syndrome evaluation were recorded.

Sample size was calculated using G* Power 3.1 software (14). The power analysis assumed a 5% significance level ($\alpha = 0.05$), 80% power ($1 - \beta = 0.80$) and a moderate effect size (Cohen's $h = 0.4$). GA sample size of 60 patients per group was calculated to provide 80% power to detect the expected difference between the two groups with no long and long sleep duration (14).

Categorical variables were expressed as numbers and percentages. Continuous variables were presented as mean $\pm$ standard deviation or median (range of quartiles). Chi-square test was applied for categorical variables. Fisher's exact test was applied in cases that did not fulfil the chi-square criteria. Student's t-test, a parametric test, was used for normally distributed continuous variables. Mann Whitney-U test was used for the comparison of non-normally distributed variables. SPSS-22 statistical programme was used for the analysis and $p < 0.05$ was considered statistically significant (15).

Results

In our study, 107 geriatric patients with no long sleep duration (≤ 8 hours) and 67 geriatric patients with long sleep duration (> 8 hours) were included. There was no significant difference between the two groups in terms of age and gender ($p = 0.174$, $p = 0.739$). Sleep duration was 6.52 ± 1.19 h/day in the no long sleep duration group and 9.10 ± 0.88 h/day in the long sleep duration group, and this difference was statistically significant ($p < 0.001$). There was no significant difference between the two groups in terms of number of chronic diseases and number of medications ($p = 0.256$, $p = 0.154$). There were no significant differences between the two groups in terms of hypertension, diabetes mellitus, coronary artery disease, osteoporosis, hypothyroidism, asthma, hyperlipidaemia, chronic obstructive pulmonary disease, atrial fibrillation, benign prostatic hyperplasia and incontinence ($p = 0.342$, $p = 0.443$, $p = 0.325$, $p = 0.575$, $p = 0.892$, $p = 1.000$, $p = 0.433$, $p = 0.475$, $p = 0.572$, $p = 0.538$, $p = 0.713$; respectively). Detailed analysis is given in Table 1.

Table 1. Comparison of demographic data and chronic diseases of patients with no long/long sleep duration

	Patients with no long sleep duration (≤ 8 hours)	Patients with long sleep duration (> 8 hours)	p
Number of patients	107	67	
Gender (Female /male)	76 / 31	46 / 21	0.739
Age*	69.42 $\pm$ 10.58	71.56 $\pm$ 9.12	0.174
Sleep Duration*	6.52 $\pm$ 1.19	9.10 $\pm$ 0.88	<0.001
Number of chronic diseases*	2 (1-3)	2 (1-3)	0.256
Number of Drugs *	2 (1-4)	2 (2-4)	0.154
Hypertension	56 (52%)	40 (59%)	0.342
Diabetes Mellitus	20 (19%)	15 (23%)	0.443
Coronary Artery Disease	8 (8%)	2 (3%)	0.325
Osteoporosis	13 (20%)	10 (25%)	0.575
Hypothyroidism	16 (15%)	10 (16%)	0.892
Asthma	5 (5%)	3 (5%)	1.000
Hyperlipidemia	22 (20%)	10 (15%)	0.433
Chronic Obstructive Pulmonary Disease	4 (4%)	4 (6%)	0.475
Atrial Fibrillation	12 (%11)	9 (%14)	0.572
Benign Prostatic Hyperplasia	9 (9%)	3 (5%)	0.538
Incontinence	4 (4%)	3 (5%)	0.713

*Data are shown as mean $\pm$ standard deviation (SD) or median(interquartile intervals), Statistically significant P values are indicated as bold

When we analysed the results of sleep duration and comprehensive geriatric assessment; basic and instrumental activities of daily living were lower in the group with longer sleep duration, but this difference was not statistically significant ($p=0.110$, $p=0.117$). Malnutrition rate was 35% in the group with long sleep duration and 21% in the no long sleep duration group. In the MNA-SF test for malnutrition assessment, the values of the group with longer sleep duration were lower and this difference was statistically significant ($p=0.046$). The FRAIL questionnaire for frailty and the geriatric depression scale for depression assessment

were both higher in patients with longer sleep duration, but this difference was not significant ($p=0.208$, $p=0.062$). Mini mental test was lower in patients with longer sleep duration, but this difference was not statistically significant ($p=0.094$). Sarcopenia rate was 49% in the group with long sleep duration and 33% in patients with no long sleep duration, and this difference was statistically significant ($p=0.041$). The SARC-F questionnaire, which is a sarcopenia screening test, was also statistically significantly higher in the group with long sleep duration ($p=0.020$). Detailed analysis is given in table 2.

Table 2. Comparison of comprehensive geriatric assessment results of patients with no long /long sleep duration

	Patients with no long sleep duration (≤ 8 hours)	Patients with long sleep duration (> 8 hours)	p
Number of patients	107	67	
Sarcopenia	36 (33%)	33 (49%)	0.041
Basic Activities of Daily Living *	5.81 $\pm$ 0.87	5.43 $\pm$ 1.54	0.110
Instrumental Activities of Daily Living *	7.70 $\pm$ 1.19	7.20 $\pm$ 1.98	0.117
MNA-SF score*	12.57 $\pm$ 1.81	12.00 $\pm$ 1.82	0.046
FRAIL score*	2 (1-2)	2 (1-3)	0.208
SARC-F score*	1 (0-3)	3 (1-4)	0.020
Mini Mental Test score*	27.34 $\pm$ 2.80	26.21 $\pm$ 3.88	0.094
Geriatric Depression Scale *	2 (0-5)	3 (2-5)	0.062

*Data are shown as mean $\pm$ standard deviation (SD) or median(interquartile intervals), Statistically significant P values are indicated as bold

When the group with long sleep duration and the no long sleep group were compared in terms of laboratory values, there was no statistically significant difference in haemoglobin A1c, ferritin, creatinine, haemoglobin, TSH, 25-Hydroxy Vitamin-D, Vitamin B12, folic acid, CRP and sedimentation rate ($p=0.484$, $p=0.295$, $p=0.095$, $p=0.585$, $p=0.184$,

$p=0.062$, $p=0.477$, $p=0.412$, $p=0.155$, $p=0.721$; respectively). Neutrophil/lymphocyte ratio was higher in patients with long sleep duration than in patients with no long sleep duration and this difference was statistically significant ($p=0.009$) (See Table 3).

Table 3. Laboratory values of patients with no long/long sleep duration

	Patients with no long sleep duration (≤ 8 hours)	Patients with long sleep duration (> 8 hours)	p
Hemoglobin A1c (%)*	6.0 $\pm$ 1.1	5.9 $\pm$ 0.6	0.484
Ferritin (ng/ml)*	56 (31-89)	46 (24-90)	0.295
Creatinine (mg/dL)*	0.8 $\pm$ 0.3	1.0 $\pm$ 0.5	0.095
Hemoglobin (g/dl)*	12.8 $\pm$ 1.3	12.5 $\pm$ 1.5	0.585
TSH (μ U/ml)*	2.1 (1.3-2.8)	1.8 (1.1-2.6)	0.184
25-Hydroxy Vitamin-D (μ g/L)*	25 (20-32)	23 (15-29)	0.062
Vitamin B12 (pg/ml)*	330 (243-469)	320 (229-435)	0.477
Folic acid (ng/mL)*	8.0 $\pm$ 4.3	7.5 $\pm$ 3.6	0.412
Neutrophil/lymphocyte ratio	2 (1.5-2.6)	2.4 (1.9-2.9)	0.009
CRP (mg/L)*	2.6 (1.0-5.5)	2.7 (1.2-8.9)	0.155
Sedimentation rate (mm/h)*	14 (7-25)	15 (6-30)	0.721

*Data are shown as mean $\pm$ standard deviation (SD) or median(interquartile intervals), Statistically significant P values are indicated as bold

Discussion

Sleep is the most important time period that determines our quality of life. In geriatric age group, the importance of sleep increases even more. Because, apart from chronic diseases, geriatric syndromes affect the quality of life and mortality in geriatric individuals. When we look at the results of this study, there is a statistically significant relationship with sarcopenia and malnutrition among geriatric syndromes. Sarcopenia and malnutrition are directly related to morbidity and mortality in geriatric individuals.

When we reviewed the studies on the relationship between sarcopenia and sleep duration in the literature; a correlation was found between long sleep duration and sarcopenia in the meta-analysis published by Li et al. in 2023 (16). Smith et al. have analysed sarcopenia and sleep duration in a study conducted in low- and middle-income countries and determined a significant relationship between long sleep duration and sarcopenia (17). In a study reported in Korea, sarcopenia was found to be independently associated with long sleep duration (18). Similarly, there is a significant relationship between sarcopenia and long sleep duration in our study.

In a study conducted in China investigating sleep duration and nutritional status in geriatric patients, the MNA-SF test was used to screen for malnutrition and it was shown that long sleep duration increased the risk of malnutrition (19). In addition, sarcopenia and malnutrition are two intertwined geriatric syndromes; based on this relationship, Malnutrition-Sarcopenia Syndrome is defined in the literature (20). In our study, a significant relationship was found between malnutrition and sleep duration. Malnutrition and sarcopenia were the two geriatric syndromes with a significant statistical relationship with sleep duration.

When we look at the articles showing the relationship between sleep duration and inflammation; in the review by Irwin et al. long sleep duration was associated with an increase in systemic inflammation markers, while short sleep duration was not found to be associated (21). In our study, there was no statistical significance with CRP, sedim, ferritin, but neutrophil/lymphocyte ratio was statistically significantly associated with long sleep duration.

This significance may be due to sleep-related diseases (such as obstructive sleep apnea syndrome). Therefore, it is very difficult to establish a causal relationship.

In our study, the geriatric depression scale score was higher in the long sleep duration group, but this difference was not statistically significant. The relationship between long sleep duration and depression is a controversial issue in the literature. In a study conducted in China in 1429 women over 60 years of age, the probability of depressive symptoms was found to be statistically significantly higher in women with long sleep duration (over 8 hours) (22). A web-based cross-sectional survey was applied to 8698 participants in Japan and it was found that long sleep was not associated with depression (23). These different results may be due to methodological differences, sample characteristics and depression assessment tests used. A prospective and controlled study may provide clearer information on this issue.

Limitation

The limitations of our study include the absence of a questionnaire and clinical evaluation related to sleep quality in addition to sleep duration.

Conclusion

Our study showed the relationship between long sleep duration and sarcopenia and malnutrition among geriatric syndromes in geriatric patients. Malnutrition and sarcopenia in geriatric patients are important because they are associated with morbidity and mortality. Therefore, sleep duration should be questioned in the examination of geriatric patients and screening for malnutrition and sarcopenia should not be forgotten if sleep duration is long.

Ethical Approval: Ethical approval was obtained from the ethics committee of Health Sciences University (Date 22.12.2023-Number 352- Health Sciences University).

Author Contributions:

Concept: A.A.S., S.D., V.S.

Literature Review: A.A.S., S.D.

Design : A.A.S., S.D., V.S.

Data acquisition: A.A.S., S.D., V.S.

Analysis and interpretation: A.A.S., S.D., V.S.

Writing manuscript: A.A.S.

Critical revision of manuscript: A.A.S., S.D., V.S.

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A New Score for the Identification of Circadian Blood Pressure Pattern in Hypertensive Patients

Hipertansif Hastalarda Sirkadiyen Kan Basıncı Paterninin Belirlenmesi için Yeni Bir Skor

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Abstract

Background: Non-dipper hypertension is characterised by a decrease of less than 10% in nocturnal blood pressure compared to daytime levels. It is known that non-dipper hypertension is associated with higher mortality than dipper hypertension. Therefore, in this study, we aimed to investigate the correlation between the easily calculable LANR score in the diagnosis of non-dipper HT.

Materials and Methods: A total of 524 patients diagnosed with HT who were admitted to the a cardiology clinic were included in this study. Demographic data, 24-hour ambulatory blood pressure monitoring, echocardiographic, and laboratory data were obtained from hospital archives. The formula LANR = lymphocytes × albumin / neutrophils was used to calculate the LANR index. Patients were categorized into two groups, namely LANR<23 and LANR>23.

Results: When baseline demographic characteristics and laboratory parameters were compared, no significant difference was found between the two groups except neutrophils, lymphocytes and C reactive protein. CAR and NLR were found to be high in the non-dipper HT group, while HALP and LANR were found to be low. In addition, in stepwise multivariate analyses performed to determine the predictors of the prognostic process in non-dipper HT patients, CAR (odds ratio: 1.420, 95% confidence interval: 1.106-1.823, P<0.001) and LANR (odds ratio: 0.583, 95% confidence interval: 0.493-0.690, P<0.001) were identified as independent predictors of HT in non-dipper HT.

Conclusions: This study showed lower LANR, HALP scores and higher CAR, NLR scores in non-dipper HT patients compared with dipper HT patients. Furthermore, LANR and CAR were identified as independent predictors of non-dipper HT. In addition, the rate of non-dipper hypertension was reported to be significantly higher in patients with LANR<23 than in individuals with LANR>23. In conclusion, a low LANR index can be used as an early warning model to identify patients with non-dipper HT.

Keywords: Lymphocytes, Albumin, Neutrophils, Dipper, Non-dipper, Hypertension

Öz

Amaç: Non-dipper hipertansiyon, gece kan basıncının gündüz seviyelerine kıyasla %10'dan daha az azalması ile karakterizedir. Non-dipper hipertansiyonun dipper hipertansiyona göre daha yüksek mortalite ile ilişkili olduğu bilinmektedir. Bu nedenle, çalışmamızda kolayca hesaplanabilen LANR skorunun non-dipper hipertansiyonun tanısındaki ilişkisinin araştırılması amaçlanmıştır.

Materyal ve Metod: Bu çalışmaya bir kardiyoloji kliniğine başvuran ve hipertansiyon tanısı almış toplam 524 hasta dahil edilmiştir. Hastaların demografik verileri, 24 saatlik ambulatuvar kan basıncı monitörizasyonu sonuçları, ekokardiyografi ve laboratuvar verileri hastane arşivlerinden elde edilmiştir. LANR indeksini hesaplamak için lenfosit × albümin / nötrofil formülü kullanılmıştır. Hastalar LANR<23 ve LANR>23 olacak şekilde iki gruba ayrılmıştır.

Bulgular: Başlangıçtaki demografik özellikler ve laboratuvar parametreleri karşılaştırıldığında, nötrofil, lenfosit ve C-reaktif protein düzeyleri dışında iki grup arasında anlamlı bir farklılık saptanmamıştır. Non-dipper hipertansiyon grubunda CAR ve NLR değerleri yüksek, HALP ve LANR değerleri ise düşük bulunmuştur. Ayrıca, non-dipper hipertansiyon hastalarında prognostik süreci öngören faktörleri belirlemek amacıyla yapılan aşamalı çok değişkenli analizlerde CAR (odds oranı: 1.420, %95 güven aralığı: 1.106–1.823, P<0.001) ve LANR (odds oranı: 0.583, %95 güven aralığı: 0.493–0.690, P<0.001) bağımsız öngörücüler olarak tanımlanmıştır.

Sonuç: Bu çalışma, non-dipper hipertansiyon hastalarında dipper hipertansiyon hastalarına kıyasla daha düşük LANR ve HALP skorları ile daha yüksek CAR ve NLR skorlarının bulunduğunu göstermiştir. Ayrıca, LANR ve CAR indeksleri non-dipper hipertansiyon için bağımsız öngörücüler olarak belirlenmiştir. Ek olarak, LANR<23 olan hastalarda non-dipper hipertansiyon oranının LANR>23 olan bireylere göre anlamlı derecede daha yüksek olduğu saptanmıştır. Sonuç olarak, düşük LANR indeksi, non-dipper hipertansiyon hastalarını erken dönemde tanımlamak için kullanılabilecek bir erken uyarı modeli olarak değerlendirilebilir.

Anahtar Kelimeler: Lenfositler, Albümin, Nötrofiller, Dipper, Non-dipper, Hipertansiyon

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Introduction

Hypertension (HT) is characterized by persistently elevated blood pressure measurements in the systemic arteries. It is a modifiable risk factor for mortality and morbidity from all causes and cardiovascular disease worldwide (1,2). The pathophysiology of HT is multifactorial in etiology, involving both behavioral and environmental factors, genes, endocrine pathways, and different organ types (kidney, cardiovascular, and neurological systems) (3). HT pathologies in these systems are the underlying cause of the disease. When HT is not effectively controlled, it may lead to HT induced end-organ damage and adverse cardiovascular diseases.

In a healthy population, arterial blood pressure demonstrates a diurnal pattern, reaching a maximum in the morning and undergoing a gradual decrease throughout the day until a minimum is reached at night. This phenomenon is a result of the influence of the circadian rhythm on human biology and pathology (3). A significant proportion of the functional units of human metabolism are under the control of the biological clock and demonstrate a circadian rhythm. The term "diurnally oscillating systems" is employed to denote the vascular and cardiovascular systems, as well as blood pressure.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is a significant diagnostic tool for assessing the daily rhythm of arterial blood pressure. Compared to other blood pressure measurement methods, ABPM provides superior prognostic value. A dipper hypertension pattern is defined as a decrease of more than 10% in nocturnal blood pressure compared to daytime levels. In contrast, a non-dipper HT pattern is characterized by a nocturnal blood pressure decline of less than 10% (4,5). Non-dipper HT has been associated with a higher incidence of cardiovascular morbidity and mortality (6). Although the exact pathophysiological mechanisms of non-dipper HT are not fully understood, current evidence suggests that increased inflammation and elevated platelet activity may contribute to its adverse outcomes, including end-organ damage and cardiovascular events (5,6).

Serum albumin concentration, an established biomarker for nutritional status, has been shown to have prognostic value in non-dipper HT patients, as reported in previous studies (5,6). The LANR index is a newly developed biomarker calculated using serum albumin level and neutrophil-to-lymphocyte ratio (NLR) (7). A number of prior investigations have demonstrated that the LANR index functions as an independent prognostic index in patients diagnosed with different malignancies and chronic obstructive pulmonary disease (7,8). The HALP score, an innovative biomarker calculated as hemoglobin (g/L) $\times$ albumin (g/L) $\times$ lymphocytes (10^9 /L) / platelets (10^9 /L), was developed by Chen et al. in 2015 to prognosticate patients with gastric cancer. The HALP score, which is comprised of hemoglobin, albumin, lymphocytes, and platelets, has recently been defined as a marker reflecting the state of nutrition and inflammation, especially in geriatric patients.

A substantial body of research has demonstrated its capacity to serve as a significant predictor of mortality, particularly among patients afflicted with cancers of the stomach, bladder, prostate, and kidney, as well as stroke. Anemia and hypoalbuminemia are indicators of malnutrition, lymphocytes are indicators of inflammation, and high platelets are indicators of the risk of thromboembolism and atherosclerotic lesions. These indicators have been shown to be associated with mortality. However, a review of the literature revealed no studies that have examined the prognostic value of LANR and HALP Score in non-dipper HT patients.

A review of the literature has previously demonstrated a significant correlation between inflammatory biomarkers and various indices, as well as patient prognosis, in patients with non-dipper HT. Concurrently, earlier studies have demonstrated the prognostic value of parameters such as the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP) to albumin ratio (CAR) in patients with non-dipper HT (9–11). The aim of the present study was to investigate the association between the LANR index and HALP score and non-dipper HT.

Although inflammatory biomarkers such as the NLR and CAR have previously been studied in the context of non-dipper hypertension, there is currently a lack of evidence regarding the prognostic utility of more comprehensive nutritional and inflammatory indices, such as the LANR index and HALP score, in this patient population. To the best of our knowledge, no prior studies have specifically evaluated the relationship between these novel biomarkers and non-dipper HT.

Therefore, the present study aims to fill this gap by investigating the association between the LANR index, HALP score, and the non-dipper blood pressure pattern. By exploring these newly developed indices, this study seeks to provide additional prognostic tools that may enhance the risk stratification and management of patients with non-dipper hypertension.

Materials and Methods

Study design and subject

The study was administered at a single medical center between 2024 and 2025. The participants of the study were selected through a retrospective observational study. The inclusion criteria for the study population were patients who had been diagnosed with HT by ABPM. Finally, the total population of the study comprised 524 patients diagnosed with HT. Patients with coronary artery disease, active malignancy, hyperthyroidism, mild or severe valvular disease, heart failure, chronic renal failure, left ventricular hypertrophy, chronic obstructive pulmonary disease, congenital heart disease, or active infection were excluded from the study. Patients for whom data could not be accessed and whose analyses failed to converge were excluded from the study. The local ethics committee approved the study protocol. The protocol was

prepared in accordance with the ethical guidelines for human experimentation of the Declaration of Helsinki (2013).

Data collection

The diagnosis of hypertension was made on the basis of office blood pressure measurements in accordance with the ESC 2024 guidelines, with systolic blood pressure (SBP) defined as ≥ 140 mmHg and diastolic blood pressure (DBP) as ≥ 90 mmHg (1). Patients whose nocturnal blood pressure physiologically decreased by more than 10% compared to daytime values were classified as having dipper hypertension, whereas patients whose nocturnal blood pressure decreased by less than 10% or never decreased were classified as having non-dipper hypertension. For the diagnosis of non-dipper hypertension, 24-hour ABPM devices were used and hypertension was defined by ABPM as 24-hour mean blood pressure $\geq 135/85$ mmHg during the day or $\geq 120/70$ mmHg at night (1). Daytime measurements were taken at 15-minute intervals between 6:00 am and 10:00 pm, while nighttime measurements were taken at 30-minute intervals between 10:00 pm and 6:00 am. Patients were instructed to continue their daily routine and to avoid excessive physical activity during ABPM follow-up. Nocturnal BP fall has been calculated using the following formula Nocturnal systolic or diastolic BP fall (%) = (mean waking SBP/DBP - mean sleeping SBP/DBP) $\times$ 100/mean waking systolic BP (12).

Laboratory parameters

Following the acquisition of patients' baseline characteristics, a range of blood tests were performed. These included assessments of haemoglobin, creatinine, sodium, potassium, urea, uric acid, fasting plasma glucose, aspartate and alanine aminotransferase, albumin, CRP and thyroid-stimulating hormone. Furthermore, the NLR (Neutrophil / lymphocyte [$10^9/L$]), CAR (CRP [mg/dl] and Alb [g/L]), HALP (Haemoglobin [g/L] $\times$ Albumin [g/L] $\times$ Lymphocyte count [$10^9/L$] / Platelet count [$10^9/L$]) and LANR (lymphocyte [$10^9/L$] $\times$ albumin [g/L] / neutrophil [$10^9/L$]) were calculated from the haemoglobin and biochemical parameters.

Statistical analysis

All statistical analyses were performed using SPSS 22.0. Descriptive statistics were generated for categorical variables, with the frequency (percentage) of each category being calculated. The Kolmogorov-Smirnov test was applied to determine the normality of data. The data, which was normally distributed, was presented as the mean $\pm$ standard deviation and compared using an independent sample t-test. Non-normally distributed continuous data was presented as median (25th-75th interquartile range) and compared with Mann-Whitney U test. Stepwise multivariable logistic regression analysis was performed using univariate and multivariate models. Possible risk factors and included into the full multivariate model, and independent predictors were determined according to the multivariate logistic regression analysis. The optimal cut-off value and area under curve (AUC) of

the NLR, CAR, HALP and LANR was determined with receiver.

Results

The study included a total of 524 hypertensive patients. According to the 24h holter recording, 245 (46.7%) patients had dipper HT while 279 (53.2%) patients had non-dipper hypertension. It was observed that the main characteristics were similar between the two groups. Only BMI was found to be higher in the non-dipper hypertension group (25.77 $\pm$ 3.63 vs. 27.24 $\pm$ 4.07, $P<0.001$). Furthermore, 24-hour SBP was found to be higher in the non-dipper hypertension group than in the dipper hypertension group (150.01 $\pm$ 9.65 vs. 152.44 $\pm$ 12.68, $P=0.015$) (Table 1).

Table 1. Comparison of baseline characteristics of the study groups

	Dipper (n= 245)	Non-dipper (n= 279)	P
Age, years	53.0 $\pm$ 12.5	52.9 $\pm$ 12.4	0.945
Gender, male (%)	94 (38.4)	121 (43.4)	0.245
Diabetes mellitus (%)	31 (12.7)	45 (16.1)	0.260
Smoking (%)	87 (35.5)	86 (30.8)	0.255
KAH (%)	18 (7.3)	15 (5.4)	0.354
CVO (%)	8 (3.3)	5 (1.8)	0.279
BMI, kg/m ²	25.77 $\pm$ 3.63	27.24 $\pm$ 4.07	<0.001
Heart rate, /dk	78.01 $\pm$ 12.69	78.89 $\pm$ 11.47	0.409
24-h SBP, mmHg	150.01 $\pm$ 9.65	152.44 $\pm$ 12.68	0.015
24-h DBP, mmHg	86.00 $\pm$ 10.62	87.62 $\pm$ 12.63	0.114

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CAD: Coronary artery disease; CVO: Serebrovasküler olay (Cerebrovascular event); LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index.

Laboratory variables of the study groups are presented in Table 2. There was no statistically significant difference between the laboratory parameters except CRP, neutrophils, lymphocytes, NLR, CAR, HALP and LANR (Table 2). CRP (1.60 [0.80-3.45] vs. 2.10 [1.20-4.40], $P=0.004$) and neutrophils (4.54 $\pm$ 1.94 vs. 5.30 $\pm$ 2.15, $P<0.001$) were higher in the non-dipper hypertension group, whereas lymphocytes (2.37 $\pm$ 0.74 vs. 2.21 $\pm$ 0.91, $P=0.032$) were higher in the dipper hypertension group (Table 2). In addition, NLR (1.79 [1.36-2.34] vs. 2.26 [1.73-3.40], $P<0.001$) and CAR (0.34 [0.18-0.79] vs. 0.51 [0.30-1.18], $P<0.001$) calculated by simple biochemical parameters were higher in the non-dipper hypertension group, whereas HALP (56.60 [40.50-72.30] vs. 41.10 [28.00-58.90], $P<0.001$) and LANR (25.68 [19.39-34.68] vs. 17.02 [11.35-24.72], $P<0.001$) were higher in the dipper hypertension group. All of these values are statistically significant (Table 2).

Table 2. Comparison laboratory parameters of the study groups

	Dipper (n= 245)	Non-dipper (n= 279)	P
Urea, mg/dl	29.17 ± 10.47	31.06 ± 11.67	0.053
Uric acid, mg/dl	5.18 ± 1.55	5.25 ± 1.45	0.604
Creatinine, mg/dl	0.86 ± 0.19	0.88 ± 0.41	0.411
Sodium, mEq/L	140.1 ± 2.71	140.2 ± 2.69	0.657
Potas- sium, mEq/L	4.39 ± 0.38	4.35 ± 0.39	0.221
AST, U/L	18.00 (13.25-22.00)	17.00 (13.00-21.00)	0.096
ALT, U/L	17.00 (13.00-23.00)	12.00 (17.00-25.00)	0.882
Albumin, g/dl	4.61 ± 0.39	3.98 ± 0.82	0.268
CRP, mg/dl	1.60 (0.80-3.45)	2.10 (1.20-4.40)	0.004
TSH, mU/L	1.91 ± 1.23	1.78 ± 1.53	0.286
WBC, x10 ³ /μL	7.75 ± 2.24	7.99 ± 2.26	0.226
Neutrophil, x10 ³ /μL	4.54 ± 1.94	5.30 ± 2.15	<0.001
Lymphocyte, x10 ³ /μL	2.37 ± 0.74	2.21 ± 0.91	0.032
Hemoglobin, g/dl	13.65 ± 1.71	13.78 ± 1.76	0.069
Platelets, x10 ³ /μL	262 (222-308)	274 (228-321)	0.158
TSH, mU/L	1.91 ± 1.23	1.78 ± 1.53	0.286
NLR	1.79 (1.36-2.34)	2.26 (1.72-3.40)	<0.001
CAR	0.34 (0.18-0.79)	0.51 (0.30-1.18)	<0.001
HALP	56.60 (40.50-72.30)	41.10 (28.00-58.90)	<0.001
LANR	25.68 (19.39-34.68)	17.02 (11.35-24.72)	<0.001

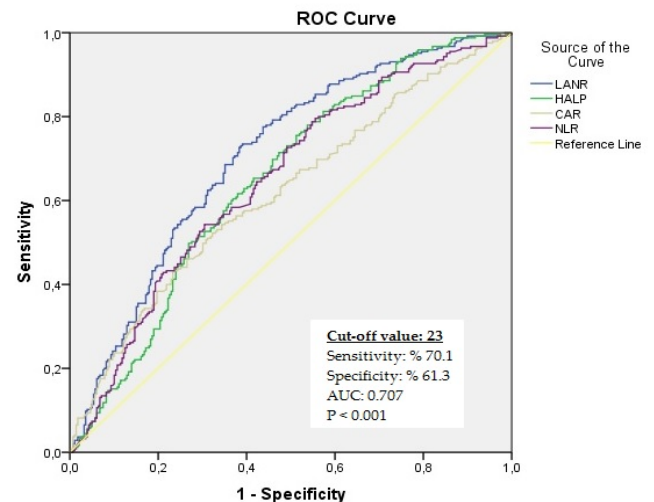
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; TSH: Thyroid stimulating hormone; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; CAR: C-reactive protein to albumin ratio; LANR: Lymphocyte × albumin / neutrophil ratio; HALP: Hemoglobin × albumin × lymphocyte / platelet score.

Table 3. Stepwise Multiple Linear Regression Analysis for Predictor of Non-dipper Hypertension

Variables	OR	95% confidence interval	P value
CAR	1.420	1.106-1.823	0.006
LANR	0.583	0.493-0.690	<0.001

CAR: C-reactive protein albumin ratio; LANR: Lymphocyte × albumin / neutrophil ratio

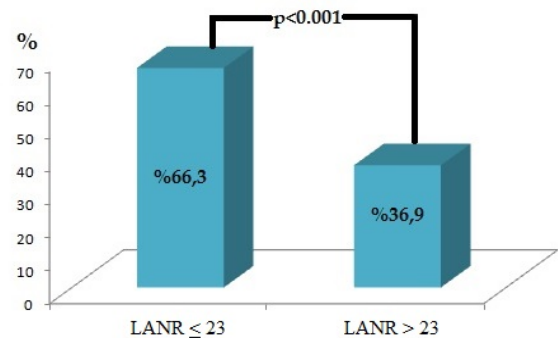
Stepwise multivariate analyses were used to determine the independent predictors of non-dipper status. Age, hemoglobin, smoking, NLR, CAR, HALP and LANR were included in stepwise multivariate regression analysis; only CAR (odds ratio: 1.420, 95% confidence interval: 1.106-1.823, $P < 0.001$) and LANR (odds ratio: 0.583, 95% confidence interval: 0.493-0.690, $P < 0.001$) were found to be independent predictors of non-dipper hypertension (Table 3). In addition, ROC analysis was performed to calculate the NLR, CAR, HALP and LANR cut off values and the best AUC to predict non-dipper hypertension. In the ROC analysis, LANR was found to be the best predictor of non-dipper hypertension. LANR ≤ 23 predicted the non-dipper status with a sensitivity of 71.9% and specificity of 61.3 (AUC:0.707, $P < 0.001$) (Figure 1).



NLR: Neutrophil to lymphocyte ratio, CAR: C-reactive protein albumin ratio

Figure 1. ROC curve analysis of NLR, CAR, HALP, LANR scores for predicting the development of Non-dipper hypertension.

When our study population was divided into two groups according to this cut-off value (those patients with LANR ≤ 23 and LANR > 23), it was detected that the frequency of non-dipper status was significantly higher in patients with LANR ≤ 23 than in patients with LANR > 23 ($P < 0.001$) (Figure 2).

**Figure 2.** Comparison of the frequency of Non-dipper Hypertension between LANR score ≤ 23 and > 23 groups.

Discussion

A comprehensive analysis of the study's outcomes revealed that patients with non-dipper hypertension exhibited significantly elevated levels of CRP, neutrophil, NLR, and CAR ratios, in contrast to those with dipper hypertension, who showed significantly lower levels of these indicators. Conversely, lymphocyte, HALP and LANR ratios were found to be significantly lower in non-dipper hypertensive patients when compared to dipper hypertensive patients. Using stepwise multivariable regression analysis, CAR and LANR were found to be independent predictors of non-dipper hypertension. In ROC analysis, a new immune-nutritional index LANR was found to be the best predictor of non-dipper hypertension with a sensitivity of 71.9% and specificity of 61.3% at a cut-off value of 23.

ABPM is a more valuable tool for demonstrating the diurnal rhythm of arterial blood pressure than conventional blood

pressure monitoring. The physiological dipper pattern is characterised by a mean decrease in nocturnal blood pressure of more than 10% relative to daytime blood pressure on a ABPM (4). A decrease of less than 10% in nocturnal blood pressure compared to daytime blood pressure is defined as non-dipper hypertension. This condition has been shown to be associated with a high incidence of cardiovascular mortality and morbidity (5,6). It is therefore important to reveal the pathophysiologic mechanisms that may be responsible for increased cardiovascular risk in order to prevent cardiovascular events, make early diagnoses and plan treatment. The primary pathophysiologic mechanism is thought to be platelet activation, atherosclerotic events and inflammatory responses. LANR, comprising lymphocytes, albumin and neutrophils, has been defined as a rapidly available, cost-effective laboratory hematology marker and an index of the immune system and inflammatory process. The present study shows that the LANR index is a powerful predictive parameter in patients with non-dipper hypertension. To the best of our knowledge, this is the first study to evaluate the prognostic significance of the LANR index in patients with non-dipper hypertension. However, given the rapidly evolving nature of scientific research, the possibility of prior unpublished or less widely recognized studies cannot be entirely excluded.

The term 'LANR' was first defined by Liang X. et al. (7), who demonstrated its value as a prognostic indicator in patients with resectable colorectal cancer. The study concluded that LANR may serve as a useful reference to help these patients decide on a treatment plan. Serum albumin levels have been shown to influence the circadian rhythm of blood pressure (13). Serum albumin levels are a vital indicator for assessing nutritional status and are negatively correlated with C-reactive protein levels. C-reactive protein has been identified as a significant inflammatory risk marker in the process of vascular atherosclerosis (3,13).

The HALP score was first introduced in 2015 by Chen et al (14) to prognostically predict gastric cancer patients. This score is a valuable tool in the field of oncology, providing researchers and clinicians with a novel method to assess the inflammatory status of patients. The study showed that the HALP score decreased significantly with poor immune response, suggesting that the HALP score may be an important marker for assessing the inflammatory status of patients. A number of studies have previously examined the HALP score in cardiovascular patient groups. These studies have shown that a low HALP score has prognostic significance in predicting in-hospital mortality in cases of ST-elevation myocardial infarction, mortality in acute heart failure patients and overall mortality in cardiovascular diseases (15-17).

Previous studies have found that patients with non-dipper HT exhibit high CAR values and that CAR is independently correlated with non-dipper hypertension (10,18). Concurrently, one study revealed that patients diagnosed with non-dipper hypertension showed significantly higher NLR levels

than cases of dipper hypertension (10). In addition, a separate relationship between HT and neutrophil levels was shown in one study (19). In our study, the fact that neutrophils and CRP were high in the non-dipper HT group and that NLR and CAR were high in the non-dipper HT group is an indicator of increased inflammation in the non-dipper HT group. Accordingly, the increased mortality in the non-dipper HT group can be attributed to this increased inflammation. All these parameters are in line with the literature (10,18,19). In addition, albumin shows antioxidant and anti-inflammatory properties (20,21). In our study, albumin was found to be lower in the non-dipper HT group, but this was not statistically significant.

As demonstrated in the present study, these results are consistent with the findings of preceding research. Specifically, the study found that neutrophil, NLR, CRP, and CAR levels were significantly elevated, while lymphocyte levels were reduced, in the non-dipper HT group. In fact, all these findings support the increased inflammatory response in non-dipper HT patients as suggested by studies in the literature (5,9,10,11,13). Due to the complex pathophysiology of non-dipper HT, the more inflammatory parameters are included in the scores used, the more accurate the results. In this context, neither NLR nor HALP seems to be an independent predictor of non-dipper HT. When CAR and LANR scores, which were found to be independent predictors of non-dipper HT in our study, were analysed, we found that LANR score showed non-dipper HT with a better sensitivity and specificity in the ROC analysis. Our study shows that LANR score, which is an inflammatory indicator in non-cardiac diseases and is associated with mortality, is a good indicator of inflammation in non-dipper HT patients. Thus, we think that the LANR score, which is calculated with simple biochemical parameters, will enable the early recognition of non-dipper HT patients and the related increase in mortality can be prevented.

In clinical practice, the LANR index may be considered an additional prognostic tool in the evaluation of hypertensive patients undergoing ambulatory blood pressure monitoring. Based on our findings, a LANR value below 23 could suggest a higher likelihood of exhibiting a non-dipper blood pressure pattern. Therefore, we propose that the LANR index could be particularly useful in hypertensive patients with suspected non-dipper profiles or those presenting with high cardiovascular risk. Patients with a LANR score below this threshold might benefit from closer monitoring, early therapeutic interventions, and more aggressive cardiovascular risk management strategies. Future prospective studies are warranted to further validate the clinical applicability of this cut-off value.

The present study was subject to some limitations. First, it was performed retrospectively with a relatively small number of patients. Retrospective studies inherently carry the risk of selection bias and information bias. Although strict inclusion and exclusion criteria were applied and patients were selected consecutively, the potential for unrecognized

confounding factors that may affect the results cannot be entirely excluded. Second, a longer follow-up period and collection of data on long-term prognosis could have provided additional information that would have increased the value of our study. Third, although chronic inflammatory disease, malignancy, and hematologic diseases were excluded, there may be patients who have not yet been diagnosed and these could not be excluded. Fourthly, the study did not include detailed data regarding the medical treatments received by the patients, such as antihypertensive therapies, statins, or anti-inflammatory agents. The absence of this information is a notable limitation, as certain medications could potentially influence systemic inflammation markers, serum albumin levels, or other laboratory parameters assessed in this study. Consequently, the lack of medication data may have introduced a degree of confounding that could affect the interpretation of the association between LANR and HALP scores and non-dipper hypertension. Nevertheless, considering that no statistically significant differences were observed in the demographic characteristics between groups, it is likely that the distribution of medical treatments was relatively balanced across the study groups. Finally, more detailed echocardiographic parameters and their correlation with the LANR index could have increased the clinical significance of the study.

In conclusion, the LANR score is a cost-effective, widely implemented, readily accessible, and reproducible test that has emerged as a marker of systemic inflammatory response. This evaluation may facilitate the diagnosis of non-dipper HT patients at elevated risk of cardiovascular incidents in the early stages, thereby enabling the implementation of an early treatment strategy to reduce complications. Although the predictive value of the LANR index demonstrated only moderate-to-high discriminatory power, it remains clinically significant and valuable when used in conjunction with other clinical parameters. In addition, we think that our study will shed light on prospective and large studies to be conducted in the future.

Ethical Approval: Ethical approval of the study was obtained with the decision of Izmir Bozyaka Training and Research Hospital Health Research Ethics Committee dated 06.02.2025 and numbered 2025/14.

Author Contributions:

Concept: H.F., A.N.E.

Literature Review: H.F., A.N.E.

Design : H.F., A.N.E., L.D.

Data acquisition: H.F., A.N.E., L.D.

Analysis and interpretation: H.F., A.N.E.

Writing manuscript: H.F., A.N.E.

Critical revision of manuscript: H.F., A.N.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

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A Retrospective Analysis of Lung Cancer Diagnosis and Clinical Features During the COVID-19 Pandemic

COVID-19 Pandemisi Döneminde Akciğer Kanseri Tanısı ve Klinik Özelliklerinin Retrospektif Analizi

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Abstract

Background: The COVID-19 pandemic has disrupted healthcare systems and potentially delayed the diagnosis of progressive diseases such as lung cancer. This study aimed to evaluate the impact of the pandemic on access to healthcare among lung cancer patients and to analyze the types and stages of lung cancer diagnosed during this period compared to the pre-pandemic era.

Materials and Methods: This retrospective comparative study included 209 patients diagnosed with lung cancer at Harran University Chest Diseases and Oncology Clinics: 52 before the pandemic and 157 during the pandemic. Demographic and clinical data, including age, gender, smoking status, cancer type, diagnostic method, and stage, were collected from hospital records. Statistical analyses were performed using SPSS v.26, with significance set at $p < 0.05$.

Results: There were no significant differences between groups in age, gender, or smoking status ($p > 0.05$). The rate of advanced-stage diagnoses (Stage 4A–4B) significantly increased during the pandemic (63.7% vs. 44.2%; $p = 0.031$), with Stage 4B cases nearly doubling. Additionally, the number of patients without definitive staging increased. Adenocarcinoma (31.8%) and squamous cell carcinoma (25.5%) were the most common types. Bronchoscopy (29.9%) and FOB+EBUS (29.3%) were the most frequently used diagnostic methods. During the pandemic, a relative increase was observed in the use of less invasive procedures such as transthoracic biopsy and thoracentesis.

Conclusions: The findings indicate that the COVID-19 pandemic contributed to delays in lung cancer diagnosis, as evidenced by a higher rate of late-stage presentations. These results underscore the need for resilient diagnostic systems and proactive strategies to ensure timely cancer diagnosis during healthcare crises.

Keywords: Lung cancer, COVID-19 pandemic, Diagnosis delay, Cancer staging

Öz

Amaç: COVID-19 salgını sağlık sistemlerini bozmuş ve akciğer kanseri gibi ilerleyici hastalıkların teşhisini geciktirmiştir. Bu çalışmanın amacı, salgının akciğer kanseri hastaları arasında sağlık hizmetlerine erişim üzerindeki etkisini değerlendirmek ve bu dönemde teşhis edilen akciğer kanserinin türlerini ve evrelerini pandemi öncesi döneme göre analiz etmektir.

Materyal ve Metod: Bu retrospektif karşılaştırmalı çalışmaya Harran Üniversitesi Göğüs Hastalıkları ve Onkoloji Kliniklerinde akciğer kanseri teşhisi konan 209 hasta dahil edildi: 52'si pandemiden önce ve 157'si pandemi sırasında. Yaş, cinsiyet, sigara içme durumu, kanser türü, tanı yöntemi ve evre dahil olmak üzere demografik ve klinik veriler hastane kayıtlarından toplandı. İstatistiksel analizler SPSS v.26 kullanılarak yapıldı ve anlamlılık $p < 0,05$ olarak belirlendi.

Bulgular: Yaş, cinsiyet ve sigara kullanımı açısından gruplar arasında anlamlı fark bulunmadı ($p > 0,05$). Pandemi döneminde ileri evre (Evre 4A–4B) tanı oranı anlamlı şekilde artmış (%63,7 vs. %44,2; $p = 0,031$) ve Evre 4B oranı yaklaşık iki katına çıkmıştır. Ayrıca evrelemesi yapılamayan vaka sayısı artmıştır. Adenokarsinom (%31,8) ve skuamöz hücreli karsinom (%25,5) en sık görülen tiplerdi. Bronkoskopi (%29,9) ve FOB+EBUS (%29,3) en yaygın tanı yöntemleri olup; pandemi döneminde transtorasik biyopsi ve torasentez gibi daha az invaziv girişimlerde göreceli artış izlenmiştir.

Sonuç: Bulgular, COVID-19 pandemisinin akciğer kanseri tanısında gecikmelere katkıda bulunduğunu, bunun da geç evre başvurularının daha yüksek oranda görülmesiyle kanıtlandığını göstermektedir. Bu sonuçlar, sağlık krizleri sırasında zamanında kanser teşhisini sağlamak için dayanıklı tanı sistemlerine ve proaktif stratejilere olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: Akciğer kanseri, COVID-19 pandemisi, Tanı gecikmesi, Kanser evreleme

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Introduction

The COVID-19 pandemic has profoundly impacted healthcare systems, significantly reducing the frequency of patient visits to healthcare institutions. During this period, individuals primarily sought medical care in emergency situations, resulting in delays in the diagnosis and treatment of numerous diseases (1). Evidence from the literature indicates that these disruptions in healthcare access pose substantial risks, particularly for progressive diseases such as cancer. Delays in diagnosis for conditions like cancer can severely compromise patient health outcomes and limit available treatment options (2, 3).

Lung cancer, one of the most prevalent malignancies worldwide, represents a significant clinical challenge requiring early detection and intervention. Its progression markedly deteriorates patients' overall health and quality of life while complicating treatment processes. Early diagnosis is therefore critical for improving prognosis and ensuring timely intervention (4). However, lung cancer is predominantly diagnosed at advanced stages, significantly affecting treatment outcomes and survival rates. Advanced-stage lung cancer has a very poor prognosis, with a five-year survival rate of only around 5% (5).

Despite these critical insights, the impact of COVID-19 on oncological patients, including those with lung cancer, has been inadequately explored in the existing literature. Notably, there has been a lack of comprehensive analysis regarding how the pandemic influenced lung cancer patients' access to healthcare services. This gap is significant for understanding how healthcare systems can better prepare for future crises and develop sustainable care models for oncological patients.

The aim of our study is to evaluate the impact of the pandemic on lung cancer patients' access to healthcare services and to analyze the types and stages of lung cancer diagnosed during this period. Accordingly, we have identified the following research questions:

How did the COVID-19 pandemic affect diagnosis delays for lung cancer patients?

What are the types of cancer and stages of patients diagnosed with lung cancer during the pandemic period?

Materials and Methods

This retrospective comparative study was conducted with the approval of the Harran University Ethics Committee (Ethics Committee Decision No. HRÜ/24,17,02; Date:04/11/2024) and adhered to the principles of the Declaration of Helsinki. The study included patients diagnosed with lung cancer at Harran University Chest Diseases and Oncology Clinics during the pre-COVID and COVID-19 pandemic periods.

Patients with a histopathologically confirmed diagnosis of lung cancer and complete, accurate medical records within the defined time frames were included. Exclusion criteria comprised incomplete or erroneous data, lack of staging information, or a primary diagnosis other than lung cancer.

Data were retrospectively extracted from the hospital's digital medical records and patient files. The collected variables included age, gender, smoking status, lung cancer type, diagnostic method, and cancer stage.

Information regarding gender (male/female), age (recorded as a continuous variable), and smoking status (categorized as "yes" or "no") was collected for each patient. Lung cancer types were grouped into eight main categories: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, metastatic carcinoma, large cell neuroendocrine carcinoma, carcinoid tumor, mesothelioma, and suspicious malignancy. The diagnostic methods assessed in the study included endobronchial ultrasonography (EBUS), bronchoscopy, trans-thoracic needle biopsy, flexible bronchoscopy combined with EBUS (FOB+EBUS), surgical biopsy, and thoracentesis. Cancer staging was based on the standard TNM classification system, ranging from stage 1B to stage 4B, as documented in patient records. Cases without definitive staging information were categorized separately as "uncertain staging." All data were anonymized, and patient confidentiality was strictly preserved.

Statistical analyses were conducted using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables as frequencies and percentages. Group comparisons between the pre-COVID and COVID-19 periods were performed using the chi-square (χ^2) test for categorical variables. The significance level was set at $p < 0.05$.

Results

A total of 209 patients diagnosed with lung cancer were included in the study: 52 in the pre-COVID period and 157 during the COVID-19 pandemic. There was no statistically significant difference between the two groups in terms of age, sex, or smoking status ($p > 0.05$ for all comparisons) (Table 1).

A significant shift was observed in cancer stage distribution between the two periods. During the COVID-19 period, 63.7% of patients were diagnosed at advanced stages (Stage 4A and 4B), compared to 44.2% in the pre-COVID period. Notably, Stage 4B cases were markedly more common during the pandemic (47.1%) than before (28.8%). Conversely, early-stage diagnoses (Stages 1B to 3A) were relatively more frequent prior to the pandemic (Figure 1). This difference in cancer staging between the two timeframes was statistically significant ($p = 0.031$), suggesting a potential delay in diagnosis during the COVID-19 pandemic. Furthermore, 20% ($n=31$) of cases diagnosed during the pandemic had undetermined staging due to pathologically suspicious or metastatic conditions, which may reflect incomplete diagnostic workups or delays in accessing comprehensive evaluations. While adenocarcinoma remained the most frequently diagnosed subtype in both periods (28.8% pre-COVID vs. 31.8%

during COVID), the proportion of squamous cell carcinoma and small cell carcinoma diagnoses decreased during the pandemic (32.7% to 25.5% and 32.7% to 19.1%, respectively). In contrast, rare subtypes such as carcinoid tumors, large cell neuroendocrine carcinoma, and mesothelioma

were more frequently identified during the COVID period. These findings suggest a shift in histological subtype detection patterns, possibly influenced by diagnostic delays or changes in referral and access patterns (Table 2).

Table 1. Patient Clinical Features

	Pre-Covid Mean $\pm$ SD or n (%)	During-Covid Mean $\pm$ SD or n (%)	p
Age (years)	59.47 $\pm$ 10.26	61.72 $\pm$ 11.99	0.8969*
Sex			
Male	45 (86.5%)	133 (84.7%)	0.4536 ⁺
Female	7 (13.5%)	24 (15.3%)	
Smoking status			
Yes	41 (78.8%)	127 (80.9%)	0.9041 ⁺
No	11 (21.2%)	30 (19.1%)	

*Independent samples t-test

⁺Chi-square

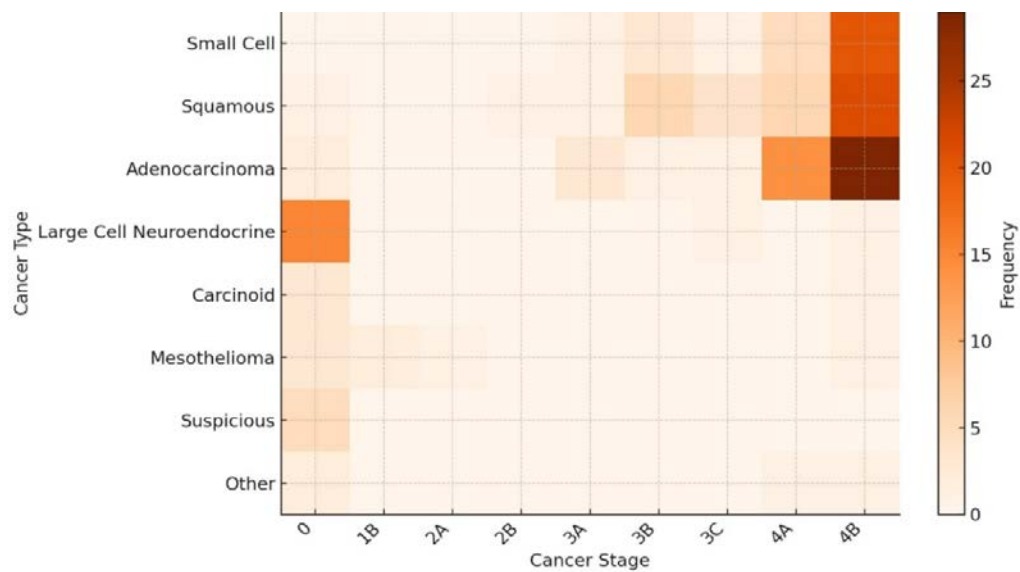


Figure 1. Cancer Stages by Type

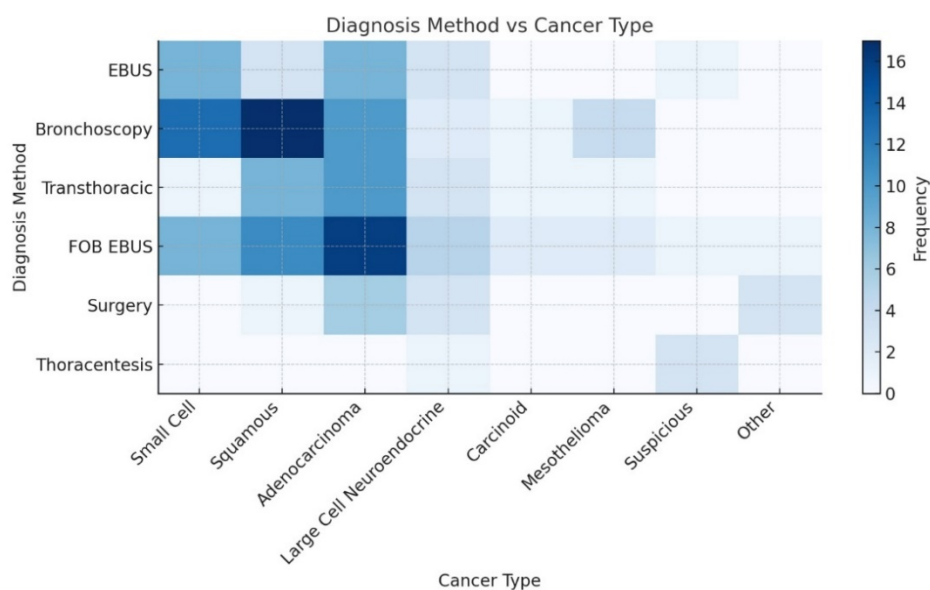


Figure 2. Diagnostic Methods by Cancer Type

The distribution of diagnostic methods remained generally consistent across both time periods. Bronchoscopy and flexible bronchoscopy with endobronchial ultrasound (FOB+EBUS) continued to be the most commonly employed procedures (Figure 2). However, a slight increase was noted in the use of less invasive approaches, such as transthoracic needle biopsy (15.4% vs. 15.3%) and thoracentesis (1.9% vs.

2.5%) during the COVID period. The proportion of surgical diagnoses slightly decreased. These shifts may reflect adaptations to minimize aerosol-generating procedures and preserve healthcare resources during the pandemic (Table 3).

Table 2. Lung Cancer Types

Type	Pre-Covid n (%)	During-Covid n (%)	p
Adeno	15 (%28.8)	50 (31.8%)	0.1198*
Squamous	17 (%32.7)	40 (25.5%)	
Small	17 (%32.7)	30 (19.1%)	
MET	-	17 (10.8%)	
Carcinoid	1 (%1.9)	7 (4.5%)	
Suspicious	1 (%1.9)	5 (3.2%)	
Large Cell Neuroendocrine	1 (%1.9)	4 (2.5%)	
Mesothelial	-	4 (2.5%)	

*Chi-square

Table 3. Cancer Diagnosis Methods Distribution

Type	Pre-Covid n (%)	During-Covid n (%)	p
Bronchoscopy	16 (30.8%)	47 (29.9%)	0.9917
FOB EBUS	17 (32.7%)	46 (29.3%)	
Transthoracic	8 (15.4%)	24 (15.3%)	
EBUS	6 (11.5%)	23 (14.6%)	
Surgery	4 (7.7%)	13 (8.3%)	
Thoracentesis	1 (1.9%)	4 (2.5%)	

*Chi-square

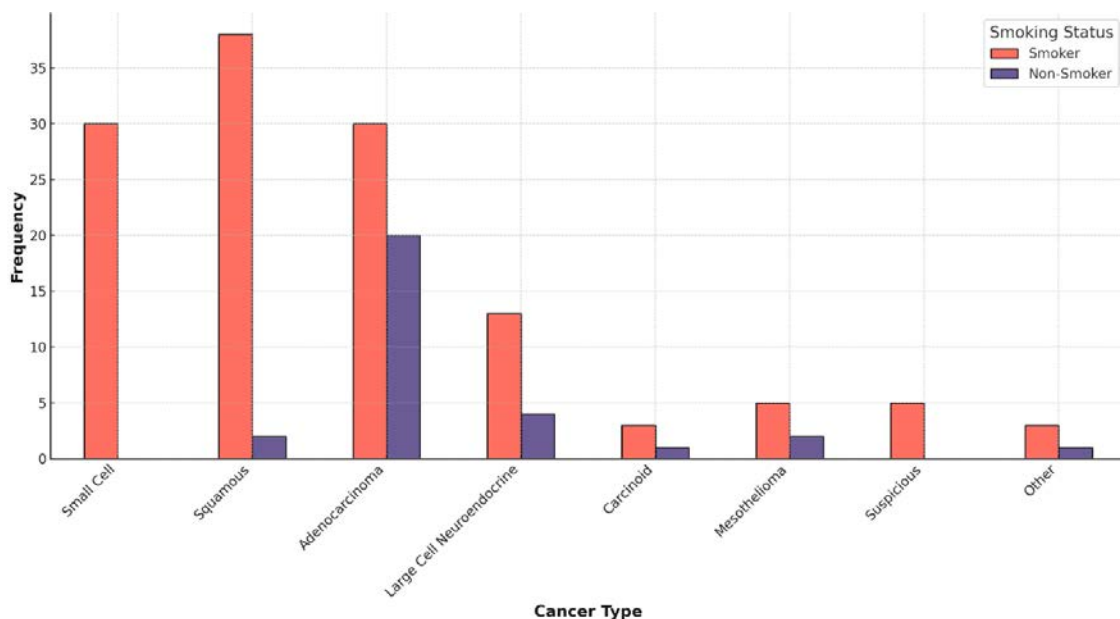


Figure 3. Smoking Status Frequencies by Cancer Type

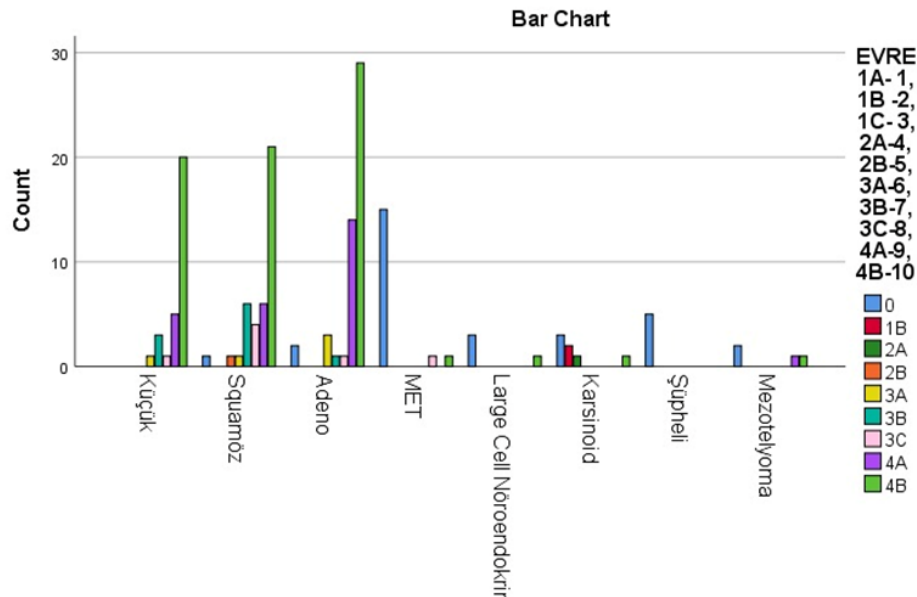


Figure 4. Subtypes of lung cancer and their distribution according to stage

Discussion

In this study, the clinical and diagnostic features of 156 patients diagnosed with lung cancer during the COVID-19 pandemic were evaluated and the effects of the pandemic on lung cancer diagnosis were analyzed. In our study, During the COVID-19 period, 63.7% of patients were diagnosed at advanced stages (Stage 4A and 4B), compared to 44.2% in the pre-COVID period. Notably, Stage 4B cases were markedly more common during the pandemic (47.1%) than before (28.8%). Conversely, early-stage diagnoses (Stages 1B to 3A) were relatively more frequent prior to the pandemic. This difference in cancer staging between the two timeframes was statistically significant ($p = 0.031$), suggesting a potential delay in diagnosis during the COVID-19 pandemic. Interruptions in access to health services and restrictions on invasive diagnostic methods during the COVID-19 pandemic may have contributed to these results.

It was determined that COVID-19 period 65.79% of our patients were Stage 4 compared to 44.2% in the pre-COVID period. This rate shows that a large portion of patients have lost the chance of curative treatment at the time of diagnosis. While it is reported in the literature that advanced stage rates in lung cancer diagnosis are high regardless of the pandemic (44% Stage III and IV), the higher rate in our study (65.79%) suggests that COVID-19 may have further increased diagnostic delays (6, 7). The disruption of cancer screening programs during the pandemic and the hesitation of patients to seek healthcare

services may have increased the rates of diagnosis at advanced stages (8). The fact that adenocarcinoma is diagnosed more frequently at advanced stages supports the information that this type is usually clinically silent and is noticed at advanced stages with diagnostic delays (9). While adenocarcinoma remained the most frequently diagnosed subtype in both periods (28.8% pre-COVID vs. 31.8% during COVID),

the proportion of squamous cell carcinoma and small cell carcinoma diagnoses decreased during the pandemic (32.7% to 25.5% and 32.7% to 19.1%, respectively). In contrast, rare subtypes such as carcinoid tumors, large cell neuroendocrine carcinoma, and mesothelioma were more frequently identified during the COVID period. These findings suggest a shift in histological subtype detection patterns, possibly influenced by diagnostic delays or changes in referral and access patterns (Table 2).

It has been stated in the literature that adenocarcinoma can develop independently of smoking, along with genetic and environmental factors (10, 11). However, the fact that adenocarcinoma was also common in individuals who smoke in our study suggests that the effect of smoking on this subtype should be re-evaluated. It has been determined that there is a strong relationship between smoking and squamous cell cancer, and adenocarcinoma is common in both smokers and non-smokers. The literature supports the fact that squamous cell cancer is particularly sensitive to carcinogens in cigarette smoke and is more common in smokers (12, 13). The fact that a large portion of the patients with adenocarcinoma in our study were smokers suggests that this subtype may be affected by smoking along with factors other than smoking. It is conceivable that geographical and environmental factors may have been effective in these results. An increase in the incidence of adenocarcinoma may have been observed, especially during periods when smoking increased. It is known that the COVID-19 pandemic has restricted access to healthcare services and reduced the use of invasive diagnostic methods. In our study, all of the time the most commonly used diagnostic methods were endobronchial ultrasonography (EBUS) and bronchoscopy, but it is thought that the diagnostic processes may have been prolonged in some patients due to the limited use of these methods during the pandemic

(14, 15). Measures to reduce the risk of infection during aerosol-generating procedures may have delayed the timely application of diagnostic methods. This situation may have made it difficult to detect early-stage cancers in particular and contributed to the increase in advanced-stage diagnosis rates (16-18).

Likewise, many oncology services were turned into pandemic clinics, as was the case in our country, which caused difficulties for diagnosed patients in accessing chemotherapy. The fear of being vulnerable to the pandemic due to the chemotherapeutics given also prevented patients from receiving treatment.

Our study is one of the rare studies that evaluate the effects of healthcare interruptions specific to this period, as it examines patients diagnosed with lung cancer during the COVID-19 pandemic. It examines the relationship between cancer stages and types in detail, revealing clinical differences in diagnosis processes. However, being a retrospective study limits the capacity to evaluate causal relationships. Our study is based on data obtained from a single center, which limits the generalizability of the results.

Conclusion

Our study reveals in detail the effects of the COVID-19 pandemic on lung cancer diagnosis and treatment processes. The fact that a large proportion of patients are diagnosed at an advanced stage shows that the pandemic causes delays in diagnosis, which limits the chances of curative treatment for patients. In order to increase early diagnosis and intervention opportunities, cancer screening programs need to be made more resilient to extraordinary situations. Multicenter studies with larger sample sizes are critical to assess the long-term effects of the pandemic and prepare healthcare services for future crises.

Ethical Approval: This retrospective comparative study was conducted with the approval of the Harran University Ethics Committee (Ethics Committee Decision No. HRÜ/24,17,02; Date:04/11/2024)

Author Contributions:

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Safety of Elective Inguinal Hernia Repair in the Geriatric Population: A Retrospective Analysis

Geriatrik Popülasyonda Elektif İnguinal Herni Onarımının Güvenliği: Retrospektif Analiz

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Abstract

Background: Inguinal hernia (IH) repair is generally considered safe with low morbidity and mortality; however, the risk increases in geriatric patients due to the prevalence of comorbid conditions. This study aims to compare the outcomes of elective versus emergency IH repair in elderly patients.

Materials and Methods: Patients aged 65 years and older who underwent surgery for IH at Balıklıgöl State Hospital and Akçakale State Hospital between 01.12.2022 and 01.02.2024 were retrospectively reviewed. The patients were divided into two groups as emergency (G-EM) and elective (G-EL) surgery. Age, gender, comorbidities, type of operation, length of hospitalization and postoperative complications were recorded. Postoperative complications were recorded as wound infection, seroma and ileus.

Results: The study included 72 patients. Sixty-one (84.7%) patients were in the G-EL group and 11 (15.3%) were in the G-EM group. The G-EL group was composed entirely of males, with a mean age of 70.9 years (range: 65-86), while the G-EM group included 6 males (54.5%) and 5 females (45.5%), with a mean age of 71.2 years (range: 65-89). The length of hospitalization was significantly shorter in the G-EL group (1.39 ± 0.62 days) compared to the G-EM group (4.50 ± 2.51 days, $p < 0.001$). Postoperative complications were occurred in 5 (45.6%) patients in the G-EM group and in 7 (11.5%) patients in the G-EL group, a significant difference was found ($p=0.015$). No mortality was observed in both groups.

Conclusions: Although IH repair in the geriatric population is a concern due to comorbidities, we recommend elective mesh hernia repair for patients diagnosed with inguinal hernia to avoid the high complication rate after emergency repair as seen in our study and in the literature.

Keywords: Geriatrics, Inguinal Hernia, Complications, Surgery

Öz

Amaç: Kasık fıtığı (İH) onarımı genellikle düşük morbidite ve mortalite ile güvenli kabul edilir; ancak, komorbid durumların yaygınlığı nedeniyle geriatrik hastalarda risk artar. Bu çalışmanın amacı yaşlı hastalarda elektif ve acil İH onarımının sonuçlarını karşılaştırmaktır.

Materyal ve Metod: 01.12.2022 ile 01.02.2024 tarihleri arasında Balıklıgöl Devlet Hastanesi ve Akçakale Devlet Hastanesi'nde İH nedeniyle ameliyat edilen 65 yaş ve üzeri hastalar retrospektif olarak incelendi. Hastalar acil (G-EM) ve elektif (G-EL) cerrahi olmak üzere iki gruba ayrıldı. Yaş, cinsiyet, eşlik eden hastalıklar, ameliyat türü, hastanede yatış süresi ve ameliyat sonrası komplikasyonlar kaydedildi. Ameliyat sonrası komplikasyonlar yara enfeksiyonu, seroma ve ileus olarak kaydedildi.

Bulgular: Çalışmaya 72 hasta dahil edilmiştir. Altmış bir (%84,7) hasta G-EL grubunda ve 11 (%15,3) hasta G-EM grubundaydı. G-EL grubu ortalama 70,9 yaş (dağılım: 65-86) ile tamamen erkeklerden oluşurken, G-EM grubu ortalama 71,2 yaş (dağılım: 65-89) ile 6 erkek (%54,5) ve 5 kadın (%45,5) içermektedir. Hastanede yatış süresi G-EL grubunda (1.39 ± 0.62 gün) G-EM grubuna (4.50 ± 2.51 gün, $p < 0.001$) kıyasla anlamlı olarak daha kısaydı. Ameliyat sonrası komplikasyonlar G-EM grubunda 5 (%45,6) hastada görülürken, G-EL grubunda 7 (%11,5) hastada görülmüştür ve anlamlı bir fark bulunmuştur ($p=0,015$). Her iki grupta da mortalite gözlenmedi.

Sonuç: Geriatrik popülasyonda İH onarımı komorbiditeler nedeniyle endişe verici olsa da, çalışmamızda ve literatürde görüldüğü gibi acil onarım sonrası yüksek komplikasyon oranından kaçınmak için inguinal herni tanısı alan hastalara elektif mesh herni onarımını öneriyoruz.

Anahtar Kelimeler: Geriatri, İnguinal Herni, Komplikasyon, Cerrahi

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Introduction

Inguinal hernia (IH) is a disease seen in all age groups and requires more than 20 million operations annually worldwide (1). As an age group, it is common in childhood and advanced ages (2). Increased intra-abdominal pressure and abdominal wall weakness are effective in its formation (3). Inguinal hernia has a high prevalence in the elderly population (≥ 65 years) due to abdominal wall weakness, benign prostatic hyperplasia, chronic cough and chronic constipation (4).

Physical examination is usually sufficient for the diagnosis of inguinal hernia. Ultrasound (USG) and magnetic resonance imaging (MRI) can be used as additional methods for diagnosis in suspicious cases or in female patients (5).

Surgery is the only curative treatment for inguinal hernia and patients with symptoms should always be advised to undergo surgery. A 2020 international guideline recommended a “watchful waiting” strategy for asymptomatic or minimally symptomatic inguinal hernia (IH) patients, especially for male patients at low risk of developing into an emergency. However, it has been reported that most patients will need surgery in time (6).

In surgical techniques, open repair without mesh and Lichtenstein tension-free mesh, or laparoscopic or robotic methods such as Total Extra Peritoneal (TEP) and Trans Abdominal Pre-Peritoneal (TAPP) can be used (7).

In addition, morbidity and mortality rates related to surgery and anesthesia increase in patients aged 65 years and older (8). Therefore, surgical treatment tends to be postponed in asymptomatic or mildly symptomatic patients aged 65 years and older with a diagnosis of inguinal hernia (8). When urgent inguinal hernia repair is needed, morbidity and mortality rates also increase (9).

In this study, we aimed to compare the results of elective and emergency IH repair in geriatric patients.

Materials and Methods

Patients aged 65 years and older who underwent surgery for IH between 01.12.2022 and 01.02.2024 at Balıklıgöl

State Hospital and Akçakale State Hospital were retrospectively reviewed. Patients were operated with open technique Lichtenstein tension-free mesh repair. The patients were divided into two groups as emergency (G-EM) and elective (G-EL) surgery group. Age, gender, comorbidities, type of operation, length of hospitalization and postoperative complications were recorded. Postoperative complications that developed during hospitalization or within 30 days after discharge were recorded as wound infection, seroma and ileus. Patients whose information was not clearly available were excluded from the study.

The operations were performed by 2 general surgeons with 5 years of experience in inguinal hernia surgery.

Statistical Analysis

Statistical analysis of our study was performed with SPSS 18 program. Kolmogorov-Smirnov test was used to determine the distribution of numerical data. Independent-samples t-test was used for comparison in groups with normal distribution and Chi-square test was used for comparison of non-numerical data. P values < 0.05 were considered statistically significant.

Results

The study included 72 patients. Of the patients, 61 (84.7%) were in the G-EL group and 11 (15.3%) were in the G-EM group. All patients in the elective group were male and the mean age was 70.9 years (65-86). In the emergency group, 6 (54.5%) were male, 5 (45.5%) were female and the mean age was 71.2 (65-89) years (Table-1). All patients in the G-EL group had inguinal hernia while 27.3% (n=3) patients in the G-EM group had femoral hernia. In the G-EL group, 42.6% had Coronary Artery Disease (CAD), 27.9% had Chronic Obstructive Pulmonary Disease (COPD) and 8.2% had Benign Prostatic Hypertrophy (BPH). In the G-EM group, 81.8% had CAD, 45.5% had COPD and 27.3% had BPH as comorbidities (Figure 1). The rate of comorbidity was higher in the emergency group compared to the elective group.

Table 1. Comparison of groups according to results

	G-EL	G-EM
Men	61	6
Women	0	5
Age (mean)	70.9	71.2
Hernia Type		
• Inguinal	61	8
• Femoral	0	3
Bowel Resection	0	3
Hospitalization	1.4 gün	4.5 gün
Postoperative Complications	7	5
• Seroma	5	3
• İleus	1	2
• Wound infection	1	0

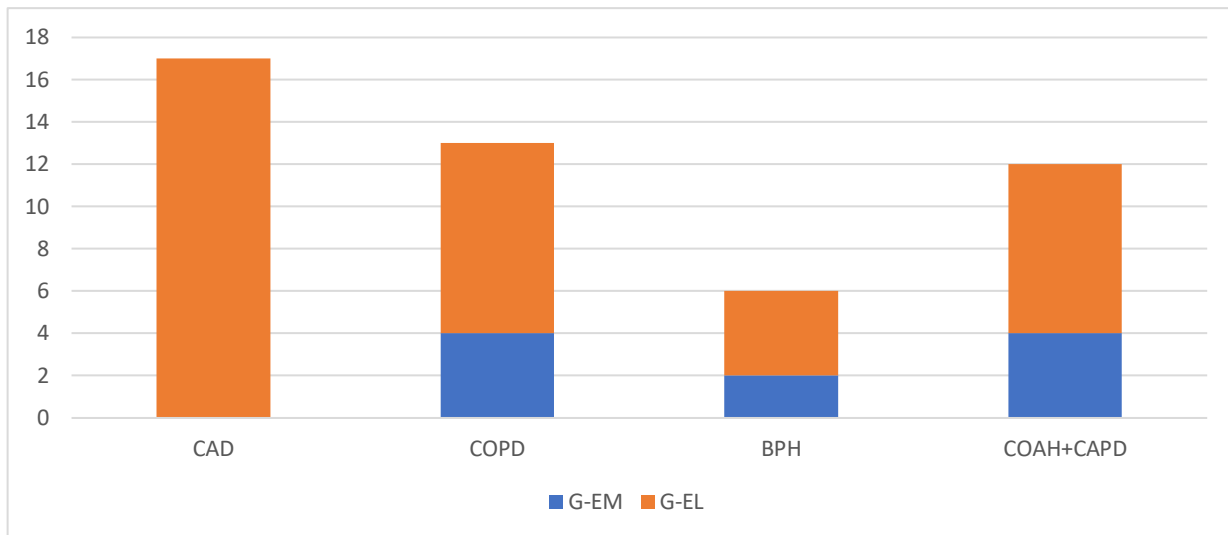


Figure 1. Distribution groups according to comorbid diseases

Both groups were operated under spinal anesthesia. All patients in the G-EL group and 8 (72.7%) patients in the G-EM group underwent mesh hernia repair. Small bowel resection operation was performed in 3 (27.3%) patients in the G-EM group. The duration of hospitalization was 1.39 ± 0.62 days in the G-EL group and 4.5 ± 2.51 days in the G-EM group, which was statistically significant ($p < 0.001$). There was no difference between the gender of the patients and the development of complications ($p = 0.191$). Postoperative complications were observed in 5 (45.6%) patients in the G-EM group and in 7 (11.5%) patients in the G-EL group, a significant difference was found ($p = 0.015$). No mortality was observed in both groups.

Discussion

The risk factors for inguinal hernia (IH) include male gender, advanced age, low body mass index, pre-existing abdominal wall muscle weakness, and increased intra-abdominal pressure (10). In our study, the majority of patients were male.

The development of inguinal hernia is more common in elderly patients compared to the general population due to a weakened abdominal wall and comorbid conditions that increase intra-abdominal pressure, such as chronic obstructive pulmonary disease (COPD), benign prostatic hyperplasia (BPH), and chronic constipation (11). In elderly patients, the incidence of emergency hernia repair increases due to prolonged life expectancy and delayed surgeries, which may lead to fatal outcomes.

Although morbidity and mortality rates in surgical repair of inguinal hernia are generally low, decision-making by surgeons becomes more challenging in geriatric patients due to the coexistence of comorbid diseases. In our study, the high rate of comorbidities in patients operated on under emergency conditions supports the possibility that some

surgeries may have been postponed by surgeons due to concerns about postoperative complications.

Işıl et al. found that 21% of patients who underwent emergency surgery for IH required bowel resection, which was deemed statistically significant (12). In our study, the rate of small bowel resection in three (27.3%) patients in the emergency group was consistent with the literature. The difference between the groups was statistically significant, as reported in previous studies that showed increased postoperative complications and prolonged hospitalizations in patients who underwent emergency IH repair (9, 13).

While general anesthesia is typically preferred in emergency situations, local or regional anesthesia is the preferred option for elective hernia repair, particularly in elderly patients with significant comorbidities (14). General anesthesia has been associated with increased morbidity and mortality rates in the geriatric population (15). Meta-analyses have reported the complication rate following inguinal hernia (IH) surgery in elderly patients as ranging from 21.9% to 28.9%, with mortality rates ranging from 1.2% to 6%. In our study, the complication rate was found to be statistically significantly higher in the emergency group, with no mortality observed among our patients (16).

A limitation of our study is its retrospective design and the relatively small sample size. Multicenter, prospective studies with larger patient populations would provide more robust and comprehensive data, offering clearer and more valuable insights into the management of inguinal hernia in the geriatric population.

Conclusion

While inguinal hernia (IH) repair in the geriatric population poses challenges due to the presence of comorbidities, we recommend elective mesh hernia repair for patients diagnosed with inguinal hernia. This approach is suggested to

mitigate the high complication rates associated with emergency repairs, as observed in our study and supported by the existing literature.

Ethical Approval: Ethics committee approval was obtained from the Harran University Clinical Research Ethics Committee on October 21, 2024, with decision number HRU/24.16.54.

Author Contributions:

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An Examination of the Sociodemographic and Clinical Characteristics of Cases Presenting to the Child Psychiatry Clinic after the Kahramanmaraş Earthquakes

Kahramanmaraş Depremi Sonrası Çocuk Psikiyatrisi'ne Başvuran Olguların Sosyodemografik Ve Klinik Özelliklerinin İncelenmesi

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Abstract

Background: On February 6, 2023, two devastating earthquakes with magnitudes of 7.7 and 7.6 struck Kahramanmaraş, Türkiye. Children and adolescents are among the most vulnerable groups to experience significant psychosocial impacts following such disasters. Given Türkiye's large pediatric population, understanding the mental health outcomes in this group is of national importance. Post-earthquake psychiatric symptoms and disorders in children may include depression, anxiety, post-traumatic stress symptoms, behavioral issues, cognitive regression, attention deficits, academic decline, and learning difficulties. This study aims to contribute to the literature by examining the sociodemographic characteristics, clinical profiles, psychiatric diagnoses, and treatment approaches among pediatric patients affected by the Kahramanmaraş earthquakes.

Materials and Methods: This retrospective study reviewed the medical records of 164 children and adolescents who were diagnosed under ICD code X34 (victims of earthquake) and presented to Elazığ Fethi Sekin City Hospital the child psychiatry outpatient clinic between February 2023 and February 2024.

Results: The most common presenting complaints were anxiety, school avoidance, and earthquake-related fears (31.1%). The most frequently identified psychiatric conditions were neurodevelopmental disorders (totaling 34.1%), including ADHD (17.6%), intellectual disability (7.3%), autism spectrum disorder (4.3%), and specific learning disorder (3.6%), as well as anxiety disorders (15.9%). Acute stress disorder, according to DSM-5, was diagnosed in 66% of the cases.

Conclusions: As expected, there was a high prevalence of neurodevelopmental and internalizing psychiatric disorders following the earthquakes. Prospective, long-term follow-up studies assessing the enduring impact of the Kahramanmaraş earthquakes on children and adolescents in Türkiye are warranted.

Keywords: Disaster, Trauma, Earthquake, Child psychiatry, Adolescent mental health, Türkiye

Öz

Amaç: 6 Şubat 2023 tarihinde, Türkiye'nin Kahramanmaraş ilinde 7.7 ve 7.6 büyüklüğünde iki yıkıcı deprem meydana gelmiştir. Çocuklar ve ergenler, bu tür afetlerin ardından en fazla psikososyal etkilenebilirliğe açık gruplardan biridir. Türkiye'nin büyük çocuk nüfusu göz önüne alındığında, bu yaş grubundaki ruh sağlığı sonuçlarının anlaşılması ulusal düzeyde önem taşımaktadır. Deprem sonrasında çocuklarda depresyon, anksiyete, travma sonrası stres belirtileri, davranış sorunları, gelişimsel gerileme, dikkat eksikliği, akademik başarıda düşüş ve öğrenme güçlükleri gibi psikiyatrik semptom ve bozukluklar ortaya çıkabilir. Bu çalışma, Kahramanmaraş depremlerinden etkilenen çocuk ve ergenlerin sosyodemografik özelliklerini, klinik profillerini, psikiyatrik tanıları ve tedavi yaklaşımlarını inceleyerek literatüre katkı sağlamayı amaçlamaktadır.

Materyal ve Metod: Bu retrospektif çalışmada, Şubat 2023 ile Şubat 2024 tarihleri arasında Elazığ Fethi Sekin Şehir Hastanesi çocuk ve ergen psikiyatrisi polikliniğine başvuran ve ICD kodu X34 (deprem mağduru) tanısı alan 164 hastanın dosya kayıtları incelenmiştir.

Bulgular: En sık başvuru şikayetleri anksiyete, okuldan kaçınma ve depreme bağlı korkular (% 31,1) olarak belirlenmiştir. En yaygın psikiyatrik bozukluklar; dikkat eksikliği ve hiperaktivite bozukluğu (% 17,6), zihinsel yetersizlik (% 7,3), otizm spektrum bozukluğu (% 4,3) ve özgül öğrenme güçlüğü (% 3,6) gibi nörogelişimsel bozukluklar (toplam % 34,1) ile anksiyete bozuklukları (%15,9) olmuştur. Vakaların % 66'sında DSM-5 kriterlerine göre akut stres bozukluğu tanısı konmuştur.

Sonuç: Depremler sonrasında, öngörüldüğü gibi nörogelişimsel ve içselleştirilmiş psikiyatrik bozuklukların yaygın olduğu görülmüştür. Türkiye'de çocuk ve ergenlerin Kahramanmaraş depremlerinden uzun vadeli etkilenimlerini değerlendirecek ileriye dönük izlem çalışmalarına ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Afet, Travma, Deprem, Çocuk psikiyatrisi, Ergen ruh sağlığı, Türkiye

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Introduction

Two major earthquakes, with magnitudes of 7.7 and 7.6, struck the province of Kahramanmaraş on February 6, 2023 (1). These earthquakes primarily affected eleven provinces, with Kahramanmaraş being the epicenter. The Kahramanmaraş earthquakes were the most devastating in Türkiye since the Erzincan (Mw: 7.9) and Kocaeli-Gölcük (Mw: 7.6) earthquakes of the 20th century (1). Nearly 50,000 people lost their lives, and approximately 200,000 were injured in these disasters (2). Beyond the significant loss of life and property, earthquakes also have profound psychological, social, physical, and economic consequences (3). Among those most vulnerable to the psychosocial impacts of earthquakes are children and adolescents. Given Türkiye's large child and youth population, this issue carries critical national importance (4). Earthquake-related factors—such as physical injury, bereavement, displacement, loss of home and possessions, educational disruption, separation from peers, and forced relocation—can have serious psychological effects on children and adolescents (5). The negative impact may persist both in the short and long term, with trauma symptoms potentially emerging even years after the event (6). Previous studies have documented a range of psychiatric symptoms and disorders in children following earthquakes, including depression, anxiety, post-traumatic stress disorder (PTSD), difficulties with anger, cognitive regression, attention problems, decreased academic performance, and learning difficulties (4,6–12). Research conducted after the 1999 Gölcük earthquake in Türkiye examined the sociodemographic and clinical characteristics, as well as psychiatric diagnoses, of affected children and adolescents (4,6,11). In a study by Kılıç et al., PTSD symptoms were evaluated in 800 children aged 8–14 and their families. The findings indicated a link between children's PTSD severity and the presence of PTSD in other family members, particularly paternal depression (11). Another study by Çelebi Oncu et al. used incomplete story tasks with 103 children—some exposed to the earthquake and some not—and found that trauma-related symptoms persisted even two years later among the exposed group (6). Similarly, Bal et al. reported that nearly 70% of 293 children and adolescents displayed moderate to severe PTSD symptoms following the earthquake (4).

The current study aims to contribute to the literature by investigating the sociodemographic features, clinical presentations, psychiatric diagnoses, and treatments of children and adolescents affected by the Kahramanmaraş earthquakes. It is expected that internalizing problems—such as anxiety, depression, acute stress disorder, and PTSD—will be common among this population. Furthermore, we anticipate a high prevalence of neurodevelopmental disorders, as these conditions frequently lead to referrals to child and adolescent psychiatry outpatient clinics.

Materials and Methods

Patient

Retrospective review of the archive files of 164 children and adolescents who presented to the child psychiatry outpatient clinic of Elazığ Fethi Sekin City Hospital between February 2023 and February 2024 was conducted. These individuals underwent complete diagnostic interviews and were subsequently diagnosed as victims of the earthquake under ICD code X34. Patients who met the inclusion criteria for this descriptive, cross-sectional, and retrospective study were selected. The inclusion criteria required that patients have a documented presenting complaint, a psychiatric diagnosis based on DSM-5, complete sociodemographic and clinical data necessary for the study, as well as disease severity and post-treatment improvement scores according to the Clinical Global Impression (CGI) Scale. Patients with missing sociodemographic or clinical data in their files were excluded from the study.

Study Procedures

The study was designed as a descriptive, cross-sectional, and retrospective study. Ethical approval was obtained from the Firat University Ethics Committee (approval letter number 2024/05-05, dated March 21, 2024) before the initiation of the study. Patient archive files were reviewed, and sociodemographic data, psychiatric diagnoses, treatments, pre-treatment and post-treatment disease severity using the Clinical Global Impression Scale, and post-treatment recovery scores were assessed.

Demographic Variables and Clinical Severity

The parameters examined in the patient archive files included: age, sex, city of origin, the presence of any loss in the nuclear family or among close relatives, a previous history of presentation to a child psychiatry clinic, any diagnoses and treatments provided, medical history, presence of any known psychiatric illness, psychiatric illnesses in the family, whether the individuals experienced the earthquakes, the extent of damage to the home (minor/moderate/severe), whether relocation to a different city occurred, the exhibition of acute stress disorder symptoms, psychiatric diagnoses following presentation, and treatments administered. Disease severity prior to and after treatment, as well as recovery scores post-treatment, were evaluated using the CGI Scale in patients who attended follow-up. All these parameters were routinely assessed in the patient files, and no additional parameters were utilized in the study.

Psychological Measures

Clinical Global Impression Scale: Developed by William Guy in 1976, the Clinical Global Impression Scale consists of three items: disease severity, improvement, and side effects. Disease severity is rated on a scale from 1 to 7,

with 1 representing normal (not ill) and 7 indicating severe illness. The improvement score also ranges from 1 to 7, with 1 indicating much improvement, 4 representing no change, and 7 indicating very much worse. Side effect severity is rated from 1 (none) to 4 (side effects so severe that they impact the patient's life). In this study, CGI disease severity and improvement scores were utilized to assess the clinical outcomes. (13).

Statistical Analysis

Statistical analysis was performed using the Social Sciences Statistical Package version 21.0 (SPSS 21.0). Since the sample size was greater than 50, the Kolmogorov-Smirnov test for single samples was employed to assess the distribution of continuous variables. The chi-square test was used to compare categorical variables between two independent groups. The Student's t-test was applied for continuous variables that demonstrated a normal distribution, while the Mann-Whitney U test was used for those that did not follow a normal distribution. The paired-samples t-test was employed to compare normally

distributed continuous variables between two dependent groups, and the Wilcoxon signed rank test was used for non-normally distributed variables. A p-value of less than 0.05 was considered statistically significant for all analyses..

Results

A total of 164 earthquake victims were included in the study, with boys constituting 55.5% (n = 91) and girls 44.5% (n = 73). The mean age of the victims at the time of their first visit to the child psychiatry clinic was 10.87 ± 4.03 years. Of the 164 earthquake victims, 59.8% (n = 98) were from the city of Elazığ, while 40.2% (n = 66) had relocated from other cities. The demographic and clinical characteristics, including age, sex, city of origin, whether relocation occurred due to the earthquakes, medical history, and family history of psychiatric illness, are presented in Table 1.

Table 1. Earthquake victims' sociodemographic data

		Earthquake victims Mean ±SD
Age (years, n=164)		10.87 ±4.03
Sex	Female	73 (44.5%)
	Male	91 (55.5%)
City of origin	Elazığ	98 (59.8%)
	Malatya	49 (29.9%)
	Adıyaman	7 (4.3%)
	Kahramanmaraş	6 (3.7%)
	Hatay	4 (2.4%)
Did the victims have to change their city of residence?	Yes	67 (40.9%)
	No	97 (59.1%)
Medical illness	Yes	14 (8.5%)
	No	150 (91.5%)
Psychiatric illness in the family	Yes	9 (5.5%)
	No	155 (94.5%)

n= number of cases, SD: standard deviation

Among the victims, 14 (8.5%) had an accompanying medical condition, including 3 who developed compartment syndrome after being trapped under debris. The remaining 11 patients were diagnosed with various conditions, including type 1 diabetes mellitus, epilepsy, cerebral

palsy, neutropenia, type 2 diabetes mellitus, mitochondrial myopathy, and contact dermatitis. Additionally, psychiatric illnesses such as anxiety disorder or major depressive disorder were present in the mothers or fathers of 9 (5.5%) of the victims.

Table 2. Sociodemographic Data

		n(%)
Presentation to the child psychiatry clinic	Yes	89 (54.3%)
	No	75(45.7%)
Did the victim feel the earthquake?	Yes	163(99.4%)
	No	1(0.6%)
Did the home suffer moderate /severe damage?	Yes	58(35.4%)
	No	106(64.6%)
Acute stress disorder	Yes	109(66.5%)
	No	55(33.5%)

n= number of cases

Table 3. Presentation Complaints and Psychiatric Diagnoses

	n(%)
Presentation Complaints	
Language problems	1(0.6%)
Anger, behavioral problems	7(4.3%)
Anxiety, school phobia, fear of earthquakes	51(31.1%)
Sleep problems	4(2.4%)
Attention deficit, hyperactivity	4(2.4%)
Unhappiness, missing the deceased, grief	2(1.2%)
Prescription of medication	13(7.9%)
Skin picking, obsessions, hair pulling	1(0.6%)
Multiple complaints	81(49.4%)
Psychiatric Diagnoses	
Acute Stress Disorder	17(10.4%)
Anxiety Disorder, Selective Mutism, School Phobia, Conversion	26(15.9%)
Post-Traumatic Stress Disorder	9(5.5%)
Neurodevelopmental Disorders: Chronic Tic Disorder, Language Problems, ASD, ADHD, ID, SLD, Stuttering	56(34.1%)
Grief, Major Depressive Disorder	14(8.5%)
Sleep, Behavioral Problems, Anger,	9(5.5%)
Infantile masturbation	
Multiple Diagnoses	32(19.5%)
Trichotillomania, Skin Picking, OCD	1(0.6%)

n= Number of cases, ASD: Autism Spectrum Disorder, ADHD: Attention Deficit Hyperactivity Disorder, ID: Intellectual Disability, SLD: Specific Learning Disorder, OCD: Obsessive Compulsive Disorder

The majority of the patients (84.2%) presented to the child psychiatry clinic within the first three months following the earthquake, with the remaining 15.8% presenting within nine months. However, nearly half of the patients (49.4%) did not attend any follow-up visits. A total of 30 (18.3%) patients attended the second follow-up, 17 (10.4%) attended the third, and 11 (6.7%) attended the fourth. Twenty-five (15.1%) patients attended the 5th-15th follow-up appointments.

Table 2 summarizes data regarding exposure to the earthquakes, whether the patients felt the tremors, the severity of damage to their homes, and whether they exhibited symptoms of acute stress disorder.

The most common complaints presented were anxiety, inability to attend school, and fear of future earthquakes

(31.1%). The most frequent psychiatric diagnoses observed were neurodevelopmental disorders, with a total frequency of 34.1%, including Attention Deficit Hyperactivity Disorder (ADHD) at 17.6%, Intellectual Disability at 7.3%, Autism Spectrum Disorder (ASD) at 4.3%, Specific Learning Disability at 3.6%, and Anxiety Disorders at 15.9%. The presenting complaints and psychiatric diagnoses of the victims are shown in Table 3.

Regarding pharmacological treatment, combination therapies (22.6%) were the most commonly prescribed, with selective serotonin reuptake inhibitors (SSRIs) being the most frequently used drug class (21.3%). The details of the drug therapies administered are summarized in Table 4.

Table 4. Treatments

	n(%)
Antipsychotic	27(16.5%)
SSRI (Sertraline Reuptake Inhibitor)	35(21.3%)
Methylphenidate/Atomoxetine/Clonidine/Guanfacine	18(11%)
Supportive/special education/Melatonin/language therapy	35(21.3%)
Combination	37(22.6%)
Propranolol	9(5.5%)

n= number of cases

The analysis revealed that loss among nuclear family members ($p < 0.001$), close relatives ($p < 0.001$), and friends ($p < 0.001$) was significantly higher in victims who had relocated from outside Elazığ compared to those from the city. These findings, as well as the follow-up

rates at the child psychiatry outpatient clinic, are presented in Table 5.

Finally, Clinical Global Impression (CGI) disease severity scores significantly decreased among victims who re-

ceived drug therapy ($p < 0.001$), with the majority benefiting from the treatment. The earthquake victims' pre-

and post-treatment CGI scores and improvement scores are shown in Table 6.

Table 5. Distribution of earthquake victims by province and child psychiatry outpatient clinic follow-up rates

		Elazığ (n:98)	Other Provinces(n:66)	X ²	p
		n(%)	n(%)		
Loss of nuclear family	Yes	3(3.06%)	40(60.61%)	67.511	p<0.001*
	No	95(96.9%)	26(39.40%)		
Loss of close relative	Yes	2(2.04%)	46(69.70%)	87.203	p<0.001*
	No	96(97.96%)	20(30.30%)		
Loss of friends	Yes	5(5.10%)	47(71.21%)	79.603	p<0.001*
	No	93(94.90%)	19(28.79%)		
Number of presentations to the child psychiatry clinic 1		41(41.8%)	40(60.6%)	5.558	P=0.018*
More than 1 (range 2-15)		57(58.2%)	26(39.4%)		

n= number of cases, p*= Pearson Chi-Square Test p value, p**= Fisher's exact test p value Note: Statistically significant results are shown in bold.

Table 6. Distributions of CGI pre- and post-treatment scores and CGI improvement score

Earthquake victims using drug therapy	CGI disease severity pre-treatment (n:77)	CGI disease severity post-treatment (n:77)	z	P
	Median (25%-75%)	Median (25%-75%)		
	4(4-4)	2(2-3)	-7.974	<0.001*
	CGI improvement scores	n(%)		
	1	15(9.1%)		
	2	44(26.8%)		
	3	16(9.8%)		
	4	2(1.2%)		

n=number of cases, p*= Mann-Whitney U test p value, p value Note: Statistically significant results are shown in bold.

Discussion

This study predicted that internalizing problems such as anxiety, depression, acute stress disorder, and post-traumatic stress disorder (PTSD) would be commonly observed following the Kahramanmaraş earthquakes. It was also anticipated that neurodevelopmental disorders would be particularly prevalent, as these are frequently encountered in child psychiatry outpatient settings. In the present study, the most frequent presenting complaints were anxiety, school phobia, and fear of earthquakes (31.1%). These findings are consistent with previous research indicating that anxiety and depressive symptoms are among the most common post-earthquake complaints reported in child psychiatry clinics (8,14). Most patients in our sample presented with multiple co-occurring complaints. Psychiatric diagnoses made after the earthquakes under ICD code X34 included neurodevelopmental disorders (34.1%), anxiety disorders, selective mutism, school phobia, and conversion disorder (15.9%). In routine clinical settings, neurodevelopmental disorders are among the most frequently diagnosed conditions in child psychiatry (15). Moreover, 54.3% of the earthquake victims in our sample had a documented history of prior consultation with child psychiatry clinics. Given that neurodevelopmental disorders typically emerge in early childhood and require long-term follow-up and intervention, it is expected that they would remain a common diagnosis post-disaster. The elevated rate of post-disaster presentations among children

with neurodevelopmental disorders in this study highlights the psychological vulnerability of this group and underscores their increased need for psychological support.

Early intervention and sustained psychosocial support are particularly crucial for this population in the aftermath of disasters. Previous studies have identified acute stress disorder, PTSD, depression, and anxiety as the most common psychiatric conditions following earthquakes (9,11,14,16–22). The variations across studies may be attributed to differences in methodology, particularly the use of self-report scales, which can introduce bias. For example, studies following the 1999 Gölcük earthquake utilized scales such as the PTSD and anxiety-depression inventories (4,11) many of which relied on subjective self-reporting. In the present study, the most frequently prescribed medications were combination therapies, particularly selective serotonin reuptake inhibitors (SSRIs), which align with the predominant psychiatric diagnoses observed. Notably, 7.9% of the patients presented solely for medication refills and reported no current symptoms. These individuals had previously been under psychiatric care but were unable to access medications due to collapsed homes, displacement, or other earthquake-related disruptions. Acute stress disorder was diagnosed in 66.3% of the patients, a finding that is consistent with the 70% prevalence reported in post-earthquake studies (23). While 59.8% of the patients in this study were originally from Elazığ, 40.2% had relocated there from other affected provinces. Patients from

Elazığ had significantly higher rates of both initial presentation and follow-up. CGI disease severity scores decreased significantly among the victims using drug therapy, and the majority benefited significantly from the treatment. In contrast, those who had relocated from other provinces experienced significantly higher rates of bereavement involving nuclear family members, relatives, and friends. These losses, coupled with displacement and disruption of social networks, likely contributed to greater psychosocial difficulties and reduced continuity of care. The majority of patients (84.2%) sought psychiatric care within the first three months following the earthquakes. However, only about half (50.6%) continued with follow-up visits. Although most initial consultations occurred early in the post-disaster period, follow-up care extended over the course of one year. While psychosocial support and intervention programs following disasters typically span about six months (24), the current study suggests a need for extended services. Previous research has also demonstrated that the psychological impact of major earthquakes can persist for years (6).

A major strength of this study is its original contribution in capturing the post-earthquake mental health needs of children and adolescents in a region like Elazığ, which experienced significant in-migration following the disaster. The study also provides valuable insights into psychiatric service utilization over a one-year period. However, several limitations should be acknowledged, including its retrospective and single-center design, relatively small sample size, absence of structured diagnostic interviews, and exclusion of patients with incomplete records. These factors may limit generalizability and introduce sampling bias. Future prospective, multi-center studies with long-term follow-up are needed to better understand the enduring mental health effects of the Kahramanmaraş earthquakes on children and adolescents in Türkiye.

In conclusion, given Türkiye's geographic vulnerability to earthquakes, identifying the most common psychiatric complaints and diagnoses in children and adolescents post-disaster is essential for planning timely interventions and allocating resources effectively. In addition to post-disaster response, greater emphasis should be placed on preparing children and adolescents psychologically prior to disasters and ensuring the continuity of mental health care afterward.

Ethical Approval: The study was approved by Firat University Non-interventional Clinical Research Ethical Committee (Decision no: 2024/05-05, Date: 21.03.2024).

Author Contributions:

Concept: N.S.G.Ü.

Literature Review: N.S.G.Ü.

Design : N.S.G.Ü.

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Analysis and interpretation: N.S.G.Ü.

Writing manuscript: N.S.G.Ü.

Critical revision of manuscript: N.S.G.Ü.

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Şanlıurfa Eyyübiye İlçesi Anaokullarındaki Öğrencilerde İntestinal Parazit Prevalansı

Prevalence of Intestinal Parasites in Şanlıurfa Eyyübiye Preschool Education Institutions

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Öz

Amaç: Çalışmada, Şanlıurfa Eyyübiye ilçesinde bulunan anaokulu öğrencilerinde bağırsak parazitlerinin görülme sıklığı ve parazit varlığı ile ilişkili etmenlerin incelenmesi amaçlanmıştır.

Materyal ve metod: Araştırmanın evreni, Raosoft örneklem hesaplama formülü kullanılarak %5 hata ve 0.5 olasılıkla çalışmada örneklem büyüklüğü 372 olarak hesaplanmıştır (<http://www.raosoft.com/samplesize.html>). Eyyübiye ilçesi anaokullarına devam eden 11637 öğrenciden random olarak seçilen 372 anaokulu öğrencisinden alınan gaita ve selofan bant örnekleri incelenmiştir. Parazitlerle ilişki etmenlerin belirlenebilmesi için hazırlanan anket formları değerlendirilmiştir. Dışkı örnekleri öncelikle makroskopik olarak incelenmiş olup daha sonra serum fizyolojik ve lugol ile hazırlanan dışkı preparatlarında, ışık mikroskopunda protozoon trofozoit, kistleri ve helmint yumurtaları incelenmiştir. Ayrıca örnekler formaldehit - etil asetat çöktürme yöntemi uygulandıktan sonra serum fizyolojik ve lugol ile hazırlanan preparatlarla mikroskopta incelenmiştir. Selofan bantlar *Enterobius vermicularis* ve *Taenia saginata* tespiti açısından mikroskopta incelenmiştir. İstatistiksel analiz için SPSS version 17 ve chi-squared testi kullanılmıştır. $p < 0.05$ istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Çalışılan 372 örnekten 277'sinde parazit varlığı saptanmıştır. Alınan gaita örneklerinin %23.3'ünde *Ascaris lumbricoides*, %19.3'ünde *Taenia saginata*, %47'sinde *Giardia intestinalis*, %13.7'sinde *Hymenolepis nana*, %1.8'inde *Trichuris trichiura* saptanmıştır. Toplanan selofan bant örneklerinin %23.3'ünde *Enterobius vermicularis* tespit edilmiştir. Parazit varlığı ile ilişkili etmenlerin analizi sonucunda bağırsak paraziti görülme riskini artıran faktörler arasında, anne-baba eğitim durumlarının düşük oluşu, gelir düzeyinin düşük olması, ailedeki birey sayısının fazlalığı, beslenme ve hijyen alışkanlıkları ve tırnak yeme alışkanlığı olduğu saptanmıştır.

Sonuç: Öğrencilerin ve ailelerin parazitlerin bulaş yolları hakkında bilgilendirilmesi, hem okul ortamında hem de evde sanitasyonun sağlanması parazit bulaşını azaltabilir. Özellikle dezavantajlı grupların bulunduğu riskli bölgelerde, parazitlerden korunma konusunda hem ailelere hem de çocuklara eğitimler düzenlenmesinin, çocukların hijyen konusunda bilinçlendirilmelerinin sağlanmasının ve parazit taramaları yapılmasının, parazit yoğunluğunu azaltabilecek uygulamalardan olduğu düşünülmektedir.

Anahtar Kelimeler: Parazit, Öğrenci, Prevalans, Tek sağlık

Abstract

Background: Our study aimed to examine the frequency of intestinal parasites and the factors associated with the presence of parasites in kindergarten students in Şanlıurfa Eyyübiye district.

Materials and Methods: The population of the research was calculated as 372, with a 5% error and 0.5 probability, using the Raosoft sample calculation formula (<http://www.raosoft.com/samplesize.html>). Stool and cellophane tape samples taken from 372 kindergarten students randomly selected from 11637 students attending kindergartens in Eyyübiye district were examined. Survey forms prepared to determine the factors associated with parasites were evaluated. Stool samples were first examined macroscopically, and then, after applying the formaldehyde-ethyl acetate precipitation method, protozoan cysts and helminth eggs were examined under the microscope with preparations prepared with physiological saline and Lugol. Cellophane tapes were examined under microscope for the detection of *Enterobius vermicularis* and *Taenia saginata*. Statistical data analysis was performed using SPSS version 17, and chi-squared (χ^2) tests. p -value < 0.05 was considered statistically significant.

Results: The presence of parasites was detected in 277 of the 372 samples studied. *Ascaris lumbricoides* was detected in 23.3% of the stool samples, *Taenia saginata* in 19.3%, *Giardia intestinalis* in 47%, *Hymenolepis nana* in 13.7%, and *Trichuris trichiura* in 1.8%. *Enterobius vermicularis* was detected in 23.3% of the collected cellophane tape samples. As a result of the analysis of the factors associated with the presence of parasites, it was determined that the factors that increase the risk of intestinal parasites are the low education level of the parents, low income level, high number of family members, nutrition and hygiene habits, and nail biting habits.

Conclusions: Informing students and families about the transmission of parasites, ensuring sanitation both in the school environment and at home can reduce parasite transmission. Especially in risky areas where disadvantaged groups are located, it is thought that organizing training for both families and children on protection against parasites, raising children's awareness about hygiene and performing parasite screening are among the practices that can reduce the density of parasites.

Keywords: Parasites, Students, Prevalence, One health

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Giriş

İntestinal parazit enfeksiyonları neredeyse tüm dünyaya dağılmış olup, birçok bölgede yüksek prevalans oranlarında bulunabilmektedir. Çoğunlukla yeterli su ve sanitasyon olanaklarının bulunmadığı gelişmekte olan ülkeleri etkileyen önemli bir halk sağlığı sorunudur. Dünyada yaklaşık 3,5 milyar insanın intestinal parazitlerden etkilendiği, 450 milyon insanda enfeksiyonların semptomatik seyrettiği ve yıllık yaklaşık 200 bin insanın öldüğü bildirilmektedir (1,2).

Türkiye’de rapor edilen intestinal parazit oranlarında farklı bölgelerde beslenme ve kişisel hijyen alışkanlıklarına, sosyoekonomik duruma bağlı olarak farklılık görülebilmektedir. Parazit bulaşı sıklıkla fekal oral yolla enfekte yiyecekler ve içeceklerin alınması ile meydana gelirken düşük sosyoekonomik koşullar ve kişisel hijyenin kötü olmasının toplumda parazit enfeksiyonlarının yayılmasında önemli epidemiyolojik faktörler olduğu düşünülmektedir (3,4).

İntestinal parazit enfeksiyonları çocuklarda ciddi komplikasyonlara neden olabilir. Kronik etkileriyle ortaya çıkan anemi, çeşitli vitamin eksiklikleri, yetersiz beslenme, büyüme-gelişme geriliği gibi fiziksel ve zihinsel sorunlar oluşturabilir (5,6).

Farklı coğrafik bölgelerde intestinal parazitlerin prevalansı üzerine yapılan çalışmalar, kontrol ve korunma politikalarının belirlenmesi açısından önemlidir. Çalışmada, Şanlıurfa Eyyübiye ilçesinde bulunan anaokulu öğrencilerinde bağırsak parazitlerinin görülme sıklığı ve parazit varlığı ile ilişkili etmenler olarak, cinsiyet, anne-baba eğitim düzeyi, beslenme alışkanlıkları, sosyo-ekonomik düzey, tuvalet alışkanlıkları, evde birlikte yaşayan kişi sayısı, parazit hastalıklarında görülebilen belirtiler ve kişisel hijyen alışkanlıkları gibi bilgilerin incelenmesi amaçlanmıştır.

Materyal ve Metod

Çalışmaya başlamadan önce, Etik Kurul izni 5.08.2024 tarih ve HRÜ/24.11.47 sayılı etik kurul kararı ile Harran Üniversitesi Klinik Araştırmalar Etik Kurulunca onaylanmıştır. Şanlıurfa İl Milli Eğitim Müdürlüğü’nden çalışma izni (Çalışma izin numarası: MEB.TT.2024.001067/27.08.2024) alınmıştır. Araştırmanın evreni, Raosoft örneklem hesaplama formülü kullanılarak %5 hata ve 0.5 olasılıkla çalışmada örneklem büyüklüğü 372 olarak hesaplanmıştır (<http://www.raosoft.com/samplesize.html>). Eyyübiye ilçesi anaokullarına devam eden 11637 öğrenciden random olarak seçilen 372 anaokulu öğrencisinden alınan örnekler incelenmiştir.

Okul ziyaretlerinde öğrencilerle bir araya gelinip bağırsak parazitleri ve bulaş yolları hakkında bilgi verilmiştir. Parazitlerle ilişkili etmenlerin belirlenebilmesi için hazırlanan anket formları, çalışmanın içeriği ile ilgili bilgilendirmenin yapıldığı Veli onam formları, gaita kapları ve selofan bantlar verilip ilgili bilgilendirmeler yapılmıştır.

Ertesi sabah gaita ve selofan bant örnekleri toplanarak Mikrobiyoloji laboratuvarında incelemeye başlanmıştır. Dışkı örnekleri öncelikle makroskopik olarak incelenmiş daha sonra protozoonlar ve helmint yumurtalarının korunması için %10 formaldehit içeren tüplere alınmıştır. Formaldehit- etil asetat çöktürme yöntemi uygulandıktan sonra, protozoon kistleri ve helmint yumurtaları, serum fizyolojik ve lugol ile hazırlanan preparatlarla mikroskopta incelenmiştir. Selofan bantlar *Enterobius vermicularis* ve *Taenia saginata* tespiti açısından mikroskopta incelenmiştir.

İstatistiksel analiz için SPSS 17 (SPSS Inc., Chicago, IL, USA) paket programı ki-kare (χ^2) testi kullanılmıştır. Kategorik değerler için frekans (%) analizi yapılmıştır. $p < 0.05$ değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

Çalışmaya alınan gaita örneklerinin %23.3’ünde *Ascaris lumbricoides*, %19.3’ünde *Taenia saginata*, %47’sinde *Giardia intestinalis*, %13.7’sinde *Hymenolepis nana*, %1.8’inde *Trichuris trichiura* saptanmıştır. Toplanan selofan bant örneklerinin %23.3’ünde *Enterobius vermicularis* tespit edilmiştir (Tablo 1). Çalışılan örneklerin %37’sinde tek parazit, % 21.2’sinde ikili parazit, %14.5’inde üçlü parazit varlığı saptanmıştır (Tablo 2). Çalışmaya katılan öğrencilerin %56.8’i kadın, %43.1’i erkektir. Sosyodemografik özellikler incelendiğinde annelerin %88.2’sinin lise öncesi eğitime sahip olduğu, %11.7’sinin lise ve sonrası eğitime sahip olduğu görülmüştür. Babaların ise %75’i lise öncesi eğitim, % 25’i lise ve sonrası eğitime sahiptir. Meslek durumlarına bakıldığında annelerin tamamının ev hanımı, babaların %58 ’inin işsiz, %27’sinin çiftçi ve tarım işçisi olduğu belirlenmiştir. Ailelerin %54.9’unun aylık gelirinin 5 bin tl den az olduğu ve %86.2’sinin gelirinin ihtiyaçlarını karşılamaya yetmediğini belirttiği saptanmıştır. Ankete katılanların %82.3’ü bağırsak parazitleri konusunda bilgileri olmadığını belirtmişlerdir. Parazitolojik enfeksiyonlarda görülebilecek belirtilerden %82.3’ünde anemi, %31.3’ünde iştahsızlık, %27.4’ünde ağızdan salya akması, %23.52’sinde karın ağrısı, %21.5’inde anüste kaşıntı, %19.6’sında büyüme gelişme geriliği olduğu görülmüştür. Bölgemizde sıkça tüketilen çiğköftenin yeme sıklığı da sorgulanmış ve %60.7’sinin ayda 1-2 kez, %33.3’ünün ayda 3-4 kez çiğköfte tükettiği belirlenmiştir.

Parazit varlığı tespit edilen öğrencilerin %84’ünün evde 5 ve daha fazla sayıda kişiyle yaşadıkları tespit edilmiştir.

Analiz sonucunda bağırsak paraziti görülme riskini artıran faktörler arasında anne-baba eğitim durumlarının düşük oluşu, gelir düzeyinin düşük olması, ailedeki birey sayısının fazlalığı, beslenme ve hijyen alışkanlıkları ve tırnak yeme alışkanlığı olduğu saptanmıştır.

Sosyodemografik özelliklerin bazıları ile parazit varlığı arasındaki ilişki Tablo 3’te gösterilmiştir.

Tablo 1. Çalışmada saptanan parazit türleri ve oranları

Parazit Türü	%	Pozitif örnek sayısı	Toplam örnek sayısı
<i>Giardia intestinalis</i>	47,0	175	372
<i>Ascaris lumbricoides</i>	23,3	87	372
<i>Enterobius vermicularis</i>	23,3	87	372
<i>Taenia saginata</i>	19,3	72	372
<i>Hymenolepis nana</i>	13,7	51	372
<i>Trichuris trichiura</i>	1,8	7	372

Tablo 2. Çoklu parazit saptanan örneklerin yüzdesi

Parazit birlikteliği	Örnek sayısı	Yüzde oranı
2'li parazit	79 örnek	% 21,2
3'lü parazit	58 örnek	% 15,5
Tek parazit	138 örnek	% 37

Tartışma

Bağırsak parazitlerinin sıklığı, yapılan çalışmalarda bölge-lerin coğrafik özelliklerine, sosyoekonomik ve sosyokültürel alışkanlıklara göre farklılık göstermektedir. Okul öncesi ve ilköğretim çağındaki öğrencilerin beslenme ve kişisel hijyen alışkanlıkları parazit bulaşının engellenmesi açısından çok önemlidir. Bu açıdan toplu yaşanan alanlarda hijyen alışkanlıklarının çocuklara kazandırılması gerekmektedir. Türkiye’de farklı illerde ilköğretim çağındaki çocuklarda yapılan çalışmalarda farklı parazit türleri ve sıklığı bildirilmektedir. Kocaeli’de %39, Denizli’de %10.2, Eskişehir’de %32.3, Sivas’ta %71.2, Hakkari’de %57.8, Ordu’da %57, Van’da %64.4, Mardin’de %36.9, Malatya’da %22.5 olarak ilköğretim çağındaki öğrencilerde saptanan parazit sıklığı bildirilmiştir (7-14).

Şanlıurfa’da 2001-2005 yılları arasında yapılan çalışma sonuçlarına göre, öğrencilerde bağırsak parazitleri sıklığının gecekondü bölgesinde %80, apartman bölgesinde %53 olduğu belirtilmiştir. Bu parazitler arasında *Ascaris lumbricoides*’in %45, *Trichuris trichiura*’nın %15-20, *Hymenolepis nana*’nın %10-15 ve *Taenia*’nın %5 oranında görüldüğü saptanmıştır. Öğrencilere parazit ilacı dağıtılmasından sonra yapılan kontrol çalışmasında ise bağırsak parazitleri sıklığının gecekondü bölgesinde %35, apartman bölgesinde ise %6.4 olarak saptandığı bildirilmiştir (15).

Şanlıurfa’da 0-72 ay yaş aralığında çocuklarda yapılan bir çalışmada ise, çocukların %58’inde bir veya birden fazla bağırsak paraziti saptandığı bildirilmiştir. Parazit enfeksiyonu saptanan çocukların %55.2’sinde tek parazit saptanırken, %44.8’inde birden fazla bağırsak paraziti varlığı rapor edilmiştir (16).

Şanlıurfa’da tarım işçisi 6-59 ay yaş aralığındaki çocuklarda yapılan bir çalışmada ise %55.4 oranında bağırsak paraziti saptandığı bildirilmiştir. Çalışmada en yüksek orana sahip parazit *Giardia intestinalis* (%37.2) olarak saptanmıştır (17). Benzer şekilde Güneydoğu Anadolu bölgesi illerinde tarım işçisi 6 yaş altındaki çocuklarda yapılan diğer bir çalışmada ise %44.6 oranında parazit saptandığı belirtilmiştir (18).

Afrika’da yapılan bir çalışmada, ilköğretim çağındaki öğrencilerde %32.2, Etiyopya’da %55.8, İran’da %42.5, Pakistan’da %82 olarak parazit prevalansı rapor edilmiştir (6,19-21).

Sunulan çalışmada en yüksek sayıda parazit %47 oranı ile *Giardia intestinalis* olarak saptanmıştır. Güneydoğu Anadolu (%47.97), Şanlıurfa (%42.53), Kocaeli (%15), Hakkari (14.9), Denizli’de (31.6) ve Elazığ’da (%6.6) yapılan çalışmalarda da *Giardia intestinalis* en yüksek oranda bulunmuştur (6-8,18,16,11,22). *Giardia intestinalis* saptanma oranları çeşitli çalışmalarda sırasıyla %13.9, %14.8, %6, %6.3 olarak bildirilmiştir (5,6,9,20).

İkinci sırada %23.3 oranı ile *Enterobius vermicularis* ve *Ascaris lumbricoides* parazitleri saptanmıştır. *Ascaris lumbricoides* saptanma oranları ise %39, %37.8, %2, %40.9, %4.3, %18.3 gibi değişen oranlarda yapılan çalışmalarda bildirilmiştir (5,6,9-11,16). Çalışmada meyve sebze tüketimi ile ilgili sorulan sorulara verilen cevaplarda %80 oranında meyve sebzelerin sudan geçirilerek tüketildiği belirtilmiştir. Yalnızca sudan geçirilerek sebze meyvelerin tüketilmesinin parazit sayısındaki artışa neden olabileceği düşünülmektedir.

Enterobius vermicularis saptanma oranları, % 6.4, %10, %29.6, %3.2, %31, %27.5, %37.84, %2.1, %6.8 olarak çeşitli çalışmalarda bildirilmiştir (6-10,16,18,22,23). Parazitiz belirlenileri ile sorulan sorulara ağızdan salya akması ve anüste kaşıntı olması cevabını veren öğrencilerin %47.3’ünde *Enterobius vermicularis* pozitif olarak saptanmıştır. *Enterobius vermicularis* saptanan örneklerin %75’inde bu belirtilerin bildirildiği görülmüştür.

Çalışmada incelenen örneklerde *Taenia saginata* parazit yüzdesi %19.3 olarak saptanmıştır. Ülkemizde yapılan çalışmaların birçoğunda *Taenia saginata* ya hiç saptanmamış ya da düşük oranlarda saptanmıştır (7-11). Şanlıurfa’da yapılan bir çalışmada *Taenia saginata*’nın varlığı %11.6 olarak bildirilmiştir (17). Güneydoğu Anadolu bölgesinde yapılan diğer bir çalışmada ise *Taenia saginata* %27.03 oranında saptanmıştır (18).

Tablo 3. Sosyodemografik özellikler ve parazit görülme sıklığı arasındaki ilişki

Demografik özellikler	Toplam	Parazit saptanan		Parazit saptanmayan		P değeri
	n	n	%	n	%	
Cinsiyet						
Kadın	211	160	75	51	25	χ^2 :0.06
Erkek	161	117	72	44	28	p:0.79
Baba eğitim durumu						
Öğrenim görmeyen- ilköğretim	277	226	81.5	51	19.5	χ^2 :14.61
Lise	58	36	71	22	29	p: 0.023
Lisans ve üstü	44	15	34	29	66	
Baba meslek						
İşsiz-Serbest	219	175	80	44	20	χ^2 :4.51
Memur	30	15	50	15	50	p: 0.20
Tarım işçisi-Çiftçi	102	80	78.6	22	21.4	
Emekli	21	7	33.3	14	66.6	
Anne eğitim durumu						
Öğrenim görmeyen- ilköğretim	328	262	80	66	20	χ^2 :9.58
Lise	22	15	66.7	7	33.3	p: 0.008
Lisans ve üstü	22	-	-	22	100	
Evde yaşayan kişi sayısı						
1-4	51	21	41	30	59	χ^2 :5.02
5-7	248	189	76.5	58	23.5	p: 0.008
8 den fazla	73	66	90	7	10	
Bağırsak parazitleri konusunda bilgi						
Evet	66	44	66.6	22	33.3	χ^2 :0.35
Hayır	306	233	76.2	73	23.8	p: 0.5
Parazitoz belirtileri						
Kansızlık var	87	58	66.7	29	33.3	χ^2 :0.50
Kansızlık yok	285	219	76.9	66	23.1	p: 0.4
Büyüme gelişme geriliği var	73	66	90	7	10	χ^2 :1.57
Büyüme gelişme geriliği yok	299	211	70.5	88	29.4	p: 0.2
Anüste kaşıntı var	73	73	100	-	-	χ^2 :4.25
Anüste kaşıntı yok	299	204	68.2	95	31.7	p: 0.03
Karın ağrısı var	80	58	72.7	22	27.3	χ^2 :0.2
Karın ağrısı yok	292	219	75	73	25	p: 0.8
İştahsızlık var	110	73	66.3	37	33.6	χ^2 :0.68
İştahsızlık yok	262	204	77.8	58	22.2	p: 0.4
İshal var	29	22	76	7	24	χ^2 :0.01
İshal yok	343	255	74.3	88	25.6	p: 0.9
Ağızdan salya akması var	87	73	83.3	14	16.7	χ^2 :0.64
Ağızdan salya akması yok	285	204	71.5	81	28.4	p: 0.4
Kabızlık var	36	29	80.5	7	19.4	χ^2 :0.08
Kabızlık yok	336	248	78.9	88	26.1	p: 0.7
Aylık çiğ köfte tüketim sayısı						
1-2	226	160	71	66	29	χ^2 :23,059
3-4	124	95	76.6	29	23.3	p: 0.00
5 den fazla	22	22	100	-	-	
Meyve ve sebzelerin tüketimi						
Sirkeli suda bekleterek	30	15	50	15	50	χ^2 :1.48
Sudan geçirerek	292	226	77.5	66	22.5	p: 0.4
Suda bekleterek	50	36	72	14	28	
Ailede çocukların yatak durumları?						
Çocuklar aynı yatakta yatar	182	153	84	29	16	χ^2 :2.32
Çocuklar ayrı ayrı yatar	190	124	65.2	66	34.7	p: 0.12
Hayvan besleme durumu						
Evet	36	36	100	-	-	χ^2 :1.89
Hayır	336	240	71.4	96	28.5	p: 0.16
Kullanılan içme suyu						
Şebeke suyu	329	248	75.3	81	24.6	χ^2 :0.92
Kuyu suyu	7	7	100	-	-	p: 0.63
Hazır su	36	22	60	14	40	
Tırnak yeme alışkanlığı						
Var	146	139	95	7	5	χ^2 : 7.27
Yok	226	138	61	88	38.9	: 0.007

Bölgemizde çiğköfte tüketiminin fazla olması *Taenia saginata* sayısının yüksekliğinin sebebi olabilir. Öğrencilere sorulan sorulara verilen cevaplara göre, aylık çiğköfte tüketim sayısı 1-2 olan öğrencilerin %71'inde, 3-4 olan öğrencilerin %76.6'sında, aylık tüketilen çiğköfte sayısı 5 ten fazla olan öğrencilerin tamamında *Taenia saginata* parazit varlığı belirlenmiştir. Çiğköfte tüketim sayısına göre parazit oranındaki artış istatistiksel olarak anlamlı bulunmuştur ($p<0.05$).

Çalışmada %13.7 oranında *Hymenolepis nana*, %1.8 oranında *Trichuris trichiura* parazit varlığı saptanmıştır. Çeşitli çalışmalarda *Hymenolepis nana* oranları %5, %8.6, %0.2, %3.2, %3.5, %5.7, %1.9 (5-8,11,16,23) olarak *Trichuris trichiura* ise, %60.9, %10.6, %4.9 oranlarında rapor edilmiştir (5,6,10).

Çalışmada % 21.2 oranında 2'li parazit, %15.5 oranında 3'lü parazit varlığı saptanmıştır.

Tırnak yeme alışkanlığı bulunduğu belirtilen öğrencilerin %88.2'sinde parazit varlığı tespit edilmiştir. Tırnak yeme alışkanlığı ile parazit varlığı arasındaki ilişki istatistiksel olarak anlamlı bulunmuştur ($p<0.05$). El hijyeninin sağlanmaması ve elin sürekli ağızda tutulması, kirli eller yoluyla parazit bulaşını kolaylaştırmaktadır.

Çalışmada anne ve baba eğitim düzeyi arttıkça, çocuklarda parazit enfeksiyonunun azaldığı saptanmıştır ($p<0.05$). Anne-baba eğitim düzeyinin artmasıyla, beslenme, yaşanan evin durumu, gelir durumunun artması, kişisel hijyen sağlanması konularında daha uygun ortam oluşturulması sağlanmış olabilir. Ayrıca çocukların eğitimi konusunda anne-babalarda farkındalığın daha yüksek olması beklenebilir.

Parazit saptanan öğrencilerin %84'ünün evde 5 ve daha fazla sayıda kişiyle yaşadıkları tespit edilmiştir. Evde yaşayan kişi sayısı arttıkça kişiye özel eşya kullanımının azalması, çocuğa yeterli ilginin gösterilememesi, tuvalet-banyo gibi ortamların daha sıklıkla kullanılmasının parazit enfeksiyonlarının bulaşına zemin hazırlamış olabileceği düşünülmektedir.

Parazit varlığı ile ilgili saptadığımız faktörler ışığında, anne-baba eğitim düzeyi, gelir durumu, kişisel hijyen alışkanlıkları, beslenme tarzı gibi konuların önemli olduğunu söyleyebiliriz. Öğrencilerin ve ailelerin parazitlerin bulaş yolları hakkında bilgilendirilmesi, hem okul ortamında hem de evde sanitasyonun sağlanması parazit bulaşını azaltabilir. Özellikle dezavantajlı grupların bulunduğu riskli bölgelerde, parazitlerden korunma konusunda hem ailelere hem de çocuklara eğitimler düzenlenmesinin, çocukların hijyen konusunda bilinçlendirilmelerinin sağlanmasının ve parazit taramaları yapılmasının, parazit yoğunluğunu azaltabilecek uygulamalardan olduğu düşünülmektedir.

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Relationship Between Coronary Collateral Circulation and The Presence of Bendopnea in Patients with Ischemic Low Ejection Fraction Heart Failure

İskemik Düşük Ejeksiyon Fraksiyonlu Kalp Yetmezliği Olan Hastalarda Koroner Kollateral Dolaşım ile Bendopne Varlığı Arasındaki İlişki

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Abstract

Background: Coronary collateral circulation(CCC) is a physiological protective mechanism that develops as a result of critical coronary artery stenosis and ischemia. Bendopnea, shortness of breath upon bending forward, is linked to poor cardiac index, increased pulmonary capillary wedge pressure, and coronary artery disease. This study aims to investigate the relationship between coronary collateral circulation and the presence of bendopnea in patients with ischemic low ejection fraction heart failure.

Materials and Methods: The cross-sectional study screened 1024 patients diagnosed with heart failure with low ejection fraction after coronary angiography between January 2023 and January 2024, and 259 met the inclusion criteria. Inclusion criteria for the study were defined as having stable coronary artery disease and low ejection fraction heart failure (LVEF<40%) Patients were categorized into bendopnea+ and bendopnea- groups. Rentrop classification was used as a basis for the evaluation of CCC

Results: There were 158 patients (mean age: 74.1±12.9 years, % 66.4 male) in the bendopnea+ group, while there were 101 patients (mean age: 67.2±14.2 years, %70.2 male) in the bendopnea- group. Bendopnea+ patients were older and had a higher number of NYHA class 3-4 individuals(p<0.001). NT-proBNP(p=0.001) and uric acid levels(p=0.001) were significantly higher in the bendopnea+ group. The Gensini score(p=0.001) and poor collateral circulation(p=0.001) were significantly higher in the bendopnea+ group. Systolic pulmonary artery pressure (sPAP) was notably higher in the bendopnea+ group (p=0.001). Regression analyses identified age(OR: 1.355 %95 CI:1.212-1.517 p=0.001), NT-proBNP(OR: 1.252 %95 CI:1.195-1.412 p=0.001), NYHA class 3-4(OR: 1.245 %95 CI:1.195-1.412 p=0.001), Gensini score(OR: 1.328 %95 CI:1.213-1.515 p=0.001), and poor collateral circulation(OR: 1.318 %95 CI:1.162-1.441 p=0.001) as independent risk factors for bendopnea. **Conclusions:** The study concludes that insufficient coronary collateral circulation is an independent risk factor for bendopnea in ischemic heart failure patients.

Keywords: Bendopnea, Ischemic Heart Failure, Coronary Collateral Circulation

Öz

Amaç: Koroner kollateral dolaşım (KKK), kritik koroner arter stenozu ve iskemisi sonucu gelişen fizyolojik bir koruyucu mekanizmadır. Öne eğilince nefes darlığı olan bendopne, kötü kardiyak indeks, artmış pulmoner kapiller kama basıncı ve koroner arter hastalığı ile bağlantılıdır. Bu çalışma iskemik düşük ejeksiyon fraksiyonlu kalp yetmezliği olan hastalarda KKK ve bendopne varlığı arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Materyal ve Metod: Kesitsel çalışmaya Ocak 2023 ile Ocak 2024 arasında koroner anjiyografi sonrası düşük ejeksiyon fraksiyonlu kalp yetersizliği tanısı konulan 1024 hasta tarandı ve 259'u dahil etme kriterlerini karşıladı. Çalışmaya dahil edilme kriterleri stabil koroner arter hastalığı ve düşük ejeksiyon fraksiyonlu kalp yetmezliği (LVEF<40%) olması olarak tanımlandı. Hastalar bendopne+ ve bendopne- gruplarına ayrıldı. KKK değerlendirmesi için Rentrop sınıflandırması kullanıldı

Bulgular: Bendopne+ grubunda 158 hasta (ortalama yaş: 74,1±12,9 yıl, % 66.4 erkek) varken, bendopne- grubunda 101 hasta (ortalama yaş: 67,2±14,2 yıl, %70.2 erkek) vardı. Bendopne+ hastalar daha yaşlı ve daha fazla sayıda NYHA sınıf 3-4 birey vardı (p<0.001). NT-proBNP (p=0.001) ve ürik asit(p=0.001) düzeyleri bendopne+ grubunda anlamlı olarak daha yüksekti. Gensini skoru(p=0.001) ve zayıf kollateral dolaşım(p=0.001) bendopne+ grubunda anlamlı olarak daha yüksekti. Sistolik pulmoner arter basıncı (sPAP) bendopne+ grubunda belirgin olarak daha yüksekti (p=0.001). Regresyon analizleri, bendopne için bağımsız risk faktörleri olarak yaş(OR: 1.355 %95 CI:1.212-1.517 p=0.001), NT-proBNP(OR: 1.252 %95 CI:1.195-1.412 p=0.001), NYHA sınıf 3-4 (OR: 1.245 %95 CI:1.195-1.412 p=0.001), Gensini skoru(OR: 1.328 %95 CI:1.213-1.515 p=0.001), ve zayıf kollateral dolaşımı(OR: 1.318 %95 CI:1.162-1.441 p=0.001) saptadı.

Sonuç: Çalışmada, yetersiz koroner kollateral dolaşımın iskemik kalp yetmezliği hastalarında bendopne için bağımsız bir risk faktörü olduğu sonucuna varılmıştır.

Anahtar kelimeler: Bendopne, İskemik Kalp Yetmezliği, Koroner Kollateral Dolaşım

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Introduction

Coronary collateral circulation (CCC) is a physiological protective mechanism that develops as a result of critical coronary artery stenosis and ischemia. Well-developed coronary collateral circulation reduces myocardial ischemia and anginal symptoms and preserves cardiac functions (1). In stable and acute coronary artery disease (CAD) patients, it leads to a reduction in the infarct area, a decrease in the development of ventricular aneurysms, preservation of ventricular functions, and a decrease in mortality and morbidity in both the short and long term (2). Numerous studies have found a direct proportional relationship between good collateral circulation and left ventricular functions in heart failure patients (3). Additionally, studies have shown that the presence of collateral circulation has a significant impact on left ventricular reverse remodeling after percutaneous coronary intervention and coronary artery bypass graft surgery (4).

As a result of heart failure, numerous symptoms arise depending on the type and severity of the disease. Shortness of breath and its various types (orthopnea, paroxysmal nocturnal dyspnea, exercise dyspnea) are the main symptoms of acute heart failure (5). Bendopnea, also known as flexi-dyspnea, has recently been described as the development of shortness of breath within 30 seconds when leaning forward in patients with systolic and decompensated heart failure. Although its exact etiology is not known, it is thought to occur due to increased ventricular pressure resulting from increased abdominal and intrathoracic pressure when leaning forward (6). Additionally, it has been closely associated with poor cardiac index, increased pulmonary capillary wedge pressure, right heart pressure, and pulmonary artery pressure. Studies have shown that the presence of bendopnea in patients with systolic heart failure is associated with a low quality of life and a poor prognostic indicator in the long term (7). Furthermore, it has been closely associated with many cardiovascular diseases, such as the prevalence of coronary artery disease and surgical outcomes. However, there is no study in the literature showing the relationship between coronary collateral circulation and ischemic low ejection fraction heart failure patients (8). The aim of this study is to investigate the relationship between coronary collateral circulation and the presence of bendopnea in patients with ischemic low ejection fraction heart failure.

Materials and Methods

This study was designed as a cross-sectional study. After obtaining local ethics committee approval, 1024 patients diagnosed with ischemic low ejection fraction heart failure after coronary angiography between January 2023 and January 2024 were screened. Patients who underwent coronary angiography due to stable coronary artery disease were studied. Inclusion criteria for the study

were defined as having stable coronary artery disease and low ejection fraction heart failure (LVEF<40%)(9). Patients who were diagnosed with stable CAD according to the criteria recommended by the European Society of Cardiology (21) and who underwent coronary angiography and were determined to have coronary stenosis of 95% or more in at least one major coronary vessel were included in the study (22). All patients included in the study had angina or angina-equivalent symptoms, and coronary angiography indications were established with positive non-invasive tests (exercise stress test, stress echocardiography, and myocardial perfusion scintigraphy). The study was conducted in accordance with the Declaration of Helsinki.

Patients under the age of 18, those receiving steroid treatment, those with chronic kidney or liver failure, those with systemic inflammatory disease, those with a decompensation condition, those with acute coronary syndrome, those with severe valvular disease, those who have had coronary artery bypass surgery, those who have previously undergone percutaneous coronary intervention for any reason and patients with abnormal serum electrolyte values were not included in the study. Any patients who could not bend forward because of any muscular or joint diseases or any other problems were excluded. At the end of the exclusion criteria, 259 patients were included in the study. (Figure 1: The study flowchart).

To assess the presence of bendopnea, patients were asked if they experienced shortness of breath while bending forward in a sitting position. If patients developed headache, dizziness, or syncope, they were instructed to stop bending and were given appropriate treatment. These patients were excluded from the study. The presence or absence of bendopnea and the onset time were recorded.

All patients were thoroughly evaluated for hyperlipidemia, diabetes mellitus, smoking, asthma, and Chronic Obstructive Pulmonary Disease (COPD). All medications used by the patients were thoroughly reviewed. Hematological, biochemical and serological values were obtained and recorded from peripheral blood samples taken after a 12-hour fast. Chronic kidney failure was defined as having a glomerular filtration rate of less than 60 for more than three months. For diabetes mellitus, patients taking antidiabetic medication, having fasting blood glucose levels above 126 mg/dL in at least two measurements, or an HbA1c>6.5 were considered. Hyperlipidemia was defined as having a low-density lipoprotein (LDL) level >160 mg/dL or taking statin medication. The diagnostic criterion for Chronic Obstructive Pulmonary Disease was defined as having an FEV1(Forced Expiratory Volume)/FVC (Forced Vital Capacity) < 70% or FEV1< 70% after inhaled bronchodilator administration.

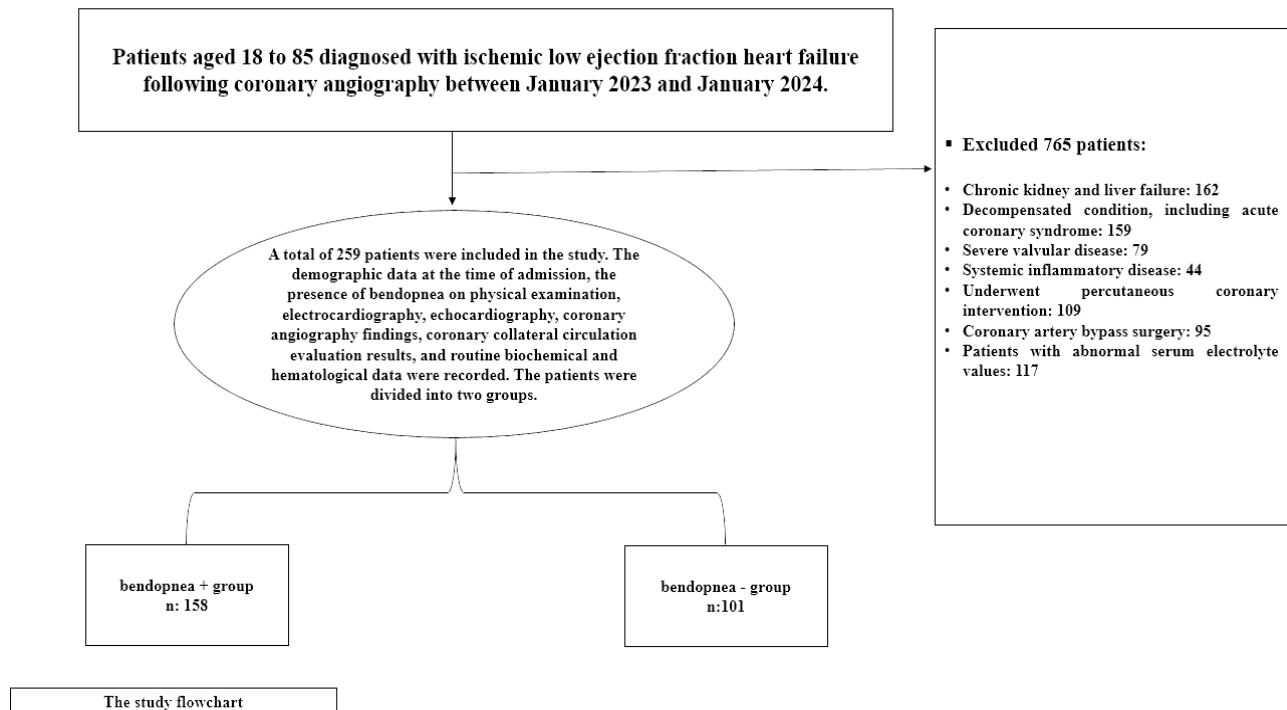


Figure 1. The study flowchart

Evaluation of Laboratory Findings

Complete blood count, renal function tests, lipid parameters, serum glucose, uric acid, blood urea nitrogen (BUN), high-sensitivity C-reactive protein (CRP) levels were recorded, and glomerular filtration rate and creatinine clearance (CrCl) were calculated.

Echocardiographic Evaluation

The echocardiographic examination of all patients included in the study was performed using an iE33 cardiac ultrasound system (Philips Healthcare) and a 2.5 to 5 MHz probe system. Ejection fraction was measured using the modified Simpson method. HFrEF occurs when the left ventricular ejection fraction (LVEF) is 40% or less(9).

Evaluation of Coronary Angiography

Coronary angiography was performed using the Allura Xper FD 10 (Philips Healthcare). Angiography was performed by puncture of the femoral artery with 6F Judkins standard right and left catheters. Iodixanol was used as the radiological contrast agent. At least four projections for the left coronary system and at least two projections for the right coronary system were recorded in digital and analog formats. Two independent cardiologists examined the coronary angiography results without knowing patient characteristics. The culprit vessel (stenosis of $\geq 95\%$) areas were divided and recorded according to three groups: right coronary artery, left descending artery, and circumflex coronary artery. Rentrop classification was used as a basis for the evaluation of CCC. Rentrop grade 0 is accepted as the absence of collateral flow, grade 1 is defined as the presence

of side branches without an occluded main coronary artery, grade 2 is defined as partial visibility of an occluded main coronary artery and grade 3 is defined as complete visibility of an occluded main coronary artery. Consistent with previous studies, Rentrop grades 0 and 1 were accepted as poor collateral flow, whereas Rentrop grades 2 and 3 were accepted as good collateral flow(10).

Evaluation of CAD Severity

Gensini scoring was used to grade the extent and severity of atherosclerosis in the coronary arteries for all patients. According to the degree of angiographic stenosis, 1 point was given for 1% to 25% stenosis, 2 points for 26% to 50% stenosis, 4 points for 51% to 75% stenosis, 8 points for 76% to 90% stenosis, 16 points for 91% to 99% stenosis, and 32 points for 100% total occlusions. The Gensini score was calculated by multiplying these scores by the coefficient defined for each segment of the coronary arteries and summing the results. The segments and their coefficients were as follows: 5 for the left main coronary artery, 2.5 for the proximal segment of the left coronary artery, 1.5 for the mid segment, 1 for the apical segment, 1 for diagonal 1, and 0.5 for diagonal 2; 2.5 for the proximal segment of the circumflex coronary artery, 1 for the distal segment, 1 for the obtuse marginal, 1 for the posterior descending artery if left dominant, 0.5 for the posterolateral artery, and 1 for the right coronary artery (proximal, mid, and distal segments), as well as the posterior descending artery (9).

Statistical Analysis

SPSS Statistics for Windows (version 25.0; IBM) and Amos (version 24.0; IBM) statistical packages were used to analyze the data. Descriptive statistics (mean [SD], median [IQR], No. [%]) for categorical and continuous variables were reported. Homogeneity of variances, one of the assumptions of parametric tests, was tested using the Levene test. The normality assumption was tested using the Shapiro–Wilk test. To assess differences between the two groups, the independent t-test was used when the assumptions of the parametric tests were met, whereas the Mann-Whitney U test was used when they were not. A p-value of < .05 was considered statistically significant. Univariate analysis was used to calculate the association of different variables with CCC. Variables for which the unadjusted p-value in the logistic regression model was < .05 were identified as potential risk markers and included in the full multivariate model.

Results

A total of 259 patients were included in this study. Patients were divided into two groups: bendopnea+ and bendopnea-. There were 158 patients (mean age: 74.1±12.9 years, % 66.4 male) in the bendopnea+ group, while there were 101 patients (mean age: years: 67.2±14.2, %70.2 male) in the bendopnea- group. No gender difference was observed between the groups, but the bendopnea+ group

was statistically older (p=0.001). In terms of symptoms, the number of New York Heart Association (NYHA) class 3-4 patients was statistically higher in the bendopnea+ group (p=0.001). No differences were found between the groups when comparing patients' medical histories and treatments. The basic characteristics of the patients are shown in Table 1.

When the laboratory values of the patients were examined, no differences were observed between the groups in terms of hemoglobin, white blood cells, and renal function values. The N-terminal pro brain natriuretic peptide (NT-proBNP) (p=0.001) and Uric Acid levels (p=0.001) was statistically higher in the bendopnea+ group (Table 2).

No differences were found when comparing echocardiographic features. When comparing angiographic features, the Gensini score and poor collateral circulation were statistically higher in the bendopnea+ group (p=0.001). Additionally, in the bendopnea+ group, Systolic Pulmonary Artery Pressure (sPAP) was statistically significantly higher compared to the bendopnea- group (p= 0.001) (Table 3).

In univariate and multivariate regression analyses, age (OR: 1.355 %95 CI:1.212-1.517 p=0.001), NT-proBNP (OR: 1.252 %95 CI:1.195-1.412 p=0.001), NYHA class 3-4 (OR: 1.245 %95 CI:1.195-1.412 p=0.001), Gensini score (OR: 1.328 %95 CI:1.213-1.515 p=0.001), and poor collateral circulation (OR: 1.318 %95 CI:1.162-1.441 p=0.001) were observed as independent risk factors for bendopnea (Table 4).

Table 1. The basic characteristics

	Bendopnea+ N:158	Bendopnea- N:101	P
Demographic and Risk Factors			
Age, years, n(%)	74.1±12.9	67.2±14.2	<0.001
Male, n(%)	105(66.4)	71(70.2)	0.121
Smoking status, n (%)	43 (27.2)	35(34.6)	0.627
COPB, n (%)	32(20.2)	22(21.7)	0.123
Diabetes Mellitus, n (%)	91(57.5)	64(63.7)	0.341
Hypertension, n (%)	78(49.3)	54(53.4)	0.681
Hyperlipidemia, n (%)	52(32.9)	30(29.7)	0.607
Medical Treatments			
ACEI (n, %)	71(44.9)	48(47.5)	0.232
ARB (n, %)	16(1)	11(1)	0.345
Beta blockers (n, %)	32(2)	23(2)	0.226
Statins (n, %)	30(1.8)	24(2.3)	0.426
Acetylsalicylic acid (n, %)	12 (0.7)	9(0.8)	0.369
Oral antidiabetic drugs (n, %)	72 (45)	52(51)	0.638
Insulin (n, %)	42 (26)	34(33)	0.494
NYHA class 3-4	76 (48.1)	44(43.5)	0.001

COPB: Chronic Obstructive Pulmonary Disease, **ACEI:** Angiotensin-Converting Enzyme Inhibitors, **ARB :** Angiotensin Receptor Blockers, **NYHA:** New York Heart Association

Table 2. Comparison of laboratory parameters

	Bendopnea+ N:158	Bendopnea- N:101	P value
Laboratory measurements			
Hb (mg/dl)	13.2±1.15	12.5±2.18	0.256
Glucose (mg/dl)	160.6±51.6	154.9±55.8	0.589
WBC (x10 ⁹)	10.1±3.12	11.1±2.11	0.321
Lymphocyte Count (x10 ⁹)	2.3±1.1	2.8±1.4	0.254
Cr (mg/dL)	1.1±0.28	0.96±0.23	0.412
Na (mmol/L)	138.6±7.2	140.1±5.51	0.541
K (mmol/L)	4.61±1.35	4.27±1.1	0.789
Üric Acid	7.12±1.1	5.73±2.4	0.001
Total Protein (g/dL)	6.51±1.51	6.61±1.38	0.168
Calcium (mg/dL)	9.72±1.9	9.51±1.71	0.207
CRP(mg/L)	2.18 ±0.66	2.33±1.12	0.124
NT-proBNP (ng/l)	1450± 752	1059±851	0.001
HDL-C (mg/dL)	151±42.2	142±40.8	0.888
LDL-C (mg/dL)	47±12.8	46±11.5	0.133
Total Cholesterol (mg/dL)	189.5±55.8	178±51.2	0.432

Hb: Hemoglobin, **WBC:** White blood cells, **Cr:** Creatinine, **Na:** Sodium, **K:** Potassium, **CRP:** C-reactive protein, **NT-proBNP :** N-terminal pro brain natriuretic peptide, **HDL-C:** High-density lipoprotein cholesterol, **LDL-C:** Low-density lipoprotein cholesterol, **LVEF:** Left ventricular ejection fraction

Table 3. Comparison of echocardiographic, electrocardiographic, and angiographic features

	Bendopnea+ N:158	Bendopnea- N:101	P value
Echocardiographic features			
LA diameter (mm)	35 ± 5.8	34±6.6	0.741
LV diastolic diameter (mm)	59±7	58±9	0.789
LV sistolik diameter (mm)	47±11	46±10	0.124
RV Dilatation(%)	34(%21)	35(%34.6)	0.258
sPAP (mmHg)	48±14	41±12	0.001
LVEF(%)	38±4.5	36±5.1	0.251
Electrocardiographic features			
Heart Rate (/min)	81±17	82±17	0.541
QRS Duration (ms)	120±31	121±32	0.894
Angiographic Features			
Gensini score	80±5.9	91±8.1	0.001
Poor collateral circulation (Rentrop class 0-1)(%)	40±6.9	25±7.5	0.001
Culprit vessel			0.098
LAD	41(%40.5)	69(%43.6)	
LCX	28(%27.7)	43(%26.0)	
RCA	32(%31.8)	49(%30.4)	

LA: Left Atrium, **LV:** Left Ventricle, **RV:** Right Ventricle, **sPAP:** Systolic Pulmonary Artery Pressure, **LVEF:** Left Ventricular Ejection Fraction, **LAD:** Left Anterior Descending Artery, **LCX:** Left Circumflex Artery, **RCA:** Right Coronary Artery

Table 4. The effects of different variables on bendopnea in univariate and multivariate logistic regression analyses

	OR	95% CI	p	OR	%95 CI	P value
Age	1.231	1.109-1.412	0.001	1.355	1.212-1.517	0.001
NYHA class 3-4	1.356	1.224-1.514	0.001	1.245	1.195-1.412	0.001
NT-proBNP	1.257	1.112-1.377	0.001	1.252	1.185-1.322	0.001
Gensini score	1.215	1.102-1.312	0.001	1.328	1.213-1.515	0.001
Poor collateral circulation	1.211	1.101-1.310	0.001	1.318	1.162-1.441	0.001
Uric acid	1.235	0.941-1.311	0.411			
sPAB	1.314	0.944-1.432	0.259			
Diabetes Mellitus	1.187	0.954-1.352	0.654			
Gender	1.254	0.923-1.411	0.451			
Hypertension	1.121	0.898-1.332	0.369			

OR: Odds Ratio, CI: Confidence Interval, NYHA: New York Heart Association, NT-proBNP : N-terminal pro brain natriuretic peptide, sPAB : systolic pulmonary artery pressure

Discussion

This study is the first to investigate the relationship between coronary collateral circulation and bendopnea in patients with ischemic low ejection fraction heart failure. At the end of the study, poor collateral circulation was shown to be an independent risk factor for the presence of bendopnea.

In addition, our study demonstrated that advanced age, high NT proBNP, decreased functional capacity, and extensive coronary artery disease are independent risk factors for the development of bendopnea. With advanced age, there is an increase in comorbidities, the prevalence of coronary artery disease, increased left ventricular end-systolic pressure, decreased functional capacity, and increased pulmonary artery pressure. In the study by Kaya H. et al., aging was observed as an independent risk factor for bendopnea (11). NT-proBNP is released as a result of increased cardiac filling pressure and is directly proportional to ventricular pressure. Studies on advanced-stage heart failure have shown a close relationship between high NT-proBNP levels and bendopnea. Decreased functional capacity is closely related to increased left ventricular filling pressure and decreased cardiac index and studies on bendopnea have observed that decreased functional capacity is an independent risk factor for bendopnea. The only study investigating the relationship between the prevalence of coronary artery disease and bendopnea was conducted by Saylik F. et al. In this study, the prevalence of coronary artery disease was observed as an independent risk factor for bendopnea (OR: 3.82), and mortality was found to be 2.21 times higher (12). In the study conducted by Rodriguez et al., the presence of bendopnea in patients with severe aortic stenosis was found to be an independent risk factor for postoperative mechanical ventilator need and prolonged hospital stays (13).

The presence of coronary collateral circulation not only reduces myocardial damage but also decreases mortality

and the incidence of low cardiac output syndrome. Meier et al. demonstrated that the presence of collaterals reduces mortality by 35% (14). The positive effect of collateral circulation on left ventricular functions in coronary artery diseases has been shown in many studies. In a study conducted by Hirai et al., it was observed that left ventricular functions improved in the chronic period in the patient group with adequate collateral circulation, despite thrombolytic administration without reperfusion, while no change was observed in the patient group without adequate collateral circulation (15). Additionally, Habib et al. observed better left ventricular functions in patients with good collateral circulation in coronary artery disease patients (16). In a study conducted by Meier, Stefoana et al., an increase in left ventricular pressures was observed in the patient group without sufficient coronary collaterals during the iatrogenic 60-second occlusion of the coronary arteries in a study group of 50 patients with no difference in left ventricular ejection fraction (17).

Shortness of breath is the most important symptom in heart failure patients. Previously, exercise dyspnea, orthopnea and paroxysmal nocturnal dyspnea (PND) were defined. Bendopnea, a recently defined symptom in heart failure patients, is considered shortness of breath within 30 seconds of bending forward in patients with advanced-stage heart failure. Although its etiopathogenesis is not fully known, it is thought to be related to increased intra-abdominal and intra-aortic pressure upon bending forward. Bendopnea was introduced into the clinical literature in 2014 by Thibodeau et al. It was observed in 29 out of 102 patients (28%). Cardiac catheterization studies showed increased left ventricular filling pressure, pulmonary capillary wedge pressure and right atrial pressure in the presence of bendopnea. While all patients showed an increase in pulmonary capillary wedge pressure and right atrial pressure upon bending, there was no change in car-

diac index in patients without bendopnea, whereas a statistically significant decrease was observed in patients with bendopnea. Additionally, it was observed three times more frequently in patients with high pulmonary capillary wedge pressure and low cardiac index. However, no association was found between bendopnea and patients with high pulmonary capillary wedge pressure and normal cardiac index (18). Trinidad et al. found that the presence of bendopnea was closely related to increased PND, orthopnea, and jugular venous pressure (JVP), and particularly noted that short-term mortality was 2.3 times higher in patients with advanced-stage heart failure (19). In a meta-analysis of six studies on heart failure, Pranata B. et al. observed that orthopnea was 3.02 times, PND 2.76 times, abdominal fullness 7.5 times, and advanced-stage heart failure 7.5 times more common in the presence of bendopnea, with short- and long-term mortality being 2.21 times higher (20). In our study, the presence of insufficient coronary collateral circulation was observed as an independent risk factor for bendopnea in patients with ischemic heart failure.

Limitations

The study had some limitations. Firstly, it was a single-center, cross-sectional study. The research was conducted with a relatively small patient group. Due to data loss, many patients were excluded from the study. The results of the study need to be supported by randomized controlled trials.

Conclusion

In our study, the presence of insufficient coronary collateral circulation was observed as an independent risk factor for bendopnea in patients with ischemic heart failure.

Ethical Approval: Ethical approval was obtained from the İzmir Bakırçay University Non-Invasive Clinical Research Ethics Committee with the application number 2065 (date: 26/02/2025).

Author Contributions:

Concept: İ.K, F.S.

Literature Review: İ.K, F.S.

Design : İ.K, F.S.

Data acquisition: İ.K, F.S.

Analysis and interpretation: İ.K, F.S.

Writing manuscript: İ.K, F.S.

Critical revision of manuscript: İ.K, F.S.

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Comparison of Supine and Prone Positions in PCNL Operations Performed in Isolated Kidney Upper Pole Access

İzole Böbrek Üst Pol Akses Yapılan PCNL Operasyonlarında Supin ve Prone Pozisyonlarının Karşılaştırılması

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Abstract

Background: Renal stones larger than 2 cm in the upper pelvical system are usually managed with Percutaneous Nephrolithotomy (PCNL) operation, but there are unclear as to which position should be used. In our study, we aimed to compare the preoperative-peroperative and postoperative data of patients who underwent PCNL with isolated renal upper pole access in supine and prone position.

Materials and Methods: The study included 20 Supine PCNL and 45 Prone PCNL cases who underwent isolated renal upper pole access for renal calculi. Age, gender, body mass index (BMI) were evaluated from demographic data. Radiological findings such as stone-skin distance, stone density, stone size and volume were recorded. Total operation time, access time and fluoroscopy time were recorded from peroperative data. In the postoperative period, the duration of hospital stay and complications according to Clavien Dindo classification were recorded. Non-contrast computed tomography was performed at the 1st postoperative month and the stone-free status of the patients was evaluated.

Results: There was no statistical difference in demographic data in terms of age, gender, BMI, ASA scores in both groups. The total operation time was 75.95±28.7 min in supine PCNL group and 92.48±23.4 min in prone PCNL group (p<0.001). Access time was 11.6±5.12 min in supine PCNL group and 9.2±3.7 min in prone PCNL group (p<0.001). Fluoroscopy time was 3.6±1.2 min in the supine PCNL group and 2.5±1.1 min in the prone PCNL group and was statistically longer (p<0.001). There was no difference in complications between the groups. Grade>2 complications according to Clavien Dindo classification were more frequent in supine PCNL patients (p:0.03). Stone-free status was 70% in supine PCNL patients and 77.7% in prone PCNL patients and was higher in the prone PCNL group (p:0.01).

Conclusions: In patients undergoing PCNL for isolated upper pole stone, the operation time is longer when prone PCNL is performed, but higher stone-free rates are obtained in these patients. Grade >2 complications are less common in prone PCNL for renal upper pole calculi.

Keywords: PCNL, Supine position, Prone position, Renal calculi, Stone surgery

Öz

Amaç: Üst pelvikalsiyel sistemde 2 cm'den büyük böbrek taşları genellikle Perkütan Nefrolitotomi (PCNL) operasyonu ile tedavi edilir ancak hangi pozisyonda olması gerektiği konusunda belirsizlikler vardır. Çalışmamızda supin ve prone pozisyonunda izole böbrek üst pol akses ile PCNL yapılan hastaların preoperatif-peroperatif ve postoperatif verilerinin karşılaştırılması amaçlanmıştır.

Materyal ve Metod: Çalışmaya böbrek taşı için izole böbrek üst polüne akses yapılan 20 Supin PCNL ve 45 Prone PCNL vakası dahil edildi. Hastaların demografik verilerinden yaş, cinsiyet, vücut kitle indeksi (VKİ) değerlendirildi. Radyolojik bulguların taş-cilt mesafesi, taşın dansitesi, taşın büyüklüğü ve volümü kaydedildi. Peroperatif verilerinden total operasyon süresi, akses süresi ve floroskopi süresi kaydedildi. Postoperatif süreçte ise hastaların hastanede kalış süresi, Clavien Dindo sınıflamasına göre komplikasyonları belirtildi. Operasyon sonrası 1. ay Non-kontrast Bilgisayarlı Tomografi çekilerek hastaların taşsızlık durumu değerlendirildi.

Bulgular: Her iki grupta demografik verilerden yaş, cinsiyet, VKİ, ASA skorları açısından herhangi bir istatistiksel fark izlenmedi. Peroperatif verilerden operasyon süresi supin PCNL grubunda 75.95±28.7 dk, prone PCNL grubunda 92.48±23.4 dk olup daha uzundu (p<0.001). Akses süresi Supin PCNL grubunda 11.6±5.12 dk, Prone PCNL grubunda ise 9.2±3.7 dk idi (p<0.001). Floroskopi süresi ise Supin PCNL grubunda 3.6±1.2 dk, prone PCNL hastalarında ise 2.5±1.1 dk olup istatistiksel olarak daha uzundu (p<0.001). Gruplar arasında komplikasyonlar açısından fark izlenmedi. Clavien Dindo sınıflamasına göre Grade>2 komplikasyonlar Supin PCNL hastalarında daha sıkı (p:0.03). Taşsızlık durumu supin PCNL hastalarında %70, prone PCNL hastalarında %77.7 olup Prone PCNL grubunda daha yüksek izlendi (p:0.01).

Sonuç: İzole üst pol taşı nedeniyle PCNL uygulanan hastalarda prone PCNL uygulandığında operasyon süresi daha uzundur ancak bu hastalarda daha yüksek taşsızlık oranları elde edilmektedir. Böbrek üst pol taşı için PCNL operasyonunda Prone PCNL'de Grade >2 komplikasyonlar daha az görülmektedir.

Anahtar Kelimeler: PCNL, Supin pozisyon, Prone pozisyon, Böbrek taşı, Taş cerrahisi

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Introduction

Renal stone disease is a common urological problem worldwide (1). Percutaneous Nephrolithotomy (PCNL), which is one of the renal stone surgical methods, is performed especially for stones larger than 2 cm (2). In PCNL operations, supine or prone positions are used according to the surgeon's preference (3). In PCNL procedures for upper pole stones, both positions have their own advantages and disadvantages (4). Prone position provides a wider operation area by keeping the renal system in a stable position, and the supracostal and intracostal access are more feasible in this position (5).

In the supine position, simultaneous interventions with combined retrograde intrarenal surgery (RIRS) can be performed more easily. However, nephroscopic manipulation may be limited due to the mobility of the renal cavity for upper pole stones in the supine position (6).

There are limited studies in the literature on the success and complications of PCNL operations for isolated upper pole stones. In this study, we aimed to evaluate which position has a higher stone free rate (SFR), which position has fewer complications and which position is more applicable in clinical practice in isolated upper pole kidney stones.

Materials and Methods

This study was approved by our institutional ethical review committee (Decision No: 2024/05-11, Date: 04.06.2024). All patients gave their written consent before participating in the study. We retrospectively reviewed the cases of PCNL between January 2018 and January 2024.

The exclusion criteria were as follows: Renal stones other than isolated upper pole, patients with stones <2 cm, history of neuromuscular disease, congenital renal anomaly, coagulopathy, morbid obesity and skeletal deformity. After the exclusion criteria, the study was designed with 20 supine PCNL and 45 prone PCNL cases with access to the upper pole of the kidney.

Demographic data including age, gender, body mass index (BMI), American Society of Anaesthetists (ASA) score; pre-operative evaluations including degree of hydronephrosis, stone characteristics on Kidney-Ureter-Bladder (KUB) graphy, stone density, stone volume, stone-skin distance (SSD); intraoperative data including access, fluoroscopy, total operation time; postoperative data including length of hospital stay (LOS), residual stone status and complications, need for additional treatment at 1-month follow-up, and SFR were obtained from electronic patient files and recorded in a database. All patients received prophylactic antibiotherapy with second generation cephalosporins. Patients with growth in preoperative urine culture were treated with antibiotics until sterile urine culture results were obtained. In axial NCCT, 3 distances were measured from the centre of the stone to the skin surface: horizontal, vertical and 45° between the first 2 measurements. The average of these 3 measurements was accepted as the SSD. Stone density (HU) was calculated by the point value at the

centre of the stone. Stone volume was determined using the ellipsoid formula ($0.167 \times \pi \times L \times W \times W \times H$) (7).

In both methods, a 5f ureteral catheter was inserted into the ureter and the anatomy of the pelvis and calyx structures was better demonstrated by fluoroscopy-guided retrograde pyelography with contrast material. After pyelography, fluoroscopy-guided puncture needle (18 gauge, Boston Scientific Corporation, Natick, MA) was used to access the appropriate upper calyx. After placement of the guide wire (SensorTM Guide Wire, Boston Scientific), the tract was dilated using amplatz dilators and a 30 Fr amplatz sheath (Karl Storz, Tutlingen, Germany) was inserted. Renal access time was defined as the time from retrograde pyelography to puncture of the desired calyx, expansion of the tract with fascial dilators, and placement of the Amplatz sheath. Fluoroscopy time was measured as the total fluoroscopy time used during the operation. Operative time was measured as the time from the sterile draping of the patient to the insertion of the nephrostomy tube or Double J catheter. SFR was defined as the absence of residual stones on Non-Contrast Computer Tomography (NCCT) 1 month after the operation or the largest stone size of the residual stone <4 mm. Clavien-Dindo Classification was used for complications (8).

Operation Technique

Supine Percutan Nephrolithotomy

After induction of general anaesthesia, a 5 Fr ureteral catheter was inserted into the renal pelvis with fluoroscopy, in Modified Galdakao Valdivia position. Renal access was obtained through the renal calyx with a fluoroscopy-guided puncture needle (18 Gauge, Boston Scientific Corporation, Natick, MA). After placement of the guide wire (SensorTM Guide Wire, Boston Scientific), the tract was dilated using amplatz dilators and a 30 Fr amplatz sheath (Karl Storz, Tutlingen, Germany) was inserted. A 28 Fr nephroscope was inserted through the amplatz. Stone was directly identified and fragmented into smaller parts using a 3.4-Fr Pneumatic Lithotripter (Vibrolity, Elmed, Ankara, Turkey). Large fragments of fragmented stones that could fit into the Amplatz sheath were removed with stone forceps. After the decision to end the operation, an 8 f nephrostomy tube was placed in all patients. A 4.8 Fr JJ catheter was placed according to the surgeon's preference.

Prone Percutan Nephrolithotomy

The patient was given general anesthesia and the patient was placed in the lithotomy position and cystoscopy was performed. Preferably, open-ended 5 Fr ureteral catheter was placed in the ureter on the planned side of the operation. After the ureteral catheter was left in the pelvis, the urethral catheter was inserted and the ureteral catheter was fixed to the catheter. Then, the patient was carefully placed in the prone position. When the patient was placed in the prone position, silicone pillows were placed on the

chest area, both flank areas, and under the feet, especially to prevent lung compression. Renal access was obtained through the renal calyx with a fluoroscopy-guided puncture needle (18 Gauge, Boston Scientific Corporation, Natick, MA). After placement of the guide wire (SensorTM Guide Wire, Boston Scientific), the tract was dilated using amplatz dilators and a 30 Fr amplatz sheath (Karl Storz, Tutlingen, Germany) was inserted. A 28 Fr nephroscope was inserted through the amplatz. Stone was directly identified and fragmented into smaller parts using a 3.4-Fr Pneumatic Lithotriptor (Vibrolity, Elmed, Ankara, Turkey). Large fragments of fragmented stones that could fit into the Amplatz sheath were removed with stone forceps. After the decision to end the operation, an 8 f nephrostomy tube was placed in all patients. A 4.8 Fr JJ catheter was placed according to the surgeon's preference.

Statistical Analysis

The data were evaluated in the statistical package program IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA). The normal distribution of the data of numerical variables was evaluated with the Shapiro Wilk normality test and Q-Q graphs. Categorical variables were given as frequency and percentage. Descriptive statistics are given as Mean $\pm$ Standard Deviation and Median (IQR) values. The

mean differences between two related groups of normally distributed data were compared by independent ttest, and the Mann Whitney U test was used to compare non-normally distributed data. The relationship between categorical variables was evaluated with the Pearson Chi-Square test in $r \times c$ tables. A value of $p < 0.05$ was considered statistically significant.

Results

There was no statistical difference in demographic data in terms of age, gender, BMI, ASA scores in both groups. The mean age was 51.1 ± 18.4 years in supine PCNL patients and 47.2 ± 17.5 years in prone PCNL patients. There was no difference between the groups in terms of stone structure, degree of hydronephrosis, localisation of the stone, laterality of the stone, volume and density of the stone, and stone-skin distance between the findings obtained in preoperative radiological evaluations with KUB graphy and NCCT. The stone volume was 6715.7 ± 1647.6 mm³ in the supine PCNL group and 7132.8 ± 1881.5 mm³ in the prone PCNL patients, which was higher in the prone PCNL patients, although there was no statistical difference. Quantitative data related to demographic and radiological findings of the patients are shown in Table 1.

Table 1. Comparison of demographic data and radiological features of the stone between both groups

	Group 1 (Supine PCNL) (n=20)	Group 2 (Prone PCNL) (n=45)	
	Mean $\pm$ SD	Mean $\pm$ SD	p value
Age (years)	51.1 $\pm$ 18.4	47.2 $\pm$ 17.5	0.217
BMI (kg/m ²)	23.1 $\pm$ 4.8	25.2 $\pm$ 5.7	0.109
Sex (M/F) n (%)	15 (75) / 5 (25)	32 (71.1) / 13 (28.9)	0.872
ASA Class n (%)			
1	4 (20)	9 (20)	
2	11 (55)	26 (57.7)	0.982
3	5 (25)	10 (22.2)	
Structure of the stone			
Opaque	15 (75)	33 (73.3)	
Semi opaque	4 (20)	9 (20)	0.741
Non-opaque	1 (5)	3 (6.6)	
Stone Side (Left/Right)	11 (55) / 9 (45)	21 (46.6) / 24 (53.4)	0.091
Stone Volume (mm ³)	6715.7 $\pm$ 1647.6	7132.8 $\pm$ 1881.5	0.079
Stone density (HU)	978.1 $\pm$ 401.7	1014.8 $\pm$ 489.89	0.111
Stone skin distance (cm)	11.8 $\pm$ 3.1	10.9 $\pm$ 2.9	0.816

Among the peroperative data, the operation time was 75.95 ± 28.7 min in the supine PCNL group and 92.48 ± 23.4 min in the prone PCNL group ($p < 0.001$). Access and fluoroscopy time were statistically longer in the supine PCNL group (11.6 ± 5.12 min and 3.6 ± 1.2 min) than in the prone PCNL group (9.2 ± 3.7 min and 2.5 ± 1.1 min) ($p < 0.001$). There was no difference between the groups in terms of d-j stent placement rates and complications. Grade >2

complications were more frequent in supine PCNL patients ($p:0.01$). SFR was 70% in supine PCNL patients and 77.7% in prone PCNL patients ($p:0.03$). There was no statistical difference between the groups in terms of length of hospital stay and additional treatment of residual stones. Data on the comparison of peroperative and postoperative values of the patients are shown in Table 2.

Table 2. Comparison of Perioperative and Postoperative Data between both groups

	Group 1 (Supine PCNL) (n=20)	Group 2 (Prone PCNL) (n=45)	
	Mean±SD	Mean±SD	p value
Access time	11.6±5.12	9.2±3.7	<0.001
Fluoroscopy screening time (min)	3.6±1.2	2.5±1.1	<0.001
Operation time (min)	75.95±28.7	92.48±23.4	<0.001
Access Location			
-Supracostal	14 (70)	37 (82.2)	<0.001
-Infrakostal	6 (30)	8 (17.7)	
DJ stent insertion n (%)	7 (35)	18 (40)	0.802
Clavien Dindo , n (%)			
1	3 (15)	6 (13.3)	0.102
2	2 (10)	4 (8.8)	
3A	2 (10)	2 (4.4)	
3B	1 (5)	1 (2.2)	
Grade >2 Complications, n (%)	3 (15)	3 (6.6)	0.03
Length of stay in hospital (days)	1.7±0.8	1.8±0.9	0.463
Stone Free Rate n (%)	14 (70)	35 (77.7)	0.01
Additional treatment n (%)	4 (20)	8 (17.7)	0.239
Additional type of treatment n (%)			
ESWL	1 (5)	2 (4.4)	0.184
F-URS-URS	3 (15)	5 (11.1)	
PCNL	0 (0)	1 (2.2)	

Discussion

In this study, the different aspects of supine and prone positions in patients undergoing PCNL with isolated upper pole access for renal calculi were analysed in detail.

Upper calyx access for PCNL is generally used for stones with special anatomy such as staghorn stones, large upper calcal stones, and stones in anomalous kidneys (9). The first step of successful PCNL is to establish a properly placed nephrostomy tract (10). The advantage of upper pole access is direct access to most of the intrarenal collecting system and upper ureter, so upper pole access is one of the ways to ensure good stone clearance (11). Upper pole access can be performed by both supracostal and infracostal approaches. Although supracostal access provides direct access to the stones in the upper pole of the kidney, it may increase the risk of pleural injury and haemothorax (12). In the prone position, the advantages of supracostal access include a steeper nephroscopic angle and an optimal field of view for a larger stone load (13-14). In our study, supracostal access was performed in 82.2% of patients in the prone position and 70% in the supine position for upper pole stones, and it was observed that more supracostal access was provided in the prone position.

The most important indicator of success in PCNL operations is the SFR (15). In the literature, Astroza et al. (16) used upper pole access more frequently in the prone position in staghorn stones and the SFR was 59.2% in the prone position and 48.4% in the supine position in staghorn stones. Tefekli et al. (12) reported an SFR of 77.1% in patients who underwent isolated upper pole access. Soares et al. (5) found an SFR of 84.8% with supracostal access and 84.4% with infracostal access in their series of 329 isolated upper pole accesses. In a study by Bulut et al. (17) on the comparison of supine and prone PNL during the learning curve period,

SFR rates were found to be 80% in the supine position and 64% in the prone position. In the literature, it is obvious that the surgical success varies according to the position in PCNL operation performed to isolated upper pole stones. In our study, SFR in isolated upper pole stones was 77.7% in prone PCNL and 70% in supine PCNL patients and this difference was clinically significant. In our opinion, this difference is due to the fact that supracostal access can be performed more easily in the prone position.

Although the main aim of PCNL operations is to provide stone-free operation, short surgical time and fewer complications in the per-postoperative period are also important points (18). Surgical time in PCNL operations consists of 3 parts as access time, fluoroscopy time and total operation time. Oner et al. (19) found a total operation time of 37.5 min and a fluoroscopy time of 3.4 min in their PCNL series in which they applied isolated upper pole accessory. Sofer et al. (20) reported an operation time of 90 min in supine position and 110 min in prone position in patients in whom they performed PCNL by reaching the upper calyx. Kumar et al. (21) reported an operation time of 51.8 min in the supine position in patients who underwent isolated upper pole access in the supine position. In our study, the duration of access, fluoroscopy and total operation time in the supine and prone positions were 11.6, 3.6, 75.9 and 9.2, 2.5, 92.4, respectively. Total operative time was longer in the prone position, whereas access and fluoroscopy time were shorter. In addition, Desoky et al. (22) compared the supine and prone PCNL methods and found that the operative time was statistically significantly shorter in the supine position, but there was no significant difference in SFR, postoperative complication rates, postoperative pain, and hospital stay. Also, Jamil et al. (23) reported that supine PCNL

required shorter operating time, shorter hospital stay, and less analgesia treatment than percutaneous nephrolithotomy performed in the prone position. We think that the change of the patient's position affects the duration of the operation in the prone position.

In terms of complications, both positions have their own advantages and disadvantages. Since upper pole access can be performed with a steeper angle in the prone position, complication rates have been reported to be lower compared to the supine position (24-25). Soares et al. (5) found a Clavien Grade 3-4 complication rate of 17.6% in patients who underwent supracostal upper pole access in the prone position and 1.9% in patients who underwent infracostal access. In addition, there were concerns about increased colonic injury due to more lateral access in the supine position, but Liu et al. showed that there was no significant difference between both methods in their meta-analysis (26). Kekre et al. (27) performed PCNL with supracostal access in a series of 102 patients, 79.5% of the patients were stone-free and 9.8% of the patients had intrathoracic complications such as hydrothorax, pneumothorax or hydropneumothorax requiring intercostal drainage. Radecka et al. (28) found a nephropleural fistula rate of 3.3% after supracostal PCNL. In our study, no difference was observed between all groups in terms of total complications. Grade>2 complications were observed in 3 patients in both patient groups with a rate of 15% in Prone patients and 6.6% in Supine PCNL patients. The higher rate of Grade>2 complications, especially in Prone patients, may be due to the surgeons attempting more supracostal access.

The main limitations of our study are its retrospective design, the fact that it was performed in a single centre and the small number of cases. Another limitation is the use of standard 30 F Amplatz in PCNL operations. Complication rates may be reduced with lower width Amplatz dilators.

Conclusion

In PCNL operations performed with upper pole access, although prone PCNL has a longer operation time, a higher stone-free rate is obtained. Grade>2 complications are less common in prone PCNL.

Ethical Approval: The study was approved by The University of Health Sciences, Tepecik Training and Research Hospital Ethical Committee, Izmir, Turkey (Decision No: 2024/05-11, Date: 04.06.2024).

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Data acquisition: Y.A., S.B., F.D., M.G.

Analysis and interpretation: B.E.

Writing manuscript: Y.A., S.B., O.K., M.G.

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Evaluation of the Effects of Fovea Capitis Femoris Localization and Morphometry on the Femoral Head

Fovea Capitis Femoris Lokalizasyonun ve Morfometrisinin Femur Başı Üzerine Olan Etkilerinin Değerlendirilmesi

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Abstract

Background: The fovea capitis femoris (FCF) is a distinct depression on the femoral head, serving as the insertion point for the ligamentum capitis femoris and potentially allowing vascular entry. Avascular necrosis and degenerative illnesses, as well as hip biomechanics, may be impacted by anatomical differences of the FCF. This study aimed to analyze the morphometric features and quadrant-based localization of the FCF and assess their relationships with femoral head geometry.

Materials and Methods: Seventy-one adult dry femurs were examined. The mediolateral images were standardized. Morphometric parameters—including transverse and longitudinal diameters, depth, area, and perimeter—were measured using a digital caliper and ImageJ. Femoral head surface area and perimeter were also recorded. The location of the FCF was determined using a quadrant-based model. Statistical analysis involved ANOVA and Hochberg's GT2 for post-hoc test.

Results: Type II was the most common FCF configuration (64.8%), while Type I, III, and V were each found in 7.0% of cases. Type V showed the highest area and perimeter values, whereas Type I had the lowest. Significant differences were observed among types for longitudinal length ($p = 0.005$), area ($p = 0.001$), and perimeter ($p = 0.001$). Type I exhibited a significantly more compact profile, possibly indicating reduced ligament attachment and vascular ingress.

Conclusions: FCF morphology varies according to its structural type and may influence both ligamentous anchorage and vascular supply. Understanding these variations may aid in surgical planning and radiological assessment, particularly in procedures involving the femoral head.

Keywords: Femur, Femur head, Fovea capitis femoris, Hip joint, Ligamentum capitis femoris

Öz

Amaç: Fovea capitis femoris (FCF), femur başı üzerinde yer alan belirgin bir çöküntü olup, ligamentum capitis femoris'in distal tutunma noktasını oluşturmaktadır ve aynı zamanda vasküler yapıların girişine olanak tanıyan bir geçit işlevi görmektedir. FCF'nin anatomik varyasyonları, kalça eklemi biyomekanik özelliklerini etkileyebileceği gibi avasküler nekroz ve dejeneratif hastalıklar gibi patolojik durumların gelişiminde de rol oynayabilir. Bu çalışmanın amacı, FCF'nin morfometrik özelliklerini ve kadran temelli lokalizasyonunu analiz etmek ve bu parametrelerin femur başı geometrisi ile olan ilişkisini değerlendirmektir.

Materyal ve Metod: Çalışmada yetmiş bir erişkin kuru femur incelenmiştir. Femur başlarının standardize mediolateral görüntüleri elde edilmiştir. Transvers ve longitudinal çaplar, derinlik, alan ve çevre gibi morfometrik parametreler dijital kumpas ve ImageJ yazılımı kullanılarak ölçülmüştür. Ayrıca femur başının yüzey alanı ve çevre uzunluğu da kaydedilmiştir. FCF'nin lokalizasyonu, kadran temelli bir model kullanılarak sınıflandırılmıştır. Elde edilen veriler, ANOVA ve Hochberg'in GT2 post-hoc testi ile istatistiksel olarak analiz edilmiştir.

Bulgular: FCF konfigürasyonları arasında en sık gözlenen tip Tip II olup, olguların %64,8'ini oluşturmaktadır. Tip I, III ve V konfigürasyonları ise her biri %7,0 oranında tespit edilmiştir. En yüksek ortalama alan ve çevre değerleri Tip V'de, en düşük değerler ise Tip I'de saptanmıştır. Longitudinal uzunluk ($p = 0,005$), alan ($p = 0,001$) ve çevre ($p = 0,001$) değişkenleri açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmuştur. Tip I konfigürasyonunun daha kompakt morfolojik bir yapıya sahip olması, ligamentöz tutunma alanının ve vasküler girişin daha sınırlı olabileceğini düşündürmektedir.

Sonuç: FCF'nin morfolojik yapısı, tipolojik sınıflamasına bağlı olarak anlamlı varyasyonlar göstermektedir. Bu varyasyonlar, ligamentum capitis femoris'in tutunma potansiyelini ve femur başının vaskülarizasyonunu etkileyebilir. Söz konusu morfometrik farklılıkların cerrahi planlamada ve radyolojik değerlendirmelerde dikkate alınması, özellikle femur başını içeren girişimlerde komplikasyonların azaltılmasına katkı sağlayabilir.

Anahtar Kelimeler: Femur, Femur başı, Fovea capitis femoris, Kalça eklemi, Ligamentum capitis femoris

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Introduction

The fovea capitis femoris (FCF) is a distinct anatomical structure located on the posteroinferior aspect of the femoral head, forming a shallow depression that serves as the attachment site for the ligamentum capitis femoris (ligamentum teres)-a ligament thought to contribute to both mechanical stability and limited vascular support of the femoral head (1-3). Although the ligament's functional role has been debated, especially in adults, the anatomical region of its insertion, the FCF, has attracted increasing attention due to its potential involvement in pathological processes such as avascular necrosis, developmental dysplasia of the hip, and osteoarthritic changes (4-6).

The FCF may also contain small vascular foramina, which provide entry points for vessels that supply the femoral head with an additional blood supply, especially in the early stages of life, in addition to being a ligament attachment site. (7, 8). Disruption of these vascular channels, especially in the setting of femoral neck fractures or corticosteroid use, has been implicated in the pathogenesis of osteonecrosis. Therefore, the morphology and dimensions of the FCF may not only reflect normal anatomical variation but also provide clues to underlying vascular integrity and biomechanical stress distribution across the femoral head. Several anatomical and radiological studies have explored the shape, presence, or absence of the FCF in relation to ligament integrity, degenerative conditions, and congenital anomalies. Sampatchalit et al. (9) reported that degenerative hypertrophy of the ligamentum capitis femoris is often associated with wider and deeper FCFs, while Cerezal et al. (1) described hypoplastic or absent FCFs in cases of congenital ligament absence. However, despite the established anatomical significance of this region, detailed morphometric analyses of the FCF with femoral head morphology remain to be disclosed. Given that the FCF resides directly on the femoral head surface, it is reasonable to hypothesize that variations in the size and shape of the femoral head—including parameters such as the total surface area—might influence the morphological characteristics of the FCF, such as its transverse and vertical diameters, depth, area, and perimeter (10, 11). Understanding this anatomical relationship could provide deeper insight into the spatial organization of proximal femoral structures and the biomechanical and clinical significance of the FCF.

Current approach aimed to reveal the potential influence of femoral head geometry on the morphometric characteristics of the FCF. The findings of this study are likely to contribute to a better understanding of anatomical variations in this region and serve as a potential reference in radiological assessments, preoperative surgical planning, and anthropological identification.

Materials and Methods

This study was conducted on a total of 71 dry femora obtained from the Anatomy Department of Bilecik Seyh Edebali and Eskisehir Osmangazi Universities Faculty of Medicine. Specimens exhibiting any form of deformation likely to compromise measurement accuracy were excluded from the analysis. Information regarding the age and sex of the specimens was unavailable, and it was not possible to determine whether the right and left femurs originated from the same individual. Morphological and morphometric characteristics of the FCF and femoral head were assessed using methodologies established in previous studies (12).

Standardized mediolateral digital photographs of the femoral heads were obtained for morphometric evaluation. During image acquisition, a millimetric calibration ruler was placed adjacent to each specimen to ensure accurate scaling. All photographs were taken with the medial aspect of the femoral head facing the camera, and the femoral neck axis was carefully aligned parallel to the camera lens to maintain consistent mediolateral orientation across all samples. Morphometric evaluations were performed using a digital caliper (Koodmax digital carbon fiber caliper, China; sensitivity 0.01 mm) and Image J software (National Institutes of Health, USA) following proper calibration based on the ruler included in each image. The same researcher repeated the measurements three times, and mean values were used in the study.

Locational Typing of the FCF Based on Mediolateral Imaging

The anatomical localization of the FCF was evaluated based on mediolateral images of the femoral head. For this purpose, each femoral head image was digitally divided into four quadrants- anterosuperior, anteroinferior, posterosuperior, and posteroinferior by superimposing vertical and horizontal lines intersecting at the center of the femoral head using ImageJ software. According to the quadrant in which the FCF was predominantly located, five distinct localization types were defined (Figure 1).

Measurement of the Femoral Head and FCF Parameters

The area was calculated based on the circular contour surrounding the femoral head observed in mediolateral digital images. In addition to area measurement, the perimeter of the femoral head was also assessed using the same mediolateral images to provide a comprehensive evaluation of femoral head geometry (Figure 2).

The morphometric parameters of the FCF were defined and measured in accordance with previous anatomical studies (12). All linear measurements were performed using a digital caliper while area and perimeter calculations were obtained through ImageJ software on standardized mediolateral digital images. The anatomical landmarks and measured morphometric parameters of the FCF are illustrated in Figure 2.

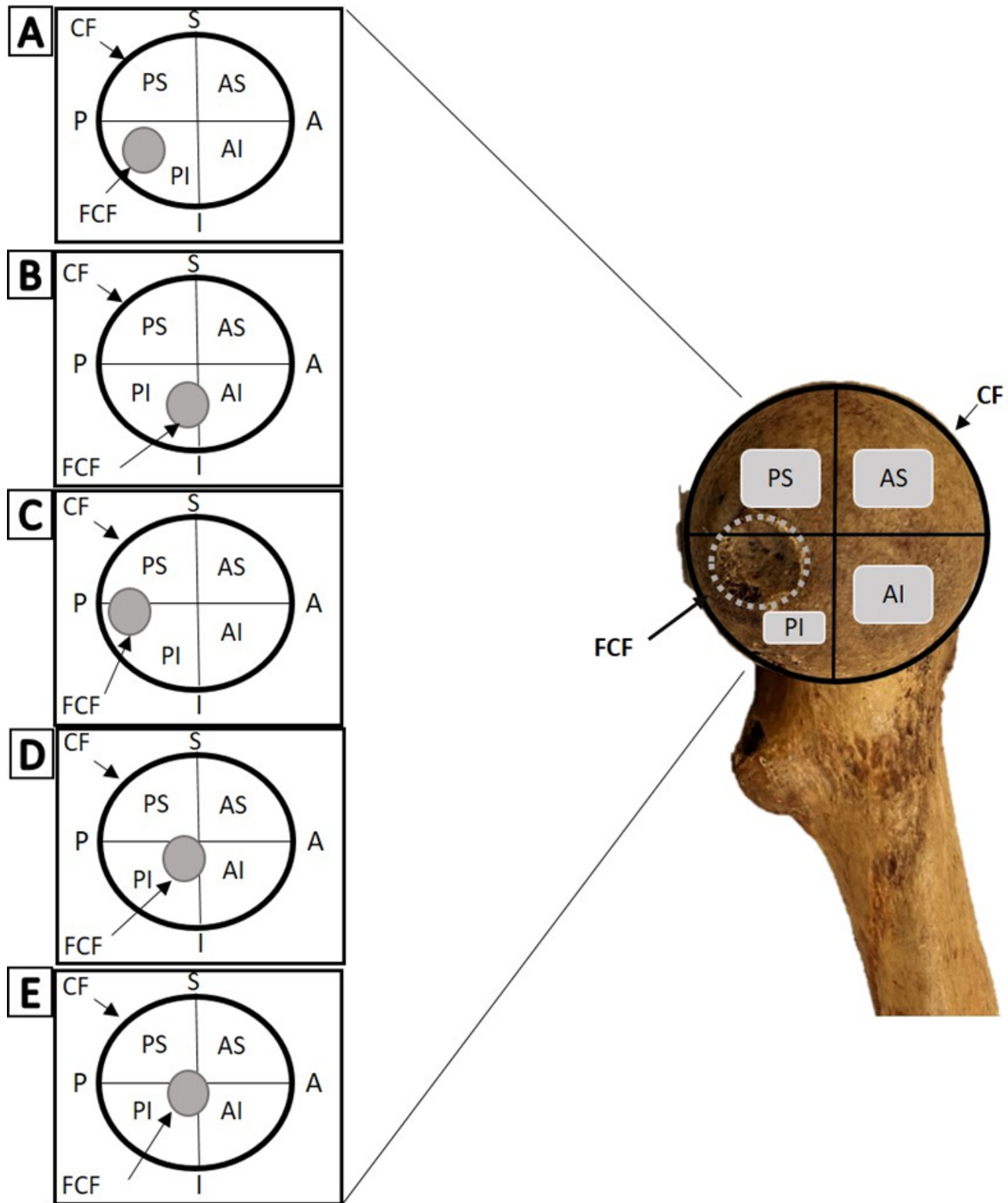


Figure 1. The localization types of the fovea capitis femoris (FCF) are illustrated based on its position on the femoral head (caput femoris, CF). The femoral head is divided into four anatomical quadrants: anterosuperior (AS), anteroinferior (AI), posterosuperior (PS), and posteroinferior (PI). The FCF, delineated by a dashed circle, is primarily located within the posteroinferior quadrant, but five distinct localization types (Type 1–Type 5) are defined according to the position of its center. Subfigures (A–E) demonstrate these types: (A) Type 1 localization, (B) Type 2 localization, (C) Type 3 localization, (D) Type 4 localization, and (E) Type 5 localization. The orientation of the femoral head is marked with directional labels: anterior (A), posterior (P), superior (S), and inferior (I).

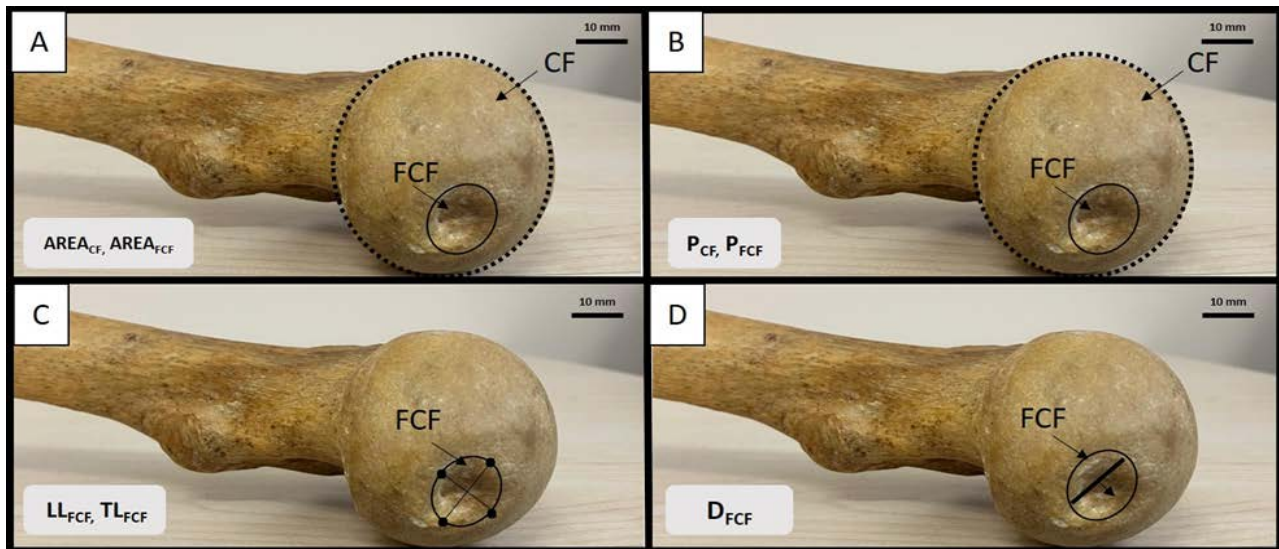


Figure 2. Representative views of the proximal femur showing the morphometric assessment of the fovea capitis femoris (FCF) in relation to the caput femoris (CF). **(A)** Measurement of the total surface area of the femoral head ($AREA_{CF}$) and the surface area of the fovea capitis ($AREA_{FCF}$). **(B)** Perimeter measurements of the femoral head (P_{CF}) and the fovea capitis (P_{FCF}). **(C)** Evaluation of the longest longitudinal length (LL_{FCF}) and transverse length (TL_{FCF}) of the fovea. **(D)** Measurement of the depth of the fovea capitis femoris (D_{FCF}). All parameters were measured digitally using high-resolution calibrated images. Scale bars represent 10 mm.

- **Longitudinal Length of the FCF (LL_{FCF}):** The longest diameter of the FCF was measured directly using a caliper.
- **Transverse Length of the FCF (TL_{FCF}):** The shortest diameter of the FCF, oriented perpendicular to the longitudinal axis, was measured with a caliper.
- **Depth of the FCF (D_{FCF}):** The vertical distance from the deepest point of the FCF to the imaginary plane connecting the foveal margins was measured by a caliper.
- **Area of the FCF ($AREA_{FCF}$):** The area was calculated as the surface area enclosed by the geometric shape surrounding the foveal margins, based on mediolateral digital images analyzed via ImageJ.
- **Perimeter of the FCF (PER_{FCF}):** The perimeter was computed based on the traced outline of the FCF on digital images using ImageJ software.

Statistical Analysis

The statistical evaluation was carried out using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was performed to assess the normality of the data distribution for each variable. Variables were analyzed using one-way analysis of variance (ANOVA) to determine statistically significant differences among the study groups. For post-hoc pairwise comparisons, Hochberg's GT2 test was applied, which is suitable for situations with unequal sample sizes between groups. A significance threshold of $p < 0.05$ was adopted for all statistical tests.

Results

The bone numbers and percentages of the typing made according to FCF shapes were given in Table 1. Among the 71 femoral heads analyzed, Type II was the most frequently observed configuration (64.8%, $n=46$) while Types I, III, and V were less common (7.0% each, $n=5$). Descriptive statistics for all morphometric parameters across shape types—including mean $\pm$ standard deviation and minimum-maximum values—were summarized in Table 2. Type V exhibited the highest mean values for both area (27.6 mm²) and perimeter (67.1 mm) of the FCF, whereas Type I had the lowest values in nearly all variables.

The one-way ANOVA revealed statistically significant differences between shape groups in three parameters: longitudinal length (LL) of the FCF ($p = 0.005$), area of the FCF ($p = 0.001$), and perimeter of the FCF ($p = 0.001$) (Table 3). No significant differences were observed in TL or depth values across groups.

According to the post-hoc analysis, femoral heads with Type I FCF demonstrated significantly lower LL values compared to all other groups. Furthermore, significant differences in area and perimeter were observed between Type I and Type II versus Types III, IV, and V, suggesting a measurable distinction in foveal morphology across these categories.

These findings indicated that more compact and less expansive FCF shapes (e.g., Type I) tend to present with smaller morphometric profiles, which may be relevant in understanding anatomical variation, ligament insertion area, or possible vascular implications.

Table 1. Bone numbers and percentages measured according to FCF typing

Type I	Type II	Type III	Type IV	Type V	Total Number
5 (7.0%)	46 (64.8%)	5 (7.0%)	10 (14.2%)	5 (7.0%)	71

Table 2. Descriptive statistics of the parameters evaluated according to groups (mm and mm²)

Type		Perimeter of the CF	Area of the CF	LL of the FCF	TL of the FCF	Depth of the FCF	Area of the FCF	Perimeter of the FCF
Type I	Mean±SD	136.6±9.5	137.0±1.84	12.00±0.71	10.40±1.19	3.24±0.61	10.6±2.0	38.1±4.0
	Min. - Max.	128.4-152.2	121.0-164.0	10.90-12.80	9.70-12.50	2.40-4.10	8.7-13.5	32.9-42.1
Type II	Mean±SD	137.9±11.6	148.0±21.7	16.52±3.09	12.88±2.09	2.40±0.73	15.2±5.6	47.0±9.3
	Min. - Max.	115.3-159.0	100.8-188.8	12.30-24.80	9.20-18.40	1.00-3.80	3.3-29.3	26.8-68.3
Type III	Mean±SD	137.5±15.6	151.9±25.0	19.06±4.49	12.86±2.49	2.50±0.66	23.4±9.2	61.0±12.8
	Min. - Max.	120.4-159.2	115.9-185.1	14.60-25.70	10.10-15.10	1.60-3.30	12.9-34.3	46.8-72.3
Type IV	Mean±SD	146.7±16.7	166.8±26.9	17.61±3.58	11.99±3.23	2.67±0.59	24.7±8.3	59.7±9.7
	Min. - Max.	109.7-171.0	117.2-204.3	11.60-24.30	7.90-18.20	1.40-3.50	12.6-41.6	44.4-77.4
Type V	Mean±SD	140.5±10.1	148.0±17.5	19.40±5.33	14.24±3.20	2.50±0.82	27.6±7.5	67.1±4.0
	Min. - Max.	125.8-152.5	118.9-166.2	11.80-26.80	10.30-17.60	1.90-3.70	21.1-39.3	61.9-73.22

Table 3. ANOVA Table for the comparison of the variables

		Sum of Squares	df	Mean Square	F	p
LL of the FCF	Between Groups	184.388	4	46.097	4.101	0.005*
	Within Groups	741.859	66	11.240		
	Total	926.247	70			
Area of the FCF	Between Groups	1678.137	4	419.534	10.693	0.001*
	Within Groups	2589.535	66	39.235		
	Total	4267.672	70			
Perimeter of the FCF	Between Groups	4105.928	4	1026.482	12.308	0.001*
	Within Groups	5504.259	66	83.398		
	Total	9610.187	70			

df = degree of Freedom, F=Fisher Statistic, *p-values < 0.05

Discussion

The present work aimed to provide a comprehensive morphometric and localization-based evaluation of the FCF using dry femoral specimens. The findings revealed notable differences in FCF measurements across localization types, particularly in longitudinal length, area, and perimeter values. The predominance of the posteroinferior quadrant localization is consistent with previous anatomical reports, supporting the notion that the FCF occupies a relatively fixed position on the femoral head. However, variations in its morphometric dimensions among subtypes suggest that not only its location but also its size and shape may differ substantially between individuals. Numerous anatomical studies have consistently described the FCF as residing in the posteroinferior quadrant of the femoral head, a finding corroborated by the present study. In all specimens examined, the FCF was identified within this region, supporting the notion that its localization is relatively constant across individuals. Perumal et al. pointed out (8) this positional tendency in their assessment of dry femurs; however, they did not provide a detailed quadrant-based classification or morphometric correlation. Similarly, Ceynowa et al. (13) emphasized the surgical relevance of the posteroinferior FCF localization, particularly in hip arthroscopy, where it serves as a reliable intraoperative landmark. The consistent anatomical positioning observed in our study reinforces the clinical utility of the FCF, not only as a point of

reference in imaging and surgical procedures, but also as a potential indicator of preserved vascular architecture, especially in the context of femoral head viability and reconstructive planning. The reproducibility of its location further supports the integration of the FCF in standardized anatomical mapping protocols, particularly in orthopedic and anthropological applications.

The present study revealed that Type I FCFs, characterized by a compact configuration, exhibited the smallest values across multiple morphometric parameters, including longitudinal length, area, and perimeter. This finding aligns with the results reported by Sampatchalit et al. (9), who demonstrated a correlation between the thickness of the ligamentum capitis femoris and the dimensions of the FCF. According to their MRI-based investigation, larger and deeper foveae were associated with hypertrophied ligaments while smaller foveae were typically linked to thinner or degenerative ligaments. These results support the notion that ligamentous loading and biomechanical stress may influence foveal morphology, potentially through adaptive responses or developmental shaping mechanisms.

Moreover, the reduced surface area in Type I configurations may imply a narrower insertion point for the ligament, which in turn could impact the mechanical stability of the hip joint in certain positions, particularly during flexion and external rotation. Additionally, since the fovea also accommodates minor vascular foramina, its smaller size may correspond to limited vascular ingress, a factor

of clinical relevance in conditions such as avascular necrosis of the femoral head, where compromised blood flow plays a central role in pathogenesis (1, 9). These interpretations highlight the multifactorial significance of foveal morphometry-where size not only reflects anatomical variation but also serves as a potential marker for ligament integrity and vascular support. As such, the identification of smaller Type I FCFs in anatomical studies could inform both radiological evaluations and preoperative planning in orthopedic practice.

Based on the present analysis, Type II FCFs, characterized by a round morphology, were the most frequently observed configuration, accounting for 64.8% of the cases. This high prevalence suggests that Type II may represent the "average" or typical anatomical structure, offering a balanced form that provides both structural support and vascular function. Similar distributions have been reported in previous anatomical studies conducted on both cadaveric specimens and radiological imaging, indicating that circular or near-circular foveae are the most common variant (14). The moderate longitudinal length, area, and perimeter values observed in Type II FCFs suggest that this morphology offers adequate surface for ligament attachment and sufficient space for vascular foramina. Its symmetrical shape and frequent occurrence make it a dependable anatomical landmark in arthroscopic and radiological procedures, especially during femoral neck fracture repair or joint-preserving surgeries. The structural balance of Type II may reduce mechanical stress while ensuring vascular continuity, highlighting its relevance in both anatomical assessment and surgical planning.

As observed in this research, Type V FCFs demonstrated the highest mean values for both area and perimeter, suggesting a morphologically broader and more expansive structure. This anatomical configuration might have provided a wider surface area for the insertion of the ligamentum capitis femoris, potentially enhancing the ligament's functional capacity. Cerezal et al. highlighted the role of the ligamentum teres in contributing to hip joint stability, particularly during flexion, adduction, and external rotation, and emphasized its relevance in both surgical planning and pathological assessment (1).

Moreover, a larger foveal surface may accommodate a greater number or size of vascular foramina, which serve as entry points for small vessels supplying the femoral head. Zhao et al. reported that the absence or reduction of nutrient foramina in the FCF may compromise vascular inflow to the femoral head and is a potential risk factor for osteonecrosis, particularly following trauma or corticosteroid therapy (15). This suggests that a broader foveal morphology, as seen in Type V FCFs, could correlate with enhanced vascular supply and may confer a protective advantage in terms of femoral head viability.

Collectively, these findings imply that larger FCF morphologies may offer dual clinical advantages by providing a

more robust site for ligamentous anchorage and enhancing vascular access to the femoral head. Recognition of such anatomical variations may prove valuable in arthroscopic navigation, preoperative surgical planning, and risk stratification for conditions such as avascular necrosis or femoral head dislocation.

Additionally, the femoral head surface area and perimeter measurements obtained in this study are generally consistent with previously reported morphometric investigations. Notably, the average femoral head perimeter values align closely with those reported by Perumal et al. and Yazar et al. supporting the comparability of measurement techniques (8, 12). These studies documented average perimeter lengths in the range of 135–145 mm, which closely match the mean values recorded in our sample. These findings suggest that assessing femoral head surface area and perimeter is not only relevant for morphometric documentation but also carries clinical importance. Accurate evaluation of femoral head geometry plays a critical role in orthopedic procedures such as total hip arthroplasty, avascular necrosis assessment, and prosthesis planning (13, 16).

The morphometric characteristics of FCF are not only clinically relevant but also hold significance in anthropological research. Individual variations observed in FCF morphology may enhance the utility of the femoral head in forensic identification, including sex determination, age estimation, and population-based comparisons. Perumal et al. reported that FCF morphology can vary with age and sex, suggesting its potential value in forensic anthropology (8). These findings highlight that, beyond its surgical and radiological importance, the FCF may serve as a functional anatomical marker in the osteological assessment of human remains. Morphometric variability of the femoral head reflects individual variation and may serve as a useful parameter in studies on age estimation, sex determination, or population differences. As such, femoral head dimensions may be considered valuable reference data in larger-scale anthropological analyses (17).

In conclusion, this study presented a morphometric and localization-based evaluation of the FCF in relation to femoral head geometry. Significant differences in FCF measurements-particularly in longitudinal length, area, and perimeter-were observed across quadrantal localization types. Type I FCFs showed the smallest dimensions, suggesting limited ligament attachment surface and vascular access, which may have clinical implications in cases such as avascular necrosis, femoral neck fractures, and hip dysplasia.

Given that the FCF often serves as the only consistently visible arthroscopic landmark, a detailed understanding of its morphology is essential for accurate surgical navigation and graft placement in hip-preserving procedures. These findings might also inform radiological interpretation and preoperative planning. Future studies incorporating radiological and clinical data are needed to further

explore the diagnostic and prognostic value of FCF morphology.

Strengths and Limitations of the Study

One of the primary strengths of this study is the use of dry femoral specimens, which allowed for precise morphometric evaluation without interference from soft tissue structures. This enabled the accurate delineation of anatomical landmarks and reliable measurement of surface-based parameters. However, a notable limitation is the lack of demographic data—specifically age and sex—associated with the specimens. As a result, it was not possible to assess potential morphometric variations based on demographic subgroups, which may influence the generalizability of the findings across different populations.

Ethical Approval: This study does not include experiments on human participants or humans/animals. Since the skulls belong to the Department of Anatomy, there is no ethical committee decision. The authors affirm that the study was conducted in accordance with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions.

Author Contributions:

Concept: H.G.

Literature Review: H.G.

Design : H.G., N.T.C.

Data acquisition: H.G.

Analysis and interpretation: N.T.C.

Writing manuscript: H.G., N.T.C.

Critical revision of manuscript: H.G., N.T.C., Y.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Pleural Fluid Gas Analysis in Diagnosing and Differentiating Pulmonary Diseases

Plevral Sıvı Gaz Analizinin Pulmoner Hastalıkların Tanısında ve Ayırımında Kullanımı

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Abstract

Background: This study aimed to evaluate pleural fluid gas parameters in patients with different underlying pulmonary diseases to assess their diagnostic implications.

Materials and Methods: This study conducted at Akdeniz University Pulmonology Department and Harran University Pulmonology Department. The retrospective study included 118 patients with pleural effusion confirmed via imaging between January 2018 and December 2024. Pleural fluid samples collected by thoracentesis underwent gas analysis (pO₂, pCO₂, pH, HCO₃) and standard biochemical and cytological evaluations. Comparative analysis of gas characteristics was performed across diagnostic categories with a significance threshold of p < 0.05.

Results: In this study, 87 of 118 patients underwent arterial blood gas analysis, with a mean age of 66.4±14.2 years and 72.4% being male. Acidic, normal, and alkaline pleural fluid pH values were observed in 25.3%, 26.4%, and 48.3% of patients, respectively. Most effusions were exudative (83.9%), and unilateral (81.6%), with malignancy (29.9%), pneumonia (35.6%), and heart failure (16.1%) being the leading causes. Among pneumonia cases, 45.1% had complicated effusions or empyema. Transudative effusions were associated with older age, higher pH, and lower LDH, pCO₂, and protein levels (p<0.05). Compared to other causes, pneumonia-related effusions were more likely to be exudative, occur in males, and have higher protein levels. Malignant effusions showed significantly higher HCO₃ and protein levels (p<0.05).

Conclusions: Pleural fluid gas analysis may offer valuable diagnostic insights, particularly in differentiating infectious from non-infectious effusions.

Keywords: Pleural Fluid Analysis, Pneumonia, Pulmonary Diseases

Öz

Amaç: Bu çalışma, farklı altta yatan pulmoner hastalıkları olan hastalarda plevral sıvı gaz parametrelerini değerlendirek tanılabilirliklerini incelemeyi amaçlamaktadır.

Materyal ve Metod: Akdeniz Üniversitesi ve Harran Üniversitesi Göğüs Hastalıkları Bölümü'nde gerçekleştirilen bu retrospektif çalışma, Ocak 2018 ile Aralık 2022 arasında görüntüleme ile doğrulanmış plevral efüzyonu olan 118 hastayı içermektedir. Torasentez ile toplanan plevral sıvı örneklerine gaz analizi (pO₂, pCO₂, pH, HCO₃) ve standart biyokimyasal ve sitolojik değerlendirmeler yapıldı. Gaz özellikleri, tanı kategorileri arasında karşılaştırmalı olarak analiz edildi ve anlamlılık eşiği p < 0,05 olarak belirlendi.

Bulgular: Bu çalışmada, 118 hastanın 87'sine arteriyel kan gazı analizi uygulandı; hastaların ortalama yaşı 66,4±14,2 yıl olup, %72,4'ü erkekti. Plevral sıvı pH değeri hastaların %25,3'ünde asidik, %26,4'ünde normal ve %48,3'ünde alkalen olarak saptandı. Plevral sıvıların büyük çoğunluğu (%83,9) ekssüdatif ve %81,6'sı unilateraldı. En sık nedenler malignite (%29,9), pnömoni (%35,6) ve kalp yetmezliği (%16,1) olarak belirlendi. Pnömoni tanısı alan olguların %45,1'inde komplike efüzyon veya ampiyem vardı. Transüdatif efüzyonlar daha ileri yaş, daha yüksek pH ve daha düşük LDH, pCO₂ ve protein düzeyleri ile ilişkiliydi (p<0,05). Pnömoniye bağlı efüzyonlar, diğer nedenlere kıyasla daha çok erkeklerde görülmekte, daha yüksek protein düzeylerine sahip olmakta ve daha sık ekssüdatif özellik göstermekteydi. Malignite grubunda ise HCO₃ ve total protein düzeyleri anlamlı olarak daha yüksekti (p<0,05).

Sonuç: Plevral sıvı gaz analizi, özellikle enfeksiyöz ve enfeksiyöz olmayan efüzyonları ayırt etmede yararlı tanılabilir bilgiler sunabilir.

Anahtar Kelimeler: Plevral efüzyon, Pnömoni, Pulmoner hastalıklar

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Introduction

Pleural effusion is a common manifestation in various pulmonary diseases, including pneumonia, empyema, tuberculosis, malignancy, and heart failure (1–7). The evaluation of pleural fluid characteristics is crucial for diagnosing the underlying cause of the effusion. Traditionally, pleural fluid analysis includes the assessment of its physical, chemical, and cytological properties (4,5,7–9). However, the analysis of pleural fluid gas characteristics, such as oxygen (pO₂) and carbon dioxide (pCO₂) levels, has not been extensively explored. A few studies have thoroughly investigated pH as a characteristic of pleural fluid gas (10–12). Pleural fluid pH is a crucial diagnostic marker, particularly in distinguishing complicated parapneumonic effusion, where pH is typically below 7.0 (10,13). It also serves to differentiate between malignant and tuberculous effusions; a pH below 7.30 strongly suggests tuberculosis, while a value above 7.30 favors malignancy. The biochemical profile of pleural fluid—including pH, pCO₂, pO₂, HCO₃⁻, and glucose—varies depending on the total white blood cell (WBC) count and the integrity of the pleura (10). Because blood gas analyzers are widely available in clinical settings, pH and gas measurements can offer rapid, cost-effective diagnostic support compared to culture-based methods (14). An animal study reported that peritoneal fluid pH, PCO₂, and PO₂ levels could distinguish bacterial infections from other etiologies (15).

The potential diagnostic value of pleural fluid gas analysis lies in its ability to provide insights into the metabolic and respiratory status of the pleural space. Alterations in pleural fluid gas tensions could reflect local pathophysiological processes, such as increased metabolic activity of pleural cells, impaired gas diffusion, or abnormal vascular permeability (8,16–18). This study aims to investigate the pleural fluid gas characteristics in patients with different pulmonary diseases and to evaluate their diagnostic implications.

Materials and Methods

Study Design and Population

This retrospective study was conducted at Akdeniz University Pulmonology Department and Harran University Pulmonology Department between Jan 1, 2018 and December 31, 2024. The study included patients presenting with pleural effusion, confirmed by chest X-ray or ultrasound, who underwent thoracentesis for diagnostic purposes. Patients with a history of recent thoracic surgery, chest trauma, or known pleural disease were excluded.

Sample Collection

Pleural fluid samples were obtained via thoracentesis under sterile conditions. Each patient provided informed consent prior to the procedure. Approximately 50–100 mL of pleural fluid was collected in heparinized syringes to prevent clotting. Samples were immediately transported to the laboratory for analysis. There was no need for ice as they are measured immediately.

Pleural Fluid Gas Analysis

Pleural fluid gas analysis was performed using a blood gas analyzer. The following parameters were measured: Partial pressure of oxygen (pO₂), Partial pressure of carbon dioxide (pCO₂), pH, Bicarbonate (HCO₃⁻).

In addition to gas analysis, pleural fluid was subjected to standard biochemical and cytological analysis, including: Total protein, Lactate dehydrogenase (LDH), Glucose, Cell count and differential, Gram stain and culture, cytological examination.

The cause of pleural effusion was primarily determined based on pathological examination, culture growth, and/or clinical-radiological-biochemical assessments, if available.

Pneumonia was defined as the presence of cough, sputum production, fever (>38°C), elevated acute-phase reactants (e.g., C-reactive protein or procalcitonin), and radiographic evidence of pulmonary infiltration on chest imaging (X-ray or computed tomography).

Complicated Pleural Effusion and Empyema Classification

Pleural fluid samples were further evaluated for the presence of complicated parapneumonic effusion or empyema. Empyema was defined as pleural fluid with purulent appearance or positive Gram stain/culture. Complicated parapneumonic effusion was identified based on low pleural fluid pH (<7.20), low glucose (<40 mg/dL), or loculated effusion on imaging. These definitions were used to categorize the pneumonia-related effusions.

Data Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The pleural fluid gas parameters were compared across different diagnostic categories using appropriate statistical tests (e.g., independent t-test, chi-square test). In the chi-square analysis, due to the insufficient number of cases for each cause of pleural effusion, the other groups were combined and compared with the pneumonia group. Similarly, the malignancy group was compared with the combined of other groups. Statistical significance was set at $p < 0.05$.

Results

In this study, a total of 118 patients were evaluated. Of these patients, 87 underwent arterial blood gas analysis. The average age of the patients was 66.4 years, with a standard deviation of 14.2 years. Among these 87 patients, 24 were female (27.6%) and 63 were male (72.4%). Pleural fluid analysis showed that 22 patients (25.3%) had acidic pleural fluid, 42 patients (48.3%) had alkaline pleural fluid, and 23 patients (26.4%) had pleural fluid within the normal range. In the medical histories, 27 patients (31%) had a history of malignancy, 35 patients (40.2%) had hypertension, 17 patients (19.5%) had heart failure, and 18 patients (20.7%) had diabetes mellitus.

Pathological examination of the pleural fluid revealed malignancy in 5 (5.7%) patients, and pleural fluid cultures showed bacterial growth in 7 (8.0%) patients. Regarding the nature of

the pleural fluid, 14 (16.1%) patients had transudative pleural fluid, while 73 (83.9%) had exudative pleural fluid. Chest X-rays indicated unilateral pleural effusion in 71 (81.6%) patients and bilateral pleural effusion in 16 (18.4%) patients. Additionally, 54 (62.1%) patients had a history of smoking. Based on further investigations, the pleural effusion was attributed to malignancy in 26 patients (29.9%), heart failure in 14 patients (16.1%), pneumonia in 31 patients (35.6%), and the cause remained undetermined in 16 patients (18.4%).

Among the 31 patients diagnosed with pneumonia, 8 patients (25.8%) were classified as having empyema, and 6 patients (19.3%) had complicated parapneumonic effusions without frank empyema. Thus, a total of 14 patients (45.1%) with pneumonia had either complicated effusions or empyema. The remaining 17 patients (54.9%) had uncomplicated parapneumonic effusions. The basic characteristics of the patients are provided in Table 1.

Table 1. The basic characteristics of the patients

	Features	n	%
Sex	Male	63	72.4
	Female	24	27.6
pH	Asidic	22	25.3
	Alkalic	42	48.3
	Normal	23	26.4
Light	Transudative	14	16.1
	Exudative	73	83.9
Smoking	Current/exsmoker	54	62.1
	Nonsmoker	23	26.4
	Unknown	10	11.5
X-ray	Unilateral	71	81.6
	Bilateral	16	18.4
Culture growths	Positivity	7	8.0
Pathologic examintaion	Diagnostic	5	5.7
Pleural fluid etiology	Malignancy	26	29.9
	Heart failure	14	16.1
	Pneumonia	31	35.6
	Unknown	16	18.4
		Mean	sd
Age	years	66.4	14.2
Pleural fluid	pH	7.39	0.19
	pCO ₂ (mmHg)	42.5	16.3
	pO ₂ (mmHg)	119.7	31.4
	hCO ₃ (mmol/L)	25.1	5.8
	Total protein (g/L)	30.9	16.4
	LDH (U/L)	562.8	1005.3
	Albumin (g/L)	35.4	9.3
	White blood cell (thousand/mm3)	2.1	1.4

When comparing transudative and exudative fluids, it was found that patients with transudative effusion were older (73.8 vs 67.2, $p=0.035$) and had higher pH (7.48 vs 7.38,

$p=0.001$), and lower LDH levels (142 vs 640, $p=0.001$), pCO₂ levels (36.5 vs 43.7, $p=0.009$) and total protein levels (28.0 vs 31.5, $p=0.039$) (Table 2).

Table 2. Comparison of transudative and exudative fluids

	Transudative (n=14)	Exudative (n=73)	p
Age, yr (mean±sd)	73.8±7.9	67.2±11.7	0.035
pH (mean±sd)	7.48±0.1	7.38±0.2	0.001
pCO ₂ , mmHg (mean±sd)	36.5±6.3	43.7±17.4	0.009
pO ₂ , mmHg (mean±sd)	123.0±31.9	119.1±31.5	0.670
hCO ₃ , (mmol/L) (mean±sd)	27.4±6.5	26.1±5.9	0.137
LDH ,(U/L) (mean±sd)	142.3±68.7	640.9±1077.4	0.001
Total protein (g/L) (mean±sd)	28.0±11.3	31.5±17.4	0.045
Albumin, (g/L) (mean±sd)	18.7±5.6	22.7±6.6	0.039
White blood cell (mean±sd)	1.6±1.1	1.3±1.1	0.573
Male n(%)	10 (71.4)	53 (72.6)	0.580
Alkalic n(%)	9 (64.3)	33 (45.2)	0.214
Malignancy n(%)	5 (35.7)	22 (30.1)	0.450
Hypertension n(%)	7 (50.0)	28 (38.4)	0.300
Diabetes mellitus n(%)	5 (35.7)	13 (17.8)	0.126
Heart failure n(%)	8 (57.1)	9 (12.3)	0.001
Unilateral fluid n(%)	12 (85.7)	59 (80.8)	0.500
Current/exsmoker n(%)	10 (71.4)	44 (60.3)	0.152

Compared to patients with other conditions (e.g., heart failure, malignancy), those diagnosed with pneumonia had higher pleural fluid protein levels ($p=0.032$), a higher proportion of males ($p=0.013$), and a greater likelihood of exu-

dative effusion ($p<0.001$) (Table 3). When comparing malignancy to other causes, the HCO_3 level ($p=0.001$) and total protein level ($p=0.036$) were higher in the malignancy group (Table 4).

Table 3. Comparison of pleural fluid properties according to etiology (pneumonia vs others)

	Pneumonia (n=31)	Others (n=56)	p
Age, yr (mean±sd)	65.7±15.6	66.9±13.6	0.346
pH (mean±sd)	7.34±0.2	7.42±0.1	0.062
pCO ₂ , mmHg (mean±sd)	45.1±18.7	41.1±17.7	0.163
pO ₂ , mmHg (mean±sd)	113.8±31.8	123.0±31.0	0.197
hCO ₃ , (mmol/L) (mean±sd)	25.5±6.2	26.8±5.8	0.153
Total protein, (g/L) (mean±sd)	35.8±14.3	28.1±17.1	0.032
LDH, (U/L) (mean±sd)	633.5±1199.3	518.5±872.2	0.399
Albumin, (g/L) (mean±sd)	21.1±5.5	22.5±7.1	0.305
White blood cell (mean±sd)	1.1±1.1	1.5±1.1	0.287
Male n(%)	28 (87.5)	35 (63.6)	0.013
Alkalic n(%)	13 (40.6)	29 (52.7)	0.099
Hypertension n(%)	12 (37.5)	23 (41.8)	0.434
Diabetes mellitus n(%)	7 (21.9)	11 (20.0)	0.521
Exudative n(%)	32 (100)	41 (74.5)	<0.001
Unilateral fluid n(%)	27 (84.4)	44 (80.0)	0.419
Current/exsmoker n(%)	23 (71.9)	31 (56.4)	0.223

Table 4. Comparison of malignant and non-malignant pleural effusions

	Malignant (n=27)	Others (n=60)	p
Age, yr (mean±sd)	65.3±8.3	67.0±16.3	0.603
pH (mean±sd)	7.42±0.1	7.38±0.2	0.324
pCO ₂ , mmHg (mean±sd)	40.9±7.9	43.3±18.9	0.530
pO ₂ , mmHg (mean±sd)	120.8±29.2	119.2±32.6	0.827
hCO ₃ , (mmol/L) (mean±sd)	28.6±4.7	23.7±5.7	0.001
Total protein, (g/L) (mean±sd)	36.8±11.1	28.4±17.7	0.036
LDH, (U/L) (mean±sd)	335.8±308.2	649.8±1158.2	0.205
Albumin, (g/L) (mean±sd)	21.9±7.4	16.1±9.5	0.009
Male n(%)	20(74.1)	43 (71.7)	0.517
Alkalic n(%)	15 (55.6)	27 (45.0)	0.565
Hypertension n(%)	8 (29.6)	27 (45.0)	0.132
Diabetes mellitus n(%)	7 (25.9)	11 (18.3)	0.296
Exudative n(%)	22 (81.5)	51 (85.0)	0.450
Unilateral fluid n(%)	19 (70.4)	52 (86.7)	0.067
Current/exsmoker n(%)	17 (63.0)	37 (61.7)	0.725

Discussion

This study provides a comprehensive analysis of pleural fluid gas characteristics in patients with various pulmonary diseases, highlighting their potential diagnostic implications. Our findings underscore the significance of pleural fluid gas analysis as an adjunct to traditional pleural fluid evaluations. In our study, it was found that patients with pneumonia had pleural fluid with higher protein levels, and a greater likelihood of exudative effusion compared to other groups. Additionally, malignancy group had pleural fluid with higher protein levels and HCO_3 levels.

The observation that patients with transudative pleural effusions were older and had higher pH, lower LDH levels, albumin levels and total protein levels aligns with existing literature. Transudative effusions are often associated with systemic conditions like heart failure, which predominantly affects older populations. The elevated biochemical markers

in transudative effusions reflect the underlying pathophysiology, where systemic factors lead to fluid accumulation without significant local inflammation. In addition to pleural fluid gas analysis, the evaluation of hematological and biochemical parameters such as C-reactive protein (CRP), mean platelet volume (MPV), and platelet count has been shown to aid in differentiating exudative from transudative effusions. These parameters, when used alongside traditional criteria, may enhance diagnostic accuracy in determining the etiology of pleural effusions (19).

In inflammatory events, phagocytic activity results in acid accumulation, leading to a decrease in pH (8). In pleural effusions caused by tuberculosis or other microorganisms, pH is consequently low. In patients with pneumonia, pleural fluid analysis revealed distinct characteristics compared to those with other underlying conditions. Pneumonia-associated effusions exhibited lower pH, higher pCO₂, and lower

HCO₃ levels, indicating a more acidic environment and altered gas exchange within the pleural space. Various studies in the literature have shown that in infectious conditions like tuberculosis, pH decreases, while in malignancies, pH remains above 7.30 (10,20,21). The pCO₂ measured in pleural fluid, like pH, is significant in diagnosing infectious diseases (11,22). However, our study found that the pH in pneumonia patients was not significantly lower compared to other conditions. This discrepancy may be due to the timing of pleural fluid sampling, as pH levels can fluctuate depending on the stage of infection and treatment status. Additionally, variations in host immune response and bacterial virulence could influence the extent of acid production within the pleural space.

In parapneumonic effusion, the presence of diffuse inflammation of the pleural membrane decreases free gas exchange between blood and pleural fluid through the inflamed membrane. As a result, the pH of parapneumonic effusion is lower than normal because CO₂ in the pleural fluid cannot diffuse freely. Sobhey et al. (10) attributed the reduction in pleural fluid pH to the buildup of glucose metabolism byproducts, specifically CO₂ and lactic acid. In our study, pCO₂ levels in patients diagnosed with pneumonia were found to be higher than the normal range. However, when compared to other etiologies, this difference was not statistically significant. One possible explanation is the substantial proportion of cancer patients in the non-pneumonia group, which may have influenced the overall results. Malignant effusions are typically associated with less pronounced metabolic activity and a relatively stable pleural environment, potentially mitigating differences in pCO₂ levels. Additionally, variations in disease severity and the timing of pleural fluid sampling could have contributed to the observed findings. Notably, approximately one-fourth of pneumonia cases in our cohort were diagnosed as empyema, a condition characterized by intense inflammation and purulent fluid accumulation. Among the 31 patients with pneumonia, 8 cases (25.8%) were diagnosed with empyema based on clinical and radiological findings. In these patients, the pleural fluid was characterized by a purulent appearance, markedly low pH, and elevated pCO₂ levels. Given that empyema represents a severe inflammatory process within the pleural space, it is expected to cause significant alterations in pleural fluid gas parameters. The presence of empyema in this subgroup likely contributed to the overall acid-base imbalance observed in the pneumonia cohort. Furthermore, when evaluating the clinical significance of pleural gas parameters, it is important to consider such complicating factors, as they may distort the interpretation of results. Therefore, future studies should aim to separately analyze uncomplicated parapneumonic effusions and empyema cases to better elucidate their respective gas profile characteristics. These factors highlight the complexity of pleural fluid acid-base balance and suggest that multiple mechanisms influence pH and gas exchange in different pathological conditions. Some studies have highlighted that pleural fluid pCO₂ levels

may be lower and pO₂ levels higher in malignant diseases (10). However, in our study, there were no statistically significant differences in pleural fluid pH, pCO₂, or pO₂ levels between malignant diseases and other conditions. Although there were no statistically significant differences in pleural fluid gas characteristics between patients with malignancy and those with other causes, identifying malignancy through pathological examination of pleural fluid remains crucial. The ability to diagnose malignancy from pleural fluid highlights the importance of careful cytological evaluation, in addition to biochemical and gas analyses.

Our findings align with previous reports suggesting that the pleural fluid pH and gas parameters are not solely disease-specific but are also influenced by pleural integrity and the inflammatory environment (10–12). While empyema exhibits markedly low pH due to intense neutrophilic infiltration and diffuse pleural inflammation, malignant and transudative effusions may retain near-normal pH levels owing to preserved regions of healthy pleura that allow for effective gas exchange (10,11). Interestingly, post-pleurodesis malignant effusions demonstrate lower pH despite a lower WBC count, likely due to fibrosis-induced impairment of gas diffusion rather than cellular inflammation (10). Additionally, the technical reliability of blood gas analyzers for pleural pH and pCO₂ assessment has been validated, although anaerobic sample handling remains essential to avoid artificial pH elevation (11). These insights emphasize the combined importance of pleural pathophysiology and sample handling in interpreting pleural fluid gas analysis.

HCO₃ is another parameter that can be analyzed in pleural fluid. In the study by Sobhey and Naglaa, it was reported that HCO₃ levels were the lowest in malignant diseases and the highest in empyema. In our study, due to the limited number of patients, a direct comparison of all groups was not feasible. Contrary to the findings of Sobhey and Naglaa (10), in our study, HCO₃ levels were found to be higher in malignant patients compared to other diseases.

Despite the valuable findings, this study has limitations, including its retrospective design and the relatively small sample size. Additionally, investigating the role of other gas parameters, such as oxygen and carbon dioxide levels, in different stages of pulmonary diseases could provide a deeper understanding of the pathophysiological processes at play.

Conclusion

In conclusion, pleural fluid gas analysis, when combined with traditional biochemical and cytological evaluations, offers a robust approach for diagnosing and understanding the underlying causes of pleural effusions. The distinct gas characteristics associated with different pulmonary diseases highlight the potential of this method in clinical practice, ultimately improving patient outcomes through more accurate diagnosis and targeted treatments. It is important to note that the interpretation of pleural fluid gas analysis results should be done in conjunction with other diagnostic tests, such as imaging studies and clinical examination.

Ethical Approval: The study protocol was approved by the Institutional Review Board (IRB) of Akdeniz University (06.03.2025/225). All procedures were conducted in accordance with the Declaration of Helsinki and local regulations. Patient confidentiality was maintained throughout the study.

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Literature Review: F.Ü., A.G.Ç., B.K., H.T.

Design : İ.K., F.Ü.

Data acquisition: A.G.Ç., B.K. H.T.

Analysis and interpretation: F.Ü.

Writing manuscript: F.Ü., A.G.Ç.

Critical revision of manuscript: İ.K., F.Ü., H.T.

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Triglyceride Glucose Index: As A Glycemic Control Indicator

Glisemik Kontrol Belirteci Olarak Trigliserid Glukoz İndeksi

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Abstract

Background: Type-2 Diabetes Mellitus (T2DM) continues to be the most common endocrine disease today. Easily accessible, accurate and reproducible markers are needed in addition to the accepted markers to evaluate insulin resistance (IR) and glycemic control. Therefore, our study aimed to evaluate the use of triglyceride glucose index (TyGI) as an indicator for insulin resistance and glycemic control.

Materials and Methods: Triglyceride (TG), HbA1c, fasting blood glucose (FBG), and total insulin (TI) values of 953 samples, studied simultaneously in our Faculty of Medicine Hospital Laboratory between March 2023 and August 2023, were retrospectively evaluated. The patients were divided into two groups as good and/or poor glycemic control regarding their HbA1c, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values. Receiver Operating Characteristic (ROC) analysis was performed to assess the ability of TyGI to discriminate between good and/or poor glycemic control for each of HOMA-IR and HbA1c. Statistical significance level was accepted as $p < 0.05$. Multivariate logistic regression analysis was performed as well.

Results: A total of 953 patients; with the mean age of 40.83 ± 16.78 participated in the study. According to gender, all parameters except age ($p: 0.613$) showed significant differences ($p < 0.001$). There were significant differences for FBG, HbA1c, HOMA-IR, TI, TG and TyGI parameters according to cut-off values in all two study groups ($p < 0.001$). TG showed high positive correlation with TyGI ($r: 0.796$, $p < 0.001$) and moderate positive correlation with FBG ($r: 0.616$, $p < 0.001$) for both study groups, but low positive correlation with the others. TyGI, had a high selectivity and specificity for HOMA-IR with ≥ 8.76 cut-off value (AUC:0.72, Se:65%, Sp:70% ($p < 0.001$: 95% CI:0.69-0.75)). In ROC analysis, TyGI had the highest AUC value for HbA1c, and the lowest for HOMA-IR group. The risk of poor glycemic control for HOMA-IR in men is 2.247 times higher than in women. As age increases by one unit, the risk of poor glycemic control for HOMA-IR increases by 1.045 times.

Conclusions: TyGI was significantly raised in incident T2DM patients with poor glycemic control. TyGI can act as a simple and useful markers that have the strong predictive capability to identify insuline resistance and anticipate the development of incident T2DM.

Keywords: Diabetes Mellitus, Insulin Resistance, Glycemic Control, Triglyceride, Glucose

Öz

Amaç: Tip-2 Diyabetes Mellitus (T2DM) günümüzde en yaygın endokrin hastalık olmaya devam etmektedir. İnsülin direncini (İD) ve glisemik kontrolü değerlendirmek için kabul görmüş belirteçlere ek olarak kolay erişilebilir, doğru ve tekrarlanabilir belirteçlere ihtiyaç duyulmaktadır. Bu nedenle çalışmamızda insülin direnci ve glisemik kontrol için bir göstergesi olarak trigliserid glukoz indeksinin (TyGI) kullanımını değerlendirmeyi amaçladık.

Materyal ve Metod: Mart 2023 ile Ağustos 2023 tarihleri arasında Tıp Fakültesi Hastanesi Laboratuvarımızda eş zamanlı olarak incelenen 953 örneğin trigliserid (TG), HbA1c, açlık kan şekeri (AKŞ) ve toplam insülin (TI) değerleri geriye dönük olarak incelendi. Hastalar; HbA1c ve homeostasis model değerlendirilmesiyle tahmin edilen insülin direnci (HOMA-İD) değerleri açısından iyi glisemik kontrol ve/veya kötü glisemik kontrol olmak üzere iki gruba ayrıldı. TyGI'nin, HOMA-İD ve HbA1c'nin her biri için iyi ve/veya kötü glisemik kontrol arasında ayırım yapabilme yeteneğini değerlendirmek amacıyla Duyarlılık ve Özgüllük Analizi (DÖA) yapıldı. İstatistiksel anlamlılık düzeyi $p < 0.05$ olarak kabul edildi. Ayrıca çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Çalışmaya yaş ortalaması 40.83 ± 16.78 olan toplam 953 hasta katıldı. Cinsiyete göre yaş ($p: 0.613$) hariç tüm parametreler anlamlı farklılıklar gösterdi ($p < 0.005$). Her iki çalışma grubunda da kesme değerlerine göre AKŞ, HbA1c, HOMA-İD, TI, TG ve TyGI parametreleri için anlamlı farklılıklar vardı ($p < 0.001$). TG, her iki çalışma grubu için de TyGI ile yüksek pozitif korelasyon ($r: 0.796$, $p < 0.001$) ve AKŞ ile orta derecede pozitif korelasyon ($r: 0.616$, $p < 0.001$) gösterdi ancak diğerleri ile düşük pozitif korelasyon gösterdi. TyGI, ≥ 8.76 kesim değeri (Eğri Altı Alan (EAA):0.72, Duyarlılık:%65, Seçicilik:%70 ($p < 0.001$: %95 GA:0.69-0.75)) ile HOMA-İD için yüksek seçiciliğe ve duyarlılığa sahipti. TyGI; HbA1c için en yüksek EAA'ya ve HOMA-İD grubu için ise en düşük EAA'ya sahipti. Erkeklerde HOMA-İD için kötü glisemik kontrol riski kadınlara göre 2.247 kat daha fazladır. Yaş bir birim arttıkça, HOMA-İD için kötü glisemik kontrol riski 1.045 kat artmaktadır.

Sonuç: TyGI, kötü glisemik kontrole sahip yeni T2DM hastalarında önemli ölçüde yükselmiştir. TyGI, insülin direncini belirlemek ve yeni T2DM gelişimini önceden tespit etmek için güçlü öngörücü yeteneğe sahip basit ve kullanışlı bir belirteç olarak işlev görebilir.

Anahtar Kelimeler: Diabetes Mellitus, İnsülin Direnci, Glisemik Kontrol, Trigliserit, Glukoz

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Introduction

Type-2 Diabetes Mellitus (T2DM), characterized by chronic hyperglycemia, can cause damage to different organ systems and lead to life-threatening health complications. (1). Obesity, a poor diet, and a sedentary lifestyle are major risk factors for T2DM (2, 3). According to various regional and nationwide studies, the total prevalence of DM in Türkiye is between 12.7% and 14.7% (4-7). T2DM diagnosis and treatment are costly and can be a significant burden to people. (8).

Good glycemic control is very important in the management of diabetes, as it reduces the risk of complications. Insulin resistance (IR) is characterized by decreased insulin sensitivity of peripheral tissues. IR, which plays an important role in the pathogenesis of metabolic syndrome and diabetes, can occur 10 to 20 years before the definitive diagnosis of T2DM (9). Glycated hemoglobin A1c (HbA1c), reflects average blood glucose in patients over approximately 3 months. Keeping HbA1c below 7% of target value has been shown to reduce vascular complications of diabetes (10, 11). In patients with T2DM, the risk of cardiovascular disease (CVD) increases by 18% for every 1% increase in absolute HbA1c value.(12). Diabetic dyslipidemia is another risk factor for CVD in diabetic patients. It is characterized by a decrease in high-density lipoprotein cholesterol (HDL-C), an increase in triglycerides (TG), and postprandial lipemia. Apart from these, the more atherogenic small, dense LDL is converted from low-density lipoprotein cholesterol (LDL-C) (13).

Multivariate scores developed to identify those at high risk of diabetes among healthy individuals are based on a combination of risk factors (metabolic syndrome, first-degree relative with diabetes, history of gestational diabetes, etc.), but they generally have poor predictive value (14). In order to accurately predict future diabetes, early circulatory biomarkers such as high-sensitivity C-reactive protein, interleukin-6, or tumor necrosis factor-alpha can be used (15). However, they are also inefficient for screening and are inconvenient and costly to use in daily laboratory practice.

In order to evaluate insulin sensitivity, the medical profession has therefore looked for substitute, indirect biomarkers. Strong predictive ability, high specificity, and sensitivity make Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Fasting Insulin (FI) popular surrogate markers for IR assessment. However, although being more practical than the hyperinsulinemic-euglycemic clamp technique, they are still difficult to use in day-to-day situations (16, 17). Since insulin is not measured in every hospital, and due to transportation problems of blood samples from small family medicine offices to the hospital laboratories or HOMA-IR measurement handicaps, the quest for easier biomarkers to incorporate into a routine test is ongoing. Because measurement of triglyceride, and glucose levels is common and reasonably priced, TyGI can be calculated more frequently in clinical practice (18).

For all these reasons, new markers are needed to identify people at high risk of developing diabetes. Early and effective diabetes identification can prevent early morbidity and increase

patient well-being. Large epidemiological studies demand non-invasive and cost-effective diagnostics to identify and prevent T2DM. Triglyceride-glucose index (TyGI) is a new marker associated with insulin resistance and helps to identify those at high risk of chronic complications in people with T2DM who are still asymptomatic. The TyGI was proposed by Guerrero-Romero et al.(19) as a surrogate marker of insulin resistance measured by the hyperinsulinemic-euglycemic clamp test (20, 21). The TyGI is an accurate biomarker of insulin resistance and can be used to predict diabetes risk. It is simple to collect and quantify in clinical settings or large-scale epidemiological research. Several studies have identified a significant correlation between the TyGI and the risk of developing T2DM in China (22, 23), Singapore (24), Europe (25, 26), Korea (21, 27), Thailand (28), and Iran (29, 30).

Data indicating the significance of TyGI in incident T2DM is still lacking in Türkiye. Hence, the present study was designed to investigate the association of TyG index with HbA1c and insulin resistance in T2DM.

Materials and Methods

After taking approval of the ethical committee, this cross-sectional retrospective study was conducted in the Tokat Gaziosmanpaşa University Medical Faculty Hospital. All 953 participants aged between 18-75 years old, had blood tests for fasting blood glucose (FBG), The homeostatic model assessment for insulin resistance (HOMA-IR), HbA1c, Total Insulin (TI), and TG levels between March-August 2023 were included in the study. Their TyGIs were calculated. We excluded participants age under 18 years, having chronic thyroid disease, liver diseases, chronic kidney disease, hematological disorders or malignancies, systemic inflammatory or infectious diseases, history of metabolic or bariatric surgery and use of anti-inflammatory or steroid therapy.

Participants were grouped on the basis of HOMA-IR and HbA1c values and evaluated according to their cut-off values as 2.7 and 5.7 respectively. After evaluating the qualitative variables, we looked at the distributions of the quantitative variables. The relationship between the significant variables and TyGI was evaluated for each HOMA-IR and HbA1c group. We defined the cut-off values and ROC curves of TyGI for each study group. Then, we performed logistic regression analysis of the selected variables based on our study groups.

All the information of the patients were collected retrospectively from our hospital data system (ENLIL HBYS Co. Türkiye). Cobas c501 (Roche Diagnostics, GmbH, Mannheim, Germany) instrument was used to estimate HbA1c, FBG, TG, levels. Serum TI estimation was performed on Cobas e411 (Roche Diagnostics, GmbH, Mannheim, Germany). HOMA-IR was derived by the formula "Fasting Insulin(FI): ($\mu\text{U/L}$) $\times$ FBG (mg/dL) / 405 (31). The Following formula was used to calculate TyGI: [Serum TG(mg/dL) $\times$ FBG(mg/dL) / 2] (19).

Descriptive analyzes were conducted to provide information about the general characteristics of the study groups. Data for

continuous variables are presented as mean±standard deviation; Data regarding categorical variables are given as n (%). When comparing the means of quantitative variables between groups, the Significance of the Difference Between Two Means test is used. ROC analysis was used to determine performance measures in predicting TyGI, HOMA-IR and HbA1c variables. P values were considered statistically significant when calculated to be less than 0.05. Ready-made statistical software was used in the calculations (SPSS 22.0 Chicago, IL, USA).

Results

A total of 953 patients; with the mean age of 40,83±16,78 participated in the study (Table 1 and 2). According to gender, all

parameters, except age (p: 0,613) and TI (p: 0.005), showed significant differences (p<0.005) (Table 2).

In Table 3, except age, all other variables showed significant differences according to the HOMA-IR cut-off value of 2.7 (p<0.001). In Receiver Operating Characteristic (ROC) analysis, TyGI, had the high sensitivity and selectivity for HOMA-IR with ≥8,76 cut-off value (AUC:0,72, Se:65%, Sp:70% (p<0.001: 95% CI:0,69-0,75)) (Table 4). In both study groups, TyGI showed high positive correlations with TG (r: 0,796, p<0.001), moderate positive correlations with FBG (r: 0,616, p<0.001) and low positive correlations with others in pairwise correlations (Table 5).

Table 1. Distribution of qualitative variables

		n	%
HOMA-IR group	<2,7	379	39,8%
	≥2,7	574	60,2%
HbA1c (%) group	<5,7	568	59,6%
	≥5,7	385	40,4%

Table 2. Distribution of quantitative variables by gender

Variables	Gender			P
	Total	Female (n=652)	Male (n=301)	
Age (Year)	40,83±16,78	41,02±15,74	40,43±18,86	0,613
HbA1c (%)	5,96±1,49	5,83±1,37	6,24±1,69	<0,001
TyGI	8,87±0,67	8,77±0,62	9,07±0,72	<0,001
FBG (mg/dL)	97,4[90-112]	96[89-108,05]	101[92-122,5]	<0,001*
HOMA-IR	3,2[2,08-5,22]	3,12[2,07-4,95]	3,49[2,14-6,62]	0,010*
TI (mIU/mL)	12,63[8,14-19,36]	12,57[8,13-18,73]	13,28[8,14-20,98]	0,298*
TG (mg/dL)	127[93,3-179]	121,75[86-166]	142,5[107-207]	<0,001*

Data are shown as mean±Standard deviation or median[Quartile 1-Quartile 3].Independent Samples t test was used. *:Mann Whitney U test was used. FBG: Fasting Blood Glucose, TI: Total Insulin, TyGI: Triglyceride glucose index.

ROC analysis curves, for TyGI regarding HOMA-IR, and HbA1c groups were shown in Figure 1 and 2, respectively. In multivariate logistic regression analysis, the risk of having poor glycemic control for HOMA-IR in men is significantly 2.247 times higher than in women (p=0.022). Each unit increase in age and FBG significantly increases the risk of poor glycemic control by 1.056 and 1.045 fold for HOMA-IR, respectively (p=0.001) (Table 6).

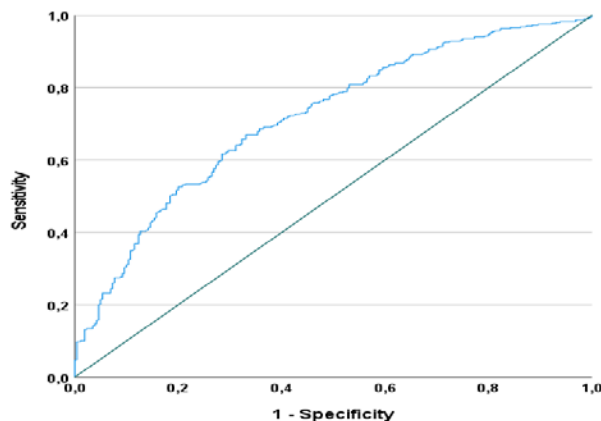


Figure 1. ROC analysis of TyGI for HOMA-IR (≥8,76 cut-off value (AUC:0,72, Se:65%, Sp:70% (p<0.001: 95% CI:0,69-0,75))

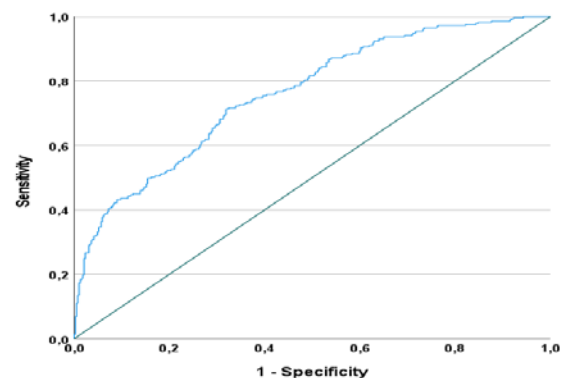


Figure 2. ROC analysis of TyGI for HbA1c (≥8,98 cut-off value (AUC:0,85, Se:84%, Sp:70% (p<0.001: 95% CI:0,82-0,87))

In Table 7, except age, all other variables showed significant differences according to the HbA1c cut-off value of 5.7 (p<0.001). In ROC analysis, TyGI, had the high sensitivity and selectivity for HbA1c with ≥8,98 cut-off value (AUC:0,85, Se:84%, Sp:70% (p<0.001: 95% CI:0,82-0,87)) (Tables 8). Every unit increase in age and FBG significantly increases the risk of poor glycemic control by 1.063 and 1.110 fold for HbA1c, respectively (p<0.001) (Table 9).

Table 3. Distribution of quantitative variables according to HOMA-IR groups

Variables	Total	HOMA-IR group		P
		<2,7	≥2,7	
	Mean±SD	Mean±SD	Mean±SD	
Age (Year)	40,83±16,78	40,16±17,01	41,84±16,4	0,130
HbA1c (%)	5,96±1,49	5,69±1,3	6,14±1,58	<0,001
TyGI	8,87±0,67	8,57±0,53	9,06±0,68	<0,001
FBG (mg/dL)	97,4[90-112]	92[87-99,4]	102[93-122]	<0,001*
TI (mIU/mL)	12,63[8,14-19,36]	7,78[5,32-9,36]	17,7[13,79-25,12]	<0,001*
TG (mg/dL)	127[93,3-179]	109[77-141,95]	145,1[107-204]	<0,001*

Data are shown as mean±Standard deviation or median[Quartile 1-Quartile 3].Independent Samples t test was used. *:Mann Whitney U test was used. FBG: Fasting Blood Glucose, TI: Total Insulin, TyGI: Triglyceride glucose index.

Tablo 4. ROC analysis results for HOMA-IR

Variable	Cut-off	AUC (95% CI)	Se	Sp	PPV	NPV	p
TyGI	≥8,76	0,72 (0,69-0,75)	0,65	0,70	0,76	0,57	<0,001

AUC: Area Under Curve, PPV:Positive predictive value, NPV: Negative predictive value, Se: Sensitivity, Sp: Specificity

Table 5. Pairwise correlation between variables with TyGI for HOMA-IR

		Total	HOMA-IR <2.7	HOMA-IR ≥2.7
		TyGI	TyGI	TyGI
Age (Year)	r	0,331*	0,431*	0,365*
	p	<0,001	<0,001	<0,001
HbA1c (%)	r	0,582*	0,492*	0,599*
	p	<0,001	<0,001	<0,001
FBG(mg/dL)	r	0,616*	0,500*	0,626*
	p	<0,001	<0,001	<0,001
HOMA-IR	r	0,353*	0,162*	0,313*
	p	<0,001	0,009	<0,001
TI (mIU/mL)	r	0,232*	-0,070	0,128*
	p	<0,001	0,264	0,009
TG (mg/dL)	r	0,796*	0,850*	0,770*
	p	<0,001	<0,001	<0,001

Pearson correlation coefficient was used.

Table 6. Logistic regression analysis of selected variables by HOMA-IR group

Model	Univariate				Multivariate			
	p	Odds Ratio	95% C.I.for Odds Ratio		p	Odds Ratio	95% C.I.for Odds Ratio	
			Lower	Upper			Lower	Upper
Gender (F/M)	0.026	1.382	1.040	1.835	0.022	2.247	1.051	4.504
Age (Year)	0.130	1.007	.986	1.002	0.001	1.056	1.033	1.081
HbA1c	<0.001	1.293	1.154	1.449	0.213	0.660	0.343	1.269
FBG (mg/dL)	<0.001	1.016	1.010	1.021	0.007	1.045	1.012	1.079
TG (mg/dL)	<0.001	1.009	1.006	1.012	0.884	1.002	0.979	1.025
TyGI	<0.001	3.916	2.869	5.347	0.374	2.320	.363	14.823

Reference category: Women for Gender

Table 7. Distribution of quantitative variables according to HbA1c group

Variables	Total	HbA1c group		p
		<5.7	≥5.7	
Age (Year)	40,83±16,78	34,72±14,82	49,84±15,4	<0,001
HbA1c (%)	5,96±1,49	5,22±0,27	7,05±1,84	<0,001
TyGI	8,87±0,67	8,61±0,53	9,22±0,68	<0,001
FBG (mg/dL)	97,4[90-112]	95[88,9-104]	189[149-263]	<0,001*
HOMA-IR	3,2[2,08-5,22]	3,11[2,02-4,86]	4,38[2,88-8,92]	<0,001*
TI (mIU/mL)	12,63[8,14-19,36]	13,03[8,44-19,93]	10,66[5,72-17,3]	<0,001*

TG (mg/dL)	127[93,3-179]	123,1[92-172,1]	148[117-228]	<0,001*
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Data are shown as mean±Standard deviation or median[Quartile 1-Quartile 3].Independent Samples t test was used. *:Mann Whitney U test was used. FBG: Fasting Blood Glucose, TI: Total Insulin, TyGI: Triglyceride glucose index.

Table 8. ROC analysis results for HbA1c

Variable	Cut-off	AUC (95% CI)	Se	Sp	PPV	NPV	p
TyGI	≥8,98	0,85 (0,82-0,87)	0,84	0,7	0,32	0,96	<0,001

AUC: Area Under Curve, PPV:Positive predictive value, NPV: Negative predictive value, Se: Sensitivity, Sp: Specificity

Table 9. Logistic regression analysis of selected variables according to HbA1c group

	Univariate				Multivariate			
	p	Odds Ratio	95% C.I.for Odds Ratio		p	Odds Ratio	95% C.I.for Odds Ratio	
			Lower	Upper			Lower	Upper
Gender	0.004	1.503	1.140	1.982	0.864	0.930	0.408	2.120
Age (Year)	<0.001	1.067	1.056	1.078	<0.001	1.063	1.033	1.094
FBG(mg/dL)	<0.001	1.094	1.078	1.109	<0.001	1.110	1.059	1.164
HOMA-IR	<0.001	1.125	1.084	1.167	0.133	0.664	0.389	1.134
TI (mIU/mL)	0.002	1.012	1.005	1.020	0.149	1.111	0.963	1.283
TG (mg/dL)	<0.001	1.005	1.003	1.007	0.739	1.003	0.984	1.023
TyGI	0.001	6.004	4.292	8.399	0.074	4.414	0.865	22.530

Reference category: Women for Gender

Discussion

In our study, high levels of TyGI were found in patients with uncontrolled T2DM. Furthermore, TyGI also revealed a significant correlation with high TG, HbA1c, FBG, and HOMA-IR levels suggesting that TyGI can be used independently as a significant variable to determine the increased risk of developing incident T2DM. In ROC analysis, TyGI, had a high sensitivity and selectivity for HOMA-IR and HbA1c groups with cut-off values of ≥8,76, and ≥8,98 respectively. Increase in age and FBG showed significantly high poor glycemic control risk in terms of both HOMA-IR and HbA1c.

IR and β -cell dysfunction are main characteristics of T2DM (3). Fat cells and adipose tissue, which produce a number of cytokines and hormones take a central role in metabolism of glucose and lipids (32). During fasting, fat cells hydrolyze TGs and release them as free fatty acids (FFAs) and glycerol, which are taken up and oxidized by skeletal muscle and liver while during feeding, they synthesize and store TGs (33). Muscle, liver, fat, pancreatic β -cells, and other tissues contribute to hyperglycemia and hyperlipidemia when IR is present (34). Glucokinase activity and glucose-stimulated insulin secretion in islets are reduced by TGs during hypertriglyceridemia (35). Hyperglycemia causes the islet cells, which already have a weaker antioxidant capacity themselves, to be exposed to continuous oxidative stress (36). Therefore, β -cell failure may be due to glucose toxicity and lipotoxicity (34). Newly published studies have suggested that TyGI is associated with IR and can be used as a reliable and useful surrogate indicator to define IR (15). Many studies have reported the association between TyGI and the occurrence of diabetes in patients (22, 30). This association persisted regardless of obesity status. The predictive value of TyGI was comparable to metabolic health.

However, few studies have evaluated the risk of diabetes based on the TyGI and its selectivity potential. In accordance with our study, Babic et al. (9) observed that TyGI increased

in patients with high HbA1c levels and TyGI was significantly independently associated with HbA1c. In the same study, the positive relation between TyGI and uncontrolled glucose

levels proposed that TyGI could be used as an independently significant indicator in predicting the development and progression of insulin resistance. Another contribution of their study is that TyGI may also be a good surrogate indicator of glycemic control in addition to HbA1c. Both are routinely measured in clinical laboratories, are inexpensive, and reflect different cardiometabolic abnormalities, which are the main reasons for their use. The fact that they are not available in most primary care settings in low-income countries and are relatively expensive makes HbA1c weaker. Therefore, an alternative index that is inexpensive and routinely available may potentially be used by primary care physicians in the follow-up of T2DM patients and in the screening of prediabetic patients.

TyGI was shown to be significantly increased in patients with poor glycemic control and significantly associated with HbA1c in the study of Hameed et al. (37). Additionally, they showed that TyGI had the largest AUC in identifying diabetics with poor glycemic control. In our, in accordance with this study, TyGI had large AUC for identifying poor glycemic control on the basis of HbA1c.

Lee et al. (38) have shown that a single TyGI determined at any given time can be a predictor of the risk of developing diabetes, that changes in TyGI levels over time affect the risk of developing diabetes, and that changes in metabolic health status, particularly in nonobese individuals, may be an independent risk factor for future diabetes. Our study showed a single time point measurement not changes in the TyGI levels, so we can only talk about risk of developing diabetes.

Liu et al.(39) and Zhang et al.(22) showed a significant association between TyGI and T2DM in normal-weight Chinese

patients, which was evident for women of all age groups and elderly men. Additionally, women tend to have higher hepatocellular lipids compared to men, both in the fasting state and after glucose and lipid loading. Visceral fat tissue increases significantly for both sexes as people age, which may increase the risk of T2DM (40). Our study found significant positive associations between TyGI and IR indicators like HbA1c, HOMA-IR, and TI. This association was also present for age of all men and women, but contrary to former studies, men tend to have higher T2DM developing risk than women.

Guerrero-Romero et al. (19) was the first to propose TyGI instead of HOMA-IR. TyGI showed high sensitivity (96.5%) and specificity (85.0%) for the diagnosis of insulin resistance in Mexican people compared to the hyperinsulinemic-euglycemic state. TyGI showed moderate correlation with HOMA-IR. In the study of Simental-Mendía et al. (41) which included 748 apparently healthy participants, the sensitivity and specificity of TyGI in determining IR were 84.0% and 45.0%, respectively. The association between TyGI and incident T2DM has been reported in several studies (24, 28). In consistence with these studies, TyGI had 70% selectivity and 65% sensitivity for IR and it was a functional indicator of IR in our study.

Janghorbani et al. (42) reported that in the Iranian population, they found an increased risk of incident T2DM above 8.43 in men and 8.19 in women for TyGI. This risk may be up to five times greater in individuals in the top quartile of TyGI compared to those in the bottom quartile in both men and women. In our study, we determined an elevated risk for T2DM over 8.76 of TyGI for HOMA-IR. The risk of T2DM in men is 2.247 times higher than in women. The risk also increases by age for 1.045 times.

In a study conducted in a Brazilian population, and the TyGI appeared to outperform HOMA-IR in clinical practice (20). A 4-year retrospective longitudinal study in Koreans found that a high TyGI at baseline was associated with the development of T2DM, independent of obesity status (21). Therefore, the TyGI may be clinically important in preventing incident T2DM.

Strengths of the study include a large community-based sample size across a wide age range, high participation rates, standardized high-quality clinical and laboratory procedures, and adjustment for numerous potential confounding factors.

Its limitations are that the study was a retrospective cross-sectional study and its relationship with incident T2DM complications was not evaluated.

In conclusion, we think that TyGI is a valuable marker that reflects the degree of insulin resistance and can be easily calculated from routine laboratory data and predicts future diabetes risk in both obese and non-obese men and women. Therefore, our data should be validated in other populations for this marker to find more application in practice.

Ethical Approval: Ethical approval of the study was obtained with the decision of Tokat Gaziosmanpaşa University Medical Faculty Clinical Researches Ethics Committee dated 26.10.2023 and numbered 23-KAEK-251.

Author Contributions:

Concept: M.K.

Literature Review: M.K.

Design: M.K., O.D.

Data acquisition: M.K.

Analysis and interpretation: M.K., O.D.

Writing manuscript: M.K.

Critical revision of manuscript: M.K., O.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Selective Computed Tomography Use in Pediatric Head Trauma: Clinical Challenges and Recommendations for Children Under Two Years

Pediatric Kafa Travmasında Seçici Bilgisayarlı Tomografi Kullanımı: İki Yaş Altı Çocuklarda Klinik Zorluklar ve Öneriler

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Abstract

Background: Head trauma in children under two years of age is a significant public health concern frequently encountered in emergency departments. Due to the unique anatomical and physiological characteristics of this age group, accurate clinical evaluation and appropriate management remain challenging. This study aimed to examine the epidemiological characteristics, clinical presentations, imaging practices, and clinical outcomes of pediatric head trauma cases in this vulnerable age group. Additionally, it assessed adherence to established international clinical guidelines and sought to provide practical suggestions to minimize the unnecessary use of computed tomography (CT) imaging.

Materials and Methods: In this retrospective observational study, medical records of 2,074 pediatric patients aged 0–24 months who presented to the emergency department of a tertiary care training and research hospital with head trauma between January 1, 2015, and December 31, 2015, were analyzed. Data collected included patient demographics, mechanisms of injury, clinical findings, Glasgow Coma Scale (GCS) scores, indications for CT imaging and results, and clinical follow-up information. All data were analyzed using descriptive statistics, logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: Falls were the most common mechanism of injury, accounting for 64.6% of cases. CT scans were performed in 64.6% of the patients; however, clinically significant intracranial injuries were detected in only 10.4%. Loss of consciousness (OR=1.75) and scalp hematoma (OR=1.62) were identified as the strongest independent predictors of positive CT findings. ROC analysis demonstrated moderate predictive performance (AUC=0.72), indicating that clinical assessment alone provides limited accuracy in guiding imaging decisions.

Conclusions: Despite well-established international guidelines, CT scans continue to be overused in pediatric head trauma cases among children under two years of age. Implementing structured clinical decision tools such as the *Pediatric Emergency Care Applied Research Network (PECARN)* criteria, along with targeted educational programs for healthcare providers and parents, is critical to minimizing unnecessary radiation exposure, enhancing patient safety, and improving clinical outcomes. Future studies should investigate alternative imaging modalities, such as rapid-sequence MRI, and structured observation protocols to better determine their practicality and effectiveness. Ultimately, reducing unnecessary CT use requires a multifaceted approach that includes strict adherence to guidelines, structured educational initiatives, active parental involvement, and exploration of safer imaging methods. Such a comprehensive strategy will help ensure optimal care and improved patient safety in pediatric head trauma.

Keywords: Pediatric Head Trauma, Computed Tomography, PECARN Guidelines, Emergency Department, Radiation Exposure

Öz

Amaç: İki yaşından küçük çocuklarda kafa travması, acil servislerde sık karşılaşılan önemli bir halk sağlığı sorunudur. Bu yaş grubunun kendine özgü anatomik ve fizyolojik özellikleri nedeniyle, doğru klinik değerlendirme ve uygun yönetim stratejileri önemli bir güçlük olmaya devam etmektedir. Bu çalışma, iki yaş altı çocuklarda görülen kafa travması olgularının epidemiyolojik özelliklerini, klinik bulgularını, görüntüleme uygulamalarını ve klinik sonuçlarını değerlendirmeyi amaçlamıştır. Ayrıca, uluslararası klinik kılavuzlara uyum düzeyini belirleyerek gereksiz bilgisayarlı tomografi (BT) kullanımını azaltmaya yönelik pratik öneriler sunmayı hedeflemiştir.

Materyal ve Metod: Retrospektif, gözlemsel nitelikteki bu çalışmada, 1 Ocak – 31 Aralık 2015 tarihleri arasında üçüncü basamak bir eğitim ve araştırma hastanesi acil servisine kafa travması nedeniyle başvuran 0–24 ay arasındaki 2074 çocuğun tıbbi kayıtları incelendi. Hastaların demografik özellikleri, travma mekanizmaları, klinik bulguları, Glasgow Koma Skalası (GKS) skorları, BT görüntüleme endikasyonları ve sonuçları ile klinik izlem verileri kaydedildi. Toplanan veriler tanımlayıcı istatistikler, lojistik regresyon ve ROC analizleri kullanılarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 2074 hastanın en sık travma mekanizması düşme olarak saptandı (%64,6). Hastaların %64,6'sına BT uygulandı; ancak bunların yalnızca %10,4'ünde klinik olarak anlamlı intrakraniyal bulgular tespit edildi. Pozitif BT bulguları açısından en güçlü belirleyiciler bilinç kaybı (OR=1,75) ve saçlı deri hematomu (OR=1,62) olarak belirlendi. ROC analizi, klinik değerlendirmenin tek başına görüntüleme kararı vermede orta düzeyde güvenilir olduğunu gösterdi (AUC=0,72).

Sonuç: Uluslararası kılavuzlara rağmen, iki yaş altı pediatrik kafa travması vakalarında BT kullanımı halen gereğinden fazladır. Gereksiz radyasyon maruziyetini en aza indirmek, hasta güvenliğini artırmak ve klinik sonuçları iyileştirmek için *Pediatric Acil Bakım Uygulamalı Araştırma Ağı (PECARN)* gibi yapılandırılmış klinik karar protokollerinin uygulanması ve sağlık profesyonelleri ile ebeveynlere yönelik eğitim programlarının hayata geçirilmesi kritik öneme sahiptir. Gelecekteki çalışmalar, hızlı-sekanslı MR gibi alternatif görüntüleme yöntemlerinin ve yapılandırılmış gözlem protokollerinin uygulanabilirliğini ve etkinliğini daha detaylı olarak incelemelidir. Nihayetinde, gereksiz BT kullanımının azaltılması, kılavuzlara tam uyum, yapılandırılmış eğitim programları, aktif ebeveyn katılımı ve daha güvenli görüntüleme yöntemlerinin araştırılmasını içeren çok yönlü bir strateji gerektirir. Böyle bir yaklaşım, pediatrik kafa travmalarında optimal bakım ve hasta güvenliğini sağlayacaktır.

Anahtar Kelimeler: Pediatrik Kafa Travması, Bilgisayarlı Tomografi, PECARN Kılavuzları, Acil Servis, Radyasyon Maruziyeti

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The study was derived from a 2016 medical specialty thesis titled "Evaluation of head trauma patients under two years of age presenting to the emergency department," registered under number 914640 at the National Thesis Center.

Introduction

Head trauma is among the most frequent reasons for pediatric emergency department visits worldwide, especially in children younger than two years of age. Due to specific anatomical and physiological features at this age - including incomplete skull ossification, a relatively larger head-to-body size ratio, and developmental immaturity - infants and toddlers are highly vulnerable to serious intracranial injury even from apparently minor trauma (1, 2). Clinical assessment and management decisions in this population are particularly challenging because of limited verbal communication and often nonspecific symptoms (3, 4).

Computed tomography (CT) is a critical diagnostic tool for detecting traumatic brain injuries in children; however, it carries substantial risks associated with ionizing radiation. Childhood exposure to CT scan radiation has been linked to an increased long-term risk of malignancies, underscoring the need to avoid unnecessary CT use (5-7). This creates a complex clinical dilemma, as physicians must balance the imperative of not missing a potentially life-threatening injury against the risks associated with unnecessary imaging.

A pivotal development in the rational management of pediatric head trauma has been the creation of the Pediatric Emergency Care Applied Research Network (PECARN) clinical prediction rule. Derived from the largest prospective pediatric head injury study to date, PECARN is designed to identify children at very low risk of clinically important traumatic brain injury (ciTBI), allowing for safe avoidance of CT scanning in such cases (8). The rule is particularly notable for its validation in infants under two years of age, where it incorporates key high-risk indicators such as a Glasgow Coma Scale score less than 15, altered mental status, palpable skull fracture, and non-frontal scalp hematoma. In this high-vulnerability group, the PECARN algorithm has demonstrated nearly 100% sensitivity and negative predictive value for ciTBI, with multiple validation studies confirming its reliability and safety across diverse emergency department settings (8, 9). Subsequent multicenter research from different healthcare systems has also reinforced the robust performance of PECARN, supporting its use as a standard of care for selective imaging in pediatric head trauma (10). The widespread implementation of PECARN in clinical protocols has been associated with significant reductions in unnecessary CT scans without an increase in missed clinically important injuries, highlighting its critical role in improving both diagnostic accuracy and patient safety (10-13).

Despite the availability of these evidence-based guidelines, CT imaging continues to be over-utilized in the management of pediatric head trauma in real-world practice (11). In our setting, as in many others, the excessive use of CT in young children may stem from medicolegal concerns (physicians' fear of missing a diagnosis) as well as

the inherent difficulty of accurately assessing neurological status in preverbal patients. These factors can contribute to variability in practice and may lead clinicians to order CT scans even when clinical decision rules suggest that imaging is not necessary, thereby increasing children's exposure to radiation.

Therefore, the present study aimed to provide detailed epidemiological data, clinical characteristics, and imaging outcomes for children under two years old presenting with head trauma at a tertiary emergency department. Additionally, we sought to evaluate adherence to international head trauma guidelines in this context and to discuss strategies for reducing unnecessary radiation exposure in this vulnerable patient group.

Materials and Methods

Study Design and Setting

This study was a retrospective observational analysis of pediatric head trauma cases. We reviewed the records of patients aged 0-24 months who presented with head injury to the emergency department of a tertiary care center in Turkey between January 1, 2015 and December 31, 2015. The hospital is a high-volume referral center for pediatric emergencies, including trauma. During the study period, no formal institutional protocol (such as PECARN) was mandated for pediatric head trauma imaging; decisions to perform a CT scan were made according to the treating physician's clinical judgment and prevailing standard practices.

Data Collection

Data were collected retrospectively from electronic medical records using a structured form. The variables recorded included patient demographics (age, sex), mechanism of injury (e.g., fall, blunt trauma, motor vehicle collision, suspected abuse), clinical findings on presentation (such as loss of consciousness, vomiting, scalp hematoma, irritability or abnormal behavior), initial GCS score, indications for obtaining a CT scan (if performed), the results of cranial CT imaging, and patient outcomes (disposition from the emergency department, need for hospital admission, or death).

Inclusion and Exclusion Criteria

We included all patients between 0 and 24 months of age who presented with isolated head trauma (with or without minor extracranial injuries). Patients with polytrauma involving other major injuries, those with incomplete medical records, or those who were transferred to another facility for specialized care were excluded from the analysis to maintain a focused and reliable dataset. A total of 2,293 eligible patients were identified during the study period; of these, 219 were excluded based on the criteria above, leaving 2,074 patients in the final study cohort.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to summarize patient demographic and clinical characteristics. Logistic regression analysis was conducted to identify independent predictors of clinically significant findings on CT (such as skull fractures or intracranial hemorrhages). Variables for the regression model were chosen based on clinical relevance and initial univariate analyses. We reported odds ratios (OR) with 95% confidence intervals (CI) for significant predictors. The discriminatory ability of clinical features to predict CT outcomes was further evaluated using ROC curve analysis. The area under the ROC curve (AUC) was calculated as an aggregate measure of test performance. An AUC of 0.5 indicates no discrimination (no better than chance), whereas an AUC of

1.0 indicates perfect discrimination; we interpreted the AUC values using conventional thresholds (e.g., ~0.7 as moderate accuracy). A p-value < 0.05 was considered statistically significant for all analyses.

Results

Patient Characteristics

A total of 2,074 pediatric patients aged 0-24 months were included in the study (after excluding 219 cases that did not meet the inclusion criteria). The cohort was 55.2% male (n = 1,145), and the mean age was 13.4 ± 6.1 months. The vast majority of injuries were minor, with 99.9% of patients (n = 2,072) presenting with a mild traumatic brain injury (GCS 13-15). Only 2 patients (0.1%) had severe trauma with GCS ≤ 8 on arrival. Table 1 summarizes the demographic and clinical characteristics of the study population

Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	Number (n=2074)	Percentage (%)
Gender (Male)	1145	55.2
Mean age (months $\pm$ SD)	13.4 ± 6.1	-
Injury Mechanism		
Falls	1340	64.6
Blunt trauma	493	23.8
Motor vehicle accidents	40	1.9
Suspected child abuse	3	0.1
Clinical Findings		
Scalp hematoma	348	16.8
Scalp laceration	327	15.8
Vomiting	217	10.5
Irritability or abnormal behavior	191	9.2
Loss of consciousness	77	3.7
Glasgow Coma Scale (GCS)		
Mild (13–15)	2072	99.9
Severe (≤ 8)	2	0.1
Hospital admission rate	127	6.1
Mortality	2	0.1

Mechanisms of Injury

Falls were by far the most common mechanism of head injury, accounting for 64.6% of cases (n = 1,340) (Figure 1). Other documented mechanisms included blunt trauma (23.8%, n = 493), motor vehicle collisions (1.9%, n = 40, often involving the child as a passenger in car accidents), and suspected non-accidental trauma (child abuse), which was rare (0.1%, n = 3). The predominance of falls highlights the typical injury pattern in this age group, where infants and toddlers often fall from furniture, beds, or while being carried.

Clinical Findings on Presentation

Notably, 39.7% of patients (n = 824) had no remarkable clinical symptoms or signs reported at presentation, despite the history of head injury. Among those who did exhibit symptoms or exam findings, the most frequent was scalp hematoma, observed in 16.8% of patients (n = 348). Scalp lacerations were present in 15.8% (n = 327), and vomiting was documented in 10.5% (n = 217). Irritability or other changes in behavior (suggestive of possible concussion in a preverbal child) were noted in 9.2% (n = 191).

A history of loss of consciousness (even a brief LOC, as could be determined from witness accounts) was recorded in 3.7% of cases ($n = 77$) (Figure 2).

It is important to note that in many infants it can be challenging to ascertain symptoms like headache or dizziness; thus, these percentages likely underestimate the true prevalence of milder symptoms that cannot be communicated by the patient.

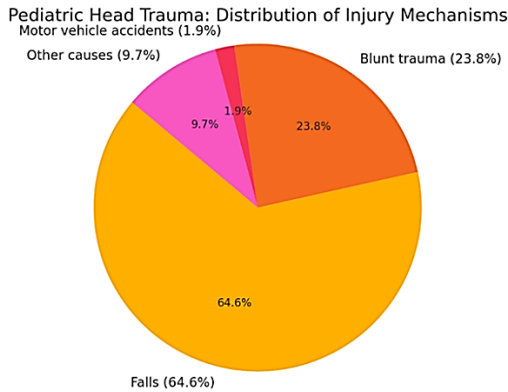


Figure 1. Distribution of Injury Mechanisms in Pediatric Head Trauma ($n = 2,074$)

CT Imaging Utilization

Out of the 2,074 patients, 1,340 (64.6%) underwent CT imaging of the head during the initial evaluation (Figure 3). The decision to perform a CT was made by the treating emergency physician based on clinical judgment, as per our institutional practice.

Nearly all of the patients who received a CT scan had presented with a mild TBI (GCS 13–15), reflecting that many scans were done in cases with relatively good initial neurological status. Among those who had a head CT, clinically significant findings (i.e., traumatic injuries identified on CT) were present in 140 patients, yielding a positive scan rate of 10.4% among imaged children (or 6.8% of the entire cohort). In other words, approximately 9 out of 10 scanned infants had no acute traumatic pathology visible on CT.

CT Findings

The most common significant injury detected on CT was a linear skull fracture, which was found in 97 patients (7.2% of scanned patients, corresponding to 4.7% of the total cohort). The second most common finding was intracranial hemorrhage, identified in 37 patients (2.8% of those who had CT, 1.8% of total) (Figure 4).

Based on the detailed analysis of cranial CT findings, isolated epidural hematoma was identified in 5 patients (0.4% of all scanned), while isolated subdural hematoma was detected in 8 patients (0.6%). Isolated subarachnoid hemorrhage (SAH) was observed in 9 cases (0.7%), and

cerebral contusion was present in 5 patients (0.4%). Additionally, several patients exhibited combined lesions, such as linear skull fracture with epidural hematoma ($n = 4$), subdural hematoma ($n = 4$), or subarachnoid hemorrhage ($n = 3$). No cases of diffuse axonal injury were observed in this cohort (Table 2). These findings indicate that, in children under two years of age, intracranial hemorrhages detected on CT were predominantly focal events—most commonly epidural, subdural, or subarachnoid in nature, often associated with skull fractures or contusions. The absence of diffuse axonal injury and the generally low frequency of severe parenchymal involvement reflect the predominance of low-energy trauma mechanisms and the rarity of extensive brain injury in this young population.

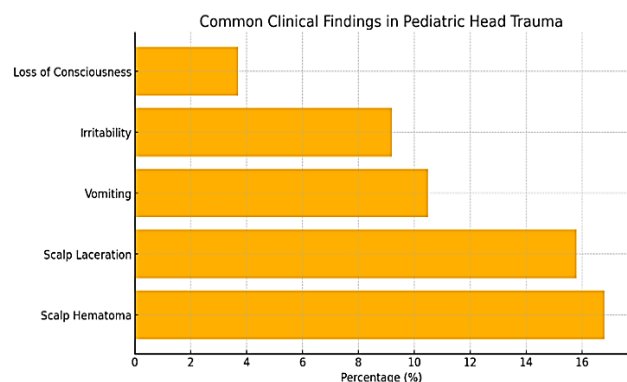


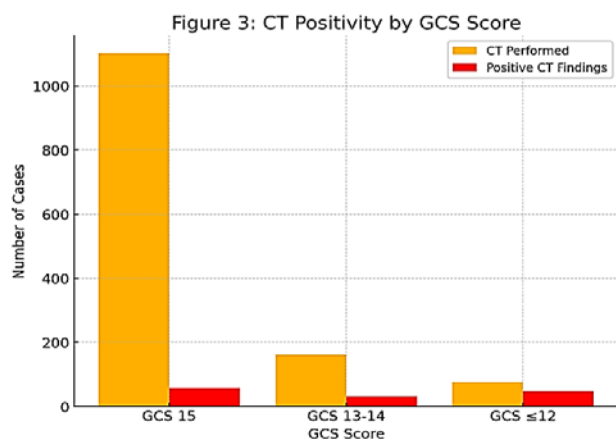
Figure 2. Common Clinical Findings in Pediatric Head Trauma and their frequencies.

Predictors of Positive CT Results: We performed a logistic regression analysis to determine which clinical variables were independently associated with having a positive CT scan (i.e., showing a skull fracture or intracranial injury). The analysis revealed two significant predictors: loss of consciousness and scalp hematoma. Patients with a reported loss of consciousness had an OR = 1.75 (95% CI: 1.30–2.32, $p < 0.01$) for a positive CT finding, meaning they were about 1.75 times more likely to have an injury on CT than those without an LOC, holding other factors constant. Similarly, patients who had a scalp hematoma on exam had an OR = 1.62 (95% CI: 1.22–2.18, $p < 0.01$) for a positive CT. These two factors remained significant in the multivariable model, whereas other clinical features did not. Notably, other symptoms such as vomiting or irritability (which were relatively common in the cohort) were not found to be independent predictors of intracranial injury after controlling for the presence of LOC and scalp hematoma. Table 3 presents the summary of CT findings and the odds ratios for key clinical predictors. To assess the overall performance of these clinical factors in predicting traumatic brain injuries, we conducted an ROC curve analysis.

Table 2. Distribution of Cranial CT Findings, Including Intracranial Hemorrhage Subtypes, in Patients Under Two Years Old.

CT Finding	Number of Patients (n)	% of Total Patients (n=2,074)	% of Patients with CT (n=1,340)
Isolated linear skull fracture	86	4.1%	6.4%
Isolated depressed skull fracture	9	0.4%	0.7%
Linear + depressed fracture	2	0.1%	0.1%
Isolated epidural hematoma	5	0.2%	0.4%
Isolated subdural hematoma	8	0.4%	0.6%
Isolated subarachnoid hemorrhage (SAH)	9	0.4%	0.7%
Isolated intraparenchymal hemorrhage	2	0.1%	0.1%
Cerebral contusion	5	0.2%	0.4%
Linear fracture + epidural hematoma	4	0.2%	0.3%
Linear fracture + subdural hematoma	4	0.2%	0.3%
Linear fracture + subarachnoid hemorrhage (SAH)	3	0.1%	0.2%
Depressed fracture + subdural hematoma	1	0.0%	0.1%
Linear fracture + SAH + subdural hematoma	1	0.0%	0.1%
Traumatic cerebral edema	1	0.0%	0.1%
No acute traumatic finding (Normal CT)	1,200	57.9%	89.6%
CT not performed	734	35.4%	—
Total	2,074	100%	100%

The aggregate predictive ability of the clinical assessment (using the combination of features in our model) was moderate, with an area under the curve (AUC) of 0.72 (95% CI ~0.68–0.76). This AUC suggests that while our model was better than chance at identifying which patients had injuries, there were considerable limitations to its accuracy. In practical terms, an AUC of 0.72 indicates that there is overlap between the clinical profiles of children with and without injuries — no perfect separation. Therefore, using clinical judgment alone (even when informed by the predictors identified) would result in some missed injuries or, alternatively, a high rate of scans to catch all injuries.

**Figure 3.** Proportion of Patients Undergoing CT Imaging, Stratified by GCS Score.

Based on the ROC analysis, we evaluated potential decision thresholds to translate this model into practice. Table 4 summarizes the diagnostic performance (sensitivity and specificity) of different approaches to deciding which patients should undergo CT imaging:

As shown in Table 4, our actual practice in this cohort (which involved liberal use of CT at the physicians' discretion) achieved nearly 100% sensitivity for detecting significant injuries, but at the cost of a very low specificity (~38%), meaning many children without injuries were scanned. The PECARN rule, if it had been strictly applied to our patients, would also have achieved 100% sensitivity (no missed injuries) with a moderate improvement in specificity (~53% of those without injury would avoid scanning). Using a simple two-factor rule based on our study's predictors (scanning if either LOC or a scalp hematoma is present) could further improve specificity to roughly 86%, but with a slight drop in sensitivity (we estimate ~93% in our dataset) as a few injuries would have been missed by this narrower criterion. Conversely, a very strict rule of scanning only if both LOC and scalp hematoma were present yields a very high specificity (~98%) but misses the majority of injuries (sensitivity ~20%), and thus would be an unsafe strategy. These analyses underscore the trade-offs involved in decision-making: rules that achieve higher sensitivity invariably do so at the expense of more false positives (lower specificity), whereas tightening criteria to improve specificity risks missing significant injuries.

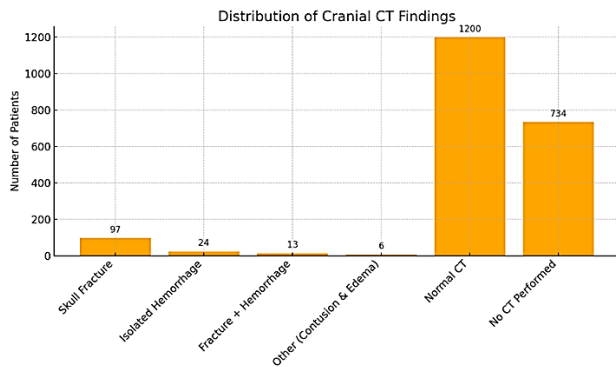


Figure 4. CT Utilization and Positive Findings (number of CT scans performed versus how many showed positive traumatic findings).

Patient Disposition and Outcomes

Despite the relatively low rate of significant findings on CT, a subset of patients required further care. In our cohort, 127 children (6.1%) were admitted to the hospital for observation or treatment following the emergency evaluation. The criteria for admission typically included

the presence of a significant injury on CT, worrisome symptoms (like persistent vomiting or lethargy), or other clinical concerns such as suspected abuse. The vast majority of hospitalized patients were observed and managed conservatively; only a very small number required any neurosurgical intervention (for example, one patient underwent evacuation of an epidural hematoma).

The overall outcomes were favorable in this population. The mortality rate in this study was extremely low. There were 2 deaths (0.1% of the total sample). Both fatal cases involved severe mechanisms: one infant suffered a fatal head injury in a high-speed motor vehicle accident, and the other was a child who fell from a significant height (greater than two stories). These cases underscore that while uncommon, severe trauma can result in catastrophic outcomes even in this young age group. Importantly, no deaths or life-threatening complications occurred among children who were initially sent home from the emergency department without a CT; both fatalities were among those appropriately identified as high risk, who underwent CT scanning and were admitted, but unfortunately succumbed to their injuries despite intervention.

Table 3. Summary of CT Findings and Odds Ratios for Clinical Predictors of Positive CT Results.

CT Scan Outcome	Number of Patients (% among scanned)	Clinical Predictor	OR (95% CI)	p-value
CT performed (total scanned)	1,340 (100%)	Loss of consciousness	1.75 (1.30–2.32)	< 0.01
– Positive for trauma	140 (10.4%)	Scalp hematoma	1.62 (1.22–2.18)	< 0.01
• Skull fracture	97 (7.2%)	Vomiting	1.10 (0.80–1.52)	0.55
• Intracranial hemorrhage	37 (2.8%)	Irritability/behavior change	0.96 (0.67–1.37)	0.82
– No acute traumatic finding	1,200 (89.6%)			

(The table shows that only loss of consciousness and scalp hematoma were significantly associated with positive CT findings in the multivariate model; other factors like vomiting and irritability did not show a statistically significant independent effect.)

Table 4. Sensitivity and Specificity of Different Imaging Decision Strategies for Detecting Clinically Important Brain Injury on CT.

Imaging Decision Strategy	Sensitivity (%)	Specificity (%)
Actual clinical practice (physician judgment; CT obtained in 64.6% of patients)	~100	~38
PECARN rule (under age 2; recommend CT if any PECARN risk factor present)	100	53
Presence of either loss of consciousness or scalp hematoma (CT if either present)	~93	~86
Presence of both loss of consciousness and scalp hematoma (CT only if both present; very strict/high-specificity)	~20	~98

Abbreviations: CT = computed tomography; LOC = loss of consciousness; PECARN = Pediatric Emergency Care Applied Research Network.

* The “either LOC or scalp hematoma” approach reflects a simple rule where CT is recommended if the patient has either a history of loss of consciousness or a scalp hematoma. The “both LOC and scalp hematoma” approach recommends CT only if both findings are present, representing a very restrictive, high-specificity and low-sensitivity strategy.

Discussion

This study demonstrates the significant challenges in managing head trauma in infants and toddlers and highlights the persistent overuse of CT imaging in this population. Despite the existence of clearly defined international guidelines that advocate for selective imaging, we found that nearly two-thirds of children under two with head injury underwent CT scanning, while only about one-tenth

of those scans identified clinically significant intracranial injuries. Our findings mirror those of previous reports which have noted high rates of CT utilization for minor pediatric head trauma in emergency settings, both in Turkey and internationally (11,12). The tendency toward liberal imaging in these cases appears to be driven by multiple factors. Emergency physicians face the “when in doubt, scan” dilemma — a combination of fear of missing a

rare but serious injury (and the potential medicolegal repercussions of such an oversight) and the difficulty of assessing subtle neurological signs in a non-verbal, uncooperative infant — which can tilt the decision in favor of performing a CT “just to be safe.” These real-world pressures can at times override guideline recommendations and contribute to variability in practice, leading to more frequent scanning than what objective decision rules would call for. Reducing this gap between guidelines and practice is a key challenge that needs to be addressed through education, system-level protocols, and culture change.

Our data provide insight into the epidemiology and risk factors of head trauma in young children. Falls were the predominant mechanism of injury (64.6% of cases), which is consistent with epidemiological patterns reported in other regions (14). Young children are naturally prone to falls due to their developing motor skills and lack of danger awareness, and they often fall from furniture, caregivers’ arms, or down stairs. The high proportion of falls underscores the importance of preventive strategies, such as educating parents and caregivers about home safety (for example, never leaving an infant unattended on elevated surfaces, using safety gates for stairs, etc.). By contrast, intentional trauma (suspected non-accidental injury) was very uncommon in our series (only 3 cases, 0.1%), but this should not lead to complacency; clinicians must remain vigilant for signs of abuse in any infant with an inconsistent history or injury pattern, as abusive head trauma can be easily missed and carries high morbidity and mortality (2).

Despite the overall low rate of serious intracranial injuries in our cohort, the CT utilization rate was high, reflecting the clinical uncertainty in evaluating these patients. We identified loss of consciousness and scalp hematoma as the strongest clinical predictors of a positive CT scan. These findings align well with established pediatric head trauma decision rules. In fact, both of these factors feature prominently in the PECARN criteria for children under two years: the PECARN rule considers a GCS < 15 or any signs of altered mental status (which includes loss of consciousness or extreme drowsiness) and palpable skull fractures or scalp hematomas (especially non-frontal) as high-risk features that warrant CT (8). Our results reinforce that these two elements are important red flags for clinicians. It is noteworthy that other common symptoms like vomiting and irritability did not show independent predictive value for intracranial injury in the multivariate analysis (15). This does not mean those symptoms are unimportant — rather, in many cases they co-occur with the stronger predictors (or are absent in many injured children), reducing their apparent standalone impact when adjusted for other factors. Moreover, the presence of vomiting or behavioral changes can still influence a physician’s decision to observe a child more closely or to image, especially if such symptoms persist or worsen.

The ROC analysis (AUC = 0.72) in our study highlights the limitations of clinical judgment alone in accurately distinguishing which infants have serious head injuries. An AUC in the low 0.7 range indicates only moderate accuracy — meaning there is a considerable overlap in clinical presentation between children with and without injuries. In practical terms, to achieve near-perfect sensitivity (catch all true injuries), one would have to accept a high false-positive rate (scanning many children who are uninjured). Conversely, focusing on high specificity (scanning only those very likely to be injured) would inevitably miss some injuries given the overlap. This finding underscores why structured decision rules are so valuable: they intentionally err on the side of sensitivity. For example, the PECARN rule for under-2-year-olds achieves ~99–100% sensitivity for clinically important TBI (8), accepting a lower specificity to ensure almost no serious injuries are missed. Using such rules can standardize care and reduce unnecessary CT scans by identifying low-risk children who can be safely managed without imaging. Indeed, real-world validation studies have confirmed that the PECARN clinical prediction rules perform reliably in practice, reinforcing their value for routine use (13). Studies comparing rule-guided decisions to unstructured physician judgment have shown that decision aids can match or improve upon clinician accuracy, while also reducing variability in practice (16). In our context, better adherence to PECARN or similar guidelines could have avoided many of the CT scans performed on children who ultimately had normal findings, without compromising safety. When we retrospectively applied the PECARN criteria to our dataset, it achieved a sensitivity of 100% and a negative predictive value of 100% for detecting clinically important intracranial injuries (no ciTBI cases would have been missed). However, the specificity of the rule in this cohort was approximately 53%, with a positive predictive value of about 13%. In other words, roughly half of the children without a significant injury would have undergone CT scanning under strict PECARN-based criteria. This trade-off highlights the challenge in balancing the imperative to catch all serious injuries against the need to avoid exposing children to unnecessary radiation. Given the priority of safety in this age group, most clinicians and guidelines favor maximizing sensitivity (at the expense of specificity) to ensure that nearly no dangerous injuries are missed.

It is also important to discuss the role of symptoms like vomiting and irritability in the evaluation of head trauma. In our study, neither of these symptoms was an independent predictor of injury on CT after accounting for other factors. This is in line with research that has specifically examined vomiting in head-injured children. Isolated vomiting (vomiting in the absence of other high-risk signs such as altered mental status or signs of skull fracture) has been found to be rarely associated with significant traumatic brain injury (15). Borland et al. reported that children with minor head trauma who present with vomiting

but no other risk factors have an exceedingly low rate of ciTBI, and therefore an observation approach can be justified in lieu of immediate CT (15). Our findings support this: many infants in our cohort who vomited once or twice were managed with observation and did well, which is consistent with the notion that brief, isolated vomiting can be managed safely without radiation in otherwise low-risk cases. Similarly, irritability or behavior change is a very subjective and non-specific sign in infants. It can stem from pain (like a scalp hematoma), hunger, or general distress, and not necessarily from a head injury. While persistent or severe irritability should raise concern (especially if a child cannot be consoled, which could indicate increased intracranial pressure), mild irritability did not correlate strongly with CT findings in our data. These observations underscore the importance of considering the overall clinical picture rather than any single symptom in isolation. Infants with isolated symptoms and no other worrisome findings can often be safely observed, whereas those with multiple risk factors or a concerning exam should be imaged.

In light of the risks associated with CT, alternative management strategies and imaging modalities are important to explore. For example, in infants with open fontanelles, cranial ultrasound can be performed at the bedside to identify skull fractures or intracranial hemorrhage without radiation exposure, making it a useful screening tool in selected minor head trauma cases (17, 18). Emerging technologies like near-infrared spectroscopy (NIRS) have also shown promise in detecting intracranial hematomas noninvasively (17). However, one of the most promising imaging alternatives is the use of rapid-sequence MRI as an alternative to CT for head trauma evaluation. MRI, of course, does not involve ionizing radiation and thus would eliminate the radiation risk. Traditionally, MRI has been impractical in the acute trauma setting for young children due to long scan times and the need for the child to remain still (often requiring sedation). However, recent advances have led to the development of fast MRI protocols that can be completed in only a few minutes. Studies have demonstrated the feasibility and safety of performing quick brain MRIs in children with head injuries, showing that it is possible to obtain diagnostic-quality images without sedation in many cases (19). Furthermore, investigators have reported that using rapid MRI in place of CT can substantially decrease radiation exposure for pediatric head trauma evaluation (20). Moreover, evidence from comparative studies is very encouraging: a fast MRI can detect most clinically significant injuries that a CT can, including skull fractures and intracranial hemorrhages, with high accuracy (21). For example, a 2019 multicenter study found that fast MRI had excellent agreement with CT for identifying traumatic brain injuries in young children, missing only a very small fraction of injuries that were mostly minor or clinically insignificant.

While MRI in the emergency setting is not yet widely available (it requires specific protocols and immediate radiology support), these developments suggest a potential paradigm shift in the future. If rapid MRI can be implemented broadly, we could markedly reduce children's exposure to CT-related radiation. However, obstacles such as scanner availability, the need for radiologist expertise at off-hours, and the logistics of scanning an agitated toddler still need to be addressed. In the meantime, the judicious use of CT (when clearly indicated) and reliance on observation and clinical judgment for low-risk cases remain the mainstay of management.

Another well-recognized strategy to reduce unnecessary CT scans is the use of structured observation periods in the emergency department. Instead of immediately scanning every head-injured infant, a clinician may choose to observe the child for several hours to see if symptoms evolve or improve. This approach can filter out children who were initially symptomatic from the stress of the injury but are not truly intracranially injured – these children often improve with observation and can be discharged without ever undergoing CT. Research has shown that implementing observation protocols significantly reduces CT utilization without increasing missed injuries or adverse outcomes (22). In practice, many experienced clinicians already do this intuitively (for example, observing a child who had a brief LOC or one episode of vomiting but is now alert and playful in the ED). Formalizing such observation strategies as part of a guideline can further encourage their use.

Limitations

We acknowledge several limitations. First, this was a retrospective single-center study conducted at a tertiary care hospital using data from 2015, which may limit the generalizability of our findings to other settings or current practice and introduce potential information bias due to reliance on incomplete medical records. Second, we did not directly measure adherence to clinical decision rules (for example, by retrospectively applying PECARN criteria to each case), so guideline compliance was assessed only indirectly via overall imaging rates. In this context, a multicenter study by Babl et al. (2017) (10) directly comparing pediatric head trauma decision rules highlights the value of such analyses, but conducting a similar comparison was beyond our scope. Third, human factors such as medicolegal concerns or clinician risk tolerance were not captured in our data because we did not survey physicians; thus, we could only infer these influences from existing literature and clinical experience rather than measure them directly. Fourth, we lacked systematic data on observation duration for patients managed without CT and did not conduct any follow-up beyond the acute hospital visit, limiting our ability to detect delayed complications in those not scanned. Finally, as an observational study, we can identify associations but cannot establish

causation. Despite these limitations, our findings align with those of larger studies and known trends (for example, high fall rates and a low yield of CT in mild head injuries), suggesting that our results are generalizable to similar clinical settings and can inform ongoing efforts to improve pediatric head trauma assessment.

Conclusion

Children under two years of age with head trauma continue to undergo CT imaging at high rates, even though international guidelines (such as PECARN) advise a more selective approach. Our study underscores that the majority of these scans do not find serious injuries, highlighting an opportunity to improve decision-making and avoid exposing infants to ionizing radiation unnecessarily. The drivers of CT overuse in this context include uncertainty in clinical evaluation of very young children, the difficulty of interpreting subtle signs in a preverbal patient, and concerns about medicolegal risks of missing an injury. Given the particular vulnerability of this age group to the long-term harms of radiation, it is imperative that emergency care providers strictly adhere to validated clinical decision rules for head trauma. By following these guidelines, clinicians can maintain a near-zero miss rate for significant injuries while safely reducing the number of CT scans.

To bridge the gap between evidence-based recommendations and practice, a multifaceted strategy is needed. Educational initiatives should be implemented to train and remind healthcare professionals about the proper use of head trauma algorithms and the risk trade-offs involved with CT imaging. Such training can increase physicians' confidence in identifying low-risk patients who can be observed instead of immediately scanned. In parallel, parental education is crucial – families should be informed about the rationale for avoiding unnecessary CT scans (emphasizing the radiation risks) and be made partners in the observation process when appropriate. Clear communication and written instructions on what warning signs to look for at home can empower parents and reduce their anxiety when a decision is made to forego imaging. Additionally, hospitals and healthcare systems should consider adopting protocols that encourage structured observation for mild head injuries and provide decision support tools to aid clinicians in adhering to guidelines. Where resources allow, exploring the use of rapid MRI techniques could offer a radiation-free diagnostic alternative for equivocal cases, although this requires infrastructural support.

In summary, effectively reducing unnecessary CT scans in infants with head trauma will require a comprehensive approach that combines rigorous guideline adherence, provider and caregiver education, and innovation in diagnostic methods. By doing so, we can ensure that children receive optimal care – benefiting from the life-saving capabilities of CT when needed, but shielded from its potential harms when it is not.

Ethical Approval: The study was approved by the local Institutional Ethics Committee (Approval No: 50, Date: 09.02.2016). Because this was a retrospective review of de-identified patient records, informed consent was not required. Confidentiality of patient data was maintained throughout the study in accordance with the principles of the Declaration of Helsinki.

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Analysis and interpretation: M.Ş., Ö.L.A., H.A.D.

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Optimizing Sedation Protocols Through Early Postoperative Mobilization: A Retrospective Analysis

Postoperatif Hızlandırılmış Mobilizasyonun Sedasyon Protokolleri Üzerine Etkisi: Retrospektif Bir Analiz

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Abstract

Background: Sedation depth during surgery significantly impacts postoperative outcomes. Deeper sedation levels are associated with delayed recovery, increased complications, and higher mortality rates. Optimizing sedation protocols is essential for improving patient outcomes. We aimed to evaluate the effects of mild versus deep sedation on postoperative recovery, complications, and mortality in elective surgical patients.

Materials and Methods: This retrospective cohort study analyzed postoperative outcomes based on sedation depth in patients undergoing elective surgery. The study was conducted at a tertiary university hospital, specifically at Gaziantep City Training and Research Hospital, Department of Anesthesiology and Reanimation. A total of 320 adult patients (≥ 18 years) who underwent elective surgeries under sedation between 2023 and 2025. Patients were divided into two groups: Group A (mild sedation) and Group B (deep sedation). Inclusion criteria included complete medical records and documented postoperative mobilization data. Exclusion criteria were ICU admissions postoperatively and incomplete records. The primary outcome measures included time to first mobilization, length of hospital stay, and mortality rates. Secondary outcome measures encompassed the incidence of complications, including pulmonary embolism, infection, and thrombosis, as well as postoperative pain levels and patient satisfaction scores.

Results: Patients in Group A exhibited faster mobilization (12.5 ± 3.7 hours vs. 18.8 ± 4.1 hours, $p < 0.001$), shorter hospital stays (3.6 ± 1.1 days vs. 5.1 ± 1.3 days, $p < 0.001$), and lower mortality rates (4.9% vs. 11.3% , $p = 0.03$) compared to Group B. Deep sedation was a significant risk factor for mortality (OR: 2.8, 95% CI: 1.8–4.4, $p = 0.01$), with higher propofol and fentanyl doses contributing to adverse outcomes. Delayed mobilization (OR: 1.18 per hour, $p = 0.008$) and prolonged hospital stays (OR: 1.32 per day, $p = 0.001$) further increased mortality risk.

Conclusions: Mild sedation protocols are associated with improved postoperative outcomes, including faster recovery, fewer complications, and reduced mortality. Tailored sedation strategies and early mobilization programs are critical for optimizing perioperative care.

Keywords: Sedation depth, Postoperative outcomes, Mild sedation, Deep sedation, Early mobilization

Öz

Amaç: Cerrahi sırasında sedasyon derinliği, postoperatif sonuçlar üzerinde önemli etkilere sahiptir. Derin sedasyon seviyeleri; iyileşmenin gecikmesi, komplikasyonların artması ve mortalite oranlarının yükselmesiyle ilişkilidir. Sedasyon protokollerinin optimize edilmesi, hasta sonuçlarını iyileştirmek açısından kritik öneme sahiptir. Bu çalışmada, elektif cerrahi uygulanan hastalarda hafif ve derin sedasyonun postoperatif iyileşme, komplikasyonlar ve mortalite üzerine etkilerini değerlendirmeyi amaçladık.

Materyal ve Metod: Bu retrospektif kohort çalışmada, 2023–2025 yılları arasında Gaziantep Şehir Hastanesi Anesteziyoloji ve Reanimasyon Kliniği'nde elektif cerrahi geçiren 320 yetişkin hasta (≥ 18 yaş) değerlendirildi. Hastalar sedasyon derinliğine göre iki gruba ayrıldı: Grup A (hafif sedasyon) ve Grup B (derin sedasyon). Dahil edilme kriterleri; eksiksiz tıbbi kayıtların ve postoperatif mobilizasyon verilerinin mevcut olmasıydı. Postoperatif yoğun bakım ünitesine yatırılan ve eksik kayıtları olan hastalar çalışma dışı bırakıldı. Birincil sonuç ölçütleri; ilk mobilizasyona kadar geçen süre, hastanede kalış süresi ve mortalite oranlarıydı. İkincil sonuç ölçütleri ise; pulmoner emboli, enfeksiyon, tromboz gibi komplikasyonların insidansı, postoperatif ağrı düzeyleri ve hasta memnuniyeti puanlarıydı.

Bulgular: Hafif sedasyon uygulanan Grup A'da, ilk mobilizasyona geçiş süresi daha kısa (12.5 ± 3.7 saat vs. 18.8 ± 4.1 saat, $p < 0.001$), hastanede kalış süresi daha az (3.6 ± 1.1 gün vs. 5.1 ± 1.3 gün, $p < 0.001$) ve mortalite oranı daha düşüktü (4.9% vs. 11.3% , $p = 0.03$) (Grup B'ye kıyasla). Derin sedasyon, mortalite için anlamlı bir risk faktörüydü (OR: 2.8, %95 GA: 1.8–4.4, $p = 0.01$) ve yüksek doz propofol ve fentanyl kullanımı olumsuz sonuçlara katkı sağladı. Gecikmiş mobilizasyon (OR: 1.18/saat, $p = 0.008$) ve uzamış hastane yatışı (OR: 1.32/gün, $p = 0.001$) da mortalite riskini artıran faktörler olarak belirlendi.

Sonuç: Hafif sedasyon protokolleri, daha hızlı iyileşme, daha az komplikasyon ve daha düşük mortalite oranları ile ilişkilidir. Kişiyi özel sedasyon stratejileri ve erken mobilizasyon programları, perioperatif bakımın optimize edilmesinde kilit rol oynamaktadır.

Anahtar Kelimeler: Sedasyon derinliği, Postoperatif sonuçlar, Hafif sedasyon, Derin sedasyon, Erken mobilizasyon

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Introduction

Sedation is a cornerstone of perioperative care, aiming to ensure patient comfort, immobility, and safety during surgical procedures. However, the depth of sedation has significant implications for postoperative outcomes, with deeper sedation levels often associated with delayed recovery, increased complications, and higher mortality rates (1). The choice of sedation protocol involves balancing the need for sufficient anesthetic depth with minimizing potential adverse effects, particularly in high-risk patient populations (1, 2).

The impact of sedation depth extends beyond the intraoperative period, influencing key recovery parameters such as time to mobilization and hospital length of stay. Deep sedation has been shown to prolong emergence times, delay mobilization, and increase the risk of complications such as venous thromboembolism and infections (3, 4). Conversely, mild sedation protocols are increasingly recognized for their role in enhancing recovery and improving outcomes by reducing physiological stress and promoting early mobilization (5).

Despite the growing body of evidence linking sedation depth to postoperative outcomes, limited data exist on its specific impact in diverse surgical populations. Furthermore, the interaction between sedation depth and patient-specific factors, such as ASA score and BMI, remains under-explored. Addressing these gaps is critical for developing tailored sedation strategies that optimize patient safety and recovery.

This study aims to evaluate the effects of sedation depth on postoperative outcomes, focusing on mortality, recovery time, and complications. By analyzing a comprehensive dataset, we seek to provide insights into the benefits of mild sedation protocols and propose evidence-based recommendations for improving perioperative care.

Materials and Methods

Study Design and Population

This retrospective study analyzed data from patients who underwent elective surgery under deep sedation between 2023 and 2025. Data were extracted from the electronic health records (EHR) and anesthesia tracking system of a tertiary university hospital, ensuring comprehensive and accurate documentation. The study included patients aged 18 years or older with complete medical records who underwent elective surgery under deep sedation. Eligible patients had documented postoperative early mobilization data. Patients were excluded if they required intensive care unit admission postoperatively, had incomplete or erroneous medical records, or experienced specific postoperative complications that precluded adherence to the standard mobilization protocol. The types of surgical procedures included general surgery (e.g., cholecystectomy, hernia repair), orthopedic surgery (e.g., knee/hip arthroscopy, spinal surgery), and urologic surgery (e.g., TUR-P, nephrectomy).

These procedures were classified as minor or major based on operative duration and invasiveness. The classification was used to evaluate its impact on mobilization and mortality. A flow diagram of patient selection and grouping is presented in Figure 1 to enhance transparency of the study design.

Groups

Patients were categorized into two groups based on the sedation protocols employed during their surgical procedures. Group A (mild sedation) included patients who received mild sedation with propofol at an infusion rate of 1–2 mg/kg/hour and low-dose fentanyl ($\leq 1 \mu\text{g/kg}$). Group B (deep sedation) comprised patients who received deep sedation with propofol at an infusion rate of 2–4 mg/kg/hour and high-dose opioids, such as fentanyl ($> 1 \mu\text{g/kg}$) or remifentanyl. In standard clinical practice, sedation depth is ideally assessed using validated scales such as the Ramsay Sedation Scale or the Richmond Agitation-Sedation Scale (RASS). However, in our retrospective dataset, these scores were not consistently recorded. Therefore, we defined sedation depth based on sedative and opioid dosages, as described in previous retrospective studies with similar constraints.

Data Collection

Demographic data, including age, sex, and body mass index (BMI), were recorded along with comorbidities such as diabetes mellitus and hypertension. Sedation-related data included the sedation protocols applied, drug dosages, sedation duration, and emergence time. Postoperative outcomes were evaluated based on time to mobilization, length of hospital stay, ASA Score (I-II/III-IV), and complications such as pulmonary embolism, infection, and fever. Additional clinical metrics, including pain scores measured by the Visual Analog Scale (VAS) and patient satisfaction scores, were also documented. Early mobilization was defined as the patient's ability to ambulate or be mobilized to a sitting position in a chair within the first 24 hours following surgery. Delayed mobilization was defined as initiation of these activities beyond 24 hours postoperatively. These definitions were based on enhanced recovery after surgery (ERAS) protocols to ensure consistency and clinical relevance.

Statistical Analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 27. Descriptive statistics were presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and frequencies (n) and percentages (%) for categorical variables. Independent t-test or Mann-Whitney U test were used for continuous variables. Chi-square test was used for categorical variables. Logistic regression analysis was used to assess the risk of postoperative complications. A p-value < 0.05 was considered statistically significant.

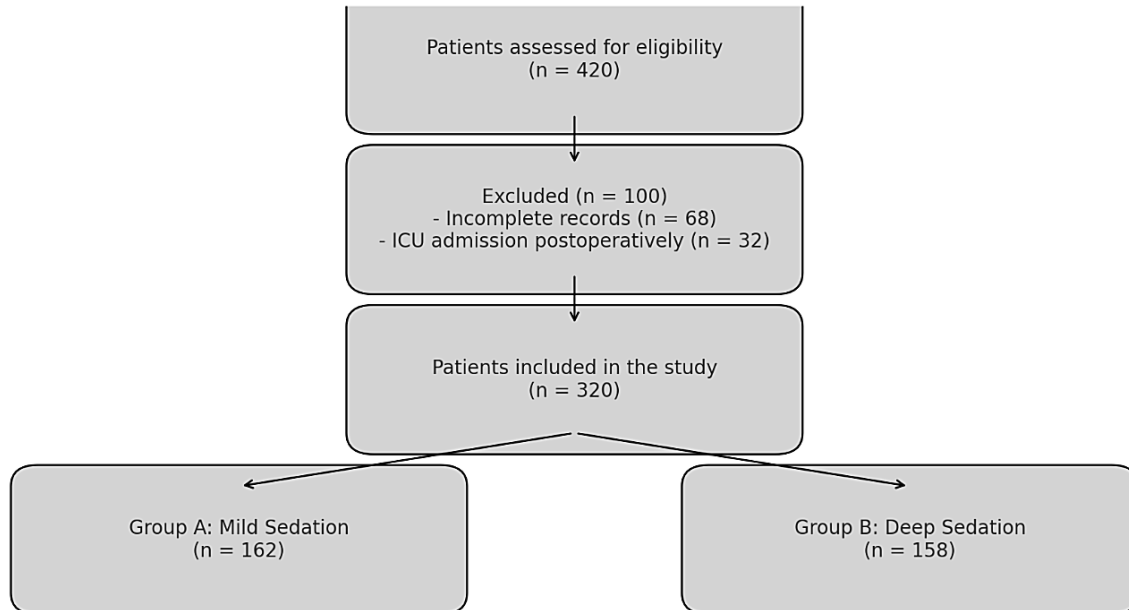


Figure 1. Flow diagram of patient selection and grouping. Out of 420 patients initially assessed, 100 were excluded due to incomplete records (n = 68) or ICU admission postoperatively (n = 32). A total of 320 patients were included and divided into two groups based on sedation depth.

Results

Comparison of demographic and baseline characteristics between the groups was shown in table 1. The mean age of patients was similar, with Group A (Mild Sedation) reporting 52.1 ± 15.2 years and Group B (Deep Sedation) at 52.5 ± 14.6 years ($p = 0.68$). Baseline characteristics were similar between the mild sedation (Group A) and deep sedation (Group B) groups. There were no significant differences in age, gender, BMI, smoking status, or the prevalence of comorbidities such as diabetes mellitus and hypertension (all $p > 0.05$). Additionally, ASA scores and the distribution of surgery types (major vs. minor) were comparable between the groups, suggesting a balanced baseline profile (Table 1).

Comparison of sedation and sedation parameters between the groups was shown in table 2. Group B (Deep Sedation) received higher doses of both propofol and fentanyl compared to Group A (Mild Sedation). Specifically, the propofol infusion rate in Group B was significantly elevated at 3.3 ± 0.4 mg/kg/hr, compared to 1.6 ± 0.3 mg/kg/hr in Group A ($p < 0.001$). Similarly, fentanyl doses were markedly higher in Group B, averaging 1.5 ± 0.3 µg/kg, while Group A received a mean dose of 0.9 ± 0.2 µg/kg ($p < 0.001$). Despite similar sedation durations, the emergence times varied considerably. Group B experienced significantly prolonged emergence, with a mean time of 15.4 ± 3.5 minutes, compared to 8.6 ± 2.2 minutes in Group A ($p < 0.001$) (Table 2.).

Table 1. Comparison of demographic and baseline characteristics between the groups

Characteristic	Group A (N=162) (Mild Sedation)	Group B (N=158) (Deep Sedation)	p-value
Mean Age (years)	52.1 ± 15.2	52.5 ± 14.6	0.68
Gender (Male/Female) (%)	55% (89) / 45% (73)	57% (90) / 43% (68)	0.77
BMI (kg/m ²)	26.3 ± 3.1	26.7 ± 3.2	0.55
Diabetes Mellitus (%)	20.4% (33)	21.5% (34)	0.82
Hypertension (%)	25.9% (42)	26.3% (42)	0.65
Smokers (%)	18.5% (30)	19.0% (30)	0.47
ASA Score (I-II/III-IV) (%)	85% (138) / 15% (24)	82% (129) / 18% (29)	0.33
Surgery Type (Major/Minor) (%)	60% (97) / 40% (65)	58% (91) / 42% (67)	0.41
General Surgery	74 (45.6%)	67 (42.4%)	
Orthopedic Surgery	50 (30.8%)	50 (31.6%)	
Urologic Surgery	38 (23.6%)	41 (26.0%)	

Table 2. Comparison of sedation and sedation parameters between the groups

Parameters	Group A (Mean ± SD) (Mild Sedation)	Group B (Mean ± SD) (Deep Sedation)	p-value
Propofol Infusion Rate (mg/kg/hr)	1.6 ± 0.3	3.3 ± 0.4	<0.001
Fentanyl Dose (µg/kg)	0.9 ± 0.2	1.5 ± 0.3	<0.001
Sedation Duration (min)	122 ± 29	125 ± 28	0.18
Emergence Time (min)	8.6 ± 2.2	15.4 ± 3.5	<0.001

Postoperative outcomes, including time to mobilization, hospital stay, complication rates, and mortality, are summarized in Table 3. Patients in the mild sedation group (Group A) demonstrated significantly better postoperative outcomes compared to the deep sedation group (Group B). Specifically, time to mobilization was markedly shorter in Group A (12.5 ± 3.7 hours) than in Group B (18.8 ± 4.1

hours; $p < 0.001$). Hospital stay was also significantly reduced in Group A (3.6 ± 1.1 days) versus Group B (5.1 ± 1.3 days; $p < 0.001$). Moreover, the overall complication rate was significantly lower in Group A (11.7%) compared to Group B (23.1%; $p = 0.01$). Mortality was also reduced in the mild sedation group (4.9%) relative to the deep sedation group (11.3%; $p = 0.03$) (Table 3.).

Table 3. Comparison of postoperative outcomes between the groups

Outcomes	Group A (N=162) (Mild Sedation)	Group B (N=158) (Deep Sedation)	p-value
Time to Mobilization (hours)	12.5 ± 3.7	18.8 ± 4.1	<0.001
Length of Hospital Stay (days)	3.6 ± 1.1	5.1 ± 1.3	<0.001
Overall Complication Rate (%)	11.7% (19)	23.1% (37)	0.01
Pulmonary Embolism (%)	2.5% (4)	6.3% (10)	0.08
Infections (%)	5.6% (9)	10.8% (17)	0.07
Thrombosis (%)	1.9% (3)	4.4% (7)	0.09
Mortality (%)	4.9% (8)	11.3% (18)	0.03

Comparison of pain and satisfaction scores between the groups is presented in Table 4. Patients in Group A reported significantly lower postoperative pain (VAS: 3.1 ±

1.0 vs. 4.8 ± 1.2, $p < 0.001$) and higher satisfaction scores (8.5 ± 1.3 vs. 7.3 ± 1.4, $p < 0.001$) compared to Group B (Table 4.).

Table 4. Comparison of pain and satisfaction scores between the groups

Measure	Group A (Mean ± SD) (Mild Sedation)	Group B (Mean ± SD) (Deep Sedation)	p-value
VAS Pain Score	3.1 ± 1.0	4.8 ± 1.2	<0.001
Patient Satisfaction Score	8.5 ± 1.3	7.3 ± 1.4	<0.001

Table 5. Logistic regression analysis results for mortality

Variable	Odds Ratio (OR)	95% CI	p-value
Deep Sedation	2.8	1.8–4.4	0.01
Age	1.05	0.98–1.13	0.08
BMI	1.12	1.03–1.23	0.03
Diabetes Mellitus	1.3	0.92–1.85	0.02
Hypertension	1.2	0.88–1.63	0.18
Smoking	1.4	1.00–1.96	0.05
ASA Score III-IV	1.6	1.10–2.33	0.02
Time to Mobilization (hours)	1.18	1.06–1.31	0.008
Length of Hospital Stay (days)	1.32	1.15–1.52	0.001
Overall Complication Rate (%)	2.0	1.25–3.20	0.015
Propofol Infusion Rate (mg/kg/hr)	1.9	1.30–2.80	0.03
Fentanyl Dose (µg/kg)	1.7	1.20–2.60	0.04
Emergence Time (min)	1.5	1.10–2.20	0.02

Logistic regression analysis results for mortality were shown in table 5. Deep sedation emerged as a significant risk factor, with an odds ratio (OR) of 2.8 (95% CI: 1.8–4.4, $p = 0.01$), highlighting the association between sedation depth and adverse outcomes. Similarly, BMI was found to be a significant predictor, with an OR of 1.12 (95% CI: 1.03–

1.23, $p = 0.03$), suggesting that higher body mass index increases mortality risk. Patients with ASA Score III-IV had an elevated risk, reflected by an OR of 1.6 (95% CI: 1.10–2.33, $p = 0.02$), emphasizing the impact of preoperative health status on postoperative outcomes. Time to mobilization and length of hospital stay were also significant predictors.

For every hour of delayed mobilization, the odds of mortality increased by 18% (OR: 1.18, 95% CI: 1.06–1.31, $p = 0.008$). Similarly, longer hospital stays were associated with an increased risk of mortality, with an OR of 1.32 (95% CI: 1.15–1.52, $p = 0.001$). Overall complication rates were strongly linked to mortality, with a twofold increase in risk (OR: 2.0, 95% CI: 1.25–3.20, $p = 0.015$). Among sedation parameters, higher propofol infusion rates (OR: 1.9, 95% CI: 1.30–2.80, $p = 0.03$), increased fentanyl doses (OR: 1.7, 95% CI: 1.20–2.60, $p = 0.04$), and prolonged emergence times (OR: 1.5, 95% CI: 1.10–2.20, $p = 0.02$) were all significant contributors to mortality. These findings suggest that deeper sedation levels, excessive opioid administration, and delays in recovery exacerbate adverse outcomes (Table 5).

Discussion

This study highlighted significant associations between sedation depth and key postoperative outcomes, including recovery time, complication rates, and mortality. The findings revealed that deep sedation was independently associated with a higher risk of mortality, delayed mobilization, and prolonged hospital stays. Furthermore, higher doses of anesthetic agents, such as propofol and fentanyl, were linked to adverse outcomes, including increased complication rates and extended emergence times. In contrast, mild sedation protocols were associated with faster recovery, fewer complications, and improved patient satisfaction. These results underscored the critical role of optimizing sedation depth to improve postoperative outcomes and minimize mortality risk in surgical patients.

Recent studies have highlighted the impact of sedation depth on postoperative outcomes, particularly mortality. Our study's finding that deep sedation was independently associated with a higher risk of mortality aligned with prior research. Su et al. conducted a meta-analysis comparing sedation with general anesthesia in patients undergoing percutaneous procedures and found that lighter sedation was associated with lower in-hospital and 30-day mortality rates, particularly in cardiac and macrovascular surgeries (6). While Su et al.'s findings were based on a relatively homogeneous patient population undergoing cardiac and macrovascular procedures, our study involved a broader and more heterogeneous surgical group. Although this limits the direct comparability, the consistent trend observed across both studies strengthens the argument for the potential advantages of lighter sedation. Nevertheless, we recognized the need for future research to confirm these effects within specific surgical subgroups. Phillips et al. observed an increased risk of adverse outcomes with deep sedation protocols, reporting an odds ratio of 2.5 for mortality in patients receiving high propofol doses during major surgeries (7). Zhuang et al. reported no significant differences in long-term mortality between deep and light sedation protocols but noted increased postoperative complications with deeper sedation (8). This discrepancy may stem

from variations in patient populations, surgical procedures, and definitions of sedation depth across studies. Our findings contributed to this evidence by reinforcing the short-term risks associated with deep sedation while suggesting that careful adjustment of sedation protocols may mitigate these risks.

Excessive use of anesthetic agents, such as propofol and fentanyl, has been strongly associated with adverse postoperative outcomes. In our study, higher propofol infusion rates were linked to an increased risk of mortality. Cascella et al. stated that elevated propofol doses significantly delayed emergence and prolonged mechanical ventilation, contributing to increased rates of complications such as pulmonary embolism and postoperative delirium (9). In our study, fentanyl doses were associated with higher odds of mortality. In a multicenter study by Mercado et al., which reported that higher opioid dosing during surgery was linked to an elevated risk of respiratory depression, extended recovery room stays, and greater postoperative pain (10). Excessive propofol and opioid administration can delay emergence by prolonging sedation levels and suppressing physiological recovery mechanisms (9). Pederson et al. stated that delayed emergence increases the risk of postoperative immobility, which can lead to complications such as thrombosis and infections (11). Additionally, high doses of opioids, such as fentanyl, may exacerbate these effects by causing respiratory depression and impairing the ability to resume normal physiological activities (9, 12). Our findings contributed to the growing evidence supporting the need for balanced dosing strategies to optimize recovery and minimize complications. Reducing reliance on excessive anesthetic agents while maintaining adequate sedation levels may improve both short- and long-term postoperative outcomes.

Our study identified ASA Score III-IV as a significant predictor of mortality, underscoring the importance of preoperative health status in determining postoperative outcomes. Hackett et al. demonstrated that higher ASA scores were associated with increased risks of complications and mortality in patients undergoing major surgeries, particularly those involving cardiopulmonary bypass (13). Higher ASA scores reflect greater systemic disease burden, which may impair the body's ability to tolerate surgical stress and recover effectively (14). In addition to ASA score, BMI was also found to be an independent predictor of mortality in our study. Obesity has been consistently linked to worse surgical outcomes in the literature (15). Gurunathan et al. reported that higher BMI was associated with prolonged operative times, increased risk of wound infections, and higher rates of thromboembolic events (16). Obesity complicates surgical recovery by exacerbating comorbid conditions such as diabetes and hypertension and increasing the likelihood of respiratory and cardiovascular complications. The combined impact of high ASA scores and elevated BMI highlighted the need for careful preoperative risk stratification. Leis et al. stated that patients with both high ASA

scores and obesity face compounded risks of perioperative complications and mortality (17). Additionally, although type of surgery is a well-known determinant of postoperative outcomes, our analysis revealed no significant differences in the distribution of major and minor surgeries between the two groups. This supports the interpretation that sedation depth, rather than surgical severity, played a key role in influencing postoperative mobilization and mortality. While the primary pathology and the nature of surgical intervention undoubtedly influence outcomes, we controlled for these variables in our analysis through ASA scoring, comorbidity data, and classification of surgical procedures as major or minor. These served as surrogate indicators of disease burden and surgical intensity. Importantly, even after these adjustments, sedation depth consistently emerged as an independent predictor of poor outcomes. This suggested that, although not the sole determinant, sedation strategy plays a substantial role in postoperative recovery and mortality risk.

While surgery type, disease severity, and comorbidities are known to influence postoperative outcomes, we accounted for these factors in our multivariate logistic regression analysis. Variables such as ASA score, BMI, diabetes, hypertension, and type of surgery were included in the model to adjust for confounding. Despite these adjustments, deep sedation remained an independent predictor of mortality and delayed recovery. This suggested that sedation depth contributes significantly to outcomes, independent of surgical complexity or baseline risk.

Deep sedation has been increasingly recognized as a contributor to adverse postoperative outcomes due to its impact on physiological recovery and mobilization. One key mechanism is delayed emergence, which prolongs immobility, increasing the risk of venous thromboembolism and pulmonary complications. Prolonged sedation delays the initiation of normal postoperative activities, exacerbating the risk of thrombosis due to venous stasis and impairing pulmonary function by reducing lung expansion and clearance of secretions (18, 19). Sakr et al. reported that patients with prolonged emergence times had a twofold increase in the risk of pulmonary embolism and pneumonia compared to those who emerged more rapidly from sedation (20). Additionally, deep sedation may suppress physiological responses, leading to systemic inflammation and impaired tissue recovery. Ivascu et al. showed that prolonged exposure to high doses of anesthetics such as propofol increased levels of pro-inflammatory cytokines, contributing to delayed wound healing and higher infection rates (21). These effects are compounded by the depressive effects of opioids, which may further impair respiratory function and exacerbate immune dysregulation. In contrast, mild sedation protocols are associated with reduced risks of these complications by promoting faster recovery and earlier mobilization. Light sedation minimizes the time to emergence, enabling patients to resume physiological functions more

quickly, thereby reducing the risks of thrombosis and respiratory complications (22). A study by Shehabi et al. showed that mild sedation protocols were associated with a 30% reduction in the incidence of venous thromboembolism and postoperative infections compared to deeper sedation (23). Additionally, lighter sedation is less likely to suppress immune responses, thereby facilitating better recovery and fewer systemic complications.

Optimizing sedation depth can play a pivotal role in enhancing patient outcomes and reducing healthcare costs. Tailored sedation strategies should be developed based on individual patient profiles. Patients with high ASA scores or elevated BMI—both of which were significant predictors of mortality in our study—may benefit from lighter sedation to mitigate the compounded risks of deep sedation and pre-existing vulnerabilities (17). Early mobilization programs should also be prioritized as part of perioperative care to minimize complication rates. Early mobilization has been shown to significantly reduce the risk of venous thromboembolism, pulmonary complications, and prolonged hospital stays (24). The results of this study have implications for future clinical guidelines on sedation protocols. Incorporating evidence-based recommendations for mild sedation and early mobilization into standardized surgical care pathways can improve patient safety and outcomes. Additionally, guidelines should encourage the use of sedation scales and monitoring tools to adjust sedation depth dynamically during surgery.

This study has some limitations. Being a single-center study and the lack of standardized sedation scale data (e.g., Ramsay or RASS) limited our ability to objectively quantify sedation depth. As a result, we relied on dosage-based criteria, which may be less precise in capturing the full clinical spectrum of sedation. Additionally, while we adjusted for key confounders in the regression model, the retrospective nature of the study limits our ability to control for all unmeasured variables, such as intraoperative blood loss or exact disease etiology. Future prospective, multicenter studies are necessary to validate these findings and further explore tailored sedation protocols that optimize patient outcomes.

In conclusion, this study demonstrated that deep sedation significantly increases mortality risk, delays recovery, and is associated with higher rates of postoperative complications. In contrast, mild sedation protocols were shown to reduce mortality, shorten recovery times, and improve overall patient outcomes. These findings underscore the importance of tailoring sedation strategies to individual patient profiles, balancing adequate sedation with the need for rapid recovery and minimized risks. Implementing evidence-based sedation practices and early mobilization protocols can play a critical role in optimizing perioperative care and improving surgical outcomes.

Ethical Approval: The study was designed as a descriptive, retrospective investigation. Ethical approval was received from Health Science University local ethics committee (approval number: 15.12.2024/12-1).

Author Contributions:

Concept: E.E.

Literature Review: E.E.

Design : E.E.

Data acquisition: E.E.

Analysis and interpretation: E.E.

Writing manuscript: E.E.

Critical revision of manuscript: E.E.

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Machine Learning Based Investigation of Relation Between Patient and Glabellar Wrinkle Characteristics

Hasta Özellikleri ile Glabellar Kırışıklık İlişkisinin Makine Öğrenimi Tabanlı İncelenmesi

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Abstract

Background: The skin around the glabella area is the region most affected by the underlying muscle activity during facial expressions and wrinkling. Although glabellar lines or wrinkles are commonly considered a cosmetic concern in the facial region, objective clinical assessment of this condition remains important. This study investigated the relationship between various patient characteristics, potentially reflecting lifestyle and physiological factors, and glabellar wrinkle patterns, which were categorized according to distinct muscle contraction types described in the literature.

Materials and Methods: Data were collected from a total of 870 patients. One of the study's primary objectives was to explore the potential of using multiple patient-related variables in a machine learning-based prediction system while identifying the most influential characteristics associated with glabellar wrinkles. Multiple supervised machine learning algorithms were employed to uncover potentially nonlinear associations and identify the most informative predictors, including Naïve Bayes, Random Forest, Logistic Regression, and K-Nearest Neighbors. Each model was tested across all possible feature subsets to evaluate their predictive performance.

Results: The study aimed to demonstrate that a machine learning-based approach could be functional for the early prediction of glabellar wrinkles. The analysis revealed significant associations between patient characteristics, such as age, gender, education, marital status, and occupation, and distinct glabellar wrinkle patterns. Furthermore, the machine learning models demonstrated that these characteristics could be used to predict wrinkle types with considerable performance. In the best scenario, separating the U-type pattern from others, an F1 score of 0.71 was achieved using K-Nearest Neighbors, supporting the potential for early identification and personalized intervention planning.

Conclusions: The study confirmed that specific patient characteristics are strongly related to the formation of different glabellar wrinkle types. In addition, machine learning-based predictive systems showed promising performance, indicating their potential use in supporting clinicians with personalized cosmetic assessments and early intervention strategies.

Keywords: Artificial Intelligence, Skin Aging, Machine Learning, Demography

Öz

Amaç: Glabella bölgesindeki deri, yüz ifadesi ve kırışıklık oluşumu sırasında alttaki kas aktivitesinden en çok etkilenen alanlardan birisidir. Glabellar çizgiler veya kırışıklıklar genellikle kozmetik kaygı nedeni olabilmekle birlikte, bu çizgi ve kırışıklıkların klinik açıdan nesnel değerlendirilmesi önem taşımaktadır. Bu çalışmada, hastaların yaşam tarzı ve fizyolojilerini yansıtabilecek çeşitli özellikleri ile literatüre göre sınıflandırılmış glabellar kırışıklık karakterleri arasındaki ilişki araştırılmıştır.

Materyal ve Metod: Bu çalışmada toplam 870 hastadan veri toplanmıştır. Çalışmada öncelikli olarak hastaları karakterize eden birden fazla değişkenin makine öğrenmesi tabanlı bir tahmin-teşhis sisteminde kullanılabilirliğinin araştırılması hedeflenmiştir, bu doğrultuda glabellar kırışıklıklarla ilişkili olabilecek en etkili özelliklerin belirlenmesi amaçlanmıştır. Naïve Bayes, Rastgele Orman, Lojistik Regresyon ve K-En Yakın Komşular gibi farklı kılavuzlu makine öğrenmesi algoritmaları kullanılarak, doğrusal olmayan potansiyel ilişkilerin ortaya çıkarılması hedeflenmiştir, en ilintili değişkenler belirlenmiştir. Her modelin tahmin performansı, tüm olası özellik alt kümeleri üzerinde test edilmiştir.

Bulgular: Çalışmada, glabellar kırışıklık karakterinin önceden tahmini için makine öğrenimi temelli bir yaklaşımın işlevsel olabileceğinin gösterilmesi amaçlanmıştır. Analiz sonuçları; yaş, cinsiyet, eğitim, medeni durum ve meslek gibi hasta özellikleri ile glabellar kırışıklık karakteri arasında önemli ilişkiler olduğunu göstermektedir. Ayrıca çalışmada, bu özelliklerle kırışıklık tiplerinin öngörülebilirliği araştırılmış, U tipi desen için K-En Yakın Komşu algoritmasıyla 0.71 F1 skoru elde edilmiştir. Bu sonuç, erken teşhis ve kişiselleştirilmiş planlama açısından yöntemin potansiyelini ortaya koymaktadır.

Sonuç: Çalışma, belirli hasta özelliklerinin farklı glabellar kırışıklık türlerinin oluşumuyla önemli derecede ilintili olduğunu doğrulamıştır. Ayrıca makine öğrenimi tabanlı potansiyel bir teşhis ve kestirim sisteminin bu özellikler ile yüksek performanslı sınıflama yapması otomatik sınıflayıcıların kişiselleştirilmiş kozmetik değerlendirme ve erken müdahale için destek potansiyeline işaret etmektedir.

Anahtar Kelimeler: Yapay Zekâ, Cilt Yaşlanması, Makine Öğrenmesi, Demografi

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Introduction

The glabella region between the eyebrows is subject to increased muscle activity during facial expressions associated with emotions such as anger and irritation (1). Due to its anatomical location and underlying muscular dynamics, this area has become a focal point in cosmetic dermatology (2). One widely used treatment modality is botulinum toxin injection, which requires careful planning and precise application (3). A clear understanding of its anatomy, combined with identifying patient characteristics that contribute to wrinkling, forms the basis for aesthetic procedures targeting this region and a critical foundation for proactively preserving its cosmetic integrity.

In one study, authors noted that age and gender significantly influence the formation of glabellar lines due to anatomical and physiological differences, which may impact the treatment approach (4). Additionally, it has been highlighted that age, gender, ethnicity, and skin sensitivity play a significant role in facial aging and should be considered when planning cosmetic procedures (5). Moreover, an extensive twin study by Rexbye et al. demonstrated that various lifestyle-related factors, such as smoking, sun exposure, body mass index, and social status, significantly influence perceived facial aging, with distinct patterns observed between genders (6).

At this point, computer-aided investigation holds excellent potential for identifying the most influential attributes. Accordingly, numerous previous studies have implemented automated classification and estimation methods to make predictions related to facial wrinkles, aging, and cosmetic outcomes. For instance, Shah et al. showed that machine learning can effectively analyze facial features to predict cosmetic treatment needs, underscoring the potential of computer-aided methods in facial assessment (7). Recent surveys have further supported the potential of automated systems for facial wrinkle detection and analysis, highlighting the broader role of machine learning in cosmetic evaluation tasks (8). In another study, Kim et al. proposed a semi-automatic labeling and deep learning-based detection system for facial wrinkles, demonstrating the capability of AI models to extract wrinkle-related patterns from facial images reliably (9).

In recent years, computer-aided methods have shown strong potential for identifying important factors in facial aging and wrinkle formation. Several studies have used machine learning techniques to analyze facial features and predict cosmetic needs. Although the present study does not involve facial images or image processing, machine learning was applied to evaluate patient-related characteristics. The goal was to identify the factors most strongly associated with glabellar wrinkle types based on muscle contraction patterns defined in previous research. The analysis pipeline involved balancing the class distributions, trying out different feature combinations, and evaluating performance using F1 scores. This allowed us to identify which feature-method setups performed best in distinguishing wrinkle patterns and to explore whether such predictions could have clinical value.

Materials and Methods

Original Data

The data analyzed in this study were collected from 870 participants, including male and female volunteers aged between 18 and 74. Based on predefined criteria, individuals who had undergone any surgical or medical procedures (such as botulinum toxin injections) in the facial region or who had a history of facial trauma were excluded.

Glabellar wrinkle types were determined based on the classification proposed by Lima et al. (10). Accordingly, participants were asked to frown, and five distinct wrinkle patterns were identified: V-shaped, U-shaped, omega-shaped, converging arrows, and inverted omega-shaped lines.

All procedures, assessments, and data collection processes were carried out in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine at Çukurova University on June 2, 2023 (approval number 134/44).

This study is also supported by the Çukurova University Scientific Research Projects Unit under project number TSA-2024-16787 and is derived from this project.

Analyzed Attributes

This study examined several patient-related attributes to explore their potential association with the severity of glabellar wrinkles. The dataset comprised the following variables:

Age: A normalized continuous variable ranging from 0 to 1, representing the patient's age. Although age is often assumed to be normally distributed, a Shapiro-Wilk test ($W = 0.943$, $p < .001$) showed a significant deviation from normality. The corresponding histogram in Figure 1 illustrates this skewed distribution.

No transformation was applied since all possible feature combinations were tested during model evaluation. Age is considered one of the key factors in wrinkle formation due to long-term muscle activity and decreasing skin elasticity with age.

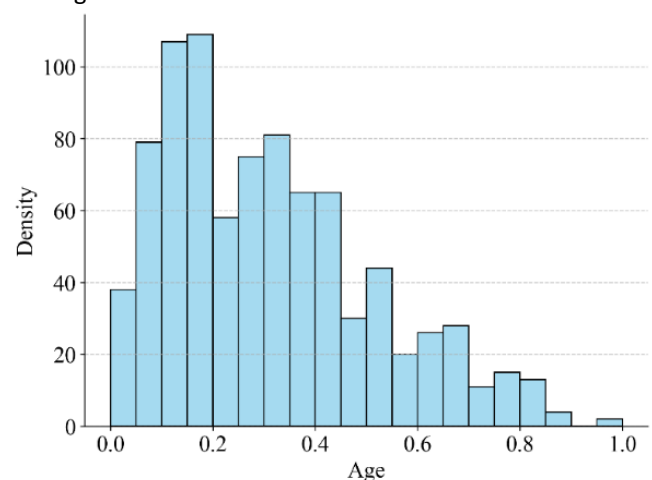


Figure 1. Histogram of the normalized Age variable. The distribution is right-skewed, indicating a deviation from normality.

Gender: A categorical binary variable (Female, Male). Gender-based anatomical and hormonal differences are known to influence the pattern and depth of facial wrinkles.

Education: A categorical variable denoting the level of education, categorized as primary school and below, high school, university, and postgraduate education. It was included as a potential lifestyle-related indicator, reflecting differences in health awareness, stress exposure, and access to skincare practices.

Marital Status: A categorical binary variable representing the individual's marital status (Single, Married). Social and emotional factors related to marital status have been suggested to influence aging processes and perceived stress, which may, in turn, affect skin health.

Occupation: A categorical binary variable corresponding to the patient's occupational status (Employed, Unemployed). It was considered due to its potential relevance to environmental exposure (e.g., sunlight, stress, or physical activity), which are recognized factors in facial aging.

Glabellar Contraction Pattern: The target variable in this study represents the pattern of muscle contraction in the glabellar region, classified based on facial expressions observed during animation. Following the classification proposed by Lima et al., this categorical variable includes five primary types: "U", "V", "Omega", "Inverted Omega", and "Converging Arrows". Each pattern is associated with a different combination of muscle activity involving the corrugator supercilii, depressor supercilii, procerus, and orbicularis oculi muscles (10). This classification system has allowed us to group the facial dynamics within our region of interest accurately.

These attributes were selected due to their potential role in wrinkle formation, either directly through biological mechanisms or indirectly via lifestyle and environmental influences. Subsequently, the contribution and predictive importance of each variable were assessed using various machine learning algorithms. Figure 2 visualizes the distribution of glabellar contraction patterns across four demographic characteristics to provide an overview of the dataset.

Machine Learning Based Investigation

An experimental algorithm was implemented to determine the most effective subset of features for each classification scenario. Accordingly, all possible non-empty combinations of the available features were evaluated. For each feature subset, every classifier was trained and tested using a stratified 80/20 train-test split. The accuracy of each model was recorded, and the combination yielding the highest performance was reported for each scenario. It should be noted that, to transform the multi-class glabellar contraction pattern into a machine learning-compatible structure, several binary grouping scenarios were defined. These scenarios grouped glabellar types based on different clinical perspectives. The four binary grouping scenarios were created to explore glabellar wrinkle classifications based on clinical rele-

vance. These groupings reflect variations in wrinkle symmetry, distribution, and severity. For example, comparing type 1 with types 2–5 allows investigation of the most distinct contraction pattern, while other splits (e.g., 1–2 vs. 3–5) reflect increasing asymmetry or complexity in wrinkle formation. Such divisions may inform personalized treatment strategies or early signs of muscular imbalance. The following split strategies were applied:

- Types 1 and 2 vs. Types 3, 4, and 5
- Types 1, 2, and 3 vs. Types 4 and 5
- Type 1 vs. Types 2, 3, 4, and 5
- Types 1 to 4 vs. Type 5

For each scenario, a binary variable was created and balanced using random under-sampling to ensure equal class representation. The balanced datasets were used to evaluate the classification performance of multiple models. The overall workflow of the implemented experimental classification scheme is visualized in Figure 3.

This approach has allowed a comprehensive exploration of the interactions between demographic variables and glabellar pattern classification.

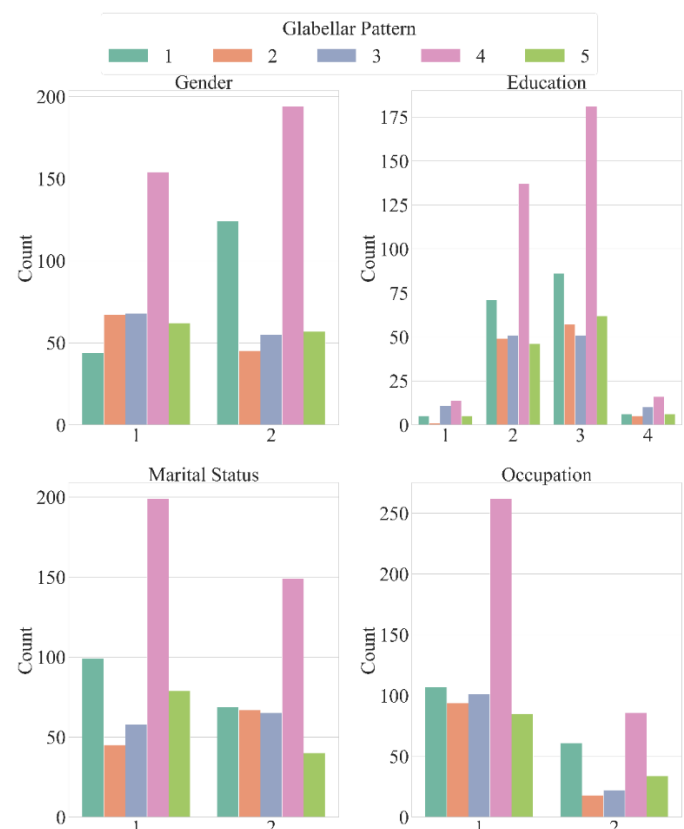


Figure 2. Glabellar contraction types shown by gender, education, marital status, and occupation.

Implemented Classifiers

This study used four supervised machine learning methods to classify glabellar wrinkle types. Each classifier was specifically chosen because of its proven performance in similar prediction tasks and suitability for the type of data collected. Naive Bayes is a probabilistic classification method grounded

on Bayes' theorem (11). It assumes that predictor variables (patient characteristics in this study, such as age, gender, education, marital status, and occupation) independently contribute to wrinkle type (12). While this assumption may not always hold perfectly true in reality, Naive Bayes often performs effectively in practice, especially with categorical and relatively small-sized feature sets.

Random Forest is an ensemble learning method that constructs multiple decision trees using random subsets of data and features (13). Combining predictions from these trees reduces the risk of overfitting and often achieves higher accuracy (14). This robustness makes it particularly valuable for identifying the most critical patient characteristics contributing to wrinkle patterns.

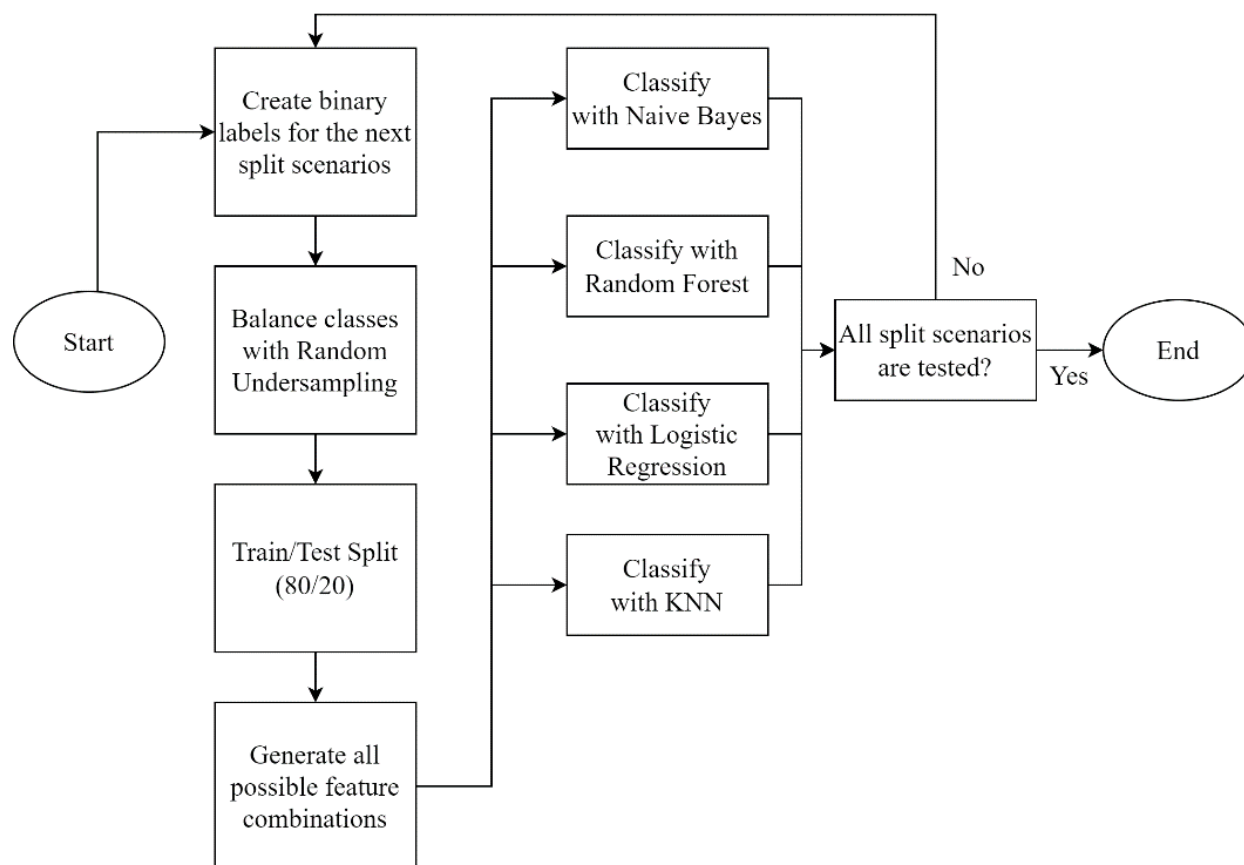


Figure 3. Workflow of the classification process applied to glabellar wrinkle patterns.

Logistic Regression is a widely used linear classification method primarily suited for binary prediction tasks (15). This method calculates the probability of an observation belonging to a specific category based on its predictor variables (16). Due to its straightforward nature and interpretability, Logistic Regression can provide insights into linear relationships between patient characteristics and glabellar wrinkle patterns. However, it performs best when predictor variables have linear relationships with the outcome and when categorical variables are numerically appropriately encoded. In this study, categorical variables were represented numerically without specific encoding methods, such as one-hot encoding, which might influence the interpretability and predictive performance of the Logistic Regression model. Lastly, K-Nearest Neighbors (KNN) is a classification method that assigns the class label of an observation by examining the labels of its closest neighbors in the feature space. The final prediction is based on the majority class among these

neighbors (17). KNN relies heavily on distance calculations, which typically perform best with numerical data (18). In this study, categorical variables were used directly in numeric form without special preprocessing. This approach can potentially impact the accuracy of the distance calculations and, consequently, reduce the predictive performance of KNN compared to other methods. Nonetheless, KNN serves as an intuitive and simple comparative baseline to evaluate how effectively wrinkle types can be predicted based solely on the direct numerical similarity of patient characteristics. All classifiers were evaluated under identical conditions, using the same training-test splits and feature subsets, to ensure comparability of results and provide reliable conclusions about which patient characteristics best predict glabellar wrinkle patterns.

Results

Four binary classification scenarios, each representing a different grouping of contraction patterns, were tested to evaluate the predictive capability of demographic attributes on glabellar wrinkle classification. For each scenario, all possible non-empty combinations of five features (Age, Gender, Education, Marital Status, and Occupation) were evaluated using four supervised learning methods: Naive Bayes, Random Forest, Logistic Regression, and K-Nearest Neighbors. Random

under-sampling was applied to ensure class balance before training.

To make sure the evaluations were fair and not affected by class imbalance, each scenario was tested using training and test sets that included equal numbers of positive and negative samples. This balancing was done separately for each scenario. Model performances were compared based on their F1 scores, and the best feature-method combination for each setup was recorded. Table 1 shows the classification results and related details for all scenarios.

Table 1. Best performing classification split scenarios are presented

Split	Train Size	Test Size	Best F1 Score	Best Method	Best Features
[1, 2] vs [3, 4, 5]	448	112	0.597	NB	('Education', 'Occupation')
[1, 2, 3] vs [4, 5]	644	162	0.667	KNN	('Gender',)
[1] vs [2, 3, 4, 5]	268	68	0.710	KNN	('Gender', 'Occupation')
[1, 2, 3, 4] vs [5]	190	48	0.694	KNN	('Age', 'Gender', 'Occupation')

In addition to the F1 score, other performance metrics were calculated for the best-performing classification scenario. The model achieved a sensitivity of 0.97, indicating a strong ability to detect positive cases. However, specificity was relatively low (0.24), which reduced the overall accuracy (0.60) and MCC (0.30). These results suggest that while the model is highly responsive to U-type wrinkles, its ability to identify non-U types correctly is limited.

To confirm the consistency of the best-performing setup, a 5-fold stratified cross-validation was applied using the K-Nearest Neighbors algorithm with Gender and Occupation as predictors. The model achieved F1 scores ranging from 0.66 to 0.89 across folds, with an average F1 score of 0.84. These results support the generalizability of the model beyond a single train-test split.

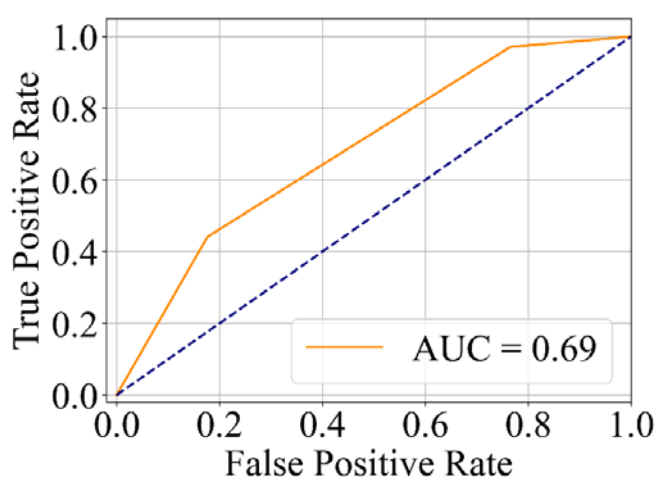


Figure 4. ROC curve for the best resulted feature combination and classifier in the one-versus-rest classification of glabellar type 1.

The ROC curve for the best-performing scenario, where glabellar wrinkle type 1 was compared against types 2 to 5 using the KNN classifier, is shown in Figure 4. The model achieved an F1 score of 0.71 and an AUC of 0.69 using only Gender and Occupation as features.

To further investigate the discriminative power of each feature in the most successful split scenario, a principal component analysis (PCA) was performed for all features. The loadings of the first principal component (PC1), which captures the maximum variance in the data, are visualized in Figure 5. The highest positive contribution to PC1 was observed from the Occupation variable, followed by Gender, whereas Education exhibited a strong negative loading. This pattern supports the classification results obtained in Scenario 3 ([1] vs [2, 3, 4, 5]), where the best F1 score was achieved using Gender and Occupation as predictors.

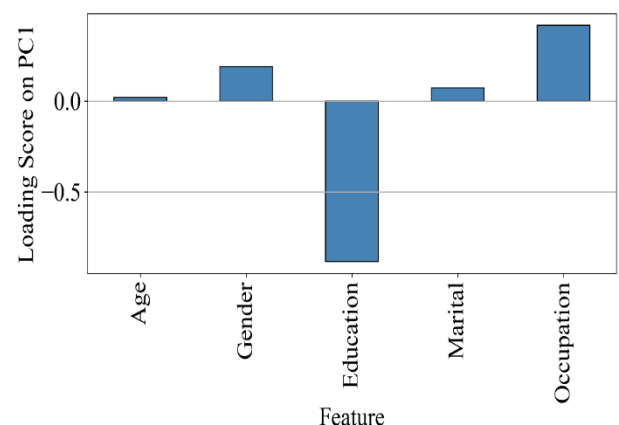


Figure 5. PC1 loadings from PCA applied to the most successful classification scenario, showing the contribution of each feature to the main variance axis.

Discussion

The present study aimed to exploit the predictive relationship between patient characteristics and glabellar wrinkle patterns through supervised machine learning algorithms. While previous clinical studies have focused primarily on descriptive or comparative statistics to understand muscle contraction patterns in the glabellar region, supervised classifiers were implemented in our study to investigate the degree of relation between wrinkle characteristics and individual-level attributes such as age, gender, and lifestyle indicators while evaluating the different grouping scenarios.

Our findings indicate that best resulting classification was performed with one-versus-rest scenario where the "U-type" contraction was separated from others (Table 1). With this scenario, gender and occupation emerged as the most influential predictors in differentiating glabellar wrinkle types, particularly in the one-versus-rest scenario where the "U-type" contraction was separated from others. The predictive capacity of these features is supported by PCA results, where they demonstrated high contributions to the main variance component. This is consistent with prior research indicating gender-related anatomical and hormonal influences on facial muscle behavior. For instance, Luebberding et al. revealed that wrinkle formation patterns differ significantly between males and females, with men exhibiting earlier and more pronounced glabellar lines, while women experience an accelerated development of wrinkles post-menopause, likely due to hormonal shifts (19). Additionally, occupational status may reflect cumulative exposure to environmental factors like stress or UV radiation, which are known contributors to facial aging (20). Moreover, the ROC curve analysis for this scenario showed an AUC of 0.69, reflecting a moderate but meaningful ability to distinguish the "U-type" contraction from other wrinkle patterns.

The best classification performance ($F1 = 0.71$) was achieved using the KNN algorithm, suggesting that nonlinear relationships and local proximity in the feature space are relevant when modeling facial muscle dynamics. To check the consistency of the results, a 5-fold stratified cross-validation was applied to the best-performing scenario. The model showed stable performance across folds, with an average F1 score of 0.84, supporting that the results are not dependent on a single train-test split. However, the overall moderate F1 scores across all models and scenarios suggest that patient characteristics alone may only partially explain glabellar wrinkle patterns. Other factors, such as genetic predisposition, emotional expressivity, or skin type, may also play significant roles and merit further exploration.

In this study, a set of supervised classifiers including Naive Bayes, Random Forest, Logistic Regression, and K-Nearest Neighbors was implemented. While these algorithms provided meaningful results, future studies incorporating a broader range of classifiers may help improve the generalizability and robustness of the findings. The model demonstrated strong sensitivity in detecting U-type wrinkles; however, its relatively low specificity suggests a tendency to

overpredict this class, which should be addressed in future improvements.

The research presented by Lima et al. highlights the complexity of facial muscle interactions and the need for individualized evaluation. It emphasizes that contraction patterns in the glabellar, forehead, and periocular regions are interconnected and influenced by demographic factors (10). Our findings complement these observations by demonstrating that such contraction groupings can be partially predicted based on basic demographic and lifestyle characteristics.

One major strength of our study is the comprehensive evaluation of all feature subsets across multiple classifiers, allowing for an unbiased investigation into variable importance. Nevertheless, limitations include the lack of facial imaging data, which could have enriched the analysis with direct morphological cues. Moreover, excluding skin phototypes and sun exposure levels may have prevented a more complete understanding of extrinsic aging effects.

The step-by-step analysis pipeline implemented in this study enabled a systematic examination of how patient characteristics are associated with different types of glabellar wrinkles. By balancing the dataset in each scenario, testing all possible feature combinations, and evaluating models with consistent performance metrics, the approach ensured fairness and comparability across setups. This structure also enabled the identification of the most informative features and the selection of suitable algorithms for each grouping. While relatively simple, the pipeline offers a practical framework for exploring classification problems where the underlying relationships may vary across clinically meaningful subgroups.

Future research should consider integrating facial imaging with structured patient data, using deep learning architectures to improve prediction accuracy. Additionally, expanding the dataset to include ethnically and geographically diverse populations could enhance the generalizability of the findings.

Conclusion

This study demonstrates that glabellar wrinkle patterns are influenced by demographic factors such as gender and occupation and that machine learning can serve as a valuable tool in predicting these patterns with reasonable accuracy. By identifying key individual attributes associated with specific contraction types, our findings may contribute to a more personalized approach in cosmetic dermatology, where individualized treatment planning is increasingly emphasized. Furthermore, this study offers a data-driven perspective on the behavioral dynamics of facial muscles, which may complement clinical observations and support future research aiming to optimize aesthetic interventions.

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Ethical Approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine at Çukurova University on June 2, 2023 (approval number 134/44).

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Literature Review: Ç.C., A.G.K., D.M.B., E.E.S., YT., M.G.B.

Design : Ç.C., A.G.K., D.M.B., E.E.S., YT., M.G.B.

Data acquisition: Ç.C., A.G.K., D.M.B., E.E.S., YT., M.G.B.

Analysis and interpretation: Ç.C., A.G.K.

Writing manuscript: Ç.C., A.G.K.

Critical revision of manuscript: Ç.C., A.G.K.

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3T MRI-Based Regional Mapping of Magnetization Transfer Ratio in Normal Brain Tissue: A Study of White and Grey Matter Differences

3 Tesla MRI Kullanılarak Normal Beyin Dokusunda Bölgesel Manyetizasyon Transfer Oranı Haritalaması: Beyaz ve Gri Madde Farklılıklarının İncelenmesi

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Abstract

Background: This study aimed to establish normal regional Magnetization Transfer Ratio (MTR) values in white and grey matter using 3-Tesla MRI in healthy adult subjects, with a particular focus on cortical and deep brain structures. It also aims to assess the variability of these values and provide a baseline for further pathological studies.

Materials and Methods: Seventy healthy volunteers (28 females, 42 males, mean age 28 years) were included. MRI scans were performed using a 3.0 Tesla MRI scanner. Conventional cranial MRI sequences were acquired, followed by Magnetization Transfer Imaging (MTI) with off-resonance pulses. MTR maps were generated from proton density-weighted images obtained with and without magnetization transfer pre-pulses. Measurements were performed in 31 white matter and 9 grey matter regions, with additional assessments of CSF for noise control. Statistical analysis was carried out to compare MTR values across different brain regions.

Results: The mean MTR value was significantly higher in white matter (23.9 ± 0.21) compared to grey matter (17.3 ± 0.77). The corpus callosum had the highest MTR values within the white matter, particularly in the splenium, while the thalamus exhibited the highest MTR values in the grey matter. Regional variations were observed, with higher MTR values in the occipital and temporal lobes and lower values in the frontal and parietal lobes. MTR measurements showed excellent intra-observer (ICC > 0.9) and good inter-observer reliability (ICC 0.80–0.90).

Conclusions: This study provides detailed MTR mapping of normal brain tissue, highlighting significant regional differences between white and grey matter. The findings offer valuable baseline data for assessing structural changes in CNS diseases and for evaluating the efficacy of therapeutic interventions. MTR measurements demonstrate high reproducibility, making this technique a reliable tool in clinical and research applications for monitoring pathological alterations in the central nervous system.

Keywords: Magnetization Transfer Ratio, MTR, 3.0 Tesla, Magnetization Transfer Imaging, brain.

Öz

Amaç: Bu çalışmanın amacı, sağlıklı yetişkin deneklerde 3 Tesla manyetik rezonans görüntüleme (MRG) kullanarak beyaz ve gri cevherde normal bölgesel Manyetizasyon Transfer Oranı (MTO) değerlerini, özellikle kortikal ve derin beyin yapılarına odaklanarak belirlemek, bu değerlerin değişkenliğini değerlendirmek ve daha ileri patolojik çalışmalar için bir temel oluşturmaktır.

Materyal ve metod: Çalışmaya dahil edilen 70 sağlıklı gönüllünün (28 kadın, 42 erkek, ortalama yaş 28) MRG taramaları 3.0 Tesla MRG tarayıcısı kullanılarak gerçekleştirildi. Konvansiyonel kranial MRG sekanslar elde edilmiş, ardından rezonans dışı darbelerle Manyetizasyon Transfer Görüntüleme yapıldı. MTR haritaları, manyetizasyon transferi ön darbeleriyle ve bunlar olmadan elde edilen proton yoğunluk ağırlıklı görüntülerden oluşturuldu. Ölçümler, görüntü kontrolü için ek BOS değerlendirmeleriyle birlikte 31 beyaz cevher ve 9 gri cevher bölgesinde gerçekleştirildi. Farklı beyin bölgelerindeki MTO değerlerini karşılaştırmak için istatistiksel analiz yapıldı.

Bulgular: Ortalama MTO değeri beyaz cevherde ($23,9 \pm 0,21$) gri cevhere ($17,3 \pm 0,77$) kıyasla önemli ölçüde daha yüksekti. Korpus kallozum, beyaz cevher içinde, özellikle spleniumda en yüksek MTO değerlerine sahipken, talamus gri cevherde en yüksek MTO değerleri saptandı. Oksipital ve temporal loblarda daha yüksek MTO değerleri ve frontal ve parietal loblarda daha düşük değerlerle bölgesel farklılıklar gözlemlendi. MTO ölçümleri mükemmel gözlemci içi (ICC > 0,9) ve gözlemciler arası iyi güvenilirlik (ICC 0,80–0,90) gösterdi.

Sonuç: Bu çalışma, normal beyin dokusunun ayrıntılı MTO haritalamasını sunarak beyaz ve gri cevher arasındaki önemli bölgesel farklılıkları vurgulamaktadır. Bulgular, MSS hastalıklarındaki yapısal değişiklikleri değerlendirmek ve terapötik müdahalelerin etkinliğini değerlendirmek için değerli temel veriler sunmaktadır. MTO ölçümleri yüksek tekrarlanabilirlik gösterir ve bu tekniği merkezi sinir sistemindeki patolojik değişiklikleri izlemek için klinik ve araştırma uygulamalarında güvenilir bir araç haline getirir.

Anahtar Kelimeler: Manyetizasyon Transfer Oranı, MTO, 3.0 Tesla, Manyetizasyon Transfer Görüntüleme, beyin.

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Introduction

Magnetic resonance imaging (MRI) is a radiological tool which offers a sensitive, safe, and non-invasive way of imaging for central nervous system (CNS) diseases and monitoring the pathological alterations (1). The composed contrast in conventional MRI sequences results from the proton density of free-water molecules, and different relaxation characteristics of protons in water molecules. Thus, conventional MRI provides high sensitivity and low specificity for the detection of pathologies. Disease-related changes in water content or normal tissue losses due to edema, inflammation, infection, tumor cell infiltration, demyelinating diseases such as gliosis and other diseases which may cause neuronal damage can produce similar signal changes. Also, there is a proton pool which is tightly bounded to lipid membrane or proteins. Due to their very short T2 time, these protons are not visible in conventional MR images. Magnetization transfer imaging (MTI) is a MRI technique which can be used to collect indirect information about this bound proton pool and obtain information about a pathological entity (1-3).

The pre-pulse method is used to selectively saturate the bound proton pool by using the resonance characteristics or differential T2 time of the free and bound protons. This saturation is transferred into free water protons in processes such as chemical transversion or spin diffusion, which result in significant decrease in the tissue signal intensity. Therefore, the size of this effect is known as the magnetization transfer ratio (MTR), which represents the quantity and nature of macromolecules in the areas of interest. It has been used increasingly to evaluate CNS-related diseases. In addition, it has a potential to investigate the efficacy of new experimental methods in multiple sclerosis (MS). The effects of variables such as age, sex, brain region, or dominant hemisphere on MTR values and other MTR-influencing variables should be known to interpret these studies accurately (4-13). In this study, we defined MTI method and referred clinical applications particularly in the field of neuroradiology. To serve a model for further pathological studies, we aimed to map regional MTR values in the normal white/grey matters (cortical-deep) in a group of adults using 3-Tesla MRI.

In light of these considerations, this study aims to explore the regional variations in Magnetization Transfer Ratio (MTR) values across different areas of the brain, particularly within the white and grey matter, using 3-Tesla MRI. By focusing on the normal cortical and deep regions in a cohort of healthy adults, we seek to establish baseline MTR values that can serve as reference points for future research into various CNS pathologies. This detailed mapping will help enhance the understanding of the relationship between tissue composition and MTR, further supporting its clinical applications in evaluating neurodegenerative and demyelinating diseases, such as multiple sclerosis.

Materials and Methods

Study Population

The study included a total of 70 volunteer healthy subjects without any pathology, as confirmed by conventional MRI. None of the subjects had any complaints. Before entering into the MRI room, all metal objects or accessories were removed. Exclusion criteria were as follows: having medical devices or equipment (internal fixation, metallic cover heart pacemakers, etc.) which can interfere with MRI imaging; age outside the pre-specified interval (range, 20 to 40 years); having measurement artifacts (confirmed by cerebrospinal fluid [CSF]); having a parenchymal pathology in conventional series, systemic disease, and chronic symptoms. The ethics committee approved the protocol of the study (Bakırköy Sadi Konuk Hospital, Ethics Committee, Number:2015/04/05). A written informed consent was obtained from each subject. The study was conducted in accordance with the principles of the Declaration of Helsinki.

MRI protocol

Images from all subjects were acquired in supine position with a 3.0 Tesla MRI Signal HD scanner (Siemens, MAGNETOM Verio, Germany) by using a head coil. Initially, the routine cranial MRI protocol was applied to all subjects; then, MTI sequencing was performed on subjects who fulfilled the inclusion criteria. For conventional images, preview images were acquired to determine the sections in the axial-sagittal and coronal planes. In accordance with the cranial MRI protocol, we obtained axial T1-weighted turbo spin echo (TSE) sequences, axial and coronal T2-weighted TSE sequences, axial fluid attenuated inversion recovery (FLAIR) sequences, and sagittal T1-weighted TSE sequence diffusion-weighted images and apparent diffusion coefficient (ADC) maps through this images.

Two different proton density-weighted images were obtained with/without using an off-resonance magnetization pre-pulse with the identical variables and the identical localization in the axial plane to create MTR map in the MTI. The following variables were used: TR: 2400 ms, TE: 18 ms, flip angle: 150°, field of view (FOV) 220*180*180 mm, reconstruction matrix 128*128, voxel size: 1.88*1.88*3.00. Saturation pre-pulse was an off-resonance pulse with a frequency offset of 500 kHz and bandwidth of 488 Hz/px. Images of 70 sections were used to screen the whole brain. Thirty-five sections were obtained by using the MTI pulse, and 35 sections were obtained without using the MTI pulse. After MRI, images were processed with MTR equation and, then, sent to workstations for analysis. The specific absorption rate (SAR) values were within the range of Food and Drug Administration-approved limits during measurements.

Image Analysis

All cross-sectional images were evaluated in syngo Acquisition Workplace-ICS Tower 11E by using the Syngo.via (Siemens Healthcare, Germany) software. The images were evaluated by two independent radiologists with nine (E.K.) and eight (V.K.) years of neuroradiology experience. The readers who performed the measurements evaluated the images independently and separately. In addition, for intra-observer variability, the same measurements were performed by the readers a second time at one-month intervals. Interobserver variability was evaluated by averaging the measurements made by the readers at different times. First, conventional images were analyzed to confirm the absence of underlying pathologies. Then, to provide process standardization, a guide list and image maps of measuring range were created. The MTR maps and T1-weighted images were measured after synchronization. The areas of interest in the MTR maps in all subjects were analyzed and saved accordingly. Both hemispheres were measured individually, and midline structures were measured alone. The MTR values were measured in the right/left hemispheres, white matter/grey matters (cortical-deep), all localizations in the white matter and supra and infratentorial compartments of the grey matter. The regional differences and mean MTR values with standard deviation (SD) of measured areas were statistically analyzed. In addition, MTR values of CSF samples were measured to provide noise control, and subjects with high noise values (CSF value >3 pu) were excluded. A total of 80 measurements were obtained from each subject; nine areas from the grey matter (i.e., cerebellum, temporal lobe, parietal lobe, precentral gyrus, occipital lobe, frontal lobe, head of the caudate nucleus, globus pallidus, putamen and thalamus) and 29 areas from the white matter (i.e., pericallosal area, brachium pontis, tectum, tegmentum, optic tract, middle and lateral cerebellar peduncles, central white matter of frontal lobe, frontal lobe U-fibers (subcortical WM), parietal lobe central WM, parietal lobe subcortical WM, temporal lobe central WM, temporal lobe subcortical WM, optical radiation, occipital lobe central WM, occipital lobe subcortical WM, internal capsule; anterior and posterior crus and genu, external capsule, corpus callosum genu and splenium, centrum semiovale, corona radiata, parasagittal subcortical WM, periventricular WM, pons, and cerebellar WM) were taken bilaterally and three midline WM (i.e., anterior commissure, fornix and body of corpus callosum) were taken unilaterally. The measurements of one CSF and total 79 parenchymal areas were evaluated with circular regions of interest (ROIs). The selected ROIs were chosen to cover both cortical and deep regions commonly involved in neurodegenerative and demyelinating diseases. The ROIs were between 0.5 mm² and 25 mm² depending on the region. The subjects with high CSF values (> 3pu) were also excluded.

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Variables were classified as either categorical or continuous. Categorical variables were presented as counts and percentages (%), while continuous variables were expressed as mean $\pm$ standard deviation. The intraobserver and interobserver agreement for MTR values in normal brain tissue were assessed using the intra-class correlation coefficient (ICC). ICC values were interpreted as follows: <0.4, poor agreement; 0.4–0.75, moderate agreement; 0.75–0.9, good agreement; and >0.9, excellent agreement (14–16). For example, the intra-observer ICC for the splenium of the corpus callosum was 0.94, indicating excellent reliability. Statistically, a p-value of <0.05 was considered significant for all analyses.

Results

A total of 70 subjects were included in the study. Of these subjects, 28 (40%) were females, and 42 (60%) were males. The mean age was 28 years (range, 20 to 40 years). For male subjects, the mean age was 29 years and 26.5 years for males and females, respectively.

Parenchymal MTR values of 41 areas (31 white matter areas, nine grey matter areas, and CSF) were measured for all 70 subjects. Thirty-seven parenchymal measurements were evaluated bilaterally, and three midline measurements were evaluated unilaterally (80 measurements for each subject). The mean MTR value in the white matter was higher, compared to the grey matter. The mean pu values for the grey matter and white matter were 17.3 ± 0.77 (SD) and 23.9 ± 0.21 (SD), respectively. The MTR maps showed homogeneous and uniform suppressions in the white matter and grey matter. In the grey matter, the lowest MTR values were obtained from the cerebellum and frontal lobe, while the highest values were obtained from the thalamus and globus pallidus. In the white matter, the lowest MTR values were obtained from the tectum, optic tracts, fornix, and anterior commissure, while the highest values were obtained from the corpus callosum, posterior crus, and centrum semiovale. In the comparison of the lobes, the highest mean MTR value was detected in the occipital and temporal lobes for the grey matter, whereas the white matter MTR value of the temporal lobe was higher than the other lobes. The mean MTR value in the subcortical white matter was lower, compared to the central white matter. According to the classification of the values of the, lowest to highest values were obtained from the anterior crus, anterior genu, and posterior crus, respectively. Values for the corpus callosum were homogenous, while the highest parenchymal MTR values were obtained from the corpus callosum splenium, followed by the corpus callosum genu. In the brainstem, suppression of the tectum was higher, compared to the mesencephalon and tegmentum.

In addition, higher values were observed in the lateral crus cerebri, compared to the medial crus cerebri. The MTR values in pons and tegmentum values were similar, which also

showed similarities to the MTR values in the white matter cerebellum. The MTR values in caudate nucleus and putamen values were close, while MTR values in globus pallidus were slightly higher. However, MTR values in the thalamus were higher, compared to the aforementioned regions. Tables 1 and 2 present the measurements performed by two different radiologists at two separate time points for white matter, along with the ICC values indicating intra- and inter-observer reliability.

Similarly, Tables 3 and 4 display the measurements performed by the same radiologists at two different time points for gray matter, along with the corresponding ICC values for intra- and inter-observer reliability. And the figures show the parenchymal levels at which the measurements were made.

The images in figures 1, 2, 3, 4, 5 and 6 show measurements in different regions.

Table 1. Intra-observer reliability of measurements of magnetic transfer rates from white matter

Localisation	Magnetisation Transfer Ratio (Reader 1)			Magnetisation Transfer Ratio (Reader 2)		
	First measurement	Second measurement	R%	First measurement	Second measurement	R%
1. Corpus Callosum body	24.3±0.5	24.8±1.1	93.8	24.4±1.2	24.9±1.1	90.1
2. Pericorpus callosum WM	24.5±0.7	24.1±0.7	91.2	23.9±0.7	24.1±0.6	84.1
3. Brachium pontis	23.2±0.8	23.3±0.7	96.1	23.0±0.6	22.8±0.8	87.2
4. Tectum	21.7±0.6	22.0±1.0	93.2	22.2±0.9	22.1±1.0	86.3
5. Tegmentum	23.1±0.7	23.0±0.9	96.8	23.1±0.9	22.9±0.9	90.2
6. Optic tract	22.0±1.0	21.4±1.5	97.8	21.7±1.4	21.4±1.2	83.7
7. Cerebral peduncul medial	23.5±0.9	23.6±1.3	97.7	23.4±1.2	23.9±1.2	86.7
8. Cerebral peduncul lateral	24.2±0.8	24.3±1.3	98.2	24.1±1.2	24.3±1.2	87.9
9. Frontal lobe central	24.1±0.9	24.8±0.9	88.7	24.5±1.0	24.6±0.9	92.1
10. Frontal lobe subcortical	23.6±0.9	24.3±0.9	87.1	24.1±0.8	24.2±0.8	89.1
11. Parietal lobe central	24.5±1.1	25.2±1.0	89.2	24.8±1.2	24.8±0.9	96.7
12. Parietal lobe subcortical	24.3±0.5	24.5±0.8	97.8	24.3±0.9	24.2±0.9	94.1
13. Temporal lobe central	25.0±0.6	25.7±1.0	90.1	25.3±1.3	25.3±1.1	97.1
14. Temporal lobe subcortical	24.5±0.8	25.1±1.1	91.2	24.7±1.2	24.5±0.9	94.2
15. Optic radiations	24.7±0.7	25.1±0.9	93.1	24.8±1.1	24.8±1.2	97.1
16. Occipital lobe central	24.5±0.9	24.9±0.8	92.5	24.6±0.8	24.7±0.7	96.2
17. Occipital lobe subcortical	24.0±1.1	24.3±0.8	95.2	24.1±0.9	24.3±0.8	93.4
18. Internal Capsul anterior Crus	24.2±0.8	23.5±1.1	89.8	23.4±1.1	23.5±0.9	97.5
19. Internal Capsul genu	24.6±0.7	24.6±1.0	98.7	24.3±1.1	24.6±1.1	89.8
20. Internal Capsul posterior Crus	25.3±0.7	25.5±0.9	96.2	25.1±1.2	25.3±1.1	95.2
21. External Capsul	23.0±0.5	23.1±0.8	97.1	23.1±0.7	22.5±0.9	92.1
22. Corpus Callosum genu	25.9±0.8	26.0±0.9	93.1	25.5±1.3	26.1±0.8	92.8
23. Corpus Callosum splenium	26.1±0.8	26.5±1.0	94.0	26.1±1.2	26.5±1.1	96.1
24. Fornix	21.8±0.7	21.6±1.1	96.4	21.9±1.2	21.2±1.0	87.4
25. Centrum semiovale	25.1±0.4	24.9±0.7	95.1	24.6±0.9	24.8±0.9	89.1
26. Corona radiata	24.2±0.5	24.3±0.9	97.1	24.1±0.9	24.1±0.8	96.5
27. Parasagital subcortical WM	24.1±0.4	23.9±1.0	96.3	23.8±0.9	23.7±0.7	97.4
28. Periventricular WM	24.0±0.6	23.8±0.9	94.1	23.6±0.8	23.7±0.8	98.1
29. Anterior commissur	21.4±0.9	21.3±1.4	97.3	21.6±1.3	21.2±1.1	92.1
30. Pons	23.2±0.6	22.7±0.8	93.9	22.7±0.7	22.4±0.7	98.1
31. Cerebellum	23.2±0.6	22.7±0.8	94.2	22.6±0.7	22.4±0.8	96.0

%R Relative coefficient of reliability

Table 2. Inter-observer reliability of measurements of magnetic transfer rates from white matter

Localisation	Magnetisation Transfer Ratio		
	Reader 1 average measurement	Reader 2 average measurement	R%
1. Corpus Callosum body	24.6±0.8	24.5±1.1	84.4
2. Pericorpus callosum WM	24.3±0.7	24.0±0.6	83.2
3. Brachium pontis	23.2±0.7	22.9±0.7	87.2
4. Tectum	21.9±0.8	22.1±1.0	86.1
5. Tegmentum	23.0±0.8	23.0±0.9	89.2
6. Optic tract	21.7±1.3	21.5±1.3	87.8
7. Cerebral peduncle medial	23.6±1.1	23.6±1.2	87.7
8. Cerebral peduncle lateral	24.3±1.1	24.2±1.2	88.2
9. Frontal lobe central	24.5±0.9	24.6±0.9	88.3
10. Frontal lobe subcortical	23.9±0.9	24.2±0.8	85.4
11. Parietal lobe central	24.8±1.0	24.7±0.9	84.7
12. Parietal lobe subcortical	24.4±0.7	24.2±0.9	87.8
13. Temporal lobe central	25.2±0.8	25.2±1.1	89.1
14. Temporal lobe subcortical	24.9±0.9	24.6±1.0	83.2
15. Optic radiations	24.9±0.8	24.7±1.2	87.1
16. Occipital lobe central	24.7±0.8	24.7±0.8	82.5
17. Occipital lobe subcortical	24.1±0.8	24.2±0.8	85.2
18. Internal Capsule anterior Crus	23.8±1.0	23.5±0.9	89.8
19. Internal Capsule genu	24.6±0.8	24.5±1.0	90.7
20. Internal Capsule posterior Crus	25.4±0.9	25.2±1.0	90.2
21. External Capsule	23.0±0.9	22.8±0.8	87.1
22. Corpus Callosum genu	26.0±0.9	25.8±0.8	83.1
23. Corpus Callosum splenium	26.3±0.9	26.3±1.1	94.3
24. Fornix	21.7±0.9	21.5±1.0	86.4
25. Centrum semiovale	25.0±0.5	24.7±0.9	82.1
26. Corona radiata	24.3±0.7	24.1±0.8	87.1
27. Parasagittal subcortical WM	24.0±0.8	23.7±0.8	86.3
28. Periventricular WM	23.9±0.9	23.7±0.7	89.1
29. Anterior commissure	21.3±1.3	21.3±1.2	90.3
30. Pons	22.9±0.8	22.5±0.8	82.9
31. Cerebellum	22.9±0.7	22.5±0.8	87.2

%R Relative coefficient of reliability

Table 3. Intra-observer reliability of measurements of magnetic transfer rates from gray matter

Localisation	Magnetisation Transfer Ratio (Reader 1)			Magnetisation Transfer Ratio (Reader 2)		
	First measurement	Second measurement	R%	First measurement	Second measurement	R%
Cerebellum	13.6±1.4	13.8±1.4	92.7	13.2±1.1	13.6±1.2	91.8
Temporal lobe	16.7±1.4	16.5±1.4	97.3	16.3±1.2	16.1±1.4	96.3
Parietal lobe	16.2±1.9	16.3±1.7	95.4	16.0±1.1	16.2±1.7	94.4
Occipital lobe	16.2±1.4	15.9±1.2	90.8	16.0±1.3	15.8±1.3	91.4
Frontal lobe	14.2±1.6	14.3±1.3	94.9	14.0±1.4	14.5±1.2	93.9
Caudate nucleus	18.7±1.1	18.8±1.0	94.5	18.6±1.3	18.9±1.1	93.5
Globus pallidus	19.6±1.4	19.5±1.1	90.4	19.4±1.6	19.4±1.2	91.8
Putamen	22.5±1.1	22.3±0.9	91.0	21.5±1.1	22.1±0.8	90.0
Thalamus	22.9±1.1	22.6±0.9	87.9	22.6±1.4	22.4±0.9	91.9

%R Relative coefficient of reliability

Table 4. Inter-observer reliability of measurements of magnetic transfer rates from gray matter

Localisation	Magnetisation Transfer Ratio		
	Reader 1 average measurement	Reader 2 average measurement	R%
Cerebellum	13.7±1.4	13.4±1.2	89.7
Temporal lobe	16.6±1.4	16.2±1.4	87.3
Parietal lobe	16.6±1.9	16.1±1.7	85.4
Occipital lobe	16.0±1.4	15.9±1.3	91.8
Frontal lobe	14.3±1.6	14.3±1.2	91.9
Caudate nucleus	18.7±1.1	18.7±1.1	92.5
Globus pallidus	19.5±1.4	19.4±1.4	90.5
Putamen	22.4±1.1	21.8±0.8	89.8
Thalamus	22.7±1.1	22.5±0.9	88.9

%R Relative coefficient of reliability

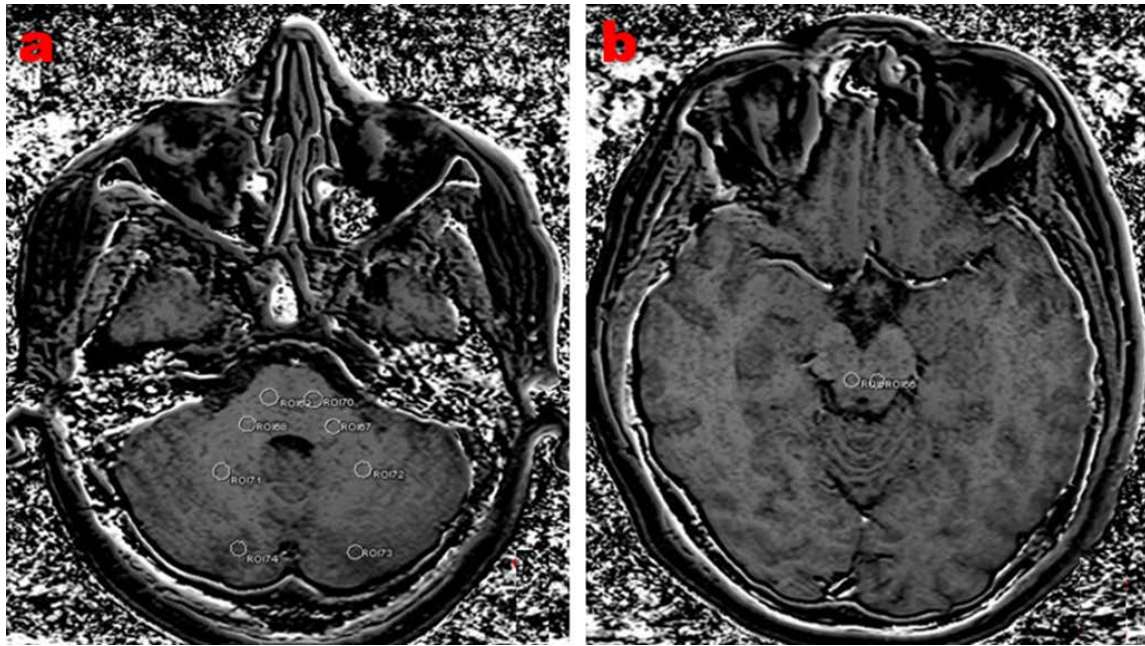


Figure 1. a) MTR measurement level from down to up. Pons level measurement examples: ROI 67-68: right and left middle, cerebellar pedunculus, ROI 69-70: Pons right and left half, ROI 71-72: right and left cerebellar white matter, ROI 73-74: right and left cerebellar gray matter **b)** inferior mesencephalic level. ROI 55-56: right and left Tegmentum

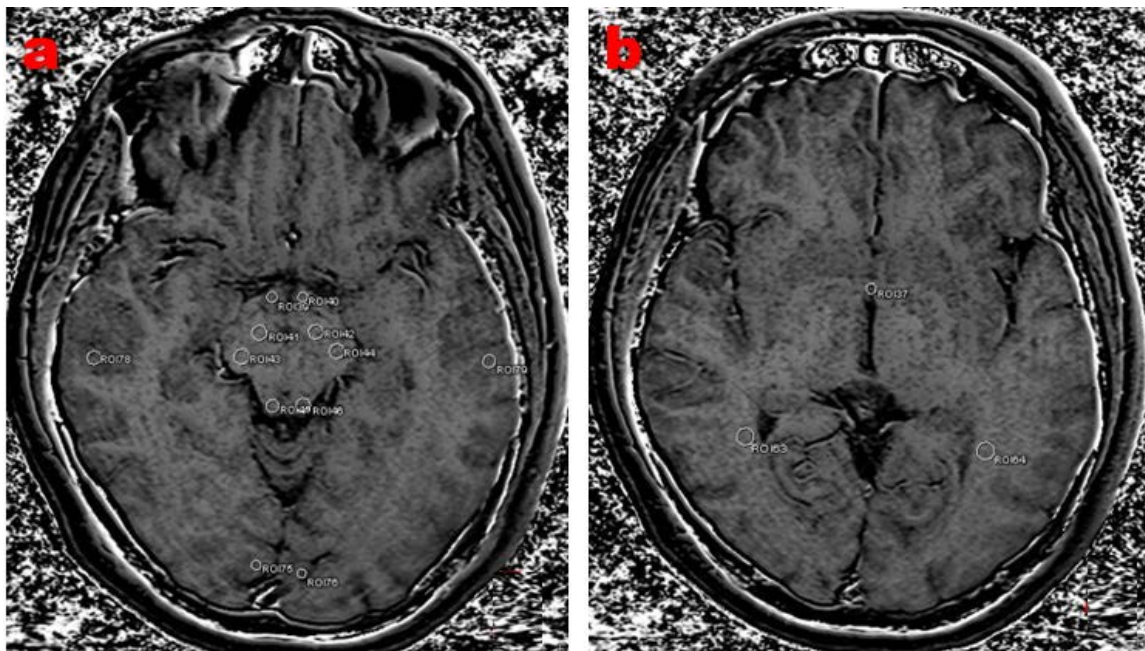


Figure 2. a) Superior mesencephalic level ROI 39-40: right and left optic tractus, ROI 41-42: right and left crus cerebri medial, ROI 43-44: right and left crus cerebri lateral, ROI 45-46 right and left half of tectum, ROI 75-76: right and left occipital gray matter, ROI 78 79: right and left temporal gray matter. **b)** Cerebrum basal level ROI 37: anterior commissur, ROI 63-64: right and left optic radiations

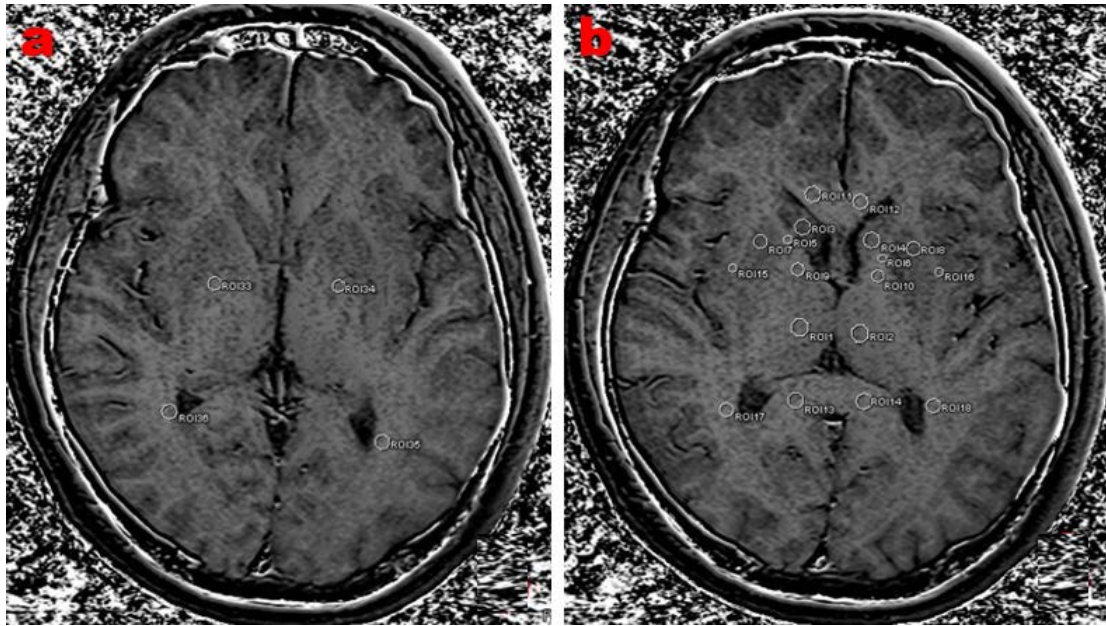


Figure 3. a) Inferior basal ganglia level. ROI 33-34: right and left globus pallidus, ROI 35-36: right and left periventricular white matter
b) basal ganglia level
ROI 1-2: right and left thalamus ROI 3-4: right and left head of caudat nucleus
ROI 5-6: Right and left capsula interna anterior crus
ROI 7-8: Right and left putamen ROI 9-10: right and left capsula interna genu
ROI 11-12: Right and left halves of corpus Callosum genu
ROI 13-14: Right and left halves of Corpus Callosum splenium ROI 15-16: Right and left external capsule, ROI 17-18: Right and left periventricular white matter

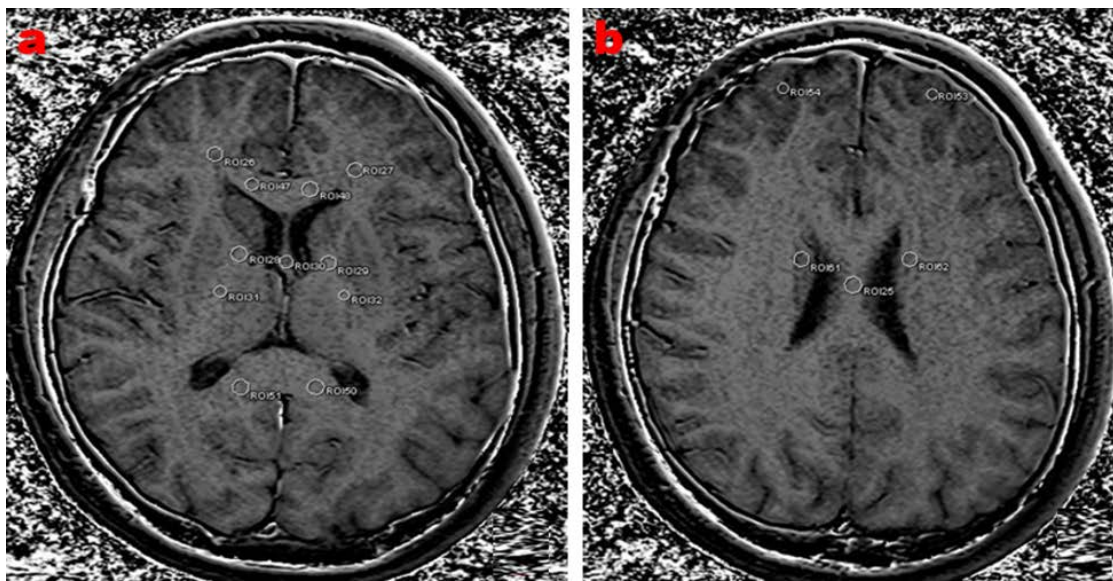


Figure 4. a) Upper basal ganglia level ROI 26-27: right and left pericorpus callosum
ROI 28-29: right and left internal capsule genu, ROI 30: Fornix, ROI 31-32: right and left internal capsule posterior krus ROI 47-48: Right and left halves of Corpus Callosum genu
ROI 50-51: Right and left halves of corpus callosum splenium. b) Upper ventricular level. ROI 25: body of corpus callosum, ROI 51-52: right and left corona radiata, ROI 53-54: right and left frontal gray matter

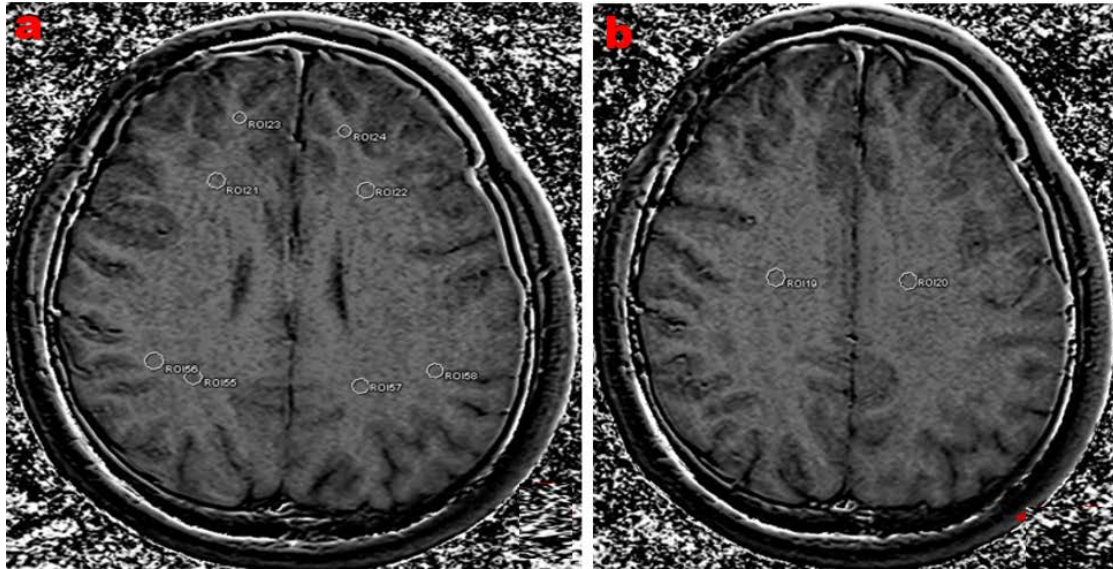


Figure 5. a) Supraventricular level. ROI 21-22: right and left frontal deep white matter, ROI 23-24: right and left frontal subcortical white matter, ROI 55-57: right and left parietal deep white matter, ROI 56-58: right and left parietal subcortical white matter. b) upper centrum semiovale level. ROI 19-20: right and left parietal gray matter.

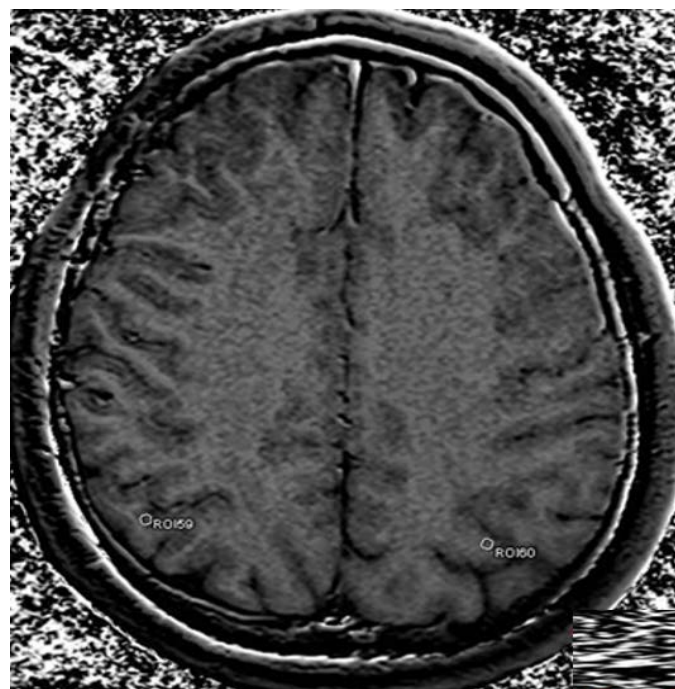


Figure 6. Centrum semiovale level. ROI 19-20: right and left centrum semiovale

Discussion

Tissue-contrast mechanisms in conventional MRI depend on three major features: density of free water protons, spin-lattice (T1), and spin-spin (T2) relaxations. Indeed, conventional MRI has low specificity in terms of detecting pathological processes. On the contrary, MTI has a unique contrast mechanism, which allows monitoring the macromolecule bound protons, which are not visible in conventional MRI (4). The MTR values in the brain have shown

promise in detecting the structural damages of the white matter, demyelinating pathologies, particularly in disease such as MS (5,6,12,13). Regional MTR values and its variations of the normal brain should be known to understand how and what extent demyelinated white matter diseases alter the MTR values, which is considered more specific to structural white matter injury.

In this study, we identified regional MTR values in the normal white/grey matters (cortical-deep) in adults and evalu-

ated differences in the regional MTR values. We also discussed variations and possible reasons of these variations. We selected off-resonance MTI pulses with spin echo-based sequences to obtain MTR measurements. For dividing the brain into different zones, we used the table by Mehta et al. (17) with minor modifications, as it is helpful to evaluate more brain regions rather than other available methods (17,18).

Previous studies have demonstrated that MTR values vary among anatomic structures in the normal brain (1,17,18). The MTR values in the normal white matter are relatively high, compared to the grey matter (1,17,19). Moreover, MTR values show variations across different regions in the white matter; the highest MTR values are seen in the corpus callosum (1,17,20). The MTR value of the deep white matter is relatively low, compared to the corpus callosum. Different lobes have similar values. Subcortical U-fibers have lower MTR values. The highest MTR value in the grey matter is detected in the thalamus. Compared to thalamus, caudate nucleus, globus pallidum and putamen have similar, but relatively lower MTR values (17). Regional variations in myelination are accompanied by regional variations in MTR values. In addition, physiological age-related changes in MTR values have been observed in developing and adult brain (21,24). In another study, Engelbrecht et al. showed age-dependent alterations in the MTR values in pediatric brain regions (22). The causes of the differential saturation are elevated myelination and galactocerebroside concentration due to the maturation (22). Mehta et al. (17) reported no significant differentiation between two-hemisphere, while Silver et al. (1) obtained higher values from left hemisphere. The differential MTR of the normal brain may be related to the fiber density, degree of myelination, degree of tissue hydration, and vascularization. The age-dependent and age-independent variations in MTR values in the normal brain should be considered in the analysis of regional MTR values in the affected brain.

In the present study, we used lower offset frequency (500 Hz) off-resonance pulse to decrease energy depolarization and as a result our MTR values were lower, compared to the previous findings. Our findings on the regional variations are consistent with findings of Mehta et al. (17) similar to previous studies; we observed higher MTR values in the white matter, compared to the grey matter (Tables 1,2,3 and 4-Figures 1, 2, 3, 4, 5 and 6). The degree of myelination, cerebroglycosides, phosphatidylcholine, and cholesterol in the white matter may have played a role in these results. Moreover, we found the highest MTR values in the corpus callosum. Within the corpus callosum, the highest MTR value was detected in the splenium (Tables 1 and 2-Figure 2). According to the literature data, corpus callosum has the highest MTR value within the white matter. Within the corpus callosum, Mehta et al. (1) observed the highest MTR value in genu, while Silver et al. (1) and Garcia et al. (25) found the highest MTR value in the splenium. Corpus callo-

sum has a large number (about 300 million fibers) of myelinated commissural fibers, which results in higher MTR values (26). Similar to Mehta et al. (17), we observed higher MTR values in the deep white matter, compared to the subcortical white matter at the lobar level (Tables 1 and 2-Figure 3).

Furthermore, the MTR values in the temporal and occipital lobes of the white matter were higher, compared to parietal and frontal lobes in our study (Tables 1 and 2-Figure 5). These results are also consistent with the findings of Mehta et al. (17). On the other hand, Silver et al. (1), Garcia et al. (25) and Tozer et al. (27) reported higher values in the frontal lobe. The MTR values in the periventricular white matter were similar, and MTR values in the centrum semiovale were higher, consistent with the literature (Tables 1 and 2-Figures 2 and 3). In the internal capsule, as in the studies of Mehta et al. (17) and Garcia et al. (25), we observed the highest value in the anterior crus, followed by the anterior genu, and posterior genu (Tables 1 and 2-Figure 2). The MTR values in the posterior crus were higher, compared to the lobes of deep and superficial white matter (Tables 1 and 2-Figures 2 and 3). Long and myelinated corticospinal tract fibers, which start from the primer motor cortex, constitute fibers of posterior crus, and the higher posterior crus values may be related to this.

In the evaluation of the structures of the posterior fossa white matter, we observed similar MTR values in pons, cerebellum, and brachium pontis, which were higher, compared to tectum and tegmentum. The lowest MTR values were observed in the tectum (Tables 1 and 2-Figure 1). There is no available data on MTR values in the pons and cerebellum in the literature. Mehta et al. (17) determined MTR values in tectum, tegmentum and brachium pontis. Contrary to our findings, the authors determined the highest MTR value in the tectum. Similar to Mehta et al. (17), we found higher MTR values in the lateral region of cerebral crus, compared to the medial region (Tables 1 and 2-Figure 1). This can be due to the presence of fibers coming from posterior crus of internal capsule, whereas fibers coming from anterior crus of internal capsule and frontopontin fibers are present in the medial region.

Similar to the literature data, we determined the highest MTR value in the grey matter in the thalamus (Tables 3 and 4-Figure 2). A potential explanation for this finding is the presence of many afferent and efferent fibers in the thalamus (26). Consistent with the previous findings, we determined higher MTR values in the grey matter of the temporal lobe and the occipital lobe, which were lower compared to the basal ganglia (Tables 3 and 4-Figure 1).

In the comparison of the MTR values among basal ganglia, the highest value was found in the thalamus, followed by globus pallidus, putamen, and head of caudate nucleus (Tables 3 and 4-Figure 3). These findings are consistent with Garcia et al. (25); however, Mehta et al. (17) observed similar MTR values in the putamen and caudate nucleus, and higher MTR values, compared to the globus pallidus. Similar

to Garcia et al. (25), we found higher MTR values in the basal ganglia, compared to the other lobes. However, Mehta et al. (17) reported higher MTR values in the temporal lobe, compared to the globus pallidus.

Nonetheless, this study has a certain limitation as data were obtained from only a group of middle-aged individuals. Therefore, we were unable to evaluate the effect of age and dominance. However, we believe that our findings are highly valuable, as we used 3T-MRI to contribute to further studies.

In our study, we demonstrated that Magnetisation Transfer Ratio (MTR) measurements exhibit intra-observer agreement exceeding 90% (excellent agreement) and inter-observer agreement ranging between 80% and 90% (good agreement). These findings indicate that MTR measurements are highly reproducible and can yield reliable and accurate results even when performed by different observers. The results support the utility of MTR as a standardized measurement tool in both clinical practice and research settings.

Limitations

One limitation of this study is the relatively small sample size, which may affect the generalizability of the findings to the broader population. Additionally, while 3-Tesla MRI provides high-resolution imaging, the sensitivity of the MTR technique to detect subtle pathological changes in tissue composition may be limited by factors such as the resolution of the MRI scanner and the influence of motion artifacts. Furthermore, the cross-sectional design of the study prevents the assessment of longitudinal changes in MTR values over time, which could provide more insights into disease progression or the effects of treatment. Although hemispheric dominance was not assessed, previous studies have reported minimal impact of dominance on MTR values (28). Finally, other factors, such as individual variations in hydration status, medication use, or comorbidities, were not controlled for and could influence the MTR measurements.

Conclusion

In conclusion, MTR measurement has the potential to evaluate pathological and physiological structural alterations in CNS *in vivo*, and the method is an invaluable tool which can provide enhanced sensitivity and specificity in the evaluation of the pathological processes. In addition, MTR measurement has the potential to evaluate response to treatment, and therapeutic efficacy. On the other hand, biological variations in the normal brain regions should be considered in the interpretation of these findings. Therefore, we conclude normal MTR values in different brain regions to use as indices in further studies in which 3T MRI will be used with the variables described in this study.

Ethical Approval: This study was approved by the Clinical Research Ethics

Committee of the Bakırköy Sadi Konuk Training and Research Hospital (Ethical Committee approval number: 2015/04/05 Date: 23/02/2015).

Author Contributions:

Concept: E.K., V.K., M.T., E.İ.

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Design: E.K., M.T., T.K.

Data acquisition: M.T. E.Ç., T.K.

Analysis and interpretation: E.K., M.T.

Writing manuscript: E.K., M.T., V.K.

Critical revision of manuscript: E.K., M.T., T.K.

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A Bibliometric Analysis of 4269 Articles Published on Laparoscopic Sleeve Gastrectomy in Journals Indexed in Scientific Citation Index-Expanded Between 2000-2023

2000-2023 Yılları Arasında, Scientific Citation Index Tarafından İndekslenen Dergilerde, Laparoskopik Sleeve Gastrektomi Üzerine Yayınlanan 4269 Makalenin Bibliyometrik Analizi

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Abstract

Background: Especially; In the last decade, the prestige of laparoscopic sleeve gastrectomy among surgeons and patients has increased, and the demand to get knowledge was accelerated. Holistic evaluation of scientific publications, including publication and citation metrics, is the definition of "Bibliometrics". In the present research, we aimed to analyze the most cited articles about LSG, published between the years 2000-2020, with respect to the database of Web of Science.

Materials and Methods: We used the search engine of Clarivate Analytics®, Web of Science Core Collection, by using the keyword "Laparoscopic sleeve gastrectomy", and by choosing the "Topic" section on January 1, 2020. Only "Articles" in "English" were included in the study protocol. The publication rates, according to years, countries, journal categories, organizations, authors and publication number, citation, and h-index data were evaluated. Also, publication metrics were evaluated in terms of Gross Domestic Product (GDP), Gross Domestic Product per capita (GDPpp), and Human Development Index (HDI) of the countries.

Results: The most productive countries, scientific journals, and authors are USA, Obesity Surgery, and Schauer PR, respectively. A weak positive correlation was found between publication numbers and GDP ($r=0.370$, $p<0.05$), also positive correlations with (GDPpp) and HDI ($r=0.359$, $p>0.05$; $r=0.603$, $p>0.05$; respectively).

Conclusions: This study shows the avalanching publication productivity concerning LSG, over the last twenty years. Bibliographic analysis will contribute to facilitating researchers' further research.

Keywords: Bibliometrics, Sleeve gastrectomy, Laparoscopic sleeve gastrectomy, Bariatric surgery

Öz

Amaç: Özellikle son on yılda laparoskopik sleeve gastrektominin (LSG) cerrahlar ve hastalar arasındaki prestiji artmış ve bilgi edinme talebi hızlanmıştır. "Bibliyometri", yayın ve atıf ölçütleri dahil olmak üzere bilimsel yayınların bütünsel değerlendirmesi olarak tanımlanır. Bu çalışmada 2000-2023 yılları arasında yayınlanan LSG ile ilgili en çok atıf alan makaleleri Web of Science veri tabanına bağlı olarak incelemeyi amaçladık.

Materyal ve Metod: 1 Ocak 2023'de Clarivate Analytics®, Web of Science Core Collection arama motorunda "Topic" bölümünü seçilerek "Laparoskopik sleeve gastrectomy" anahtar kelimesi arama için kullanıldı. Yalnızca "İngilizce" de "Makaleler" çalışma protokolüne dahil edildi. Yıllara, ülkelere, dergi kategorilerine, kuruluşlara, yazarlara ve yayın sayısına göre yayın oranları, atıf ve h-indeksi verileri değerlendirildi. Ayrıca, ülkelerin Gayri Safi Yurtiçi Hasıla (GSYİH), Kişi Başına Gayri Safi Yurtiçi Hasıla (GSYİHpp) ve İnsani Gelişme Endeksi (İGE) açısından yayın ölçütleri değerlendirildi.

Bulgular: En üretken ülkeler, bilimsel dergiler ve yazarlar sırasıyla ABD, Obesity Surgery ve Schauer PR' idi. Yayın sayıları ile GSYİH arasında zayıf bir pozitif korelasyon ($r = 0.370$, $p < 0.05$), ayrıca (GDPpp) ve HDI ile pozitif korelasyon (sırasıyla $r = 0.359$, $p > 0.05$; $r = 0.603$, $p > 0.05$) bulundu.

Sonuç: Bu çalışma, son yirmi yılda LSG ile ilgili araştırmaların verimliliğinin çığ gibi arttığını göstermektedir. Bibliyografik analiz, araştırmacıların bundan sonraki araştırmalarının kolaylaşmasına katkı sağlayacaktır.

Anahtar Kelimeler: Bibliyometri, Sleeve gastrektomi, Laparoskopik sleeve gastrektomi, Bariatrik cerrahi

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Introduction

Obesity is associated with serious comorbidities and mortality and remains a major health problem. (1). With the increasing popularity of bariatric surgical procedures, the number of patients applying for surgical procedures has continued to increase significantly (2). Also, laparoscopic sleeve gastrectomy (LSG) is an effective, promising method for treating obesity (3,4).

The 1991 National Institutes of Health (NIH) consensus statement about body mass index and bariatric surgery did not address some techniques and advancements, including procedures like LSG (5). However, nearly two decades after the consensus of NIH, the American Society for Metabolic and Bariatric Surgery (ASMBS) affirmed LSG as an acceptable alternative option of ASMBS, insurance coverage for LSG started, and the International Classification of Diseases, 9th Revision, Clinical Modification code for this procedure established in 2011 (6,7). Following these developments, the prestige of LSG amongst surgeons and patients has risen. Accordingly, the demand for learning about LSG has increased (5,8).

Bibliometry means a holistic definition of scientific publications (9). Evaluation of citations to scientific articles is a bibliographic process. This analysis is created in the assessment of collaboration between scientists, published publications, various institutions, or countries (10). The internet accelerated on-line access to scientific databases or publications. For this reason, the amount of publication in scientific databases has also increased (11). Bibliometric studies lead to collaboration between authors, publications, and active journals from different countries, resulting in the formation of a guide for researchers (10). But there are no studies in the literature that measure the productivity of scientific articles about an obesity treatment method with markers and scales that measure the socio-economic well-being levels of countries producing scientific publications focusing on LSG.

With this research, we intend to measure the studies announced in the Web of Science (WOS) database, concerning LSG, written from 2000 to today. Our second aim is to assess if there is a relationship between the United Nations Development Statistics and bibliometric outcomes about this issue.

Materials and Methods

We obtained the data in this study from Clarivate Analytics®, Web of Science Core Collection (<http://apps.webof-knowledge.com>), which compiling citations and categorizing academic effects globally (12). We researched by using the keyword "*Laparoscopic sleeve gastrectomy*", and by choosing the "*Topic*" segment on January 1, 2020. We categorized the upcoming data in order of publication time, which is the WOS default. Only articles with English and journals indexed as "Scientific Citation Index Expanded" in WOS were included in the study.

The website of the WOS analysis function was used to evaluate the data. The parameters used in the assessment of the publication rates were publication time, the countries that were the source of the publication, journal category, the institutions where the authors practice. Besides, the number of publications, citations received, and h-index information was determined. Publication metrics were evaluated in terms of "*Gross Domestic Product (GDP)*, *Gross Domestic Product per capita (GDPpp)* and *Human Development Index (HDI)*" of the countries.

GDP and GDPpp: Data was obtained from the website of *The World Bank, 2018 statistics* (<https://data.worldbank.org/indicator>).

HDI: Data was collected from the *United Nations "Human Development Indices and Indicators 2018 Statistical Update"*.

We applied the GNU operating system- PSPP software program for statistical estimation. We practiced descriptive statistical techniques for estimating the data. Spearman's rank-order correlation analysis was applied to measure the strength of a monotonic relationship between paired data. The estimate of correlation was recognized as $0.26 < r < 0.49$: low correlation; $0.50 < r < 0.69$: moderate correlation; $0.70 < r < 0.89$ high correlation; $0.90 < r < 1.00$: Very high correlation. Statistical significance was taken as $p < 0.05$ (13).

Results

Range of Publications: Between 2000-2020, 4681 publications have been published about LSG. When we classify the publications according to their types, we found 4396 (93.3%) articles, 205 (4.3%) proceedings paper, 79 (1.6%) early access article, and 1 (0.2%) book chapter.

Language: The distribution of the articles according to language, English: 4269 (91.1%), German: 47 (1%), Spanish: 41 (0.8%), French: 27 (0.6%), Korean: 3 (0.06%), Polish: 3 (0.06%), Hungarian: 2 (0.04%), Italian: 1 (0.02%), Slovenian: 1 (0.02%), and language of the two articles were unspecified. In our study, only articles in English were used.

Range of Citations: The H-index of 4269 articles written in English was 107. The publication and citation measurements, according to years, were shown in Figure 1. The list of five most productive countries in 5-years periods; 2000-2004: USA, Austria, Australia, Canada, Switzerland; 2004-2009: USA, France, Germany, Greece, Spain; 2009-2014: USA, Italy, France, Spain, Germany; 2014-2019: USA, France, Italy, Turkey, China.

It was seen that 20339 (including self-citations) citations were made from the articles focusing on LSG in the time interval that is the subject of the study. Publication and citation measurements, according to countries, were shown in Table 1. Publications on LSG appear to be scarce in Africa, South Asia, and Central Asia. An ongoing increase in the number of citations and publications has been observed over the years (Figure 1).

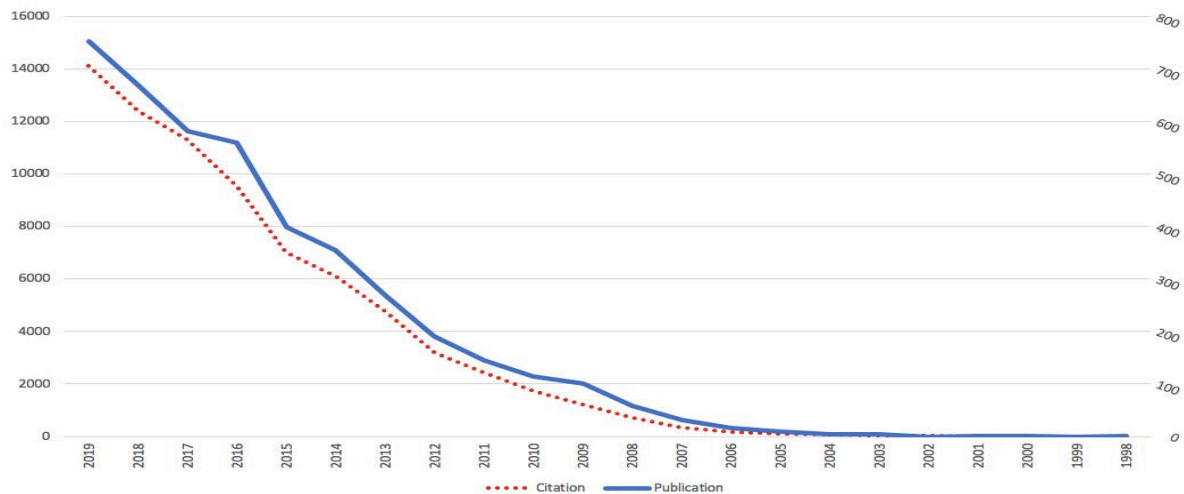


Figure 1. Publication and citation metrics according to years

The information obtained from the WOS shows that journals that publish on surgical or endocrine-metabolic diseases are the most focused journals on this topic (77.4 and 9.4, respectively). These journals are also leaders in citation (74% and 22.7%, respectively) (Table 2).

Top journals: The most publications on LSG are from 10 surgery-focused journals. *Obesity Surgery* is the most productive/ active journal in all evaluation categories. The metrics of productivity are shown in Table 3.

Most active authors: Nine of the ten most productive authors are surgeons. The most prolific authors are shown in Table 4.

Top organizations: Cleveland Clinic Foundation, Assistance Publique Hôpitaux Paris APHP, and Harvard University are the most active organizations about the LSG topic. Seven of the fifteen most productive organizations are health providers from the USA. Israel, England, and France are other productive countries on this topic (Table 5).

Analysis of correlation between publication statistics and gross domestic product/ Human development index: There was a weak positive correlation between publication numbers and Gross Domestic Product ($r=0.370$, $p<0.05$), also positive correlations with GDPpp and HDI ($r=0.359$, $p>0.05$; $r=0.603$, $p>0.05$; respectively). Additionally, a weak negative

correlation found between publication number and obesity incidence of the countries ($r=-0.151$, $p>0.005$) (Table 6).

Table 1. Publication and citation metrics according to countries

Country	Publication n (%)	Citation n (%), Mean $\pm$ SD (min-max)	h-index
USA [†]	1440 (33.77)	7159 (36.33) 21.72 $\pm$ 66.01 (0-1201)	150
France	334 (7.8)	1143 (5.8) 14.26 $\pm$ 24.15 (0-212)	35
Italy	280 (6.5)	1232 (6.25) 20.47 $\pm$ 52.02 (0-695)	38
Spain	238 (5.5)	956 (4.85) 19.57 $\pm$ 34.74 (0-313)	35
The U.K.	209 (4.9)	1485 (7.53) 16.04 $\pm$ 32.89 (0-289)	31
PRC [†]	202 (4.7)	1250 (6.34) 9.82 $\pm$ 24.62 (0-270)	23
Germany	185 (4.3)	1154 (5.85) 19.24 $\pm$ 31.32 (0-260)	32
Turkey	176 (4.1)	442 (2.24) 4.2 $\pm$ 17.3 (0-203)	10
Canada	156 (3.6)	908 (4.6) 16.9 $\pm$ 43.3 (0-407)	50
Israel	146 (3.4)	304 (1.54) 14.5 $\pm$ 25.7 (0-187)	23

[†] USA: United States of America, U.K.: United Kingdom, PRC: People's Republic of China

Table 2. Publication and citation metrics of top ten category according to Web of Science

Journal Category	Publication n (%)	Citation n (%), Mean $\pm$ SD (min-max)
Surgery	3303 (77.4)	15085 (74), 17.4 $\pm$ 42.68 (0-793)
Endocrinology Metabolism	403 (9.44)	4633 (22.7), 16.83 $\pm$ 39.91 (0-496)
Gastroenterology Hepatology	274 (6.41)	2708 (13.2), 13.09 $\pm$ 24.07 (0-172)
Nutrition Dietetics	217 (5.08)	2667 (13), 15.53 $\pm$ 40.17 (0-496)
Medicine General Internal	203 (4.75)	3684 (18), 23.07 $\pm$ 112.14 (0-1201)
Nursing	94 (2.2)	136 (0.6), 1.51 $\pm$ 3 (0-15)
Medicine Research Experimental	73 (1.7)	393 (1.9), 5.53 $\pm$ 12.79 (0-98)
Pediatrics	49 (1.1)	439 (2.1), 12.67 $\pm$ 22.81 (0-129)
Pharmacology Pharmacy	49 (1.1)	381 (1.8), 8.39 $\pm$ 12.15 (0-63)
Multidisciplinary Sciences	48 (1.1)	740 (3.6), 16.48 $\pm$ 63.51 (0-442)

Table 3. Publication and citation metrics of top ten journals

Journal	Publication n (%)	Citation n (%), Mean±SD (min-max)	h-index
Obesity Surgery	1372 (32.1)	9771 (47.9), 20±50.37 (0-793)	72
Surgery for Obesity and Related Diseases	663 (15.5)	5538 (27.1), 15.3±29.9 (0-471)	47
Surgical Endoscopy and Other Interventional Techniques	248 (5.8)	3851 (18.8), 23.6±41.9 (0-416)	38
Bariatric Surgical Practice and Patient Care	83 (1.9)	116 (0.56), 1.4±2.7 (0-15)	6
Journal of Laparoendoscopic Advanced Surgical Techniques	69 (1.6)	438 (2.14), 6.7±10 (0-44)	13
Annals of Surgery	50 (1.1)	2801 (13.7), 79.7±118.5 (0-539)	28
Journal of Gastrointestinal Surgery	45 (1)	730 (3.58), 17.4±28.1 (0-118)	15
Surgical Laparoscopy Endoscopy Percutaneous Techniques	44 (1)	425 (2.08), 10.8±15.9 (0-72)	11
American Surgeon	40 (0.9)	221 (1.08), 5.8±7.9 (0-28)	11
Videosurgery and Other Miniinvasive Techniques	40 (0.9)	238 (1.16), 7.9±11.5 (0-61)	10

Table 4. Publication and citation metrics of top ten authors

Author name	Publication n (%)	Citation n (%) mean±SD (min-max)	Nation	Institution	Expertise	h-index
Schauer PR	75 (1.7)	3250 (15.9) 59.37±179.8 (0-1201)	USA [†]	Cleveland Clinical Foundation	Surgery	25
Brethauer SA	64 (1.4)	2952 (14.4) 59.53±191.8 (0-1201)	USA [†]	Cleveland Clinical Foundation	Surgery	22
Lee WJ	57 (1.3)	1107 (5.4) 28.84±42.36 (0-263)	Taiwan	Min-Sheng General Hospital	Surgery	22
Aminian A	55 (1.2)	1765 (8.6) 39.95±135.79 (0-845)	USA [†]	Cleveland Clinical Foundation	Surgery	16
Gagner M	46 (1)	1832 (8.9) 62.59±95.35 (0-501)	Canada	University of Montreal	Surgery	25
Seeley RJ	43 (1)	1059 (5.2) 40.93±75.17 (0-442)	USA [†]	University of Cincinnati	Surgery	19
Szomstein S	41 (0.9)	1018 (4.9) 30.59±41.28 (0-168)	USA [†]	Cleveland Clinical Foundation	Surgery	18
Regimbeau JM	39 (0.9)	493 (2.4) 17±27.28 (0-154)	France	University of Picardie Jules Verne	Surgery	15
Rosenthal RJ	39 (0.9)	1426 (7) 47.05±85.6 (0-471)	USA [†]	Cleveland Clinical Foundation	Surgery	18
Le Roux CW	37 (0.8)	662 (3.2) 20.19±35 (0-184)	Ireland	University College of Dublin	Pathology	14

[†] USA: United States of America**Table 5.** Publication and citation metrics of most productive organizations

Organization	Publication, n (%)	Nation
CLEVELAND CLINIC FOUNDATION	172 (3.71%)	USA
ASSISTANCE PUBLIQUE HOPITAUX PARIS APHP	121 (2.61%)	FRANCE
HARVARD UNIVERSITY	108 (2.33%)	USA
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE	90 (1.94%)	FRANCE
UNIVERSITY OF CALIFORNIA SYSTEM	90 (1.94%)	USA
CENTRO DE INVESTIGACION BIOMEDICA EN RED	82 (1.77%)	SPAIN
SACKLER FACULTY OF MEDICINE	73 (1.57%)	ISRAEL
TEL AVIV UNIVERSITY	73 (1.57%)	ISRAEL
SAPIENZA UNIVERSITY ROME	72 (1.55%)	ITALY
IMPERIAL COLLEGE LONDON	69 (1.49%)	ENGLAND
UNIVERSITY OF MICHIGAN	68 (1.46%)	USA
UNIVERSITY OF LONDON	64 (1.38%)	ENGLAND
UNIVERSITY OF CINCINNATI	61 (1.31%)	USA
CORNELL UNIVERSITY	60 (1.29%)	USA

Table 6. Publication numbers and gross domestic product/ human development index relation

Nation	Article n (%)	GDP* (\$)	GDPpp** (\$)	Population (n)	HDI**	Incidence of obesity (%)	Average BMI (kg/m ²)
USA	1440 (33.77)	20544	62694	329064917	0.924	36.2	28.8
FRANCE	334 (7.8)	2778	41463	65129728	0.901	21.6	25.3
ITALY	280 (6.5)	2084	34483	60550075	0.880	19.9	26
SPAIN	238 (5.5)	1419	30370	46736776	0.891	23.8	26.7
The U.K.	209 (4.9)	2855	42943	67530172	0.922	27.8	27.3
PRC	202 (4.7)	13608	9770	1433783686	0.752	6.2	23.9
GERMANY	185 (4.3)	3948	47603	83517045	0.936	22.3	26.3
TURKEY	176 (4.1)	771	9370	82319724	0.791	32.1	27.8
CANADA	156 (3.6)	1713	46232	37411047	0.926	29.4	27.2
ISRAEL	146 (3.4)	370	41715	8883800	0.903	26.1	26.3

*Gross domestic product (Billion \$), **Gross domestic product per capita, ***Human development index

† USA: United States of America, U.K.: United Kingdom, PRC: People's Republic of China

GDP, GDPpp, Population: Data was obtained from the website of The World Bank, 2018 statistics (<https://data.worldbank.org/indicator>)

HDI: Data was collected from the United Nations "Human Development Indices and Indicators 2018 Statistical Update".

Discussion

According to the data we obtained in our study, publication productivity related to LSG has been increasing in the last two decades. Our outcomes show that researchers have an increasing interest in morbid obesity and LSG procedure. The determination of this progress shows the importance of bibliographic analysis, which will facilitate researchers in their further studies.

The number of publications on LSG has increased like snowballs after initiation of insurance coverage at the end of the first decade of the twentieth-first century (14), especially in the USA. France, Italy, Spain, and the United Kingdom are other leading countries that follow the US in the publication productivity on LSG. This finding is anticipated if the massive funds and the high number of research centers designated for researching the morbid obesity in the USA are recognized. Simultaneously, the enrichment of the undeveloped/developing nations such as the People's Republic of China and Turkey was remarkable. In 2019, the Chinese scientist declared an "obesity prevention program" to identify primary steps to be taken to control future obesity problem in China, which eventually would lead to an obesity-related chronic disease epidemic (15). Like China, the Turkish Ministry of Health initiated a new structuring process by "Fighting Obesity and Control Program" to fight the upcoming epidemic in 2010 (16). Increasing awareness of developing countries like the People's Republic of China and Turkey about the forthcoming obesity epidemic has attracted scientists' attention. Despite this improving productivity, publications focusing on LSG are scarce in Africa, South Asia, and Middle Asia. Our outcomes are similar to previous studies (10,17), reporting that the number of publications was lower in these regions (Figure 1). The low socio-economic level is the reason why the African, South, and Middle Asian countries are lagging in producing scientific publications on obesity.

We think that the increase in scientific articles focusing on LSG also directly correlates with the long and mid-term national health programs beginning to define obesity as a severe

life-threatening condition. Like Turkey and the People's Republic of China, in many European countries' health policy-makers have developed programs to raise awareness and fight obesity (18-21). However, it was not easy for society to adapt to these programs. In the "Fighting Fat, Fighting Fit" campaign performed in Britain, 30% of participants recognized healthy lifestyle messages, but less than 1% advised medical professionals to adopt the suggested behavioral modifications (20). Similarly, the campaign executed in the Netherlands did not have adequate power to establish behavioral changes in people (19). Despite all the unfavorable conditions, we think that the number of campaigns against obesity and scientific publications related to obesity should increase gradually. The literature suggests that raising general knowledge and awareness of potential health risks are the initial steps in stopping the spread of diseases as obesity (16,22). An analysis among the journals showed that *Obesity Surgery*, published by the "International Federation for the Surgery of Obesity and metabolic disorders" since 1991, was the most productive journal in LSG. In many bibliometric studies, *Obesity Surgery* is ranked at the top in the number of both publications and citations (10,23). This journal aims to publish original researches, clinical reports, guidelines, historical notes, invited commentaries, letters to the editor, medicolegal issues, meeting abstracts, modern surgery/technical innovations, new concepts, reviews, scholarly presentations, and opinions about obesity, obesity-related comorbidities, and treatment options. The author, Schauer PR, has the highest publication productivity about the topic LSG. His study "Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes" was published in 2012, and had the highest citation numbers per year (Total citation: 1167, Citation per year: 145.8) (24). Schauer PR et al. evaluated 150 patients and aimed to compare the success of intensive medical therapy and surgical treatment to achieve glycemic control in obese patients with type 2 diabetes. The topic of morbid obesity is often considered as the subject of endocrinology, and surgical treatment methods were ignored in much of the

twentieth century. First reports about surgical therapy of the morbid obesity are published in the second half of the twentieth century, but they remained uncertain until the 1990s. Kremen performed the first metabolic surgery in 1954 (25); from this date to 1994, many modifications of bariatric procedures were reported, but none of them gained widespread acceptance (26-29). Alan Wittgrove performed the first laparoscopic gastric bypass surgery in 1994 (30). Scopinaro is the first who mentioned about sleeve gastrectomy procedure as a part of the biliopancreatic diversion procedure (31). In the first decade of the twentieth-first century, LSG was accepted as a surgical technique of morbid obesity treatment with low perioperative morbidity, maintained digestive continuity, and was comfortable converting to other bariatric surgeries (32). GDP is one of the most common indicators used to determine the economic level of a country. It depicts the cumulative result of income and expense in dollars over a period and includes different determinants, such as consumption and investment. Many authors have explored the relationship between obesity problem or its surgical treatment and GDP. Cazzo et al. investigated the correlation between GDP and the number of bariatric procedures and revealed a direct correlation (33). Norte et al. (34) and Oddo et al. (35), who obtained similar results, observed that economic changes occurring negatively could change diet quality and increase the risk of obesity. HDI emphasizes that people and their capability should be used as a criterion that evaluates not only the country's financial growth but also the development of that country. It is the average measurement of essential parameters such as long healthy life, intellectual level, and standard of living in people's development process. Gupta et al. found a significant correlation between HDI and obesity (36). Yach et al. (37) also showed that developing countries have been undergoing rapid "obesogenic". But none of the researchers evaluated if there is a relationship between socio-economic parameters and publishing productivity. In our study, we found a positive correlation between the countries' publications on LSG and GDP, GDPpp, and HDI values. The study of Gehanno JF et al. (38) is the most similar to our research in the literature. Gehanno et al. evaluated the relationship between socio-economic factors and publications focusing on childhood obesity. Identical to the presented study, they found a significant association between publication productivity on childhood obesity and HDI. Increasing the social and economic levels would cause an increase in the supply separated by the governments for scientific programs and researches.

This is the first study focusing on the bibliographic analysis of English publications published on LSG in SCI-E journals. The fact that it does not contain any database other than WOS, which is the most reliable source for accessing and classifying scientific publications (39), is the most critical factor that limits our study. Also, evaluating only English articles is another challenge that limits the study. However, the authors were unable to interpret and assess articles other than English. Therefore, multicenter research is required, including articles in other languages.

Conclusion

Many people have been suffering and will suffer from morbid obesity and comorbid diseases caused by morbid obesity, which can be effectively treated only by surgical procedures. For this reason, it is imperative to cooperate globally and support them on strategies to be applied in obesity prevention and treatment and new scientific approaches in this regard. The most crucial weapon in the battle against the obesity epidemic is scientific publications and the progress that these publications will cause.

The present study demonstrates the avalanching publication productivity concerning LSG, a popular treatment method of morbid obesity, over the last twenty years. Because of this progress, a bibliographic analysis will contribute to facilitating researchers' further research. The necessary support should be increased for the developing or undeveloped countries to publish scientific studies on obesity, obesity-related comorbidities, and treatment methods.

Ethical Approval: All procedures performed in studies were following the Helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions:

Concept: U.E.

Literature Review: U.E.

Design : U.E.

Data acquisition: U.E.

Analysis and interpretation: U.E.

Writing manuscript: U.E.

Critical revision of manuscript: U.E.

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A Case of Hysterical Paralysis/Conversion Disorder with Triplegia After General Anesthesia

Genel Anestezi Sonrası Tripleji ile Seyreden Histerik Paralizi/Konversiyon Bozukluğu Olgusu

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Abstract

Conversion disorder manifests as physical symptoms arising from an underlying psychological condition. Classified as a somatoform disorder, it is relatively rare. Common triggers include significant stress, emotional trauma, childhood physical or sexual abuse and neglect, a personal or family history of mental health disorders, or a history of neurological disease with similar symptoms. The disorder is diagnosed when unexplained physical/neurological symptoms -such as paradoxical paralysis, seizures, pain, or sensory deficits involve one or more muscle and sensory systems. These symptoms are interpreted as unconscious adaptations to difficult situations. Various psychological stressors, such as anesthesia and surgery, can cause sudden clinical manifestations of conversion disorder even in patients with no previous psychological diagnoses. In the postoperative period, conversion disorder should be considered in the differential diagnosis of unexplained neurologic symptoms while meticulously excluding organic causes. However, the surgery itself and the experience of anesthesia can also be sources of stress and trauma, contributing to the development of postoperative conversion disorder symptoms. When conversion disorder is suspected, psychiatric consultation should be sought, and treatment should be initiated as soon as possible. Early intervention and a multidisciplinary approach are essential for achieving a positive outcome in such cases.

Keywords: Conversion Disorder, General Anesthesia, Paralysis

Öz

Konversiyon bozukluğu, altta yatan psikolojik bir bozukluğun fiziksel semptomlarla ifade edilmesidir. Somatoform bir hastalık olarak tanımlanır ve nadir görülür. Tetikleyici faktörler arasında yakın zamanda yaşanan önemli stres veya duygusal travma, çocuklukta fiziksel veya cinsel istismar ve ihmal, kişisel veya ailesel ruh sağlığı bozukluğu öyküsü veya benzer semptomlara neden olan nörolojik hastalık öyküsü yer alır. Konversiyon bozukluğu, bir veya daha fazla kas ve duyu sistemini içeren paradoksal felç, nöbetler, ağrı ve/veya duysal noksanlıklar gibi açıklanamayan fiziksel ve/veya nörolojik semptomlar olduğunda teşhis edilir. Zor durumlara adaptasyon durumlarında biliş dışı kaynaklanan semptomlar olarak yorumlanmaktadır. Anestezi ve ameliyat gibi çeşitli tetikleyiciler ve psikolojik stresler, daha önce psikolojik bozukluğu olmayan hastalarda konversiyon bozukluğun ani klinik belirtilerine neden olabilir. Ameliyat sonrası dönemde açıklanamayan nörolojik semptomları olan hastalarda konversiyon bozukluğu ayırıcı tanıda düşünülmeli ve organik nedenler titizlikle dışlanmalıdır. Bununla birlikte, ameliyatın kendisi ve anestezi deneyimi de bir stres ve travma kaynağı olabilir ve ameliyat sonrası konversiyon bozukluğu semptomlarının gelişiminde rol oynayabilir. Semptomlar konversiyon bozukluğuna bağlı olduğu düşünüldüğünde, psikiyatristlere danışılmalı ve tedaviler mümkün olan en kısa sürede başlatılmalıdır. Bu tür vakalarda olumlu sonuç için erken müdahale ve multidisipliner yaklaşım şarttır.

Anahtar Kelimeler: Humerus, Processus supracondylaris, Foramen supratrochlearis, Morfometrik, Varyasyon

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Introduction

Hysterical paralysis is a form of conversion disorder. When a patient presents with paralysis, the diagnosis must be confirmed through imaging and electrophysiological to rule out organic causes. Postoperative conversion disorder can affect motor and/or sensory functions and, in some cases, cause temporary loss of consciousness. It is diagnosed by excluding neurological, metabolic, or iatrogenic causes occurring after surgery.

Conversion disorder is reported to have a higher prevalence rate of 5-14% among general hospital patients, compared to 1-3% among psychiatric outpatients, and 5-25% among psychiatric inpatients (1). However, these rates are not specific to the perioperative period, and a direct association with anesthesia or surgery has not been established. There are limited reports addressing cases of conversion disorder associated with anesthesia techniques. These include cases of conversion disorder in pediatric patients after general anesthesia and in adults after spinal anesthesia or epidural anesthesia (2, 3-8).

This case highlights the importance of considering conversion disorder in the differential diagnosis of postoperative neurological symptoms to ensure early diagnosis and appropriate management. To our knowledge, this is the first reported case of conversion disorder manifesting as triplegia after general anesthesia.

Case

A 28-year-old, 48 kg female patient underwent anesthesia premedication for lithotripsy to treat a left renal mid-pole localized stone. She had no significant systemic and neurologic disease preoperatively, and no psychiatric evaluation was performed before surgery.

Following the procedure under general anesthesia, the patient complained that she could not feel or move both legs and her left arm upon waking. Before the surgical procedure, midazolam was administered intravenously at a dose of 0.02 mg/kg as premedication. Anesthesia was induced with a slow intravenous infusion of propofol at a dose of 2 mg/kg after adequate monitoring. For maintenance, sevoflurane was delivered continuously at a concentration of 1.0-2.0% via inhalation following intubation.

During the procedure, the patient was positioned in the standard lithotomy position. A 9.5 Fr semi-rigid renoscope was used for initial access. A DJ stent, which had been placed one month earlier for prestrutting purposes, was visualized in the bladder and removed using foreign body forceps. A sensor guidewire was advanced under fluoroscopic guidance through the left ureteral orifice into the left kidney, followed by the insertion of the 9.5 Fr renoscope into the distal ureter. A safety guidewire was also placed under fluoroscopic control. No access sheath was utilized.

A 1.5 cm stone in the mid-pole of the left kidney was fragmented using laser lithotripsy. No additional stones were detected. Subsequently, a 4.7 Fr DJ stent (28 cm) was pla-

ced using the Seldinger technique under fluoroscopic guidance, and a 16 Fr Foley catheter was inserted. The operation lasted 45 minutes. During the procedure, an isotonic saline solution (0.9% NaCl) was used as the irrigation fluid. A 30-watt holmium: YAG (Ho:YAG) laser device (MegaPulse 30+) was employed, delivering energy via a 272-micron laser fiber. For flexible ureterorenoscopy, a single-use digital flexible ureterorenoscope was preferred. As prophylactic antibiotic therapy, 1 g of ceftriaxone was administered intravenously.

Upon emergence from anesthesia, the patient was fully awake but unable to move her left arm and both legs and was unresponsive to painful stimuli. Reflexes were normal in all four extremities, with no hyperreflexia or hypotonia. Routine blood biochemistry, hemogram, electrolytes, renal function, and thyroid function tests were all within normal limits. Brain MRI, diffusion MRI, and spinal cord MRI were unremarkable. Nerve conduction studies demonstrated normal motor and sensory nerve conduction velocities, combined muscle action potentials, and bilateral tibial and left ulnar/median F responses. Needle EMG of both legs, thighs (L2-S1), and left upper extremity (C5-T1) was also unremarkable. Bilateral tibial and median SEP responses were within normal limits. Given the normal white blood cell count, absence of fever, and isolated neurological findings, cerebrospinal fluid testing was not performed.

Neurophysiological and radiological examinations ruled out stroke, hemorrhage, mass lesions, or other structural causes of paresis. On the second day of hospitalization, the patient started to move her right leg and was able to walk while dragging her left leg. However, her left arm remained immobile. On the third day of admission, a psychiatrist was consulted to investigate potential psychosomatic causes. The psychiatrist diagnosed the patient with postoperative conversion disorder. Instead of medical treatment, rehabilitation with physical therapy, supportive care, and psychotherapy were implemented. The patient was discharged after one week without any residual neurological deficits.

Discussion

Conversion disorder is classified as a type of somatoform disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (9). It presents with symptoms such as paradoxical paralysis, seizures, sensory deficits, and pain that cannot be explained by typical neuroanatomical and physiological mechanisms (9, 10).

A review of the literature shows that the relationship between anesthesia type and the development of conversion disorder remains unclear, with ongoing uncertainty about whether anesthesia plays a protective or causal role. Some researchers suggest that surgical stress or trauma may be a triggering factor for functional neurologic symptoms. It is also noteworthy that this disorder develops under propofol sedation. Stone et al. even suggested propofol sedation as a therapeutic option for severe symptoms of

conversion disorder (11). In addition, a previous case of postoperative conversion disorder after moderate-to-deep sedation with propofol has been documented (12). This case is important in demonstrating that conversion disorder can occur independently of general or central neuraxial anesthesia. Although the impact of anesthesia on conversion disorder remains unclear, further research will help us better understand its role and develop more effective prevention and treatment strategies.

Regardless of the type of anesthesia administered, conversion disorder should be considered in the postoperative period. The patient should be approached with a multidisciplinary strategy, taking into account their psychosocial status in addition to a detailed neurological and metabolic evaluation. Diagnosis requires a detailed psychiatric interview, assessment of psychosocial stressors, and differentiation from other psychiatric disorders such as somatic symptom disorder, anxiety disorders, or depression.

A detailed preoperative evaluation of the patient's mood, anxiety levels, trauma history, and stress factors may help identify patients at risk. In our case, no preoperative psychiatric evaluation was performed.

When symptoms do not follow typical neuroanatomical and physical patterns, conversion disorder should be considered after ruling out organic causes. Early psychiatric consultation and appropriate treatment -including psychotherapy and supportive care- are crucial in preventing prolonged hospital stays and improving patient outcomes.

Conclusion

Our case shows that conversion disorder should be considered in patients exhibiting unexplained physical and/or neurological symptoms after all other potential causes have been ruled out, particularly in cases requiring urgent intervention. When symptoms are suspected to stem from conversion disorder, it is essential to consult psychiatrists and initiate treatments promptly to facilitate patient rehabilitation.

Ethical Approval: An 'Informed Consent Form' was obtained from the patient. The identity of the patient was kept confidential.

Author Contributions:

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Sol Vokal Kord Paralizisinin Nadir Bir Nedeni: Ortner Sendromu

A Rare Cause Of Left Vocal Cord Paralysis: Ortner Syndrome

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Öz

Vokal kord paralizileri intra ve ekstralarengal patolojilere bağlı olarak ortaya çıkabilen bir klinik bulgudur. Ekstralarengal patolojilerden Ortner sendromu olarak da bilinen kardiyovokal sendrom, kardiyovasküler patolojilere bağlı olarak gelişen sol vokal kord paralizisidir. 3 aydır ses kısıklığı yakınması bulunan 48 yaşında kadın hasta, fizik muayenesinde sol vokal kord paralizisi saptanması üzerine kontrastlı boyun manyetik rezonans incelemesi ve kontrastsız toraks bilgisayarlı tomografi incelemesi yapılmış herhangi bir patoloji saptanmamıştır. Hastanın ek olarak obezitesinin olması ve nefes darlığı yaşıyor olması nedeni ile kardiyoloji bölümüne konsulte edilmiş yapılan transtoraksik ekokardiyografide pulmoner arter hipertansiyonu tanısı almıştır. Ek patoloji saptanmayan hasta Ortner sendromu tanısı almıştır. Pulmoner arter hipertansiyonu olan hastada kardiyak ve pulmoner hastalıklar araştırıldı. Arteriyel hipertansiyona bağlı sekonder pulmoner arter hipertansiyonu olarak düşünüldü ve medikal tedavi başlandı. Pulmoner arter hipertansiyonu ilk ölçümlerde 50 mmHg iken tedavi sonrası 3. ay kontrolünde 28mmHg ölçüldü. Sol vokal kord paralizisi ise halen devam etmekte ancak hastanın nefes darlığı ve ses kısıklığı şikayeti azaldı. Ses kısıklığı ile başvuran hastaların değerlendirilmesinde etiolojide ekstralarengal patolojiler dikkate alınmalı, pulmoner arter hipertansiyonu gibi kardiyak hastalıklar akıldan tutulmalıdır.

Anahtar Kelimeler: Ortner sendromu, Pulmoner arter hipertansiyonu, Ses kısıklığı, Vokal kord paralizisi

Abstract

Vocal cord paralysis is a clinical finding that can occur due to intra- and extralaryngeal pathologies. Cardio-vocal syndrome, also known as Ortner syndrome among extralaryngeal pathologies, is left vocal cord paralysis that develops due to cardiovascular pathologies. A 48-year-old female patient who had a complaint of hoarseness for 3 months underwent a contrast-enhanced neck magnetic resonance imaging and non-contrast thorax computerized tomography examination upon detection of left vocal cord paralysis during physical examination, and no pathology was detected. In addition to the patient's obesity and shortness of breath, the cardiology department was consulted and a transthoracic echocardiography was performed, and pulmonary artery hypertension was diagnosed. No additional pathology was detected in the patient and Ortner syndrome was diagnosed. Cardiac and pulmonary diseases were investigated in the patient with pulmonary artery hypertension. It was considered as secondary pulmonary arterial hypertension due to arterial hypertension and medical treatment was started. Pulmonary arterial hypertension was measured as 50 mmHg in the first measurements and 28 mmHg in the 3rd month control after treatment. Left vocal cord paralysis still continues, but the patient's complaints of shortness of breath and hoarseness have decreased. In the evaluation of patients presenting with hoarseness, extralaryngeal pathologies should be taken into consideration in the etiology and cardiac diseases such as pulmonary arterial hypertension should be kept in mind.

Keywords: Hoarseness, Ortner syndrome, Pulmonary arterial hypertension, , Vocal cord paralysis

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Giriş

Vokal kord paralizisinin hem laringeal hem de larinks dışı birçok sebebi mevcuttur. 2005'lu yıllara kadar etiolojide en sık neden malignite olduğu düşünülmekteydi ancak son yıllarda vokal kord paralizisinin en sık nedeni iatrojenik olduğu kabul edilmektedir (1,2).

Etiolojide nadir olarak görülen Ortner sendromu ise kardiyovasküler patolojilere bağlı olarak gelişen sol vokal kord paralizisidir. İlk olarak 1897'de Ortner tarafından mitral stenozla bağlı sol vokal kord paralizisi bildirilmiştir. Mitral stenoz dışında da birçok kardiyovasküler hastalıkla ilişkili olduğu bildirilmiştir (3,4).

Olgu

3 aydır ses kısıklığı ve nefes darlığı yakınması bulunan 48 yaşında kadın hasta, herhangi bir sebep olmaksızın aniden ses kısıklığı ve nefes darlığı şikayeti ile kliniğimize başvurdu. Şikayetin başlangıcında üst veya alt solunum yolu enfeksiyonu düşündüren bulgu yoktu. Hastanın bilinen hastalık öyküsü ve kullandığı ilaç bulunmamaktaydı. Alınan anamnezde hastanın vücut kitle indeksi 33,9 hesaplanmış olup obezite saptanmıştır.

Fizik muayenesinde, yapılan fleksibl fiberoptik nazo-faren-golarengoskopide larinkste başka patoloji olmaksızın sol vokal kordun median pozisyonda paralitik olarak saptanması üzerine kontrastlı boyun ve beyin manyetik rezonans (MR) incelemesi ve kontrastlı toraks bilgisayarlı tomografi (BT) incelemesi yapılmış ve raporları normal olarak yorumlandı (Şekil 1).

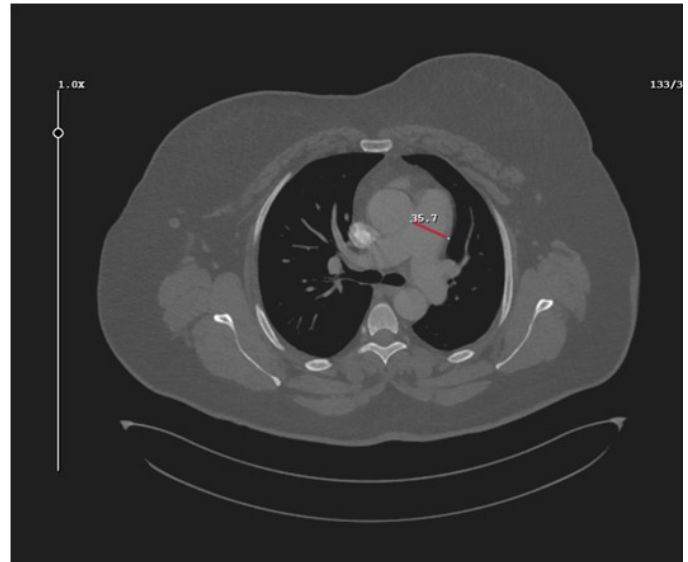


Şekil 1. Hastanın flexibl laringoskopi ile muayenesinde sol vokal kordun median pozisyonda hareketsiz duruşu.

Hastanın ek olarak obezitesinin olması ve nefes darlığı yaşıyor olması nedeni ile kardiyoloji bölümüne konsulte edildi. Yapılan transtorasik ekokardiyografide pulmoner arter basıncı 50 mmHg ölçüldü, orta derece mitral yetmezlik saptandı ve tansiyon ölçümleri 190/110mmhg olarak saptandı. Hasta hipertansiyona sekonder pulmoner arter hipertansiyonu ve buna bağlı sol vokal kord paralizisi yani Ortner sendromu tanısı aldı. Daha sonra hastanın toraks BT incelendiğinde normalde 29 mm den küçük olması gereken pulmoner arter çapı 35.7 mm ölçüldü yani hastanın pulmoner arter dilatasyonu da vardı (Şekil 2).

Hastanın kardiyoloji tarafından uygulanan 3 aylık medikal tedavi sonrası kontrolünde pulmoner arter basıncı 28 mmHg ölçüldü. Tansiyon takipleri normal sınırlardaydı. Hafif düzey mitral yetmezlik hala mevcuttu. Ses kısıklığı şikayeti ve nefes darlığı şikayeti azaldı ancak vokal kord paralizisi devam etmekteydi.

Hastadan; radyoloji görüntülerinin, muayene fotoğrafının ve bahsi geçen bütün klinik bilgilerinin yayın amaçlı kullanılabacağına dair onam alınmıştır.



Şekil 2. Hastanın toraks BT incelemesinde pulmoner trunksun dallara ayrıldığı yerdeki çap ölçümü.

Tartışma

Vokal kordların hareketi laringeal kaslar tarafından sağlanır. Krikotiroid dışındaki vokal kord hareketini sağlayan kaslar rekürren laringeal sinir tarafından innerve edilir. Sağ rekürren laringeal sinir ile sol rekürren laringeal sinir seyri farklıdır. Sağ rekürren laringeal sinir sağ subklavyen arteri çaprazlayıp trakeoözafageal oluktan larinkse girer. Sol rekürren laringeal sinir ise sol aortikopulmoner aralıktan ligamentum arteriozumdan geçerek trakeoözafageal oluktan ilerleyip larinke ulaşır. Sol rekürren laringeal sinirin seyri daha uzun olduğundan hasar görme ihtimali sağ rekürren laringeal sinire göre daha fazladır (1,2).

Vokal kord paralizi sinir iletimindeki kesinti sonucu aynı taraf laringeal kaslarda hareket görülmemesi durumudur. Tek veya çift taraflı olabilir (2). Etiyolojide 2005 li yıllara kadar en sık neden maligniteler olduğu düşünülmekteydi ancak son yıllarda vokal kord paralizisinin en sık nedeni iatrojenik olduğu kabul edilmektedir (2). Bunun yanı sıra sarkoidoz ve sistemik lupus eritematozus gibi inflamatuvar hastalıklar, varisella ve Lyme gibi enfeksiyöz hastalıklar; inme, myastenia gravis, multiple sklerozis gibi nörolojik rahatsızlıklar etiolojide suçlanmaktadır. Herhangi bir sebep bulunamayan vokal kord paralizileri ise idiopatik olarak kabul edilmektedir (1-3).

Etiyolojide çok nadir olarak sol laringeal sinirin anatomik pozisyonundan dolayı kardiyotorasik patolojiler de sol vokal kordun hareketini etkilemektedir. Bunlardan Ortner sendromu olarak da bilinen kardiyovokal sendrom, kardiyovasküler patolojilere bağlı olarak gelişen sol vokal kord paralizisidir (4). Ortner sendromunun semptomları ses kısıklığı, dispne, öksürük ve disfaji gibi nonspesifiktir. Patofizyolojisine gelince rekürren laringeal sinirin anatomisi ile ilişkilidir. Sinirin aortikopulmoner aralıktan geçerken sıkışması sonucu meydana gelir (3-5). Verma ve ark. yaptığı sistematik bir derlemede 1955-2021 yılları arasında Ortner sendromu olarak yayınlanan makalelerden 117 hastayı çalışmalarına dahil etmiştir. Derlemede Ortner sendromunun her yaş grubundan olabileceği saptanmıştır. Etiyolojide ise birinci sırada aort anevrizması ve pulmoner arter hipertansiyonu yer almaktadır (5).

Pulmoner arter hipertansiyonu tanısı pulmoner arter basıncı ölçümü ile olmaktadır. Pulmoner arter basıncı normalde 10-18 mmHg arasındadır. Pulmoner arter basıncının istirahatte 25 mmHg, eforla 30 mmHg üzeri basınç ölçümü pulmoner arter hipertansiyonu tanısı aldırır (6,7). Bizim olgumuzda pulmoner arter basıncı 50 mmHg olarak ölçülmüştür. Bunun dışında akciğer grafisinde veya BT de pulmoner arter trunkusunda genişleme izlendiğinde pulmoner arter hipertansiyonundan şüphe edilmelidir. Pulmoner arter trunkusunun dallara ayrıldığı kesitte trunkusa 90 derece dik olarak çekilen doğru parçasının uzunluğu 29 mm üzerinde ise pulmoner arter dilatasyonu düşünülmeli ve pulmoner arter hipertansiyonu akla gelmelidir (6,7). Bizim olgumuzda toraks BT'sinde pulmoner trunkus ölçümü 35.7 mm dir ve pulmoner arter dilatasyonu mevcuttur.

Pulmoner arter hipertansiyonunun birçok sebebi mevcuttur. Bizim olgumuzda primer hipertansiyona bağlı olduğu düşünülmüştür. Hastaya kardiyoloji kliniği tarafından medikal tedavi başlanmış ve 3 aylık takip neticesinde dramatik iyileşme gözlenmiştir. Hastanın ses kısıklığı ve nefes darlığı şikayeti azalmış ancak vokal kord paralizi devam etmektedir. Hastanın hem kardiyoloji hem de kulak burun boğaz kliniği tarafından takibi devam etmektedir.

Sonuç olarak, ses kısıklığı ile başvuran hastaların değerlendirilmesinde etiolojide larinks dışı patolojiler dikkate alınmalı, pulmoner arter hipertansiyonu gibi kardiyovasküler hastalıklar akılda tutulmalıdır.

Etik onam: Hastadan; radyoloji görüntülerinin, muayene fotoğrafının ve bahsi geçen bütün klinik bilgilerinin yayın amaçlı kullanılacağına dair onam alınmıştır.

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A Surgical Surprise During Laparoscopic Transabdominal Preperitoneal Repair; Undescended Testis

Laparoskopik Transabdominal Preperitoneal Onarım Sırasında Cerrahi Bir Sürpriz; İnmemiş Testis

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Abstract

Undescended testis (cryptorchidism) is a common congenital anomaly in childhood but rarely seen in adults. Inguinal hernia can occasionally coexist with undescended testes, although such a presentation is uncommon in adult patients. We report a rare case of a 28-year-old male with a right inguinal hernia who was found to have an atrophic testis within the hernia sac during laparoscopic transabdominal preperitoneal (TAPP) repair. The patient had a history of bilateral orchiopexy in infancy. Preoperative ultrasonography did not detect the undescended testis. Intraoperatively, orchiectomy was performed following urology consultation, and the TAPP procedure was completed successfully. The postoperative course was uneventful, and pathology revealed an atrophic testis without malignancy. This case highlights the importance of preoperative suspicion and the benefits of the laparoscopic approach in managing such coexisting pathologies in adults.

Keywords: Cryptorchidism, Inguinal Hernia, Laparoscopy, Orchiectomy, TAPP

Öz

Kriptorşidizm, skrotumda testislerin olmaması olarak tanımlanır. Bu durum erkek çocuklarda yaygın olsa da yetişkin hastalarda nadirdir. Kriptorşidizm ve kasık fıtığı arasındaki ilişki çocukluk çağında sıklıkla görülür ancak yetişkinlerde veya yaşlılarda nadirdir (1,2). Bu çalışmada, hem kriptorşidizm hem de kasık fıtığı teşhisi konulan yetişkin bir erkek hasta laparoskopik cerrahi teknikleri kullanılarak başarıyla tedavi edildi (3). Hasta laparoskopik transabdominal preperitoneal onarım ve orşiektomi prosedürlerine tabi tutuldu. Ameliyat sonrası herhangi bir komplikasyon gelişmedi ve hasta ameliyattan sonraki ikinci gün taburcu edildi. Patolojik incelemede malignitesi olmayan atrofik bir testis ortaya çıktı. Takip sırasında herni tekrarı görülmedi. Yetişkin hastalarda kasık fıtığı ve kriptorşidizmin kombine patolojisinde laparoskopik yaklaşım uygulanabilir bir seçenek sunar ve tanı ve tedavide çeşitli avantajlar sağlar.

Amacımız inguinal herniye eşlik eden kriptorşidizm olgularında minimal invaziv yaklaşımın avantajını ve postoperatif sonuçları vurgulamaktır.

Anahtar Kelimeler: Kriptorşidizm, Kasık Fıtığı, Laparoskopi, Orşiektomi, TAPP

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Introduction

Cryptorchidism is defined as the absence of testes in the scrotum. Although this condition is common in male children, it is rare in adult patients. The association between cryptorchidism and inguinal hernia is frequently observed in childhood but is uncommon in adults or the elderly (1,2). In this study, an adult male diagnosed with both cryptorchidism and inguinal hernia was successfully managed using laparoscopic surgical techniques (3). The patient underwent laparoscopic transabdominal preperitoneal repair and orchiectomy procedures. No postoperative complications developed, and the patient was discharged on the second day post-operation. Pathological examination revealed an atrophic testis with no malignancy. No recurrence of hernia was observed during follow-up. The laparoscopic approach in combined pathology of inguinal hernia and cryptorchidism in adult patients offers a feasible option and provides several advantages in diagnosis and treatment.

Our aim is to emphasize the advantage of a minimally invasive approach and postoperative outcomes in cases of cryptorchidism associated with inguinal hernia.

Case

A 28-year-old male patient with no known disease was admitted to our general surgery clinic with a swelling in his right groin that had persisted for six months. Physical examination revealed incisions in both inguinal regions from previous operations. The patient reported having surgery for an undescended testis as an infant, and no testis could be palpated in the right scrotum.

A reducible right inguinal hernia was present, and the left testis was observed within the scrotum. With ultrasound findings supporting the physical examination, surgery using the laparoscopic transabdominal preperitoneal (TAPP) technique was decided. Preoperative ultrasonography identified a right inguinal hernia but did not report an undescended testis. The patient had a history of bilateral orchiopexy in infancy.

During surgical exploration, no defect was observed in the left inguinal canal. An indirect hernia, which included the right inguinal canal and the testis herniating lateral to the inferior epigastric vessels, was identified. After reducing the hernia sac, an atrophic testis was found along with the spermatic cord and testicular vessels (Figure 1).

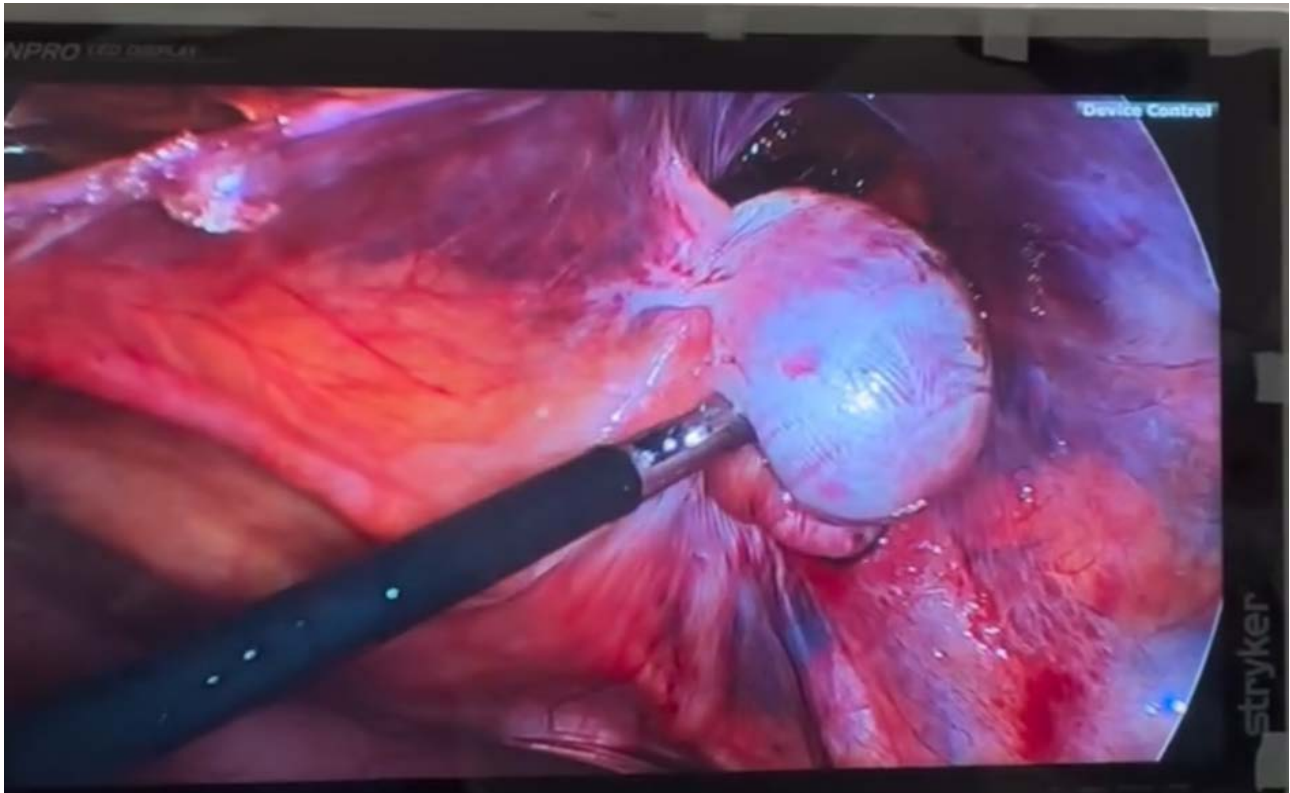


Figure 1. Laparoscopic view of the undescended testis

The urologist was invited to the perioperative case. Given the atrophic structure of the testis, primary excision was recommended and performed. The informed consent process included the possibility of orchiectomy in case of intraoperative detection of an atrophic or ectopic testis.

The TAPP procedure was applied. The surgery lasted 80 minutes, and the patient was discharged on the second postoperative day without complications. Histopathological examination reported an atrophic testis. No signs of recurrence were detected in imaging during the 6 and 12-month follow-ups.

Discussion

Cryptorchidism is the most common congenital anomaly of male genitalia, affecting approximately 1% of one-year-old boys (1). It is characterized by one or both testes remaining in the abdomen or inguinal canal since birth (5). Although the condition typically presents in childhood, undiagnosed cases may persist into adulthood (2). Inguinal hernia is seen in about 7% of children with cryptorchidism (1). While this association is frequent in pediatric patients, it can also be observed in adults (3). Untreated cryptorchidism has the potential to impair spermatogenesis, primarily because germ cells in the undescended testis begin to deteriorate after the first year of life. Furthermore, after puberty, the functionality of undescended testes diminishes, and fertility rates generally decline even after orchiopexy procedures (3).

Laparoscopic repair of inguinal hernias is considered the standard of care, especially for bilateral inguinal hernias (6, 7). Compared to open surgery, laparoscopic approaches offer numerous advantages, including less postoperative pain, a lower risk of surgical site infection, and higher rates of early discharge. Additionally, laparoscopic methods increase the possibility of detecting and repairing ipsilateral or contralateral hernias (8).

In this case, the operation duration was recorded as 80 minutes. The postoperative period progressed smoothly, and the patient was discharged on the second day. No recurrence of hernia was observed during the one-year follow-up. These results support the efficacy and safety of laparoscopic repair and emphasize the importance of this approach in managing cryptorchidism and related conditions. Several case reports in the literature have highlighted the management of adult patients with coexistent inguinal hernia and cryptorchidism. Fujishima et al. described the totally extraperitoneal (TEP) approach in combination with orchiectomy, emphasizing the feasibility of treating both conditions under a single laparoscopic view (4). Similarly, Ungureanu et al. presented a series of adult patients treated with laparoscopic techniques, underlining the importance of preoperative diagnosis and intraoperative flexibility (3). In rare cases, an undescended testis may be incidentally discovered during hernia surgery, as noted by Sepulveda et al., and careful dissection and urology consultation are essential to avoid complications (7). While TEP is another minimally invasive option, the TAPP approach may be more suitable in uncertain anatomical situations or when intra-abdominal visualization is preferred. The choice between TEP and TAPP may depend on surgeon experience, available equipment, and intraoperative findings.

Conclusion

This case demonstrates the feasibility and safety of simultaneous laparoscopic hernia repair and orchiectomy in adult patients with cryptorchidism. The laparoscopic approach offers both diagnostic and therapeutic advantages in rare coexisting conditions.

Ethical Approval: Informed consent form was obtained from the patient (February 21, 2025).

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Variation of Musculocutaneous Nervi Branching to Median Nerve and not Piercing Coracobrachialis Muscle; Case Report

Nervus Medianus'a Dal Veren ve Musculus Coracobrachialis'i Delmeyen Nervus Musculocutaneus Varyasyonu; Olgu Sunumu

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Abstract

The fifth and sixth (and sometimes the fourth) cervical spinal nerves merge to form the superior trunk, and the superior trunk and the anterior part of the median nerve merge to form the fasciculus lateralis. Fasciculus lateralis is divided into two branches as lateral cord and musculocutaneous nerve. The musculocutaneous nerve pierces the coracobrachialis muscle and then travels between the brachialis muscle and the biceps brachii muscle. Variations in anatomical structures are common. However, nerve variations occur more rarely in these structures. These variations are anatomically and clinically important. This case report was detected during routine dissection of a male cadaver in the Department of Anatomy, Karabuk University Faculty of Medicine. For dissection, the fossa axillaris, arm and forearm of both upper extremities were dissected. During dissection, it was found that the musculocutaneous nerve in the left upper extremity continued without piercing the coracobrachialis muscle and gave a connecting branch to the median nerve. There are limited case studies on this nerve variation and studies show that this variational condition is important for surgical operations in this region. Therefore, this study is important for both surgical and clinical sciences.

Keywords: Musculocutaneous nerve, Coracobrachialis muscle, Median nerve, Variation

Öz

Beşinci ve altıncı (bazen de dördüncü) servikal spinal sinirler birleşerek truncus superior'u, truncus superior ile nervus medianus'un ön bölümü de birleşerek fasciculus lateralis'i meydana getirir. Fasciculus lateralis'te radix lateralis ve nervus musculocutaneus olmak üzere iki dala ayrılır. Nervus musculocutaneus'da musculus coracobrachialis kasını deler ve sonrasında musculus brachialis ile musculus biceps brachii arasında seyreder. Anatomik yapılarda varyasyonlar gözüken bir durumdur. Fakat bu yapılar içerisinde sinir varyasyonları daha nadir olarak ortaya çıkmaktadır. Bu varyasyonlarda anatomik ve klinik açıdan önemlidir. Bu olgu sunumu Karabük Üniversitesi Tıp Fakültesi Anatomi Anabilim dalı'nda yer alan erkek kadavranın rutin diseksiyonu sırasında tespit edildi. Diseksiyon için her iki üst extremitenin de fossa axillaris'i, kol ve ön kol bölgesi diseke edildi. Diseksiyon sırasında sol üst extremitede yer alan nervus musculocutaneus'un musculus coracobrachialis'i delmeden devam ettiği ve nervus medianus'a birleştirici bir dal verdiği bulundu. Bu sinir varyasyonu ile ilgili sınırlı vaka çalışması bulunmakta olup çalışmalar bu varyasyonel durumun bu bölgedeki cerrahi operasyonlar için önemli olduğunu göstermektedir. Bundan dolayı bu çalışma hem cerrahi bilimler için hem de klinik bilimler için önem arz etmektedir.

Anahtar Kelimeler: Nervus musculocutaneus, Musculus coracobrachialis, Nervus medianus, Varyasyon

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Introduction

The fasciculus lateralis branch of the plexus brachialis usually divides at the infraclavicular level (lower level of the musculus pectoralis minor) into two branches, the lateral cord of the median nerve (MN) and the musculocutaneous nerve (MCN). The lateral cord of the MN is thick and the MCN is thin. The thin MCN pierces the coracobrachialis muscle and innervates the brachialis muscle and biceps brachii muscles. It then superficialises just above the epicondylus lateralis and continues as cutaneous antebrachii lateralis nervi (1-3).

Nerve variations in the upper extremity are important for invasive interventions in this region and for the evaluation of symptoms related to nerve variation (4, 5). Because anaesthetic blocks, trauma, nerve transpositions, vascular surgeries, surgical procedures applied in this region may damage the median nerve and loss of limb function may occur (6). Connecting branches between MCN and MN are encountered during routine dissection by anatomists and have been reported by many researchers (7).

The aim of this study is to present a case report of a connecting branch between MCN and MN and to emphasise the importance of this variational condition.

Case

This case report was found during routine dissection of an adult male cadaver in Karabük University Faculty of Medicine, Department of Anatomy. For routine dissection of the cadaver;

1. The skin, adipose tissue and fascia in the pectoral region, shoulder region, arm and forearm were dissected.
2. Superficial veins were dissected.
3. Pectoral muscles were dissected.
4. Biceps brachii muscle was dissected.
5. Fossa axillaris was dissected.
6. Plexus brachialis and its vessels were dissected.

During dissection, it was observed that the MCN in the left upper extremity continued its course without piercing the m. coracobrachialis and gave a connecting branch to the MN (Figure 1).

Discussion

Variations in the course and branching of the plexus brachialis are common and these variations are important in surgical interventions (8-10). One of these variations is the connecting branch between MCN and MN. The formation of this connecting branch is a congenital condition. Muscles develop from the mesenchyme in the intrauterine period and the axons of the spinal nerves grow distally and reach the mesenchyme. During this process, some variational conditions may occur (10).

Nerve variations between MCN and MN are anatomically classified into 5 types. In type 1, there is no connecting branch between MCN and MN. In type 2, part of the lateral cord merges with the MCN and gives a connecting branch to

the MN distally. In type 3, the lateral cord merges with the MCN and gives a branch distally to the MN. In type 4, the lateral cord merges with the MCN and then reaches the MN. It then follows the MN for some time and then leaves the MN as a lateral branch. In type 5, the MCN is absent. The connecting branches between MCN and MN are also classified into 3 types. In type 1, the connecting branch is proximal to the coracobrachialis muscle. In type 2, the connecting branch is distal to the coracobrachialis muscle. The connecting branch and MCN do not pass through the coracobrachialis muscle (5, 10-12).

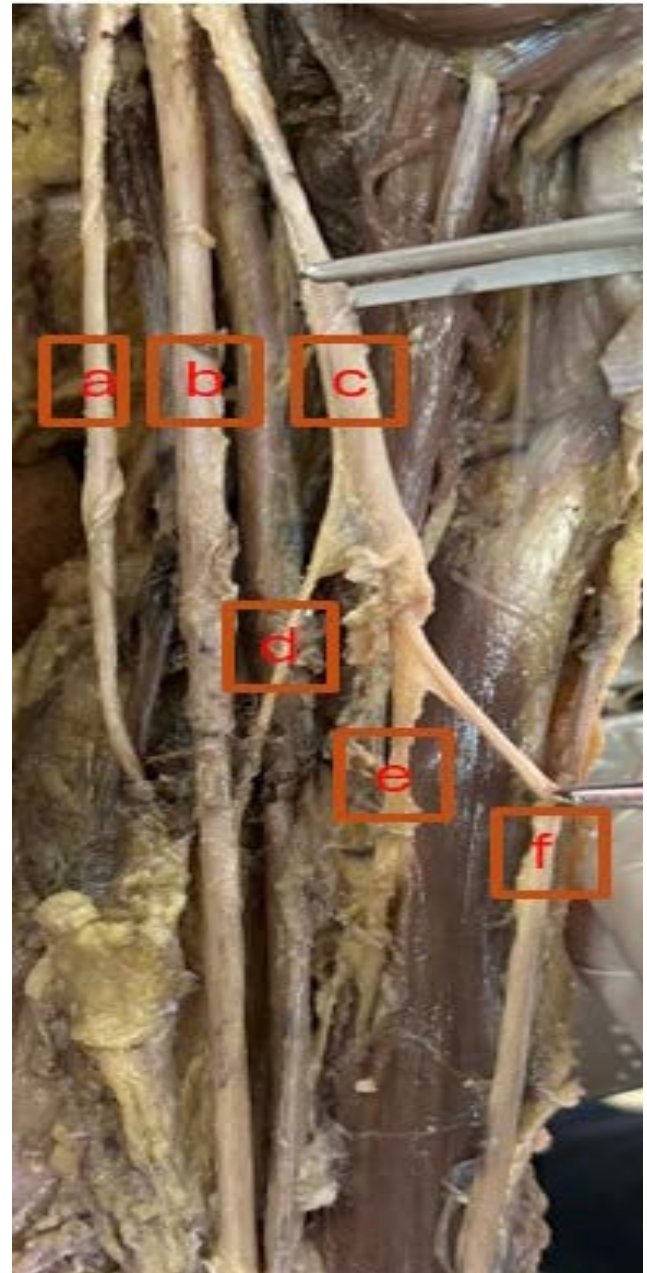


Figure 1. Connecting branch of the musculocutaneous nerve to the median nerve (a: ulnar nerve b: median nerve c: musculocutaneous nervi d: joining branch, e: brachial branch, f: cutaneous antebrachii lateralis nervi)

Venieratos and Anagnostopoulou studied 79 cadavers and found 22 connecting branches between MCN and MN in 16 of them. Of these, 6 were found to be bilateral. According to the classification of the joining branch between the MCN and MN, 9 of them were found as Type 1, 10 as Type 2 and 3 as Type 3 (13). Basar et al. In their study on a 42-year-old male cadaver, they found a connecting branch between the MCN and the MN with a length of 8 cm and a diameter of 3 mm (14). Sarikcioglu et al. In a 60-year-old male cadaver, they found a connecting branch between MCN and MN on the left side (15). Choi et al. In their study on 138 cadavers, 14 branches with fusion between MCN and MN, 53 branches with one connecting branch, 5 branches with 2 connections, 1 branch with both fusion and 1 branch were found (16).

Conclusion

The connecting branches between MCN and MN are important for surgeons, anaesthetists and orthopaedists in the treatment of upper extremity pain, surgical interventions, regional anaesthesia applications. In addition, these connecting branches are important in anatomical variational studies. In conclusion, we believe that this case report will contribute to anatomists, surgeons, anaesthetists and orthopaedists.

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Analysis and interpretation: Y.S, H.Ş.E, N. Y.

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