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Harran Üniversitesi Tıp Fakültesi Dergisi
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. Özette 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 istatiksel 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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1) Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III, İstanbul Üniversitesi C errahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-1650.
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Web sitesi;
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

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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 cümlenin 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. Mikroskobik 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. Bununlar 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 kurumdan alınan izin belgesi de ayrıca sisteme yüklenmelidir).
- Olgu Sunumu- Serisinde hastanın açık kimliği paylaşılmamalı ve hastadan yayına izin verildiğine dair “Aydınlatılmış onam formu”nun 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

INFORMATION FOR AUTHORS

The journal is the publication organ of Harran University Faculty of Medicine. Please read the following explanations when preparing an article for our journal. Harran University Faculty of Medicine Journal publishes clinical and experimental studies, letters to the editor, clinical case reports, technical and educational invited reviews, original images with the latest developments in medicine, video disease identification questions and letters to the editor that contribute to medical science and academic studies. Authors are not charged any fee during the article evaluation and publication process.

Acceptance for publication is based on the decision of at least two reviewers and the editorial committee. All kinds of publication rights of the articles accepted for publication belong to the journal. This right is determined with the signature of all authors with a specially designed publication right transfer form. The journal is published 3 times a year. The publication language of the journal is Turkish or English. English abstract is mandatory for Turkish articles and Turkish abstract is mandatory for English articles. The submitted manuscripts must be original and must not have been published in any journal before (Oral presentations and posters presented at scientific congresses are excluded). All kinds of responsibilities (ethical, scientific, legal, etc.) of the articles published in the journal belong to the authors. Articles that do not comply with the Spelling Rules and have a similarity rate of more than 25% in the plagiarism program are not evaluated.

WRITING RULES

Manuscripts submitted for publication should be written in Microsoft Word program. All articles, figures and graphics should be sent electronically. Except for the cover page, the names of the institutions and authors should not be mentioned anywhere in the manuscript.

All manuscripts should be arranged as follows.

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

The article part (excluding abstract, references, tables, figures and captions) of research review articles should not exceed 4000 words in total, the abstract should not exceed 400 words, references should not exceed 40, and the number of tables and figures should not exceed 10. The limits are summarized in the table below. Case reports should consist of the following sections: Title, English title, Turkish and English abstract, introduction, presentation of the case(s), discussion and references. Case reports should not exceed 8 pages in total. Articles on technical and medical developments and image presentations of original subjects should not exceed 2 pages.

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 **	-		-	-

**Excluding abstract, references, tables, figures and title*
***No limit is applied.*

PREPARATION OF ARTICLES

The text should be written in a simple and understandable style, adopt a scientific writing style and avoid unnecessary repetitions. The text should be written in Times New Roman 12-point font, double-spaced. Pages should be numbered in the lower right corner.

1 - TITLE PAGE

The title and short title of the manuscript should appear on the cover page. Both titles should be written in Turkish and English. The title of the article should not exceed 100 characters and the short title should not exceed 50 characters. The names, surnames, institutions, e-mail addresses and ORCID ID numbers of all authors who contributed to the study should be clearly written.
If the study has been presented in any congress before, the name of the congress, time (day-month-year and place of the congress) should be indicated.
If the study is derived from a graduate thesis, the date and thesis number (National Thesis Center) should be indicated.
At the bottom of the title page, the name, surname, open address, postal code, telephone and e-mail address of the author to be contacted should be written.

2- FULL TEXT

Full texts to be reviewed by the referees during the evaluation process should be uploaded to the system as a single file. The full text file should consist of the following sections and should be organized in this order.

a) Abstracts

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- Results
- Conclusions
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- Materials and Methods
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- Discussion.

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Website
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Araştırma Makalesi / Research Article

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Research Article / Araştırma Makalesi

Differentiating Multiple Myeloma and Osteolytic Bone Metastasis on Spinal CT Scan: A Comprehensive Study Using Convolutional Neural Network

Spinal BT Taramasında Multipl Miyelom ve Osteolitik Kemik Metastazının Ayırt Edilmesi: Konvolüsyonel Sinir Ağı Kullanan Kapsamlı Bir Çalışma

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Abstract

Background: Accurate differentiation of spinal multiple myeloma (MM) and osteolytic metastatic bone tumor (OMBT) can be challenging. Usually, imaging methods, laboratory tests, and biopsy are performed for the correct diagnosis. In this study, we aimed to differentiate CT images from patients with MM and OMBT using CNN models.
Materials and Methods: 3707 CT images of 91 patients (1886 OMBT images and 1821 MM images; 46 males and 45 females; mean age: 61.2 years) obtained between January 2015 and January 2023 were reviewed. 2667 images were randomly selected for the training set, 740 for the validation set, and 300 for the test set. A transfer learning approach was used based on DenseNet121, DenseNet169, EfficientNetB0, MobileNet, MobileNetV2, VGG16, and Xception CNN architectures. The performance of the models was evaluated.
Results: When the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, F1 score, and kappa measurements of the models in the MM and OMBT differentiation are evaluated, the most successful ones are MobileNetV2, MobileNet, and VGG16, with accuracy of 88%, 86.33%, and 86%, respectively.
Conclusions: Our study showed that CNN-based artificial intelligence models can differentiate MM and OMBT on CT images.

Keywords: Artificial Intelligence, Multiple Myeloma, Spinal Metastasis

Öz

Amaç: Spinal multipl miyelom (MM) ve osteolitik metastatik kemik tümörünün (OMKT) doğru bir şekilde ayırt edilmesi zorlayıcı olabilir, genellikle doğru tanı için görüntüleme yöntemleri, laboratuvar testleri ve biyopsinin kombinasyonu uygulanır. Bu çalışmada, MM ve OMKT hastalarından elde edilen BT görüntülerini CNN modelleri kullanarak ayırt etmeyi amaçladık.
Materyal ve Metod: Ocak 2015 ile Ocak 2023 arasında elde edilen 91 hastanın (1886 OMKT görüntüsü ve 1821 MM görüntüsü; 46 erkek ve 45 kadın; ortalama yaş: 61,2 yıl) 3707 BT görüntüsü incelendi. Eğitim seti için 2667, doğrulama seti için 740, test seti için 300 görüntü rastgele seçildi. DenseNet121, DenseNet169, EfficientNetB0, MobileNet, MobileNetV2, VGG16 ve Xception CNN mimarilerine dayanan bir transfer öğrenimi yaklaşımı kullanıldı. Modellerin performansı değerlendirildi.
Bulgular: Modellerin MM ve OMKT ayrımındaki duyarlılık, özgüllük, pozitif prediktif değer, negatif prediktif değer, doğruluk, F1 skoru ve kappa ölçümleri değerlendirildiğinde, en başarılı modeller sırasıyla %88, %86,33 ve %86 doğruluk oranları ile MobileNetV2, MobileNet ve VGG16 olmuştur.
Sonuç: Çalışmamızda CNN tabanlı yapay zekâ modellerinin BT görüntülerinde MM ve OMKT'yi ayırt edebileceğini gösterdik.

Anahtar Kelimeler: Yapay Zekâ, Multipl Miyelom, Spinal Metastaz

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Introduction

Multiple myeloma (MM) is the most common primary malignant bone tumor while the most common malignant bone tumor is metastatic cancer (1). Both are generally seen in patients over 40 years old and present themselves with multiple osteolytic lesions (2). The most common site of osteolytic metastatic bone tumors (OMBT) is the spine where MM also generally presents itself (3). Distinguishing between these two entities is crucial, as their management strategies significantly differ, with implications for patient prognosis and overall survival.

Accurate identification of spinal lesions can be challenging, usually a combination of imaging methods, laboratory tests, and biopsy is performed for the correct diagnosis (4). Recent advancements in machine learning, specifically Convolutional Neural Networks (CNNs), have revolutionized the field of medical imaging analysis (5, 6). CNNs can automatically learn and extract relevant features from images, enabling them to discern intricate patterns and make accurate predictions. By leveraging this technology, we aim to develop a CNN-based approach that can effectively differentiate between spinal lesions in MM and OMBT using computed tomography (CT) scans which is the primary diagnostic imaging modality for MM, as proposed by the International Myeloma Working Group (IMWG) (4). Such an approach could streamline the diagnostic process, provide prompt and accurate identification of the underlying pathology, and guide appropriate treatment decisions.

In this study, we aimed to differentiate CT images from patients with MM and OMBT using different CNN models. To the best of our knowledge, this is the first study in the literature aimed at differentiating CT images of these two entities using CNN. We anticipate that our CNN-based approach will exhibit high sensitivity and specificity, offering a reliable and efficient tool for distinguishing between MM and OMBT in routine clinical practice. This study demonstrates the potential of the use of artificial intelligence technologies in cancer diagnosis and will form an important basis for future studies in the field of spinal lytic tumors.

Materials and Methods

This retrospective study was approved by the university institutional review board (Application no: 2023/18-19) and was conducted under the Declaration of Helsinki. Patient consent was waived.

Patient selection:

Non-contrast-enhanced spinal CT images of patients with MM and OMBT between January 2015 and January 2023 were evaluated.

Previous spinal surgery, unknown pathology diagnosis, and artifacts that impair diagnostic quality were exclusion criteria from the study. CT images were obtained from two scanners (Philips Brilliance 64; Philips Medical Systems, Best, The Netherlands, and Siemens SOMATOM Definition AS+, Siemens Healthcare, Germany).

Patient dataset:

All images on CT scans were evaluated by two neuroradiologists with seven years of neuroradiology experience (M.K.S. and Y.K.C.). DICOM images were analyzed with Sectra Workstation version 23.2.2.5087 and ProbelViewer programs. The spinal CT slices demonstrating pathology specific to OMBT and MM were manually selected through the interfaces of the programs. Images without pathology were excluded. Images were converted from DICOM (Digital Imaging and Communications in Medicine) format to JPEG (Joint Photographic Experts Group) format. The demographic data of the cases were anonymized. Selected images for both were divided into the relevant class. A dataset was created using a total of 3707 images, including 1886 OMBT images and 1821 MM images. 2667 images were randomly selected for the training set, 740 images for the validation set, and 300 images for the test set.

Training and validation:

The transfer learning method was used to differentiate MM and OMBT. DenseNet121, DenseNet169, EfficientNetB0, MobileNet, MobileNetV2, VGG16, and Xception, among the models that showed high performance in the ImageNet competition, were selected as the CNN models in which the transfer learning approach will be used. Xception accepts a 299x299 pixel image as its input shape, while in other models the input shape was 224x224 pixels. CT images were resized as accepted by the models and presented from three channels. The classifier layers of CNN models have been fine-tuned. The last classifier layers of the CNN models were replaced with two fully connected layers of 512 and 256 nodes, respectively. Rectified Linear Unit (ReLU) and SoftMax were used as the activation function. Pretrained weights from ImageNet were applied. The batch number was selected as 16. Epoch is set to 100 for all CNN models. The pipeline and architecture of the fine-tuned models are shown in figure 1.

Google Colaboratory (Colab), an open-source cloud-based tool owned by Google, was used for training, and testing all models.

Results

In our study, spinal CT images of 39 (43%) patients with MM and 52 (57%) patients with OMBT were reviewed. The causes of OMBT included in the study were: lung cancer (n=18), breast cancer (n=18), gastrointestinal cancer (n=7), hepatocellular cancer (n=2), neuroendocrine cancer (n=1), renal cell cancer (n=1) and prostate cancer (n=1). The primary cancer of 3 metastatic patients was unknown. In total, 45 (49%) of 91 cases were female and 46 (51%) were male. The mean age was 61.2 years (standard deviation ±5.6). All demographic data are shown in table 1.

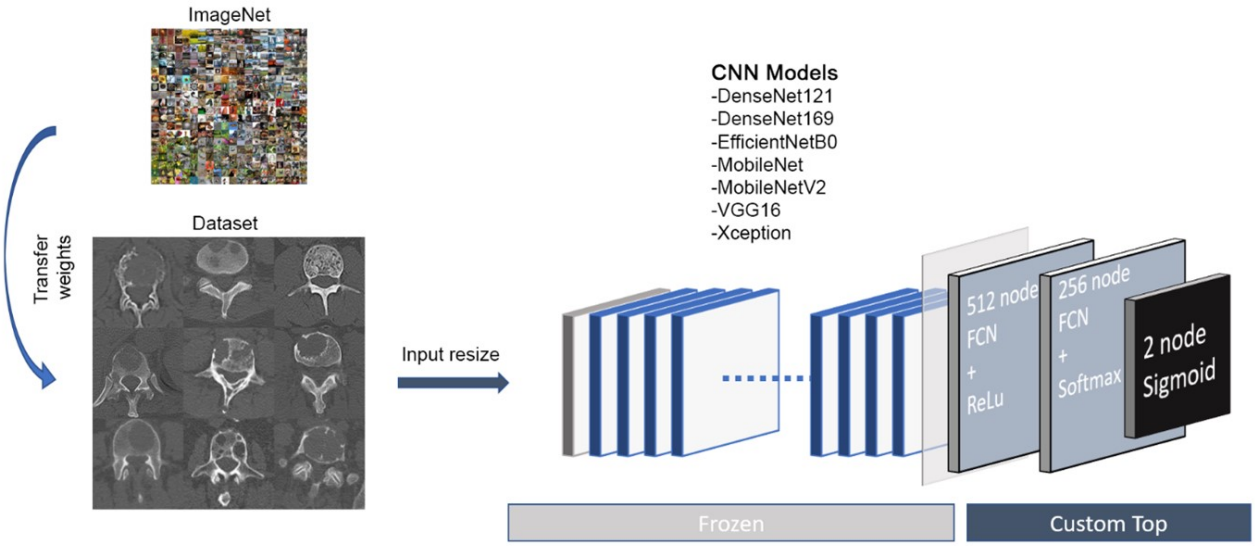

Figure 1. Artificial intelligence pipeline

Table 1. Demographics

	Myeloma	Metastasis	Total
Gender (n, %)			
Male	21 (53.8%)	25 (48.1%)	46 (50.5%)
Female	18 (46.2%)	27 (51.9%)	45 (49.5%)
Total	39 (100%)	52 (100%)	91 (100%)
Age (mean, Interval, Standard Deviation)	63.1 (23-83)	59.8 (34-85)	61.2 (23-85, ±5.6)

Performance of CNN models:

The highest accuracy rate in the CNN models we created in the differentiation of MM and OMBT was obtained in MobileNetV2 with 88%, and the lowest accuracy rate was obtained in EfficientNetB0 with 74.67%. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, F1-score, and kappa values obtained from the confusion matrix of the models are given in Table 2 and Figure 2 for each model. In addition, the ROC curve of the models is shown in figure 3.

Learning in the training graphs of pre-trained CNN models started after the first epochs and stabilized at 10-40 epochs. When the loss graphs of the CNN models are evaluated, it is seen that the loss decreases progressively in both training and validation sets, which shows that there is no overfitting problem. The accuracy and loss graphs for the fine-tuned models with the top three are presented in figure 4.

Table 2. Evaluation of models in MM and OMBT differentiation

	DenseNet121	DenseNet169	EfficientNetB0	MobileNet	MobileNetV2	VGG16	Xception
Statistic	Value	Value	Value	Value	Value	Value	Value
Sensitivity	79.89%	80.86%	78.46%	84.28%	83.93%	81.03%	69.59%
Specificity	91.27%	86.23%	71.76%	88.65%	93.18%	92.86%	85.85%
Positive Predictive Value	92.67%	87.33%	68.00%	89.33%	94.00%	94.00%	90.00%
Negative Predictive Value	76.67%	79.33%	81.33%	83.33%	82.00%	78.00%	60.67%
Accuracy	84.67%	83.33%	74.67%	86.33%	88.00%	86.00%	75.33%
F1 Score	0.858	0.8397	0.7286	0.8673	0.8868	0.8704	0.7849
kappa	0.693	0.667	0.493	0.7227	0.760	0.720	0.507

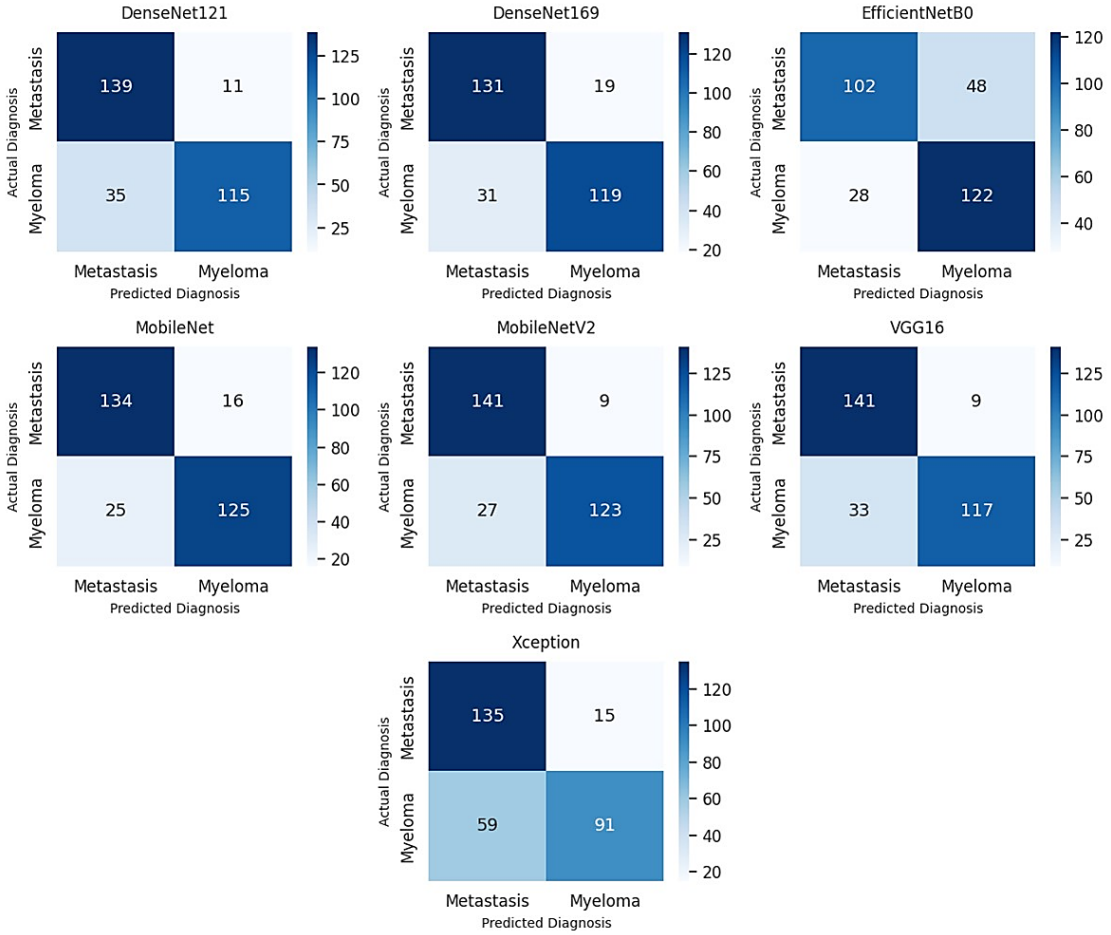

Figure 2. Confusion matrices of the models

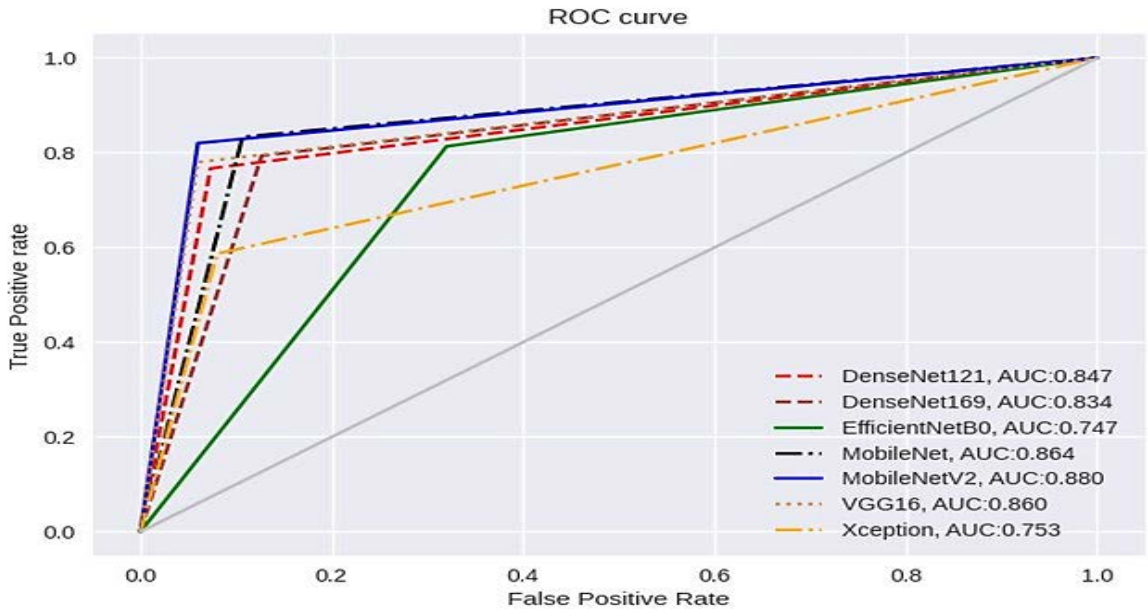

Figure 3. Roc curves of the models

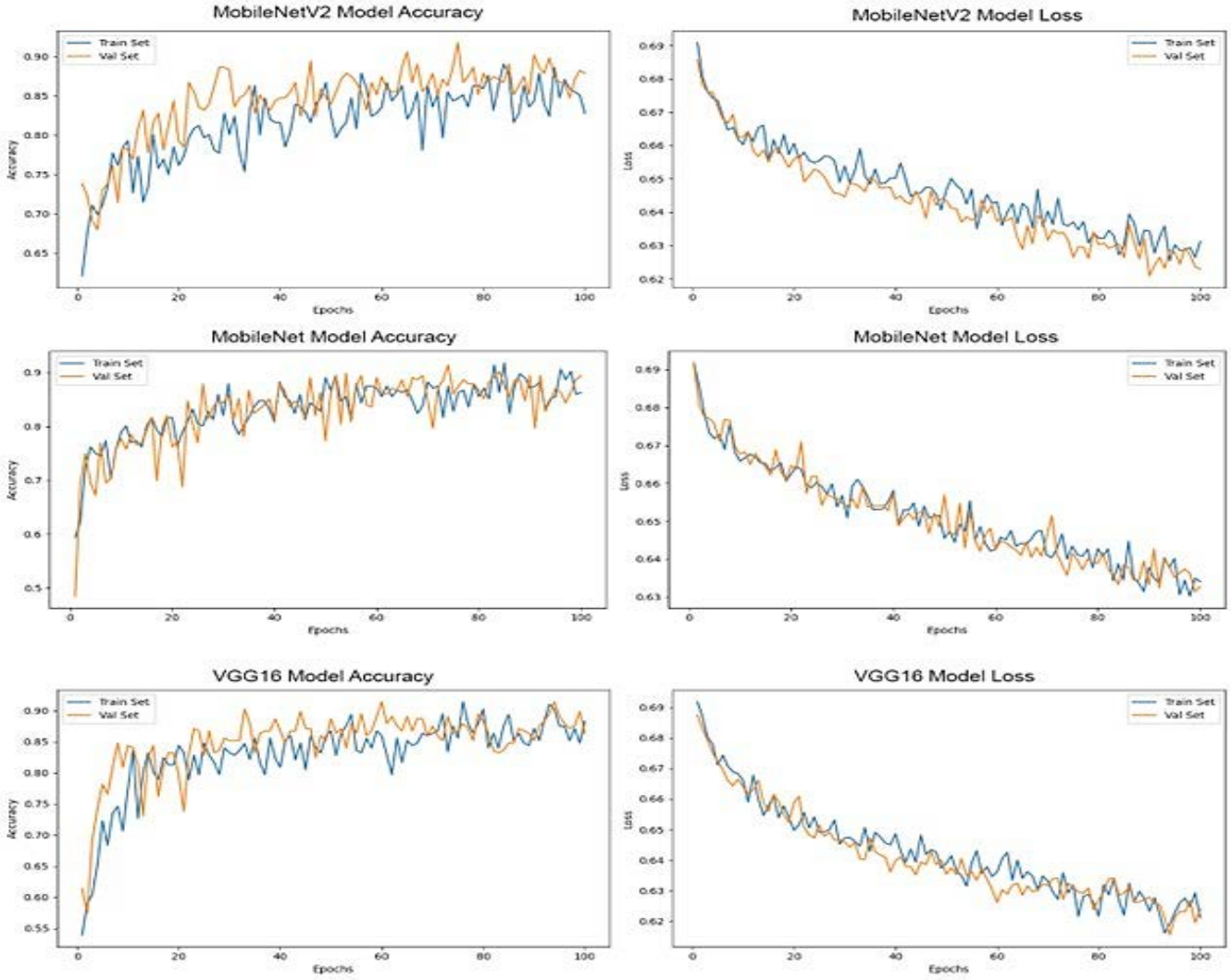

Figure 4. Accuracy and lose graphs

Discussion

In daily practice, CT scans for spinal bones are used a lot. Osteolytic bone lesions are the most commonly seen lesions in the spine. The spinal lesions detected on CT scans have both benign and malignant causes. The differential diagnosis of malignant causes includes MM and OMBT. Histopathological diagnosis of lesions with bone biopsy is the gold standard examination for benign and malignant tumors. Since the histopathological examination is an invasive procedure, clinical and radiological examinations play an important role in the diagnosis and follow-up of the disease in the differentiation of spinal lesions (7). Differentiation of MM and OMBT has an important role in the treatment planning of the patient. In patients with no prior known disease, radiological differentiation of MM and OMBT is very challenging. Moreover, publications are stating that pathologically diagnosed spinal bone lesions can be missed by the radiologist up to 24% (8). MM and OMBT are difficult to distinguish from each other in conventional radiology, therefore CNN-based deep learning models may have benefits such as increasing diagnostic accuracy and shortening the diagnosis time for these diseases.

In our study, CNN-based deep learning models were applied to differentiate the MM from OMBT. In our study, the accuracy of the VGG16 model was 86%, the accuracy of MobileNet was 86%, and the accuracy of the MobileNetV2 model was 88%. We used images from two different CT devices. The use of images from more than one CT device shows that the success of the models is generalizable. To the best of our knowledge, our study is the first study in the literature that uses CNN-based deep learning models to differentiate spinal MM and OMBT in CT. Among our CNN models, the most successful was the fine-tuned MobileNetV2 with 88% accuracy. The least successful model was EfficientNetB0. According to an article on the Keras API website, the difficulty of defining hyperparameters may cause EfficientNet variants to perform less successfully in classification tasks with fewer classes (9). In addition, there are studies in the literature showing that MobileNetV2 is more successful than EfficientNet in binary classification problems (10,11).

In a similar study, Lang et al. assessed lung cancer and other organ metastases in spinal bones using artificial intelligence

in DCE-MRI images. In their research, the accuracy achieved with conventional CNN ranged from 0.61 to 0.74, with a mean of 0.71 and a standard deviation of 0.043. In our study, all the CNN models employed demonstrated higher accuracy than the results reported by Lang et al. The improved performance of our models could be attributed to the use of the transfer learning approach. In this approach, the ImageNet dataset is utilized to pre-train the CNN, and the acquired functional weights are subsequently applied to the training of new custom datasets. As a result, this approach enhances the success of the models. Another possible explanation for the superior performance of our model may be the use of CT images instead of MRI. Because MRI imaging parameters may vary in different centers. MRI signals can be influenced by various parameters which can lead to magnetic field inhomogeneity. Moreover, CT images are more standardized than MRI images and are not affected by other signal differences, which may account for this outcome (12).

Xiong et al. used lumbar MRI images to distinguish between spinal metastasis and MM by texture analysis. In this study, they found that machine learning-based texture analysis can differentiate metastasis and MM in the lumbar spine. In their study, they achieved accuracy, sensitivity, and specificity performance of 0.815, 0.879, and 0.790, respectively, in the validation cohort with the Artificial Neural Networks classifier on T2WI images (13). Our study used CNN-based deep learning models, which are more advanced artificial intelligence techniques compared to the ones used in this study. Moreover, while the highest accuracy in this study was 81.5% in the validation set, in our study the accuracy was higher in the external validation set. Another advantage of our study is the ability to distinguish between OMBT and MM not only in lumbar vertebrae but also in thoracic vertebrae.

Baykara et al. aimed to differentiate MM and OMBT by histogram analysis using ADC maps in MRI images. They mentioned that the lower ADC values in myeloma patients compared to metastasis can be used in this differentiation (14). The deep learning approach is more feasible than histogram analysis. CNN models used in our study offer suggestions that will facilitate fast, effective, and clinical functioning.

There are deep learning studies performed to detect lesions in spinal bones. These studies can distinguish spinal lesions as lytic, sclerotic, and mixed types. It has also been shown that deep-learning models can detect spinal metastasis at a high rate (15,16). The aim of the studies in the literature is generally for lesion detection. Our study is the first to demonstrate successful differentiation of MM and OMBT using CT images in spinal bone lesions with CNN-based deep learning models.

Chen et al. evaluated MRI images in the differentiation of spinal MM and lung cancer metastasis by radiomics and deep learning model. Their study shows that the deep learning model has a stronger capability in differential diagnosis than that of the radiomics model and radiologist assessment (7). In our study, the differentiation of MM and OMBT is not limited to lung cancer metastasis. Another advantage of our study is that this distinction can be made successfully in CT, which is cheaper than MRI.

There are publications in the literature that aim to differentiate spinal MM and OMBT. Among these publications, Mutlu et al., in their study of 207 patients with CT images, defined that features such as homogeneity of the lesion, high density, perilesional sclerosis, and border features may be useful in the differentiation of MM and OMBT. Despite the features that help in distinguishing these two conditions, they concluded that the distinction is not very clear in most patient groups (17). In addition, the subjective nature of the defined features is another diagnostic challenge. The use of deep learning models can yield useful findings in lesion differentiation. Subjective evaluation will be prevented thanks to the automation made with deep learning models. In addition to the conventional findings, our study shows artificial intelligence applications can make a significant contribution to this differentiation.

There are some limitations in our study. Although the loss graphs of the models in both the training and validation sets show a decreasing trend, indicating no over-fitting problem, the use of multiple images from the same patient may have resulted in higher model performance than expected. Furthermore, given the limited number of patients in our dataset despite the large number of images, further comprehensive studies are required such as including data from more diverse sources or a prospective study setup.

Consequently, it is very difficult to distinguish between MM and OMBT with CT images in daily practice. Our study showed that CNN-based artificial intelligence models can contribute to conventional radiological evaluations in this distinction with high success. Thanks to technological developments in models and artificial intelligence programs, the distinction between MM and OMBT will be easier.

Ethical Approval: *For this retrospective study, Institutional Review Board approval was obtained from the Non-Invasive Clinical Research Ethics Committee with the application number 2023/18-19 (date: 5/31/2023).*

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Concept: M.K.S.
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Design : M.K.S., Y.K.C., A.B.
Data acquisition: M.K.S., Y.K.C.,
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Writing manuscript: M.K.S., R.B., A.B.
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Research Article / Araştırma Makalesi

Evaluation of Behaviours Towards Rational Drug Use in University Students

Üniversite Öğrencilerinde Akılcı İlaç Kullanımına Yönelik Davranışların Değerlendirilmesi

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Abstract

Background: Rational drug use is the use of drugs that meet patients' clinical needs, in doses appropriate to their individual requirements, for the correct duration and at the lowest cost. Irrational drug use poses significant health and economic problems. Due to various factors such as inability to apply healthcare institutions, financial difficulties, stress and exposure to social media and the internet, which encourage self-medication university students tend to engage in irrational drug use. This research seeks to investigate the behaviors associated with rational drug use among students enrolled in health and non-health disciplines at Gaziantep University.
Materials and Methods: A survey was conducted with 1638 students studying at Gaziantep University between January and June 2018. The survey form consisted of 53 questions that evaluated sociodemographic characteristics and behaviors related to rational drug use. The findings were compared and evaluated among all participants, student groups studying in the health and non-health fields and additionally, among student groups studying in the medical faculty and other health field faculties.
Results: The rate of non-prescription drug use among university students has been determined as 64.2%. The most frequently used non-prescription drug groups are analgesics (51.7%), cold drugs (12.5%), vitamins (6.4%) and antibiotics (5.4%). The frequency of non-prescription drug use is significantly higher among health field students compared to non-health field students and among medical students compared to other health field students ($p<0.05$). The use of drug based on the recommendation of acquaintances is significantly higher among non-health field students compared to health field students ($p<0.05$). Among all participants, the rate of non-prescription antibiotic use for flu or cold is 44.4%, with non-health field students using non-prescription antibiotics for flu/cold more frequently than health field students ($p<0.05$). More than half of the students use alternative products/treatments, with the most frequently used being nutritional supplements (33.5%) and herbal products (20.0%). Additionally, 20.2% of the students have been determined to use drug/products outside of drug to enhance exam performance during exam periods, with the most frequently used being methylphenidate (5.1%) and multivitamins (5%).
Conclusions: Irrational drug use behaviors are widely observed among university students, who are the architects of the future. Health field students act more rationally compared to non-health field students, especially in terms of antibiotic use. To enhance awareness of rational drug use, it is essential to carry out research and educational initiatives in collaboration with health authorities, universities, professional healthcare providers, and the media.

Keywords: Rational drug use, University students, Behaviour of drug use

Öz

Amaç: Akılcı ilaç kullanımı, hastaların klinik ihtiyaçlarını karşılayan ilaçları, bireysel gereksinimlerine uygun dozlarda, doğru süreyle ve en düşük maliyetle kullanmasıdır. İlaçların akılcı olmayan kullanımları sağlık ve ekonomi açısından önemli sorunlara yol açmaktadır. Üniversite öğrencileri çeşitli nedenlerle sağlık kuruluşlarına başvuramama, ekonomik sıkıntı, stres ve kendi kendine tedaviyi teşvik eden sosyal medya ve internet ortamına maruziyet gibi sebeplerle akılcı olmayan ilaç kullanımına yönelmektedir. Bu çalışmada, Gaziantep Üniversitesi'nde sağlık alanındaki ve sağlık alanı dışındaki fakültelerde eğitim alan öğrencilerin akılcı ilaç kullanımına yönelik davranışlarının incelenmesi amaçlanmıştır.
Materyal ve Metod: Gaziantep Üniversitesi'nde öğrenim gören 1638 öğrenciye 2018 yılının Ocak ve Haziran ayları arasında anket yapılmıştır. Anket formu, öğrencilerin sosyodemografik bilgilerini ve akılcı ilaç kullanımı ile ilgili davranışlarını değerlendiren 53 soruyu kapsamaktadır. Bulgular tüm katılımcılarda, sağlık alanında ve sağlık alanı dışında öğrenim gören öğrenci gruplarında ve ayrıca, tıp fakültesi ile tıp fakültesi dışındaki sağlık alanı fakültelerinde eğitim almakta olan öğrenci gruplarında karşılaştırılarak değerlendirilmiştir.
Bulgular: Üniversite öğrencileri arasında reçetesiz ilaç kullanım oranı %64.2, reçetesiz en sık kullanılan ilaç grupları analjezikler (%51.7), soğuk algınlığı ilaçları (%12.5), vitaminler (%6.4) ve antibiyotikler (%5.4) olarak belirlenmiştir. Reçetesiz ilaç kullanım sıklığı, sağlık alanı öğrencileri arasında sağlık alanı dışındakilere göre ve tıp fakültesi öğrencilerinde diğer sağlık alanı öğrencilerine oranla anlamlı olarak daha yüksektir ($p<0.05$). Tanıdık tavsiyesi ile ilaç kullanımı sağlık alanı dışı öğrencilerinde sağlık alanı öğrencilerine oranla daha yüksektir ($p<0.05$). Tüm katılımcılarda grip ya da soğuk algınlığında reçetesiz antibiyotik kullanımı %44.4 oranında olup sağlık alanı dışı öğrencileri sağlık alanı öğrencilerine göre daha sık grip/soğuk algınlığında reçetesiz antibiyotik kullanmaktadır ($p<0.05$). Öğrencilerin yarısından fazlası alternatif ürün/tedavi kullanmakta ve en sık besin destekleri (% 33.5) ve bitkisel ürünler (% 20.0) kullanılmaktadır. Ayrıca, öğrencilerin %20.2'sinin sınav dönemlerinde sınav performansını arttırmak amacıyla ilaç/ilaç dışı ürün kullandığı ve bu amaçla en sık metilfenidat (% 5.1) ve multivitaminlerin (% 5) kullanıldığı belirlenmiştir.
Sonuç: Geleceğin mimarı olan üniversite öğrencileri arasında akılcı olmayan ilaç kullanımı davranışları yaygın bir şekilde gözlenmektedir. Sağlık alanı öğrencileri sağlık alanı dışı öğrencilere göre özellikle antibiyotik kullanımı olmak üzere daha rasyonel davranmaktadır. Akılcı ilaç kullanımı farkındalığının arttırılabilmesi amacıyla sağlık otoritelerinin, üniversitelerin, profesyonel sağlık çalışanlarının ve medyanın iş birliği ile akılcı ilaç kullanımına yönelik araştırmaların ve eğitimlerin yapılması önem taşımaktadır.

Anahtar Kelimeler: Akılcı ilaç kullanımı, Üniversite öğrencileri, Ilaç kullanım davranışı

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Introduction

Rational drug use is defined as the use of drugs appropriate for the clinical needs of patients in doses that meet their individual requirements, in sufficient time, at the lowest cost to themselves and the society (1).

Rational drug use involves several key steps: making the correct diagnosis, determining treatment goals and treatment options, choosing the suitable treatment, correctly prescribing drug if drug therapy is warranted, initiating treatment by providing clear information and instructions to the patient, evaluating the prognosis and monitoring and assessing treatment outcomes. Throughout the process of rational drug use, it is critical to consider non-pharmacological treatment options, conduct a comprehensive analysis of drugs in terms of efficacy, appropriateness, safety and cost, minimize potential risks, inform the patient and ensure their participation in the treatment process (2, 3).

Globally, more than half of all medicines are prescribed, dispensed or sold inappropriately, half of the patients do not use their drugs correctly and one-third of the world's population lacks access to essential medicines (4).

Rational drug use plays a fundamental role in preventing polypharmacy, inappropriate self-medication, non-adherence to treatment, inappropriate prescribing according to clinical guidelines, prolonged disease duration, antibiotic resistance, drug-drug interactions, adverse events and increased treatment costs (5).

University students tend to use drugs irrationally due to factors such as financial difficulties, inability to access healthcare facilities for various reasons, stress and exposure to social media and the internet which promote self-medication (6, 7). Since university students represent a significant social group that constitue the country's future, improving their awareness and behaviors regarding rational drug use can significantly contribute to the sustainable development of society. This research seeks to identify the behaviors related to rational drug use among university students enrolled in health and non-health fields at Gaziantep University.

Materials and Methods

The population for this cross-sectional descriptive study includes 25,204 students enrolled in various faculties at Gaziantep University, specifically in Medicine, Arts and Sciences, Dentistry, Law, Fine Arts, Engineering, Theology, and Economics and Administrative Sciences, as well as in the Nursing and Midwifery Departments of the Faculty of Health Sciences, the School of Physical Education and Sports, and the Vocational School of Health Services, during the period from January to June 2018. With a precision of 5% and a confidence level of 95%, the minimum number of participants required to estimate a prevalence of 50% has been calculated to be 379.

The researchers prepared a questionnaire based on relevant literature (6, 8-10), which was then administered through face-to-face interviews with 1,638 students who consented to participate in the study from January 20 to June 20, 2018. The questionnaire comprises 53 questions that evaluate the sociodemographic characteristics of the participants and their behaviors related to rational drug use. The data were analyzed using descriptive statistics and the Chi-square test through the SPSS 26 for Windows software package. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Gaziantep University Clinical Research Ethics Committee, with decision number 38, dated 18 January 2018.

Results

A total of 1,638 students took part in the study, with 722 (44.1%) enrolled in healthcare-related faculties and 916 (55.9%) in non-healthcare-related faculties. 357 (49.4%) of the health field students are studying at the faculty of medicine. Of all participants, 56.8% are female, 57% are 21 years old or younger, 45.4% are in good economic condition, 87.1% have health insurance, 23% smoke, 22.4% use alcohol and 92% do not have any chronic diseases (Table 1).

The students' behaviors regarding drug procurement are shown in Table 2 and the procured drug groups are illustrated in Figure 1, which includes only the primarily marked drug groups. 64.2% of participants use non-prescription drugs, with the most frequently procured being painkillers (51.7%), cold drugs (12.5%), vitamins (6.4%), and antibiotics (5.4%). Health field students (70.5%) use non-prescription drugs significantly more than non-health field students (59.2%) and procure painkillers, cold drugs, vitamins, and gastrointestinal system drugs without a prescription at a higher rate ($p<0.05$). 50.8% of students use drugs with the advice of relatives or friends, with painkillers (42.7%) being the most frequently used, followed by cold drugs (9.5%) and antibiotics (6.7%). Non-health field students (53.8%) use drugs with advice from acquaintances significantly more than health field students ($p<0.05$). Painkillers are more frequently used in the non-health field group, while vitamins and allergy drugs are used more often in the health field group ($p<0.05$). Participants recommend drugs to acquaintances at a rate of 54.9%, with the most recommended being analgesics (43.2%), cold drugs (18.4%) and antibiotics (10.1%). Health field students (59.4%) recommend drugs significantly more often than non-health field students (51.3%) and they recommend painkillers, antibiotics, cold drugs and vitamins at a higher rate ($p<0.05$). It was found that 63.9% of participants obtained a prescription or purchased drugs without being ill, thinking they might need them, with the most commonly obtained drugs being analgesics (50.7%), cold drugs (21.4%), stomach drugs (21.4%), antibiotics (16.1%), vitamins (16.1%) and psychiatric drugs (8.7%).

Table 1. Sociodemographic characteristics of university students.

Demographic characteristics	Total (1638), n (%)	Health field (722) n (%)	Non-health field (916) n (%)
Gender			
Woman	930 (56.8)	445 (61.6)	485 (52.9)
Male	708 (43.2)	277 (38.4)	431 (47.1)
Age			
21 years and younger	934 (57)	423 (58.6)	511 (55.8)
22 years and older	704 (43)	299 (41.4)	405 (44.2)
Economic situation			
Poor	562 (34.3)	177 (24.5)	385 (42)
Moderate	332 (20.3)	139 (19.3)	193 (21.1)
Good	744 (45.4)	406 (56.2)	338 (36.9)
Health insurance			
Avaliable	1426 (87.1)	668 (92.5)	758 (82.8)
Not avaliable	212 (12.9)	54 (7.5)	158 (17.2)
Smoking status			
Smoker	376 (23)	138 (19.1)	238 (26)
Nonsmoker	1262 (77)	584 (80.9)	678 (74)
Alcohol use			
Yes	367 (22.4)	178 (24.7)	189 (20.6)
No	1271 (77.6)	544 (75.3)	727 (79.4)
Presence of chronic disease			
Yes	131 (8)	60 (8.3)	71 (7.8)
No	1507 (92)	662 (91.7)	845 (92.2)

Table 2. Students' attitudes towards supplying drug.

	Total (1638) n (%)	Health field (722) n (%)	Non-health field (916) n (%)	P value
Use of non-prescription drug				
Yes	1051 (64.2)	509 (70.5)	542 (59.2)	χ^2=22.534, p= 0.001
No	587 (35.8)	213 (29.5)	374 (40.8)	
Use of drug on the recommendation of acquaintances				
Yes	832 (50.8)	339 (47)	493 (53.8)	χ^2=7.620. p= 0. 006
No	806 (49.2)	383 (53)	423 (46.2)	
Recommending drug to acquaintances				
Yes	899 (54.9)	429 (59.4)	470 (51.3)	χ^2=10.720, p= 0. 001
No	739 (45.1)	293 (40.6)	446 (48.7)	
Purchasing drug without being ill				
Yes	1046 (63.9)	455 (63)	591 (64.5)	χ^2=0.394, p= 0.530
No	592 (36.1)	267 (37)	325 (35.5)	

While there was no significant difference between health field students (63%) and non-health field students (64.5%) in this behavior (p>0.05), health field students more frequently procured cold drugs (p<0.05) (Table 2 and Figure 1).

Students' responses regarding antibiotic use are shown in Table 3. 44.4% of participants use antibiotics without a prescription for flu or cold, with this behavior observed more frequently in non-health field students (48.4%) than in health field students (39.3%) (p<0.05). The rate of quiting the prescribed antibiotics before finishing them was 81% among students and non-health field students (84.7) left the prescribed antibiotics before finishing them at a higher rate than health field students (76.2) (p<0.05). The most common reason for stopping antibiotics before finishing them was recovery (32.4%). This reason was more prevalent among non-health field students, while forgetfulness was a more frequent cause for discontinuation among health field students. (p<0.05) (Table 3).

Table 4 presents students' behaviors related to drug use. Among them, 85.4% reported receiving information from a doctor/pharmacist about the prescribed drug, 65.4% had no issues obtaining drugs, 44% preferred the cheaper option among drugs with the same effect, 97.5% used their drugs as directed by doctor and 93.9% read the drug instructions. Health field students preferred cheaper drugs more often, while non-health field students more frequently had issues obtaining prescription drugs and asked for information from the doctor/pharmacist (p<0.05) (Table 4).

Table 3. Students' responses about the use of antibiotics.

	Total (1638) n (%)	**Health field (722) n (%)**	**Non-health field (916) n (%)**	**P value**
Use of non-prescription antibiotics for flu or cold				
Yes	727 (44.4)	284 (39.3)	443 (48.4)	χ^2=13.329, **p=0.001**
No	911 (55.6)	438 (60.7)	473 (51.6)	
The situation of stopping a prescribed antibiotic before finishing it.				
Yes	1326 (81)	550 (76.2)	776 (84.7)	χ^2=19.092, **p=0.001**
No	312 (19)	172 (23.8)	140 (15.3)	
The reason for stopping a prescribed antibiotic before finishing it*				
Recovery	618 (37.7)	242 (32.4)	376 (41)	χ^2=9.744, **p=0.002**
Feeling well	464 (28.3)	203 (26.3)	261 (27.5)	χ^2=0.028, p=0.866
Forgetfulness	129 (7.9)	76 (10.5)	53 (5.8)	χ^2=12.505, **p=0.001**
Allergy	25 (1.5)	8 (1.1)	17 (1.9)	χ^2=1.503, p=0.220
Aiming to avoid excessive drug use	147 (9.0)	67 (9.3)	80 (8.7)	χ^2=0,147, p=0,701
Other	31 (1,9)	11 (1.5)	20 (2.2)	χ^2=0.947, p=0,331

**More than one answer was given.*

Table 4. Students' behaviors related to drug use.

	Total (1638) n (%)	**Health field (722) n (%)**	**Non-health field (916) n (%)**	**P value**
The situation of using the drug as directed by the doctor/pharmacist				
Yes	1597 (97.5)	710 (98.3)	803 (87.7)	χ^2=3,742. p=0. 053
No	41 (2.5)	12 (1.7)	113 (12.3)	
The situation of paying attention to taking the drug on an empty/full stomach				
Yes	1611 (98.4)	715 (99)	896 (97.8)	χ^2=3.670, p=0. 055
No	27 (1.6)	7 (1)	20 (2.2)	
The situation of paying attention to taking the drug on time				
Yes	1517 (92.6)	675 (93.5)	842 (91.9)	χ^2=1.453, p=0. 228
No	121 (7.4)	47 (6.5)	74 (8.1)	
The situation of paying attention to the drug dosage				
Yes	1591(97.1)	709 (98.2)	882 (96.3)	χ^2=5.292, p=0.021
No	47 (2.9)	13 (1.8)	34 (3.7)	
The situation of paying attention to the use of the drug with other drugs				
Yes	1523 (93)	673 (93.2)	850(92.8)	χ^2=0. 108, p=0. 742
No	115 (7)	49 (6.8)	66 (7.2)	
The situation of preferring the cheaper option among drugs with the same effect				
Yes	720 (44)	384 (53.2)	336 (36.7)	χ^2=44.645, **p=0.001**
No	918 (56)	338 (46.8)	580 (63.3)	
The situation of experiencing problems in obtaining prescription drugs				
Yes	567 (34.6)	221 (30.6)	346 (37.8)	χ^2=9.154, **p=0. 002**
No	1071 (65.4)	501 (69.4)	570 (62.2)	
The situation of asking the doctor/pharmacist for information about the drug				
Yes	1399 (85.4)	596 (82.5)	803 (87.7)	χ^2=8.478, **p=0. 004**
No	239 (14.6)	126 (17.5)	113 (12.3)	
The situation of reading the drug instructions				
Yes	1538 (93.9)	687 (95.2)	851 (92.9)	χ^2=3.561, p=0. 059
No	100 (6.1)	35 (4.8)	65 (7.1)	

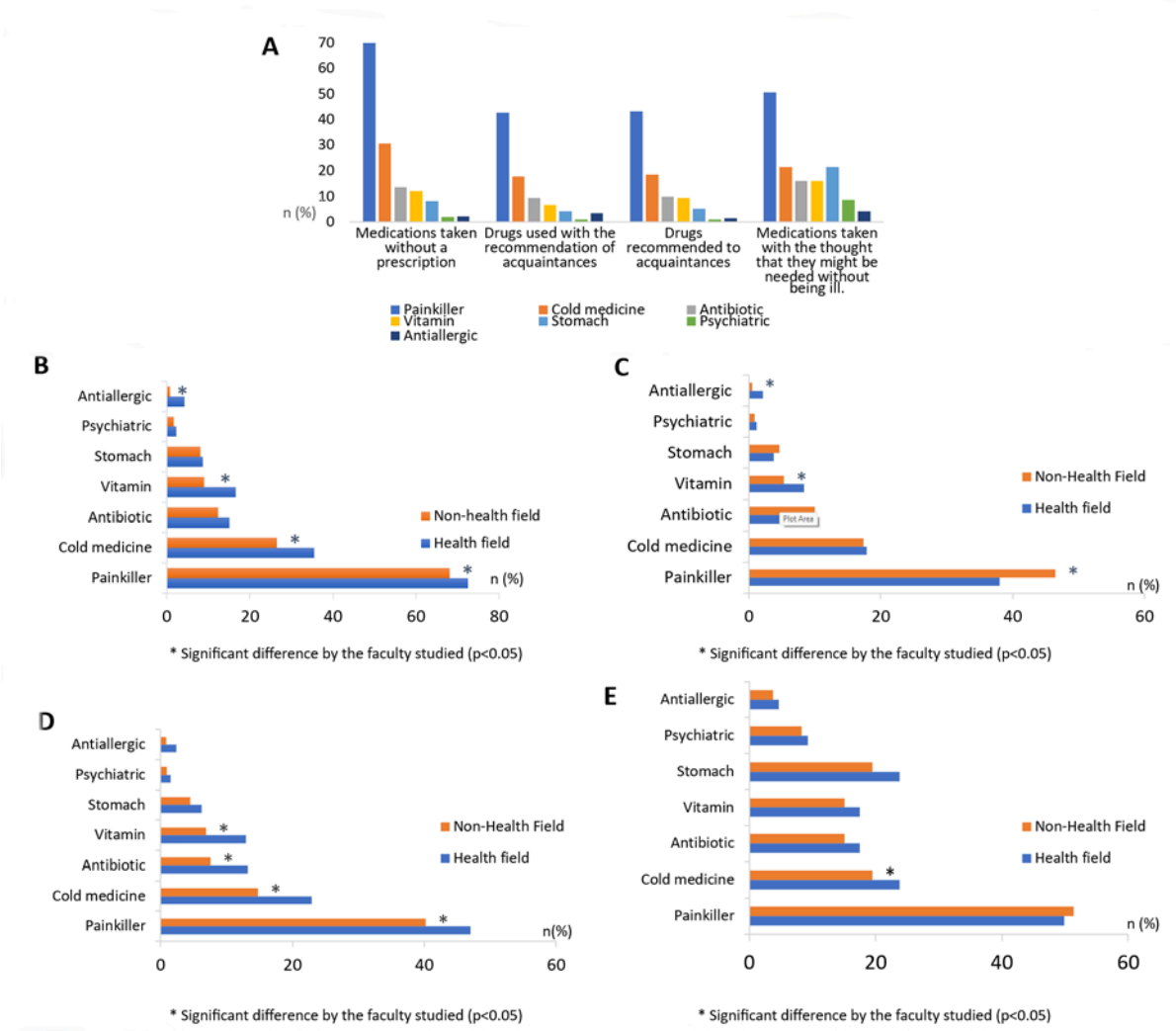

Figure 1. A. Students' behaviors in supplying drug. B. Distribution of non-prescription drug groups according to the type of faculty. C. Distribution of drug groups taken based on the recommendation of acquaintance according to the type of faculty. D. Distribution of drug groups recommended to acquaintance according to the type of faculty. E. Distribution of drug groups prescribed/purchased with the thought that they may be needed without being ill according to the type of faculty. Multiple responses have been given to all questions related to drug groups.

The responses of students regarding the occurrence of side effects, the lack of benefit from the drug, storage conditions of drugs and the status of unused drugs are presented in Table 5. Students most frequently reported consulting a doctor (41.3%) when they experienced any side effects from the drugs they used and they most commonly stopped using the drug (41%) when they did not benefit from it. Students most frequently stored drugs at room temperature (62%) and in the refrigerator (33%), and least frequently according to the temperature conditions specified in the usage instructions/package (4.9%). Of the participants, 64.2% disposed of expired unused drugs, 25.9% left them at home, 6.8% gave them to a hospital/health center/pharmacy and 3.1% gave them to someone in need. Non-health field students (45.9%) reported stopping the drug when they did not benefit from it at a higher rate than health field students (34.9%) ($p<0.05$). Health field students (%30.9) more frequently reported leaving unused drugs at home compared to non-health field students (%21.9) ($p<0.05$)

The students' use of alternative products/treatments and drug/products outside of drug to enhance exam performance is presented in Table 6. The frequency of using drug/products outside of drug to enhance exam performance was 20.2% overall, 21.2% among health field students and 19.4% among non-health field students, with no significant difference ($p>0.05$). Alternative product/treatment usage was 52.1% overall, 54.4% among health field students and 50.3% among non-health field students, also showing no significant relationship with faculty type ($p > 0.05$). The drug/products outside of drug used, in order of frequency, were methylphenidate (5.1%), multivitamins (5%), B vitamin complexes (4.4%), caffeine-containing energy drinks (2.7%), modafinil (1.6%), propranolol (1.0%), passiflora (0.7%), coenzyme Q10 (0.7%), and ginkgo biloba (0.3%). Alternative products/treatments included nutritional supplements (33.5%), herbal products (20.0%), cupping therapy (1.8%), acupuncture (1.6%), reflexology (1.5%), neural therapy (1.0%), mesotherapy (0.7%), and

hypnosis (0.2%). The types of alternative products/treatments and drug/products outside of drug differed significantly between health field and non-health field students ($p < 0.05$). Methylphenidate, multivitamins and energy drinks were more frequently used by health field students, while nutritional supplements and herbal treatments were more frequently used by non-health field students ($p<0.05$) (Figure 2).

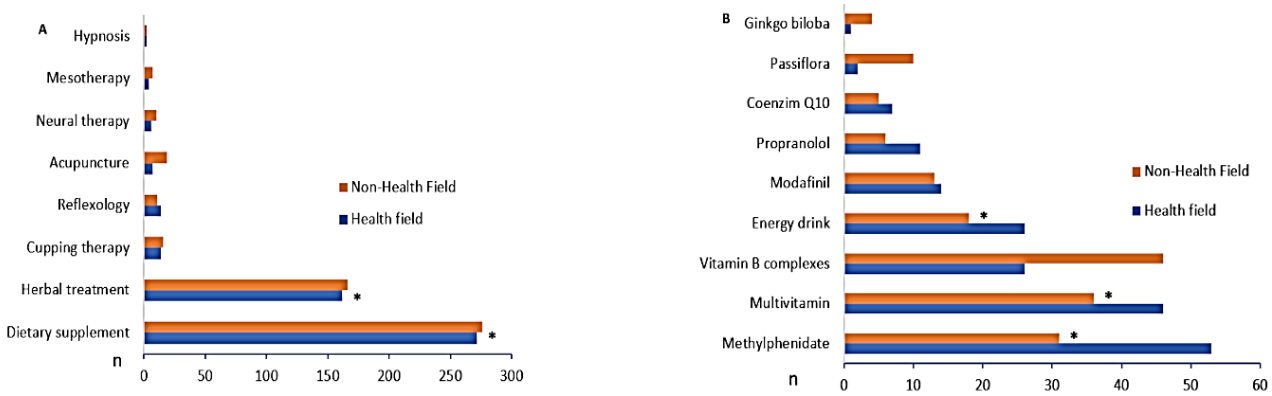

Figure 2. A. Comparison of alternative products/treatment types used by students between health and non-health students. B. Comparison of drugs/products used to increase exam success during the exam period between health and non-health students. In the questions regarding drugs/non-drug products and alternative products/treatment types, multiple responses were allowed.
*= p<0.05.

Table 5. Responses regarding the storage locations of drugs at home, the status of unused drugs and the situation of not benefiting from the drug.

	Total (1638) n (%)	**Health field (722) n (%)**	**Non-health field (916) n (%)**	**P value**
Responses regarding the situation of the drug causing side effects.				
I stop taking the drug	583 (35.6)	244 (33.8)	339 (37)	
I apply to the doctor	677 (41.3)	304 (42.1)	373 (40.7)	
I continue to use (the drug)	27 (1.7)	15 (2.1)	12 (1.3)	χ^2=3.032, p=0. 0552
I stop taking the drug and apply to the doctor	349 (21.3)	158 (21.9)	191 (20.9)	
Other	2 (0.1)	1 (0.1)	1 (0.1)	
Responses regarding the situation of not benefiting from the drug				
I stop taking the drug	672 (41)	252 (34.9)	420 (45.8)	
I apply to the doctor	577 (35.2)	277 (38.4)	300 (32.8)	χ^2=21.291, **p=0. 001**
I continue to use drug	106 (6.5)	52 (7.2)	54 (5.9)	
I stop taking the drug and apply to the doctor	282 (17.2)	140 (19.4)	142 (15.5)	
Other	1 (0.1)	1 (0.1)	0 (0.0)	
Storage locations of drugs at home				
Room temperature	1016 (62)	454 (62.9)	562 (61.4)	
In the refrigerator	541 (33)	231 (32)	310 (33.8)	χ^2=0.654. p=0. 721
According to the temperature specified in the instructions/packaging	81 (4.9)	37 (5.2)	44 (4.8)	
Responses regarding the status of unused drugs				
I throw it away if it has expired	1052 (64.2)	432 (59.8)	620 (67.7)	
It stays at home	424 (25.9)	223 (30.9)	201 (21.9)	χ^2=22.377, **p=0. 001**
I give it to the hospital/health clinic/pharmacy	111 (6.8)	39 (5.4)	72 (7.9)	
I give it to someone in need	51 (3.1)	28 (3.9)	23 (2.5)	

Table 6. Participants' use of drug/product outside of drug to enhance exam performance during exam periods and alternative products/treatments.

	Total (1638) n (%)	**Health field (722) n (%)**	**Non-health field (916) n (%)**	**P value**
Use of drug/product outside of drug to enhance exam performance during exam periods				
Yes	331 (20.2)	153 (21.2)	178 (19.4)	
No	1307 (79.8)	569 (78.8)	738 (80.6)	χ2=0.775, p=0.379
Use of alternative products/treatments				
Yes	854 (52.1)	393 (54.4)	461 (50.3)	
No	784 (47.9)	329(45.6)	455 (49.7)	χ2=2.726, p=0.099

Table 7 outlines the rational drug use behaviors of medical and non-medical health field students. Medical students reported significantly higher rates of using non-prescription drugs including analgesics, cold drugs, vitamins, stomach drugs and antihistamines compared to non-medical health field students ($p < 0.05$). However, the use of non-prescription antibiotics for flu and cold symptoms was significantly lower among medical students ($p < 0.05$). There was no significant difference between the two groups in the use of drug/products outside of drug to enhance exam performance ($p > 0.05$), although medical students reported using modafinil more frequently than non-medical health field students during exam periods ($p < 0.05$) (Table 7).

Table 8 compares certain behaviors related to rational drug use among students based on their sociodemographic characteristics. Behaviors such as getting a prescription/purchasing drug without being sick, choosing the cheaper option among drugs with the same effect, reading drug instructions and using drug/products outside of drug to enhance exam performance showed significant differences according to gender ($p<0.05$). Women more frequently get prescriptions or purchase drugs without being sick and read drug instructions, while men more often choose cheaper drugs with the same effect and use non-prescription drug/products outside of drug to enhance exam success ($p<0.05$). Individuals aged 22 and older obtain medicines without a prescription and use drug/products outside of drug for exam success more frequently than those aged 21 and younger ($p<0.05$). Economic status also showed significant differences: students with good economic status more often obtained non-prescription drugs and used drug/products outside of drug during exam periods, while those with poor economic status faced more difficulties in obtaining drugs ($p<0.05$). Participants without health insurance more frequently used non-prescription antibiotics for flu/cold and had more difficulties obtaining drugs compared to those with insurance ($p<0.05$). Those with chronic diseases showed significantly higher usage of alternative products/treatments than those without such conditions ($p<0.05$) (Table 8).

Table 7. Comparison of certain behaviors related to rational drug use between medical students and students from non-medical health fields.

	Medical students (n=357), n %	**Non-medical health field students (n=365), n %**	**P value**
Those who take medicine without a prescription	276 (77.3)	233 (63.8)	χ^2=15.757 **p=0.001**
Medicines taken without a prescription**			
Pain killers	223 (62.5)	192 (52.6)	χ^2=7.182 p=**0.007**
Antibiotic	22 (6.2)	18 (4.9)	χ^2=0.523 p=0.470
Cold drug	85 (23.8)	27 (7.4)	χ^2=37.093 p=**0.001**
Vitamin	68 (19.0)	4 (1.1)	χ^2=64.784 p=**0.001**
Stomach drug	24 (6.7)	3 (0.8)	χ^2=17.457 p=**0.001**
Psychiatric drug	7 (2.0)	3 (0.8)	χ^2=1.714 p=0.190
Allergy drug	25 (7.0)	13 (3.6)	χ^2=4.286 p=**0.038**
Those who prescribed/purchase medicine without being ill	230 (64.4)	225 (61.6)	χ^2=0.599 p=0.439
Those who prefer cheaper alternatives with the same effect	204 (57.1)	180 (49.3)	χ^2=4.441 p=0.097
Those who had problems obtaining prescribed drug	99 (27.7)	122 (33.4)	χ^2=2.754 p=**0.035**
Those who read the instructions before using the drug	338 (94.7)	349 (95.6)	χ^2=0.345 p=0.557
Those who use non-prescription antibiotics for cold/flu	118 (33.1)	166 (45.5)	χ^2=11.678 p=**0.001**
Those who use alternative products/treatments	203 (56.9)	189 (51.8)	χ^2=1.878 p=0.171
Those who use medicine/products to enhance exam performance	82 (23.0)	71 (19.5)	χ^2=1.337 p=0.248
Medicines/products used to enhance exam performance**			
Methylphenidate	31 (8.7)	22 (6.0)	χ^2=1.872 p=0.171
Multivitamins	31 (8.7)	15 (4.1)	χ^2=6.329 p=0.012
Vitamin B complex	17 (4.8)	9 (2.5)	χ^2=2.741 p=0.098
Energy drink	11 (3.1)	15 (4.1)	χ^2=0.550 p=0.458
Modafinil	12 (3.4)	2 (0.5)	χ^2=7.513 p=**0.006**
Propranolol	7 (2.0)	4 (1.1)	χ^2=0.900 p=0.343
Passiflora	0 (0.0)	2 (0.5)	χ^2=1.962 p=0.161
Coenzyme Q10	4 (1.1)	3 (0.8)	χ^2=0.168 p=0.722*
Ginkgo biloba	1 (0.3)	0 (0.0)	χ^2=0.168 p=0.494*

** Fischer exact test has been used.*

***More than one answer was given.*

Table 8. Comparison of Students' Behaviors Towards Rational Drug Use According to Their Sociodemographic Characteristics.

Demographic characteristics	Those who take drug without a prescription	Those who purchase drug without being ill	Those who prefer cheaper drug	Those who had problems obtaining drug	Those who read the instructions	Those who use non-prescription antibiotics for cold/flu	Those who use alternative products	Those who use drug/product to enhance exam performance
Gender								
Female	597 (64.2)	630 (67.7)	382 (40.1)	299 (32.1)	889 (95.6)	407 (43.8)	494 (52.8)	172 (18.5)
Male	454 (64.1)	416 (58.8)	358 (47.8)	268 (37.8)	649 (91.7)	320 (45.2)	363 (51.3)	159 (22.5)
Test	χ^2=0.001 p=0.977	χ^2=14.06 **p=0.001**	χ^2=7.274 **p=0.026**	χ^2=5.827 p=0.054	χ^2=10.802 **p=0.001**	χ^2=0.335 p=0.563	χ^2=0.374 p=0.541	χ^2=3.915 **p=0.048**
Age								
≤21	573 (61.3)	600 (64.2)	392 (42.0)	309 (33.1)	875 (93.7)	430 (46.0)	477 (51.1)	169 (18.1)
≥22	478 (67.9)	446 (63.4)	328 (46.6)	258 (36.6)	663 (94.2)	297 (42.2)	377 (53.6)	162 (23.0)
Test	χ^2=7.487 **p=0.006**	χ^2=1.37 p=0.711	χ^2=3.479 p=0.062	χ^2=2.253 p=0.133	χ^2=0.170 p=0.680	χ^2=2.412 p=0.120	χ^2=0.990 p=0.320	χ^2=6.019 **p=0.014**
Economic Status								
Poor	316 (56.2)	349 (62.1)	240 (42.7)	221 (39.3)	525 (93.4)	284 (50.5)	282 (50.2)	103 (18.3)
Moderate	214 (64.5)	223 (67.2)	146 (44.0)	130 (39.2)	319 (96.1)	143 (43.1)	178 (53.6)	55 (16.6)
Good	521 (70.0)	474 (63.7)	334 (44.9)	216 (29.0)	694 (93.3)	300 (40.3)	394 (53.0)	173 (23.3)
Test	χ^2=26.529 **p=0.001**	χ^2=2.337 p=0.311	χ^2=0.622 p=0.733	χ^2=18.77 **p=0.001**	χ^2=3.492 p=0.174	χ^2=13.814 p=0.001	χ^2=1.355 p=0.508	χ^2=8.241 **p=0.016**
Health Insurance								
Yes	914 (64.1)	912 (64.0)	617 (43.3)	462 (32.4)	1347 (94.5)	617 (43.3)	743 (52.1)	285 (20.0)
No	137 (64.6)	134 (63.2)	103 (48.6)	105 (49.5)	191 (90.1)	110 (44.1)	111 (52.4)	46 (21.7)
Test	χ^2=0.022 p=0.881	χ^2=0.045 p=0.833	χ^2=2.118 p=0.146	χ^2=23.92 **p=0.001**	χ^2=6.136 p=**0.013**	χ^2=5.554 **p=0.018**	χ^2=1.355 p=0.508	χ^2=0.336 p=0.562
Chronic Illness								
Yes	92 (70.2)	83 (63.4)	59 (45.0)	55 (42.0)	125 (95.4)	55 (42.0)	80 (68.3)	35 (26.7)
No	959 (63.3)	963 (63.9)	661 (43.9)	512 (34.0)	1413 (93.8)	672 (44.6)	774 (51.4)	296 (19.6)
Test	χ^2=2.278 p=0.131	χ^2=0.015 p=0.901	χ^2=0.068 p=0.795	χ^2=3.417 p=0.065	χ^2=0.578 p=0.447	χ^2=0.332 p=0.565	χ^2=4.552 **p=0.033**	χ^2=3.742 p=0.053
Smoking								
Yes	242 (64.4)	256 (68.1)	170 (45.2)	138 (36.7)	338 (89.9)	167 (44.4)	185 (53.0)	104 (27.7)
No	809 (64.1)	790 (62.6)	550 (43.6)	429 (34.0)	1200 (95.1)	560 (44.4)	669 (53.0)	227 (18.0)
Test	χ^2=0.008 p=0.927	χ^2=3.778 p=0.052	χ^2=0.313 p=0.576	χ^2=0.939 p=0.333	χ^2=13.631 **p=0.001**	χ^2=0.001 p=0.989	χ^2=1.684 p=0.194	χ^2=16.808 **p=0.001**
Alcohol use								
Yes	269 (73.3)	249 (67.8)	196 (46.0)	137 (37.3)	338 (92.1)	172 (46.9)	189 (51.5)	110 (30.0)
No	782 (61.5)	797 (62.7)	551 (43.4)	430 (33.8)	1200 (94.4)	555 (43.7)	665 (52.3)	221 (17.4)
Test	χ^2=17.159 **p=0.001**	χ^2=3,261 p=0.071	χ^2=0.841 p=0.359	χ^2=1.540 p=0.215	χ^2=2.664 p=0.103	χ^2=1.181 p=0.576	χ^2=0.077 p=0.277	χ^2=27.972 **p=0.001**

Discussion

Significant progress in rational drug use has been achieved in our country through awareness-raising activities conducted under the National Rational Drug Use Action Plan. Universities, health professionals and the pharmaceutical industry have also contributed to the efforts of health authorities in raising awareness of rational drug use in society. In our study, a questionnaire consisting of questions related to drug use is applied to 1,638 students studying in health field and non-health field faculties at Gaziantep University, aiming to determine the contributions of ongoing efforts to enhance awareness regarding rational drug use in our country and to identify and compare the rational drug use behaviors of students in health field and non-health field education.

In this research, the rate of non-prescription drug use among university students is 64.2%. In studies involving university students studying in health field and non-health field in our country, the rate of non-prescription drug use is reported as 23.2% in Erzincan and 35.4% in Istanbul (11, 12). In these studies, the frequency of non-prescription drug use has been determined to be lower compared to our study. This difference may be due to the varying regions where the research was conducted. Additionally, since the specified studies inquire about non-prescription drug use over a certain period, specifically in the last month, this one-month period may not allow for the evaluation of non-prescription drug use as a habit. The prevalence of self-medication among university students worldwide is reported to be 70.1% (13). This finding is higher than the frequency rate of non-prescription drug use obtained in our study. The behav-

ior of non-prescription drug use may vary depending on socioeconomic characteristics, the type of faculty studied, the drug legislation in the countries where the studies are conducted or the effectiveness of the authorities responsible for regulating the pharmaceutical market. The frequency of non-prescription drug use among university students determined in our study is similar to the results of other studies in the literature (14-16). Moreover, in a study conducted at the national level in our country in 2016, it was shown that the frequency of non-prescription drug use in the general population (80.48%) was higher than the rate we determined (17). The education that university students receive may contribute to the development of rational drug use behaviors.

In our study, participants were categorized into two age groups: 21 years and under and 22 years and over. The frequency of non-prescription drug use was significantly higher among those aged 22 years and over compared to those 21 years and under ($p<0.05$). In the study conducted by Osemene et al.(18), it has been determined that the frequency of self-medication among students shows a significant difference according to age, consistent with the findings we obtained. However, in some studies evaluating university students, the frequency of non-prescription drug use has not been associated with age (19, 20).

The frequency of non-prescription drug use in our study was higher among health field students (70.5%) compared to non-health field students (59.2%) ($p < 0.05$). Additionally, medical students (77.3%) used non-prescription drugs more frequently than non-medical health field students (63.8%) ($p < 0.05$). Similar findings were reported by Sharma et al. (21) and Klemenc-Ketis et al.(22) who found a higher frequency of self-medication among students in the health field. In contrast, Rahimisadegh et al. (23) found no significant difference between medical and non-medical students while Sawalha et al. (24) reported that self-medication was more common among students outside the health field. The higher frequency of non-prescription drug use among students in health field faculties can be attributed to their access to more information about diseases and drugs in their curriculum, leading to greater self-confidence.

In our study, analgesics were the most frequently used non-prescription drugs (51.7%), which aligns with previous research (25-27). Additionally, the Drug Surveillance Report-6 published by the Turkish Medicines and Medical Devices Agency (TITCK) in 2018 stated that, consistent with our findings, analgesics were the most frequently sold group of non-prescription drugs, accounting for 37.55% (28). This may be due to analgesics affordability, ease of access and perception of having fewer side effects. After analgesics, the most commonly used non-prescription drug categories were cold medicines (12.5%), vitamins (6.4%) and antibiotics (5.4%). In studies examining rational drug use among university students in our country, it has been reported that the frequency of non-prescription antibiotic use has gradually decreased over the years (11, 29, 30). This situation indicates that the prohibition of non-prescription antibiotic sales in pharmacies and the efforts to increase rational antibiotic use in the community, conducted within the framework of the Rational Drug Use Action Plan 2014-2017 by the Ministry of Health, have been effective (31).

We also found that non-prescription drug categories varied by field of study, with health field students more frequently obtaining analgesics, cold medicines, vitamins and stomach drugs without a prescription compared to non-health field students ($p<0.05$). However, there was no significant difference between the groups regarding the frequency of use of psychiatric and antiallergic drugs without a prescription. This finding we obtained is consistent with other studies in the literature which reported that the groups of medicines taken without prescription differed between students studying in health and non-health fields. It was reported that health field students used analgesics, antibiotics, antiallergic drugs, herbal products and laxatives more frequently and cold medicines and decongestants less frequently in self-medication compared to non-health field students (24, 32, 33).

In our study, the use of drugs based on family/friend/acquaintance advice has been associated with the type of faculty studied and it has been determined that the use of drugs based on acquaintance advice is higher among non-health field students compared to health field students ($p<0.05$). Alshogran et al. (33) similarly found that non-medical students were more likely to follow friends' recommendations for self-medication. While health field students were less likely to use drugs recommended by acquaintances, they were more likely to recommend drugs to others ($p<0.05$). This situation may stem from the thought that health field students have a sufficient level of medical knowledge due to their education.

In our study, the rate of non-prescription antibiotic use among students for flu or cold is 44.4%, observed more frequently among non-health field students (48.4%) than health field students (39.3%) ($p<0.05$). Additionally, non-medical health field students (45.5%) use non-prescription antibiotics for flu/cold at a higher rate than medical students (33.1%) ($p<0.05$). The rate of quitting prescribed antibiotics before finishing them is 81%, more frequent among non-health field students (84.7%) than health field students (76.2%) ($p<0.05$). The inappropriate prescribing of antibiotics, their use in inappropriate dosages, their use in the treatment of non-bacterial infections, self-medication and their excessive use lead to an increase in antibiotic resistance, which is defined as a global health problem and the spread of antibiotic resistance, limiting the effectiveness of treatments for infectious diseases (34-36). Literature examination reveals that, parallel to our findings, Shahpawee et al. (37) reported that 41% of students deemed antibiotic use appropriate for treating viral diseases like flu and colds, while Şahin et al. (32) found that non-health field students used non-prescription antibiotics for flu and cold more fre-

quently than health field students. Identifying antibiotic usage behaviors among university students can serve as an effective means to encourage rational antibiotic practices and mitigate antibiotic resistance. In our study, the frequency of non-prescription antibiotic use for flu and cold among university students is high, indicating a need for education and initiatives to raise awareness about rational antibiotic use. The high rate of discontinuation of antibiotic treatment in our study indicates that compliance with treatment, especially antibiotic treatment, is not achieved in university students.

In our study, we found that 34.6% of the students had problems in obtaining prescribed drug, those with poor (39.3) and moderate (39.2) economic status had significantly more problems in obtaining drug than those with good (29) economic status and those without health insurance (49.5) had significantly more problems in obtaining drug than those with (32.4) ($p<0.05$). Özyiğit et al. (29) reported in their 2015 study that 15% of students experienced problems in obtaining drugs. With the Health Transformation Program implemented in 2003 in our country, different health insurances were unified under one umbrella and their coverage was expanded, improving access to healthcare services. A positive relationship has been identified between having health insurance and the use of prescribed drugs, while individuals with poor economic conditions are more likely to use drugs without a prescription instead of with one (17).The finding from our study that 34.6% of students, particularly those without health insurance and those with poor economic status, experience problems in obtaining drugs may increase irrational drug use behaviors, such as non-prescription drug use and self-medication with antibiotics.

We determined that the behaviour of preferring the cheaper one among the drugs with the same effects was observed in 44% of university students and was significantly associated with gender and the type of faculty ($p<0.05$), whereas it was not associated with the presence of health insurance ($p<0.05$). We found that males preferred cheaper alternatives more frequently than females (47.8% vs. 40.1%, respectively) and students in the health field made this choice more often than those in the non-health field (53.2% vs. 36.7%, respectively) ($p<0.05$). In a study by Kukula (38) involving 640 medical faculty students, the rate of preferring cheaper drugs among those with the same effects was reported to be 31.88%. Generic drug use is a practice that can reduce the cost of treatment. As shown in our study, while it is pleasing that health field students prefer cheaper alternatives from drugs with the same effects, 56% of all students not choosing these options indicates a need for further research to increase awareness regarding generic drug practices.

In our study, the rate of students reading medication instructions was 93.9%. Women (95.6%) read instructions more than men (91.7%) ($p<0.05$). Consistent with our findings, Kurt et al. (39) reported that 56.5% of university students read instructions, while 27.7% did so sometimes. Moreover Taş (40) found that 84.2% of students read the medication leaflet. Alshogran et al. (33) associated the reading of instructions with the type of faculty studied, but our study did not find such a relationship.

The frequency of alternative product use in our study was 52.1%, with nutritional supplements (33.5%) and herbal products (20.0%) being the most commonly used. Consistent with our study, the literature indicates that the use of alternative products/treatments is prevalent among university students, with nutritional supplements and herbal products being among the most commonly utilized types of alternative treatments/products (41). These products are marketed as harmless through labels such as natural and herbal and are readily available for purchase online. However, there are numerous case reports of severe side effects associated with these products (42). Therefore, it is important that students are specifically informed about the use of alternative product/ treatments in rational drug use education programs.

We found that 20.2% of the students used drugs/product outside of drug to enhance exam performance during exam periods, with the most commonly used being methylphenidate (5.1%), multivitamins (5%), B vitamin complexes (4.4%), high-caffeine energy drinks (2.7%), and modafinil (1.6%). While the use of such products did not vary by field of study, health field students used methylphenidate, multivitamins and energy drinks more frequently than non-health field students and medical students used modafinil more often than other health field students ($p<0.05$). A study in France with medical students and physicians found a 33% prevalence of psychostimulant use to enhance academic performance, including vitamin C, caffeine-containing supplements, prescription, and illicit psychostimulants (43). In a study with 1,056 students in our country, only prescription psychostimulants, such as methylphenidate and modafinil, were assessed, with a reported prevalence of 8.4% (44) The frequency of using drugs/product to enhance academic performance may vary based on participant profiles, evaluated substances and the country of the study. Although central nervous system stimulant drugs are safe and effective within their indications, the undesirable effects associated with their non-medical use are not known. Therefore, it is necessary to increase efforts to detect the use of drugs without proper knowledge of their safety, incorrect duration of use and use without indication as well as to prevent such irrational drug use behaviors. The data from our study showing that the frequency of using drug/products outside of drug to enhance exam performance was significantly higher in males than in females ($p<0.05$) aligns with the literature (45). This higher frequency in males may be due to their greater tendency for risk-taking. We also found that students who use alcohol and tobacco were more likely to use drugs to enhance exam performance ($p<0.05$). This supports Şekerci et al. (44) which indicated that psychostimulant use was more prevalent among university students who consume alcohol and tobacco.

Compared to previous studies evaluating rational drug use among university students in Turkey, this study has the characteristic of being the study with the largest sample size to our knowledge. Previous studies on rational drug use in Turkey have mainly focused on students studying in the field of health. In our study, data on the rational drug use behaviours of students studying both in and out of the health field were presented. The main limitation of our study is that it was conducted solely on the selected sample.

In conclusion, our study found that irrational drug use behaviors were prevalent among university students. It has been demonstrated that students in the health field exhibit more rational behaviors, particularly regarding antibiotic use, compared to students in non-health fields. To increase awareness of rational drug use, it is essential to provide trainings on rational drug use in cooperation with health authorities, universities, healthcare professionals and the media.

Ethical Approval: *Ethical approval of the study was obtained with the decision of Gaziantep University Clinical Research Ethics Committee dated 18.01.2018 and numbered 38.*

Author Contributions:
Concept: Z.D., B.A., F.S.S., B.A.
Literature Review: Z.D., B.A., F.S.S., B.A.
Design : Z.D., B.A., F.S.S., B.A.
Data acquisition: Z.D., B.A., F.S.S., B.A.
Analysis and interpretation: Z.D., B.A., F.S.S., B.A.
Writing manuscript: Z.D., B.A., F.S.S., B.A.
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Research Article / Araştırma Makalesi

The Effect of the Covid 19 Pandemic on the Antibiotic Resistance Levels of *Staphylococcus aureus* Strains

Covid 19 Pandemisinin *Staphylococcus aureus* Suşlarının Antibiyotik Direnç Düzeylerine Etkisi

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Abstract

Background: *Staphylococcus aureus* is a significant human pathogen that can cause a diverse range of diseases, from mild skin and soft tissue infections sepsis. The aim of this study was to retrospectively compare the antibiotic resistance status of *S. aureus* strains and the change in the prevalence of methicillin-resistant *S. aureus* (MRSA) before, during and after the Coronavirus Disease 2019 (COVID-19) pandemic in our hospital.
Materials and Methods: The present study was designed to encompass three cross-sectional phases before COVID-19 pandemic (1 January 2018 to 31 December 2019, two years), the pandemic period (11 March 2020 to 10 March 2022, two years), and the post-pandemic phase (5 May 2023 to 31 December 2023, seven months). In the study, the incidence and antibiotic resistance status of *S. aureus* strains cultured and identified from various clinical samples were retrospectively analyzed using data from the hospital laboratory information system.
Results: As a result of the study, when the antibiotic resistance status of *S. aureus* strains was examined, it was determined that gentamicin resistance had a resistance rate of 4% in the pre-pandemic period and 6.9% in the pandemic period. A downward trend was observed in MRSA rates during the pandemic. A higher MRSA prevalence was observed before the pandemic compared to the following two periods (p=0.093). In addition, a higher MRSA prevalence was observed in the intensive care unit in the pre-pandemic period compared to other wards (p=0.075).
Conclusions: The decrease in MRSA prevalence during the pandemic period may be due to a number of factors, such as the implementation of quarantine measures, improved hand hygiene practices and meticulous attention to contact precautions. The increase in gentamicin resistance rates observed during the pandemic period may be due to excessive intensive use of antibiotics.

Keywords: MRSA, Antibiotic resistance, COVID-19 Pandemic, *Staphylococcus aureus*

Öz

Amaç: *Staphylococcus aureus*, hafif seyirli deri ve yumuşak doku enfeksiyonlarından sepsise kadar çok çeşitli hastalıklara neden olabilen önemli bir insan patojenidir. Bu çalışmada, hastanemizde Koronavirüs Hastalığı 2019 (COVID-19) pandemisi öncesinde, sırasında ve sonrasında *S. aureus* suşlarının antibiyotik direnç durumu ile metisilin dirençli *S. aureus* (MRSA) prevalansındaki değişimin retrospektif olarak karşılaştırılması amaçlanmıştır.
Materyal ve Metod: Bu çalışma, COVID-19 pandemisi öncesi (1 Ocak 2018- 31 Aralık 2019, 2 yıl), pandemi dönemi (11 Mart 2020- 10 Mart 2022, 2 yıl) ve pandemi sonrası (5 Mayıs 2023- 31 Aralık 2023, 7 ay) olmak üzere üç kesitsel evreyi kapsayacak şekilde tasarlanmıştır. Çeşitli klinik örneklerden kültürlenen ve tanımlanan *S. aureus* suşlarının insidansı ve antibiyotik direnç durumu, hastane laboratuvar bilgi sistemindeki veriler kullanılarak retrospektif olarak analiz edilmiştir.
Bulgular: Çalışma sonucu olarak *S. aureus* suşlarının antibiyotik direnç durumu incelendiğinde gentamisin direncinin, pandemi öncesi dönemde %4, pandemi döneminde ise %6.9 direnç oranına sahip olduğu tespit edilmiştir. Pandemi süresince MRSA oranlarında bir düşüş eğilimi görülmüştür. Pandemi öncesinde, sonraki iki döneme kıyasla daha yüksek bir MRSA prevalansı gözlenmiştir (p=0,093). Ek olarak pandemi öncesi dönemde yoğun bakım ünitesinde diğer servislere kıyasla daha yüksek bir MRSA prevalansı gözlenmiştir (p=0,075).
Sonuç: Pandemi döneminde MRSA prevalansındaki azalmanın, karantina önlemlerinin uygulanması, gelişmiş el hijyeni uygulamaları ve temas önlemlerine titizlik gösterilmesi gibi bir dizi faktörden kaynaklanabilir. Pandemi döneminde gentamisin direnç oranlarında gözlenen artış, aşırı yoğun antibiyotik kullanımına bağlı olabilir.

Anahtar Kelimeler: MRSA, Antibiyotik direnci, COVID-19 Pandemisi, *Staphylococcus aureus*

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Introduction

Staphylococcus aureus is an important human pathogen that can cause a wide spectrum of diseases ranging from mild skin and soft tissue infections to sepsis. The emergence of methicillin-resistant strains has led to a higher risk of morbidity and mortality as well as limited treatment options (1). Methicillin resistance is caused by the acquisition of mecA/mecC genes located in a mobile genetic element that can be integrated into chromosome (2). In methicillin-resistant *S. aureus* (MRSA) isolates, penicillin-binding proteins (PBPs) 2a and 2c, encoded by these genes, cause the bacteria to show a lower affinity for beta-lactam antibiotics (3-4).

In an institution providing healthcare services, the prevalence of Hospital acquired MRSA (HA-MRSA) is accepted as an indicator of the general infection rate. It is stated that one of the main transmission sources of MRSA in hospitals is the hands of healthcare workers (1).

Antimicrobial resistance (AMR) was among the biggest public health problems in the twenty-first century before the COVID-19 outbreak. During the pandemic, increased hand hygiene, decreased international travel and elective hospital procedures were expected to reduce the development and spread of antimicrobial resistance in the short term, but the disruption of standard healthcare services resulted in more widespread and uncontrolled antibiotic use (5). The pandemic process has further increased the burden of infection control and prevention strategies used in the management of AMR. Due to the contagious nature of the pathogen, many different measures have been taken to prevent its spread, which have not been seen before (6). These measures, which were applied only in high-risk units before the pandemic period, ensured that the pandemic was controlled at various levels, while other areas where patient care was provided and control programmes for other hospital-acquired infections were damaged (7). This situation led to a change in priority and disruption of infection control measures during the pandemic, and it was determined that inappropriate use of antimicrobial agents before and during the pandemic contributed negatively to the formation and spread of resistance (8-10).

Continuous monitoring of microorganisms and regular updating antibiotic resistance patterns are required to maintain infection control practices in hospitals. During the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) epidemic, it was reported that MRSA rates increased in healthcare settings (11). Considering this information, this study was designed as a single-centre and retrospective study to obtain information about the antibiotic resistance status of *S. aureus* and MRSA strains isolated before and after the COVID-19 pandemic in our hospital and to make comparisons.

Materials and Methods

Period of the research

The World Health Organization (WHO) declared that the global health emergency announced on 30 January 2020 for the COVID-19 pandemic caused by SARS-CoV-2 ended on 5 May 2023. On the other hand, WHO emphasises that COVID-19 is still a global health threat (12). With the detection of the first COVID-19 case in Turkey on 10 March 2020, the pandemic has shown its effect very rapidly in our country (13). In this study, the results of various clinical specimens in which *S. aureus* strains were found to grow after culture and identification tests in three cross-sectional periods: before the COVID-19 pandemic (1 January 2018-31 December 2019, two years), during the pandemic period (11 March 2020-10 March 2022, two years) and after the declaration of the end of the global health emergency; after the pandemic (5 May 2023-31 December 2023, 7 months) were compiled retrospectively from the hospital laboratory information system as a single center.

Inclusion criteria

In this study, among various clinical samples sent to of Sivas Cumhuriyet University Medical Faculty Application and Research Hospital Microbiology Laboratory, if more than one bacterial agent grew from the same type of sample belonging to a patient, only the antimicrobial susceptibility result of the first bacterial strain was evaluated.

Laboratory

Various clinical samples sent to of Sivas Cumhuriyet University Medical Faculty Application and Research Hospital Microbiology Laboratory for culture procedures were routinely cultured on 5% sheep blood agar and Eosine Methylene Blue (EMB) agar media and incubated in an oven at 35-37°C for 24-48 hours. Sterile body fluids were inoculated into BD BACTEC Peds Plus/F (Becton Dickinson, USA) culture bottles by the manufacturer's recommendations and incubated in BD BACTEC 9120 (Becton Dickinson, USA) blood culture device. Blood agar was passage from the bottles with a positive signal and incubated in an oven at 35-37°C for 24-48 hours. After incubation, the isolated agents were identified by MALDI Biotyper Microflex LT (Bruker Daltonics, Germany) automated system based on matrix-mediated laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) and antimicrobial susceptibility profiles were analyzed by BD Phoenix 100 (Becton Dickinson, USA). Antimicrobial susceptibilities of the strains were evaluated in accordance with the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, v.13.1). The presence of methicillin resistance in *S. aureus* isolates was accepted as Minimum Inhibition Concentration (MIC) value '>4 mg/L' for cefoxitin.

For erythromycin-resistant and clindamycin-susceptible *S. aureus* isolates, the presence of inducible clindamycin resistance was investigated in accordance with EUCAST recommendations (the D phenomenon). In the presence of inducible clindamycin resistance, the isolate was considered resistant except for short-term treatment of less serious skin and soft tissue infections (14).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) v.23.0, (IBM Co., USA) package program was used to evaluate the data obtained from this study. Numerical variables were given as frequency (n) and percentage (%). Antimicrobial susceptibility

test results were categorised as 'susceptible' and 'resistant'. Chi-square (x^2) and Fisher's exact x^2 tests were used to evaluate the antimicrobial resistance data. $p<0.05$ was considered statistically significant.

Results

In the pre-pandemic period, *S. aureus* was grown in 1027 of the clinical samples sent to the hospital Microbiology Laboratory and MRSA was detected in 104 (10.1%) of these samples. During the pandemic period, 582 *S. aureus* were grown and MRSA was detected in 41 of them (7%), while in the post-pandemic period, 135 *S. aureus* were grown and MRSA was detected in 10 of them (7.4%). No statistically significant difference was found between the periods. ($p>0.05$). The rate of MRSA was 10.9% in the intensive care unit (ICU) and 8.1% in other wards ($p>0.05$) (Table 1).

Table 1. Frequency of MRSA in clinical samples before, during and after the COVID-19 pandemic

	Total		MRSA		*p*
	n	%	n	%	
Period					
Pre-Pandemic *	1027	58.9	104	10.1	
Pandemic **	582	33.4	41	7.0	0.093
Post-Pandemic ***	135	7.7	10	7.4	
Hospital unit					
Intensive Care Unit	479	27.5	52	10.9	0.075
Service	1265	72.5	103	8.1	
Sample					
Blood	354	20.3	36	10.2	
Respiratory samples	491	28.2	43	8.8	
Wound site	306	17.5	27	8.8	
Tissue biopsy	117	6.7	9	7.7	
Nasal swab	70	4.0	8	11.4	
BOS	6	0.3	1	16.7	0.898
Joint fluid	37	2.1	1	2.7	
Pleural fluid	10	0.6	1	10.0	
Abscess	62	3.6	4	6.5	
Urine	125	7.2	13	10.4	
Other *(aspiration materials, catheter, peritoneal fluid, ear and other swab)*	166	9.5	12	7.2	
Total	**1744**	**100.0**	**155**	**8.9**	

**1 January 2018- 31 December 2019, **11 March 2020- 10 March 2022, ***5 May 2023- 31 December 2023.*

When the antibiotic resistance rates of the isolated *S. aureus* strains were analyzed, it was found that the resistance rate of gentamicin resistance higher during the pandemic period. It was found that the resistance rate was 4% in the pre-pandemic period and 6.9% in the pandemic period. The difference between these periods was statis-
tically significant ($p=0.006$). No significant difference was detected in terms of resistance to levofloxacin, erythromycin, clindamycin, tetracycline and TMP-SMX antibiotics used before and after the pandemic ($p>0.05$). No resistance to vancomycin, teicoplanin and linezolid antibiotics was detected in the samples (Table 2).

The resistance rates of gentamicin antibiotic, whose resistance rates increased during the pandemic period, were statistically analyzed by comparing the resistance rates in the wards and ICUs, but no significant difference was found ($p>0.05$) (Table 2).

Compared to the wards, resistance rates for gentamicin, erythromycin, clindamycin and tetracycline antibiotics were statistically significantly higher in ICUs (Figure 1).

When MRSA and MSSA isolates were evaluated in terms of resistance to the antibiotics used, a much higher rate of resistance was found in MRSA isolates (Figure 2).

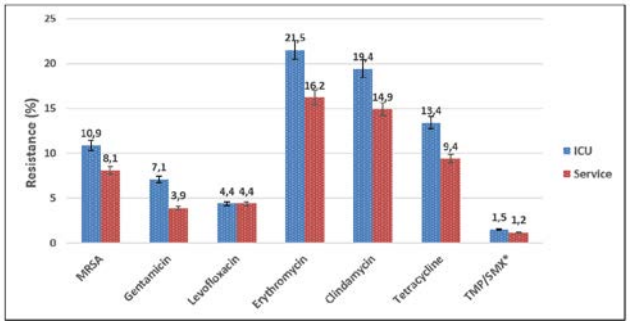

Figure 1. Comparison of resistance rates detected in *S. aureus* isolates from intensive care units (ICU) and other services [%] *Trimethoprim/sulfamethoxazole

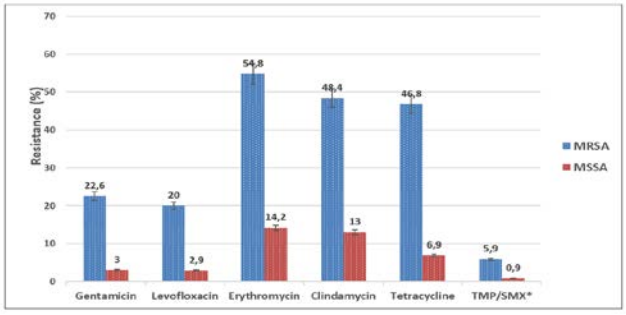

Figure 2. Distribution of resistance rates detected in *S. aureus* isolates according to methicillin susceptibility (%). *Trimethoprim/sulfamethoxazole

Table 2. Resistance rates of *S. aureus* isolates from intensive care units and other wards before, during and after the COVID-19 pandemic [n (%)]

	n	A	B	C	Total	*p*
Gentamicin	**1744**	**41 (4.0)**	**40 (6.9)**	**2 (1.5)**	**83 (4.8)**	**0.006**
ICU	479	15 (6.7)	18 (8.7)	1 (2.2)	34 (7.1)	0.286
Service	1265	26 (3.3)	22 (5.9)	1 (1.1)	49 (3.9)	**0.036**
Levofloxacin	**1744**	**46 (4.5)**	**23 (4.0)**	**8 (5.9)**	**77 (4.4)**	0.596
ICU	479	9 (4.0)	9 (4.3)	3 (6.5)	21 (4.4)	0.747
Service	1265	37 (4.6)	14 (3.7)	5 (5.6)	56 (4.4)	0.678
Erythromycin	**1712**	**174 (17.0)**	**97 (17.6)**	**31 (23.0)**	**302 (17.6)**	0.228
ICU	469	51 (22.8)	39 (19.6)	11 (23.9)	101 (21.5)	0.671
Service	1243	123 (15.3)	58 (16.5)	20 (22.5)	201 (16.2)	0.218
Clindamycin	**1712**	**161 (15.7)**	**90 (15.8)**	**29 (21.5)**	**280 (16.2)**	0.217
ICU	469	49 (21.8)	33 (16.3)	10 (21.7)	92 (19.4)	0.324
Service	1243	112 (14.0)	57 (15.5)	19 (21.3)	188 (14.9)	0.167
Vancomycin	**1744**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	-
ICU	479	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Service	1265	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Teicoplanin	**1744**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	-
ICU	479	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Service	1265	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Linezolid	**1744**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	-
ICU	479	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Service	1265	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Tetracycline	**1740**	**108 (10.6)**	**63 (10.8)**	**11 (8.1)**	**182 (10.5)**	0.649
ICU	478	36 (16.1)	23 (11.1)	5 (10.9)	64 (13.4)	0.270
Service	1262	72 (9.0)	40 (10.7)	6 (6.7)	118 (9.4)	0.445
TMP/SMX*	**1707**	**10 (1.0)**	**9 (1.5)**	**3 (2.2)**	**22 (1.3)**	0.400
ICU	473	3 (1.4)	3 (1.4)	1 (2.2)	7 (1.5)	0.918
Service	1234	7 (0.9)	6 (1.6)	2 (2.2)	15 (1.2)	0.393

*A: Before the pandemic, B: During the pandemic, C: After the pandemic, *Trimethoprim/sulfamethoxazole, ICU: Intensive Care Unit*

Discussion

Since *S. aureus* strains cause both nosocomial and community-acquired infections, antibiotic resistance data of the bacteria are of critical importance for public health. In particular, the presence and prevalence of MRSA strains with methicillin resistance necessitates the implementation of a special antimicrobial resistance management program against the bacteria (3).

It is a known fact that the COVID-19 pandemic has caused an increase in antimicrobial resistance. This is supported by several published reports (15-16). The cause is multifaceted. During the COVID-19 pandemic, prolonged hospital stays in inpatients, intensive use of antibiotics and steroids, and interventional procedures such as mechanical ventilation and catheter use have led to an increase in AMR rates (17).

The COVID-19 pandemic resulted in high rates of morbidity and mortality during the first periods when it was first observed. The presence of co-infection has been reported in a large proportion of patients in this process (16-20). Tabah and Laupland reported in their study that *S. aureus* was the most common pathogen causing super-infection and co-infection during COVID-19 and that MRSA infections increased intensely in this process (21). However, unlike the result of this study, a decreasing trend in MRSA rates during the pandemic period was found in our study. Similarly, some studies in the literature reported a decrease in *S. aureus* and MRSA rates during the pandemic period (20-22-23). This is thought to be related to the intensive control measures taken to prevent infection transmission. Quarantine practices, widespread hand hygiene awareness in the community and social distancing rules played an active role in this decrease (24).

In our study, no significant difference was found in the MRSA strain rates between periods. Similar to our study, Kahraman et al. reported that no significant difference was observed between the pre-pandemic period and the pandemic period in terms of MRSA strain rates. In our study, the increase in gentamicin resistance rates of *S. aureus* strains during the pandemic period is remarkable. In contrast to this result, Kahraman et al. found a significant decrease in gentamicin resistance rates during the pandemic period, but in parallel with our study, they reported that resistance rates did not differ between wards and ICUs (25). Aytaç et al. reported increased methicillin resistance during the pandemic period compared to the pre-pandemic period (26). In their study, Yılmaz et al. found an increased gentamicin resistance during the pandemic period compared to the pre-pandemic period, as in our study, and similarly, they did not report resistance to vancomycin, teicoplanin and linezolid antibiotics (27).

In our study, resistance rates of MRSA strains to most antibiotics did not change significantly during the pandemic. An exception was the significant decrease in cefoxitin resistance observed during the pandemic period. Different

rates of drug resistance of MRSA strains have been reported during the COVID-19 pandemic, possibly due to the diverse sample sources, populations and time periods studied (28-29).

In our study, resistance rates in MRSA isolates were higher than in MSSA isolates for all antibiotics except vancomycin,

teicoplanin and linezolid, as expected. Bahçeci et al. reported higher resistance rates for MRSA compared to MSSA for all antibiotics except vancomycin, teicoplanin, linezolid, daptomycin and tigecycline (30).

In our study, it was determined that the MRSA rates in the pre-pandemic (10.1%), pandemic (7%) and post-pandemic (7.4%) periods were similar, and there was no significant difference between the periods in terms of MRSA isolation. These results are not completely consistent with previous studies. These differences in MRSA rates between centres can be attributed to many factors such as the density and functioning of hospitals during the pandemic period, ICU rates, antibiotic use profiles, and study populations.

Furthermore, the highest MRSA distribution was found in the intensive care unit (10.9%) in this study. This result indicates that equipment-associated infections represent the highest risk for MRSA transmission (31).

Implementation of infection control measures, review of antimicrobial resistance control programs, and appropriate and rational use of broad-spectrum antibiotics are of critical importance to prevent the increasing resistance rates of bacterial infection agents such as MRSA, which are difficult to treat and have high mortality.

More comprehensive and multicenter studies are needed to see the long-term impact of the COVID-19 pandemic on the prevalence of multi-resistant bacteria, including MRSA, and the change in AMR rates. We hope that our study will contribute to the rational use of antibiotics in patients with MRSA isolation.

Limitation

In this study, not knowing whether the patients had COVID-19 or not was considered as a limitation of the study. Secondly, since it was a retrospective study, sufficient information could not be obtained about the patients (such as treatments applied, having chronic diseases). In addition, the fact that it is a single-centre study affects generalisation.

Ethical Approval: *This study was conducted with the approval of Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (dated 2024-01/05 and numbered 18.01.2024).*

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Research Article / Araştırma Makalesi

The Impact of Low Birth Weight and Gestational Age on Premature Retinopathy Outcomes

Düşük Doğum Ağırlığı ve Gebelik Yaşının Prematüre Retinopatisi Üzerindeki Etkisi

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Abstract

Background: The study aimed to investigate the incidence and treatment of retinopathy of prematurity (ROP) in premature infants, focusing on its relationship with gestational age and birth weight.
Materials and Methods: This retrospective study analyzed 1101 infants with a gestational age of 34 weeks or less and/or a birth weight of 1700 grams or less, screened for ROP between 2021 and 2023.
Results: Fifty-five infants required ROP treatment. ROP incidence was higher in lower birth weight and earlier gestational age groups. Among infants weighing 1000 grams or less, 56.1% developed ROP, compared to 43% in the 1001-1250 gram category and 28.1% in the 1251-1700 gram category. For gestational age, 53.2% of infants less than 27 weeks, 26.8% of 27-34 weeks, and 12.7% of over 34 weeks developed ROP.
Conclusions: Premature infants, especially those with very low birth weight and early gestational age, are at high risk for ROP, necessitating comprehensive screening and timely intervention.

Keywords: Retinopathy of prematurity, Birth weight, Gestational age, Laserphotocoagulation

Öz

Amaç: Çalışmanın amacı, prematüre bebeklerde prematüre retinopatisi (ROP) insidansı ve tedavisini araştırmak, özellikle gestasyonel yaş ve doğum ağırlığı ile ilişkisini incelemektir.
Materyal ve Metod: Bu retrospektif çalışma, 2021 ve 2023 yılları arasında ROP için taranan, gestasyon yaşı 34 hafta veya daha az ve/veya doğum ağırlığı 1700 gram veya daha az olan 1101 bebeği analiz etmiştir.
Bulgular: Elli beş bebek ROP tedavisi gerektirmiştir. ROP insidansı, daha düşük doğum ağırlığı ve daha erken gestasyonel yaş gruplarında daha yüksekti. 1000 gram veya daha az ağırlığındaki bebeklerin %56,1'i ROP geliştirirken, 1001-1250 gram kategorisinde %43 ve 1251-1700 gram kategorisinde %28,1 ROP geliştirmiştir. Gestasyonel yaşa göre, 27 haftadan küçük bebeklerin %53,2'si, 27-34 hafta arası bebeklerin %26,8'i ve 34 haftadan büyük bebeklerin %12,7'si ROP geliştirmiştir.
Sonuç: Prematüre bebekler, özellikle çok düşük doğum ağırlığı ve erken gestasyonel yaşa sahip olanlar, ROP için yüksek risk altındadır ve kapsamlı tarama ve zamanında müdahale gereklidir.

Anahtar Kelimeler: Prematüre retinopatisi, Doğum ağırlığı, Gebelik yaşı, Lazer fotokoagülasyon

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Introduction

Retinopathy of prematurity (ROP) is a retinal vascular disease characterized by the development of abnormal proliferation in the retinal vessels of premature infants (1,2). It was first noticed as a fibroblastic mass assembled behind the lens in premature infants. It was described as retrolental fibroplasia, referring to the pattern (3). Nowadays, it is understood that the pattern named retrolental fibroplasia in the past is Stage 5 ROP. In the 1940s and 1950s, the first ROP epidemic was experienced due to uncontrolled oxygen support and in the 1970s the second ROP epidemic was experienced due to the increase in the survival rate of very low gestational age infants as a result of medical and technological developments of the intensive care units (4,5). The frequency of retinopathy of prematurity varies according to the development levels of countries and the characteristics of neonatal intensive care units (6). In recent years, the increase in the incidence of ROP in developing countries draws attention. The most important factor in the pathogenesis of the disease is the continuation of retinal vascularization, which takes place in the relatively hypoxic intrauterine environment in the retina, under retinal hyperoxic conditions in a preterm infant (7). While the retina is avascular until the 16th week of pregnancy, the nasal retina at 36 weeks and the temporal retina at 40 weeks completes its vascularization. Therefore, in premature infants, the retina is not fully vascularized at the time of birth, and there is a peripheral avascular zone and its width varies according to the gestational age at birth (8). ROP is believed to develop through a two-stage process, although its exact pathogenesis is not fully understood. In premature infants, retinal vascularization, which begins in the intrauterine environment, is delayed by various damaging factors. These factors include prolonged hyperoxia, asphyxia, hypothermia, acidosis, and vitamin E deficiency, which are potential causes of the initial injury (9). In the early stage of ROP (phase 1), the suppression of vascular endothelial growth factor (VEGF) and erythropoietin due to hyperoxia, along with the absence of insulin-like growth factor 1 (IGF-1) and poor postnatal growth, hinders normal vascular development (10). Despite this, the retina continues to grow, leading to an unmet oxygen demand due to impaired retinal vascularization, resulting in retinal hypoxia and the onset of phase 2. During this phase, hypoxia triggers an increase in mediators such as VEGF, erythropoietin, and IGF-I, which leads to neovascularization.

Neovascularizations in the retina are observed at the vascular-avascular retinal border. First, neovascularizations cluster in the retina and form a rapidly thickening ridge tissue. If neovascularization progresses further, it may cause leakage and edema formation and retinal detachment leading to vision loss (11). In premature infants in phase-1, low IGF-1 levels in the early stages of life are usually due to prematurity itself and immature liver function rather than hypoxia. The immature liver function of premature infants leads to inadequate IGF-1 production, which negatively affects retinal vascular development. In phase-2, IGF-1 levels increase as the baby's nutrition improves and liver function improves. This increase works together with the release of VEGF caused by hypoxia to initiate the abnormal neovascularization process. While VEGF is expressed as the hypoxic retina's effort to form vessels, IGF-1 supports pathological vascular growth by increasing the effects of VEGF in this process. As a result, low levels of IGF-1 cause vascular development to lag behind, while the increase in IGF-1 and the interaction with VEGF contribute to the progression of ROP in the later period (9). These mechanisms are important in understanding the pathogenesis of the disease and determining therapeutic targets. Although our current knowledge is not sufficient to show in which infants the pathological process will occur, some risk factors have been reported in the light of clinical experience, revealing infants at risk (7). The best known risk factors are low birth weight and gestational age (10). In addition, many factors such as oxygen therapy, blood transfusion, acidosis, hypoxia, sepsis, and intraventricular bleeding have been thought to be associated with ROP (12).

Infants at risk of ROP should be screened and complications should be prevented by detecting and treating high-risk infants in a timely manner. Knowing the gestational ages and birth weights of the infants required treatment will shed light on who would be included in the screening. In this study, the rate of development and treatment of ROP in infants who were examined for ROP and the relationship of this rate with the gestational age and birth weight were examined. Appropriate screening criteria and methods for management of ROP were discussed.

Materials and Methods

Within the scope of the study, the records of 1101 infants with a birth age of 34 weeks and below and/or a birth weight of 1700 grams and below,and 34 weeks and above with a history of intensive care unit support who were examined for ROP between the years 2021-2023, were retrospectively analyzed. Before the examination, phenylephrine at 1.25% dilution and tropicamide at 0.5% dilution were dripped 3 times at 5 minutes intervals. Topical anesthesia with proparacaine hydrochloride was applied to infants with appropriate pupil dilatation. After the lids were opened with infant blepharosta, all retinal zones were examined with an indirect ophthalmoscope and +20 Diopter lens, with assistance of a scleral indentator. The subjects without retinopathy were followed up with 2-week intervals until peripheral retinal vascularization completed (approximately 45th gestational week). In cases with retinopathy, on the basis of the International PR Classification (ICROP-3) criteria[6], the severity of retinopathy between the vascular and avascular areas were described as (Stage 1 if there is a demarcation line, Stage 2 if there is a bulge or “ridge”, Stage 3 if extraretinal fibrovascular proliferation is detected, Stage 4a if there is partial retinal detachment not including the macula,Stage 4b if there is a partial retinal detachment including the macula, Stage 5

if total retinal detachment is present, Stage 5a if there is a total tractional retinal detachment but posteior pole is visualised with ophthalmoscopy,Stage 5b if there is closed funnel retinal detachment in the form of leukocoria, in which the retina is completely collected behind the lens,Stage 5c if there is a leukocoric tractional retinal detachment, in which the anterior chamber narrows and iridocorneal synechiae form, leading to corneal opacification over time). Follow-up periods of these patients were planned according to the current findings. The patients with high-risk according to the criteria of the ETROP (Early Treatment of Retinopathy of Premature) study group with pre-threshold disease signs (Plus disease with PR at any stage in Zone 1, stage 3 PR in Zone 1 without plus disease, Stage 2 or 3 PR in Zone 2 with plus disease) were underwent laser photocoagulation under general anesthesia. Surgical intervention via vitreoretinal procedures was implemented for cases presenting with retinal detachment. The cohort was stratified into distinct categories based on birth weight: ≤1000 g, 1001-1250 g, 1251-1700 g, a subtotal group (≤1700 g), 1701-2000 g, and ≥2001 g. Additionally, gestational age served as a criterion for further categorization: <27 weeks, 27-34 weeks, a subtotal group (≤34 weeks), and >34 weeks. All infants over 34 weeks or 1700 g had cardiopulmonary support treatment and considered high risk for developing ROP.These stratified groups underwent comprehensive analysis with respect to several parameters: the quantity of infants subjected to PR screening, the prevalence of PR (expressed as a percentage), the incidence of stage 3 and higher PR (percentage), the frequency of laser photocoagulation interventions (percentage), and the number of vitreoretinal surgical procedures performed. Furthermore, a comparative analysis was conducted between infants who were managed conservatively without intervention and those necessitating treatment. This analysis encompassed the number of patients in each group, their mean birth weight (including minimum and maximum values), and their average gestational age (with corresponding minimum and maximum values).

Statistics

Statistical analyses were conducted using SPSS for Windows, Version 29.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). The Shapiro-Wilks test was employed to assess the normality of variables within a single group, confirming a normal distribution (p> 0.05). Consequently, the paired t-test was utilized to compare variables between pre-operative and post-operative periods. Pearson's correlation test was applied to examine the relationships between variables. A p-value of <0.05 was considered indicative of statistical significance.

Results

A total of 1101 infants were screened for retinopathy of prematurity. The mean gestational age of these infants was 30.5±2.530.5±2.5 weeks, ranging from 23 to 36 weeks. Their mean birth weight was 1516±435.61516±435.6 grams, with a range of 610 to 2850 grams. Among the screened population, 55 infants (5%) were diagnosed with retinopathy of prematurity at stages requiring therapeutic intervention. The mean birth weight of the infants who didn't need treatment was 1528.1±483 (550-2750) g, and the mean gestational age was 30.7±2.9 (23-37) weeks. The mean birth weight of the infants required treatment was 1152.2±396 (520-2120) g, the mean gestational age was 28.3±2.3 (24-34) weeks, and it was significantly lower than the patients who did not need treatment (p<0.001, Ki square test). Table 1 shows the comparison of infants followed up without treatment and infants requiring treatment according to mean gestational age and birth weight.

Table 1. Comparison of Mean Birth Weight and Gestational Age of Infants by Treatment Status

	Number of patients	Average birth weight (minimum-maximum)	Average gestational age (minimum-maximum)
Follow-up group	n=1046 (%95)	1548,6 g (610-2850)	30,6 weeks(23-36)
Treatment group	n=55 (%5)	1142,4 g (610-2225)	27,4 weeks (23-34)
Total	n=1101	1516 g (610-2850)	30,5 weeks (23-36)

g: gram. (Chi square test, p<0,001)

Considering the groups according to their birth weights, 66 (56.1%) of 123 infants born at 1000 g and below, 118 (8%) of 273 infants born between 1001-1250 g, and 86 of 305 infants born between 1251-1700 g (PR developed in 28.1%, 42 (12.9%) of 325 infants born between 1701-2000 g, and 1 (1.3%) of 75 infants born in 2001 g and above. The frequency of ROP by birth weight and the comparison of treated patients are shown in Table 2. PR development rate was found to be significantly higher in premature infants with low birth weight (p<0.001, chi-square test).

Considering the groups according to gestational age, 114 (53.2%) of 214 infants born below 27 weeks of age, 164 (26.8%) of 612 infants born between 27-34 weeks, and 35 of 275 infants born above 34 weeks (53.2%) 12.7) developed PR was detected. The frequency of PR according to gestational age and the comparison of treated patients are shown in Table 3. PR development rate was found to be significantly higher in infants born earlier (p<0.001, chi-square test).

It was determined that requirement of treatment decreased significantly as the birth weight of the patients increased. When examined according to the gestational age, it has been detected that the indication for treatment decreases with the increase in the birth week.

Table 2. Incidence of Retinopathy of Prematurity and Treatment Interventions by Gestational Age

Gestation age (grams)	Infants scanned for ROP	Infants with ROP (%)	Percentage of Stage 3 ROP and above (%)	Percentage of laser treatment(%)	Vitreoretinal surgery numbers
≤1000	123	66 (%56,1)	23 (%18,6)	25 (%20,3)	3
1001-1250	273	118 (%43,2)	15 (%5,5)	13 (%4,7)	1
1251-1700	305	86 (%28,1)	7 (%2,3)	8 (%2,6)	1
Subtotal (≤1700)	701	270 (%38,5)	45 (%6,4)	46 (%6,5)	5
1701-2000	325	42 (%12,9)	2 (%0,6)	3 (%0,9)	1
≥2001	75	1 (%1,3)	1 (%1,3)	-	-
Total	1101	313 (%28,4)	48 (%4,4)	49 (%4,5)	6

ROP; retinopathy of prematurity

Table 3. Prevalence and Severity of Retinopathy of Prematurity Stratified by Gestational Age: Screening Outcomes and Interventions

Gestation age (grams)	Infants scanned for ROP	Infants with ROP (%)	Percentage of Stage 3 ROP and above (%)	Percentage of laser treatment(%)	Vitreoretinal surgery numbers
<27	214	114 (%53,2)	32 (%15,0)	32 (%14,9)	4
27-34	612	164 (%26,8)	14 (%2,3)	16 (%2,6)	2
Subtotal (≤34)	826	278 (%33,7)	46 (%5,6)	48 (%5,8)	6
>34 weeks	275	35 (%12,7)	2 (%0,7)	1 (%0,4)	-
Total	1101	313 (%28,4)	48 (%4,4)	49 (%4,5)	6

ROP; retinopathy of prematurity

Discussion

Retinopathy of prematurity is an increasing, significant global issue of our time. Although significant advances have come out in the treatment of PR with cryotherapy and laser photocoagulation after the 1980s, 10-15% of the cases that undergone treatment continued suffering lose of vision (13). Technological and medical advances in treatment have led to a decrease in premature mortality and an increase in morbidity. In addition, inadequate care conditions and lack of a good screening program contribute to morbidity. The increased prevalence of multiple pregnancies due to the widespread use of assisted reproductive technologies, along with the associated rise in premature birth rates, also contributes to the incidence of ROP (14, 15). Nowadays, issues related to the diagnosis and follow-up of PR have become more prominent in recent years.

Since retinopathy of prematurity is a disease that can be completely or partially treated or its progression can be prevented when diagnosed early, premature infants should be examined by establishing a good screening program in terms of the first signs of ROP (16). The American Academy of Pediatrics recommends screening for ROP in infants born with a body weight of 1500 grams or less than 30 weeks, infants"at-risk"over 30 weeks of age (eg, those who have received long-term oxygen therapy), or infants at risk between 1500-2000 grams with accompanying systemic disease (17). It is recommended to screen infants with a gestational age of 31 weeks and below in Sweden, and infants with a gestational age of 32 weeks and below or with a birth weight of less than 1500 g in England (18). It has been emphasized that these criterias in developed countries will not be very suitable for countries with a lower socioeconomic development level and that the screening limit for these infants should be kept wider and should be decided according to local population characteristics (19).

The recommendations in the consensus guide of the Turkish Neonatology Association and the Turkish Ophthalmology Association are similar. It is recommended to screen all infants with a gestational age of 34 weeks and below or with a birth weight of 1700 g and older infants with cardiopulmonary issues and high risk for ROP (20). There are various studies on this subject in our country. Mutlu et al. stated that none of the infants over 32 weeks of age needed treatment in their studies (21). Yellow Kabadayi et al. similarly reported that it would be appropriate to screen infants born under 32 weeks and 1500 grams (22). On the contrary, in studies conducted by Özbek, stage 3 and more advanced PR findings were reported in a significant number of patients born above 1500 g and 32 weeks (23). In our study, our screening criteria were similar to the recommendations in the consensus guidelines of the Turkish Society of Neonatology and the Turkish Society of Ophthalmology. On the contrary, in our study, ROP developed in 42 (12.9%) of 325 infants born over 1700 grams and in 35 (12.7%) of 275 infants born over 34 weeks. These values were apart from the scope of screening according to the USA and UK criteria. So it is inevitable to establish a specific appropriate ROP screening guideline for every different population.

In our clinic, PR screening examination is performed with binocular indirect ophthalmoscopy and patients are examined in detail. Retcam™ (Clarity Medical Systems), a camera system that can take wide-angle digital images of the retina,

and phoenix ICON (trademark of phoenix ICON) have been put into use in some clinics abroad and in our country. Since these devices allow us to record photos, they offer the possibility of archiving images. It provides us an advantage due to its ease of application and a disadvantage of its low sensitivity. However, indirect ophthalmoscopy is the gold standard method for PR screening nowadays.

The best known risk factors for the development of retinopathy of prematurity are low DA and GA. It is known that the frequency of retinopathy increases significantly especially in infants born below 1000 grams and before 28 weeks (6, 10). In a multicenter study conducted in the United States between 2000 and 2002, the frequency of PR was 68% and the frequency of severe PR was found to be 36% in preterm infants born with a birth weight of less than 1251 g, while in another study these rates were found to be 68% and 12.4%, respectively (24,25). Our study found that as birth weight increased, there was a corresponding rise in the incidence of retinopathy of prematurity, the number of infants diagnosed with Stage 3 or higher PR, and the frequency of both laser photocoagulation and vitreoretinal surgeries. There are many studies on the effect of gestational week on PR. Selim Sancak et al. found the frequency of PR as 43.5% in a 4-year period in preterm newborns with ≤ 32 weeks of gestation (25).

Neonatal care should prioritize enhanced screening for infants at high risk of severe ROP, particularly those with very low birth weight and early gestational age. This includes frequent eye examinations to facilitate early detection. Timely intervention is crucial, necessitating standardized protocols for laser treatment and ensuring neonatal units are well-equipped and staffed. Educating parents about ROP and its management is vital, as is supporting ongoing research into alternative treatments. These strategies aim to improve outcomes for vulnerable infants, highlighting the importance of vigilant care and timely intervention in neonatal practice.

Study limitations

The potential risk factors for (ROP), such as oxygen therapy, total intubation period of the premature infants, blood transfusions, acidosis, hypoxia, sepsis and intraventricular bleeding weren't analized in the study.The infants underwent anti VEGF injections were a minority of the total premature infants, so they were excluded.Additionaly, the long term results of patients underwent pars plana vitrectomy (PPV) is unknown.

Conclusion

Findings of this study draws attention to the significance of PR screening and treatment. Due to the high comorbidity of retinopathy of prematurity, it is very important that premature births with risk factors are carefully examined and infants require treatment are treated promptly. A regular screening program should be prepared by the ophthalmologist and neonatologist together. When patients are discharged from the intensive care unit, families should be informed about the examination, and the continuity of follow-up and treatment should be the joint responsibility of the ophthalmologist, pediatrician and family. Informing the families regarding the severity of the disease may cause blindness, obtaining their consent before the examination, recording the control examinations by making an appointment through the system, and recording the examination findings both in the patient files and in the computer system will minimize the legal processes that may occur.

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Ethical Approval: *This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was obtained from the Harran University Clinical Research Ethics Committee on October 4, 2021, with decision number HRU/21.17.10 during session 17.*

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Research Article / Araştırma Makalesi

Neuroradiologic Findings Associated with Tuberous Sclerosis Complex: A Comprehensive Analysis of 24 Cases

Tüberoskleroz Kompleksi ile İlişkili Nöroradyolojik Bulgular: 24 Vakanın Kapsamlı Analizi

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Abstract

Background: This study aims to comprehensively analyze the radiological findings of 24 TSC patients to determine the radiological profile of the disease and potential diagnostic and therapeutic implications.
Materials and Methods: This retrospective study was approved by the Ethics Committee of Harran University. A total of 24 genetically diagnosed TSC patients who underwent brain MRI between 2020-2024 were included. Imaging was performed using a 3 Tesla MRI scanner, employing T2 IDEAL, 3D T1 VIBRANT, and contrast-enhanced T1 sequences. Data were analyzed using IBM SPSS Statistics software, focusing on demographic characteristics and radiological findings.
Results: The study included 24 TSC patients (14 males, 10 females) with a mean age of 8.43±10.24 years (range: 1-46 years). Cortical/subcortical tubers and subependymal hamartomas were identified in all patients (100%). Radial bands were observed in 83.3%, infarctions in 50%, and corpus callosum dysgenesis in 41.6%. Subependymal giant cell astrocytoma (SGCA) was present in 12.5% of cases, while arachnoid cysts were noted in 20.8%.
Conclusions: This study revealed a higher CNS involvement rate in TSC patients compared to the literature, with a higher prevalence among male patients. These findings emphasize the importance of detailed radiological and clinical evaluations in understanding the disease. Changes in radiological findings with age and disease progression can contribute to optimizing treatment protocols.

Keywords: Tuberous Sclerosis Complex, Central Nervous System Involvement, Radiological Findings

Öz

Amaç: Bu çalışmanın amacı, 24 TSC hastasının radyolojik bulgularını detaylı bir şekilde inceleyerek hastalığın radyolojik profilini ve klinik sonuçlarla olan ilişkisini ortaya koymaktır.
Materyal ve Metod: Bu retrospektif çalışma, Harran Üniversitesi Etik Kurulu tarafından onaylanmıştır. Çalışma kapsamında 2020-2024 yılları arasında hastanemizde genetik olarak TSC tanısı konmuş ve beyin MR görüntülemesi yapılmış 24 hasta incelenmiştir. Görüntüleme, 3 Tesla MR cihazı ile gerçekleştirildi. T2 IDEAL, 3D T1 VIBRANT ve kontrastlı T1 sekansları kullanılarak radyolojik bulgular değerlendirildi. Elde edilen veriler, IBM SPSS Statistics yazılımı ile demografik özellikler ve radyolojik bulgular açısından analiz edilmiştir.
Bulgular: Çalışmaya 24 TSC hastası (14 erkek, 10 kadın) dahil edilmiştir. Hastaların yaş ortalaması 8,43±10,24 yıl olup, yaşlar 1 ile 46 arasında değişmektedir. Tüm hastalarda kortikal/subkortikal tüberler ve subependimal hamartomlar saptanmıştır (%100). Radial band %83,3, infarkt %50, korpus kallozum disgenezi %41,6 oranında tespit edilmiştir. Ayrıca, 3 hastada subependimal dev hücreli astrositom (SGCA) (%12,5) ve 5 hastada araknoid kist (%20,8) görülmüştür.
Sonuç: Çalışmamızda TSC'nin CNS tutulum oranının literatürden yüksek olduğu ve özellikle erkek hastalarda daha sık görüldüğü tespit edilmiştir. Bu bulgular, TSC'nin radyolojik ve klinik özelliklerinin daha iyi anlaşılması ve hastalık yönetimi için önem taşımaktadır. Radyolojik bulguların yaş ve hastalık süresi ile değişimi, tedavi protokollerinin optimize edilmesine katkı sağlayabilir.

Anahtar Kelimeler: Tübüloz Skleroz Kompleksi, Merkezi Sinir Sistemi Tutulumu, Radyolojik Bulgular

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Introduction

Tuberous sclerosis (TSC) is a genetic disease caused by mutations in the TSC1 and TSC2 genes and characterized by the formation of benign tumors throughout the body, including the brain, skin, kidneys, heart, lungs, and eyes. TSC is usually diagnosed in early childhood, and affected individuals may present with developmental delay, skin manifestations, or seizures. The diagnosis of the disease may be made earlier or later depending on various clinical findings (1,2). Comprehensive analysis of radiological findings plays a critical role in the early diagnosis of TSC. Cortical tubers are lesions that can cause epileptic seizures, especially in childhood, and can affect neuropsychiatric development. Subependymal giant cell astrocytomas (SGCA), commonly located in the brain ventricles, can lead to hydrocephalus and elevated intracranial pressure due to their progressive growth. Findings such as radial bands and corpus callosum dysgenesis reflect abnormalities in brain development and are often associated with cognitive dysfunction. Therefore, a thorough analysis of radiological findings serves as a cornerstone for disease management and planning targeted intervention strategies (3,4).

In this study, we aim to examine in depth the radiological findings of 24 patients diagnosed with TSC and to reveal the radiological profile of the disease and its relationship with clinical outcomes. The patients we examined were selected from various age groups and different clinical stages. This diversity will help us understand how the radiological findings of TSC may change with age and disease duration. We also aim to the MRI technique was performed with a 3 Tesla MRI scanner (GE, Milwaukee, Wisconsin, USA) for pituitary imaging on tribute to the development of more effective treatment protocols by evaluating the effects of these findings on disease progression and response to treatment (5,6).

This study aims to provide a better understanding and management of the disease by comprehensively analyzing the radiological findings of TSC. The information obtained can be used in early diagnosis, monitoring and optimization of treatment strategies for TSC. When compared with the information available in the literature, the findings of our study can make significant contributions to clinical and radiological practices related to TSC and fill the gaps in this area. In light of this information, necessary steps can be taken to better understand the complex nature of TSC and develop effective interventions (6,7).

Materials and Methods

This retrospective study was approved by the local ethics committee of Harran University (approval number: HRU/24.16.34). The patients consisted of 24 patients who underwent MRI in our hospital's Radiology department between 2020-2024 and were genetically diagnosed.

MRI scans were acquired using a 3 Tesla scanner (GE, Milwaukee, Wisconsin, USA), optimized for cerebral imaging. After acquiring localization and calibration images in three planes, T2 IDEAL (TR: 9300 ms, TE: 102 ms, FOV: 380 x 380 mm, Matrix: 352 x 288, Slice Thickness: 1 mm), 3D T1 VIBRANT (TR: 5.4 ms, TE: 2.6 ms, FOV: 380 x 380 mm, Matrix: 416 x 320, Slice Thickness: 1.4 mm) and fat-suppressed T2 (TR: 7326 ms, TE: 85 ms, FOV: 380 x 380 mm, Matrix: 224 x 224, Slice Thickness: 1 mm) images were obtained. Radiopathological findings on brain MRI images were determined by two radiologists with 5 and 10 years of neuroradiological experience by consensus.

The data analysis process was carried out using IBM SPSS Statistics software. The obtained data set was evaluated in terms of demographic characteristics, radiological findings frequencies and other relevant clinical parameters. Statistical analyses include frequency distributions and table.

Results

The study included 24 TSC patients, of which 14 (58.3%) were male and 10 (41.7%) were female. The mean age of the patients was 8.43±10.24 years. The age range spanned from a minimum of 1 year to a maximum of 46 years. All examined patients demonstrated CNS involvement. The most common findings were cortical tubers and subependymal nodules. In addition, 50% of patients were found to have brain infarct findings, which was higher than the general population. This discrepancy might stem from our patient cohort, which included individuals with more severe clinical presentations.

In this study, all of our female and male patients diagnosed with TSC had cortical/subcortical tubers and subependymal hamartomas. SGCA was observed in 3 of our patients (12.5%). Infarction was observed in 12 of our patients (50%). Corpus callosum dysgenesis was observed in 10 of our patients (41.6%). Arachnoid cyst was observed in 5 of our patients (20.8%). Cerebellar atrophy, venous anomaly and hydrocephalus were observed in only one patient (4.16%) (Table 1).

Table 1. Distribution of Neuroradiological Findings in TSC Patients (n=24)

Neuroradiological Findings	**n**	**%**
Cortical/Subcortical Tubers and Subependymal Hamartomas	24	100.0
Radial Bands	20	83.3
Infarct	12	50.00
Corpus Callosum Dysgenesis	10	41.6
SGCA	3	12,5
Arachnoid Cyst	5	20,8
Cerebellar Atrophy	1	4,16
Venous Anomaly	1	4,16
Hydrocephalus	1	4,16

SGCA: Subependymal giant cell astrocytoma

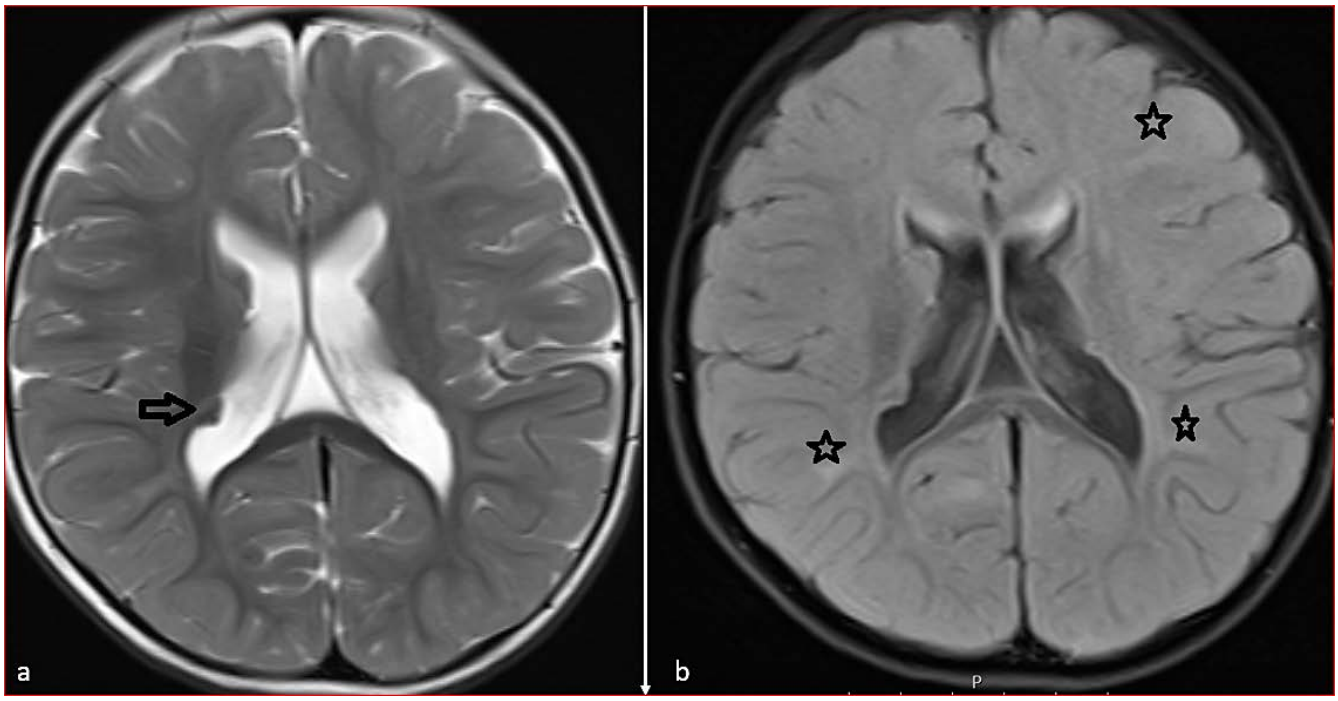

Figure 1. Brain MRI images of a 2-year-old male patient diagnosed with tuberous sclerosis. On T2W axial image, isointense nodular appearance compatible with subependymal nodule on the right lateral ventricular wall is remarkable arrow . On T2 FLAIR W axial image, patchy hyperintense areas consistent with hamartoma in the subcortical areas of bilateral cerebral hemispheres are noted (*).

Discussion

CNS involvement associated with TSC has been reported in the literature at widely varying rates. In general, CNS involvement rates vary widely depending on the genetic and phenotypic diversity of the disease. Studies in the literature show the presence of cortical tubers in 80% to 90% of TSC patients, while subependymal nodules and white matter abnormalities are seen at lower rates (8).

In our study, CNS involvement was observed in all 24 patients, indicating one of the highest rates in the literature (9). This high rate suggests that our study may have focused on a specific subgroup or that particularly severe cases may have been examined. In addition, a gender-based analysis was performed in our study and it was examined whether the findings differed according to gender. Although it is stated in the literature that TSC is seen at similar rates in both genders, it is emphasized that some clinical features may vary according to gender. The findings obtained in our study showed that CNS involvement is more common in male patients. Although this result is consistent with some studies in the literature, more detailed genetic and molecular studies are required to understand the reason for this difference (10). Since studies on the role of gender in TSC are generally conducted on a limited number of patients, it is important to support them with large-scale epidemiological studies.

It is known that CNS involvement associated with TSC can directly affect the course of the disease and treatment responses. In this context, a better understanding of CNS involvement rates and gender differences may provide important strategic information in the management of the disease. This information is crucial for early diagnosis and intervention, facilitating the development of personalized treatment approaches. We can compare the findings of CNS infarction in the literature with the results of our own study. In the literature, the prevalence of silent brain infarction (SBI) was determined as 20.2% in Asian countries, 12.4% in Europe and 15.6% in the USA. These studies revealed that age is the main determinant in the prevalence of SBI (11,12).

Signs of infarction were observed in 15 patients, reflecting a higher prevalence compared to general population rates reported in the literature. This difference may be due to differences in the selection of our study population. For example, the selection of patients with more severe symptoms or certain demographic characteristics may affect these rates. The literature also indicates that risk factors for ischemic stroke (IS) in young patients are similar to those in older populations; modifiable risk factors such as hypertension, smoking, low physical activity and hyperlipidemia are associated with an increased incidence of stroke among young people (13,14). When the distribution of patients with infarction in our study was examined according to gender, it was observed that gender does not have a significant effect on risk in the literature; however, the role of gender may become apparent in combination with certain risk factors (e.g. smoking and hypertension) (15).

This study has some limitations. First of all, the limited number of cases limits the generalizability of the findings. In addition, the lack of detailed clinical data such as seizure history

in the patients made it difficult to fully evaluate the relationship between central nervous system involvement and neurological symptoms. The lack of data on other organ involvement in the study prevented a more comprehensive analysis of the multisystemic nature of the disease. These limitations indicate that the results obtained should be supported in larger patient groups and with multidisciplinary approaches.

In conclusion, the effects of TSC on the central nervous system are an important source of morbidity in terms of neurological and neurodevelopmental disorders. Our study emphasizes the importance of clinical and radiological evaluations in TSC patients with prominent CNS involvement.

Ethical Approval: *This retrospective study was approved by the local ethics committee of Harran University (approval number: HRU/24.16.34).*

Author Contributions:
Concept: M.D.
Literature Review: M.D., M.S.B
Design : M.D.
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Araştırma Makalesi / Research Article

Mide Kanserinde Klinik Evreleme ile Patolojik Evrelemenin Karşılaştırılması ve Uyumun Değerlendirilmesi

Comparison of Clinical and Pathological Staging in Gastric Cancer and Evaluation of Their Concordance

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Öz

Amaç: Bu çalışma, mide adenokarsinomunun preoperatif evrelemesinde kullanılan farklı görüntüleme yöntemlerinin etkinliğini ve bu yöntemlerin birbirine kıyasla üstünlüklerini araştırmayı amaçlamaktadır. Elde edilen bulgular doğrultusunda, cerrahi ve tedavi planlamasında en uygun yaklaşımın belirlenmesi hedeflenmiştir.
Materyal ve metod: Bu çalışma, 2015-2021 yılları arasında cerrahi tedavi uygulanmış 226 mide adenokarsinomu hastasının verilerinin retrospektif olarak analiz edilmesiyle gerçekleştirilmiştir. Hastaların %68,1'i erkek (n=154), %31,9'u kadın (n=72) olup, yaş ortalaması 63,9 ± 11,67 yıldı. Hastalar, ameliyat öncesinde BT (Bilgisayarlı Tomografi), PET-CT (Pozitron Emisyon Tomografisi) ve EUS (Endoskopik Ultrasonografi) ile taranmış ve bu görüntüleme yöntemlerinden elde edilen sonuçlar, patolojik evreleme ile karşılaştırılmıştır.
Analiz kapsamında hastalar; Yaş, cinsiyet, tümörün lokalizasyonu, boyutu, uygulanan ameliyat tipi, klinik evre ve patolojik evre gibi değişkenler açısından değerlendirilmiştir. T evrelemesi için Kappa uyum testi, N evrelemesi için ise Binary Lojistik Regresyon analizi kullanılmıştır.
Bulgular: Patolojik evreleme ile uyumu incelendiğinde, T evrelemesinde kullanılan preoperatif görüntüleme yöntemlerinde, BT, PET-CT ve EUS'nin uyum düzeyleri sırasıyla orta düzeyde (Kappa=0,421), yüksek düzeyde (Kappa=0,523) ve en yüksek düzeyde (Kappa=0,621) olarak bulunmuştur. T evrelemesinde, en yüksek doğruluk oranı %87.1 ile EUS'un T1 evresindeyken, PET-CT ve BT ise T3 evresinde sırasıyla %72.5 ve %68.2 olarak saptandı. N evrelemesi sonuçlarına göre, en yüksek doğruluk oranı N0 evresinde tespit edildi; bu evre için doğruluk oranları BT'de %84,9, PET-CT'de %84,2 ve EUS'da %88,4 olarak saptanmıştır. Ancak EUS, büyük lezyonlar ve mide-özofagus bileşkesindeki lezyonlarda tanısal zorluklar yaratabilmektedir. Ayrıca, tümörün çapı ve lokalizasyonunun, görüntüleme yöntemleri ile patolojik evreleme arasındaki uyumsuzluk riskini artıran önemli faktörler olduğu saptanmıştır.
Sonuç: Çalışmanın sonuçları, her bir yöntemin kendine özgü güçlü yönleri olduğunu ve preoperatif evreleme sürecinde bu yöntemlerin bir arada kullanılmasının daha doğru ve kapsamlı sonuçlar sağlayabileceğini göstermektedir.

Anahtar Kelimeler: Mide Adenokarsinomu, Preoperatif Evreleme, Bilgisayarlı Tomografi, Pozitron Emisyon Tomografi-Bilgisayarlı Tomografi, Endoskopik Ultrason

Abstract

Background: This study was conducted to investigate the effectiveness of various imaging methods used for preoperative staging of gastric adenocarcinoma and to determine the relative advantages of these methods, with the aim of identifying the most suitable approach for surgical and treatment planning.
Materials and Methods: Data from 226 patients with gastric adenocarcinoma who underwent surgical treatment between 2015 and 2021 were analyzed retrospectively. Of the patients included in the study, 68.1% were male (n=154) and 31.9% were female (n=72), with a mean age of 63.9 ± 11.67 years. The patients underwent preoperative imaging using CT, PET-CT, and EUS, and the results were compared with pathological staging. Variables such as age, sex, tumor localization, size, type of surgery, and clinical and pathological stages were assessed. T staging was evaluated using the Kappa concordance test, while N staging was analyzed using Binary Logistic Regression.
Results: Concordance between pathological staging and imaging methods for T staging was found to be moderate for CT (Kappa=0.421), high for PET-CT (Kappa=0.523), and highest for EUS (Kappa=0.621). In T staging, the highest accuracy rate for EUS was 87.1% at the T1 stage, while PET-CT and CT revealed accuracy rates of 72.5% and 68.2%, respectively, at the T3 stage. According to the N staging results, the highest accuracy rate was achieved in the N0 stage; for this stage, the accuracy rates were found to be 84.9% for BT (CT), 84.2% for PET-CT, and 88.4% for EUS. However, EUS encountered issues with large lesions and the gastroesophageal junction. Tumor size and localization were identified as significant factors influencing the risk of discordance.
Conclusions: The study's results indicate that each method has unique strengths and that combining these methods in the preoperative staging process can yield more accurate and comprehensive results.

Keywords: Gastric adenocarcinoma, Preoperative staging, Computed tomography, Positron emission tomography-computed tomography, Endoscopic ultrasound

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Giriş

Mide kanseri, dünya genelinde en yaygın beşinci kanser türü olup kansere bağlı ölümler arasında üçüncü sırada yer almaktadır (1). Gastrik kanser (GK) hastalarında preoperatif dönemde doğru TNM evrelemesi, etkili bir tedavi stratejisi oluşturmak için hayati önem taşır. Bu amaçla, EUS, Kontrastlı Bilgisayarlı Tomografi (CECT) ve PET-CT gibi çeşitli görüntüleme yöntemleri kullanılmaktadır.

EUS, GK evrelemesinde yaygın bir şekilde kullanılan bir yöntemdir. Ancak, uzak lenf nodları (LN) ve büyük tümörlerin değerlendirilmesinde sınırlı kalabilmektedir (2). Kontrastlı BT, preoperatif evrelemede doğru ve etkili bir araç olarak kabul edilmekle birlikte, radyasyon maruziyeti riski taşır ve yüzeyel lezyonların tanısında sınırlı kalabilir. Ayrıca, bu yöntem genellikle LN metastazlarının değerlendirilmesinde kullanılmakta olup, geniş kesit kalınlığı ve düşük görüntü çözünürlüğü nedeniyle solunum hareketi artefaktlarına maruz kalabilir (3). Bu durum, yalnızca boyut kriterlerine dayalı nodal değerlendirmede mikroskopik nodal invazyonun tespitini ve reaktif nodların ayrımını zorlaştırmaktadır (4).

PET-CT, mide kanserinin evrelemesinde yüksek duyarlılık ve özgüllük sunan bir yöntemdir. Ancak, maliyetli olması ve geniş çapta uygulanabilirliğinin sınırlı olması nedeniyle yaygın kullanım alanı bulamamaktadır (3). Ayrıca, PET-CT sonuçları, FDG (florodeoksiglukoz) enjeksiyonu sonrası geçen süre, tümör boyutu, normoglisemi ve teknik parametreler gibi birçok faktörden etkilenmektedir (4).

Materyal ve Metod

Hasta Seçimi

Bu çalışma için gerekli etik onay, Sağlık Bilimleri Üniversitesi Adana Şehir Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (Tarih: 03/08/2023, Karar No: 2735). Retrospektif olarak yürütülen bu araştırma, 2015-2021 yılları arasında mide adenokarsinom tanısı alarak cerrahi tedavi gören toplam 226 hastayı kapsamaktadır. Çalışmaya dahil edilen hastaların 154'ü erkek, 72'si kadın olup, ortalama yaş 63.9 ± 11.67 yıl olarak belirlenmiştir.

Ameliyat öncesinde çekilen BT, PET-CT ve EUS görüntüleme sonuçları incelenmiş, demografik, klinik, histopatolojik ve radyolojik veriler retrospektif olarak toplanarak ortak bir veri tabanına kaydedilmiştir.

D1 ve D2 lenf nodu diseksiyonları, JRSSG (Japanese Research Society for the Study of Gastric Cancer) grubunun belirlediği sistematiğe göre gerçekleştirilmiştir. D1 diseksiyonu, perigastrik lenf nodlarını kapsar. Küçük kurvatur boyunca yer alan (1, 3 ve 5 numaralı istasyonlar) ve büyük kurvatur boyunca bulunan (2, 4 ve 6 numaralı istasyonlar) perigastrik lenf nodu istasyonları, N1 grubu olarak adlandırılmıştır. D2 diseksiyonu, N1 grubuna ek olarak, sol gastrik arter (no. 7), ana hepatik arter (no. 8), çöliak arter (no. 9), splenik arter ve hilus (no. 10, 11) boyunca yer alan lenf nodlarını içermektedir.

Dahil Edilme Kriterleri: Preoperatif gastroskopi ile kesin mide kanseri tanısı almış olmak, Cerrahi tedavi uygulanmış olmak (total veya subtotal gastrektomi ile D1 veya D2 lenf nodu diseksiyonu), Ameliyat öncesinde karın BT'si, ek olarak PET-CT ve EUS tetkikler yapılmış olması, Eksiksiz klinik, patolojik ve takip verilerine sahip olmak.

Hariç Tutma Kriterleri: Önceden başka bir malign tümör öyküsü veya operatif müdahale geçirmiş olmak, Birden fazla malign tümör lokalizasyonuna sahip olmak, Yetersiz klinik verilere sahip olmak, Kontrastlı BT taraması yapılmamış olmak, Eksik tıbbi kayıtlara sahip olmak, Hastanede cerrahi tedavi görmemiş veya postoperatif patolojik sonuçları mide kanseri ile uyumsuz olan hastalar, Gastrointestinal stromal tümör (GIST), nöroendokrin karsinom veya intraepitelyal neoplazi tanısı almış olmak.

Bu çalışma kapsamında, hastalar yaş, cinsiyet, tümör lokalizasyonu (üst, orta, alt), ortalama tümör boyutu, ameliyat tipi, tahmini klinik evre, patolojik evre ve tümör grade'i gibi değişkenler açısından retrospektif olarak analiz edilmiştir (Tablo 1).Çalışma, Kurumsal İnceleme Kurulu tarafından onaylanmış ve Helsinki Bildirgesi prensiplerine uygun şekilde yürütülmüştür. Retrospektif doğası nedeniyle hastalardan bilgilendirilmiş onam gereksinimi göz ardı edilmiştir.

Çalışma Tasarımı

Hastalar, kesin mide kanseri tanısı almış ve preoperatif evreleme için BT, PET ve/veya EUS taramalarına tabi tutulmuştur. Preoperatif TNM evrelemesi, Amerikan Kanser İşbirliği Komitesi (AJCC) el kitabının 8. baskısına göre gerçekleştirilmiş ve postoperatif evreleme patologlar tarafından yapılan histopatolojik incelemelerle doğrulanmıştır. Preoperatif görüntüleme yöntemlerinin doğruluğu, elde edilen sonuçların postoperatif histopatolojik evreleme ile karşılaştırılması yoluyla değerlendirilmiştir.

BT Protokolü

Hastalar, BT taramasından 6 saat önce aç kalmış ve tarama öncesinde 600-1200 ml su içmiştir. İlk olarak düz tarama yapılmış, ardından intravenöz kontrast madde uygulanmıştır. Tarama, hastaların sırt üstü pozisyonda, diyaframdan pubis simfizisine kadar yapılmıştır. Kontrastlı BT, mide duvarı kalınlaşması, tümör invazyonu, LN büyümesi ve metastatik yayılımı değerlendirmek için kullanılmıştır. Mide kanserinin evrelemesi, AJCC'nin sekizinci baskısına göre gerçekleştirilmiştir; T1: Odaklı mide duvarı kalınlaşması, T2: Mide duvarında genel kalınlaşma ve transmural tutulum, T3: Dış mide duvarının tutulumu, T4: Serozanın invazyonu veya komşu organlara yayılım. LN evrelemesinde: N1: Tümörden 3 cm mesafedeki lenf nodları, N2: Tümörden 3 cm'den daha uzak mesafedeki lenf nodları olarak değerlendirilmiştir. Metastatik yayılım, 8 mm'den büyük ve yüksek kontrastlı lezyonlar olarak tanımlanmıştır.

PET-CT protokolü

Hastalar, PET-CT taramasından 6-8 saat önce aç bırakılmış ve şekerli gıdalardan kaçınmaları sağlanmıştır. Taramadan önce hastaların 600-1200 ml su içmeleri önerilmiştir. Tarama sırasında hastalar sırt üstü pozisyonda yatmaktadır. FDG adlı radyoaktif izotop, intravenöz olarak uygulanmış ve bu işlemin ardından hastalar yaklaşık 60 dakika dinlenmiştir. Taramanın

kendisi, 30-60 dakika sürmekte olup bu süreçte hastaların hareket etmemesi sağlanmıştır. CT taraması, genellikle düşük dozda yapılmış ve elde edilen görüntüler, PET görüntüleriyle birleştirilmiştir. Görüntüler, tümörlerin ve diğer anormalliklerin değerlendirilmesi amacıyla analiz edilmiş ve sonuçlar rapor halinde sunulmuştur.

EUS Protokolü

EUS işlemi öncesinde, hastaların 12 saat boyunca aç kalmaları sağlanmış. İlk aşamada, gastroskopi ile lezyonun boyutu ve yeri değerlendirilmiş. Daha sonra, EUS kullanılarak lezyon ayrıntılı bir şekilde incelenmiştir. Lezyonların evrelemesi, Uluslararası Kanser Savaş Örgütü (UICC) tarafından belirlenen TNM kriterlerine göre yapılmış. İnvazyon derinliği, gastrik duvarın hangi katmanının etkilendiğine bağlı olarak belirlendi. Lenf nodu (LN) tutulumunda, 10 mm'den büyük, homojen hipoekoik ve net sınırlı lezyonlar, malign adenopati olarak değerlendirildi.

Histopatoloji

Histopatolojik incelemeler, Amerikan Kanser İşbirliği Komitesi (AJCC) el kitabının 8. baskısındaki TNM sınıflama kriterlerine göre gerçekleştirilmiştir. İnvazyon derinliği (pT evrelemesi): Tümörün mide duvarındaki yayılımı mikroskobik olarak değerlendirilmiştir. Lenf nodu durumu (pN evrelemesi): Lenf nodlarında tümör varlığı ve yayılımı incelenmiştir. Patolojik marjin durumu (R0/R1): Cerrahi sınırların tümörden arınmış olup olmadığı değerlendirilmiştir.

Diğer Özellikler

Tümör evrelemesinin doğruluğunu etkileyebilecek bireysel hastalık özellikleri retrospektif olarak toplanmıştır. Bu özellikler arasında yaş, cinsiyet, tümör boyutu, tümörün yeri (Üst bölge; Kardia ve fundus, orta bölge; mide gövdesi ve alt bölge; antrum ve pylor) ve tümör farklılaşma derecesi (düşük, orta, yüksek farklılaşma) yer almaktadır.

İstatistiksel Yöntem

Veriler, IBM SPSS v23 yazılımı ile analiz edilmiştir. Patoloji ve tanı yöntemlerinin T ve N evreleri arasındaki uyum, Kappa uyum testi ile değerlendirilmiştir. Patoloji ve tanı yöntemleri arasındaki uyumsuzlukların bağımsız değişkenlerle ilişkisi Binary Lojistik Regresyon analizi ile incelenmiştir. Kategorik değişkenler frekans, yüzde ve n (%) değerleri ile sunulmuş olup, anlamlılık düzeyi $p<0.050$ olarak kabul edilmiştir.

Bulgular

Değişkenlere ait tanımlayıcı istatistikler

Çalışmaya dahil edilen 226 hastanın, %68,1'i erkek (n=154), %31,9'u kadın (n=72) olup yaş ortalaması 63,9±11,67 yıl olarak tespit edilmiştir. Patolojik tümör çapı ortalaması 4,9±2,53 cm, tümör lokalizasyonu açısından en fazla %46,9'unda (n=106) alt bölgede, yapılan ameliyat tipi %53,1'ine (n=120) total gastrektomi, tümör derecesi %35,8'inde (n=81) G2, LN diseksiyon sonucunda %61,3'ünde (n=138) pozitif tespit edilmiştir (Tablo 1).

Tablo 1. Değişkenlere ait tanımlayıcı istatistikler

	Ortalama±s.sapma	Ortanca (min-mak)
Yaş	63,9±11,67	64 (26-92)
Patoloji TM çapı	4,9±2,53	4,5 (1-12)
	Frekans	**Yüzde**
Cinsiyet		
Erkek	154	68,1
Kadın	72	31,9
Lokalizasyon		
Alt	106	46,9
Orta	75	33,2
Üst	45	19,9
Ameliyat Tipi		
ST	106	46,9
T	120	53,1
Grade		
G1	75	33,2
G2	81	35,8
G3	70	31
Lap sonucu		
Negatif	87	38,7
Pozitif	138	61,3

Değişkenlere ait T evresi ile Patoloji T evresi arasındaki uyumun incelenmesi

BT, PET-CT ve EUS ile elde edilen T evreleri, patolojik T evreleri ile karşılaştırılmıştır. Patolojik T1 evresinde, hastaların %29,4'ü BT'de yanlış bir şekilde T0 olarak değerlendirilmiştir. T1 evresi için uyum oranları; BT'de %26,5, PET-CT'de %56,3, ve EUS'da %87,1 olarak bulunmuştur. T2 evresinde, uyum oranları; BT için %61,8, PET-CT için %64,7, ve EUS için %69,2'dir. T3 evresinde, BT ile uyum oranları %68,2, PET-CT ile %72,5, ve EUS ile %64,7 olarak saptanmıştır. T4 evresinde ise BT için %62,7, PET-CT için %66,7, ve EUS için %62,5 oranında doğru evreleme yapılmıştır. Patolojik evreler ile BT, PET-CT ve EUS'nin uyum düzeyleri anlamlı bulunmuş olup, sırasıyla orta düzeyde (Kappa=0,421, $p<0,001$), yüksek düzeyde (Kappa=0,523, $p<0,001$) ve en yüksek düzeyde (Kappa=0,621, $p<0,001$) uyum saptandı (Tablo 2).

Tablo 2. Değişkenlere ait T ve N evresi ile Patoloji T ve N evresi arasındaki uyumun incelenmesi

	PATOLOJİ EVRESİ				Kappa	p
	T1	**T2**	**T3**	**T4**		
BT						
T0	10 (29,4)	0 (0)	0 (0)	0 (0)		
T1	9 (26,5)	1 (2,9)	0 (0)	0 (0)		
T2	15 (44,1)	21 (61,8)	28 (26,2)	0 (0)	0,421	**<0,001**
T3	0 (0)	12 (35,3)	73 (68,2)	19 (37,3)		
T4	0 (0)	0 (0)	6 (5,6)	32 (62,7)		
PET-CT						
T1	9 (56,3)	0 (0)	0 (0)	0 (0)		
T2	7 (43,8)	11 (64,7)	11 (21,6)	0 (0)	0,523	**<0,001**
T3	0 (0)	6 (35,3)	37 (72,5)	7 (33,3)		
T4	0 (0)	0 (0)	3 (5,9)	14 (66,7)		
EUS						
T1	27 (87,1)	0 (0)	0 (0)	0 (0)		
T2	3 (9,7)	9 (69,2)	11 (32,4)	0 (0)	0,621	**<0,001**
T3	1 (3,2)	3 (23,1)	22 (64,7)	3 (37,5)		
T4	0 (0)	1 (7,7)	1 (2,9)	5 (62,5)		
	N0	**N1**	**N2**	**N3**		
BT						
N0	73 (84,9)	13 (33,3)	0 (0)	0 (0)		
N1	11 (12,8)	23 (59)	15 (40,5)	18 (28,1)	0,441	**<0,001**
N2	2 (2,3)	3 (7,7)	22 (59,5)	32 (50)		
N3	0 (0)	0 (0)	0 (0)	14 (21,9)		
PET-CT						
N0	32 (84,2)	6 (31,6)	0 (0)	1 (3,3)		
N1	6 (15,8)	11 (57,9)	6 (33,3)	5 (16,7)	0,425	**<0,001**
N2	0 (0)	2 (10,5)	10 (55,6)	17 (56,7)		
N3	0 (0)	0 (0)	2 (11,1)	7 (23,3)		
EUS						
N0	38 (88,4)	5 (29,4)	0 (0)	4 (26,7)		
N1	5 (11,6)	10 (58,8)	6 (54,5)	5 (33,3)	0,408	**<0,001**
N2	0 (0)	2 (11,8)	5 (45,5)	6 (40)		

Değişkenlere ait N evresi ile Patoloji N evresi arasındaki uyumun incelenmesi

Patolojik N evresi ile karşılaştırıldığında, BT, PET-CT ve EUS yöntemlerinin performansları farklılık göstermiştir. Patolojik N0 evresinde, hastaların %84,9'u BT, %84,2'si PET-CT ve %88,4'ü EUS ile doğru olarak sınıflandırılmıştır. Bununla birlikte, N0 hastalarının %12,8'i BT, %15,8'i PET-CT ve %11,6'sı EUS ile yanlışlıkla N1 olarak değerlendirilmiştir. Patolojik N1 evresinde, hastaların %59'u BT, %57,9'u PET-CT ve %58,8'i EUS ile doğru evrelenmiştir. Ancak, bu gruptaki hastaların %33,3'ü BT, %31,6'sı PET-CT ve %29,4'ü EUS ile yanlışlıkla N0 olarak sınıflandırılmıştır. N2 evresindeki hastalar arasında, %59,5'i BT, %55,6'sı PET-CT ve %54,5'i EUS ile doğru evrelenmiştir. Ancak, N2 hastalarının %40,5'i BT, %33,3'ü PET-CT ve %45,5'i EUS ile yanlışlıkla N1 olarak değerlendirilmiştir. Patolojik N3 evresinde, hastaların %50'si BT, %56,7'si PET-CT ve %40'ı EUS ile hatalı olarak daha düşük evrelerde (N2) değerlendirilmiştir. Bununla birlikte, bu evredeki hastaların %21,9'u BT, %23,3'ü PET-CT ile doğru sınıflandırılmıştır (Tablo 2).

Bağımsız değişkenlerin Patoloji- BT, PET-CT ve EUS T evresi uyumsuzluğuna etkisinin Binary lojistik regresyon analizi

Tümor çapı

Patolojik tümör çapındaki bir birimlik artış, hem Univariate modelde hem de Multivaryant regresyon analizinde, Patoloji-BT ve Patoloji-PET-CT T evresi uyumsuzluğu riskini artırdığı saptandı. Univariate modelde bu risk, sırasıyla 0,789 ve 0,800 kat (p<0,001 ve p=0,016) artış gösterirken; Multivaryant modelde ise bu artış 0,802 ve 0,782 kat (p<0,001) olarak saptandı. Ancak, EUS ile patolojik evre uyumsuzluğu üzerinde, her iki modelde de tümör çapının istatistiksel olarak anlamlı bir etkisi bulunmamıştır (p>0,05) (Tablo 3).

Lenf nod tutulumu

Univariate analizde, LN negatif olan hastaların, pozitif olanlara kıyasla Patoloji-BT T evresi uyumsuzluğu riskinin 1,75 kat (1/0,571) daha fazla olduğu tespit edilmiştir (p=0,045). Ancak, Multiple regresyon analizinde bu etkinin istatistiksel olarak anlamlı olmadığı görülmüştür. Patoloji-PET-CT' de T evresi uyumsuzluğu açısından, her iki modelde de LN tutulumunun anlamlı bir etkisi bulunmadı. Patoloji-EUS' T evresi uyumsuzluğu, multiple regresyon analizinde, LN negatif olanlarda uyumsuzluk riskinin 1,57 kat daha fazla olduğu saptanmıştır (p<0,001). Ancak, Univariate analizde bu etki istatistiksel olarak anlamlı bulunmamıştır (Tablo 3).

Lokalizasyon

Patoloji-BT' de T evresi uyumsuzluğu açısından, hem Univariate hem de Multiple regresyon analizlerinde anlamlı bir etki bulunmamıştır (p>0,05). Patoloji-PET-CT' de T evresi uyumsuzluğu için Univariate analizde, tümörün alt bölgede lokalize olması, orta bölgeye göre uyumsuzluk riskini 3,25 kat artırmıştır (p=0,020). Bu etki, Multiple regresyon

analizinde de benzer şekilde 3,44 kat artırmıştır (p=0,021). Patoloji-EUS' ta T evresi uyumsuzluğu açısından, tümörün üst bölgede lokalize olması, alt bölgeye göre Univariate analizde uyumsuzluk riskini 3,532 kat artırmıştır (p=0,043). Ancak, Multiple regresyon analizinde bu etkinin istatistiksel olarak anlamlı olmadığı görülmüştür (Tablo 3).

Grade

Patoloji-BT' de T evresi uyumsuzluk riski açısından, Univariate analizde G1 tümör derecesi, G3'e kıyasla uyumsuzluk riskini 2,24 kat artırmıştır (1/0,446; p=0,020). Ancak, Multiple regresyon analizinde bu etkinin istatistiksel olarak anlamlı olmadığı görülmüştür (p>0,05). Patoloji-PET-CT ve Patoloji-EUS' ta T evresi uyumsuzluğu açısından, hem Univariate hem de Multiple regresyon analizinde tümör derecesinin uyumsuzluk üzerinde anlamlı bir etkisinin bulunmadığı tespit edilmiştir (p>0,05) (Tablo 3).

Cinsiyet

Cinsiyetin, Patoloji- BT, PET-CT ve EUS' ta T evresi uyumsuzluğuna etkisi üzerinde hem Univariate hem de Multiple regresyon analizlerinde anlamlı bir etkisinin olmadığı saptandı (p>0.05) (Tablo 3).

Tablo 3. Bağımsız değişkenlerin Patoloji- BT, PET-CT ve EUS T evresi uyumsuzluğuna etkisinin Binary lojistik regresyon analizi

	UYUM		Univariate		Multiple	
	Var	Yok	OR (%95 CI)	p	OR (%95 CI)	p
Patoloji TM Çap	5,5±2,48	4,1±2,40	0,789 (0,700-0,890)	**<0,001**	0,802 (0,706 - 0,91)	**<0,001***
	5,4±2,75	4,1±2,06	0,800 (0,667-0,960)	**0,016**	0,782 (0,638 - 0,959)	**0,018****
	3,07±1,87	3,45±1,90	1,109 (0,867-1,418)	0,409	1,034 (0,793 - 1,349)	0,806***
Lap sonucu						
Negatif	45 (51,7)	42 (48,3)		Referans*		
	27 (67,5)	13 (32,5)		Referans**		
	32 (72,7)	12 (27,3)		Referans***		
Pozitif	90 (65,2)	48 (34,8)	0,571 (0,331 - 0,988)	**0,045**	0,824 (0,447 - 1,521)	0,536*
	44 (67,7)	21 (32,3)	0,991 (0,427 - 2,299)	0,984	1,171 (0,427 - 3,211)	0,759**
	31 (73,8)	11 (26,2)	0,946 (0,364 - 2,461)	0,91	0,637 (0,201 - 2,027)	**<0,001*****
Lokalizasyon						
Alt	63 (59,4)	43 (40,6)		Referans*		
	29 (56,9)	22 (43,1)		Refernas**		
	34 (82,9)	7 (17,1)		Referans***		
Orta	48 (64)	27 (36)	0,824 (0,448 - 1,517)	0,535	1,039 (0,542 - 1,99)	0,909*
	30 (81,1)	7 (18,9)	0,308 (0,114 - 0,829)	**0,020**	0,291 (0,102 - 0,833)	**0,021****
	18 (69,2)	8 (30,8)	2,159 (0,674 - 6,915)	0,195	2,247 (0,658 - 7,667)	0,196***
Üst	24 (53,3)	21 (46,7)	1,282 (0,635 - 2,588)	0,488	1,586 (0,743 - 3,384)	0,233*
	12 (70,6)	5 (29,4)	0,549 (0,169 - 1,79)	0,32	0,604 (0,174 - 2,098)	0,428**
	11 (57,9)	8 (42,1)	3,532 (1,042 - 11,979)	**0,043**	3,506 (0,967 - 12,706)	0,056***
Grade						
G1	37 (49,3)	38 (50,7)		Referans*		
	22 (66,7)	11 (33,3)		Referans**		
	30 (78,9)	8 (21,1)		Referans***		
G2	50 (61,7)	31 (38,3)	0,604 (0,319 - 1,141)	0,12	0,72 (0,367 - 1,411)	0,339*
	28 (73,7)	10 (26,3)	0,714 (0,257 - 1,985)	0,519	0,785 (0,265 - 2,326)	0,662**
	18 (69,2)	8 (30,8)	1,667 (0,533 - 5,216)	0,38	2,105 (0,606 - 7,311)	0,241***
G3	48 (68,6)	22 (31,4)	0,446 (0,227 - 0,879)	**0,020**	0,568 (0,275 - 1,173)	0,126*
	21 (61,8)	13 (38,2)	1,238 (0,455 - 3,369)	0,676	1,903 (0,596 - 6,08)	0,277**
	15 (68,2)	7 (31,8)	1,75 (0,533 - 5,745)	0,356	2,399 (0,593 - 9,698)	0,22***
Cinsiyet						
Kadın	93 (60,4)	61 (39,6)		Referans*		
	47 (67,1)	23 (32,9)		Referans**		
	36 (66,7)	18 (33,3)		Referans***		
Erkek	42 (58,3)	30 (41,7)	1,089 (0,616 - 1,924)	0,769	0,927 (0,502 - 1,712)	0,808*
	24 (68,6)	11 (31,4)	0,937 (0,392 - 2,237)	0,883	0,833 (0,315 - 2,203)	0,713**
	27 (84,4)	5 (15,6)	0,37 (0,122 - 1,123)	0,079	0,353 (0,108 - 1,148)	0,084***

Patoloji-BT, ** Patoloji-PET-CT, * Patoloji-EUS T evresi uyumsuzluk etki sonuçları*

Bağımsız değişkenlerin Patoloji- BT, PET-CT ve EUS N evresi uyumsuzluğuna etkisinin Binary lojistik regresyon analizi

Tümor çapı

Multiple regresyon analizinde, patolojik tümör çapındaki bir birimlik artışın Patoloji-BT' de N evresi uyumsuzluğunu 0,817 kat artırdığı saptanmıştır (p<0,001). Ancak, Univariate analizde bu etkinin istatistiksel olarak anlamlı olmadığı görülmüştür (p>0,05). Patoloji-EUS' ta N evresi uyumsuzluğu univariate analizinde 1.369 kat artırdığı (p<0,018), fakat Multiple regresyon analizinde anlamlı bir etkisi saptanmadı. Patoloji-PET-CT N evresi uyumsuzluğu açısından tümör çapının hem Univariate hem de Multiple regresyon analizlerinde anlamlı bir etki bulunmamıştır (p>0,05) (Tablo 4).

Lenf nod tutulumu

LN pozitif olanlarda, univariate modelde patoloji-BT, PET-CT ve patoloji-EUS ile N evresi uyumsuzluk riskleri sırasıyla

6,427 kat (p<0,001), 6,635 kat (p<0,001) ve 11,4 kat (p<0,001) artış göstermiştir. Multiple regresyon analizinde ise bu risklerde, 7,761 kat (p<0,001), 7,428 kat (p<0,001) ve 9,944 kat (p<0,001) artış saptandı. Bu sonuçlar, LN pozitifliği olan hastalarda görüntüleme yöntemleri ile patolojik evreleme arasındaki uyumsuzluğun belirgin şekilde arttığını göstermektedir (Tablo 4).

Lokalizasyon

Tümörün lokalizasyonu ile patoloji-BT T, PET-CT, EUS N evresi uyumsuzluğu açısından, hem Univariate hem de Multiple regresyon analizlerinde anlamlı bir etki bulunmamıştır (p>0,05) (Tablo 4).

Grade

Univariate analiz sonuçlarına göre, G3 tümör derecesine sahip hastalarda, G1'e kıyasla Patoloji-BT, PET-CT ve EUS N evresi uyumsuzluğu riskleri sırasıyla 3,004 kat (p=0,002), 6 kat (p=0,001) ve 4,9 kat (p=0,006) daha yüksek bulunmuştur. Multiple regresyon analizinde ise G3'ün G1'e göre Patoloji-BT N evresi uyumsuzluğu riskini 2,189 kat artırdığı tespit edilmiştir (p=0,045). PET-CT N evresi uyumsuzluğu açısından, G2 tümör derecesine sahip hastalarda, G1'e göre uyumsuzluk riski Univariate analizde 3,007 kat (p=0,040) yüksek ve Multiple regresyon analizinde 4,452 kat (p=0,015) daha yüksek bulunmuştur. G3 derecesine sahip hastalar için ise bu risk, Multiple regresyon analizinde 4,543 kat daha yüksek olarak hesaplanmıştır (p=0,016). Bu sonuçlar, özellikle yüksek tümör derecelerinde (G2 ve G3), görüntüleme yöntemleri ile patolojik evreleme arasında belirgin uyumsuzluk riskleri olduğunu göstermektedir (Tablo 4).

Cinsiyet

Cinsiyetin, Patoloji- BT, PET-CT ve EUS N evresi uyumsuzluğuna etkisi üzerine hem Univariate hem de Multiple regresyon analizlerinde anlamlı bir etkisinin olmadığı saptandı (p>0.05) (Tablo 4).

Tablo 4. Bağımsız değişkenlerin Patoloji- BT, PET-CT ve EUS N evresi uyumsuzluğuna etkisinin Binary lojistik regresyon analizi

	UYUM		Univariate		Multiple	
	Var	**Yok**	**OR (%95 CI)**	**p**	**OR (%95 CI)**	**p**
Patoloji TM Çap	5,1±2,75	4,7±2,19	0,943 (0,848-1,049)	0,28	0,817 (0,714 - 0,936)	**0,004***
	4,8±2,78	5,2±2,37	1,0507 (0,909-1,227)	0,472	0,965 (0,802 - 1,16)	0,701**
	2,77±1,55	3,8±2,18	1,369 (1,056-1,775)	**0,018**	1,348 (0,961 - 1,891)	0,083***
Lap sonucu						
Negatif	72 (82,8)	15 (17,2)	Referans*			
	33 (82,5)	7 (17,5)	Referans**			
	38 (86,4)	6 (13,6)	Referans***			
Pozitif	59 (42,8)	79 (57,2)	6,427 (3,353 - 12,318)	**<0,001**	7,761 (3,736 - 16,123)	**<0,001***
	27 (41,5)	38 (58,5)	6,635 (2,558 - 17,211)	**<0,001**	7,428 (2,427 - 22,735)	**<0,001****
	15 (35,7)	27 (64,3)	11,400 (3,92 - 33,155)	**<0,001**	9,944 (2,927 - 33,782)	**<0,001***
Lokalizasyon						
Alt	60 (56,6)	46 (43,4)	Referans*			
	29 (56,9)	22 (43,1)	Referans**			
	24 (58,5)	17 (41,5)	Referans***			
Orta	43 (57,3)	32 (42,7)	0,971 (0,534 - 1,764)	0,922	0,973 (0,486 - 1,946)	0,938*
	21 (56,8)	16 (43,2)	1,004 (0,427 - 2,36)	0,992	0,777 (0,282 - 2,138)	0,625**
	17 (65,4)	9 (34,6)	0,747 (0,27 - 2,071)	0,576	0,496 (0,135 - 1,814)	0,289***
Üst	29 (64,4)	16 (35,6)	0,72 (0,35 - 1,48)	0,371	0,715 (0,317 - 1,612)	0,419*
	10 (58,8)	7 (41,2)	0,923 (0,303 - 2,81)	0,887	0,832 (0,228 - 3,03)	0,78**
	12 (63,2)	7 (36,8)	0,824 (0,269 - 2,525)	0,734	0,388 (0,095 - 1,59)	0,188***
Grade						
G1	51 (68)	24 (32)	Referans*			
	26 (78,8)	7 (21,2)	Referans**			
	28 (73,7)	10 (26,3)	Referans***			
G2	52 (64,2)	29 (35,8)	1,185 (0,61 - 2,304)	0,617	1,461 (0,691 - 3,091)	0,321*
	21 (55,3)	17 (44,7)	3,007 (1,051 - 8,604)	**0,04**	4,452 (1,335 - 14,845)	**0,015****
	17 (65,4)	9 (34,6)	1,482 (0,502 - 4,381)	0,476	1,267 (0,337 - 4,767)	0,727***
G3	29 (41,4)	41 (58,6)	3,004 (1,523 - 5,926)	**0,002**	2,189 (1,018 - 4,707)	**0,045***
	13 (38,2)	21 (61,8)	6,0 (2,03 - 17,738)	**0,001**	4,543 (1,33 - 15,519)	**0,016****
	8 (36,4)	14 (63,6)	4,900 (1,584 - 15,162)	**0,006**	2,106 (0,521 - 8,511)	0,296***
Cinsiyet						
Kadın	88 (57,1)	66 (42,9)	Referans*			
	41 (58,6)	29 (41,4)	Referans**			
	31 (57,4)	23 (42,6)	Referans***			
Erkek	44 (61,1)	28 (38,9)	0,848 (0,479 - 1,502)	0,573	0,849 (0,437 - 1,647)	0,628*
	19 (54,3)	16 (45,7)	1,191 (0,526 - 2,697)	0,676	1,801 (0,658 - 4,932)	0,252**
	22 (68,8)	10 (31,3)	0,613 (0,244 - 1,54)	0,298	0,543 (0,171 - 1,718)	0,299***

Patoloji-BT, ** Patoloji-PET-CT, * Patoloji-EUS N evresi uyumsuzluk etki sonuçları*

Tartışma

Bu çalışma, mide adenokarsinomu olan hastalarda preoperatif evreleme yöntemlerinin (BT, PET-CT ve EUS) patolojik evreleme ile uyumunu değerlendirmiştir. Bulgular, her bir yöntemin farklı düzeylerde uyum sağladığını ve doğruluğunu etkileyen faktörlerin mevcut olduğunu göstermiştir. Mide kanserinde preoperatif evreleme, hastalara uygun tedavi stratejileri belirlenmesi ve hastalığın prognozunun tahmin edilmesi açısından kritik bir role sahiptir. Klinik evrelemenin patolojik evrelemeyle uyumu, hastanın tedaviye yanıtını ve genel sağkalımını doğrudan etkileyebilir. EUS, tümörün mide duvarına invazyonunu erken evrelerde yüksek başarıyla tespit ederken, BT, lokal tümör yaygınlığını değerlendirmede daha etkilidir. PET-CT ise LN ve uzak metastazların tespitinde diğer yöntemlere kıyasla daha üstün bir rol oynar. Mide kanserinin teşhisinde yaygın olarak kullanılan iki yöntem olan EUS ve BT karşılaştırıldığında, EUS'un kullanım kolaylığı, düşük maliyeti ve radyasyon içermemesi gibi avantajları öne çıkmaktadır (2). Bununla birlikte, yöntemin seçimi, hastanın klinik durumu ve teşhis gereksinimlerine göre belirlenmelidir.

Bilgisayarlı Tomografi, PET-CT ve EUS yöntemlerinin patolojik T evreleri ile uyumu karşılaştırıldığında, BT'nin orta düzeyde uyum sağladığı (Kappa=0,421, p<0,001), PET-CT'nin daha yüksek uyum gösterdiği (Kappa=0,523, p<0,001) ve EUS'un en yüksek uyumu sağladığı (Kappa=0,621, p<0,001) bulunmuştur. Uyumun, BT ye göre daha yüksek olduğu söylense de son zamanlarda yapılan çalışmalarda birbirine yakın olduğu belirtilmektedir (5). Araştırmamızda, EUS'un T1 evresindeki yüksek uyumu (%87.1), mide duvarının invazyon derinliğini hassas bir şekilde değerlendirebilme kapasitesini göstermektedir. EUS'un yüksek uyumu, endoskopik ultrason probunun doğrudan tümör bölgesinde olmasından kaynaklanmış olabilir. T1 ve T2 evrelerinde EUS'un en iyi sonuçları verdiği (%87.1 ve %69.2), ancak T evresi arttıkça EUS'un patolojik evre ile uyumunun azaldığı (%64.7-62.5), BT ve PET-CT'nin ise T evresi ile uyumlarının arttığı ve özellikle T3 evresinde en yüksek uyumu sağladığı (%68.2 ve %72.5) tespit edildi. Bazı çalışmalar BT'nin T evresi için EUS'a göre üstün olduğunu ifade edilse de (6), çalışmamızda T1 ve T2 evrelerinde EUS'un daha yüksek uyum sağladığı saptanmıştır. Bu nedenle, T1 ve T2 evrelerinde EUS, T3 evresinde ise BT ve PET-CT kullanımı önerilmektedir. Ancak, EUS'un deneyim bağımlı ve invaziv bir yöntem olması, sedasyon komplikasyonları, küçük eğrilikler, büyük lezyonlar ve mide-özofagus bağlantısındaki tümörlerde evrelemede hata payına neden olması, dezavantajlarındandır (6). Bu doğrultuda, preoperatif evrelemeyi en iyi sonuçları elde etmek için EUS'un yüksek doğruluğunu, BT ve PET-CT ile birlikte kullanılması önerilebilir. Mide kanserinin preoperatif evrelemesinde BT en etkili tanı aracı olsa da, mide duvarındaki bireysel farklılıklar nedeniyle tanısal doğruluk tatmin edici olmayabilir (7), doğruluk oranı %43 ila %89 arasında değişmektedir (8). Çalışmamızda BT'nin patolojik T evreleri ile uyumu orta düzeyde (%54.8) bulunmuş, Özellikle T1 evresindeki zorluklar, submukoza görüntülemesindeki eksiklikler ve ödem ile yağ birikiminin ayırt edilmesindeki güçlükler (7) nedeniyle bazı T1 evreleri %29.4 oranında T0 olarak yorumlanmıştır. EUS'un T1 evresini belirlemedeki üstünlüğü çalışmamızla uyumludur (6). EUS'un T1 ve T2 evrelerinde üstün olduğu, BT'nin ise bu evrelerde yeterince doğru tespit yapamadığı göz önüne alındığında, her iki yöntemin birlikte kullanılması daha güvenilir sonuçlar elde edilmesini sağlayabilir. Ayrıca, Üç yöntemle elde edilen uyum oranı %81,8 olarak bulunmuş ve literatürde radyolojik tetkiklerin kombinasyonunu öneren çalışmalarla örtüşmüştür (4). Bu nedenle, T evrelemesinde mümkünse bu üç yöntemin bir arada kullanılması önerilmektedir. T2, T3 ve T4 evrelerinde, her üç yöntem de patolojik evreleme ile anlamlı bir uyum göstermiştir; ancak, PET-CT'nin metabolik aktiviteyi değerlendirme yeteneği, tümör evrelemesinde önemli bir avantaj sunarak genellikle daha iyi sonuçlar vermiştir.

LN metastazı, mide kanserinin postoperatif tedavi kararları açısından en kritik göstergelerden biridir ve bu metastazların görüntüleme yöntemleriyle doğru tespiti oldukça zordur (2). Çalışmamızda, BT, PET-CT ve EUS yöntemleri arasında LN evrelemesi açısından istatistiksel olarak anlamlı bir orta düzeyde uyum bulunmuştur (p<0,001). Önemli bir bulgu olarak, her üç yöntem de N0 evresinde yüksek doğruluk oranları sergilerken (5), N1 ve üstü evrelerde doğruluk oranlarının düştüğü gözlemlenmiştir. Bu durum, özellikle ileri evrelerde metastatik lenf nodu tespitinde bazı sınırlamaların olduğunu göstermektedir. Özellikle N3 evresinde EUS'un düşük performansı, mideden 6-7 cm uzaklıkta bulunan lenf nodlarını tespit etmede yetersiz olmasından kaynaklanmış olabilir (9). BT'nin N3 evresindeki uyum oranı %21,9 gibi oldukça düşük bir seviyede bulunmuştur. Literatürde, BT ve EUS'un N evresi doğruluk oranlarının sırasıyla %50-87,9 ve %50-90 arasında değiştiği belirtilmiş olup (10, 11), çalışmamızın sonuçları bu aralıklarla uyumludur. LN, belirginse veya konglomere ise EUS ve BT'de daha net değerlendirilir, ancak perigastrik LN görünürlüğü metastaz göstergesi olmayabilir ve inflamasyondan kaynaklanmış olabilir. Bu durum, preoperatif evrelemede metastatik gibi görünen LN, patolojik evrelemede negatif veya metastatik ayrımını zorlaştırabilir.

Bulgularımız, görüntüleme tekniklerinin her birinin güçlü ve zayıf yönlerini vurgulamaktadır ve kanser evrelemesinde daha güvenilir ve duyarlı yöntemlerin geliştirilmesi gerektiğini ortaya koymaktadır. Potansiyel bir çözüm olarak, farklı görüntüleme tekniklerinin bir arada kullanılması, bu sınırlamaların aşılmasına yardımcı olabilir.

Literatürde, daha büyük tümörlerin BT ve PET-CT ile daha doğru evrelendirildiği belirtilse de (12), çalışmanız, tümör çapındaki bir birimlik artışın patolojik evreleme ile bu görüntüleme yöntemleri arasında uyumsuzluk riskini artırdığını göstermektedir. BT'nin minimal invazyonları gözden kaçırma ve PET-CT'nin metabolik aktiviteyi tam olarak yansıtma sınırlılıkları, yanıltıcı evreleme sonuçlarına yol açabilir. Ancak, EUS T evresi analizinde tümör çapının veya diferansiyasyonunun uyumsuzluk riski üzerinde anlamlı bir etki

saptanmadık. Literatür ise, büyük tümör boyutlarının ve yetersiz diferansiyasyonun, EUS ile tümör invazyon derinliğinde yanlış sonuçlara neden olabileceğini belirtmektedir (13).

Tümör lokalizasyonu açısından, orta lokalizasyondaki tümörler, PET-CT ve EUS analizlerinde alt lokalizasyondan daha yüksek uyum göstermiştir (OR=0,571; p=0,045). Preoperatif T evre belirlemesinde BT performansını değerlendirmek için yapılan tek değişkenli ve çok değişkenli lojistik regresyon analizlerinde, tümör boyutu, lokalizasyon, invazyon derinliği ve grade gibi klinikopatolojik değişkenler ile BT ile belirlenen T evresi ile patolojik T evresi arasındaki uyumsuzluk riski arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (p>0.05) (13,14). Çok değişkenli analizde diğer değişkenler kontrol edilmesine rağmen istatistiksel anlamlılığın elde edilememesi, BT performansının bu değişkenlerden bağımsız olduğunu göstermektedir. PET-CT ve EUS, alt mide bölgesinin anatomik yapısı, daha fazla çevre doku ve organ ile komşuluk ilişkisi nedeniyle, tümörün gerçek yayılımının doğru bir şekilde belirlenmesini zorlaştırabilir. PET-CT' de metabolik aktiviteyi ölçümü ön planda olduğundan, bu bölgedeki tümörlerin metabolik aktivite paternleri farlılık gösterebilmesi nedeniyle, doğru evrelemeyi güçleştirebilir. Çok değişkenli analizde, diğer faktörlerin (örneğin, tümör boyutu, derinliği, lenf nodu tutulumu, grade) dahil edilmesine rağmen, alt bölge lokalizasyonunun etkisi korunmuştur. Bu durum, alt bölge lokalizasyonunun, PET-CT ile T evre uyumsuzluğu üzerindeki etkisinin, bu diğer faktörlerden bağımsız olabileceğini göstermektedir. Üst lokalizasyondaki tümörler, özellikle EUS T evresi ile patolojik evre arasındaki uyumsuzluğu artırmış (13) (OR=3,532; p=0,043), bu etki BT ve PET-CT analizlerinde gözlenmemiştir (15). Bu durum, üst bölge tümörlerinin EUS ile daha zor evrelenmesini açıklayan anatomik yapısı ve erişim zorluğunun etkisinin, çok değişkenli modelde tümör boyutu, invazyon derinliği, lenf nodu tutulumu ve grade gibi diğer faktörler tarafından maskelendiğini göstermektedir. Bu nedenle, üst bölge lokalizasyonunun tek başına EUS ile T evre uyumsuzluğu üzerinde bağımsız bir etkisi olmadığı sonucuna varılabilir.

LN negatif olanlarda, BT ve PET-CT T evre analizlerinde anlamlı bir etki göstermemiştir. Ancak, EUS T evresi için univariate analizde pozitif LN uyumsuzluk riskini azaltmıştır (p=0,045), ancak multiple analizde bu anlamlılık kaybolmuştur. Tümör derecesi, sadece BT T evresi için univariate analizde uyumsuzluk riskini azaltıcı bir eğilim göstermiştir (15) (p=0,020), ancak multiple analizde anlamını yitirmiştir. Cinsiyetin ise BT, PET-CT ve EUS T evreleri arasındaki uyumsuzluk riski üzerinde anlamlı bir etkisi bulunmamıştır (13-15). Çalışmamız, mide kanserinde preoperatif evrelemede tümör çapı ve lokalizasyonunun BT, PET-CT ve EUS uyumunda kritik faktörler olduğunu ortaya koymuştur. Bununla birlikte, LN, tümör derecesi ve cinsiyet gibi değişkenlerin uyumsuzluk üzerindeki etkisi sınırlı kalmıştır. Preoperatif evrelemede, görüntüleme yöntemlerinin bir arada kullanılması, tanısal doğruluğu artırabilir.

Tümör derecesi açısından, G3 tümör derecesi uyumsuzluk riskini önemli ölçüde artırmıştır. Tek değişkenli analizde bu risk 3 kat artmış (p = 0,002), çoklu değişkenli analizde ise 2,2 kat artış göstermiştir (p = 0,045). Buna karşın, G1 ve G2 tümör derecelerinin uyumsuzluk üzerinde anlamlı bir etkisi bulunmamıştır. Bulgularımız, bazı önceki çalışmaların aksine, tümör diferansiyasyonunun uyumsuzluk ile anlamlı bir ilişki göstermediğini ortaya koymaktadır.

Tümör çapı, sadece çoklu değişkenli analizde uyum sağlama eğilimi göstermiştir (15) (OR = 0,817, p = 0,004), ancak univariate analizde anlamlı bulunmamıştır. Tümör lokalizasyonu ve cinsiyetin uyumsuzluk üzerindeki etkisi ise istatistiksel olarak anlamlı olmamıştır (p > 0,6) (15). Bu sonuçlar, LN ve tümör derecesinin uyumsuzluk değerlendirmelerinde önemli rol oynadığını, diğer faktörlerin etkisinin ise daha sınırlı olduğunu göstermektedir.

Sonuç

Sonuç olarak, mide adenokarsinomu olan hastalarda preoperatif evreleme yöntemleri ile patolojik evreleme arasındaki uyumu artırmak için farklı görüntüleme yöntemlerinin bir arada kullanılması ve hastaya özgü faktörlerin dikkate alınması önemlidir. Özellikle tümör çapı ve lokalizasyonu, preoperatif evreleme doğruluğunu belirlemede kritik rol oynayan faktörlerdir. Bu bulgular, klinik pratikte preoperatif evreleme stratejilerinin daha doğru ve etkili bir şekilde planlanmasına katkı sağlayabilir.

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Araştırma Makalesi / Research Article

Adolesan ve Erişkinlerde Yasadışı Madde Analiz Sonuçlarının Değerlendirilmesi

Evaluation of Illicit Substance Analysis Results in Adolescents and Adults

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Öz

Amaç: Bu çalışmada, yasadışı madde analiz sonuçlarının yaşa ve cinsiyete göre değerlendirilmesi amaçlandı.
Materyal ve metod: Bu retrospektif çalışma kapsamında, Ocak-Haziran 2023 tarihleri arasında AMATEM laboratuvarında çalışılan yasadışı madde (sentetik kannabinoid-3, kokain, opiat, benzodiazepin, kannabinoid, amfetamin, ekstazi ve eroin) analiz sonuçları hastane bilgi sisteminden elde edildi. Daha sonra madde kullanım dağılımı yaşa [Adolesan (12-17 yaş) ve erişkin (≥18 yaş)] ve cinsiyete göre belirlendi.
Bulgular: Toplam 9471 idrar örneği, farklı yaş gruplarına (adolesan yaş grubu: 254, erişkin yaş grubu: 9217) ve cinsiyete (kadın: 346, erkek: 9125) göre yasadışı madde analizi sonuçları açısından incelendi. 9471 idrar örneğinin 3724'ünde (%39.3) madde pozitifliği vardı. Adolesanlarda en yüksek madde pozitifliği oranlarının sırasıyla amfetamin (%16.1), kannabinoid (%4.7) ve benzodiyazepin (%1.6) olduğu saptandı. Erişkinlerde en yüksek madde pozitifliği oranları sırasıyla amfetamin (%29.6), kannabinoid (%12.8) ve opiat (%9.7) olarak bulundu. Amfetamin, kanabinoid ve opiat pozitiflik oranları erişkinlerde adolesanlara göre anlamlı derecede yüksekti (tümü için p<0.001). Erkeklerde ve kadınlarda en yüksek görülen madde pozitifliği oranları sırasıyla amfetamin (%29.8 ve %14.7), kanabinoid (%13 ve %3.8) ve opiat (%9.7 ve %3.5) olarak saptandı. Amfetamin, kannabinoid ve opiat pozitiflik oranlarının kadınlara kıyasla erkeklerde anlamlı derecede daha yüksek olduğu saptandı (tümü için p<0.001). Çoklu madde kullanımında en sık amfetamin–kannabinoid, ikinci sıklıkta ise amfetamin–opiat ikilisinin olduğu görüldü.
Sonuç: Her iki yaş grubu ve cinsiyette en yüksek pozitiflik oranı amfetaminde, ikinci sırada ise kannabinoid maddesinde tespit edildi. Çalışmamızın, yaşa ve cinsiyete göre madde kullanım sıklığı ve profili hakkında bilgi sağlaması nedeniyle madde kullanımına karşı etkili önleyici stratejilerin geliştirilmesinde yararlı olacağını düşünmekteyiz.

Anahtar Kelimeler: Adolesan, Amfetamin, Cinsiyet, Kannabinoid, Yasadışı madde analizi

Abstract

Background: This study aimed to evaluate the illicit substance analysis results according to age and gender.
Materials and Methods: In this retrospective study, the results of illegal substance analysis (synthetic cannabinoid-3, cocaine, opiate, benzodiazepine, cannabis, amphetamine, ecstasy and heroin) studied in the AMATEM laboratory between January 2023 and June 2023 were extracted from the hospital information system. Then, the frequency of illicit substance use was determined according to age [adolescent (12-17 years) and adult (≥18 years)] and gender.
Results: A total of 9471 urine samples were examined for illicit substance analysis results according to different age groups (adolescent age group: 254, adult age group: 9217) and gender (women: 346, men: 9125). Of 9471 urine samples, 3724 (39.3%) were substance positive. The highest substance positivity rates in adolescents were found to be amphetamine (16.1%), cannabinoid (4.7%) and benzodiazepine (1.6%), respectively. The highest substance positivity rates in adults were found to be amphetamine (29.6%), cannabinoid (12.8%) and opiate (9.7%), respectively. Amphetamine, cannabinoid and opiate positivity rates were significantly higher in adults compared to adolescents (p<0.001 for all). The most common substance positivity rates in men and women were amphetamines (29.8% and 14.7%), cannabinoids (13% and 3.8%), and opiates (9.7% and 3.5%), respectively. Amphetamine, cannabinoid and opiate positivity rates were significantly higher in men compared to women (p<0.001 for all). In polysubstance use, amphetamine–cannabinoid pairs were the most common, followed by amphetamine–opiate pairs.
Conclusions: The highest positivity rate in both age groups and gender was detected in amphetamine, followed by cannabinoid. We believe that our study will be useful in developing effective preventive strategies against substance use because it provides information about the frequency and profile of substance use according to age and gender.

Keywords: Adolescent, Amphetamine, Gender, Cannabinoid, Illicit substance analysis

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Giriş

Uyuşturucu madde kullanımı dünya çapında önemli bir halk sağlığı problemidir. Dünyadaki madde kullanıcılarının sayısı 2011 yılında 240 milyon iken, 2021 yılında 296 milyona yükseldiği tahmin edilmektedir. Bu sayı 15-64 yaş arasındaki nüfusun yaklaşık %6'sını oluşturmaktadır (1). Ülkemizde madde kullanım yaygınlığı Avrupa ülkelerine göre daha düşük olmakla birlikte (2), yapılan çalışmalarda yasadışı madde kulanım oranının yıllar içerisinde giderek artış gösterdiği bildirilmiştir (3-5). Madde kullanımı erkeklerde, hiç evlenmemiş olanlarda, psikiyatrik rahatsızlığı olanlarda ve düşük eğitim ve gelir düzeyine sahip olanlarda daha yaygındır (6). Yasadışı madde kullanımının; antisosyal kişilik bozukluğu, sorunlu kişilerarası ilişkiler ve şiddet içeren davranışlar sergileme gibi psikososyal zararları bulunmaktadır (7). Ayrıca kronik madde kullanıcılarında kardiyovasküler hastalık, akciğer hastalıkları, siroz, malignite, kan yoluyla bulaşan bakteriyel ve viral enfeksiyonlar gibi bir çok ciddi komplikasyonlar oluşabilmektedir (8).

Madde kullanımına karşı mücadelede akılcı ve etkili politikalar geliştirebilmek için madde kullanım yaygınlığı hakkında kapsamlı bilgi edinmek kritik öneme sahiptir (9,10). Ancak ülkemizde laboratuvar analizlerine dayalı madde kullanım yaygınlığını gösteren araştırmalar oldukça sınırlı olup, madde kullanımıyla mücadelede etkili önleyici stratejilerin geliştirilebilmesi için madde kullanım yaygınlığı ve profili hakkında geniş çaplı çalışmalara ihtiyaç duyulmaktadır (3,10,11). Bu bağlamda, çalışmamızda yaş ve cinsiyete göre idrarda yasadışı madde analiz sonuçlarının değerlendirilmesi ve elde edilen veriler ile literatüre katkıda bulunulması amaçlanmıştır.

Materyal ve Metod

Bu çalışma kapsamında, Ocak 2023 ila Haziran 2023 tarihleri arasında Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi bünyesinde olan AMATEM laboratuvarında 5767 kişiye ait 9471 idrar örneğinde çalışılan yasadışı madde analiz sonuçları laboratuvar bilgi sisteminden elde edildi. Daha sonra yasadışı madde kullanım dağılımı yaşa [Adolesan (12-17 yaş) ve erişkin (≥18 yaş)] ve cinsiyete göre belirlendi. İdrar örneklerinin analize uygun olup olmadığını belirlemek için dansite, pH, kreatinin ve nitrit'ten oluşan idrar bütünlük testleri yapıldı. Sağlık Bakanlığı tarafından yayımlanan madde analizi kılavuzunda idrar bütünlük testleri için tanımlanan değerlendirme kriterleri esas alınarak (12), idrar bütünlük testi uygun olmayan numuneler reddedildi. İdrar bütünlük testi yapılan ve uygunluğu doğrulanan numuneler çalışmaya dahil edildi.

Laboratuvarımızda yasadışı madde analizi kapsamında sentetik kannabinoid-3, kokain, opiat, benzodiazepin, kannabinoid ve amfetamin testleri çalışılmaktadır. Amfetamin test sonucunun pozitif çıktığı durumlarda ekstazi testi, opiat test sonucunun pozitif çıktığı durumlarda ise eroin testi çalışılmaktadır. Kannabinoid, ekstazi, kokain, amfetamin ve opiat parametreleri DRI kitleri (Microgenics, ABD) ile, eroin ve benzodiazepin parametreleri CEDIA kitleri (Microgenics, ABD) ile ve sentetik kannabinoid-3 testi ARK AB-PINACA reaktifleri (ARK Diagnostics, ABD) ile AU 480 analizöründe (Beckman Coulter, ABD) ölçüldü. İdrar taramasında kullanılan eşik değerler; opiat: 2000 ng/mL, benzodiazepin: 300 ng/mL, kokain: 150 ng/mL,amfetamin: 500 ng/mL, ekstazi: 500 ng/mL, kannabinoid: 50 ng/mL, eroin: 10 ng/mL ve sentetik kannabinoid-3: 5 ng/mL olarak kullanılmaktadır. Bu araştırma için Harran Üniversitesi Etik Kurul Komisyonu tarafından onay alındı (protokol numarası: HRÜ/24.13.17).

Çalışma verilerimiz SPSS versiyon 20 programı kullanılarak analiz edildi ve anlamlılık düzeyi $p<0.05$ olarak kabul edildi. Gruplar arasında kategorik değişkenlerin karşılaştırılmasında Pearson ki-kare testi veya Fisher ki-kare testi kullanıldı. Sonuçlar sayı ve yüzde olarak ifade edildi.

Bulgular

Toplam 5767 kişiye ait 9471 idrar numunesinde çalışılan madde analiz sonuçları incelendi. Katılımcılara ait yaş ortalaması 31.4±9.8 yıl idi. 9471 idrar örneğinin 3724'ünde (%39.3) madde pozitifliği vardı. Toplam numune sayısına göre yasadışı madde pozitifliği oranlarının ve çoklu madde kullanımının dağılım verileri Tablo 1'de verilmiştir.

Tablo 1. Analizi yapılan idrar numunelerinde görülen madde pozitiflik oranları

Madde, n (%)	**Total (N:9471)**
Amfetamin	2770 (29.2)
Kannabinoid	1196 (12.6)
Opiat	896 (9.5)
Benzodiyazepin	296 (3.1)
Kokain	13 (0.1)
Sentetik kannabinoid-3	85 (0.9)
Tekli ve çoklu madde kullanım dağılımı, n (%)	
Tek testi pozitif numune sayısı	2326 (62.5)
İki testi pozitif numune sayısı	1268 (34)
Üç testi pozitif numune sayısı	126 (3.4)
Dört testi pozitif numune sayısı	4 (0.1)
Total	3724 (100)

N: Total numune sayısı, n (%): Madde pozitifliği olan numune sayısı ve yüzdesi

En fazla pozitiflik oranı amfetamin (%29.2) maddesinde saptanırken, bunu kannabinoid (%12.6) ve opiat (%9.5) maddeleri izledi. Opiat test sonucu pozitif olan numenelerin %70.2'sinde eroin pozitifliği, amfetamin testi sonucu pozitif olan numunelerinde %4.4'ünde ekstazi pozitifliği saptandı. Madde pozitifliği olan örnekler arasında iki veya daha fazla madde pozitifliği olan örneklerin oranı %37.5 idi. Çoklu madde kullanımında en sık amfetamin- kannabinoid, ikinci sıklıkta ise amfetamin-opiat ikilisinin olduğu belirlendi.
Tablo 2'de adolesan ve erişkin yaş gruplarındaki madde pozitiflik oranları özetlenmiştir. Adolesan yaş grubunun medyan (minimum-maksimum) yaşı 16 (12-17) yıldı ve 217'si (%85.4) erkek idi. Erişkin yaş grubunun medyan (minimum-maksimum) yaşı 30 (18-84) yıldı ve 8908'i (%96.6) erkek idi. Erişkinlerde en yüksek madde pozitifliği oranı amfetamin (%29.6) maddesinde saptanırken, bunu kannabinoid (%12.8) ve opiat (%9.7) maddeleri takip etti. Adolesanlarda en yüksek madde pozitifliği oranları sırasıyla amfetamin (%16.1, kannabinoid (%4.7) ve benzodiyazepin (%1.6) olarak bulundu. Amfetamin (p<0.001), kannabinoid (p<0.001) ve opiat (p<0.001) testlerinde adolesanlara kıyasla erişkinlerde anlamlı derecede daha yüksek pozitiflik saptandı.

Tablo 2. Adolesan ve erişkinlerde madde pozitiflik oranları

Madde, n (%)	Adolesan (12-17 yaş), (N: 254)	Erişkin (≥18 yaş), (N:9217)	*P* değeri
Amfetamin	41 (16.1)	2729 (29.6)	<0.001
Kannabinoid	12 (4.7)	1184 (12.8)	<0.001
Opiat	2 (0.8)	894 (9.7)	<0.001
Benzodiyazepin	4 (1.6)	292 (3.2)	0.150
Sentetik kannabinoid-3	1 (0.4)	84 (0.9)	0.730
Kokain	–	13 (0.1)	–

N: Total numune sayısı, n (%): Madde pozitifliği olan numune sayısı ve yüzdesi

Madde kullanımının cinsiyete göre dağılımı değerlendirildiğinde, hem erkeklerde hem de kadınlarda en sık görülen madde pozitifliği oranlarının sırasıyla amfetamin (%29.8 ve %14.7), kannabinoid (%13 ve %3.8) ve opiat (%9.7 ve %3.5) olduğu bulundu. Amfetamin (p<0.001), kannabinoid (p<0.001) ve opiat (p<0.001) testlerinde kadınlara kıyasla erkeklerde anlamlı derecede daha yüksek pozitiflik tespit edildi. (Tablo 3).

Tablo 3. Cinsiyete göre madde pozitifliği oranları

Madde, n (%)	Kadın (N: 346)	Erkek (N:9125)	*P* değeri
Amfetamin	51 (14.7)	2719 (29.8)	<0.001
Kannabinoid	13 (3.8)	1183 (13)	<0.001
Opiat	12 (3.5)	884 (9.7)	<0.001
Benzodiyazepin	6 (1.7)	290 (3.2)	0.130
Sentetik kannabinoid-3	–	85 (0.9)	–
Kokain	–	13 (0.1)	–

N: Total numune sayısı, n (%): Madde pozitifliği olan numune sayısı ve yüzdesi

Tartışma

Yasadışı madde kullanımına genellikle adolesan döneminde başlanmaktadır (13). Ebeveynlerin uyuşturucu kullanımı, ebeveyn-çocuk ilişkilerinin zayıf olması, ebeveynlerin düşük eğitim seviyeleri, düşük sosyoekonomik durum, fiziksel ve cinsel istismar, akran zorbalığı (14), erkek cinsiyet ve yenilik arayışı gibi bireysel risk faktörler (15) adolesanlarda madde kullanımını tetiklemektedir. Yasadışı madde kullanımının akut ve uzun vadeli sağlık üzerinde olumsuz etkileri olduğu gösterilmiştir. Kronik madde kullanımı kardiyovasküler hastalıklara, akciğer hastalıklarına, siroza, kansere, psikotik bozukluklara ve diğer ruhsal bozukluklara yol açabilmektedir (8). Madde kullanımına karşı mücadelede etkili önleyici stratejilerin geliştirilmesi açısından, ulusal ve bölgesel düzeyde madde kullanım profilinin ve madde kullanım riski taşıyanların belirlenmesi kritik öneme sahiptir (16). Bu bağlamda, bu çalışmada hastanemiz bünyesinde bulunan AMATEM laboratuvarından elde edilen madde analiz sonuçları kullanılarak madde kullanım dağılımı yaşa ve cinsiyete göre belirlendi.

Çalışmamızda laboratuvar verilerine göre en yüksek madde pozitiflik oranlarının sırasıyla amfetamin, kannabinoid ve opiat olduğu bulundu. İki veya daha fazla madde pozitifliği olan numune oranı %37.5 idi. Çoklu madde kullanımında en sık amfetamin–kannabinoid, ikinci sıklıkta ise amfetamin–opiat ikilisinin olduğu belirlendi. Karakükcü ve arkadaşlarının Kayseri ilinde yaptığı çalışmada, 2014 yılında en yüksek madde pozitifliği oranının benzodiazepin, 2015 ve 2016 yıllarında ise amfetamin/metamfetamin olduğu bulunmuştur. Ayrıca, yıllar içinde çoklu madde kullanım oranının önemli ölçüde arttığı, en yaygın çoklu madde kullanımının amfetamin–kanabinoid grubu olduğu, bunu amfetamin–opiat grubunun izlediği bildirilmiştir (3). Atik ve Çimen, NP-İstanbul Hastanesi laboratuvar verilerine göre 2015-2020 yılları arasında en yüksek madde pozitiflik oranının esrar olduğunu belirtmişlerdir. Ek olarak, 2015 yılından bu yana amfetamin kullanımında sürekli bir artış olduğuna dikkat çekmişlerdir. İkili

madde kullanım tercihlerinin yıllara göre değişmesine rağmen çoğunlukla esrar–kokain kullanımı olduğunu bildirmişlerdir (11). Diğer bir çalışmada, Balıkesir ilinde Temmuz 2016-Kasım 2018 tarihleri arasında en yüksek madde pozitifliğinin kannabinoid olduğu, bunu ekstazi ve amfetaminin izlediği tespit edilmiştir (17). Yakın zamanda yapılan bir çalışmada ise 1 Mayıs 2022 ila 31 Mayıs 2023 tarihleri arasında Ankara Bilkent Şehir Hastanesi'nde yapılan madde analiz sonuçlarına göre, en yüksek madde pozitifliği oranının benzodiazepinlerde olduğu, bunu amfetamin ve kanabinoidlerin izlediği bildirilmiştir. Yazarlar, yüksek benzodiazepin pozitifliğinin tıbbi kullanım ve/veya yasadışı kullanımdan kaynaklandığını belirtmişlerdir (9).

Çalışmamızda madde pozitifliği oranları adolesan (12-17 yaş) ve erişkin (≥18 yaş) yaş gruplarına göre de değerlendirildi. Adolesan yaş grubunda en sık kullanılan maddelerin sırasıyla amfetamin, kannabinoid ve benzodiazepin olduğu bulundu. Erişkin yaş grubunda ise sıralama amfetamin–kanabinoid–opiat şeklinde tespit edildi. Gok ve Turhan tarafından yapılan bir çalışmada, pediatrik grupta (0-18 yaş) en yüksek madde pozitifliği benzodiazepin maddesinde, ardından amfetamin maddesinde gözlenmiştir. Erişkin (18-64 yaş) grubunda ise sıralamanın benzodiazepin–amfetamin–kannabinoid şeklinde olduğu görülmüştür (9). Aslan ve arkadaşları, 2015-2016 yıllarında çocuk ve adolesan (≤18 yaş) grubunda en sık pozitif tespit edilen maddenin kannabinoidler olduğunu, bunu amfetaminler ve benzodiazepinlerin izlediğini bildirmişlerdir (18). Çiftçi Demirci ve arkadaşları, Ocak 2011 ile Aralık 2012 tarihleri arasında İstanbul'da 11-20 yaş aralığındaki 1969 çocuk ve gencin madde analiz sonuçlarını değerlendirmişler ve en yüksek madde pozitifliğinin esrarda olduğunu, bunu solventler/inhalanlar ve ekstazinin izlediğini saptamışlardır (19). Diğer bir çalışmada, 2013-2016 yılları arasında idrar örnekleri yasadışı maddeler açısından taranan adolesanlarda en sık pozitif tespit edilen maddenin amfetamin olduğu, bunu kannabinoid ve benzodiazepin maddelerinin izlediği belirlenmiştir (4). Bu sonuçlar madde kullanım profilinin yaş gruplarına göre hem yıllara hem de bölgelere göre değişkenlik gösterdiğini ortaya koymaktadır.

Yaşın yanı sıra cinsiyetin de madde kullanım sıklığıyla ilişkili bir faktör olduğu bildirilmiştir (20,21). Çalışmamızda, önceki çalışma sonuçlarıyla uyumlu olarak (3,9,17,21), erkeklerde kadınlara kıyasla daha yüksek oranda madde kullanımının olduğunu bulduk. Ek olarak, hem kadınlarda hem de erkeklerde en yüksek madde pozitifliğinin sırasıyla amfetamin, kannabinoid ve opiat olduğunu tespit ettik. Gök ve Turhan tarafından yapılan çalışmada, her iki cinsiyette madde kullanım dağılımında ilk üç maddenin benzodiazepin–amfetamin–kannabinoid olduğu belirlenmiştir (9). Diğer bir çalışmada, 2015 yılında erkeklerde en çok pozitif tespit edilen uyuşturucu maddenin kokain olduğu, 2016-2020 yılları arasında ise kanabinoid olduğu tespit edilmiştir. Kadınlarda ise 2015 ve 2016 yıllarında en çok pozitif saptanan madde alkol olurken, sonraki yıllarda kanabinoid olduğu bildirilmiştir (11). Bu sonuçlar madde kullanımının erkeklerde kadınlara göre daha yaygın olduğunu ve her iki cinsiyet için madde kullanım profillerinin bölgelere göre farklılık gösterdiğini ortaya koymaktadır.

Bu çalışmanın en önemli kısıtlılığı, tek merkezli ve kısa bir zaman periyodundaki madde analizi sonuçlarının değerlendirilmiş olmasıdır. Diğer bir kısıtlılık ise çalışma verilerinin olgu bazlı değil, örnek bazlı olmasıdır. Ayrıca bu çalışmada madde bağımlılığına neden olabilecek ailesel, sosyal ve bireysel risk faktörlerinin değerlendirilmemiş olması da önemli bir kısıtlılıktır. Ancak çalışmamız Güneydoğu Anadolu Bölgesi'ndeki bir ilde madde kullanım dağılımını yaşa ve cinsiyete göre ortaya koyan ilk çalışmadır. Madde kullanım yaygınlığı ve profili hakkında daha doğru bilgilere ulaşmak için belirli dönemlerde yapılacak, daha geniş madde tarama panelini içeren çok merkezli çalışmalara ihtiyaç vardır.

Teşekkür

AMATEM psikiyatri hekimlerine ve laboratuvar çalışanlarına veri toplamada katkı sağladıkları için teşekkür ederiz.

Etik onam: *Harran Üniversitesi Etik Kurul Komisyonu tarafından onay alındı (tarih: 09/09/2024 - karar numarası: HRÜ/24.13.17).*

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Research Article / Araştırma Makalesi

Histopathological Analysis of Hysterectomy Materials in A Tertiary Hospital

Üçüncü Basamak Hastanede Histerektomi Materyallerinin Histopatolojik Analizi

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Abstract

Background: Hysterectomy, a frequently used surgical procedure in gynecology, entails the removal of a part or all of the uterus and is employed in treating various benign and malignant diseases. This study aims to evaluate the histopathological analyses of patients underwent hysterectomy in a tertiary hospital.
Materials and Methods: The clinical and histopathological data of 107 patients who underwent hysterectomy in Mardin training and research hospital between January and March 2024 were retrospectively analyzed. The patients' age, hysterectomy type, indication, histopathological diagnosis, and other clinical parameters were recorded.
Results: Total laparoscopic hysterectomy (TLH) was the most preferred type of hysterectomy (n=62, %57.94) and patients' age average was 49.83. Abnormal uterine bleeding (AUB) and myoma uteri was the most prevalent reasons of hysterectomy (n=47, %47.66). Among endometrial lesions, endometrial polyp was the most common (n=34, 31.77%), and among myometrial lesions, leiomyoma was the most common pathological finding (n=52, 47.27%).
Conclusions: This study revealed that the histopathological analysis results of hysterectomy materials were largely consistent with clinical diagnoses. AUB and myoma uteri were among the leading indications for hysterectomy.

Keywords: Hysterectomy, Histopathology, Myoma uteri, Endometrial polyp, Leiomyoma, uterine bleeding.

Öz

Amaç: Histerektomi, jinekolojide sıklıkla uygulanan cerrahi bir işlemdir. Uterusun bir kısmının veya tamamının çıkarılmasıdır. Çeşitli benign ve malign hastalıkların tedavisinde kullanılır. Bu çalışmanın amacı, histerektomi materyallerinin histopatolojik analiz sonuçlarını incelemek ve klinik tanılarla karşılaştırmaktır.
Materyal ve Metod: Bu çalışmada, 2024 yılı Ocak-Mart ayları arasında üçüncü basamak Mardin eğitim ve araştırma hastanesinde histerektomi uygulanan 107 hastanın klinik ve histopatolojik verileri retrospektif olarak analiz edildi. Hastaların yaş, histerektomi tipi, endikasyon, histopatolojik tanı ve diğer klinik parametreleri kaydedildi.
Bulgular: Hastaların yaş ortalaması 49,83 idi. En sık histerektomi tipi total laparoskopik histerektomi (TLH) idi (n=62, %57,94). En sık histerektomi endikasyonları anormal uterin kanam ve myoma uteri idi (n=47, %47,66). Endometriyal lezyonlar arasında en sık endometrial polip, (n=34, %31,77) myometriyal lezyonlarda ise leiomyoma en sık saptanan patolojik bulguydu (n=52, %47,27).
Sonuç: Bu çalışmada, histerektomi materyallerinin histopatolojik analiz sonuçlarının klinik tanılarla büyük ölçüde uyumlu olduğu gözlendi. Anormal uterin kanama ve myoma uteri, histerektomi endikasyonları arasında en ön sıralarda yer aldı.

Anahtar Kelimeler: Histerektomi, Histopatoloji, Endometrial polip, Uterus kanaması, Miyom

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Introduction

The uterus is a vital organ in the female reproductive system, consists of two main parts: the corpus uteri and the cervix uteri. The corpus uteri comprises the endometrium and myometrium layers. Following cesarean section, hysterectomy, the surgical removal of the uterus, ranks as the second most common major surgery globally (1). Despite the availability of conservative and medical surgical options, hysterectomy is still the most favored method for treating gynecological diseases (2). Uterine preservation should be considered when the risks outweigh the benefits of surgical removal or when there are symptoms that do not respond to successful medical therapy and impair quality of life (3).

The endometrium of the uterus sheds every month under hormonal influence. The most common reasons for patients to visit gynecologists include vaginal bleeding, discharge, pelvic pain, irregular menstruation, and postmenopausal bleeding, along with lesions in the corpus and cervix. While numerous treatment options, including conservative and medical surgical interventions, are available today, hysterectomy remains among the most preferred methods for addressing gynecological issues (3).

Hysterectomy is a widely performed gynecological surgical procedure. It allows definitive diagnosis of all uterine and cervical pathology. By facilitating the retrieval of sufficient samples from the essential and suspected regions, it assists in diagnosing a variety of lesions without encountering any sampling inaccuracies.

The objective of this study is to explore the diverse gross and histopathological findings of the uterus and cervix in hysterectomy specimens collected, and to examine their correlation with clinicopathological factors.

Materials and Methods

Study Population: This study included 107 patients who underwent hysterectomy at Mardin Training and Research Hospital between January 2024 and March 2024.

Inclusion Criteria:

- Patients were aged 30 years and over.
- All patients with uterine and/or cervical hysterectomy indications were included in the study.
- The surgical method and type (abdominal, vaginal, laparoscopic) were not considered.

Exclusion Criteria:

- Hysterectomies performed for obstetric reasons

Processing of Hysterectomy Material:

- Hysterectomy materials were transferred to 10% fresh formalin in a 1:10 ratio in the operating room.
- Macroscopic examination was performed after 24 hours of fixation.
- Sections were taken from the uterus and cervix as follows:

Uterus:

- From the fundus, corpus, and lower uterine segment
- Including endometrium, myometrium, and serosa

Cervix:

- From both cervical lips
- Including endocervix and ectocervix
- Sections were processed in an automatic tissue processor, and paraffin blocks were prepared.
- 4-micron thick sections were taken from the blocks and stained with Hematoxylin & Eosin (H&E) staining.
- Special stains (PAS) were also used when necessary.

Histopathological Examination:

- Histopathological examination was performed by an experienced pathologist.
- The findings were evaluated according to the histopathology criteria published by the World Health Organization (WHO).
- The histopathological diagnosis of each patient was compared with the clinical diagnosis.

Statistical analysis : SPSS v.20.0 statistical program was utilized for statistical analysis. The patients' ages, hysterectomy types, indications, histopathological diagnoses, and other clinical parameters were summarized using descriptive statistics.

Results

A retrospective analysis was conducted on 107 hysterectomy procedures, involving patients aged between 41 and 74 years. The most common age group which underwent hysterectomy was 41-51 years. With a mean age of 49.83 years, total laparoscopic hysterectomy emerged as the most prevalent type, accounting for 62 cases (57.94%) Table (1). The commonest indication for surgery was abnormal uterin bleeding and myoma uteri (47,66 %, 47,66%) Table (2).

Table 1. Distribution based on hysterectomy type

Type of hysterectomy	Number of cases	Percentage
Total laparoscopic hysterectomy	62	57,94 %
Total abdominal hysterectomy	40	37,38 %
Vaginal hysterectomy	3	2,80 %
Radical Total abdominal hysterectomy	2	1,86 %

Table 2. Indication for surgery

Abnormal uterine bleeding	47,66 %
Myoma uteri	47,66 %
Dermoid cyst	2,80 %
Uterine prolapse	1,86 %

Endometrial polyp emerged as the most frequent pathology among endometrial lesions, observed in 34 cases (31.77%) Table (3).

Table 3. Histopathological lesions of the endometrium

Endometrial lesions	Number of cases	Percentage
Endometrial Polyp	34	31,77 %
Endometrium in the secretory phase	29	27,10 %
Proliferative endometrium	24	22,42 %
Simple Non-atypical hyperplasia	4	3,73 %
Endometrium with decidualization	4	3,73 %
Complex Non-atypical hyperplasia	3	2,80 %
Atrophic endometrium	2	1,86 %
Simple atypical hyperplasia	2	1,86 %
Endometrial carcinoma	2	1,86 %
Atrophic endometrium and endometrial polyp	1	0,93 %
Inflammation	1	0,93 %
Complex atypical hyperplasia	1	0,93 %

The most prevalent myometrial pathology observed was leiomyoma, accounting for 51 cases (47.66%) Table (4). Chronic cervicitis stood out as the most prevalent pathology among cervical lesions, identified in 86 cases (80.37%) Table(5).

Table 4. Histopathological lesions of myometrium

Myometrial lesions	Number of cases	Percentage
Leiomyoma	51	47,66 %
Adenomyosis	36	33,64 %
Adenomyosis , Leiomyoma	10	9,34 %
Normal histology	10	9,34 %

Table 5. Histopathological lesions of the cervix

Cervical lesions	Number of cases	Percentage
Chronic cervicitis	86	80,37 %
Squamous metaplasia	13	12,14 %
Erosive cervicitis	8	7,47 %

Discussion

The uterus is an important reproductive organ that is susceptible to various benign and malignant diseases. Even though there have been significant advances in conservative and surgical interventions for uterine lesions, hysterectomy may still be necessary in some cases. The increasing number of hysterectomies can be seen in cases of prophylaxis against uterine malignancy, mild genital prolapse, and non-menopausal menorrhagia (4). Dicker asserts that hysterectomy is recommended when the benefits surpass the risks associated with preserving the uterus, or when medical treatment fails to alleviate troubling symptoms (3).

This study retrospectively examined a total of 107 hysterectomy procedures, involving individuals aged between 41 and 74 years. The age group most frequently undergoing hysterectomy fell within the range of 41 to 51 years, with a mean age of 49.83. Other studies conducted by Rather et al. and Ramchandran et al. have reported similar findings (5, 6).

Type of Hysterectomy:

Total Laparoscopic Hysterectomy emerged as the predominant type of hysterectomy in our study (TLH). This finding is consistent with other studies in the literature. TLH has been demonstrated to be a less invasive procedure than Total Abdominal Hysterectomy (TAH) and provides a shorter recovery time (7). In 2019, the American Congress of Obstetricians and Gynecologists (ACOG) reaffirmed its position, originally stated in 2017 and 2009, emphasizing the preference for the vaginal approach in women undergoing hysterectomy for benign conditions, citing its "well-documented benefits and lower complication rates" (8). The American Association of Gynecologic Laparoscopists (AAGL) and the French National College of Obstetricians and Gynecologists (CNGOF) also advocate for the vaginal or laparoscopic approach as the primary choice in this scenario (9). Nevertheless, there's a difference between what's recommended and what's actually happening in practice. Over time, there has been a decline in the utilization of the vaginal approach, from 25% of cases in 1998 to 17% in 2010 (10). Our study supports recent publications, showing a vaginal hysterectomy rate of 2.8%.

Histopathological Findings:

The most common clinical indications for hysterectomy were found to be menorrhagia, fibroid uterus, and uterovaginal prolapse.

Endometrial polyp emerged as the predominant pathology among endometrial lesions. In our study, the clinical diagnosis was confirmed in the majority of cases on pathological examination; however, polyps were more frequently observed than atrophy in endometrial lesions. This finding was different from other studies conducted. In other studies, atrophic endometrium is more frequently observed (11).

In myometrial lesions, leiomyoma was the most frequent diagnosis (47.66%). This result aligns with the findings of the study conducted by Vani et al. (12). In this study, adenomyosis ranked as the second most prevalent myometrial pathology, identified in 36 cases (33.64%). Adenomyosis is seldom diagnosed preoperatively and typically identified post-hysterectomy through histopathological examination (13).

Chronic cervicitis is a highly prevalent condition among adult women, often evident under microscopic examination. In this study, it emerged as the most frequent cervical pathology, identified in 86 cases (80.37%). These findings are consistent with other studies in the current literature (11).

Indications for Hysterectomy:

In our study, the most common indications for hysterectomy were AUB and myoma uteri. Numerous studies cite abnormal uterine bleeding as the primary clinical indication for hysterectomy, while others identify myoma as the predominant reason (14, 15).

Limitations of the Study:

Limitations of this study include its retrospective design and its conduct at a single center.

Conclusion

In this study, the histopathological analysis results of patients who underwent hysterectomy at Mardin Education and Research Hospital were evaluated. AUB and myoma uteri were among the most common indications for hysterectomy. Endometrial polyp emerged as the most frequent diagnosis among endometrial lesions, while leiomyoma was the predominant diagnosis among myometrial lesions. In our study, the clinical diagnosis was confirmed in the majority of cases on pathological examination; however, polyps were more frequently observed than atrophy in endometrial lesions.

Ethical Approval: *This study was designed in accordance with the Helsinki Declaration and approved by Mardin Artuklu University Ethics Committee (Study ethics committee number: 2024/3-22; date 05/03/2024). Purpose and methods of the study were explained to patients, and they provided written informed consent.*

Author Contributions:
Concept: Ö.T., D.F., M.İ.
Literature Review: Ö.T., D.F., M.İ.
Design : E.S.
Data acquisition: Ö.T., D.F.
Analysis and interpretation: E.S., E.Ç.
Writing manuscript: Ö.T., E.S.
Critical revision of manuscript: Ö.T., E.S., E.Ç.
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Research Article / Araştırma Makalesi

Evaluation of Vascular Structures in the Anterior Mandible with Cone Beam Computed Tomography

Konik Işınlı Bilgisayarlı Tomografi ile Anterior Mandibuladaki Vasküler Yapıların Değerlendirilmesi

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Abstract

Background: The aim of this article was to evaluate the regional frequency, location, and diameter of the lingual foramen in the anterior mandible using a retrospective analysis of clinically obtained cone-beam computed tomography (CBCT) images.
Materials and Methods: Two hundred thirty-four regions of the anterior mandible from 76 patients (41 female and 35 male) were examined retrospectively using CBCT for the presence of endosseous bony canals. The study focused on the lingual foramen, measuring both the maximum diameter of the artery and the diameter of the lingual foramen itself. Additionally, distances were measured between the lingual foramen and the alveolar ridge, tooth apex, mandibular border, and mental foramen. Data were analyzed using ANOVA and independent sample t-tests to determine statistical significance.
The distributions of the measured variables were assessed for normality prior to analysis. Normality was confirmed using appropriate statistical tests, such as the Shapiro-Wilk test, and visual inspection methods, including Q-Q plots. Since the data met the assumptions of normality, parametric tests were deemed appropriate for analysis. Consequently, ANOVA and independent sample t-tests were employed to evaluate the differences among groups and the relationships between variables. This approach allows for more robust statistical inferences, leveraging the properties of the normal distribution.
Results: The diameters of the lingual artery ranged from 0.3 mm to 1.67 mm, with the majority of lingual foramina (47.62%) located in the midline region. Notably, a quintuple canal was identified in the CBCT scans. The highest measurement of the artery diameter was statistically significant ($p < 0.01$), along with the longest distance between the lingual foramen and the alveolar ridge ($p < 0.05$), and the shortest distance between the lingual and mental foramen ($p < 0.01$), all observed on the right side. These findings highlight the anatomical variations and spatial relationships of the lingual artery and foramina, which are crucial for surgical planning in the anterior mandible.
Conclusions: The findings regarding the presence, diameter, and prevalence of vascular canals are critical for oral surgery and must be considered when planning any procedures in the anterior mandible. Notably, we report an uncommon case involving a quintuple lingual canal. To prevent potentially life-threatening bleeding during surgical interventions, it is essential to identify these vascular structures using CBCT prior to mandibular surgery. This proactive approach enhances surgical safety and reduces the risk of complications.

Keywords: Anterior Mandible, Lingual Vascular Canal, Lingual Foramen, Cone-Beam Computed Tomography

Öz

Amaç: Bu çalışmanın amacı, klinik olarak elde edilen konik ışınlı bilgisayarlı tomografi (KIBT) görüntülerinin retrospektif analizini kullanarak anterior mandibuladaki lingual foramenin bölgesel sıklığını, yerini ve çapını değerlendirmektir.
Materyal ve Metod: Yetmiş altı hastanın (41 kadın ve 35 erkek) anterior mandibulalarındaki iki yüz otuz dört bölge, endosseöz kanalların varlığı açısından KIBT'ye dayalı olarak retrospektif şekilde incelenmiştir. Lingual foramen ile ilgili olarak, arterin maksimum çapı ve lingual foramenin çapı detaylı bir şekilde ölçülmüştür. Ayrıca, lingual foramen ile alveolar sırt, diş apeksi, mandibular sınır ve mental foramen arasındaki mesafeler de hesaplanmıştır. Elde edilen veriler, istatistiksel olarak analiz edilmek üzere ANOVA ve bağımsız örneklem t-testi kullanılarak değerlendirilmiştir.
Ölçülen değişkenlerin dağılımları analizden önce normallik açısından değerlendirilmiştir. Normallik, Shapiro-Wilk testi gibi uygun istatistiksel testler ve Q-Q grafikleri gibi görsel inceleme yöntemleri kullanılarak doğrulanmıştır. Veriler normallik varsayımlarını karşıladığı için, analiz için parametrik testlerin uygun olduğu düşünülmüştür. Sonuç olarak, gruplar arasındaki farklılıkları ve değişkenler arasındaki ilişkileri değerlendirmek için ANOVA ve bağımsız örneklem t-testleri kullanılmıştır. Bu yaklaşım, normal dağılımın özelliklerini kullanarak daha sağlam istatistiksel çıkarımlara olanak tanımaktadır.
Bulgular: Bu çalışmada, lingual arter çapları 0.3 ila 1.67 mm arasında değişiklik göstermiştir. Lingual foramenlerin çoğu (47,62%) orta hat bölgesinde tespit edilmiştir. Ayrıca, KIBT taramalarında beşli kanal gözlemlenmiştir. Arter çapının en yüksek ölçümü sağ tarafta bulunurken, bu sonuç istatistiksel olarak anlamlıdır ($p < 0,01$).
Lingual foramen ile alveolar sırt arasındaki en uzun mesafe de sağ tarafta kaydedilmiştir ve bu da istatistiksel olarak anlamlı bir sonuç göstermektedir ($p < 0,05$). Lingual foramen ile mental foramen arasındaki en yakın mesafe de sağ tarafta gözlemlenmiş olup, bu ölçüm de anlamlı bulunmuştur ($p < 0,01$).
Bu bulgular, anterior mandibulada cerrahi planlama için çok önemli olan lingual arter ve foraminaların anatomik varyasyonlarını ve mekansal ilişkilerini vurgulamaktadır.
Sonuç: Vasküler kanalların varlığı, çapı ve yaygınlığı ile ilgili bulgular, oral cerrahi uygulamaları açısından önemli sonuçlar ortaya koymaktadır. Anterior mandibulada gerçekleştirilecek her türlü operasyon planlanırken bu yapılar göz ardı edilmemelidir. Bu çalışmada, beşli lingual kanala sahip nadir bir vaka sunulmuştur.
Cerrahi müdahaleler sırasında potansiyel olarak yaşamı tehdit eden kanamayı önlemek için, mandibular cerrahiden önce bu vasküler yapıları KIBT kullanarak tanımlamak esastır. Bu proaktif yaklaşım cerrahi güvenliği artırır ve komplikasyon riskini azaltır.

Anahtar Kelimeler: Anterior Mandibula, Lingual Vasküler Kanal, Lingual Foramen, Konik Işınlı Bilgisayarlı Tomografi

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Introduction

The anterior mandibular region is the most preferred site for autologous bone harvesting and dental implant placement due to its relative safety, absence of major neurovascular structures, and quality of bone density (1-4). The interforaminal area of the mandible is particularly safe for dental implants supporting fixed partial dentures or overdentures. However, recent studies have assessed the vascularization of the symphysis region concerning the risk of hemorrhage. Some findings indicate that life-threatening hemorrhage and hematoma formation in the floor of the mouth can lead to serious upper airway obstruction. Research suggests a link between these critical incidents and the presence of the lateral lingual foramen (LLF), which may be associated with injury to the vasculature of the mandibular lateral foramina during implant surgery (1,2,5,6).

Lingual foramens (LF) are small holes on the mandible's lingual surface that are commonly found in the anterior areas (5). LFs are divided into two categories based on where they are located: in or near the midline [median lingual canal (MLC)] or laterally [lateral lingual canal (LLC)] (1,7-10). The lingual artery, sublingual artery, and branches of the mylohyoid nerve, lingual nerve, and mandibular incisive nerve (8,11-13) are demonstrated to supply the MLC with its contents. A neurovascular bundle from the submental artery, inferior alveolar artery, and inferior alveolar nerve (12,14) runs through the LLC. Mandibular LF has shown significant anatomical variance in many different populations, according to previous research (6,15). To minimize neurovascular injuries on the floor of the mouth, the presence, course, morphology, and location of mandibular LF must be determined. Confirming the presence and precise location of LF is crucial for both bone harvesting and dental implant placement.

Cone-beam computed tomography (CBCT) is widely utilized for preoperative evaluation due to its high resolution, rapid imaging capabilities, and low radiation exposure. CBCT scans of skeletal structures have an error rate of less than 1%, in contrast to panoramic radiographs, which have an error rate exceeding 30% (16-18). Given these advantages, a thorough examination of the region using CBCT is essential for achieving a more accurate assessment prior to oral procedures (19).

The goal of this study was to determine the regional frequency and anatomical aspects of mandibular LF using a retrospective analysis of clinically obtained CBCT images. In this respect, careful assessment of the region is essential utilizing the technical breakthrough represented by CBCT, which provides a more precise assessment.

Materials and Methods

This retrospective study enrolled a total of 76 patients—dentulous, partially edentulous, and edentulous—who were referred to an oral surgery center. Among them, 35 were male and 41 were female, with an average age of 47 years (range 25–67). Totally, 234 endosseous arteries were examined in 228 regions of 76 patients. 76 arteries located both in the midline (M) and the right-side (R), the rest of 82 arteries were in the left-side (L) regions.

Ethical approval was obtained from the Health Sciences Ethics Committee of Near East University (YDU/2020/77-1024) on February 27, 2020. The study adhered to the ethical standards set forth by the responsible committee on human experimentation (institutional and national) and complied with the Helsinki Declaration of 1975, as revised in 2000.

Anterior region images of the mandible were acquired using a CBCT device (MORITA, Kyoto, Japan), calibrated before each patient's scan. The exposure parameters included 8.0 mA, 90 kV, an exposure time of 9.4 seconds, a slice thickness of 0.960 mm, and a voxel size of 0.160 mm^3. An experienced investigator evaluated all CBCT scans. To assess reliability and repeatability, 50 randomly selected images were re-evaluated by the same observer two weeks after the initial assessment.

CBCT images of the mandibles were used for precise evaluation prior to dental implant placement and the extraction of impacted teeth. Patients with serious pathological lesions in the mandible, severe mandibular atrophy, impacted teeth near the foramina area, or low-quality CBCT images were excluded from the study.

The LF in the interforaminal area of the mandible were examined and classified based on their location. The midline (M) location was defined as the MLC, while the location between the canine and premolar regions was designated as the LLC (20), further divided into right (R) and left (L) sides. Measurements taken from the axial mandibular CT sections included the maximum diameter of the artery, the diameter of the LF, the distance between the LF and the alveolar ridge (AR), the distance between the LF and the tooth apex (TA), the vertical distance from the mandibular border (MB) to the LF, and the distance between the LF and the mental foramen (MF). Additionally, the presence of mono, bifid, and trifid canals was determined using the axial CT sections. Distance measurements were systematically obtained using tangent lines to the AR and the mental ridge, with vertical lines drawn to ensure accuracy in assessments (Figure 1).

The distributions of the measured variables were assessed for normality prior to analysis. Normality was confirmed using appropriate statistical tests, such as the Shapiro-Wilk test, and visual inspection methods, including Q-Q plots. Since the data met the assumptions of normality, parametric tests were deemed appropriate for analysis. Consequently, ANOVA and independent sample t-tests were employed to evaluate the differences among groups and the relationships between variables. This approach allows for more robust statistical inferences, leveraging the properties of the normal distribution.

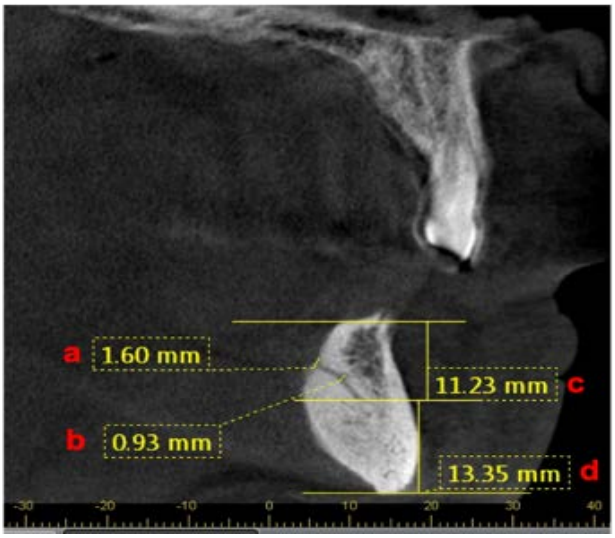

Figure 1. Linear measurements on axial mandibular CBCT sections. (a) diameter of the LF (b) maximum diameter of the artery (c) the distance between the LF and the AR (d) the distance between the LF and the MB

Results

A total of 70 participants were analyzed, with a greater number of females (n = 40) than males (n = 30) exhibiting a maximum diameter of the artery less than the mean (M = 0.71) (Table 1).

Table 1. Sex - maximum diameter of the artery crosstabulation

		<=0.71	>0.71
Sex	**Female**	40	15
	Male	30	19
	Total	70	34

The independent t-test comparisons for the distances between the lingual foramen (LF) and the mental foramen (MF) and alveolar ridge (AR) revealed no significant differences between genders (See Table 2). Specifically, the distances measured were:

Distance from LF to TA:

Female:

Mean (M) = 9.18

Standard Deviation (SD) = 3.46

Male:

M = 10.60

SD = 3.57

t-test Results:

t(26) = −1.06

p = 0.30 (not statistically significant)

Distance from LF to AR:

Female:

M = 14.45

SD = 4.54

Male:

M = 15.40

SD = 4.13

t-test Results:

t(101) = −1.10

p = 0.27 (not statistically significant)

In both cases, the p-values (0.30 and 0.27) indicate that there is no significant difference between the distances for males and females at the given alpha level (typically 0.05).

Table 2. Mean and standart deviations of distance between LF and TA, AR by gender

	Sex	n	Mean	Std. Deviation	Std. Error Mean
The distance between the LF and the TA	Female	14	9.18	3.46	0.93
	Male	14	10.60	3.57	0.95
The distance between the LF and the AR	Female	54	14.45	4.54	0.62
	Male	49	15.40	4.13	0.59

LF: Lingual foramen; TA: Tooth apex; AR: Alveolar ridge

Effect of Artery Location

One-way ANOVA revealed significant effects of artery location (Right, Left, Middle) on various measurements (Table 4):

Maximum Diameter of the Artery:

Right: M=0.96,

Left: M=0.68,

Middle: M=0.64,

Statistical Significance: F(2,101)=9.532, p<0.01 (Table 5).

Distance from LF to AR:

Right: M=17.43

Left: M=15.17

Middle: M=13.88

Statistical Significance: F(2,100)=4.33, p=0.016

Distance from LF to MF:

Right: M=11.91

Left: M=16.37

Middle: M=20.79

Statistical Significance: F(2,101)=21.28, p<0.01

Frequency of Lingual Canals

The detection rates of lingual arteries varied by location:

- Right: Not detectable in 59 patients (45.74%).
- Middle: Not detectable in 26 patients (20.15%).
- Left: Not detectable in 44 patients (34.11%).

Of the 76 patients analyzed, the frequency of lingual arteries was recorded as:

- Middle: 65.78% (50 patients).
- Left: 43.42% (33 patients).
- Right: 22.36% (17 patients).

Table 3 compares the distances between LF & TA and LF & AR, showing that there is no statistically significant difference in either case (p-values > 0.05). The mean differences (-1.41 for LF-TA and -0.95 for LF-AR) suggest small variations, but they are not meaningful. Levene's test confirms that variances are equal, meaning the variability in distances is similar across groups

Table 3. LF, TA and AR Comparison

		Levene's Test for Equality of Variances		t-test for Equality of Means			Mean Difference
		F	Sig.	t	df	Sig. (2-tailed)	
The distance between the LF and the TA	Equal variances assumed	0.03	0.87	-1.06	26	0.30	-1.41
	Equal variances not assumed			-1.06	25.76	0.30	-1.41
The distance between the LF and the AR	Equal variances assumed	0.36	0.55	-1.10	101	0.27	-.095
	Equal variances not assumed			-1.11	101	0.27	-0.95

LF: Lingual foramen; TA: Tooth apex; AR: Alveolar ridge

Table 4. LF, AR, TA, MB, MF Statistics

Variable	Mean ± SD	Median (Min - Max)
Maximum diameter of the artery	0.71 ± 0.28	0.68 (0.30 - 1.67)
Diameter of the LF	1.11 ± 0.40	1.00 (0.50 - 3.02)
Distance LF to AR (mm)	14.90 ± 4.36	15.17 (0.00 - 24.65)
Distance LF to TA (mm)	9.89 ± 3.52	10.50 (3.36 - 17.70)
Vertical distance MB to LF (mm)	11.11 ± 3.03	11.00 (0.00 - 21.28)
Distance LF to MF (mm)	17.96 ± 5.54	18.50 (1.23 - 26.39)

LF: Lingual foramen; AR: Alveolar ridge; TA: Tooth apex; MB: Mandibular border; MF: Mental foramen

Table 5. LF, AR, TA, MB and MF Comparisons

		Sum of Squares	df	Mean Square	F	Sig.
Maximum diameter of the artery	Between Groups	1.240	2	.620	9.532	.000
	Within Groups	6.567	101	.065		
	Total	7.807	103			
The distance between the LF and the AR	Between Groups	154.312	2	77.156	4.334	.016
	Within Groups	1780.315	100	17.803		
	Total	1934.626	102			
The distance between the LF and the TA	Between Groups	4.870	1	4.870	.384	.541
	Within Groups	330.147	26	12.698		
	Total	335.016	27			
Diameter of the LF	Between Groups	.157	2	.078	.493	.612
	Within Groups	16.047	101	.159		
	Total	16.204	103			
The vertical distance from the MB to the LF	Between Groups	47.211	2	23.605	2.657	.075
	Within Groups	897.403	101	8.885		
	Total	944.614	103			
The distance between the LF and the MF	Between Groups	936.544	2	468.272	21.276	.000
	Within Groups	2222.898	101	22.009		
	Total	3159.442	103			

LF: Lingual foramen; AR: Alveolar ridge; TA: Tooth apex; MB: Mandibular border; MF: Mental foramen

Discussion

Frequency and Distribution of Lingual Canals

In this study, we evaluated the frequency, distribution, and arterial diameters of bony canals within the anterior mandible using CBCT scans, as these structures are challenging to visualize through conventional radiography. Previous studies have reported the incidence of the lingual foramen in the mandible to range from 58.8% to 99.0%, findings that are consistent with our observations (18, 21-23). Gahleitner et al. reported that all patients in their study had at least one lingual canal in the anterior mandibular region (20). Among the anatomical variations observed, while the trifid mandibular canal type is relatively rare (24, 25), our investigation identified a quintuple canal type in a female patient

(Figure 2); however, this patient was excluded from statistical analyses. Gahleitner et al. classified the location of the lingual foramen as MLC and LLC, whereas we categorized it as left, midline, and right (20).

Presence of Lingual Arteries

Out of 76 patients with detectable lingual arteries, 65.78% exhibited the arteries solely on the midline of the mandible. In comparison, the frequency of lingual arteries was found to be 43.42% on the left side and 22.36% on the right side. He et al. found a presence ratio of 69.85% for lingual arteries in the middle region, which aligns with our findings (5). Tepper et al. observed that lingual arteries were located at the midline in all 70 patients studied (26). Additionally, various studies have reported a significantly higher frequency of lingual arteries in the middle section of the anterior mandible compared to the lateral aspects (8, 27, 28).

Romanos et al. noted a 9% prevalence of multiple canals (two or three) in their study (29). However, in our analysis, only five out of 76 patients (6.58%) exhibited two arteries on the left side.

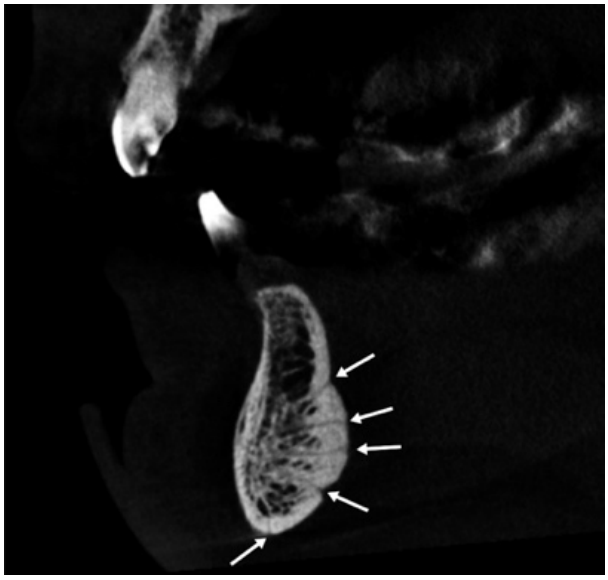

Figure 2. Quintuple lingual canal (arrows)

Diameter of Lingual Arteries

The diameter of the lingual artery is critical due to its association with the risk of significant bleeding during surgical procedures. Lustig et al. reported blood flow velocities in lingual arteries with diameters ranging from 0.18 mm to 1.8 mm, measuring between 0.7 to 3.7 ml/min (30). In our study, the diameter of the lingual arteries ranged from 0.3 mm to 1.67 mm (Figure 3). These findings underscore the necessity for CBCT imaging of the lingual arteries in the anterior mandibular region prior to surgical interventions.

Dubois et al. (31) and Kusum et al. (32) reported several cases of life-threatening bleeding in the anterior mandible during or after implant surgery.

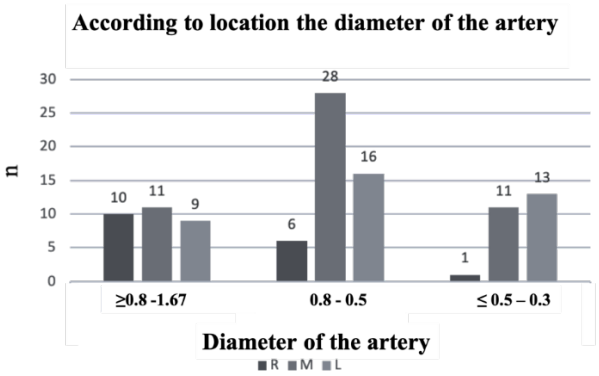

Figure 3. According to location the diameter (mm) of the artery.

Measurements from CBCT Scans

From a total of 234 CBCT scans of 76 patients, lingual arteries were detected in 105 measurements. The results indicated:

- Mono Canal: Detected in 68 measurements (64.76%, comprising 14 right, 23 midline, and 31 left) across 50 patients (65.79%).
- Bifid Canal: Identified in 24 measurements (22.86%, including 2 right, 17 midline, and 5 left) from 24 patients (31.58%).
- Trifid Canal: Found in 13 measurements (12.38%, with 1 right, 10 midline, and 2 left) across 13 patients (17.11%).

Additionally, one canal was detected in all three regions (right, midline, and left) in four patients. Among the 105 measurements of lingual arteries, 17 (16.19%) were on the right side, 50 (47.62%) were on the midline, and 38 (36.19%) were on the left side.

These findings emphasize the importance of understanding the anatomical variations and distributions of the lingual arteries in the anterior mandible, highlighting the role of advanced imaging techniques such as CBCT in surgical planning.

Conclusion

This study demonstrates that the examination of the surgical site using computed tomography, particularly prior to mandibular implant surgery, can yield valuable information. Notably, we report a rare case of a unilateral quintuple lingual canal in the symphysis region of the mandible in a female patient, a type not previously documented among multi-trunk canals.

Our findings underscore the significance of these anatomical variations for oral surgery, revealing arteries with a maximum diameter ranging from 0.3 to 1.67 mm and a 98.68% prevalence of vascular channels. Such details are crucial and should not be overlooked when working in the anterior mandible. To prevent potentially life-threatening bleeding, it is essential to detect these vessels CBCT before undertaking mandibular surgery. These findings highlight significant anatomical variations in the lingual artery influenced by both gender and anatomical location, underscoring their

importance in clinical practice.

Ethical Approval: *The ethical approval was taken from the Health Sciences Ethics Committee of Near East University (YDU/2020/77-1024) on February 27, 2020.*

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Concept: A.B., A.E.E., Ü.C.Ş., Ö.E.B.
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Data acquisition: A.B.
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Araştırma Makalesi / Research Article

Oftalmik Patolojiler ve Göz İçi Tümörlerinde Dil Farklılıklarının Yapay Zeka Chatbot Performansı Üzerindeki Etkisinin Değerlendirilmesi: ChatGPT-3.5, Copilot ve Gemini Üzerine Bir Çalışma

Assessing the Impact of Language Differences on Artificial Intelligence Chatbot Performance in Ophthalmic Pathologies and Intraocular Tumors: A Study of ChatGPT-3.5, Copilot, and Gemini

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Öz

Amaç: ChatGPT-3.5, Copilot ve Gemini yapay zeka sohbet botlarının oftalmik patolojiler ve intraoküler tümörlerle ilişkili çoktan seçmeli sorularda ki başarısına dil farklılığının etkisini araştırmak
Materyal ve metod: Oftalmik patolojiler ve intraoküler tümörlerle ilgili bilgi düzeyini test eden 36 İngilizce soru çalışmaya dahil edildi. Sertifikasyonlu çevirmen (native speaker) tarafından Türkçe çevirilerinin gerçekleştirilmesi sonrasında bu soruların hem İngilizce hem de Türkçe olarak ChatGPT-3.5, Copilot ve Gemini sohbet botlarına soruldu. Verilen cevaplar cevap anahtarı ile karşılaştırılıp doğru ve yanlış olarak gruplandırıldı.
Bulgular: ChatGPT-3.5, Copilot ve Gemini İngilizce sorulara sırası ile %75, %66,7 ve %63,9 oranında doğru cevap verdi. Bu programlar Türkçe sorulara ise sırası ile %63,9, %66,7 ve %69,4 oranında doğru cevap verdi. Sohbet botları arasında soruların Türkçe hallerini cevaplama da farklı oranda doğru cevap görüldüğü halde, istatistiksel olarak anlamlı bir fark tespit edilmedi (p>0,05).
Sonuç: Yapay zeka sohbet botlarının bilgi dağarcığının geliştirilmesinin yanında farklı dillerde aynı algıyı oluşturabilmek ve tek doğruya erişimi sağlayabilmek için farklı dilleri anlama, çevirebilme ve fikir üretebilme özelliklerinin de geliştirilmeye ihtiyacı vardır.

Anahtar Kelimeler: ChatGPT-3.5, Copilot, Gemini, Göz içi tümörler ve oftalmik patolojiler, İngilizce ve Türkçe

Abstract

Background: To investigate the effect of language differences on the success of ChatGPT-3.5, Copilot, and Gemini artificial intelligence chatbots in multiple-choice questions related to ophthalmic pathologies and intraocular tumors.
Materials and Methods: Thirty-six English questions testing knowledge about ophthalmic pathologies and intraocular tumors were included in the study. These questions were asked to ChatGPT-3.5, Copilot, and Gemini chatbots in both English and Turkish after the Turkish translations were realized by a certified translator (native speaker). The answers given were compared with the answer key and grouped as correct and incorrect.
Results: ChatGPT-3.5, Copilot, and Gemini answered the questions in English correctly at a rate of 75%, 66.7%, and 63.9%, respectively. These programs answered the Turkish questions correctly at a rate of 63.9%, 66.7%, and 69.4%, respectively. Although there were different rates of correct answers between chatbots in answering the Turkish versions of the questions, no statistically significant difference was detected (p>0.05).
Conclusions: In addition to improving the knowledge of artificial intelligence chatbots, their ability to understand different languages, translate, and generate ideas needs to be improved to create the same perception in different languages and provide access to a single truth.

Keywords: ChatGPT-3.5, Copilot, Gemini, English and Turkish, Intraocular tumors and ophthalmic pathologies

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Giriş

Yapay zeka uygulamalarının yaygınlaşması ile birlikte etkileri tıbbın tüm alanlarında izlenmeye başlanmış ve bu alanlara çok çeşitli katkılar sağlamıştır (1). Oftalmoloji alanında yaygınlaşmaya başlaması ise yaklaşık 2015 yılından sonra gerçekleşmiş, özellikle derin öğrenme tabanlı yapay zeka programlarının diyabetik retinopati, glokom gibi retinal ve optik sinir patolojilerinin tanı ve takibinde kullanılabileceğinin anlaşılması ile birlikte popülerlik kazanmıştır (2-4). Yapay zeka uygulamalarının bir diğer kolu da Büyük Dil Modeli (BDM) tabanlı programlardır. Bu programlar derin öğrenme tabanlı programlar gibi insanların öğrenme şeklini taklit etmek yerine kavramlar arasında ilişki kurma, istatistiksel modellerle analiz etme ve bunları yorumlayabilme kabiliyetine sahiptir. BDM tabanlı programlar kullanıcılar tarafından tanımlanmış olan bilgileri anlayabilir, onlarla ilgili özetler çıkarabilir ve sorulan sorulara uygun cevaplar üretebilirler (5).
Çalışmamızın amacı BDM temelli yapay zeka programları olan ChatGPT-3.5 (OpenAI), Copilot (Microsoft) ve Gemini (Google) sohbet botlarının oftalmik patolojiler ve intraoküler tümörler ile ilişkili olan çoktan seçmeli farklı dillerdeki (İngilizce ve Türkçe) aynı soruları doğru cevaplama potansiyelini değerlendirmek ve farklı dillerdeki soruların bu başarıya olan etkisini incelemektir.

Materyal ve Metod

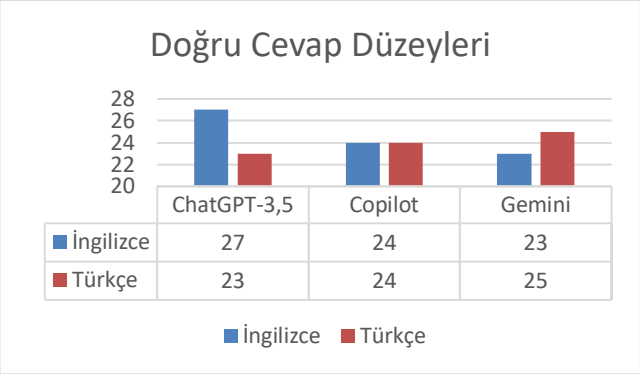
Amerikan Akademi ve Oftalmoloji 2023-2024 Basic and Clinical Science Course (BCSC) Oftalmik Patolojiler ve İntraoküler Tümörler kitabı çalışma soruları kısmında yer alan 36 sorunun tamamı çalışmaya dahil edildi (6). İngilizce olan bu sorular daha sonra sertifikasyonlu çevirmen (native speaker) tarafından Türkçeye çevrildi. Soruların İngilizce ve Türkçe versiyonları ücretsiz olarak erişim sağlanabilen ChatGPT-3.5 (OpenAI; San Francisco, CA), Copilot (Microsoft, Redmond,WA) ve Gemini (Google, Mountain View, California, United States) yapay zeka sohbet botlarına 7 Temmuz 2024 tarihinde uygulandı. Sorular sorulmadan önce yapay zeka programlarına 'Sana çoktan seçmeli sorular soracağım. Lütfen bana doğru cevap şıkkını ver.' komutu verildi. Her sorunun cevaplanmasından sonra oturum sonlandırıldı. Sohbet botlarının verdikleri cevaplar kitap arkasında yer alan cevap anahtarı ile karşılaştırılarak doğru ve yanlış olarak iki grup altında incelendi. Çalışmamızdaki veriler insan ve hayvan denekleri kaynaklı olmadığı için etik kurul onayı gerektirmemektedir.

İstatistiksel Analiz

Verilerin istatistiksel analizinde Statistical Package fort he Social Sciences sürüm 23 (SPSS Inc., Chicago, IL, USA) programı kullanıldı. Yüzdelik değerler hesaplandı. Bağımsız gruplarda nominal verilerin istatistiksel karşılaştırması için Pearson Ki-kare testi kullanıldı. Bağımlı gruplarda nominal verilerin istatistiksel karşılaştırması için McNemar testi kullanıldı. P değerinin 0,05'in altında olması anlamlılık düzeyi olarak değerlendirildi.

Bulgular

Oftalmik patolojiler ve intraoküler tümörler ile ilgili bilgi düzeyini sorgulayan 36 adet İngilizce çoktan seçmeli soru ChatGPT-3.5, Copilot ve Gemini yapay zeka sohbet programlarına uygulandı ChatGPT-3.5, sorulan soruların 27'sine (%75) doğru cevap, 9'una (%25) yanlış cevap verdi. Copilot sorulan soruların 24'üne (%66,7) doğru cevap, 12'sine (%35,3) yanlış cevap verdi. Gemini sorulan soruların 23'üne (%63,9) doğru cevap, 13'üne (%36,1) yanlış cevap verdi (Şekil 1). İngilizce soruları doğru cevaplamada her üç yapay zeka programı arasında istatistiksel anlamlı düzeyde bir fark tespit edilmedi (p=0,572 Pearson Ki-kare testi).



Şekil 1. ChatGPT-3,5, Copilot ve Gemini'nin oftalmik patolojiler ve intraoküler tümörler hakkındaki İngilizce ve Türkçe soruları doğru cevaplama düzeyleri

Aynı soruların Türkçe versiyonları ChatGPT-3.5, Copilot ve Gemini sohbet botlarına uygulandı. ChatGPT-3.5, sorulan soruların 23'üne (%63,9) doğru cevap, 13'üne (%36,1) yanlış cevap verdi. Copilot sorulan soruların 24'üne (%66,7) doğru cevap, 12'sine (%35,3) yanlış cevap verdi. Gemini sorulan soruların 25'ine (%69,4) doğru cevap, 11'ine (%30,6) yanlış cevap verdi (Şekil 1). Türkçe soruları doğru cevaplamada her üç yapay zeka programı arasında istatistiksel anlamlı düzeyde bir fark tespit edilmedi (p=0,882 Pearson Ki-kare testi).
ChatGPT-3.5 sorulan İngilizce ve Türkçe soruların 24'üne (%66,7) aynı cevabı verirken, 12'sine (%33,3) farklı cevaplar verdi. Farklı cevaplar verdiği soruların sekizi (%66,7) Türkçe sorulduğunda yanlış cevaplanırken, dördü (%33,3) Türkçe sorulduğunda doğru cevaplandı. ChatGPT-3.5'in aynı soruları İngilizce ve Türkçe olarak doğru olarak cevaplamasında istatistiksel olarak anlamlı düzeyde bir fark izlenmedi (p=0,388 McNemar testi) (Tablo 1).
Copilot sorulan İngilizce ve Türkçe soruların 26'sına (%72,2) aynı cevabı verirken, 10'una (%27,8) farklı cevaplar verdi. Farklı cevaplar verdiği soruların beşi (%50) Türkçe sorulduğunda yanlış cevaplanırken, beşi (%50) Türkçe sorulduğunda doğru cevaplandı. Copilot'un aynı soruları İngilizce ve Türkçe olarak doğru olarak cevaplamasında istatistiksel olarak anlamlı düzeyde bir fark izlenmedi (p=1,0 McNemar testi) (Tablo 1).

Gemini sorulan İngilizce ve Türkçe soruların 28'ine (%77,8) aynı cevabı verirken, sekizine (%22,2) farklı cevaplar verdi. Farklı cevaplar verdiği soruların dördü (%50) Türkçe sorulduğunda yanlış cevaplanırken, dördü (%50) Türkçe sorulduğunda doğru cevaplandı. Gemini'nin Aynı soruları İngilizce ve Türkçe olarak doğru olarak cevaplamasında istatistiksel olarak anlamlı düzeyde bir fark izlenmedi (p=0,727 McNemar testi) (Tablo 1).

Tablo 1. Yapay zeka sohbet botlarının aynı sorulara verdikleri cevaplar ve değişimleri

Cevaplar	ChatGPT-3,5 (İngilizce)	ChatGPT-3,5 (Türkçe)	Copilot (İngilizce)	Copilot (Türkçe)	Gemini (İngilizce)	Gemini (Türkçe)
Doğru	27 (%75)	23 (%63,9)	24 (%66,7)	24 (%66,7)	23 (%63,9)	25 (%69,4)
Yanlış	9 (%25)	13 (%36,1)	12 (%35,3)	12 (%35,3)	13 (%36,1)	11 (%30,6)
P değeri	0,388*		1,0*		0,727*	
Aynı cevabı üretme	24 (%66,7)		26 (%72,2)		28 (%77,8)	
Farklı cevabı üretme	12 (%33,3)		10 (%27,8)		8 (%22,2)	
Doğru-yanlış değişimi	8 (%66,7)		5 (%50)		4 (%50)	
Yanlış-doğru değişimi	4 (%33,3)		5 (%50)		4 (%50)	

**: McNemar testi*

Tartışma

ChatGPT insan düşünce yapısını taklit ederek insan benzeri cevaplar oluşturmayı amaçlayan 175 milyar gibi çok geniş bir bilgi ağı ile eğitilmiş, BDM temelli yapay zeka programları arasında bu özellikleri ile öne çıkmış ve kendisine has bir yer oluşturmuş bir yapay zeka sohbet botudur (7). En son Eylül 2021 de güncelleme alan ve internet erişimi olmayan ChatGPT-3.5 ise bu gelişim zincirinin son ücretsiz halkasını oluşturmaktadır (8). BDM grubunun diğer önemli bir temsilcisi olan ve ücretsiz erişim sağlanabilen Copilot ise Şubat 2023 tarihinde GPT-4'ün entegrasyonu ile birlikte sürekli gelişiminin devam ettiği bir yapay zeka sohbet botudur (8). Copilot sohbet botu aynı zamanda aldığı kaynakları alıntılayarak okuyucunun daha ayrıntılı bilgi edinebilmesi için bir yol gösterici olabilmektedir (8 ,9). Gemini ise BDM grubunun diğer önemli ücretsiz erişim sağlanabilen bir üyesidir. Copilotla çevrimiçi internet erişiminin olması ve sürekli güncellenmesi gibi ortak özelliklerinin yanında karşılaştığı çeşitli sorunlar karşısında kesin yanıtlar sunabilme özelliği ile benzerlerinden ayrılmaktadır (10, 11). Yapay zeka sohbet botları bu çok çeşitli avantajları göz önüne alındığında tıp eğitiminde de kendisine çok çeşitli yerler bulmuş, bilgiye hızlı erişmek isteyen, literatür taramak veya dil çevirisi yapmak isteyen tıp fakülte öğrencilerinden sağlık profesyonellerine kadar çok geniş bir alanı etkisi altında bırakmıştır (12, 13). Fakat bu programların bazı kısıtlılıklarının olması programlarının etkinliğini ve güvenilirliğini değiştirebilmektedir. Bu kısıtlılığın bir örneği çevrimiçi internet erişimi olan bu sohbet botlarının ücretli sitelere girişlerinin kısıtlılığıdır. Bu da doğru bilgi için güncel olan bilgiye erişimin aksamasına neden olacağı düşüncesidir (14, 15). Yapay zeka sohbet botlarının bu ve benzeri kısıtlılıkları düşünüldüğünde bu konuda daha ayrıntılı bilgi edinmek ve bu programlarının performanslarını incelemek amacı ile çok çeşitli konularda araştırmalar yapılmıştır. Bu konulardan biri bu programların çoktan seçmeli sorulardaki başarısını ve yeterliliğinin araştırılmasıdır. Bu konu oftalmoloji alanında sık olarak gündeme gelmiş ve yoğun bir şekilde araştırılmıştır. ChatGPT-3.5 ve ChatGPT-4.0'ın 380 oftalmoloji sorusuna verdikleri cevapları inceleyen bir araştırmada ChatGPT-3.5 soruların %55'ine doğru cevap verirken, ChatGPT-4.0 soruların %70'ine doğru cevap vermiştir. Retina ve oküler onkoloji alanındaki bilgileri sorgulayan sorulara ise ChatGPT-3.5 %54, ChatGPT-4.0 %73 oranında doğru cevap vermiştir. Araştırıcılar bu çalışmasının sonunda her ne kadar bu programların şu an için yeterli olmadıklarını belirtseler de gelecekteki gelişmelerle tıp eğitiminde önemli bir rol üstlenebileceklerini belirtmektedirler (16). ChatGPT-3.5, ChatGPT-4.0 ve insan katılımcıların 467 oftalmoloji sorusunu cevapladığı ve başarılarının değerlendirildiği çalışmada ChatGPT-3.5 %55,46, ChatGPT-4.0 %73,2 ve insan katılımcılar %58,1 oranında başarı göstermişlerdir. Oküler patolojiler ve tümörler ile ilgili sorularda ise sırası ile başarıları %45, %70 ve %58 düzeylerinde olduğu belirtilmiştir. Yazarlar sonuç olarak da yapay zeka programlarının tıp eğitimi ve uygulamalarında önemli bir araç olarak kullanılabileceği görüşünü savunmuşlardır (17). Tüm bunlara ek olarak bir başka araştırma ise Türkçe oftalmoloji sorularında ChatGPT-3.5, ChatGPT-4.0, Bing ve Bard'ın etkinliklerini araştırmışlar ve bu programların sırası ile %51, %77,5, %63 ve %45,5 doğrululuk oranlarına sahip olduklarını belirtmişlerdir ve sonuç olarak bu programların hala geliştirilmeye ihtiyacının olduğunu vurgulamışlardır (18). Yapay zeka sohbet botlarının performansının incelendiği bir farklı konu ise soruların sorulduğu bölgeye göre doğru cevaplanma düzeylerinde bir farklılığın oluşup olmadığının araştırılmasıdır. Gemini'nin farklı ülkelerin internet ağından aynı sorulardaki performansı değerlendirilmiştir. Programın performansı her ne kadar kabul edilebilir olduğu belirtilse de farklı ülkelerden erişimin başarı düzeylerini etkilediği ifade edilmiştir (19).

Bu çalışmada yapay zeka sohbet botlarının aynı soruların farklı dillerde sorulmasının başarılarını etkileyip etkilemediğini araştırmak istedik. Kendi araştırmamızda herkesin rahat erişim sağlayabileceği ve ücretsiz olduğu için gündelik hayatta daha kolay ve sık kullanılabileceğini düşündüğümüz ChatGPT-3,5, Copilot ve Gemini sohbet botlarını çalışmamıza dahil ettik. Kendi serimizde soruların İngilizce ve Türkçe cevaplamasındaki başarı oranları makul görülse bile eşit dü-

zeyde değildi. Her ne kadar farklı dillerdeki başarı oranlarında istatistiksel düzeyde anlamlı fark mevcut olmasa da ChatGPT ve Gemini'nin başarı düzeyleri birbirlerinden farklıydı. Ayrıca Copilot'un her ne kadar başarı düzeyleri aynı gibi gözükse de soru bazlı incelendiğinde aynı sorulara farklı yanıtlar ürettiklerini gözlemledik. Biz bu farklılığın sebebinin programların dil çeviri yeteneklerinin sınırlı olması ve soruları doğru yorumlama ya da erişilen bilgiyi uygun bir şekilde anlayıp, değerlendirme yeteneğinin kısıtlı olmasına bağlı olabileceğini düşünmekteyiz. Her ne kadar başarı oranları makul gözükse de dil farklılığına bağlı cevapların değişmesi araştırıcıyı bu programlara danışma sırasında kullanması gereken dil konusunda ikileme götürecek ve doğru bilgiye erişim konusunda bu programlara olan güveni zedeleyecektir.

Oftalmoloji 2023-2024 Basic and Clinical Science Course (BCSC) Oftalmik Patolojiler ve İntraoküler Tümörler kitabının çalışma soruları 36 soruyu içeriyordu ve sohbet robotlarına bunları sorduk. Soru sayısının az olmasının istatistiksel sonucun anlamlı çıkıp çıkmamasına etki edebileceğini düşünmekteyiz fakat temel bilgileri ölçen bu kitabın sorularına ilave soru eklemenin yanlış olacağı kanaatine vardık. Daha fazla soru içeren testlerde farklı değerlerin çıkıp çıkmayacağının araştırılması gerektiğini düşünmekteyiz.

Soru sayımızın azlığı, buna bağlı olarak soruların alt konu dallarına ayrılmayışı, soruların zorluk ve karmaşıklık düzeylerine göre değerlendirilmemesi, sorulara verilen cevapların sadece doğru ve yanlış olarak kategorize edilmesi ve yapay zeka programları ile insan performansının karşılaştırılıp incelenmemiş olması çalışmamızın en önemli kısıtlı yönlerini oluşturmaktadır.

Sonuç olarak çalışmamız üç farklı üretici tarafından piyasaya sürülmüş olan ChatGPT-3.5, Copilot ve Gemini adlı yapay zeka sohbet botlarının oküler patolojiler ve intraoküler tümörler ile ilgili çoktan seçmeli farklı dillerde aynı soruları cevaplamadaki performansının değerlendirildiği ilk araştırmadır. Bu programların geniş bilgilerle beslenmesi ve geliştirilmesi sıklıkla gündemde olan önemli bir konu olmakla birlikte farklı dillerde aynı soruları cevaplamadaki bu farklılıkta düzeltilmesi ve geliştirilmesi gereken diğer önemli bir hususu oluşturmaktadır. Kullanıcılar açısından tutarlı ve objektif bir ortamın sağlanması, bu programların oftalmoloji eğitiminde daha önemli sorumluluklar üstlenmesine aracılık edecektir.

Etik onam: *Çalışmamızdaki veriler, insan ve hayvan denekleri kaynaklı olmadığı için etik kurul onayı gerektirmemektedir.*

Yazar Katkıları:
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Research Article / Araştırma Makalesi

Does the Effectiveness of Cognitive Behavioural Therapy in Social Anxiety Disorder Differ According to Symptoms?

Sosyal Anksiyete Bozukluğunda Bilişsel Davranışçı Terapinin Etkinliği Semptomlara Göre Farklılık Gösteriyor Mu?

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Abstract

Background: Social anxiety disorder (SAD) presents with different symptoms and clinical appearances due to individual differences. The explanations provided by categorical models for these differences may be limited. Some individuals diagnosed with SAD may exhibit higher anxiety in performance situations, while others may exhibit higher anxiety in social situations. Our aim in this study is to evaluate the difference in symptom size in terms of clinical features and cognitive behavioural therapy (CBT) treatment effectiveness.
Materials and Methods: The records of 23 adolescents aged 12-18 who received CBT in addition to SSRI treatment for SAD between March 2022 and June 2023 were retrospectively reviewed and included in the study. Based on the information obtained from the participants' records, they were divided into two groups as generalized type (GT) and restrictive type (RT) according to their Liebowitz Social Anxiety Scale (LSAS) scores. The Children's Depression Inventory (CDI), Children's Anxiety Disorders Screening Scale (CADSS), Capa Child and Adolescent Social Phobia Scale (CASPS), and LSAS subscale scores were compared before and after CBT.
Results: When the RT (n=10) and GT (n=13) pre-treatment scale scores were compared, the CDI, CADSS, CAPSS and LSAS scores of the adolescents in the GT group were statistically significantly higher. When the LSAS subscales and CADSS scores of both groups were compared after CBT treatment, the scale scores were found to be higher in the GT group.
Conclusions: This study suggests that the effectiveness of CBT may be reduced when categorical diagnosis is made according to symptoms in SAD, especially in cases accompanied by depressive symptoms and other anxiety disorders.

Keywords: Social anxiety disorder, Adolescent, Cognitive behavioural therapy

Öz

Amaç: Sosyal anksiyete bozukluğu (SAB), bireysel farklılıklar nedeniyle farklı semptomlar ve klinik görünümlerle ortaya çıkabilir. Bu farklılıkları açıklamada kategorik modellerin sunduğu açıklamalar sınırlı kalabilir. SAB tanısı alan bireylerden bazıları performans durumlarında, bazıları ise sosyal durumlarda daha yüksek anksiyete gösterebilir. Bu çalışmadaki amacımız, klinik özellikler ve bilişsel davranışçı terapi (BDT) tedavi etkinliği açısından semptom büyüklüğündeki farklılıkları değerlendirmektir.
Materyal ve Metod: Mart 2022 ve Haziran 2023 tarihleri arasında SAB tanısıyla SSRI tedavisine ek olarak BDT alan 12-18 yaş arasındaki 23 ergenin dosyası retrospektif olarak taranarak çalışmaya dahil edilmiştir. Katılımcıların dosyalarından elde edilen bilgiler ile Liebowitz Sosyal Anksiyete Ölçeği (LSAS) puanlarına göre genelleşmiş tip (GT) ve kısıtlı tip (KT) olarak iki gruba ayrılmış ve Çocuklar için Depresyon Ölçeği (CDI), Çocuklar için Anksiyete Bozuklukları Tarama Ölçeği (CADSS), Çapa Çocuk ve Ergen Sosyal Fobi Ölçeği (CASPS) ile LSAS alt ölçek puanları BDT öncesi ve sonrası karşılaştırılmıştır.
Bulgular: BDT öncesinde GT (n=13) ve KT (n=10) gruplarının ölçek puanları karşılaştırıldığında, GT grubundaki ergenlerin CDI, CADSS, CASPS ve LSAS puanları istatistiksel olarak anlamlı derecede daha yüksek bulunmuştur. BDT sonrası LSAS alt ölçekleri ve CADSS puanları karşılaştırıldığında ise her iki grupta da ölçek puanlarının GT grubunda daha yüksek olduğu görülmüştür.
Sonuç: Bu çalışma, SAB semptomlarına göre kategorik tanı yapıldığında, özellikle depresif semptomlar ve diğer anksiyete bozuklukları eşlik eden vakalarda BDT etkinliğinin azalabileceğini düşündürmektedir.

Anahtar Kelimeler: Sosyal anksiyete bozukluğu, Ergen, Bilişsel davranışçı terapi

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Introduction

Social anxiety disorder (SAD) involves experiencing significant fear or anxiety in one or more social situations where the individual may be subject to evaluation by others. This marked fear or anxiety can arise during social interactions, being observed, or performing actions in front of others, and the person is afraid of behaving in a way that might be negatively evaluated or showing signs of anxiety (1). Researchers report that the disorder typically emerges in childhood and early adolescence and tends to become chronic and persist throughout life (2). Social anxiety is most encountered during adolescence. SSRIs and SNRIs are generally considered first-line pharmacological treatments for anxiety disorders; however, pharmacotherapy is thought to have limited efficacy in social anxiety disorder (3).

Cognitive-behavioural therapy (CBT) is seen as a highly effective therapy method for anxiety disorders in adolescents (4). In a study involving adolescents aged 15–17, including 15 girls and 11 boys, ten sessions of CBT were conducted. It was found that symptoms of SAD significantly decreased (5). Similarly, a 2020 study evaluated 12 university students with SAD using the Liebowitz Social Anxiety Scale (LSAS) after eight sessions of CBT. The results showed a significant reduction in their symptoms (6). Furthermore, several randomized controlled trials have confirmed CBT's effectiveness across various anxiety disorders (7).

However, most treatment studies exclude patients with comorbid disorders, leaving limited evidence regarding the treatment of comorbid SAD and anxiety disorders. For instance, one study found no significant differences in outcomes between SAD patients with and without comorbid Generalized Anxiety Disorder (GAD) following group CBT (8). Comorbid conditions require careful evaluation, as untreated comorbidities may result in insufficient or inappropriate treatment. CBT is generally recommended for patients with both SAD and Major Depression (MD) (9). However, research on the influence of depressive symptoms on CBT outcomes in SAD is inconsistent. Some studies suggest that higher levels of depression may reduce CBT's short-term effectiveness (11,12), while others report no significant impact of MD on CBT outcomes (13,14). Notably, one study observed worsening SAD symptoms in the long term (15). Both CBT and antidepressants are effective treatment options for SAD and comorbid conditions. However, the evidence remains insufficient, with studies often yielding inconsistent results.

It is known that individuals experiencing symptoms of social anxiety exhibit significant clinical differences. These clinical differences may manifest as variations in the environments where individuals experience anxiety or differences in the number of environments where they experience anxiety. Although it is commonly stated that people with SAD are most anxious in performance situations, it has been observed that they can experience intense anxiety in situations such as being watched while eating or encountering strangers (16,17).

Although SAD as a general concept provides an idea, psychopathology presents with different symptoms and clinical appearances due to individual differences. The explanations provided by categorical models for these differences can be limited. For this reason, the structure of the DSM, which has a categorical classification, is criticized. Efforts are being made to develop new classifications to understand and diagnose psychopathologies (18). SAD is among the psychopathologies that are difficult to explain with categorical diagnostic systems, where differences in clinical appearance cannot be distinguished by the severity of symptoms or the type and number of environments where anxiety/fear/avoidance is experienced (19).

This study aims to evaluate the clinical characteristics and treatment effectiveness of adolescents diagnosed with SAD who are treated with CBT, by classifying their treatment effectiveness according to their symptoms.

Materials and Methods

Sample

The study included 23 adolescents aged 12-18 diagnosed with SAD, whose records were retrospectively reviewed from the Recep Tayyip Erdogan Education and Research Hospital Child and Adolescent Psychiatry Clinic. These adolescents received 8-12 sessions of CBT in addition to selective serotonin reuptake inhibitors (SSRIs) as part of routine treatment. To confirm the diagnosis of SAD and rule out comorbid psychiatric disorders (e.g., psychotic disorders, bipolar disorder, tics, conduct disorders), the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL) was administered. According to the clinical evaluation based on DSM-5, adolescents with autism spectrum disorder, language development delays, intellectual disabilities, learning disorders, or those not attending formal education were excluded from the study.

The inclusion criteria for the study were as follows: being aged 12-18, having clinically normal intelligence levels, attending formal education, being literate, and having received 8-12 sessions of CBT in addition to SSRIs as part of routine treatment for a diagnosis of SAD.

Instruments

Adolescents whose data included a sociodemographic information form completed by asking questions to parents during interviews, the semi-structured interview method K-SADS-PL, and routine assessments with the Children's Depression Inventory (CDI), Children's Anxiety Disorders Screening Scale (CADSS), Capa Child and Adolescent Social Phobia Scale (CASPS), and Liebowitz Social Anxiety Scale (LSAS) prior to SSRI and CBT treatment were included in the study. The sociodemographic information form, designed by us, is a semi-structured clinical interview form completed by the researcher before administering the K-SADS-PL. It was used to collect sociodemographic information about the child and the family by asking questions to the parents.

Children's Depression Inventory (CDI)

Developed by Kovacs in 1981 to assess the level of depression in children, the CDI is the most used self-assessment tool for childhood depression (20). It is applicable to children aged 6-17. The scale consists of a total of 27 items. For each question, the child is asked to choose the most appropriate option from three choices based on their condition over the past two weeks. The scoring ranges from 0 to 2. The highest possible score on the scale is 54, and the lowest is 0. A cut off score of 19 is recommended. In Turkey, the validity and reliability study were conducted by Öy in 1991 (21).

Children's Anxiety Disorders Screening Scale (CADSS)

Developed by Birmaher et al. in 1999 to screen for anxiety disorders in childhood, the Turkish validity and reliability of the scale were established by Çakmakçı in 2004 (22,23). The scale is filled out by the child reading it themselves or having it read to them. The child is asked to mark the option that best describes them for each sentence. Each item is scored from 0 to 2. The higher the score, the higher the general anxiety level. The CADSS consists of 41 items, and a score of 25 or above is considered indicative of anxiety disorders. The scale includes subscales for somatization, panic, generalized anxiety, separation anxiety, social phobia, and school phobia.

Capa Child and Adolescent Social Phobia Scale (CASPS)

Developed by Demir et al. in 1999, the CASPS is a 25-item Likert-type self-report tool used to determine the level of social phobia in children and adolescents aged 10 and above (24). Some items on the scale address situations related to the school and classroom environment that may lead to social phobia and the reactions to these situations. The scale can score from a minimum of 25 to a maximum of 125. There is no established cut off score for the scale. High scores indicate severe symptoms of social phobia. The reliability coefficient of the scale is reported as Cronbach's $\alpha = .82$.

Liebowitz Social Anxiety Scale (LSAS)

The LSAS is a measure developed to assess fear and avoidance related to social phobia. The scale consists of a total of 24 items, with 13 items related to performance anxiety (1, 2, 3, 4, 6, 8, 9, 13, 14, 16, 17, 20, 21) and 11 items related to social situations (5, 7, 10, 11, 12, 15, 18, 19, 22, 23, 24). It is considered valid and reliable for SAD and is one of the most frequently used scales in this area (25). In Turkey, validity and reliability studies have been conducted by Dilbaz et al in 2001 (26).

Procedure

A K-SADS-PL interview was conducted with all adolescents and their parents to make diagnoses and exclude accompanying psychiatric disorders. Before CBT sessions, a sociodemographic data form was filled out by asking questions to the parents. Before CBT, the adolescents were administered the CDI, CADSS, CASPS, and LSAS scales. For those who completed at least 8 and at most 12 sessions of CBT, the CADSS, CASPS, and LSAS scales were re-administered at the final therapy session.

The research sample was divided into two groups based on their symptoms according to the subscales of the LSAS. Adolescents with scores of at least half of the maximum score on the performance anxiety and/or avoidance subscales were classified as the restricted type (RT) (n=10). Adolescents with scores of at least half of the maximum score on the performance anxiety and/or avoidance subscales, as well as scores of at least half of the maximum score on the social situation anxiety and/or avoidance subscales, were classified as the generalized type (GT) (n=13).

The routine scores of the CADSS, LSAS, and CASPS were compared for both groups before and after CBT. Additionally, the post-treatment scale scores of the two symptom-based groups were compared to evaluate the effectiveness of the treatment based on symptoms.

The study was approved by the Recep Tayyip Erdogan University Faculty of Medicine Ethics Committee (02.05.2024 decision no: 2024/89).

Statistical Analysis

The statistical analysis of the data was performed using SPSS 29 (IBM, Armonk, USA), The Shapiro-Wilk tests were used to assess the normality of data distribution. The sociodemographic data form, CDI, CADSS, LSAS subscales, and CASPS scores of the adolescents participating in the study were evaluated using descriptive statistics. The comparison of pre- and post-treatment scale scores within each group was assessed using the Wilcoxon test. Additionally, the Mann-Whitney U test was used to compare the pre-treatment and post-treatment scale scores between the two groups. The significance level was taken as $p < 0.05$.

Results

In the study, the average age of the GT group was 14.42±1.4, and the average age of the RT group was 16±0.8, with a statistically significant difference in age between the two groups. No difference was found in gender distribution between the two groups. Comparing the scale scores of the GT and RT groups, no statistically significant differences were found in the CASPS post-treatment score, the LSAS performance anxiety subscale pre-treatment, the LSAS performance anxiety subscale post-treatment, the LSAS performance-related avoidance subscale pre-treatment, or the LSAS performance-related avoidance subscale post-treatment. However, there was a statistically significant difference in pre-treatment scores on the CASPS between the two groups, with higher scores in the GT group.

The CDI score was significantly higher in the GT group. When evaluating pre- and post-treatment scores on the CADSS, a statistically significant increase was found in the GT group. Scores on the LSAS social situation anxiety subscale and the LSAS social situation avoidance subscale, both pre- and post-

treatment, were significantly higher in the GT group. The total fear score and total avoidance score on the LSAS were significantly higher in the GT group both pre- and post-treatment ($p<0.05$) (Table 1).

An evaluation of pre-and post-treatment scale scores for the GT group showed statistically significant decreases in all scale scores (Table 2). Similarly, an evaluation of pre- and post-treatment scale scores for the RT group also revealed statistically significant decreases in all scale scores (Table 2).

Table 1. Comparison of scale scores of GT and RT

	Generalized Type GT (GT) n=13 Mean±Sd.	Restricted Type RT (RT) n=10 Mean±Sd.	p
Age	14,42±1,4	16±0,8	0.05*
CASPS Before Treatment	64,67±21,2	44,82±14,1	0.019**
CASPS After Treatment	28,75±4,7	27,64±3,7	*0.379***
CDI	25,33±6,2	17,82±5,5	0.004**
CADSS Before Treatment	42,42±10,8	30±4,4	0.002**
CADSS After Treatment	22,17±5,7	16,64±3	0.016**
LSAS Anxiety About Social Situations Subscale Before Treatment	32,33±5	18,27±2,9	0.001**
LSAS Anxiety About Social Situations Subscale After Treatment	16,83±4,2	13,64±2	0.044**
LSAS Performance Anxiety Subscale Before Treatment	34,67±4,8	36±6,3	*0.833***
LSAS Performance Anxiety Subscale After Treatment	21,75±2,9	21±3,7	*0.740***
LSAS Avoidance About Social Situations Subscale Before Treatment	32,67±4,3	16,36±2,9	0.000**
LSAS Avoidance About Social Situations Subscale After Treatment	20,33±2,7	13,18±1,8	0.000**
LSAS Avoidance of Performance Status Subscale Before Treatment	31,83±4	37±6	*0.444***
LSAS Avoidance of Performance Status Subscale After Treatment	19,25±3,5	21,36±3,4	*0.151***
LSAS Total Fear Before Treatment	67±6,1	54,27±7	0.001**
LSAS Total Avoidance Before Treatment	64,5±3,7	53,45±7,7	0.001**
LSAS Total Fear After Treatment	38,58±3,8	34,73±3,6	0.023**
LSAS Total Avoidance After Treatment	39,58±3,6	34,55±4,7	0.011**

*Notes:*Independent T test; **Mann-Whitney U Test*

Abbreviations: *GT: Generalized Type, RT: Restricted Type, Std: Standard Deviation, CDI: Children's Depression Inventory, CASPS: Capa Child and Adolescent Social Phobia Scale , CADSS: Children's Anxiety Disorders Screening Scale, LSAS: Liebowitz Social Anxiety Scale*

Table 2. Examination of GT group and RT group scale scores before and after treatment

	GT (p)	RT(p)
CADSS Before-After Treatment	0.002	0.003
CASPS Before-After Treatment	0.002	0.003
LSAS Anxiety About Social Situations Subscale Before-After Treatment	0.002	0.003
LSAS Performance Anxiety Subscale Before- After Treatment	0.002	0.003
LSAS Avoidance About Social Situations Subscale Before-After Treatment	0.002	0.007
LSAS Avoidance of Performance Status Subscale Before-After Treatment	0.002	0.003
LSAS Total Fear Before -After Treatment	0.002	0.003
LSAS Total Avoidance Before-After Treatment	0.002	0.003

Notes: Wilcoxon Test

Abbreviations: GT: Generalized Type, RT: Restricted Type, CASPS: Capa Child and Adolescent Social Phobia Scale , CADSS: Children's Anxiety Disorders Screening Scale, LSAS: Liebowitz Social Anxiety Scale

Discussion

In this study, the effectiveness of CBT in treating adolescents diagnosed with SAD was evaluated by categorizing based on the prevalence of symptoms. Additionally, the impact of sub-threshold anxiety and depression symptoms on the CBT process for SAD was investigated.

In this study, when comparing the average ages of the GT and RT groups, the GT group was found to have a lower average age. The literature reports that SAD is a disorder that begins in childhood and early adolescence (27-31). McEvoy et al. (2011) found that SAD is the anxiety disorder with the earliest onset (32). It has been reported that cases of SAD with early onset are more frequently seen as subtypes compared to cases with later onset (33,34). The statistically significant difference observed between the GT and RT groups in this study, while being a confounding factor in the comparison of data, is consistent with the literature regarding early onset of generalized SAD.

When comparing pre-treatment scores of the GT and RT groups, the GT group had statistically significantly higher CDI and CADSS scores before treatment. The literature indicates that generalized SAD is not only associated with early onset but also with comorbid psychiatric disorders. It has been reported that individuals with generalized SAD experience more symptoms, which are related to comorbid psychiatric conditions (35). In a study examining the clinical impact of the age of onset of SAD in adults, those with early onset of SAD were found to have more prevalent symptoms and higher Beck Depression Inventory scores (36). Follow-up studies have specifically found that early-onset SAD may be associated with major depression (37,38). Additionally, in groups with anxiety disorders, early onset of SAD is associated with more prevalent symptoms (39). Although the K-SADS semi-structured diagnostic interview was used in this study and no comorbid psychiatric disorders were detected, the statistically significant higher CADSS and CDI scores in the GT group, indicating sub-threshold anxiety and depression symptoms, may be related to the higher prevalence of symptoms and early onset in this group. This finding is consistent with the literature.

In this study, no significant difference was found in post-treatment CASPS, pre- and post-treatment LSAS performance anxiety subscale scores, or LSAS performance-related avoidance subscale scores. These results indicate that individuals with widespread symptoms in performance anxiety and performance-related avoidance in both the GT and RT groups show similar effects in terms of performance anxiety, and are consistent with the literature (40,41).

The statistically significant higher pre-treatment scores on the CASPS, LSAS Anxiety About Social Situations Subscale, LSAS Avoidance About Social Situations Subscale, LSAS Total Fear, and LSAS Total Avoidance in the GT group indicate that this group had more widespread symptoms at the outset. In a study conducted by Koyuncu et al. in 2012, it was reported that individuals with early-onset SAD had statistically significantly higher LSAS Total Fear and Total Avoidance scores compared to those with late-onset SAD, showing more prevalent symptoms (36). The lower average age in the GT group in our study suggests that the significant elevation in scale scores for this group may be related to the higher prevalence of symptoms.

When comparing post-treatment CASPS scores between the GT and RT groups, no statistically significant difference was found. This finding may be attributed to the positive effects of CBT on SAD symptoms (42).

It was observed that post-treatment scores on the LSAS Anxiety About Social Situations Subscale, LSAS Avoidance About Social Situations Subscale, LSAS Total Fear, and LSAS Total Avoidance were higher in the GT group. These findings suggest that, similar to the literature, the effect of CBT on reducing SAD symptoms, depression, and anxiety may be less in the GT group compared to the RT group (43). However, this situation is an important confounding factor to consider in evaluating the treatment effects of CBT, given that the GT group initially had more widespread symptoms and exhibited symptoms of anxiety and depression (44). Therefore, it is crucial to consider the prevalence of initial symptoms during the treatment process, assess the presence of sub-threshold depression-anxiety, and individualize treatment plans (45). Additionally, it should be considered that providing additional interventions and support in the GT group could enhance the effectiveness of cognitive therapy (46).

In the GT group, when comparing pre-treatment and post-treatment scores on the CADSS, CASPS, LSAS Performance Anxiety Subscale, LSAS Avoidance of Performance Status Subscale, LSAS Anxiety About Social Situations Subscale, LSAS Avoidance About Social Situations Subscale, LSAS Total Fear, and LSAS Total Avoidance, a statistically significant decrease was observed in all scale scores. Similarly, in the RT group, a statistically significant decrease was observed in all scale scores when comparing pre-treatment and post-treatment scores on the CADSS, CASPS, LSAS Performance Anxiety Subscale, LSAS Avoidance of Performance Status Subscale, LSAS Anxiety About Social Situations Subscale, LSAS Avoidance About Social Situations Subscale, LSAS Total Fear, and LSAS Total Avoidance. Significant decreases were observed in both groups' pre-treatment and post-treatment scale scores. This indicates that CBT is an effective treatment method for reducing SAD symptoms. Literature shows that positive outcomes obtained from treating SAD with CBT in adolescents suggest that this therapy is a suitable and effective intervention for young people (47). A meta-analysis conducted by Kerns and Prinstein demonstrates that CBT is significantly effective in reducing symptoms in adolescents with SAD (48). This study aligns with the literature in showing that CBT is an effective method for treating SAD in adolescents.

The importance of categorizing SAD based on symptoms is also supported by the findings of this study. SAD may require different treatment approaches for individuals with varying

symptom profiles. The ways in which individuals with performance anxiety versus those exhibiting social avoidance behaviours respond to treatment, and the presence of comorbid psychiatric disorders, can differ (49). Therefore, creating more specific categories based on symptoms in SAD and adapting individualized CBT treatment plans accordingly may lead to more effective outcomes (50).

Limitations of this study include the small sample size, reliance on data from a single centre, the absence of a group receiving only CBT without pharmacotherapy, and differences in age between groups. Additionally, strengths of the study include the use of a semi-structured interview to diagnose SAD, exclusion of individuals with medical and psychiatric comorbidities, intellectual disabilities, those who cannot read and write, and those not attending formal education. The comparison of similar gender groups is also a strength. Furthermore, the fact that CBT was administered by the same therapist and that all participants were using SSRIs helped minimize potential confounding factors.

To the best of our knowledge, this study is the first to evaluate the effectiveness of CBT by categorizing symptoms in adolescents diagnosed with SAD. This research is pioneering in investigating the heterogeneity of SAD as a diagnostic category in adolescents, and in demonstrating the effectiveness of CBT with respect to symptomatic categorization and the presence of sub-threshold depression and other anxiety disorders.

This study categorized symptoms in adolescents diagnosed with SAD, evaluating the heterogeneity of the disorder and the effectiveness of CBT based on symptom prevalence. We found that in SAD, the group with widespread symptoms related to social situations had a lower age of onset and exhibited sub-threshold depression and anxiety symptoms. Post-therapy, the scale scores for this group were higher compared to the group with limited symptoms. Research on the symptom heterogeneity in SAD is limited. Given these limitations, further studies are needed to evaluate the symptom heterogeneity across various age groups, include groups not on pharmacotherapy, and clarify the effectiveness of CBT through longitudinal studies.

Ethical Approval: *The study was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Ethics Committee (02.05.2024 decision no: 2024/89).*

Author Contributions:
Concept: Y.S.N.
Literature Review: Y.S.N.
Design : Y.S.N.
Data acquisition: Y.S.N.
Analysis and interpretation: Y.S.N.
Writing manuscript: Y.S.N.
Critical revision of manuscript: Y.S.N.

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Research Article / Araştırma Makalesi

Comparison Between Manually and Automatically Calculated Analyses: Blood Gases in Pediatric Intensive Care

Manuel ve Otomatik Hesaplanan Analizlerin Karşılaştırması: Pediatrik Yoğun Bakımda Kan Gazları

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Abstract

Background: One of the most significant situations in patients with critical illness is an acid-base imbalance. Blood gas analysis is a fundamental laboratory investigation employed to assess a patient's acid-base equilibrium and oxygenation status. The accurate interpretation of the blood gas is essential for the management and treatment of disease. The aim of this study is to compare analyzes of manually and automatically calculated blood gas parameters in the pediatric intensive care unit (PICU).
Materials and Methods: This retrospective study evaluated the serum ions and blood gas parameters values at the time of admission of patients aged between 0 and 18 years who were admitted to the PICU between April and October 2023. Furthermore, the relationship between automatically (with ABL800 FLEX autoanalyzer) and manually calculated standard base excess (SBE), anion gap, and the type of blood gas samples was investigated.
Results: The study included 184 patients admitted to the PICU, of whom 105 (57.1%) were male and 79 (42.9%) female. The most common diseases were 47(25.5%) physical traumas and 43(23.4%) lower respiratory tract infections. A positive correlation was detected between the results obtained from the blood gas automatically and manually calculated values for SBE. (correlation coefficient(Cc): 0.970; p<0.001). However, a significant difference was found between the SBE automatically and manually calculation when capillary (p=0.007) or venous (p<0.001) blood gas was taken, but this difference was not found for arterial samples (p=0.089).
Conclusions: The automatic measurements of the blood gas analyser are reliable, based on this study, and we should to be say between two methods no differences automatically and manually values. Nevertheless, in cases where there is an elevated risk of base deficit in critically ill patients, it is recommended that an arterial blood gas sample be obtained.

Keywords: Acidosis, Blood gas, Pediatrics, Ion difference, Intensive care

Öz

Amaç: Kritik hastalığı olan hastalarda karşılaşılan en önemli durumlardan biri asit-baz dengesizliğidir. Kan gazı analizi, bir hastanın asit-baz dengesini ve oksijenasyon durumunu değerlendirmek için kullanılan temel bir laboratuvar incelemesidir. Kan gazının doğru yorumlanması hastalığın yönetimi ve tedavisi için önemlidir. Bu çalışmanın amacı, pediatrik yoğun bakım ünitesindeki (PYBÜ) hastalardan alınan kan gazı örneklerinde manuel ve otomatik olarak hesaplanan sonuçların karşılaştırılmasıdır.
Materyal ve Metod: Bu retrospektif çalışmada, Nisan-Ekim 2023 tarihleri arasında PYBÜ'ne yatırılan 0-18 yaş arasındaki hastaların yatış anındaki serum iyon ve kan gazı parametre değerleri incelenmiştir. Kan gazı cihazında otomatik (ABL800 FLEX otoanalizörü ile) ve manuel olarak hesaplanan standart baz açığı (SBA), anyon gap ve kan gazı örneği alım tipleri arasındaki ilişki araştırılmıştır.
Bulgular: PYBÜ'ye kabul edilen 184 hastanın 105'i (%57.1) erkek, 79'u (%42.9) kızdı. Yatış nedenleri en sık 47 (%25.5) fiziksel travmalar ve 43 (%23.4) alt solunum yolu enfeksiyonuydu. Kan gazı cihazından otomatik elde edilen sonuçlar ile SBA değeri için manuel olarak hesaplanan değerler arasında pozitif korelasyon tespit edildi (korelasyon katsayısı (Kk): 0.970; p<0.001). SBA otomatik ile manuel hesaplama arasında kapiller (p=0.007) veya venöz (p<0.001) alınan kan gazı türleri arasında istatistiksel anlamlı fark bulundu, ancak arteriyel örneklerde anlamlı fark bulunmamıştır (p=0.089).
Sonuç: Kan gazı analizörünün otomatik ölçümleri güvenilirdir. Bu çalışmaya dayanarak, iki yöntem arasında otomatik ve manuel değerler arasında anlamlı fark olmadığını söyleyebiliriz. Bununla birlikte, kritik hastalarda baz açığı riskinin yüksek olduğu durumlarda, hastadan arteriyel kan gazı örneği alınması önerilir.

Anahtar kelimeler: Asidoz, Kan gazı, Pediatri, İyon farkı, Yoğun bakım

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Introduction

One of the most serious problems affecting almost all critically patients is acid-base imbalance, and especially metabolic acidosis. This imbalance has an impact on morbidity and mortality (1). Blood gas analysis is one of the most crucial laboratory tests employed to evaluate a patient's acid-base equilibrium and oxygenation status. In addition to facilitating a diagnosis, this analysis is also employed to evaluate the patient's subsequent course of treatment and response to it (2,3). In blood gas measurement systems, some parameters such as pH, partial oxygen pressure (pO_2), partial carbon dioxide pressure (pCO_2), electrolytes [sodium (Na), potassium (K), calcium (Ca), etc.], metabolites (glucose, urea, etc.) are measured directly, while for some parameters (anion gap (AG), bicarbonate (HCO_3^-), etc.) calculation results are reported using different formulae. While some parameters, such as AG, HCO_3^-, etc. are measured directly, for some parameters the calculation results are reported using different formulae, which causes differences in the reported results between devices (4).

Bicarbonate, the second most important anion of extracellular fluid and the main component of buffering systems in blood, is one of the most important parameters used to determine the acid-base balance of blood. Standard bicarbonate concentration ($cHCO_3^-$(std)) is the bicarbonate value that should be present in the blood under 40 mmHg pCO_2 at 37°C, while actual bicarbonate concentration ($cHCO_3^-$(act)) is the instantaneous bicarbonate value of the sample calculated by the Hendersen-Hasselbalch equation using pH, pCO_2. Under normal conditions, these two values are equal to each other (4,5). In addition to bicarbonate, the formation of pH value in blood gas is influenced by other factors, including lactate derived from anaerobic metabolism and the anion gap, which is calculated based on the balance between cations and anions from intracellular and extracellular buffering systems (3). Anion gap refers to the difference between measured serum cations (positively charged particles) and anions (negatively charged particles). In routine clinical practice, the cation that is measured is sodium, while the anions are chlorine and bicarbonate. It is employed to ascertain whether metabolic acidosis is attributable to the accumulation of non-volatile acids (ketoacids, lactic acid etc.) (increased AG, normochloremic metabolic acidosis) or loss of bicarbonate (hyperchloremic metabolic acidosis, normal AG). The normal range for AG is 12 ± 4 mEq/L. In patients with low albumin, the AG should be corrected in accordance with the albumin level (6). Blood gas is important in the clinical management of patients, particularly in intensive care units, in the diagnosis, treatment, follow-up and determination of procedures to be applied (e.g. respiratory support treatments, hemodialysis) for both respiratory and metabolic disorders. It is often used in intensive care units because it is a quick, inexpensive and easy-to-use test (5,6).

The aim of this study is to compare manually and automatically calculated analyses in blood gas measurements in PICU. We also aimed to examine the relationship and correlation of pH, and bicarbonate the type of blood gas. At the same time, blood gas parameters, demographic data, diseases that caused hospitalization, and mortality status were also evaluated.

Materials and Methods

Study design

In this retrospective study, clinical data and laboratory results were collected from the electronic medical records of pediatric patients aged 1 month to 18 years who were admitted to the Aydin Adnan Menderes University Hospital PICU in April and October 2023. The characteristics of the patients, including age, gender, the primary disease of admission to the PICU, as well as the laboratory results, were reviewed. The study included patients admitted to the PICU whose blood gases, hemogram, serum ions and serum albumin values were recorded in the electronic file at the time of admission. The study excluded those who did not undergo the examinations at the same time, as well as individuals outside the 0-18 age range.

The laboratory data of a simultaneous collection of blood gas analysis (e.g., pH, pCO_2, pO_2, HCO_3) were analyzed with ABL800 FLEX autoanalyzer and blood serum chemistry (i.e., $[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca_2^+]$, $[Mg_2^+]$, $[PO_4^-]$, and albumin) data were saved. Additionally, descriptives analysis (comorbid diseases that may affect the data, previous treatments, the hospitalization periods), the type of blood gas samples were recorded. Depending on the clinical condition of the patients at the time of admission, Glasgow Coma Score (GCS), Pediatric Risk of Mortality Score III (PRISM III), primary diagnosis, congenital metabolic disease and/or renal failure, initiation of respiratory invasive/noninvasive mechanical ventilation, intravenous bicarbonate using was saved. The base excess resulting from the patient's blood gas on the blood gas analyzer was calculated and the base excess calculated manually according to their biochemical examinations was compared.

Calculation formulas of anion gap and base excess

In general, the cation measured is sodium and the anions are chlorine and bicarbonate [AG (anion gap) = Na - (HCO_3^+ Cl)]. It is used to show whether metabolic acidosis is due to accumulation of non-volatile acids (lactic acid, ketoacids, etc.) (increased AG, normochloremic metabolic acidosis) or loss of bicarbonate (normal AG, hyperchloremic metabolic acidosis) [Normal AG: 12±4 mEq/L].

In patients with low albumin level, AG should be corrected according to albumin level. In patients with hypoalbuminemia (< 3.5 g/dL), the normal anion gap is less than 12 meq/L; In patients with hypoalbuminemia, the normal anion gap is 2.5 meq/L lower for every 1 g/dL decrease in plasma albumin concentration (6).

Standard base excess (SBE), arterial lactate, serum bicarbonate and serum chloride were included to serve as a traditional approach for evaluation of acid–base disturbances. SBE was calculated from the measured pH and HCO_3^- as following;

SBE = 0.9287 x HCO_3 − 24.4 + 14.83 x (pH-7.4)

Statistical Analysis

Statistical calculations of the obtained were made with the SPSS (ver. 25.0; SPSS, USA). The suitability of the groups for normal distribution was tested with the Shapiro-Wilk. One-way analysis of variance (Oneway ANOVA) was performed to compare the three groups with each other in parameters that comply with normal distribution. Kruskal Wallis Analysis and Mann Whitney U test were performed for parameters that did not show normal distribution. The Spearman correlation test for variables with non-normal distribution and the Pearson correlation test for normal distribution determined the relationship between the parameters. Correlation analysis was performed between SBE value, manually and automatically values, and pH and AG. $p<0.05$ was considered significant.

Results

Among 184 pediatric patients admitted to the PICU between April 2023 and October 2023, 105 (57.1%) were male and 79 (42.9%) were female. When examined at the disease groups, there were most commonly 47 (25.5%) physical trauma patients and 43 (23.4%) lower respiratory tract infections. The distribution of the primary diseases that caused PICU admission is shown in Table.1.

Table 1. The distribution of the patients' primary diseases

Primary diseases	n (%)
Traumas	47 (25.5)
Lower respiratory tract infection	43 (23.4)
Postoperative care	22 (12)
Diabetic ketoacidosis	17 (9.2)
Sepsis	16 (8.7)
Status epilepticus	10 (5.4)
Postressussitative care	6 (3.3)
Oncological diseases	5 (2.7)
Intoxication	4 (2.2)
Renal diseases	3 (1.6)
Acute gastroenteritis	3 (1.6)
Ensefalitis	2 (1.1)
Congenital metabolic diseases	2 (1.1)
Cardiavasculary failure	2 (1.1)
Arrhythmias	2 (1.1)
Total	184 (100)

A total of 122 patients (66.3%) had no previously known comorbid disease. Of the subjects with a known history of chronic disease, 11 (6%) had a diagnosis of congenital metabolic disease and 5 (2.7%) had chronic renal failure.

Upon admission to the PICU, 39 patients (21.2%) required invasive mechanical ventilation, while 35 (19%) required non-invasive. The mortality rate was 9.2%. Intravenous bicarbonate was administered to 17 patients (9.2%) prior to admission and 21 patients (11.4%) during their stay in the hospital. This was due to the presence of metabolic acidosis in their blood gas analysis. Descriptive analysis of the patients included in the study and clinical and laboratory data at the PICU admission are presented in Table.2.

Table 2. Descriptive analysis, and clinical and laboratory data at the PICU admission

	Median (min-max) IQR
Age (months)	61 (1-216) 119
Glosgow coma scale	15 (3-33) 3
PRISM III	12 (1-99) 26.5
Length of stay (days)	3 (1-152) 5
pH	7.35 (6.81-7.52) 0.12
pCO_2 (mmHg)	43 (4-94.1) 12.5
HCO_3 (mmol/L)	22.9 (5.2-45.3) 6.2
Lactate (mmol/L)	1.7 (0.5-12.3) 1.4
Standard base excess	-1.2 (-26.9-21.5) 7.03
Hemoglobin (gr/dL)	10.5 (3.9-17.8) 2.8
White blood cells (10^3/mkrL)	10940 (10-58790) 8355
Platelets (10^3/µL)	287000 (24700-763000) 193000
Albumin (g/L)	36.8 (19.5-54.14) 10.6
Na (mEq/L)	139 (130-190) 5.0
K (mEq/L)	4.10 (2.1-5.9) 0.95
Cl (mEq/L)	109 (95-150) 7.0
Mg (mEq/L)	1.93 (1.07-4.04) 0.37
Ca (mEq/L)	8.30 (3-11.2) 1.15
Anion gap	7.05 (-8.3-24.5) 5.95

**PRISM III: Pediatric Risk of Mortality Score III.*

In accordance with the purpose of our study, the correlation between pH, AG (automatically and manually) and SBE (automatically and manually) values was examined. Upon examination of the blood gases, a positive correlation was identified between the results obtained from the automated and manually calculated values for the SBE (correlation coefficient (Cc): 0.970; $p< 0.001$). Upon examination of the entire pH range, an AG negative correlation was identi-

fied (Cc: 0.970; p < 0.001); but along with a positive correlation between the automatically analysed SBE (Cc: 0.794; p < 0.001) and the calculated SBE (Cc: 0.878; p < 0.001). Upon examination of all AG levels, it was found that the SBE value of the automatically analysed data set (Cc: 0.724; p < 0.001) and the calculated SBE (Cc: 0.743; p < 0.001) exhibited a negative and statistically significant correlation (Table.3).

Table 3. The general correlation between pH, AG (automatically and manually) and SBE (automatically and manually) values

Variables	Statistics Term	AG	SBE Automatically	SBE Manually
pH	**r**	-0.625	0.794	0.878
	p	<0.001	<0.001	<0.001
AG	**r**		-0.724	-0.743
	p		<0.001	<0.001
SBE Automatically	**r**	-0.724		0.970
	p	<0.001		<0.001

**AG: Anion gap, SBE: Standard base excess, r: Spearman's rho correlation coefficient, p is significant <0.05.*

Of the blood gas samples analysed, 19 (10.33%) were capillary, 140 (76.09%) were venous and 25 (13.58%) were arterial. When the automatically SBE value (p=0.493), the manually SBE (p=0.181), and AG (p=0.067) values, were examined according to whether the blood gas sample was artery, vein, or capillary, no statistically significant difference was detected (Table 4). On the contrary, if the blood gas was capillary (p=0.007) or venous (p<0.001), a significant difference was detected between the automatically SBE and manually SBE calculation, but this difference was not found in arterial blood samples (p=0.089). Depending on the type of blood gas sample, Independent-Samples Kruskal-Wallis test results of automatically SBE, manually SBE, and AG analyses are shown schematically in Figure 1.

Table 4. Comparison of BE automatically, manually and anion gap measurements among blood gas groups

Variables	Capillary (n=18)	Venous (n=140) Median (min-max) IQR	Arterial (n=25)	p value
BE Calculation Automatically	-0.1 (-14.2 - 15.8) 7.2	-1.2 (-26.9-21.5) 7.3	-0.2 (-12.8-13.0) 6.4	0.458
BE Calculation Automatically	-1.8 (-13.6-14.9) 6.5	-2.5 (-27.9-21.8) 7.4	-0.9 (-12.6-10.9) 4.9	0.197
Anion Gap	6.1 (-1.7-11.3) 5.4	7.4 (-8.3-24.5) 6.6	6.3 (-3.0-14.7) 5.4	0.067

**Kruskal-Wallis analysis used and p<0.05 considered significant.*

Discussion

The findings of our study indicate that the automated readings from the blood gas analyser are reliable source of data, as evidenced by the strong correlation between the automatically and manually values with key parameters such as pH, AG and SBE, which are appropriate to the blood gas samples obtained from pediatric patients under optimal conditions. Nevertheless, in cases where there is an elevated risk of base deficit in critically ill patients, it is recommended that an arterial blood gas sample be obtained.

In critically ill children, an investigation of acid-base imbalances is required for the majority of those admitted to the PICU (7). Disorders in oxygenation and glucose distribution throughout the body can occur in critically ill patients, depending on the underlying cause of their illness. Consequently, metabolic deteriorations, particularly metabolic acidosis with an increased anion gap, may arise as a result of the patient's elevated metabolic rate.

In pediatric patients, venous and capillary samples are also taken in addition to arterial samples due to the low number of collaterals, the risk of developing peripheral circulatory disorders, and the difficulties in obtaining them. In addition, it is important to analyze the blood gas samples taken before clotting occurs in the heparin syringes and to quickly deliver them to the location of the blood gas device under cold chain conditions to reach the correct result (2). In this study, a critical analysis was conducted on blood samples from patients in the PICU who were treated by the same PICU team. This approach ensured that the level of each sample, the injection apparatus, the method of transport to the laboratory for analysis, and the investigative process were all conducted by the same team, thereby facilitating standardisation.

The physicochemical approach to acid-base status, as developed by Peter Stewart, has been the subject of extensive study to establish the most appropriate analytical techniques for use in studies, updates and refinements in adults. Nevertheless, the majority of these studies demonstrate the potential of a physicochemical approach in pediatrics. However, they are primarily focused on the correlation between physicochemical parameters and the efficacy of the treatment, rather than pH (8-12). The present study is distinguished by its investigation of pH, AG, and automatically and manually calculated SBE levels, which have been relatively understudied in the pediatric age group.

In a study conducted by Chaiyakulsil and colleagues, the correlation between the pH levels measured in blood gas analysis and various physicochemical parameters in the PICU was

evaluated. It was reported that SBE exhibited the most significant correlation with the measured pH, whereas the single parameters, such as serum chloride and arterial lactate, demonstrated the least association. This finding indicated that a single parameter may not be sufficient for accurately assessing complex acid-base disturbances in the PICU (13). It is an established fact that unmeasurable anions and cations also have an impact on the evaluation of the clinical condition in pediatric patients. Accordingly, the present study was designed to investigate the correlation between pH, AG and SBE (both automatically and manually calculated). While AG and pH showed a negative correlation, both SBE values (automatically and manually) were found to be positively correlated with AG. Additionally, the anion gap was examined and both SBE values were found to be negatively correlated. AG increases and severe metabolic acidosis occurs due to reasons such as severe sepsis, multiple organ failure, severe metabolic imbalances in patients with severe postoperative surgery, and an increase in intracellular-extracellular ion transfer. In this case, pH decreases in case of increased AG due to physiology, and our detection of a negative correlation in the data in our study supports this situation. In the same study, Chaiyakulsil et al., found a positive correlation between blood gases and pH and physicochemical approach in the PICU (13). Similarly, in our study, a positive correlation was found between the automatically SBE value in the blood gas analyzer and the manually calculated SBE value of critically ill patients in PICU. This confirms our data in blood gas analysis.

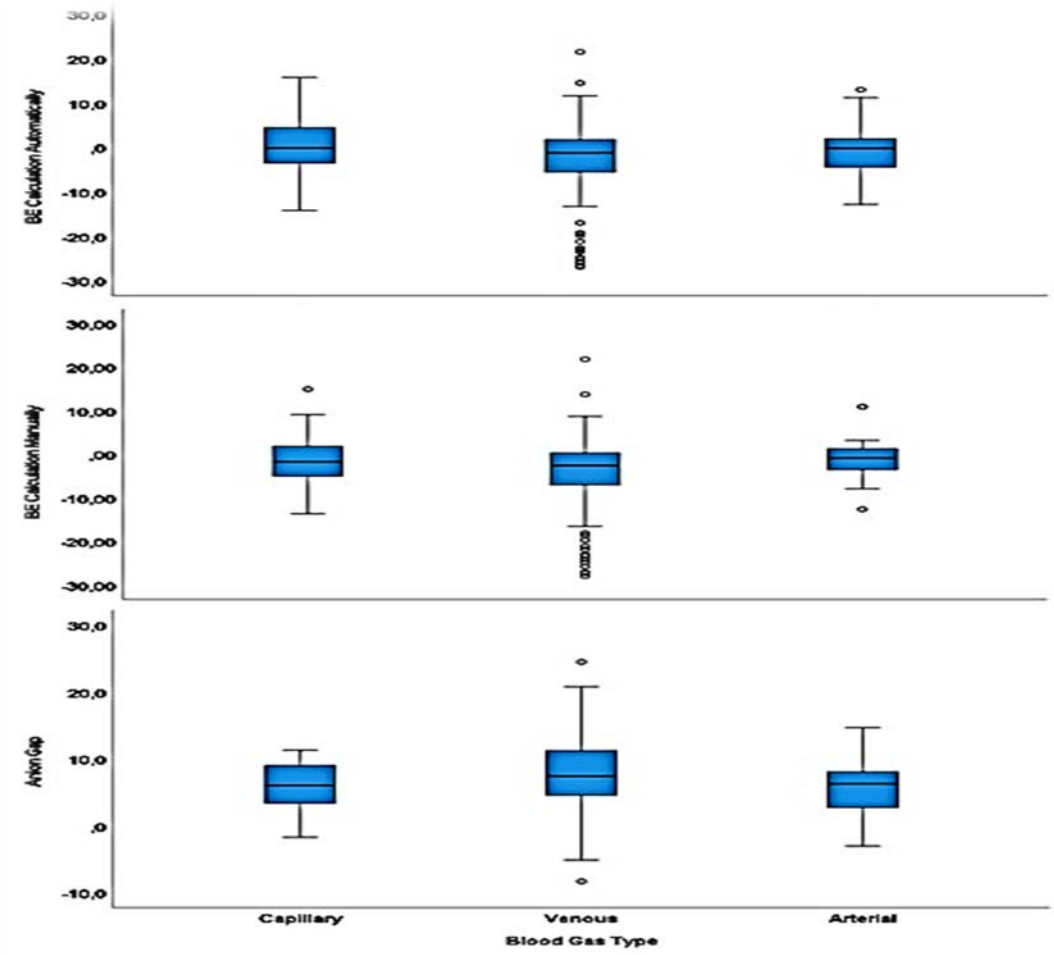

Figure 1. Comparison of BE automatically, manually and anion gap measurements between blood gas groups

The sample taken in standard blood gas analysis is arterial. However, due to the risk of arterial spasm, thrombosis, and bleeding in children, less invasive venous or capillary blood gas samples are also analyzed (7). Many studies are comparing arterial or venous blood samples. According to a study in India, there was a correlation between pH while their CO_2 concentrations were less correlative (14). With mechanical ventilation support for acute respiratory failure patients in treating from Taiwan study showed that venous samples analysis could accurately correlate values of pH, PCO_2, and HCO_3 from arterial (15). In a study conducted in Australia study with the same objective, a correlation was identified between the pH of venous and arterial blood samples at a rate of 90% (16). Similarly, in the study conducted in Turkey study demonstrated that there was a high correlation between pH, PCO_2

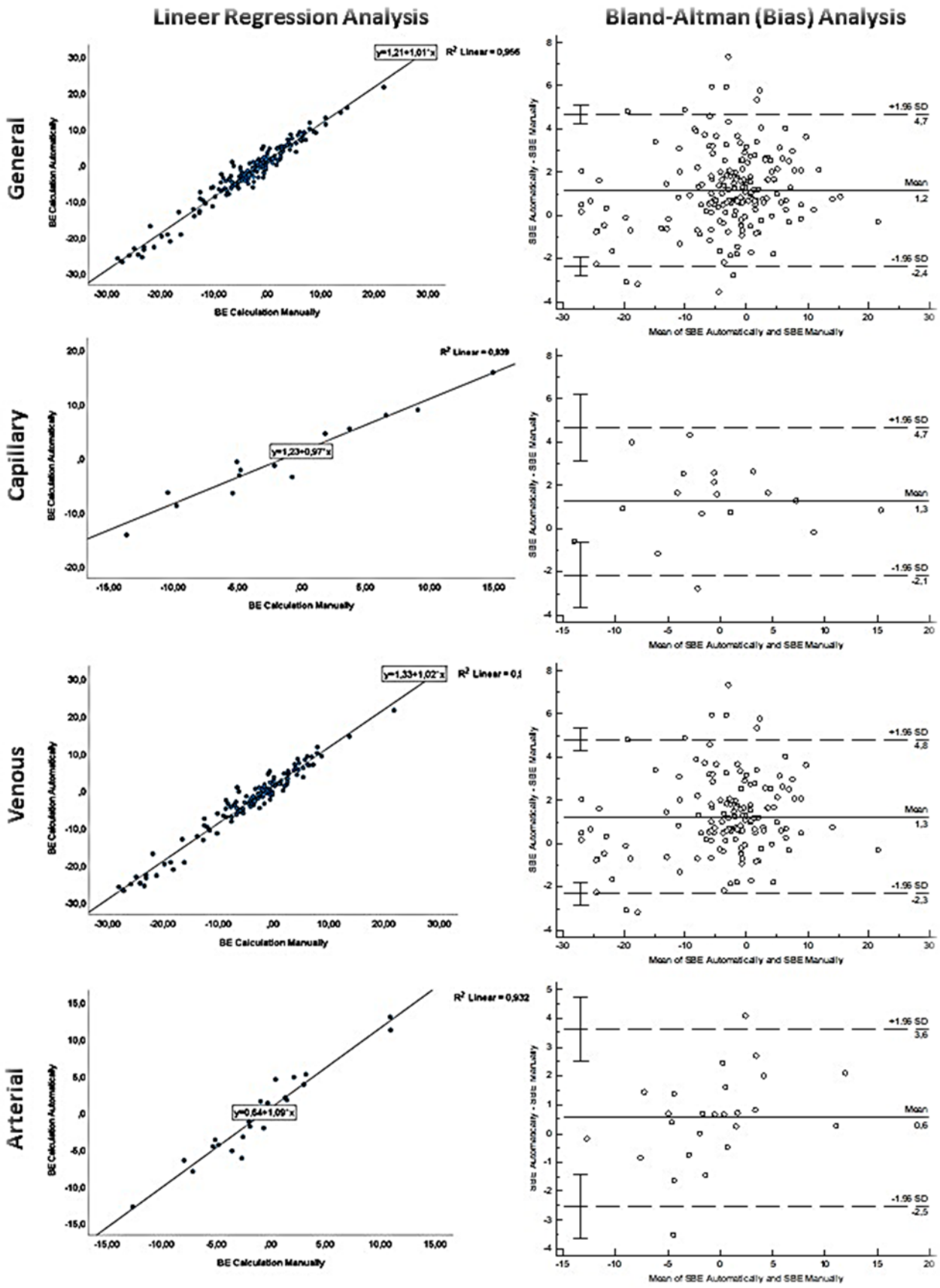

Figure 2. Correlation, regression and Bland-Altman (bias) analysis results for automatic and manual calculation of BE in general and blood gas types

and HCO_3 in both arterial and venous blood samples, including in patients with a variety of different diseases (17). On the contrary to all these studies, in Iran, acute exacerbation of chronic obstructive pulmonary disease adult patients study showed a relative correlation between arterial and venous analysis values of pH and pCO_2. Therefore, they suggested be use of arterial blood gase analysis still though sampling difficulties (18). Additionally, another study about the tricyclic antidepressants poisoning in Iran patients reported that venous pH was the only value that correlated value with arterial samples (19). In our study, we detected no statistically significant difference in the blood gas sample was artery, vein, or capillary for SBE (both automatically and manually calculation) and AG results. On the contrary, if the blood gas taken was capillary or venous, a significant difference was detected between the SBE automatically and manually calculation, but this difference was not found in arterial samples. This may be evidence that taking arterial samples in critically ill patients with high SBE values would be more beneficial in terms of clinical analysis and management, especially in pediatric patients. Although our study did not find a significant difference in SBE according to the method of the three types of blood gas sampling, when comparing manual and automated sampling, the most compatible result is arterial, followed by capillary and then venous sampling (according to lineer regression and Bland-Altman (bias) analysis). This supports the use of capillary samples in patients where arterial sampling is difficult and risky, such as neonates and infants.

This study has limitations as it is single-center and retrospective, but since the dataset covers critically ill patients of the same age group under the care of the same PICU team, we believe that it is a reliable source of information that will contribute to the existing literature on the subject. Multicenter studies covering a larger population and including specific patient groups on blood gas analysis and calculations are needed.

In conclusion, the automatic measurements of the blood gas analyser are reliable, as evidenced by the correlation between automatically and manually values with parameters such as pH, AG and SBE, which are inherent to the blood gas samples obtained from pediatric patients under optimal conditions. Nevertheless, in cases where there is an elevated risk of base deficit in critically ill patients, it is advisable to obtain an arterial blood gas sample.

Ethical Approval: *Prior to the commencement of the study, approval was granted by the Aydin Adnan Menderes University Faculty of Medicine Ethics Committee (decision dated 23/10/2023; protocol ID: 2023/182) in accordance with the ethical standards set out in the committee's guidelines*

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Araştırma Makalesi / Research Article

Lomber Mikrocerrahi ile Diskektomi Yapılan Hastalarda Tesadüfi Dural Yırtık Prognozunun İncelenmesi; Tek Merkezli Retrospektif Analiz

Prognosis of Incidental Dural Tear in Patients Who Underwent Lumbar Discectomy With Microsurgery; A Single Center Retrospective Analysis

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Öz

Amaç: Dural yırtık, lomber diskektomi sırasında en sık görülen komplikasyondur. Ek komplikasyonlara yol açabilmektedir. Çalışmamızda lomber mikrocerrahi yaptığımız hastalarda dural yırtık görülme oranını, risk faktörlerini, intraoperatif dural yırtık gelişenlerde uyguladığımız yöntemleri ve postoperatif komplikasyonları inceledik.
Materyal ve metod: Çalışmamızda hastanemizde lomber mikrocerrahi diskektomi yapılan 1845 hasta incelendi. Hastaların hangi seviyeden ve hangi taraftan opere edildikleri ve nüks diskektomi yapılıp yapılmadığı, dural yırtık gelişip gelişmediği kayıt altına alınmıştır. İntraoperatif ve postoperatif süreçler sorgulanarak istatistiki analize tabi tutulmuştur.
Bulgular: 1845 hastanın 171'inde dural yırtık gelişmiştir. Dural yırtık gelişen hastalarda yaş ortalaması 53 olarak tespit edilmiş, dural yırtık gelişmeyen hastalara göre anlamlı olarak yüksek bulunmuştur. (p<0,001) Bilateral diskektomi yapılan hastalarda dural yırtık gelişme oranı anlamlı olarak yüksek bulunmuştur. (p<0,001) Hastaların operasyon seviyeleri incelendiğinde L4-5 mesafesinden ve birden çok seviyeden yapılan operasyonlar ile nüks diskektomilerde dural yırtık gelişme oranı anlamlı olarak yüksek bulunmuştur. (p<0,001) Dural yırtık gelişen 171 hastanın 19'unda çeşitli sebepler ile tekrar yatış ya da reoperasyon ihtiyacı olmuştur.
Sonuç: Dural yırtık sonuçları itibariyle nöroşirurjiyenler için korkutucu bir komplikasyondur. Elde ettiğimiz sonuçlar dural yırtığın risk faktörleri olarak, artan yaş, L4-5 seviyesinden yapılan operasyonlar, bilateral ve çok seviye operasyonlar ile nüks operasyonları tespit etmiştir. Dural yırtık sonrası reoperasyon veya yeniden yatış gereksinimi üzerine, intraoperatif primer sütürasyon, doku grefti veya doku yapıştırıcısı uygulamanın anlamlı farklılıklar oluşturmadığını tespit ettik.

Anahtar Kelimeler: Dural yırtık, Spinal cerrahi, Beyin omurilik sıvısı(BOS) kaçağı

Abstract

Background: Dural tear is the most common complication during lumbar discectomy. It may lead to additional complications. In our study, we examined the incidence of dural tears in patients undergoing lumbar microsurgery, the risk factors, the methods we used in cases with intraoperative dural tears, and the postoperative complications.
Materials and Methods: In our study, 1845 patients who underwent lumbar microdiscectomy at our hospital were examined. The level and side of the surgery, as well as whether revision discectomy was performed and whether a dural tear occurred, were recorded. Intraoperative and postoperative processes were investigated and subjected to statistical analysis.
Results: In 171 out of 1845 patients, a dural tear occurred. The average age of patients with dural tears was found to be 53, which was significantly higher compared to patients without dural tears. (p<0,001) The rate of dural tears was significantly higher in patients who underwent bilateral discectomy. (p<0,001) When examining the operation levels, the rate of dural tears was significantly higher in surgeries performed at the L4-5 level, multiple levels, and in revision discectomies. (p<0,001) Among the 171 patients who experienced a dural tear, 19 required rehospitalization or reoperation for various reasons.
Conclusions: Dural tears are a frightening complication for neurosurgeons due to their potential outcomes. Our results identified increasing age, surgeries performed at the L4-5 level, bilateral and multiple level surgeries, and revision surgeries as risk factors for dural tears. Regarding the need for reoperation or rehospitalization following a dural tear, we found no significant differences between the application of intraoperative primary suturing, tissue grafts, or tissue adhesives.

Keywords: Dural tear, Spinal surgery, Cerebrospinal fluid leak

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Giriş

Lomber diskektomi beyin ve sinir cerrahisi pratiğinde en sık yapılan cerrahilerdendir. Standart diskektomi, mikrocerrahi veya endoskopik diskektomi tercihi cerrahın eğitimine, deneyimine ve kaynakların yeterliliğine göre değişmektedir. Tesadüfi dural yırtık, lomber diskektomi sırasında en sık görülen, sıklığı %20'lere ulaşan önemli bir komplikasyondur (1, 2). İleri yaş, diyabetes mellitus(DM), kadın cinsiyet, revizyon cerrahisi, dejeneratif omurga cerrahisi yapılan çalışmalarda risk faktörleri arasında gösterilmiştir (3). Dural yırtık gelişen hastalarda beyin omurilik sıvısı (BOS) fistülü, psödomeningosel, epidural hematom, menenjit, uzamış istirahate bağlı venöz tromboemboli gibi ek komplikasyonlar gelişebilmektedir (4). Dural yırtık geliştikten sonra olası komplikasyonların önüne geçmek için farklı yöntemler kullanılmaktadır. Sütürasyon, doku greftleri, doku yapıştırıcıları gibi uygulamaların hangisinin daha etkili olduğuna dair fikir birliği yoktur. Çalışmamızda lomber mikrocerrahi yaptığımız hastalarda dural yırtık görülme oranını, risk faktörlerini, intraoperatif dural yırtık gelişenlerde uyguladığımız yöntemleri ve postoperatif komplikasyonları inceledik.

Materyal ve Metod

Çalışmamız retrospektif kohort çalışma olarak planlanmıştır. Harran Üniversitesi etik kurulu tarafından onaylanmıştır (HRÜ/24.05.21).

Hastanemiz Beyin ve Sinir cerrahisi kliniğinde 2018-2022 yılları arasında LDH nedeni ile opere edilen 1845 hasta çalışmaya dahil edilmiştir. Hastaların verilerine hastane bilgi yönetim sistemi (HBYS) üzerinden ve ameliyat kayıt defterleri taranarak ulaşılmıştır. Çalışmaya mikroskopik yöntemle hemiparsiyel laminektomi uygulanan, tek taraflı veya bilateral, bir veya birden çok seviyeden opere edilen, ilk operasyon veya nüks nedeni ile opere edilen LDH hastaları dahil edilmiştir. Travma hastaları, spinal füzyon-fiksasyon uygulanan hastalar, total laminektomi yapılan hastalar çalışmaya dahil edilmedi. Hastalar farklı cerrahlar tarafından opere edilmiş olsa da tüm hastalara mikrocerrahi yöntemle hemiparsiyel laminektomi ve diskektomi uygulanmıştır. Tüm cerrahlar sağ ellidir. Hastalarda dural yırtık geliştiyse fasia emilebilir polydioxanone sütür ile kontinü, ciltaltı doku polyglactin sütür ile, cilt ise prolene sütür ile anatomik pozisyonda primer sütüre edilmiştir.

Hastaların demografik özellikleri ve ek hastalık olarak DM olup olmadığı tüm hastalarda sorgulandı. Hastaların hangi seviyeden ve hangi taraftan opere edildikleri ve nüks diskektomi yapılıp yapılmadığı kayıt altına alınarak birden fazla seviye veya bilateral diskektomi uygulandıysa ayrıca analiz edilmiştir. İntraoperatif dural yırtık gelişen hastalarda defekt alanına doku yapıştırıcı veya doku(yağ, kas, fasia) uygulanıp uygulanmadığı, dura sütürasyonu uygulanıp uygulanmadığı tüm hastalarda sorgulanarak kayıt altına alınmıştır. İntraoperatif dural yırtık gelişen hastalarda yatış süresi ve reoperasyon gereksinimi sorgulanarak postoperatif süreç açısından analiz edilmiştir.

İstatistiksel analizler SPSS 27.0 programında yapılmıştır. İstatistiksel anlamlılık sınırı p değerinin 0,05'ten küçük olması olarak kabul edilmiştir. Bağımsız kategorik değişkenlerin karşılaştırılmasında ki-kare ve Fisher kesinlik testleri kullanılmış değişkenler sayı ve yüzde ile sunulmuştur. Bağımsız sürekli değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov ve Shapiro-Wilk testi ile değerlendirilmiştir. Değişkenlerin normal dağılıma uymadığı belirlenmiş ve sürekli değişkenlerin karşılaştırılmasında Mann-Whitney U testi kullanılmış, bulgular ortanca ve 25 ve 75 persentil değerleri ile sunulmuştur.

Bulgular

Çalışmamıza 1845 hasta dahil edilmiş, 171 hastada dural yırtık gelişmiştir. Hastaların yaş ortalaması 47 olarak tespit edilmiştir. Dural yırtık gelişen hastalarda yaş ortalaması 53 olarak tespit edilmiş, dural yırtık gelişmeyen hastalara göre anlamlı olarak yüksek bulunmuştur (p<0,001). Hastaların %52,5 (n=969)'i erkek %47,5 (n=876)'i kadın cinsiyettedir. Dural yırtık gelişen hastalarda gelişmeyenlere göre anlamlı cinsiyet farklılığı tespit edilmemiştir. Opere edilen hastaların taraf bulgusu incelendiğinde, bilateral diskektomi yapılan hastalarda dural yırtık gelişme oranı anlamlı olarak yüksek bulunmuştur (p<0,001). Hastaların operasyon seviyeleri incelendiğinde L4-5 mesafesinden ve birden çok seviyeden yapılan operasyonlar ile nüks diskektomilerde dural yırtık gelişme oranı anlamlı olarak yüksek bulunmuştur (p<0,001) (Tablo 1).

Dural yırtık gelişen hastalar üzerinde ayrıca yapılan analizlerde postoperatif reoperasyon ihtiyacı ve tekrar yatış ihtiyacı incelenmiştir. Dural yırtık gelişen 171 hastanın 19'unda çeşitli sebepler ile tekrar yatış ya da reoperasyon ihtiyacı olmuştur. Hastaların ek hastalıkları ve demografik özellikleri incelendiğinde anlamlı bir istatistiki farklılık saptanmamıştır. Seviye ve taraf-nüks durumları da istatistiki olarak anlamlı bulunmamıştır. Tekrar operasyon geçiren hastaların %5,2 (n=1)'sinde hematom nedeni ile, %94,8 (n=18)'inde enfeksiyon veya yara yerinde akıntı nedeni ile tekrar operasyon veya yatış yapılmıştır. Hastaların ortalama yatış süresi 1,7±4,9 gün olarak bulunmuştur. 1 günden daha uzun süre yatan hastalarda ortalama yatış süresi 6,9±13,9 olarak hesaplanmıştır. Yatış süresi 1 günden daha uzun olan hastaların 13'ünde yatış süresinin 2 veya 3 gün olduğu saptanmıştır. Bu hastalarda postoperatif yara yeri takibi açısından yatış sürecinin uzatıldığı ve hastalarda ek problem olmadan taburcu edildiği tespit edildi. Bir hasta 63 gün yara yerinde akıntı ve spondilodiskit nedeni ile tekrar opere edilerek takip edildi. Bir hasta yara yeri akıntısı ve enfeksiyonu sonrası antibiyoterapi nedeni ile 16 gün, bir hasta hematom nedeni ile tekrar operasyon nedeni ile 6 gün, bir hasta optik nöropati nedeni ile 8 gün, bir hasta ise nöropatik ağrı nedeni ile 5 gün takip edildi (Tablo 2).

Tablo 1. Lomber disektomi hastaların özelliklerinin karşılaştırılması

Preoperatif özellikler	**Toplam**	**Dural yırtık yok** n (%)	**Dural yırtık var** n (%)	**p**
Cinsiyet				
Kadın	876 (47,5)	788 (47,1)	88 (51,5)	0,274[1]
Erkek	969 (52,5)	886 (52,9)	83 (48,5)	
Yaş				
Ortanca (25p-75p)	47,0 (40,0-56,0)	47,0 (39,0-56,0)	53,0 (46,0-63,0)	**<0,001[2]**
Sağ taraf				
Yok	991 (53,7)	906 (54,1)	85 (49,7)	0,270[1]
Var	854 (46,3)	768 (45,9)	86 (50,3)	
Sol taraf				
Yok	753 (40,8)	688 (41,1)	65 (38,0)	0,434[1]
Var	1092 (59,2)	986 (58,9)	106 (62,0)	
Bilateral				
Yok	1744 (94,5)	1594 (95,2)	150 (87,7)	**<0,001[1]**
Var	101 (5,5)	80 (4,8)	21 (12,3)	
L1-2				
Yok	1837 (99,6)	1667 (99,6)	170 (99,4)	0,541[3]
Var	8 (0,4)	7 (0,4)	1 (0,6)	
L2-3				
Yok	1790 (97,0)	1625 (97,1)	165 (96,5)	0,670[1]
Var	55 (3,0)	49 (2,9)	6 (3,5)	
L3-4				
Yok	1671 (90,6)	1517 (90,6)	154 (90,1)	0,810[1]
Var	174 (9,4)	157 (9,4)	17 (9,9)	
L4-5				
Yok	816 (44,2)	764 (45,6)	52 (30,4)	**<0,001[1]**
Var	1029 (55,8)	910 (54,4)	119 (69,6)	
L5-S1				
Yok	1175 (63,7)	1057 (63,1)	118 (69,0)	0,129[1]
Var	670 (36,3)	617 (36,9)	53 (31,0)	
Birden çok seviye				
Yok	1750 (94,9)	1605 (95,9)	145 (84,8)	**<0,001[1]**
Var	95 (5,1)	69 (4,1)	26 (15,2)	
Nüks				
Yok	1619 (87,8)	1485 (88,7)	134 (78,4)	**<0,001[1]**
Var	226 (12,2)	189 (11,3)	37 (21,6)	

[1] Pearson ki-kare testi kullanılmıştır.
[2] Mann-Whitney U testi kullanılmıştır.
[3] Fisher'in kesinlik testi kullanılmıştır.

Tablo 2. Dural yırtık gelişen hastalarda reoperasyon/tekrar yatış durumlarının incelenmesi

Dural yırtık hastaları	**Reoperasyon/yatış yok** n (%)	**Reoperasyon/yatış var** n (%)	**P değeri**
Cinsiyet			
Kadın	78 (51,3)	10 (52,6)	0,914[1]
Erkek	74 (48,7)	9 (47,4)	
Yaş			
Ortanca (25p-75p)	53,0 (45,3-62,8)	57,0 (46,0-63,0)	0,810[2]
Ek hastalık			
Yok	90 (59,2)	12 (63,2)	0,741[1]
Var	62 (40,8)	7 (36,8)	
DM			
Yok	132 (86,8)	16 (84,2)	0,724[3]
Var	20 (13,2)	3 (15,8)	
Sağ taraf			
Yok	75 (49,3)	10 (52,6)	0,787[1]
Var	77 (50,7)	9 (47,4)	
Sol taraf			
Yok	58 (38,2)	7 (36,8)	0,911[1]
Var	94 (61,8)	12 (63,2)	
Bilateral			
Yok	133 (87,5)	17 (89,5)	1,000[3]
Var	19 (12,5)	2 (10,5)	
L1-2			
Yok	151 (99,3)	19 (100,0)	1,000[3]
Var	1 (0,7)	0 (0,0)	
L2-3			
Yok	147 (96,7)	18 (94,7)	0,512[3]
Var	5 (3,3)	1 (5,3)	
L3-4			
Yok	136 (89,5)	18 (94,7)	0,697[3]
Var	16 (10,5)	1 (5,3)	
L4-5			
Yok	49 (32,2)	3 (15,8)	0,142[1]
Var	103 (67,8)	16 (84,2)	
L5-S1			
Yok	104 (68,4)	14 (73,7)	0,640[1]
Var	48 (31,6)	5 (26,3)	
Birden çok seviye			
Yok	130 (85,5)	15 (78,9)	0,496[3]
Var	22 (14,5)	4 (21,1)	
Doku/doku yapıştırıcısı			
Yok	13 (8,6)	0 (0,0)	-
Doku yapıştırıcısı	64 (42,1)	13 (68,4)	
Doku	9 (5,9)	0 (0,0)	
Doku yapıştırıcısı+doku	66 (43,4)	6 (31,6)	
Doku yapıştırıcısı			
Yok	22 (14,5)	0 (0,0)	0,137[3]
Var	130 (85,5)	19 (100,0)	
Doku(Kas, yağ veya fasia)			
Yok	77 (50,7)	13 (68,4)	0,144[1]
Var	75 (49,3)	6 (31,6)	
Sütürasyon ve greft/doku yapıştırıcısı			
Yok	8 (5,3)		
Tissel/doku+sütürasyon	33 (21,7)	0 (0,0)	0,157[1]
Sadece tissel/doku	106 (69,7)	5 (26,3)	
Sadece sütürason	5 (3,3)	14 (73,7)	
		0 (0,0)	
Primer Sütürasyon			
Yok	114 (75,0)	14 (73,7)	0,157[1]
Var	38 (25,0)	5 (26,3)	
Yatış süresi			
1 gün	136 (89,5)	16 (84,2)	1,000[3]
>1 gün	16 (10,5)	3 (15,8)	

[1] Pearson ki-kare testi kullanılmıştır.
[2] Mann-Whitney U testi kullanılmıştır.
[3] Fisher'in kesinlik testi kullanılmıştır.

Tartışma

Omurga cerrahisinde dural yırtık nispeten sık görülen bir komplikasyondur. Yara yerinde akıntı, bos fistülü, psödomeningosel, ve santral sinir sistemi enfeksiyonu gibi istenmeyen durumlara yol açabilmektedir (1, 2, 5). Bu çalışmada tek veya çok seviyeden lomber mikrocerrahi diskektomi uygulanan hastaları inceledik. Çalışmaya 1845 hastayı dahil ettik. 1845 hastanın 171'inde dural yırtık geliştiğini tespit ettik. Literatürde spinal cerrahi sırasında dural yırtık oranı değişken olmakla birlikte %1–17,4 arasında görülmektedir (1, 2). Bizim çalışmamızda dural yırtık görülme oranı %9,26 olarak tespit edildi. Bu oran literatür ile benzerdir. 1159 hasta üzerinde yapılan bir çalışmada dural yırtık gelişmeyen ve gelişen hastalarda yaş ortalamasını sırasıyla 40,5 ve 49,6 olarak tespit ettiler. Bir başka çalışmada dural yırtık gelişen hastalarda yaş ortalamasının daha yüksek olduğunu göstermişlerdir (6). Bizim çalışmamızda literatürle uyumlu olarak dural yırtık gelişmeyenlerde yaş ortalaması 47, gelişenlerde yaş ortalaması 53 olarak tespit edildi (p<0,001). Artan yaşla birlikte dejenerasyon bulguları olarak faset hipertrofisi, ligamentum flavum hipertrofisi ve osteofit gelişimi gibi bulgular ortaya çıkmakta ve spinal kanalda darlığa yol açmaktadır. Dural yırtık oluşmasının artan yaşla daha fazla görülmesi artan dejenerasyonla açıklanabilir (1, 7). Literatürde omurga cerrahisinde dural yırtık görülme oranının kadınlarda daha fazla olduğuna dair bilgiler mevcuttur (8, 9). Biz çalışmamızda cinsiyetin dural yırtık üzerine anlamlı bir etkisi olmadığını tespit ettik.

Spondilolistezis, jukstafaset kisti, osteofitler gibi dejeneratif bulgular ile dural yırtık görülme ihtimali artmaktadır (9). Çalışmamızda dejeneratif omurga cerrahisinden ziyade tek veya çok seviyeden yapılan hemiparsiyel laminektomi ve mikrodiskektomiye odaklandık. Lomber disk hernilerinin yaklaşık %95'i L4-5 veya L5-S1 seviyelerinde görülmektedir.(10) Yapılan çalışmalarda dural yırtığın en sık lomber seviyede ve lumbosakral bölgede görüldüğünü belirtmişlerdir (11, 12). Taylor ve ark. 106 dural yırtık hastasının %72,64'ünde L3-S1 arasında dural yırtık görüldüğünü bildirmişlerdir (13). Albayrak ve ark. yaptıkları çalışmada L3-4 düzeyinde dural yırtık oranının anlamlı olarak yüksek olduğunu bildirdi (14). Bizim çalışmamızda 171 hastanın 119'unda L4-L5 mesafesinde dural yırtık görüldü (p<0,001). Bu oran istatistiki olarak anlamlıdır. Her ne kadar üst lomber bölgede daha dar spinal kanal ve daha ince dura ile karşılaşılsa da bu operasyonların daha az sıklıkla yapılması ve cerrahın daha dikkatli olması dural yırtık oranını azaltmış olabilir. Revizyon cerrahilerinin dural yırtık ihtimalini arttırdığına dair literatürde birçok çalışma mevcuttur (3, 11, 12, 15). Bu durum muhtemelen ilk operasyon sonrası oluşan granülasyon dokuları, yapışıklıklar ve normal anatomik yapının bozulmasıyla ilişkilendirilebilir. Çalışmamızda literatürle benzer olarak nüks hastalarında dural yırtık anlamlı olarak yüksek bulundu (p<0,001). 523 hasta üzerinde yapılan bir çalışmada lomber laminektomi yapılan hastaları incelediklerinde çok seviye dekompresyon ile dural yırtık arasında istatistiki olarak anlamlı bir sonuç bulamadılar (15). Biz çalışmamızda lomber mikrodiskektomi yapılan hastalarda birden fazla seviye yapılan operasyonları tek seviye yapılan operasyonlarla, bilateral yapılan operasyonları tek taraflı yapılan operasyonlarla karşılaştırdık. Birden çok seviye mikrodiskektomi yapılan 95 hastanın 26'sında, bilateral mikrodiskektomi yapılan 101 hastanın 21'inde dural yırtık meydana geldiğini tespit ettik. Bu sonuçlar istatistiki olarak anlamlı bulunmuştur (p<0,001). Çalışmamız birden çok seviye veya bilateral yapılan diskektomilerde dural yırtık ortaya çıkma ihtimalinin daha fazla olduğunu göstermektedir.

Omurga cerrahisi sırasında meydana gelen dural yırtık beraberinde birçok sorunu da getirebilmektedir. Yapılan çalışmalarda dura yırtığı olan hastaların 90 günlük tıbbi maliyetleri, hastanede kalış süreleri ve yeniden hastaneye yatış olasılıkları daha fazla bulunmuştur (4). Dural yırtık sonrası ne kadar süre yatak istirahati gerektiği konusunda net bir bilgi yoktur. Literatürde fikir birliği olmasa da 3-5 gün arasında yatak istirahati uygulandığı belirtilmiştir (6, 16, 17). Bizim çalışmamızda hastaların ortalama yatış süresi literatüre oranla daha az görünmektedir. Bu durum muhtemelen çalışmamıza travma hastaları, spinal füzyon-fiksasyon uygulanan hastalar, total laminektomi yapılan hastaları dahil etmemiş olmamızdan kaynaklanmaktadır. Bu hastalarda daha küçük dura yırtıkları ve daha kolay onarım mümkün olabilmektedir. Ayrıca hastalarda daha küçük bir insizyonla mikrocerrahi yapılmış olması dren ihtiyacını da ortadan kaldırmış, hastaların dren takibi nedeni ile daha uzun süre yatmasının önüne geçmiştir. Çalışmamızda dural yırtık olan hastaların hangilerinde daha fazla reoperasyon/yatış olduğunu araştırdık. Bu açıdan hastaların demografik özellikleri, diskektomi seviye ve tarafları, intraoperatif doku yapıştırıcısı uygulanması, doku uygulanması ve primer onarım özelliklerini araştırdık. Choi ve ark. yaptıkları sistematik derleme çalışmada dural yırtığın lomber bölgede fazla olduğunu ve bu hastalarda daha fazla reoperasyon-enfeksiyon oranları olduğunu belirtmişler ancak seviye belirtmemişlerdir (18). Çalışmamızda diskektomi yapılan seviye ve tarafları ayrı olarak analiz ettik ancak reoperasyon veya tekrar yatış açısından anlamlı bir sonuca ulaşamadık. İntraoperatif dural yırtık geliştiğinde birçok onarım yöntemi kullanılmaktadır. Mümkünse primer sütürasyon, mümkün değilse sentetik veya biyolojik greftler, doku yapıştırıcıları, membranlar ve klipler gibi birçok materyal kullanılabilmektedir. Biz dural yırtık gelişen hastalarda mümkün olanlarda 3-0, 4-0 ipek veya polyglactin sütürler ile primer sütürasyon uyguladık. Sütürasyon uyguladıklarımıza veya uygulayamadığımız hastalarda kas, yağ veya fasia doku greftleri ile birlikte veya sadece protein bazlı(fibrin) doku yapıştırıcı (Tisseel) uyguladık. Alshameerii ve ark. yaptıkları metaanaliz çalışmasında tedavi türünden bağımsız olarak dura yırtığı tedavisi başarısızlığının toplam kombine oranını %6,1 (%4,4-%8,3) olarak tespit etti. Farklı onarım yöntemlerini karşılaştırdıklarında anlamlı bir farklılık gözlenmedi. Ancak primer sütürasyonda başarısızlık oranını daha düşük buldular (19). Choi ve ark. yaptıkları çalışmada BOS sızıntısı insidansını primer sütür ile birlikte yama uygulananlarda daha düşük bul-

dular (%5,5, 7/128). Onarım tekniği ne olursa olsun enfeksiyon veya postoperatif nörolojik defisit oranında anlamlı bir fark gözlemediler (18). Biz çalışmamızda hastalarda intraoperatif primer sütürasyon uygulananları, doku grefti veya doku yapıştırıcısı uygulananları ayrı ayrı ve kombine bir şekilde analiz ettik. Sadece sütürasyon uyguladığımız 5 hastanın hiçbrinde tekrar yatış veya operasyon ihtiyacı gelişmedi. Ancak yaptığımız analizlerde hastaların reoperasyon veya tekrar yatış gereksinimi üzerine hiçbir grupta anlamlı istatiktiksel fark bulamadık.

Çalışmamız retrospektif kohort çalışma olarak planlanmış ve HBYS üzerinden ulaşmış olduğumuz verilere dayandırılmıştır. Dural yırtık gelişen hastalarda dural yırtığın spinal kanalda lokalizasyonu ve boyutu konusunda ve uyguladığımız greftlerin boyutu konusunda net bir veri elde edemedik. Tüm bu sınırlamalara rağmen, yazarlar elde ettiğimiz sonuçların özellikle az çalışılan bir alan olan lomber mikrocerrahide dural yırtığın risk faktörleri ve yönetimi konusunda önemli olabileceğine ve literatüre katkı sunacağına inanmaktadır.

Sonuç

Lomber mikrocerrahi ile diskektomi beyin ve sinir cerrahisi pratiğinde en sık uygulanan cerrahilerdendir. Dural yırtık sonuçları itibariyle nöroşirurjiyenler için korkutucu bir komplikasyondur. Bu çalışmada lomber mikrocerrahi sırasında görülen tesadüfi dural yırtığın risk faktörlerini ve yönetimini araştırdık. Elde ettiğimiz sonuçlar dural yırtığın risk faktörleri olarak, artan yaş, L4-5 seviyesinden yapılan operasyonlar, bilateral ve çok seviye operasyonlar ile nüks operasyonları tespit etmiştir. Dural yırtık sonrası reoperasyon veya yeniden yatış gereksinimi üzerine, intraoperatif primer sütürasyon, doku grefti veya doku yapıştırıcısı uygulamanın anlamlı farklılıklar oluşturmadığını tespit ettik. Ulaştığımız sonuçların önemli olduğunu düşünmekle birlikte spnuçlarımızın prospektif çalışmalarla desteklenmesi gerektiğine inanıyoruz.

Etik onam: *Çalışmamız retrospektif kohort çalışma olarak planlanmıştır. Harran Üniversitesi etik kurulu tarafından onaylanmıştır (13/05/2024 - HRÜ/24.05.21).*

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Research Article / Araştırma Makalesi

Peer Bullying and Self-Esteem in Turkish School-Age Children Who Stutter

Okul çağı Kekemelik tanılı Çocuklarda Akran Zorbalığı ve Benlik Saygısı

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Abstract

Background: This study aims to examine the prevalence of peer bullying among Turkish-speaking school-aged children who stutter (CWS) and to explore the relationships between exposure to bullying and self-esteem, depression, and anxiety symptoms in these children.
Materials and Methods: The study included a case group of 35 children diagnosed with stuttering and a control group of 35 children with fluent speech. A speech and language therapist assessed the children in the stuttering group using the Stuttering Severity Instrument. Additionally, all children were asked to complete the Rosenberg Self-Esteem Scale (RSES), the Olweus Bully/Victim Questionnaire, and the Revised-Child Anxiety and Depression Scale (RCADS).
Results: There was a significant relationship between peer bullying experiences, self-esteem, anxiety, and depression symptoms between both groups ($p<0.05$). CWS demonstrated greater susceptibility to peer bullying compared to the control group, and they scored higher on the RSES, indicating reduced self-esteem. Furthermore, it was found that symptom scores for depressive disorder, generalized anxiety disorder, and social anxiety disorder increased in stuttering children with low self-esteem.
Conclusions: Our study demonstrated that school-aged CWS exhibit lower self-esteem and more pronounced symptoms of anxiety and depressive disorders. We believe that healthcare professionals working with the school-age CWS should assess their self-esteem and engage them in activities aimed at enhancing self-esteem, as this may help prevent the development of secondary psychopathologies such as depressive disorder, anxiety disorder.

Keywords: Peer Bullying, Self-esteem, Stuttering, Children

Öz

Amaç: Çalışmamızda Türkçe konuşan, okul çağı kekemelik tanılı çocuklarda akran zorbalığının sıklığını ve zorbalığa maruz kalma ile çocukların benlik saygısı, depresyon ve kaygı belirtileri arasındaki ilişkiyi incelemeyi amaçladık.
Materyal ve Metod: Kekemelik tanısı konulan 35 çocuk olgu grubuna, konuşması akıcı olan 35 çocuk ise kontrol grubuna dahil edildi. Kekemelik tanısı olan çocuklara, dil ve konuşma terapisti tarafından Kekemelik Şiddet Değerlendirme Aracı-4 uygulanmıştır. Çocuklar tarafından doldurulması için Rosenberg Benlik Saygısı Envanteri, Olweus Akran Zorbalığı Anketi ve Çocukluk Çağı Anksiyete Depresyon Ölçeği verilmiştir.
Bulgular: Her iki grup arasında akran zorbalığı deneyimleri, benlik saygısı, depresyon ve kaygı belirtileri arasında anlamlı bir ilişki vardı ($p<0.05$). Kekemelik tanılı çocukların, akran zorbalığına daha sık maruz kaldıkları ve daha az benlik saygısına sahip oldukları saptandı. Ayrıca, benlik saygısı düşük olan kekemelik tanılı çocuklarda depresyon, yaygın anksiyete ve sosyal anksiyete belirti puanlarının daha yüksek olduğu saptandı.
Sonuç: Çalışmamız, okul çağı kekemelik tanılı çocukların akran zorbalığına daha sık maruz kaldıklarını, daha düşük benlik saygısına, daha çok kaygı ve depresyon belirtilerine sahip olduklarını gösterdi. Okul çağı kekemelik tanısı olan çocuklar ile çalışırken akran zorbalığı ve benlik saygısının değerlendirilmesinin faydalı olacağını düşünmekteyiz. Ayrıca bu çocukların, benlik saygısını arttırmaya yönelik aktivitelere dahil edilmelerinin depresif bozukluk, kaygı bozukluğu gibi ikincil psikopatolojilerin gelişimini önlemeye yardımcı olacağını düşünmekteyiz.

Anahtar Kelimeler: Akran zorbalığı, Benlik Saygısı, Çocuk, Kekemelik

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Introduction

Stuttering is a communication disorder characterised by repetitions or prolongations of sounds, syllables, words, or hesitations or pauses that disrupt speech fluency. The American Psychiatric Association (APA) emphasizes that stuttering impacts multiple areas, including social communication, education and occupational functioning (1). Stuttering typically begins between the ages of 2 and 7, affecting 8-11% of children, and is more common in boys (2). Although most preschool children who begin stuttering recover naturally or with intervention, it is estimated that one-third continue to stutter throughout their school years and beyond (3). Recent research indicates that stuttering may be associated with various emotional and behavioural problems from childhood onwards (4, 5). Children who stutter (CWS) report experiencing more negative life events during early childhood (ages 3-4) compared to their fluent peers, including negative peer reactions in the preschool period, and higher rates of teasing, bullying, and communication difficulties during adolescence (6-8). Moreover, stuttering can limit individuals' communication skills, leading to feelings of loneliness and helplessness, and is frequently accompanied by social anxiety (4). It has also been suggested that the communicative participation of individuals with stuttering can be predicted by self-esteem, self-efficacy, and social support, in addition to the severity of speech fluency (9). Overall, the diagnosis of stuttering can profoundly impact an individual's emotional, behavioral, and cognitive well-being, regardless of age (4).

Peer bullying is conceptualized as a recurring manifestation of aggressive behavior perpetrated by an individual or group possessing greater strength or power against a comparatively weaker individual. The primary objective of such aggression is to inflict harm upon the target. Bullying can manifest in various forms, including physical bullying (e.g., pushing, hitting, kicking), verbal bullying (e.g., name-calling, teasing), cyberbullying and social or relational bullying (e.g., social exclusion, rejection from the peer group)(10). Children who stutter may encounter negative peer attitudes starting from the prescchool period and throughout the school age (11). It has also been reported that children who stutter are more likely to be victims of peer bullying than their fluent peers (12). Exposure to peer bullying during these formative years can have profound effects on the academic, social, and emotional development of children who stutter. Such experiences may contribute to the onset of social anxiety, heightened fear of negative evaluation, and diminished self-confidence (11, 12). Children who stutter are frequently targeted by peers due to their speech differences, leading to social exclusion. This exclusion plays a significant role in the development of anxiety and depression symptoms within this population (13). Studies have demonstrated that children who stutter often perceive their communication abilities as inadequate, which fosters avoidance behaviors, undermines self-confidence, and elevates social anxiety levels. Repetitive and prolonged bullying, in particular, has been shown to negatively impact self-esteem and hinder the development of social skills (13, 14). Blood and Blood (2016) reported that individuals who experienced bullying during childhood were more likely to suffer from psychosocial issues in adulthood, including social anxiety, fear of negative evaluation, and reduced life satisfaction (14). Similarly, Bernarda and Norbury (2022) found that anxiety and depression symptoms in children who stutter were significantly associated with both a negative family mental health history and experiences of bullying. Their study further revealed that bullying exacerbates anxiety symptoms, while depression symptoms tend to become more pronounced with increasing age (13).

Considering the studies in the existing literature, this study aims to:

1. Investigate the prevalence of peer bullying among school-age children who stutter and present to child psychiatry clinics.
2. Examine the impact of peer bullying on the self-esteem of these children.
3. Explore the relationship between peer bullying and the symptoms of depression and anxiety disorders in these children.

Materials and Methods

Sample

Between October 2022 and January 2023, 35 children aged 8-12 years who applied to the child psychiatry outpatient clinic and were diagnosed with developmental stuttering as a result of psychiatric examination were included in the study. Children with a diagnosis of intellectual disability and autism spectrum disorder accompanying the diagnosis of stuttering, with any known neurological, metabolic or genetic disease, with acquired stuttering, whose parents did not agree to participate in the study and whose native language was not Turkish were not included in the study. The control group in the study consisted of 35 children who visited the pediatrics outpatient clinic. These children had no neurological, psychiatric, or genetic disorders, and their speech was natural and fluent. This case-control study was approved by the ethics committee of the Health Sciences University Erzurum Regional Training and Research Hospital (2022/17-159). Written and verbal information was given to the parents of all participants before the study and their consent was obtained.

Procedure

Seventy children participating in the study underwent a standardized psychiatric interview based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) criteria (1). Additionally, a sociodemographic data form was completed for each child. Following these initial assessments, children suspected of having a fluency disorder were referred to speech-language pathologists for comprehensive evaluations.

During the speech-language pathology evaluations, which included unstructured play interaction lasting 20-30 minutes, a collaborative approach was employed. Child psychiatrists and speech-language pathologists worked together to obtain

speech samples and conduct clinical evaluations to confirm a diagnosis of childhood-onset fluency disorder (stuttering) using the DSM-5 criteria (1).

For a subset of 35 children diagnosed with stuttering by a speech-language pathologist, the Stuttering Severity Instrument-Fourth Edition (SSI-4) was administered to assess the severity of their stuttering. All participants, regardless of diagnosis, completed self-report questionnaires to measure self-esteem (*Rosenberg Self-Esteem Scale* [RSES]), bullying experiences (*Olweus Bully-Victim Questionnaire Revised Form* [OBVQ-R]), and anxiety and depression symptoms (*Revised Child Anxiety And Depression Scale* [RCADS]-Child version).

Data Collection Tools

Sociodemographic Data Form: This form was designed and applied by the researchers to collect information about the participants and their family members (age, gender, delivery time, gestational length, and family type).

Hollingshead-Redlich Scale: This scale assesses socioeconomic status (SES) based on parental occupation and educational attainment, classifying it into five levels. Scoring is based on the parent with the highest occupational and educational level, with Levels 1 and 2 indicating high SES, Level 3 representing middle SES, and Levels 4 and 5 indicating low SES (15).

***Stuttering Severity Instrument*- Fourth Edition (SSI-4):** SSI-4, developed by Riley (2009), is used to assess the severity of stuttering by speech and language therapists (16). Three categories are evaluated: frequency, duration and secondary behaviors of stuttering. The scores from all categories are summed to obtain a total score that reflects the severity of stuttering. A total score of 0–10 indicates very mild stuttering severity; 11–16 indicates mild severity; 17–26 indicates moderate severity; 27–31 indicates severe severity; and a score of 32 or above indicates very severe stuttering severity. The Turkish validity and reliability study of the scale was conducted by Mutlu et al. (17).

Rosenberg Self-Esteem Scale (RSES): RSES was developed by Morris Rosenberg in 1965 (18). The first ten questions of the scale were used to measure self-esteem in the study. Five of these ten questions consist of positive and five of negative statements. The statements are answered in a 4-point Likert scale format ranging from "strongly agree" to "strongly disagree". High scores are consistent with low self-esteem. Turkish validity and reliability studies were conducted by Çuhadaroğlu et al. (19).

Olweus Bully – Victim Questionnaire Revised Form (OBVQ-R): OBVQ was developed in 1983 and revised in 1996 by Dan Olweus (20). The scale is a self-report scale prepared for children and adolescents between the ages of 8-16 to determine the bullying situations, the type of bullying and the nature of bullying behaviour, the child's seeking help for bullying, and the reactions of adults and third parties. The questionnaire, which consists of 39 items in total, includes a detailed definition or description of bullying. Turkish validity and reliability study of the questionnaire was conducted by Sipahi and Karababa (21).

Revised-Child Anxiety And Depression Scale (R-CADS)- Child version: It was developed to evaluate anxiety disorders and major depressive disorder in children and adolescents (22). Parent and child forms are available, the child form was used in this study. The subscales include generalised anxiety disorder, separation anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive disorder and major depressive disorder. Turkish validity and reliability study was conducted by Görmez et al. (23).

Statistics

The data analysis was conducted using the SPSS 23.0 statistical program. Descriptive statistics of the evaluation results were presented as numbers and percentages for categorical variables, and as means, standard deviations, minimums, and maximums for numerical variables. The Kolmogorov-Smirnov test was employed to assess the suitability of the data for normal distribution conditions. For comparisons of numerical variables among three or more independent groups, the ANOVA test was used when the normal distribution condition was met, and the Kruskal-Wallis Analysis of Variance was used when it was not. To identify the source of significant differences between groups, the Bonferroni test, one of the post hoc test statistics, was utilized. The Spearman Correlation Test was applied to analyze the relationship between numerical variables in two groups. The Chi-square test was used to analyze differences in the rates of categorical variables among independent groups. Statistical significance was determined at the level of $p<0.05$.

Results

The case group consisted of 35 children diagnosed with developmental stuttering (mean age: 10.97 ± 2.75 years), while the control group comprised 35 children with fluent speech and no psychiatric disorders (mean age: 11.2 ± 2.41 years). Among all participants, 67% (n=47) were male. There were no significant differences between the case and control groups regarding participant characteristics such as age, gender, gestational length, delivery type, family type, and socioeconomic status ($p>0.05$) (Table 1).

The mean age at the onset of stuttering, as reported by the families of children who stutter (CWS), was 4.75 ± 2.3 years. Forty-five point seven percent of these children experienced compensatory behaviors during their speech, and 42.8% experienced bullying by peers. The types of bullying encountered by CWS included verbal (n=11), social or relational (n=6), physical (n=4), and cyber (n=4) bullying. Additionally, five individuals were both victims and perpetrators of bullying (see Table 2). Among the children in the control group, 14.3% (n=5) reported experiencing peer bullying, with two of these children identified as both bullies and victims. Verbal bullying emerged as the most prevalent type of bullying within this group (Table 2).

Table 1. Sociodemographic characteristics of the participants

Variables		Children who stutter (CWS)	Children who do not stutter (CWNS)	*p value*
Age (years± SD)		10.97 ± 2.75	11.2 ± 2.41	0.713
Gender, Male n (%)		26 (74.2)	21 (60)	0.309
Gestational length n (%)	**Premature**	2 (4.8)	3 (8.5)	0.085
	Term	33 (94.2)	32 (91.4)	
Delivery type n (%)	**Vaginal**	20 (57.1)	23 (65.7)	0.661
	C/S	12 (34.2)	11 (31.4)	
Family type n (%)	**Married**	27 (77.1)	30 (85.7)	0.059
	Divorced	3 (8.5)	2 (5.7)	
	Extended	5 (14.2)	3 (8.57)	
SES* n (%)				0.074
	Low	19 (54.2)	13 (37.1)	
	Middle	10 (28.5)	12 (34.2)	
	High	6 (17.1)	10 (28.5)	
Family history of stuttering n (%)		14 (40)		
Mean age of onset of stuttering years± SD		4.75 ± 2.3		
Compansatory behaviour during stuttering, n(%)		16 (45.7)		

CWS: Children who stutter; CWNS: Children who do not stutter SD: standard deviation
**SES: Socioeconomic status*

Table 2. Comparison of children who and who do not stutter according to peer victimization

Variables	Children who stutter	Children who do not stutter	p value
Victims n (%)	10 (28.6)	3 (8.6)	**0.029***
Both victims and bullies n (%)	5 (14.3)	2 (5.7)	
Neither victim nor bully n (%)	20 (57.1)	30 (85.7)	

*p < 0.05 is statistically significant.

The total SSI-4 score averaged 21.15 ± 8.6, with a stuttering frequency score of 11 ± 3.6, and a compensatory behavior score associated with stuttering of 5.5 ± 4.26. Among the children who stutter (CWS), 28.57% exhibited mild stuttering, 25.71% displayed moderate stuttering, and 8.57% had severe stuttering. No significant difference in stuttering severity was found between children subjected to peer bullying and those who were not (p> 0.05). However, an increase in social anxiety symptoms was observed in school-age children as the frequency of stuttering (i.e., the number of stuttered syllables in normal speech) increased (r = 0.678). No significant correlation was found between the SSI-4 scores and the Revised Children's Anxiety and Depression Scale (R-CADS) or the Rosenberg Self-Esteem Scale for the CWS (p> 0.05).

Evaluation of the participants using the R-CADS revealed that both total and subscale scores were significantly higher in children diagnosed with stuttering compared to the control group (p <0.05) (see Table 3). The Rosenberg Self-Esteem Scale (RSES) also indicated lower self-esteem in children who stutter (CWS) (p<0.05) (see Table 3). Additionally, stuttering children who experienced peer bullying had significantly higher RSES scores, indicating lower self-esteem than stuttering children who are not exposed to peer bullying. Furthermore, it was found that symptom scores for depressive disorder, generalized anxiety disorder, and social anxiety disorder increased in stuttering children with low self-esteem, with correlation coefficients of r = 0.705, r = 0.428, and r = 0.389, respectively.

Table 3. Comparison of RCADS and RSES Scale Scores of CWS and CWNS

Variables	Children who stutter (CWS)	Children who do not stutter (CWNS)	p value
R-CADS Child			
Separation Anxiety Disorder	5.5±3.92	3.85±2.45	**0.002***
Generalized Anxiety Disorder	7.46±4.81	4.2±2.45	**0.002***
Panic Disorder	6.65 ±4.78	3.08±2.62	**0.007***
Social Anxiety Disorder	10.23 ± 7.18	4.91±3.68	**0.009***
Obsessive Compulsive Disorder	5.84±3.89	3.48±2.54	**0.006***
Major Depressive Disorder	7.57±5.74	4.42±2.93	**<0.001***
Total Anxiety score	35.73±20.6	19.71±9.84	**<0.001***
Total Depression and Anxiety Score	42.88±25.39	24.08±12.04	**0.001***
RSES			
Rosenberg Self-esteem Scale	2.2±1.36	1.08±0.7	**0.001***

*CWS: Children who stutter; CWNS: Children who do not stutter; R-CADS: Revised-Child Anxiety And Depression Scale; RSES: Rosenberg Self-esteem Scale; *p < 0.05 is statistically significant.*

Discussion

The study revealed that school-aged children diagnosed with stuttering experience peer bullying more frequently than their fluent-speaking peers. Additionally, children who stutter are subjected to peer bullying exhibit lower self-esteem and more pronounced symptoms of depression, generalized anxiety disorder, and social anxiety disorder.

Existing literature consistently indicates that CWS are at a heightened risk of peer bullying compared to their fluent-speaking peers (12). A study involving 276 adults with a history of stuttering reported that 83% had experienced peer bullying during their school years (24). Similarly, research on adolescents found that 44.4% of individuals who stutter had been bullied by peers, in contrast to only 9.2% of their fluent-speaking peers (9.2%) (25). A Turkish study by Kara and Karamete (2018) found an even higher prevalence, with 84% of adults who stutter recalling experiences of peer bullying during their school years, with verbal bullying being the most common form, significantly affecting their emotional, social, academic, and professional lives (26). Moreover, Kılıçaslan et al. (2022) reported that CWS were approximately three times more likely to experience peer bullying than their fluent-speaking peers, with a bullying prevalence of 52.5% in CWS compared to 27.8% in children with fluent speech (27). In the present study, 45.7% of the 35 school-aged children diagnosed with stuttering reported peer bullying, a rate consistent with previous findings (27); albeit slightly lower than that reported by Kara and Karamete (2018) (26). The discrepancy may result from methodological differences, recall bias, or variations in the measurement scales used. Importantly, our findings revealed that the severity of stuttering did not correlate with the likelihood of experiencing peer bullying. Verbal bullying, such as teasing and name-calling, as well as social or relational bullying, including exclusion from social settings and group rejection, are more commonly observed in children who stutter (14). Consistent with the existing literature, our study identified verbal bullying as the most prevalent type, followed by social bullying. Consequently, we recommend targeted monitoring and intervention programs to prevent peer bullying in CWS, irrespective of stuttering severity.

Recent research indicates that peer bullying can contribute to various emotional and behavioral problems in individuals with stuttering (11, 25). Davis et al. (2002) observed that children who stutter experience greater social exclusion in peer interactions (28). Additionally, children with stuttering are at increased risk for both peer bullying and anxiety disorders, suggesting a bidirectional relationship between heightened anxiety symptoms and experiences of bullying (29). Adolescents with stuttering have been found to exhibit lower self-esteem compared to fluent adolescents, potentially linked to their experiences of peer bullying (25, 30). Adolescents with stuttering have been found to exhibit lower self-esteem compared to fluent adolescents, potentially linked to their experiences of peer bullying (14). Consistent with these findings, the present study demonstrated that school-aged CWS subjected to peer bullying exhibited lower self-esteem and more pronounced symptoms of depressive disorder, generalized anxiety disorder, and social anxiety disorder. These results underscore the importance of implementing interventions aimed at fostering the positive attributes of children who stutter and providing opportunities for them to demonstrate these strengths in peer settings. Such initiatives may mitigate the risk of psychiatric symptoms by enhancing self-esteem and promoting social acceptance.

In addition to the impact of peer bullying, our study highlights the elevated levels of anxiety and depressive symptoms in school-aged CWS. Previous research has established a link between stuttering and emotional or behavioral difficulties in children, which may stem from shared genetic etiology, neurobiological vulnerabilities, decreased self-efficacy, increased social rejection, and internalized stigma (4, 31). Prior studies have reported that anxiety disorders are frequently comorbid with stuttering, while depressive disorders occur less commonly. Anxiety has been shown to exacerbate speech disfluencies by increasing pause duration, fostering negative communication attitudes, and reinforcing social avoidance behaviors (32, 33). A study examining school-aged CWS found significant differences in depressive symptoms and state anxiety, though not in trait anxiety (27). Consistent with these findings, the present study demonstrated that anxiety levels and depressive symptoms are more intense in school-age CWS compared to the CWNS. Additionally, an increase in social anxiety symptoms was observed with higher frequencies of stuttering (measured by the number of syllables stuttered in normal speech) in school-aged CWS ($r = 0.678$). Given these findings, it is evident that school-aged CWS are at an elevated risk for symptoms of anxiety and depressive disorders. Consequently, follow-up by child psychiatry and the provision of psychosocial support are critical in the treatment and management of school-age CWS.

Limitations

One of the limitations of our study is that the sample group consisted of children diagnosed with stuttering who were actively seeking treatment. This selection may have led to an increased frequency of psychopathology among the participants. Future research should involve community samples to obtain a more representative understanding of stuttering's impact on psychopathology. Another limitation is that comorbid conditions such as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and others, which may coexist with stuttering, were not evaluated. Studies with larger sample sizes, that include an assessment of these comorbid conditions are needed to provide a more comprehensive analysis. Additionally, the scales used in our study were based on self-reports from

the participants. Future studies would benefit from incorporating scales that rely on feedback from parents or teachers to provide a more rounded perspective. Despite these limitations, we believe our study contributes significantly to the literature on school-age children with stuttering and their experiences with peer bullying.

Conclusion

Our study found that school-age children diagnosed with stuttering exhibit more frequent symptoms of anxiety and depressive disorders and experience high rates of peer bullying compared to their fluent-speaking peers. Furthermore, stuttering children who were bullied showed lower self-esteem and more severe symptoms of depressive disorder, generalized anxiety disorder, and social anxiety disorder. Based on these findings, we recommend providing comprehensive psychosocial support for all school-age children with stuttering. Additionally, fostering their positive attributes, raising awareness about stuttering, and implementing school-based bullying prevention programs are essential. Such measures could significantly contribute to the well-being of children with stuttering.

Ethical Approval: *Before conducting the protocol, written informed consent was obtained from the parents and the study was approved by the Ethical Committee of the Health Sciences University Erzurum Regional Training and Research Hospital with approval number 2022/17-159.*

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Research Article / Araştırma Makalesi

Inflammatory and Clinical Predictors of In-Hospital Mortality in Acute Coronary Syndrome: A Retrospective Cohort Study

Akut Koroner Sendromda Hastane İçi Mortalitenin İnflamatuar ve Klinik Tahmin Edicileri: Retrospektif Bir Kohort Çalışması

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Abstract

Background: This study aims to retrospectively analyze in-hospital mortality rates in patients diagnosed with acute coronary syndrome (ACS) and to identify independent risk factors contributing to increased mortality.
Materials and Methods: This Retrospective Single-Center Cohort Study was conducted at the Cardiology Clinic of Aktif International Hospital between January 1, 2023, and December 30, 2024. A total of 694 ACS patients were included in the study. Demographic, clinical, laboratory, and imaging data were collected. Independent risk factors for in-hospital mortality were assessed using multivariate logistic regression analysis.
Results: The in-hospital mortality rate was 2.4%. Age (p = 0.02), the frequency of diabetes mellitus (p = 0.03) and hyperlipidemia (p = 0.04), creatinine (p = 0.002) and troponin-I (p < 0.001) were significantly higher, whereas left ventricular ejection fraction (LVEF) was significantly lower (p = 0.04) in non-survivors compared to the survivors. In addition, hematological parameters such as neutrophil-to-lymphocyte ratio (NLR) (p = 0.005) and platelet-to-lymphocyte ratio (PLR) (p = 0.01) were significantly elevated in non-survivors. Multivariate logistic regression analysis demonstrated that age (odds ration [OR] = 1.05, p = 0.003), presence of diabetes mellitus (OR=1.37, p = 0.002), hypertension (OR=1.42, p = 0.001) and hyperlipidemia (OR= 1.28, p = 0.03), increased troponin-I (OR = 2.34, p < 0.001), elevated creatinine levels (OR = 1.75, p = 0.002), lower LVEF (OR = 0.89, p = 0.04), NLR (OR = 1.56, p = 0.005) and PLR (OR = 1.42, p = 0.01) were independent predictors of in-hospital mortality.
Conclusions: Our study suggests that older age, the presence of hypertension, diabetes mellitus, hyperlipidemia, renal dysfunction, elevated inflammatory markers (NLR, PLR), and reduced LVEF are independent predictors of in-hospital mortality in ACS patients. Our findings further emphasize the critical role of early revascularization in reducing mortality rates in ACS patients.

Keywords: Acute coronary syndrome, In-hospital mortality, Risk factors, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio

Öz

Amaç: Bu çalışmanın amacı, akut koroner sendrom (AKS) tanısı alan hastalarda hastane içi mortalite oranlarını retrospektif olarak analiz etmek ve mortaliteyi artıran bağımsız risk faktörlerini belirlemektir.
Materyal ve Metod: 01 Ocak 2023 - 30 Aralık 2024 tarihleri arasında Aktif International Hospital Kardiyoloji Kliniği'nde yürütülen retrospektif kohort çalışmasına 694 AKS hastası dahil edilmiştir. Hastaların demografik, klinik, laboratuvar ve görüntüleme verileri retrospektif olarak analiz edilmiştir. Hastane içi mortaliteyi etkileyen bağımsız risk faktörleri çok değişkenli lojistik regresyon analizi ile değerlendirilmiştir.
Bulgular: Hastane içi mortalite oranı %2,4 olarak bulundu. Yaş (p = 0.02), diyabetes mellitus (p = 0.03) ile hiperlipidemi (p = 0.04) sıklığı, kreatinin (p = 0.002) ve troponin-I (p < 0.001) mortalite grubunda anlamlı olarak daha yüksek iken, sol ventrikül ejeksiyon fraksiyonu (LVEF) ise daha düşük (p = 0.04) olarak tespit edildi. Ek olarak, hematolojik parametreler arasında yer alan nötrofil-lenfosit oranı (NLR) (p = 0.005) ve trombosit-lenfosit oranı (PLR) da (p = 0.01) mortalite grubunda anlamlı derecede yüksek bulundu. Çok değişkenli lojistik regresyon analizinde, yaş (OR = 1.05, p = 0.003), diabetes mellitus (OR=1.37, p = 0.002), hipertansiyon (OR=1.42, p = 0.001) and hiperlipidemi varlığı (OR= 1.28, p = 0.03), artmış troponin-I (OR = 2.34, p < 0.001), yükselmiş kreatinin seviyeleri (OR = 1.75, p = 0.002), düşük LVEF (OR = 0.89, p = 0.04), NLR (OR = 1.56, p = 0.005) ve PLR (OR = 1.42, p = 0.01) hastane içi mortalitenin bağımsız prediktörleri olarak belirlendi.
Sonuç: Çalışmamız ileri yaşın, hipertansiyon, diabetes mellitus, hiperlipidemi, renal disfonksiyon, yükselmiş inflamatuar belirteçlerin (NLR, PLR) ve azalmış LVEF'nin ACS hastalarında hastane içi mortalitenin bağımsız öngörücüleri olduğunu ileri sürmektedir. Bulgularımız ayrıca ACS hastalarında mortalite oranlarını azaltmada erken revaskülarizasyonun kritik rolünü vurgulamaktadır.

Anahtar Kelimeler: Akut koroner sendrom, Hastane içi mortalite, Risk faktörleri, Nötrofil-lenfosit oranı, Trombosit-lenfosit oranı

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Introduction

Acute coronary syndromes (ACS) are among the leading causes of death due to cardiovascular diseases worldwide, characterized by high mortality and morbidity rates (1). ACS typically occurs as a result of atherosclerotic plaque rupture and thrombus formation, leading to sudden narrowing or occlusion of the coronary arteries. ACS has a highly variable clinical course, and without timely intervention, severe complications can occur. Due to the high in-hospital mortality rates associated with ACS, early diagnosis and effective treatment strategies are of paramount importance (2).

According to the 2018 data from the Turkish Statistical Institute, cardiovascular diseases rank first among all causes of death, with ischemic heart diseases comprising the majority of these fatalities (3). ACS is broadly categorized into three types that ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (4). STEMI is characterized by complete coronary artery occlusion, resulting in higher mortality rates; however, early reperfusion therapy can significantly reduce these rates. NSTEMI, on the other hand, is usually associated with subtotal occlusion and carries a similar long-term mortality risk as STEMI (5). Unstable angina is considered a high-risk condition for myocardial infarction and requires prompt diagnosis and treatment.

Several risk factors contribute to increased mortality in ACS patients, including advanced age, male sex, hypertension, diabetes mellitus, dyslipidemia, smoking, physical inactivity, and obesity (4, 6, 7). Additionally, chronic kidney disease, elevated inflammatory markers, platelet dysfunction, and hyperglycemia have been identified as factors negatively affecting ACS prognosis. In particular, women with a high body mass index and poor stress management are at increased risk for ACS (7). Recent studies have emphasized the impact of inflammation-related biomarkers on ACS mortality. Inflammatory indicators such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have been shown to be associated with in-hospital mortality (4, 8).

In our study, we aimed to retrospectively analyze the in-hospital mortality rates in patients diagnosed with acute coronary syndrome and to identify the risk factors associated with increased mortality. By evaluating demographic characteristics, clinical findings, laboratory results, and treatment protocols, we aimed to provide a comprehensive perspective on the predictors of mortality in AKS patients. Understanding these factors may contribute to improving patient outcomes and developing more effective management strategies.

Materials and Methods

Study Design and Population

The study was approved by the Ethics Committee of Gaziantep City Hospital (2024/65, 15/05/2024). This study adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from each patient prior to their inclusion in the study. This study was designed as a retrospective cohort study, conducted at the Cardiology Clinic of Aktif International Hospital between January 1, 2023, and December 30, 2024. The study population consisted of patients diagnosed with acute coronary syndrome (ACS) within the specified period, with data collected retrospectively from electronic medical records. A total of 694 patients who met the inclusion criteria were included in the study.

The inclusion criteria encompassed patients diagnosed with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). Additionally, eligible patients were required to have complete medical records and have been admitted to the hospital during the study period. Patients were excluded if they had incomplete or missing clinical and laboratory data, were transferred from another hospital with an initial diagnosis made externally, or had a history of chronic inflammatory disease or active malignancy or were lost to follow-up before mortality assessment.

Data Collection

Data on demographic, clinical, laboratory, and treatment parameters were retrospectively extracted from hospital records. Demographic variables included age, sex, smoking status, and comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia. Clinical parameters included presenting symptoms (e.g., chest pain, dyspnea) and physical examination findings.

Laboratory findings included cardiac biomarkers such as troponin-I/T, renal function markers such as serum creatinine, and lipid profile parameters including LDL cholesterol, total cholesterol, and triglycerides. Hematological parameters such as hemoglobin levels, white blood cell count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were also analyzed.

Imaging data included electrocardiographic (ECG) confirmation of STEMI or NSTEMI and echocardiographic assessment of left ventricular ejection fraction (LVEF) and regional wall motion abnormalities. Treatment protocols included revascularization procedures such as primary percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), as well as medical therapy consisting of dual antiplatelet therapy (DAPT), heparin, beta-blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs), statins, and other adjunctive medications.

In-hospital mortality was defined as death occurring during hospitalization, with causes classified as cardiac or non-cardiac. Mortality was further categorized as early mortality (within the first 24 hours) or late in-hospital mortality.

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics (version 27, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables,

and frequencies (n) and percentages (%) for categorical variables. Comparisons between groups were performed using Student's t-test or Mann-Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. To identify independent risk factors associated with in-hospital mortality, multivariate logistic regression analysis was performed. The independent variables included age, sex, smoking status, diabetes mellitus, hypertension, hyperlipidemia, LVEF, troponin levels, creatinine levels, and inflammatory markers (NLR, PLR). The results of the logistic regression analysis were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant in all analyses.

Results

Comparison of demographic and clinical characteristics was shown in table 1. The mean age in the mortality group was significantly higher than in the survivor group (p = 0.02). Also, the frequency of diabetes (35.6% vs. 29.7%, p = 0.03) and hyperlipidemia (50.2% vs. 44.3%, p = 0.04) were significantly higher in deceased patients. Regarding gender distribution, male patients comprised the majority of the total cohort (72.3%), but the difference between the mortality and survivor groups was not statistically significant (p = 0.15). On the other hand, patients who experienced mortality had a significantly lower LVEF compared to survivors (49.3 ± 9.8% vs. 53.2 ± 10.1%, p = 0.01) (Table 1).

Table 1. Comparison of demographic and clinical characteristics

Variables	All Patients (n=694)	Mortality (+) (n=17)	Mortality (-) (n=677)	p-value
Age (mean ± SD)	65.4 ± 10.2	68.1 ± 9.5	64.7 ± 10.5	0.02
Gender (Male, %)	72.3	74.2	71.8	0.15
Smoking (%)	40.6	38.5	41.2	0.34
Hypertension (%)	65.2	70.1	64.5	0.05
Diabetes Mellitus (%)	30.8	35.6	29.7	0.03
Hyperlipidemia (%)	45.1	50.2	44.3	0.04
Body Mass Index (mean ± SD)	27.3 ± 4.2	28.1 ± 4.8	27.1 ± 4.1	0.08
Systolic Blood Pressure (mmHg, mean ± SD)	135.2 ± 18.7	138.5 ± 19.2	134.5 ± 18.4	0.11
Diastolic Blood Pressure (mmHg, mean ± SD)	78.4 ± 11.5	80.2 ± 10.9	77.9 ± 11.8	0.09
Left Ventricular Ejection Fraction (%, mean ± SD)	52.6 ± 10.4	49.3 ± 9.8	53.2 ± 10.1	0.01

Comparison of laboratory findings was shown in table 2. Patients in the mortality group had significantly higher white blood cell (WBC) counts (p = 0.001), neutrophil counts (p = 0.002), platelet counts (p = 0.04), troponin-I levels (p = 0.001) and creatinine levels (p = 0.02) compared to patients in the mortality (-) group. Also, neutrophil-to-lymphocyte ratio (NLR) (4.8 ± 1.5 vs. 3.3 ± 1.1, p = 0.01) and platelet-to-lymphocyte ratio (PLR) (135.8 ± 40.2 vs. 114.3 ± 34.7, p = 0.02) was significantly higher in the mortality group. However, no significant difference was observed between two groups in terms of glucose levels (p = 0.08) and LDL cholesterol (p = 0.09) (Table 2).

Independent risk factors affecting in-hospital mortality were shown in table 3. Advanced age was identified as an independent predictor of in-hospital mortality, with an odds ratio (OR) of 1.05 (95% CI: 1.020 - 1.080, p = 0.003), indicating that each one-year increase in age is associated with a 5% increase in mortality risk. Additionally, diabetes mellitus (OR = 1.37, p = 0.002), hypertension (OR = 1.42, p = 0.001), and hyperlipidemia (OR = 1.28, p = 0.03) were significantly associated with increased in-hospital mortality. A lower left ventricular ejection fraction (LVEF) was associated with higher mortality risk (OR = 0.89, p = 0.04). Furthermore, elevated creatinine levels (OR = 1.75, p = 0.002) were significantly correlated with increased mortality. Patients with higher troponin-I levels had a 2.34-fold increased risk of mortality (p < 0.001). Additionally, elevated inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR, OR = 1.56, p = 0.005) and platelet-to-lymphocyte ratio (PLR, OR = 1.42, p = 0.01), were significantly associated with mortality (Table 3.).

Table 2. Comparison of Laboratory Findings

Variables	All Patients (n=694)	Mortality (+) (n=17)	Mortality (-) (n=677)	p-value
White Blood Cell Count (10^9/L)	8.2 ± 2.1	10.1 ± 2.4	8.1 ± 2.0	0.001
Neutrophil Count (10^9/L)	5.6 ± 1.8	7.2 ± 2.0	5.5 ± 1.7	0.002
Lymphocyte Count (10^9/L)	2.3 ± 0.7	1.9 ± 0.6	2.4 ± 0.7	0.03
Neutrophil-to-Lymphocyte Ratio	3.4 ± 1.2	4.8 ± 1.5	3.3 ± 1.1	0.01
Platelet Count (10^9/L)	245.3 ± 58.7	210.5 ± 50.3	248.2 ± 57.5	0.04
Platelet-to-Lymphocyte Ratio	115.6 ± 35.4	135.8 ± 40.2	114.3 ± 34.7	0.02
Hemoglobin (g/dL)	13.5 ± 1.8	12.1 ± 2.0	13.6 ± 1.7	0.05
Glucose (mg/dL)	128.7 ± 45.3	140.5 ± 50.7	127.9 ± 44.8	0.08
LDL Cholesterol (mg/dL)	110.2 ± 34.5	98.4 ± 32.8	111.0 ± 34.6	0.09
Troponin-I (ng/mL)	1.87 ± 2.43	3.12 ± 2.87	1.82 ± 2.38	0.001
Creatinine (mg/dL)	1.02 ± 0.34	1.45 ± 0.40	1.01 ± 0.33	0.02

Table 3. Independent risk factors affecting in-hospital mortality

Independent Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age	1.05	(1.020 - 1.080)	0.003
Gender (Male)	1.23	(0.980 - 1.540)	0.07
Smoking	1.15	(0.890 - 1.470)	0.15
Diabetes Mellitus	1.37	(1.100 - 1.710)	0.002
Hypertension	1.42	(1.120 - 1.810)	0.001
Hyperlipidemia	1.28	(1.020 - 1.600)	0.03
Left Ventricular Ejection Fraction (LVEF)	0.89	(0.780 - 0.990)	0.04
Troponin-I	2.34	(1.750 - 3.120)	<0.001
Creatinine	1.75	(1.280 - 2.410)	0.002
Neutrophil-to-Lymphocyte Ratio (NLR)	1.56	(1.210 - 2.020)	0.005
Platelet-to-Lymphocyte Ratio (PLR)	1.42	(1.100 - 1.830)	0.01

Discussion

In our study, the in-hospital mortality rate among acute coronary syndrome (ACS) patients was 2.4%, which is within the lower range of previously reported mortality rates, varying between 2.4% and 17.7% in different studies (9, 10). This variation is influenced by several factors, including the patient population, comorbidities, and treatment strategies. For instance, in the GRACE registry, hospital mortality was reported as 7.5%, with higher rates observed in older patients and those presenting with hemodynamic instability (11). In contrast, a study by Chang et al. demonstrated an overall in-hospital mortality rate of 5.6%, emphasizing the impact of timely revascularization and evidence-based medical therapy in reducing mortality (12). The relatively lower mortality rate in our study may be attributed to improvements in early diagnosis, high rates of primary percutaneous coronary intervention (PCI), and optimized medical therapy, including dual antiplatelet therapy, statins, and aggressive secondary prevention measures (13).

Our study confirms the significant impact of aging and comorbid conditions on mortality risk in acute coronary syndrome (ACS) patients. Specifically, we found that patients with hypertension, diabetes mellitus, and hyperlipidemia had a higher risk of in-hospital mortality. These findings align with those of Fox et al., who reported that 73.8% of ACS patients had hypertension, 48.4% had diabetes, and 36.1% had hyperlipidemia, all contributing to worse clinical outcomes (9). Damluji et al. found that metabolic comorbidities significantly increased the risk of major adverse cardiovascular events (MACE) and mortality in ACS patients, emphasizing the need for aggressive risk factor management (14).

Furthermore, elevated inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been increasingly recognized as independent predictors of mortality in ACS. Our results align with these observations, as both NLR and PLR were significantly elevated in patients who succumbed during hospitalization (15). In a large-scale study, Gibson et al. demonstrated that elevated NLR was associated with a 1.6-fold increased risk of in-hospital mortality in ACS patients, further supporting the role of systemic inflammation in adverse cardiovascular outcomes (16). Another study by Rajakumar et al. confirmed that PLR was significantly higher in ACS patients with high thrombotic burden, reinforcing its value as a prognostic marker (17).

The role of early revascularization, particularly percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), in improving survival outcomes in ACS patients is well established. Our findings support previous research indicating that timely intervention limits infarct size, reduces left ventricular dysfunction, and improves overall prognosis. A meta-analysis by Kite et al. demonstrated that early invasive therapy was associated with a significant reduction in MACE and in-hospital mortality, particularly in high-risk ACS patients (18). O'Gara et al. reported that ACS patients undergoing PCI within 48 hours had significantly lower mortality rates than those receiving delayed or medical-only therapy (19).

Given our study's emphasis on early revascularization, our lower observed mortality rates likely reflect the benefits of prompt intervention and adherence to contemporary guideline-directed therapy. These findings underscore the importance of rapid assessment, aggressive risk stratification, and timely therapeutic interventions in ACS patients to improve survival outcomes.

Although hyperglycemia was not statistically significant in our study, its potential impact on cardiovascular outcomes should not be overlooked. Hyperglycemia is known to contribute to endothelial dysfunction, increased oxidative stress, and pro-inflammatory states, which may exacerbate myocardial injury and worsen prognosis in ACS patients. Previous studies have demonstrated that acute hyperglycemia is associated with increased in-hospital mortality and adverse outcomes, particularly in non-diabetic ACS patients (20, 21). Further studies with larger cohorts are needed to clarify the role of hyperglycemia in ACS prognosis.

Our study has limitations. As a single-center study, its generalizability may be limited due to variations in healthcare resources and patient management across different settings. The retrospective design carries the risk of selection bias and missing data, and unmeasured confounders like socioeconomic status and medication adherence may have influenced outcomes. Additionally, we focused on short-term in-hospital mortality without assessing long-term cardiovascular events. One of the main limitations of our study is the

inclusion of a heterogeneous ACS population comprising STEMI, NSTEMI, and UAP patients. Given that mortality rates and predictors vary across these subtypes, our results may not fully reflect the prognostic factors specific to each subgroup. While our analysis aimed to provide a comprehensive overview of in-hospital mortality in ACS patients, future studies focusing on more homogeneous cohorts, such as only STEMI or non-ST-elevation ACS, may offer more precise insights into subgroup-specific risk factors. However, our study has notable strengths. It includes a large, well-defined ACS cohort and utilizes a comprehensive dataset incorporating demographic, clinical, laboratory, and imaging parameters for detailed risk stratification. Importantly, it is among the few studies emphasizing inflammatory markers such as NLR and PLR, which are increasingly recognized as significant predictors of cardiovascular outcomes.

In conclusion, our study suggests that older age, the presence of hypertension, diabetes mellitus, hyperlipidemia, renal dysfunction, elevated inflammatory markers (NLR, PLR), and reduced LVEF are independent predictors of in-hospital mortality in ACS patients. Our findings further emphasize the critical role of early revascularization in reducing mortality rates in ACS patients. While our study provides valuable insights into ACS prognosis, further multicenter, prospective studies are needed to validate these findings and explore long-term outcomes in ACS patients. Optimizing early diagnosis, risk stratification, and personalized treatment strategies remain critical for improving survival in this high-risk population.

Ethical Approval: The study was approved by the Ethics Committee of Gaziantep City Hospital (2024/65, 15/05/2024).

Author Contributions:
Concept: M.B.
Literature Review: M.B., E.S., R.D.
Design : M.B., E.S., R.D.
Data acquisition: M.B., R.D.
Analysis and interpretation: E.S., R.D.
Writing manuscript: M.B., R.D.
Critical revision of manuscript: E.S., R.D.
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Research Article / Araştırma Makalesi

Platelet and Erythrocyte Indices and Their Impact on Prognosis in Late Neonatal Sepsis

Geç Neonatal Sepsiste, Trombosit ve Eritrosit İndeksleri ve Prognoza Etkisi

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Abstract

Background: One of the most significant causes of mortality and morbidity in newborns is neonatal sepsis. Despite all the advancements in its diagnosis and treatment, it remains a major public health issue. This study aims to evaluate the hemogram parameters of newborns admitted to the neonatal intensive care unit (NICU) with a diagnosis of late-onset neonatal sepsis, both at the start of treatment and on the 7th day.
Materials and Methods: This study was conducted in a cross-sectional manner with 89 newborns who received care and treatment for late-onset neonatal sepsis in the neonatal intensive care unit (NICU) of a university hospital between January 2017 and February 2020. Newborns between the postnatal 72nd hour and 30th day with positive blood or urine cultures were included in the study. The data of the study were obtained retrospectively in the digital environment by screening hemogram parameters, CRP levels, interventional procedure status, body fluid from which the culture was taken, culture result, initial treatment, follow-up and change in treatments, reason for hospitalization and mortality on the 1st and 7th days of sepsis.
Results: It was determined that 58.4% of the newborns were male and 50.6% were term newborns. RBC and MCH levels on the 7th day of sepsis, MCV levels on the 1st day of sepsis, HGB, HCT and PLT levels on the 1st and 7th days of sepsis were found to be statistically significantly lower in newborns who lost their lives compared to living newborns. In addition, MPV levels on the 1st day of sepsis and CRP levels on the 1st and 7th days of sepsis of newborns who died were found to be statistically significantly higher than those of living newborns.
Conclusions: As can be understood from the results, it has been proven that low RBC and MCH levels on the 7th day of sepsis, MCV levels on the 1st day of sepsis, HGB, HCT and PLT levels on the 1st day and 7th day of sepsis, and high CRP levels on the 1st day and 7th day of sepsis and MPV levels on the 1st day of sepsis should be considered as poor prognostic factors and are associated with mortality in the follow-up of newborns diagnosed with late-onset sepsis.

Keywords: Late-onset Neonatal Sepsis, Prognosis, Platelet, Erythrocyte

Öz

Amaç: Yenidoğanların mortalite ve morbiditesinin en önemli nedenlerin biri yenidoğan sepsisidir. Tanı ve tedavisindeki tüm gelişmelere rağmen önemli bir halk sağlığı sorunu olarak karşımıza çıkmaktadır. Bu araştırmada, geç başlangıçlı sepsis tanısı ile yenidoğan yoğun bakım ünitesine (YYBÜ) yatışı yapılan yenidoğanların tedavinin başlangıcı ve 7.gündeki hemogram parametrelerinin değerlendirilmesi amaçlanmaktadır.
Materyal ve Metod: Bu araştırma Ocak 2017-Şubat 2020 tarihleri arasında bir üniversite hastanesinin YYBÜ'sinde geç başlangıçlı yenidoğan sepsisi tanısıyla bakım ve tedavi almış yenidoğanlarla kesitsel tipte yürütülmüştür. Postnatal 72. saat ile 30. günler arasında olan ve kan veya idrar kültüründe üremesi olan yenidoğanlar araştırmaya dahil edildi. Araştırmanın verileri dijital ortamda retrospektif olarak sepsisin 1. ve 7. günlerinde alınan hemogram parametreleri, CRP düzeyleri, girişimsel işlem durumu, kültürün alındığı vücut sıvısı, kültür sonucu, başlangıçta uygulanan tedavi, takip ve tedavilerde yapılan değişim, yatış nedeni ve mortalite gibi durumların taranması sonucunda elde edilmiştir.
Bulgular: Yenidoğanların %58.4'ünün erkek ve %50.6'sının term bebek olduğu belirlenmiştir. Yaşamını kaybeden yenidoğanların sepsisin 7. gününde RBC ve MCH düzeyleri, sepsisin 1. gününde MCV düzeyleri ile 1. ve 7. günlerinde HGB, HCT ve PLT düzeyleri yaşayan yenidoğanlara göre istatistiksel olarak anlamlı düzeyde daha düşük saptanmıştır. Ayrıca, yaşamını kaybeden yenidoğanların sepisinin 1. gününde MPV düzeyleri ile 1. ve 7. günlerinde CRP düzeyleri yaşayan yenidoğanlara göre istatistiksel olarak anlamlı seviyede daha yüksek olarak tespit edilmiştir.
Sonuç: Sonuçlardan anlaşılacağı üzere geç başlangıçlı sepsis tanılı yenidoğanların takibinde sepisinin 7. günü RBC ve MCH düzeyleri, sepsisin 1. günü MCV düzeyleri ile sepsisin 1. günü ve 7. günü HGB, HCT ve PLT düzeylerinin düşüklüğünün ve sepsinin 1. günü ve 7. günü CRP düzeyleri ile sepsisin 1. gününde MPV düzeylerinin yüksekliğinin kötü prognostik faktör olarak değerlendirilmesi gerektiği ve mortalite ile ilişkili olduğu kanıtlanmıştır.

Anahtar Kelimeler: Geç başlangıçlı yenidoğan sepsisi; Prognoz; Trombosit; Eritrosit

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Introduction

According to the World Health Organization (WHO), nearly half of child deaths under the age of five occur during the neonatal period, making it the most vulnerable phase of life (1). Sepsis accounts for 36% of childhood deaths, with this rate being higher in low-income countries. Invasive sepsis leads to the deaths of over 1.4 million newborns annually. A significant majority of sepsis-related deaths are caused by delays in the selection of appropriate antibiotics during diagnosis and treatment. Despite the initiation of appropriate and timely antimicrobial therapy, 39% of neonatal sepsis cases result in mortality or major morbidity (2,3). Neonatal sepsis is a clinical syndrome characterized by the presence of a specific pathogen in blood cultures, showing signs of infection affecting all systems, and is defined by bacteremia (4). Despite all advancements in diagnosis and treatment, it remains a significant global public health issue and is among the primary factors causing neonatal mortality and morbidity (5).

Neonatal sepsis is categorized into three based on the time of onset: early, very late and late onset. Early-onset neonatal sepsis (EONS) occurs primarily through transplacental transmission and, more frequently, maternal-genital tract sources, while late-onset neonatal sepsis (LONS) arises from postnatal nosocomial or community-acquired factors (6-8). The incidence of EONS ranges from 0.57 to 10.96 per 1,000 live births, whereas the incidence of LONS varies between 1.6% and 51.2% (9,10). The main risk factors leading to the development of LONS include prematurity, low birth weight (LBW), admission to the intensive care unit, reliance on mechanical ventilation, frequent invasive procedures, skin infections, feeding aspiration, bottle feeding, poor umbilical care, and poor hygiene (11). There are limited studies showing the prognostic process of hematological changes (hemoglobin, hematocrit and leukocytes etc.) in LONS (12). This study was conducted to retrospectively investigate the relationship between platelet and erythrocyte indices of newborns diagnosed with LONS and treated in the neonatal intensive care unit (NICU) of a university hospital and their prognosis and mortality.

Materials and Methods

Type, Place and Time of The Research

This research is a cross-sectional study conducted on newborns diagnosed with late-onset neonatal sepsis (LONS) who were followed up and treated in the neonatal intensive care unit (NICU) of a university hospital between January 2017 and February 2020.

Population and Sample of The Study

The population of the study consists of 2,180 newborns followed up and treated in the NICU of a university hospital between January 2017 and February 2020, while the sample includes 89 newborns with positive cultures and diagnosed with LONS.

Inclusion and Exclusion Criteria

Newborn patient files were scanned digitally, and those who had positive blood or urine cultures between the 72nd hour and the 30th day postnatally were included in the study. Newborns with intraventricular hemorrhage, those who received erythrocyte or intrauterine transfusions, congenital anomalies, family history of thalassemia, and necrotizing enterocolitis were excluded from the research.

Research Protocol

The study examined the newborns' gender, gestational age, postnatal age, birth weight, mode of delivery, APGAR scores (at 1 and 5 minutes), feeding methods, , body fluids from which cultures were obtained, initial, mortality status, and the file records. When sepsis was suspected, blood samples taken were evaluated as "initial sample," and blood samples taken on the 7th day after the start of treatment were considered as "final sample."

This is our protocol for approaching newborns with suspected sepsis in the NICU.

Newborns with at least two clinical and laboratory findings had blood and urine cultures taken for suspected sepsis, and empirical antibiotics were started. Laboratory evaluations included CRP (>1.5 mg/dl), procalcitonin (≥2 ng/ml), platelet count (<100,000/mm³), immature/total NEU ratio (≥0.20), WBC count (>20,000/mm³ or <4,000/mm³), hypoglycemia (<45 mg/dl), hyperglycemia (>180 mg/dl), and metabolic acidosis (base deficit >10 mEq/L or serum lactate >2 mmol/L) (13). Clinically, evaluations were made based on respiratory abnormalities (increased ventilation or oxygen requirement, tachypnea, apnea), cardiovascular system findings (impaired peripheral perfusion, hypotension, tachycardia, bradycardia, urine output <1 ml/kg/h), gastrointestinal system findings (abdominal distension, decreased sucking, feeding intolerance), and body temperature (<36°C or>38.5°C or temperature irregularities).

Ethical Approval

Before the start of the research, ethical approval was obtained from the clinical research ethics committee of a university with decision number 19/09/15 dated 22.10.2019, along with institutional permission from the hospital where the research was conducted. Verbal consent was obtained from the parents of the newborns. The study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

The NCSS 2007 software was used for statistical analyses. Descriptive statistical values such as mean, standard deviation, median, frequency, proportion, minimum, and maximum were provided during the evaluation of research data. The normality of quantitative data was assessed using the Kolmogorov-Smirnov test, the Shapiro-Wilk test, and graphical evaluations. For comparing two groups of quantitative

data showing a normal distribution, the Student t-test was used, while the Mann-Whitney U test was applied for two groups of non-normally distributed data. The Wilcoxon Signed Ranks test was used for within-group comparisons of parameters that did not show a normal distribution. Pearson Chi-Square test and Fisher's Exact test were used for comparing qualitative data. A significance level of $p < 0.05$ was considered statistically significant.

Results

It was found that 58.4% of the newborns were male, and 50.6% were term newborns. Additionally, 67.4% were delivered by cesarean section. The average age of the newborns was found to be 6.71 ± 3.11 days. The birth weights of the newborns ranged from 1050 to 4100 grams, with an average birth weight of 2765.79 ± 666.88 grams. Among them, 58.4% had normal weight, 34.9% had low birth weight, and 6.7% had very low birth weight (Table 1).

Table 1. Descriptive Characteristics of Neonatal

Variables		n	(%)
Age (day)	Min-Max (Median)	3-20 (6)	
	Mean±Sd	6.71±3.11	
1st minute APGAR	Min-Max (Median)	4-8 (7)	
	Mean±Sd	6.93±1.04	
5st minute APGAR	Min-Max (Median)	5-10 (9)	
	Mean±Sd	8.62±1.28	
Birth weight (grams)	Min-Max (Median)	1050-4100 (2800)	
	Mean±Sd	2765.79±666.88	
	Very low	6	(6.7)
	Low	31	(34.9)
	Normal	52	(58.4)
Gender	Male	52	(58.4)
	Female	37	(41.6)
Preterm/term	Preterm	44	(49.4)
	Term	45	(50.6)
Type of birth	Vaginal	29	(32.6)
	Caesarean	60	(67.4)
Nutritional Type	Enteral	39	(43.8)
	Parenteral (longer than 7 days)	50	(56.2)
Mortality Rate	Yes	9	(10.1)
	No	80	(89.9)

Sd: Standard deviation, Min: Minimum, Max: Maximum.

Table 2 illustrates the relationship between the hemogram parameters of the newborns and mortality. It was found that the mortality rate was statistically significantly higher in newborns with low birth weight (LBW), those who were preterm, those delivered by cesarean section, and those with lower APGAR scores at 1 minute and 5 minutes, as well as in those who received parenteral nutrition. The final RBC (red blood cell) measurement values, initial MCV (mean corpuscular volume) measurement values, final MCH (mean corpuscular hemoglobin) measurement values, initial and final HGB (hemoglobin) measurement values, initial and final HCT (hematocrit) measurement values, and initial and final PLT (platelet) measurement values of the deceased newborns were found to be lower, and the differences were statistically significant. Additionally, the initial MPV (mean platelet volume) measurement values and initial and final CRP (C-reactive protein) measurement values of the deceased newborns were found to be higher, with the differences also being statistically significant (Table 2).

Table 2. The Relationship Between Hemogram Parameters of Neonatal and Mortality

			Mortality		[a]p
			No (n=80)	Yes (n=9)	
RBC (10^3/mm^3)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	2.1/ 8.8 (4.6)	3/ 7.6 (4)	0.066
		Mean±Sd	4.64±0.88	4.31±1.37	
	Final measurement (day 7 of sepsis)	Min/Max (Median)	2/ 6.2 (4.2)	2.2/ 3.8 (3.2)	0.001**
		Mean±Sd	4.12±0.81	3.12±0.57	
		[c]p	0.001**	0.021*	
	Initial-Final measurement difference	Min /Max (Median)	-4.3/ 1.3 (-0.4)	-3.8/ 0.1 (-1)	0.047*
		Mean±Sd	-0.52±0.85	-1.19±1.15	
MCV (fL)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	73.3/ 706 (100)	85.6/ 100 (96)	0.018*
		Mean±Sd	107.12±68.28	93.66±5.62	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	75.1/ 113 (94.6)	82/ 114 (89)	0.075
		Mean±Sd	94.99±7.19	91.62±9.42	
		[c]p	0.001**	0.139	
	Initial-Final measurement difference	Min /Max (Median)	-598/ 6 (-5)	-8/ 15 (-4.3)	0.314
		Mean±Sd	-12.14±66.46	-2.03±6.88	
MCH (pg)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	24.5/ 40.4 (33.6)	28/ 35.7 (31.9)	0.055
		Mean±Sd	33.69±2.71	32.03±2.34	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	18.4/ 97.6 (32.4)	26.2/ 33.7 (30.4)	0.004**
		Mean±Sd	33.57±7.93	30.26±2.24	
		[c]p	0.001**	0.017*	
	Initial-Final measurement difference	Min /Max (Median)	-13.4/ 64.9 (-1)	-3.4/ 0.1 (-2)	0.080
		Mean±Sd	-0.12±7.77	-1.77±1.22	
MCHC (g/dl)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	30.3/ 40.6 (34)	31.8/ 37.1 (33.7)	0.881
		Mean±Sd	33.9±1.7	33.88±1.77	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	28.8/ 42.9 (33.8)	31.2/ 38.1 (33.6)	0.791
		Mean±Sd	34.17±2.29	34.03±2.17	
		[c]p	0.431	0.779	
	Initial-Final measurement difference	Min /Max (Median)	-5/ 7.8 (0.2)	-2.2/ 2.1 (0.3)	0.995
		Mean±Sd	0.28±2.34	0.16±1.50	
HCT (%)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	17.8/ 60.4 (45.2)	27.2/ 50.6 (35.3)	0.005**
		Mean±Sd	45.48±8.52	37.29±6.85	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	21.5/ 59.9 (38.5)	20/ 41.1 (28)	0.001**
		Mean±Sd	39.13±7.55	28.94±7.03	
		[c]p	0.001**	0.021*	
	Initial-Final measurement difference	Min /Max (Median)	-26.3/ 11.1 (-6.4)	-17.3/ 6.2 (-7.3)	0.324
		Mean±Sd	-6.34±7.15	-8.34±7.73	
HGB (g/dl)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	1/ 19.9 (15.6)	10.1/ 16.2 (12.6)	0.002**
		Mean±Sd	15.23±3.02	12.59±1.99	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	8.2/ 19.5 (13.9)	6.5/ 13.9 (9.3)	0.001**
		Mean±Sd	13.64±2.43	9.59±2.26	
		[c]p	0.001**	0.015*	
	Initial-Final measurement difference	Min /Max (Median)	-7.7/ 8.3 (-1.8)	-5.7/ 1.3 (-3.7)	0.058
		Mean±Sd	-1.59±2.40	-2.99±2.30	
RDW (%)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	11/ 24 (14.5)	13.6/ 17.3 (14.8)	0.334
		Mean±Sd	14.92±2.03	15.20±1.09	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	1.9/ 19.2 (13.9)	12.6/ 16.6 (14.1)	0.500
		Mean±Sd	13.92±2.12	14.36±1.43	
		[c]p	0.001**	0.066	
	Initial-Final measurement difference	Min /Max (Median)	-11.7/ 6 (-0.7)	-3/ 0.6 (-0.9)	0.989
		Mean±Sd	-1.00±2.48	-0.84±1.19	

*Sd: Standart deviation, Min: Minimum, Max: Maximum, [a]Mann Whitney U Test, [c]Wilcoxon Signed Ranks Test *p<0.05**p<0.01.*

Table 2. The Relationship Between Hemogram Parameters of Newborns and Mortality (Continued)

			Mortality		[a]p
			No (n=80)	Yes (n=9)	
PLT (10^3/mm^3)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	13.3/ 979 (239.5)	6/ 322 (96)	0.003**
		Mean±Sd	269.37±164.74	117.78±122.09	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	103/ 763 (362)	6/ 255 (50)	0.001**
		Mean±Sd	375.25±131.11	71.89±78.59	
		[c]p	0.001**	0.069	
	Initial-Final measurement difference	Min /Max (Median)	-301/ 478 (86.5)	-201/ 22 (-23)	0.001**
		Mean±Sd	105.88±136.08	-45.89±73.94	
PCT (%)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	0/ 0.5 (0.2)	0/ 0.3 (0.1)	0.055
		Mean±Sd	0.21±0.10	0.13±0.11	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	0/ 0.6 (0.3)	0/ 0.2 (0.1)	0.001**
		Mean±Sd	0.28±0.10	0.10±0.08	
		[c]p	0.001**	0.401	
	Initial-Final measurement difference	Min /Max (Median)	-0.2/ 0.3 (0.1)	-0.2/ 0.2 (0)	0.023*
		Mean±Sd	0.06±0.12	-0.02±0.11	
PDW (fL)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	12.3/ 24.2 (16.2)	9.1/ 22.1 (15.6)	0.833
		Mean±Sd	16.76±3.38	15.80±3.54	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	10.2/ 24.1 (16.1)	13.2/ 24.3 (15.7)	0.395
		Mean±Sd	16.63±3.57	17.61±3.76	
		[c]p	0.903	0.441	
	Initial-Final measurement difference	Min /Max (Median)	-10.4/ 9.6 (0)	-3.1/ 15.2 (0.2)	0.514
		Mean±Sd	-0.13±3.41	1.81±5.40	
CRP (mg/dl)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	0/ 30.4 (2.1)	0/ 17.1 (7.9)	0.013*
		Mean±Sd	3.01±4.01	7.35±5.47	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	0/ 13.2 (0)	9.1/ 22.3 (12.5)	0.001**
		Mean±Sd	0.24±1.50	13.96±4.74	
		[c]p	0.001**	0.008**	
	Initial-Final measurement difference	Min /Max (Median)	-17.2/ 0 (-2.1)	3/ 9.9 (7.2)	0.001**
		Mean±Sd	-2.77±2.96	6.61±2.84	
MPV (fL)	Initial measurement (day 1 of sepsis)	Min /Max (Median)	1.1/ 12 (7)	6.5/ 15.9 (7.6)	0.020*
		Mean±Sd	7.03±1.42	9.66±3.47	
	Final measurement (day 7 of sepsis)	Min /Max (Median)	4.6/ 10.2 (7.5)	6.9/ 16.3 (8.1)	0.081
		Mean±Sd	7.43±1.13	9.46±3.43	
		[c]p	0.001**	0.678	
	Initial-Final measurement difference	Min /Max (Median)	-3.8/ 5.8 (0.3)	-6.6/ 9.2 (-0.3)	0.301
		Mean±Sd	0.40±1.35	-0.20±4.51	
WBC (10^3/mm^3)	Initial measurement (day 1 of sepsis)	Min/Max (Median)	3.3/ 90 (14.3)	6.2/57.2 (14.8)	0.629
		Mean±Sd	17.28±12.61	22.68±17.31	
	Final measurement (day 7 of sepsis)	Min/Max (Median)	5.7/23.3 (11.2)	3.4/25.8 (7.1)	0.189
		Mean±Sd	11.38±3.34	11.00±8.06	
		[c]p	0.001**	0.110	
	Initial-Final measurement difference	Min/Max (Median)	-66.7/15.4(-4.3)	-37/17.1 (-0.6)	0.187
		Mean±Sd	-5.90±11.79	-11.68±17.37	
NEU (10^3/mm^3)	Initial measurement (day 1 of sepsis)	Min/Max (Median)	1.2/ 53 (6.2)	0.5/36.6 (8.3)	0.844
		Mean±Sd	8.26±7.77	12.86±13.71	
	Final measurement (day 7 of sepsis)	Min/Max (Median)	1.3/ 11.6 (3.2)	0.5/ 12.2 (1.5)	0.105
		Mean±Sd	3.91±2.13	4.41±4.85	
		[c]p	0.001**	0.086	
	Initial-Final measurement difference	Min/Max (Median)	-50.6/ 8.2 (-2.9)	-30.3/10 (-7.4)	0.355
		Mean±Sd	-4.35±8.22	-8.46±13.13	
MON (10^3/mm^3)	Initial measurement (day 1 of sepsis)	Min/Max (Median)	0.3/ 4.4 (1.3)	0.7/ 5.3 (2.1)	0.554
		Mean±Sd	1.53±0.72	2.15±1.51	
	Final measurement (day 7 of sepsis)	Min/Max (Median)	0.5/ 3.4 (1.2)	0.2/ 6 (1.1)	0.491
		Mean±Sd	1.31±0.48	1.90±2.00	
		[c]p	0.009**	0.260	
	Initial-Final measurement difference	Min/Max (Median)	-3.7/ 2.9 (-0.1)	-2.8/ 3.9 (-0.6)	0.355
		Mean±Sd	-0.22±0.83	-0.24±1.82	

*Sd: Standart deviation, Min: Minimum, Max: Maximum, [a]Mann Whitney U Test, [c]Wilcoxon Signed Ranks Test *p<0.05**p<0.01.*

Discussion

Among the newborns followed with the diagnosis of late-onset neonatal sepsis (LONS), the final RBC levels, initial MCV levels, final MCH levels, and initial and final HGB, HCT, and PLT levels of those who passed away were found to be statistically significantly lower compared to the surviving newborns. In contrast, the initial MPV levels and the initial and final CRP measurements were found to be statistically significantly higher. In a study, it was reported that in septic patients, while hematocrit (HCT), hemoglobin (HGB), and red blood cell (RBC) counts decreased, there was no statistically significant difference in MCV levels (14). Blood loss resulting from diagnostic phlebotomy performed on newborns is one of the causes of anemia observed in the neonatal period. The shorter lifespan of red blood cells in newborns compared to adults contributes to the reduction in RBC count in newborns (15,16).

In studies conducted, it has been reported that increased red cell distribution width (RDW) is a strong and independent risk factor for mortality in critically ill neonatal patients with sepsis and septic shock (17,18). In a study evaluating RDW in cases of intrauterine growth restriction, it was found that RDW values were statistically significantly higher in preterm infants diagnosed with late-onset neonatal sepsis (LONS) compared to term infants (19).

Platelet indices used to assess platelet activation and function, such as platelet count, mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW), are also affected. In the presence of endotoxemia, it is known that there is a decrease in PLT and PCT values, along with an increase in MPV and PDW values (20). In a study investigating whether MPV (mean platelet volume) values are predictive for neonatal sepsis, it was found that MPV values increased in newborns with sepsis compared to the control group, while PCT (plateletcrit) values decreased (21). In several studies examining sepsis and its markers, it has been found that an increase in CRP (C-reactive protein) values is associated with both the severity of sepsis and mortality (21, 22). In our study, in line with the literature, CRP (C-reactive protein) values were found to be higher in newborns who experienced mortality compared to those who survived, and this difference was statistically significant.

In our study, the incidence of late-onset neonatal sepsis (LONS) was found to be higher in males compared to females. Similarly, in a study conducted in Egypt that prospectively followed newborns, it was reported that the incidence of early-onset neonatal sepsis (EONS) and LONS was higher in males than in females (23). In another study conducted in Switzerland with newborns, it was determined that the incidence of hospital- and community-acquired late-onset neonatal sepsis (LONS) was higher in males compared to females (24). It is believed that the variation of genes located on the X chromosome is the reason for this situation (25).

In a study conducted in America that examined 15,178 newborns born at or before 32 weeks of gestation and weighing less than 1500 grams, it was found that the incidence of late-onset neonatal sepsis (LONS) increased as gestational age (GA) and birth weight (BW) decreased, and that it was more common in male infants (6). Similarly, in a study conducted in Brazil with 1,506 newborns, it was reported that the frequency of late-onset neonatal sepsis (LONS) increased as gestational age (GA) and birth weight (BW) decreased (26). In contrast to the literature, our study found that the frequency of late-onset neonatal sepsis (LONS) was higher in term (50.6%) and over 2500 grams (58.4%) newborns. This situation is thought to be due to the relatively low number of premature newborns in our unit and the higher number of term newborns. In our study, the cesarean birth rate was found to be higher than the vaginal birth rate. When reviewing the literature, a similar multicenter case-control study conducted in Belgium and the Netherlands involving 755 newborns diagnosed with LONS found that 46.1% were born vaginally and 53.9% were born via cesarean section (27). As can be understood from the results, the mode of delivery, particularly cesarean section, is thought to be a potential risk factor for late-onset neonatal sepsis (LONS).

Limitations of the Study

The study's limitations include the fact that only newborns with positive cultures were included, which means that the true incidence of cases with meningitis could not be determined due to the lack of lumbar punctures performed on all newborns. Additionally, the study was retrospective and conducted only with newborns hospitalized in the neonatal intensive care unit (NICU), which represents another limitation.

Conclusions

While monitoring newborns with late-onset neonatal sepsis, it has been proven that low on day 1 of sepsis and on day 7 of sepsis levels of HGB (hemoglobin), HCT (hematocrit), and PLT (platelet) levels, along with low on day 7 of sepsis RBC (red blood cell) and MCH (mean corpuscular hemoglobin) levels, as well as low on day 1 of sepsis MCV (mean corpuscular volume) levels, and high on day 1 of sepsis MPV (mean platelet volume) levels and high on day 1 of sepsis and on day 7 of sepsis CRP (C-reactive protein) levels are associated with high mortality and poor prognostic factors.

Ethical Approval: *Before starting the study, approval from the clinical research ethics committee of a university was obtained with the decision numbered 19/09/15 dated 22.10.2019 and institutional permission from the hospital where the study was conducted. The study was conducted in accordance with the principles of the Declaration of Helsinki*

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Design : H.D., D.K.
Data acquisition: H.D.
Analysis and interpretation: H.D., D.K.
Writing manuscript: H.D.
Critical revision of manuscript: D.K.
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Araştırma Makalesi / Research Article

Adli Tıbbi Bilgi Düzeyinin, Adli Tıp Eğitimi Öncesi ve Sonrası Arasındaki Farklılığın Değerlendirilmesi

Evaluation of the Difference in Forensic Medical Knowledge Level Before and After Forensic Medicine Education

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Öz

Amaç: Tıp eğitimi sürekli bir gelişim gösteren bir süreçtir. Eğitimdeki yenilikler ve değişiklikler, öğrencilere yönelik eğitim modellerinin de sürekli gözden geçirilmesini gerektirmektedir. Bu çalışmanın amacı, Harran Üniversitesi Tıp Fakültesi 5. sınıf öğrencilerinin Adli tıbbi bilgi düzeyini, adli tıp eğitimi öncesi ve sonrası arasındaki farklılığın değerlendirilmesi ile birlikte öğrencilerin geri bildirimleri sorgulanmaya çalışılmıştır.
Materyal ve metod: 2024 yılında toplam 204 beşinci sınıf öğrencisi üzerinde yapılan bu çalışmada, öğrencilerden adli tıp stajı öncesinde ve sonrasında geri bildirim alınmıştır. Örneklem büyüklüğü $n = t^2xpxq / d^2$ formülü ile hesaplanmıştır. Her öğrenci, 13 sorudan oluşan anketi, staj öncesi ve sonrası bilgi düzeyine göre 1-9 arasında puanlayarak doldurmuştur. Veriler SPSS yazılımı ile analiz edilmiştir.
Bulgular: Öğrencilerin adli tıp bilgisi, staj öncesi ve sonrası karşılaştırıldığında anlamlı bir artış göstermiştir. Adli Tıp ve Adli Bilimler, hasta hakları, adli olgular, adli rapor düzenleme gibi konularda bilgi düzeylerinde belirgin bir iyileşme gözlenmiştir. Cinsiyete göre staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmamış olup, tabloda mevcut 13 soruda staj öncesi ve staj sonrası bilgi düzeyi arasında anlamlı farklılık saptanmıştır (p=0.000).
Sonuç: Adli tıp teorik ve pratik eğitimi, öğrencilerin adli tıp alanındaki bilgi düzeyini önemli ölçüde artış sağlamıştır. Adli Tıp eğitiminin mezuniyet öncesi dönemde daha etkin ve standartlara uygun bir şekilde verilmesi durumunda hekimlerin adli olgularla karşılaştıklarında daha donanımlı ve yetkin olmalarını sağlayacaktır.

Anahtar Kelimeler: Adli tıp eğitimi, Adli tıp, Bilgi düzeyi

Abstract

Background: Medical education is a process that is constantly evolving. Innovations and changes in education require continuous review of educational models for students. The purpose of this study is to evaluate the level of forensic medical knowledge of 5th year students of Harran University Faculty of Medicine, the difference between before and after forensic medical education, and to question the feedback of the students.
Materials and Methods: In this study conducted on a total of 204 fifth-grade students in 2024, feedback was received from the students before and after the forensic medicine internship. Sample size was calculated with the formula $n = t^2xpxq / d^2$. Each student filled out a 13-question survey by scoring 1-9 according to their knowledge level before and after the internship. The data was analyzed with SPSS software.
Results: Students' forensic knowledge showed a significant increase when compared before and after the internship. A significant improvement was observed in the knowledge levels on topics such as Forensic Medicine and Forensic Sciences, patient rights, forensic cases, and forensic report preparation. No significant difference was found between pre- and post-internship in terms of gender, and a significant difference was found between pre- and post-internship knowledge levels in the 13 questions in the table (p=0.000).
Conclusions: Theoretical and practical training in forensic medicine has significantly increased the knowledge level of students in the field of forensic medicine. If forensic medicine training is provided more effectively and in accordance with standards in the pre-graduation period, it will enable physicians to be more equipped and competent when faced with forensic cases.

Keywords: Forensic medicine education, Forensic medicine, Knowledge level

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Giriş

Tıp Eğitimi sürekli bir gelişim ve değişim göstermekte olup bu değişim, tıp fakültelerindeki eğitim modellerinin de sık sık yenilenmesini gerektirmektedir. Bu amaçla hangi eğitim yöntemlerinin daha etkili olacağı sürekli tartışma konusu olmakta, tıp eğitiminin geliştirilmesine yönelik yeni araştırmalar yapılması önerilmekte olup, bu süreçte öğrencilerin eğitim hakkındaki geri bildirimleri de bir değerlendirme kaynağı olarak eğitim modellerini şekillendirmede ve eğitim kalitesini artırmada rehber bir vasıta olarak kullanılması gerektiği ifade edilmiştir (1-3).

Günümüzde, tıp eğitiminin ne derece yeterli ve etkili olduğu, pek çok branşta olduğu gibi, bilimsel veriler ve somut kanıtlar esas alınarak değerlendirilmelidir. Söz konusu doğrultuda ağırlıklı olarak öğrenci ve akademisyenlerin tıp eğitimine dayalı eğitimle ilgili görüş ve değerlendirmelerinin istenmesi, tıp eğitimini geliştirme sürecinde yaygın bir yöntem olarak öne çıkmaktadır (4). Öğrenci geribildirimleri, eğiticilerin eğitici özelliklerinin daha iyi hale gelmesinde, gelişimine katkı sağlamasında ve yöneticiler tarafından personel ve programla dair sunulacak eğitimle ilgili stratejik kararlar almasında veri kaynağı olarak kullanılmaktadır (5). Bu geri bildirimler, mevcut eksiklerin belirlenmesi, eksiklerin giderilmesi ve yanlış uygulamaların düzeltilmesinde günümüzde yaygın bir araç olarak kullanılmaktadır (6). Yurt dışında tıp fakültelerinde yapılan çeşitli araştırmalar, öğrencilerin eğitimle ilgili görüşlerinin dikkate alındığını ve bu değerlendirmelerin eğitim programlarının yeniden şekillendirmesinde ve eğitim süreçlerini iyileştirmede rehberlik ettiğini ortaya koymaktadır (1,7,8). Türkiye'de yapılan birçok çalışmada da öğrenci geri bildirimlerinin tıp eğitiminin değerlendirilmesinde ve iyileştirilmesinde önemli bir yöntem olduğunu vurgulamaktadır (9-12).

Tıp eğitiminin etkinliğini değerlendirmek için veriye dayalı yaklaşımlar, akademisyenlerin ve öğrencilerin görüşleri dikkate alınarak değerlendirmeler yapılması, eğitim kalitesininin seviyesini yükseltmek ve daha etkili bir öğretim süreci yapılandırmak adına önemli bir yöntemdir (1,7-12). Tıp eğitiminde adli tıp eğitimi, öğrencilere gelecekteki tıbbi uygulamalarında tıbbi yasal sorumluluklarını öğrenmek ve gerektiğinde nasıl uygulaması gerektiği konularında gerekli bilgi ve becerileri kazandırdığı için lisans düzeyindeki tıp eğitiminde hayati öneme sahiptir (13).

Adli tıp, tıbbi bilgilerin hukuki alanda uygulanmasını, hekimlere ilişkin yasal meseleleri inceleyen bir bilim dalıdır. Fakültelere bağlı Adli Tıpta adli tıbbın eğitimi ve öğretimi yapılır, akademisyenler yetiştirir, Adli tıp eğitimi ülkemizde ilk kez 1839'da 2. Mahmut döneminde Mekteb-i Tıbbiye-i Şahane'de Tıbb-i Kanuni adıyla eğitim verilmeye başlanmış olup Adli Tıp eğitimi günümüze kadar pek çok gelişimler göstermiş değişikliklere uğramıştır (14).

Ülkemizde yapılan birçok çalışmada tıp fakültelerindeki adli tıp eğitiminin yetersiz olmasından dolayı hekimlerin meslek hayatlarında adli tıp hizmetlerini yürütmekte zorluk çektikleri belirtilmiştir (15-19). Ayrıca üniversitelerde verilen eğitim-öğretim standartlarında büyük farklar vardır. Bazı sınıflarda standart olmayan eğitim verilmekte olup çoğu sınıflarda yeterli pratik eğitim şartları sağlanamamaktadır (20).

Harran Üniversitesi Tıp Fakültesinde, tıp eğitiminde adli tıp eğitimi beşinci sınıflara iki haftalık staj şeklinde verilmekte olup, bu çalışmada öğrencilerin Adli tıbbi bilgi düzeyini, adli tıp eğitimi öncesi ve sonrası arasındaki farklılığı değerlendirilmesi ile birlikte öğrencilerin geri bildirimleri sorgulanmaya çalışılmıştır.

Materyal ve Metod

Çalışmanın amacına uygun olarak Harran Üniversitesi Tıp Fakültesi 5. Sınıf öğrencilerinden adli tıp staj eğitimi bitmesi sonrasında doldurulması talep edildi. 2024 yılı içerisinde toplam 204 öğrenci üzerinde yapıldı. Örneklem büyüklüğü $n = t^2xpxq / d^2$ formülü ile hesaplandı. Anket formunu doldurmayan 12 öğrenci çalışmaya dahil edilmedi. Yanıtların güvenilirliği amacıyla öğrencilerden ad, soyad ve numaralarını yazmamaları istendi. Adli tıbbi bilgi düzeyini, adli tıp eğitimi öncesi ve sonrası arasındaki farklılığı değerlendirilmek amacıyla kullanılan sorular 13 soru şeklinde düzenlenmiş olup, her sorunun karşılığında başlığın staj öncesi ve staj sonrası 1 ile 9 arasında mevcut bilgi düzeyine göre puanlama yaparak sorunun sağında bırakılan boşluğa doldurması talep edildi.

İstatistiksel Analiz

Analiz, IBM Corp. (Armonk, NY, ABD) firmasının SPSS for Microsoft Windows 21.0 yazılımı ile gerçekleştirildi. Sürekli parametreler için tanımlayıcı istatistikler ortalama ve standart sapma (SD) olarak; kategorik değişkenler için ise frekans (n) ve yüzde (%) olarak gösterildi. Verilerin analizinde Ki-kare testi ve Gruplar arasında Paired Samples Statistics ve Independent Samples testi kullanıldı. İstatistiksel anlamlılık için kabul edilebilir kriter $p<0,05$ olarak belirlendi.

Bulgular

Çalışmamızda yer alan 204 öğrencinin 103'sı erkek (%50.5) ve 101'i kız (%49.5) olarak bulundu. 'Adli Tıp ve Adli Bilimler hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 2.74±1.58, staj sonrası ortalama ± standart sapma 7.66±1.41 saptanmış olup, Adli tıp ve Adli bilimler hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000) (Tablo 1).

'Hasta hakları ve mahremiyetinin önemi hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 4,96±2,29, staj sonrası ortalama ± standart sapma 7,96±1,21 saptanmış olup, hasta hakları ve mahremiyetinin önemi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

"Hekimlerin yasal sorumlulukları hakkında bilgi düzeyi" so-

rusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 3,54±1,88, staj sonrası ortalama ± standart sapma 8,06±1,08 saptanmış olup, hekimlerin yasal sorumlulukları hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

"Adli olgular hakkında bilgi düzeyi" sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 2,64±1,63, staj sonrası ortalama ± standart sapma 7,94±1,32 saptanmış olup, adli olgular hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0.000).

'Adli olgu yönetimi hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 2,25±1,64, staj sonrası ortalama ± standart sapma 7,86±1,23 saptanmış olup, adli olgu yönetimi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Adli rapor düzenleme hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 1,79±1,55, staj sonrası ortalama ± standart sapma 7,86±1,45 saptanmış olup, adli rapor düzenleme hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

"Ahlaka karşı işlenen suçlar hakkında bilgi ve algı düzeyi" sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 3,25±1,86, staj sonrası ortalama ± standart sapma 7,62±1,37 saptanmış olup, ahlaka karşı işlenen suçlar hakkında bilgi ve algı düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

Tablo 1. Adli Tıbbi Bilgi Düzeyini Değerlendirme Anketi

	DEĞERLENDİRME SORULARI	En Az 1-2-3-4-5-6-7-8-9 En Çok ÖNCE Ort±SS	SONRA Ort±SS	P-değeri
1	Adli Tıp ve Adli Bilimler hakkında bilgi düzeyi,	2.74±1.58	7.66±1.41	**P=0.000**
2	Hasta hakları ve mahremiyetinin önemi hakkında bilgi düzeyi,	4,96±2,29	7,96±1,21	**P=0.000**
3	Hekimlerin yasal sorumlulukları hakkında bilgi düzeyi,	3,54±1,88	8,06,±1,08	**P=0.000**
4	Adli olgular hakkında bilgi düzeyi,	2,64±1,63	7,94±1,32	**P=0.000**
5	Adli olgu yönetimi hakkında bilgi düzeyi,	2,25±1,64	7,86±1,23	**P=0.000**
6	Adli rapor düzenleme hakkında bilgi düzeyi,	1,79±1,55	7,86±1,45	**P=0.000**
7	Ahlaka karşı işlenen suçlar hakkında bilgi ve algı düzeyi,	3,25±1,86	7,62±1,37	**P=0.000**
8	Adli Tıp Branşının önemi hakkında bilgi düzeyi,	3,08±1,94	6,90±1,94	**P=0.000**
9	Kimliklendirmenin önemi hakkında bilgi düzeyi,	4,54±2,20	7,59±1,70	**P=0.000**
10	Kadına şiddet ve ailenin korunması hakkındaki bilgi düzeyi,	3,42±1,89	8,17±1,12	**P=0.000**
11	Ölü muayenesi hakkında bilgi düzeyi,	3,06±1,81	7,53±1,62	**P=0.000**
12	Örnek alma usulleri-önemi hakkında bilgi düzeyi,	2,87±1,72	7,61±1,64	**P=0.000**
13	Vücut dokunulmazlığı hakkında bilgi düzeyi,	4,27±2,06	8,00±1,11	**P=0.000**

Ort: Ortalama, SS: Standart Sapma

"Adli Tıp branşının önemi hakkında bilgi düzeyi" sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 3,08±1,94, staj sonrası ortalama ± standart sapma 6,90±1,94 saptanmış olup, Adli tıp branşının önemi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Kimliklendirmenin önemi hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 4,54±2,20, staj sonrası ortalama ± standart sapma 7,59±1,70 saptanmış olup, kimliklendirmenin önemi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Kadına şiddet ve ailenin korunması hakkındaki bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 3,42±1,89, staj sonrası ortalama ± standart sapma 8,17±1,12 saptanmış olup, kadına şiddet ve ailenin korunması hakkındaki bilgi düzeyinin değişmesi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Ölü muayenesi hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 3,06±1,81, staj sonrası ortalama ± standart sapma 7,53±1,62 saptanmış olup, ölü muayenesi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Örnek alma usulleri-önemi hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 2,87±1,72, staj sonrası ortalama ± standart sapma 7,61±1,64 saptanmış olup, örnek alma usulleri-önemi hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

'Vücut dokunulmazlığı hakkında bilgi düzeyi' sorusuna tüm katılımcıların verdiği puanlar staj öncesi ortalama ± standart sapma 4,27±2,06, staj sonrası ortalama ± standart sapma 8,00±1,11 saptanmış olup, vücut dokunulmazlığı hakkında bilgi düzeyi konusunda staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmıştır (p=0,000).

Mevcut anketimizdeki 13 sorunun her biri için ayrı ayrı değerlendirme yapılmış olup, cinsiyete göre staj öncesi ve staj sonrası arasında anlamlı farklılık saptanmadı.

Tartışma

Adli tıp eğitimi, adli olgular ile mesleki sahada sık karşılaşılan durumlar olması nedeniyle tıp eğitiminde ve sonraki

mesleki hayatlarında çok önemli bir yere sahiptir (18,21). Hekimlerin mesleki hayatlarında, adli hekimlik hizmetleri ile ilgili sorumlulukları tariflenmiş olup, hekimler bu sorumluluklarını yerine getirmedikleri takdirde yasal yaptırımlar ile karşılaşabileceği belirtilmiştir (22). Çalışmamızda, adli tıp stajı öncesi ve sonrası dönem 5 öğrencilerindeki sorulan sorular ile bilgi düzeylerinde gözlemlenen değişiklikler analiz edilmiş olup, ankete katılan öğrencilerin adli tıp stajı öncesi eğitim süreçlerinde adli tıp dersi almadığı, ancak tıp eğitiminde diğer almış oldukları derslerin ders içeriklerinde mevcut anketteki sorulan sorular ile ilgili anlatımlar bulunduğu görülmüştür. Buna rağmen değerlendirmede öğrencilerin staj öncesi bilgi düzeylerinin düşük seviyede olduğu gözlenmektedir. Tokat Üniversitesi'nde yapılan bir çalışmada adli tıp stajı öncesinde verilen adli tıp ile ilgili konu başlıklarını içeren derslerin süre ve içerik açısından yetersiz olması nedeniyle, tıp öğrencilerinin adli tıp stajına başlamadan önce klinik branşlara kıyasla daha düşük bilgi seviyelerine sahip oldukları belirtilmiştir (23). Bu durum, çalışmamızdaki bulgularla da uyumlu bulunmuştur.

Tüm değerlendirme soruları için P değerleri 0.000 olarak saptanmış olup, gözlemlenen değişimlerin istatistiksel olarak anlamlı olduğunu ortaya koymaktadır. Bununla birlikte, bulgularımız, öğrencilerin Adli Tıp ve Adli Bilimler, hasta hakları, adli olgular, adli rapor düzenleme ve diğer adli konulardaki bilgi düzeylerinde staj sonrası verilen eğitimle birlikte önemli bir artış sağladığını göstermektedir. Benzer şekilde, Nilendu ve arkadaşlarının çalışmasında, kanıta dayalı adli tıp eğitiminin öğrencilerin mesleki ve hukuki farkındalıklarında anlamlı gelişmeler sağladığı rapor edilmiştir (24).

Adli tıp stajı sürecinde, çalışmaya katılan öğrencilere teorik eğitim ile pratik deneyimler bir arada sunulmuştur. Çalışmamızda özellikle "Ölü muayenesi" (3,06±1,81 → 7,53±1,62) ve "Adli rapor düzenleme" (1,79±1,55 → 7,86±1,45) gibi konularda gözlemlenen yüksek artışlar, uygulamalı eğitimin etkinliğini ortaya koymaktadır. Bu durum, Langford ve arkadaşlarının adli bilimlerde pratik becerilerin önemini vurgulayan çalışmalarıyla uyumludur (25). Benzer şekilde, Dicle Üniversitesi'nde yapılan bir çalışmada, son sınıf öğrencileri ve tıpta uzmanlık öğrencisi hekimlerin adli rapor düzenleme konusunda bilgi düzeylerinin düşük olduğu, bu nedenle daha fazla eğitime ihtiyaç duyulduğu belirtilmiştir (26).

"Adli olgu yönetimi hakkında bilgi düzeyi" (2,25±1,64 → 7,86±1,23) değerlendirmesinde gözlemlenen artışla, öğrencilerin başlangıçta bu konuda yetersiz bilgiye sahip olduklarını, ancak staj sürecinde bu bilgi düzeylerinin hızla arttığı görmekteyiz. Başlangıçtaki düşük değerin öğrencilerin konuya ilgi duymamalarından değil adli tıp ders içeriklerinin staj öncesi dönemde süre ve içerik açısından yetersiz olması nedeniyle olduğunu düşünmekteyiz. Yine Tokat Üniversitesi'nde yapılan çalışmada, "Hekimlik mesleğinizi icra ederken bir suçun işlendiğine dair fizik muayene bulgusu ile karşılaştığınızda bu hasta ile ilgili nasıl bir yol izleneceği konusunda bilginiz var mı?" sorusuna katılımcıların %36,2'sinin "ne yapacağımı bilmiyorum" yanıtını verdiği rapor edilmiştir (23). Staj süreci sırasında teorik bilgilerle pekiştirilen konulardan örneğin, "Kimliklendirmenin önemi" (4,54±2,20 → 7,59±1,70) ve "Ahlaka karşı işlenen suçlar" (3,25±1,86→ 7,62±1,37) gibi konularda da bilgi seviyesi yeterli değilken staj sonrasında bu düzey teorik eğitimle yeterli düzeyde olduğu saptandı.

'Kadına şiddet ve ailenin korunması' konusundaki bilgi düzeyindeki değişim (3,42±1,89 → 8,17±1,12), toplumsal sorumluluk ve etik meseleler hakkında farkındalık kazanımını göstermektedir. Bu bulgu, Nilendu ve arkadaşlarının adli tıp eğitiminin toplumsal bilinç artırmadaki rolünü vurgulayan çalışmalarıyla paralellik göstermektedir (24).

Sonuç

Bu çalışma, Harran Üniversitesi Tıp Fakültesi 5. sınıf öğrencilerinin Adli Tıp konuları ile ilgili bilgi seviyelerini değerlendirmek amacıyla gerçekleştirildi. Adli Tıp ve Adli Bilimler, hasta hakları ve mahremiyeti, hekimlerin yasal sorumlulukları, adli olgular ve adli olgu yönetimi gibi kritik konularda staj öncesi ve sonrası arasında belirgin bilgi artışları gözlemlenmiştir. Bu sonuçlar, mevcut Adli Tıp eğitiminin etkinliğini ve öğrencilerin mesleki becerilerini geliştirdiğini ortaya koymaktadır.

Özellikle öğrencilerin adli rapor düzenleme, ahlaka karşı işlenen suçlar ve kadına şiddet konularındaki bilgi düzeylerinde önemli gelişmeler kaydedilmiştir. Staj öncesi ve sonrası anket sonuçları, öğrencilerin Adli Tıp branşının önemini daha iyi kavradıklarını ve Adli Tıp konuları ile ilgili daha fazla bilinçlendiklerini göstermektedir. Çalışmanın bulguları, Adli Tıp eğitiminin mezuniyet öncesi dönemde daha etkin ve standartlara uygun bir şekilde verilmesi durumunda hekimlerin adli olgularla karşılaştıklarında daha donanımlı ve yetkin olmalarını sağlayacaktır.

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Araştırma Makalesi / Research Article

Hipokloröz Çözelti ile Sislemenin Sağlık Hizmeti İlişkili Enfeksiyon Hızı Üzerine Etkisi

The Effect of Fogging with Hypochlorous Solution on The Rate of Healthcare-Associated Infections

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Öz

Amaç: Sağlık Hizmeti İlişkili Enfeksiyonları önlemek için, hasta bakım alanlarının temizlenmesi ve dezenfekte edilmesi standart önlemlerin en önemli parçasıdır. Kullanılan tüm dezenfektanların aksine, hipokloröz çözelti, sodium hipoklorür ile saf suyun elektrolizi ile oluşturulduğu için güvenilir, etkin ve sterilizandır. Bu çalışmamızda hastanemizde devam eden *Acinetobacter* salgınının engellenmesinde hipokloröz çözeltinin sisleme ile uygulanmasının etkinliğini ölçmeyi amaçladık.
Materyal ve metod: Hipokloröz çözelti ile sisleme 10 yataklı bir yoğun bakım ünitesinde uygulanırken, 9 yataklı diğer yoğun bakım ünitesinde uygulanamadı. Sisleme bir ay boyunca, günde 5 kez, hastalar yataklarında tedavi almakta iken, tüm yüzeylere uygulandı. Sislemeye ek olarak rutin temizlik-dezenfeksiyon ve el hijyeni uygulamalarına devam edildi. Her iki yoğun bakım ünitesinin sisleme öncesi bir aylık dönemde ve sisleme süresince bir aylık dönemde olan kültür sonuçları ve SHİE hızları kaydedildi.
Bulgular: Sisleme uygulanmayan YBÜ'de üreme saptanan hasta sayısı %36,4'ten, %29'a düşerken, sisleme uygulanan YBÜ'de %54,5'ten %28,1'e gerilemiştir. Sisleme yapılmayan YBÜ'de 15 kültür pozitifliği, ikinci dönemde 19'a yükselirken; sisleme uygulanan YBÜ'de bu sayı 17'den 13'e gerilemiştir. Sisleme uygulanmayan YBÜ'de SHİE hızı 4,5'tan 12,9'a çıkarken, sisleme uygulanan YBÜ'de SHİE hızı 18,2'den 3,1'e gerilemiştir.
Sonuç: Hipokloröz çözelti ile sislemenin, kültür pozitifliğinde ve SHİE hızında azalma ile ilişkili olabileceği, hastalar, sağlık personeli ve tıbbi aletler açısından herhangi bir olumsuz duruma yol açmadığı sonucuna varılmıştır. Lakin konu hakkında kesin kanaate varmak için öncesi ve sonrası dönemin standardize edilmiş olduğu prospektif dizayn edilmiş çalışmalarla sonuçlarımızın desteklenmesine ihtiyaç olduğu değerlendirilmiştir.

Anahtar Kelimeler: Hipokloröz Asit, Sisleme, Dezenfektan, Çapraz Kontaminasyon, Sağlık Hizmeti İlişkili Enfeksiyon Hızı

Abstract

Background: The prevention of healthcare-associated infections hinges on the meticulous cleaning and disinfection of patient care areas, forming the cornerstone of standard precautions. Hypochlorous solution, in contrast to other disinfectants, is a unique and effective agent due to its sterile, safe, and highly efficacious nature. This is attributed to its synthesis through the electrolysis of pure water and sodium hypochloride. In this study, we sought to assess the effectiveness of fogging hypochlorous solution in curbing the ongoing *Acinetobacter* outbreak in our hospital.
Materials and Methods: The application of a hypochlorous solution by fogging was conducted in one intensive care unit with 10 beds, while this method was not employed in the other intensive care unit with 9 beds. Fogging was conducted on all surfaces five times a day for one month while patients were undergoing treatment in their beds. In addition to fogging, routine cleaning, disinfection and hand hygiene practices were maintained. Culture results and HAI rates for both intensive care units were recorded for the one-month period preceding fogging and the one-month period during which fogging was performed.
Results: The prevalence of growths among patients decreased from 36.4% to 29% in the non-fogging ICU, while a similar decline was observed in the fogging ICU, from 54.5% to 28.1%. While the culture positivity rate in the ICU without fogging increased from 15 to 19 in the second period, this number decreased from 17 to 13 in the ICU with fogging. While the rate of healthcare-associated infection (HAI) increased from 4.5 to 12.9 in the non-fogging ICU, the rate of HAI decreased from 18.2 to 3.1 in the fogging ICU.
Conclusions: It was therefore concluded that fogging with hypochlorous solution may be associated with a decrease in culture positivity and SHIE rate, and that it does not cause any adverse effects on patients, healthcare personnel or medical instruments. However, in order to reach a definitive conclusion on the subject, it was evaluated that our results need to be supported by prospectively designed studies in which the before and after periods are standardised.

Keywords: Hypochlorous Acid, Fogging, Disinfectant, Cross Contamination, Healthcare Associated İnfection Rate

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Giriş

Sağlık Hizmeti İlişkili Enfeksiyonlar (SHİE), hem mortalite ve morbiditede artış ve hem de hastanede kalış süresinde uzama sebebi ile büyük bir ekonomik yüktür (1). Dünya Sağlık Örgütü verilerine göre, hastanede yatan hastalarda SHİE gelişme riski yüksek gelirli ülkelerde %7, düşük ve orta gelirli ülkelerde ise %15 iken sadece iyi bir enfeksiyon kontrol ve önleme programları ile bu oranlar %70 oranında azaltılabilmektedir (2).

Temas ile bulaşma, SHİE'ların yayılmasında önemli rol oynamakta olup doğrudan (kişiden kişiye ek nesne ya da kişi olmaksızın aktarım) ve dolaylı temasla bulaşma olarak ikiye ayrılmaktadır. Dolaylı temas ile bulaşmada asıl kaynak, kontamine olan bir nesne ya da kişidir (3). Sağlık personelinin kontamine yüzeylere, tıbbi ekipmanlara veya hastalara el teması, çapraz kontaminasyona potansiyel olarak katkıda bulunabilir (4). Hasta bakım alanlarındaki kritik yüzeylerin temizlenmesi ve dezenfekte edilmesiyle oluşan dolaylı temas ile bulaşı azaltmak, standart önlemlerin vazgeçilmez bir parçasıdır. Özellikle hastaya en yakın ve kontamine olma olasılığı en yüksek olan alanlar ile sık dokunulan yüzeylerin temizlik ve dezenfeksiyonu çok önemlidir (5).

Dezenfektan olarak sık kullanılan sodyum hipoklorit (NaCIO) yüksek oranda sterilizan olmasının yanı sıra, güvenli ve ekonomik olması nedeniyle de çok kullanışlıdır. Ancak, metaller için oldukça aşındırıcı olması, trihalometan oluşturması ve pratik kullanım için seyreltilmesinin zor olması gibi dezavantajları vardır (6). Hipokloröz çözelti, sodyum hipoklorür ile saf suyun elektroliz yöntemi ile ayrışması ile elde edilen bir maddedir. Sodyum hipoklorit gibi hem sterilizan ve hem de güvenlidir. Ancak sodyum hipokloritten farklı olarak, hipokloröz çözelti kullanım sonrası suya dönüştüğü için insan sağlığı için en az zararlı olan dezenfektanlardandır. Bu çözeltiler hipoklorit eklenerek oluşturulmadığı için sodyum hipokloritten farklı olarak metalik korozyona da neden olmaz ve metalik maddelerin olduğu ortamlarda güvenle kullanılır (7). Hipokloröz suyun hafif asidik hali aerosol hale getirilerek sisleme şeklinde de uygulanabilir.

Bu çalışmada temizlik ve dezenfeksiyona ek olarak yoğun bakımda hasta çevresine sisleme metodu ile (aerosol) hipokloröz çözelti uygulanmasının hastanemizde devam eden *Acinetobacter* salgınının engellenmesindeki rolünü ortaya koymayı hedefledik.

Materyal ve Metod

Sisleme için kullanılan hipokloröz çözeltinin %0,02'lik kısmı elektroliz yöntemi ile sodyum klorürden elde edilmiş aktif klor, %99,98'i ise saf sudan oluşmaktaydı. Hipokloröz çözelti ile sisleme 10 yataklı bir yoğun bakım ünitesinde (YBÜ) uygulanırken, 9 yataklı diğer yoğun bakım ünitesinde gerekli izinler alınamadığı için uygulanamadı. Sisleme bir ay boyunca, günde 5 kez (08.00-12.00-16.00-20.00-24.00 olarak) uygulandı (Şekil 1). Sisleme işlemi için "ultra low volume fogging device" kullanıldı. Bu cihaz 5 litre hipokloröz çözeltiyi 27 litre/saat hızında sisleme özelliğine sahipti ve hipokloröz çözelti 03-49 mikron damla çapı ile uygulandı.

Şekil 1. Sisleme işlemi

Sisleme işlemi hastalar yataklarında tedavi almakta iken, yatak başlarına, yatak korkuluklarına, monitörlere, etajerlere, hasta başı dolaplarının üstüne ve içine ayrıca tedavi hazırlama alanları dahil olmak üzere tüm yüzeylere uygulandı. Sislemeye ek olarak rutin temizlik-dezenfeksiyon ve el hijyeni uygulamalarına devam edildi. Uygulama öncesinde ve süresince kültür alma sayısına ve süresine herhangi bir müdahalede bulunulmadı. Her iki yoğun bakım ünitesinin sisleme öncesi bir aylık dönemde ve sisleme süresince bir aylık dönemde olan kültür sonuçları ve SHİE hızları kaydedildi. Alınan kültürlerdeki ilk üremeler pozitif kültür olarak kaydedildi. Aynı materyalden tekrarlayan üremeler kaydedilmedi. Kan kültürü üremeleri, iki ayrı ekstremiteden de aynı patojen üremesi durumunda pozitif olarak kaydedildi. SHİE hızlarını hesaplamak için "Enfeksiyon hızı= (enfeksiyon sayısı/yatan hasta sayısı) x 100" formülü kullanıldı (1).

Bulgular

Sisleme öncesi dönemde ve sisleme süresince, her iki yoğun bakım ünitesinde yatan hastaların yatış tarihleri, kültür alınma tarihleri, kültürlerin alındığı materyaller, üreme sonucunda elde edilen patojenler tablo halinde sunulmuştur (Tablo 1 ve Tablo 2).

Sislemeye uygulanmayan YBÜ'de, sisleme öncesi dönemde toplamda 22 hasta yatışı olmuştur. Bu süreçte 14 (%63,6) hastanın alınan kültürlerde herhangi bir üreme saptanmaz iken, 8 (%36,4) hastada toplamda 15 kültür üremesi saptanmıştır. Kültürler alınan yerlere göre sıralandığında: yedisi trakeal aspirat kültürü (TAK), beşi idrar kültürü ve üçü kan kültürü olarak kaydedildi. Etkenlere göre sıralandığında ise en sık *Acinetobacter baumannii* üremesi saptandı. İkinci dönemde (diğer YBÜ'de sisleme yapıldığı dönemde), toplamda 31 hasta yatışı olmuştur. Bu süreçte 22 (%71) hastanın alınan kültürlerinde herhangi bir üreme saptanmaz

iken, 9 (%29) hastada toplamda 19 kültür üremesi saptanmıştır. Kültürler alınan yerlere göre sıralandığında: yedisi TAK'ta, yedisi kan kültürü ve beşi idrar kültürü olarak kaydedildi. Etkenlere göre sıralandığında yine en sık *Acinetobacter baumannii* üremesi saptandı. Diğer üremeler Tablo-1'de gösterilmiştir.

Sisleme uygulanan YBÜ'de, sisleme öncesi dönemde toplamda 22 hasta yatışı olmuştur. Bu süreçte 10 (%45,5) hastanın alınan kültürlerde herhangi bir üreme saptanmaz iken, 12 (%54,5) hastada toplamda 17 kültür üremesi saptanmıştır. Kültürler alınan yerlere göre sıralandığında: sekizi TAK, altısı idrar kültürü ve üçü kan kültürü olarak kaydedildi. Etkenlere göre sıralandığında ise en sık *Acinetobacter baumannii* üremesi saptandı. Sisleme yapılan dönemde toplamda 32 hasta yatışı olmuştur. Bu süreçte 23 (%71,9) hastanın alınan kültürlerde herhangi bir üreme saptanmaz iken, 9 (%28,1) hastada toplamda 13 kültür üremesi saptanmıştır. Kültürler alınan yerlere göre sıralandığında, yedisi TAK'ta, dördü idrar kültürü ve ikisi kan kültürü olarak kaydedildi. Etkenlere göre sıralandığında yine en sık *Acinetobacter baumannii* üremesi saptandı. Diğer üremeler Tablo-2'de gösterilmiştir.

Sisleme uygulanmayan YBÜ'de üreme saptanan hasta sayısı %36,4'ten, %29'a düşerken, sisleme uygulanan YBÜ'de %54,5'ten %28,1'e gerilemiştir. Sisleme yapılmayan YBÜ'de 15 kültür pozitifliği, ikinci dönemde 19'a yükselirken; sisleme uygulanan YBÜ'de bu sayı 17'den 13'e gerilemiştir. Sisleme uygulanmayan YBÜ'de SHİE hızı 4,5'tan 12,9'a çıkarken, sisleme uygulanan YBÜ'de SHİE hızı 18,2'den 3,1'e gerilemiştir (Tablo 3).

Tablo 1. Sisleme İle Hipokloröz Çözelti Uygulanmayan Yoğun Bakım Ünitesindeki Sisleme Öncesi ve Sisleme Uygulama Süresince Alınan Kültürler ve Sonuçları

TARİH: 05.12.2021-04.01.2022 (sisleme öncesi)				
Hasta No	**Yatış Tarihi**	**Örnek Tarihi**	**Kültür Adı**	**Patojen**
1	27.10.2021	10.12.2021	TAK	AB
		10.12.2021	İK	CA
2	14.11.2021	03.12.2021	TAK	AB
		05.12.2021	KK	BCe
3	Yeni bir kültür üremesi olmadı			
4	05.12.2021	15.12.2021	TAK	AB
5	08.12.2021	14.12.2021	İK	KP
		23.12.2021	İK	EFs
		25.12.2021	TAK	SM
6	10.12.2021	13.12.2021	TAK	AB
		13.12.2021	İK	KP
7	12.12.2021	26.12.2021	KK	EFs
		29.12.2021	İK	CA
8	Yeni bir kültür üremesi olmadı			
9	18.12.2021	27.12.2021	TAK	AB
10	Yeni bir kültür üremesi olmadı			
11	Yeni bir kültür üremesi olmadı			
12	Yeni bir kültür üremesi olmadı			
13	Yeni bir kültür üremesi olmadı			
14	Yeni bir kültür üremesi olmadı			
15	Yeni bir kültür üremesi olmadı			
16	29.12.2021	05.01.2022	TAK	KP
		05.01.2022	KK	SE
17	Yeni bir kültür üremesi olmadı			
18	Yeni bir kültür üremesi olmadı			
19	Yeni bir kültür üremesi olmadı			
20	Yeni bir kültür üremesi olmadı			
21	Yeni bir kültür üremesi olmadı			
22	Yeni bir kültür üremesi olmadı			

TARİH: 05.01.2021-04.02.2022 (sisleme dönemi)				
Hasta No	**Yatış Tarihi**	**Örnek Tarihi**	**Kültür Adı**	**Patojen**
1	05.12.2021	10.01.2022	KK	SM
2	17.01.2022	25.01.2022	KK	SA
3	Yeni bir kültür üremesi olmadı			
4	29.12.2021	13.01.2022	TAK	AB
		13.01.2022	İK	EFm
		01.02.2022	TAK	KP
		01.02.2022	İK	CA
5	Yeni bir kültür üremesi olmadı			
6	07.01.2022	19.01.2022	TAK	AB
		19.01.2022	İK	EFm
		19.01.2022	KK	SM
7	Yeni bir kültür üremesi olmadı			
8	Yeni bir kültür üremesi olmadı			
9	Yeni bir kültür üremesi olmadı			
10	Yeni bir kültür üremesi olmadı			
11	Yeni bir kültür üremesi olmadı			
12	Yeni bir kültür üremesi olmadı			
13	Yeni bir kültür üremesi olmadı			
14	28.12.2021	13.01.2022	TAK	SM
		13.01.2022	KK	SM
15	Yeni bir kültür üremesi olmadı			
16	Yeni bir kültür üremesi olmadı			
17	Yeni bir kültür üremesi olmadı			
18	Yeni bir kültür üremesi olmadı			
19	Yeni bir kültür üremesi olmadı			
20	Yeni bir kültür üremesi olmadı			
21	Yeni bir kültür üremesi olmadı			
22	Yeni bir kültür üremesi olmadı			
23	Yeni bir kültür üremesi olmadı			
24	14.01.2022	19.01.2022	TAK	AB
		27.01.2022	KK	AB
25	Yeni bir kültür üremesi olmadı			
26	Yeni bir kültür üremesi olmadı			
27	18.01.2022	20.01.2022	TAK	AB
28	Yeni bir kültür üremesi olmadı			
29	28.01.2022	03.02.2022	TAK	KP
		03.02.2022	İK	KP
		03.02.2022	KK	KP
30	Yeni bir kültür üremesi olmadı			
31	11.01.2022	27.01.2022	İK	EFm
		29.01.2022	KK	AB

TAK: trakeal aspirat kültürü, İK: idrar kültürü, KK: kan kültürü AB: Acinetobacter baumannii, CA: Candida albicans, BCe: Burkholderi cepacia, KP: Klebsiella pneumonia, EFs: Enterococcus faecalis, SM: Stenotrophomonas maltophilia, SE: Staphylococcus epidermidis, SA: Staphylococcus aureus, EFm: Enterococcus faecium

Tablo 2. Sisleme İle Hipokloröz Çözelti Uygulanan Yoğun Bakım Ünitesindeki Sisleme Öncesi ve Sisleme Uygulama Süresince Alınan Kültürler ve Sonuçları

TARİH: 05.12.2021-04.01.2022 (sisleme öncesi)				
Hasta No	**Yatış Tarihi**	**Örnek Tarihi**	**Kültür Adı**	**Patojen**
1	Yeni bir kültür üremesi olmadı			
2	Yeni bir kültür üremesi olmadı			
3	Yeni bir kültür üremesi olmadı			
4	04.11.2021	16.11.2021	TAK	RP
		29.11.2021	İK	CA
5	Yeni bir kültür üremesi olmadı			
6	19.10.2021	23.12.2021	KK	AB
7	15.12.2021	18.12.2021	TAK	CT
8	14.12.2021	24.12.2024	İK	CP
9	05.12.2021	16.12.2021	İK	CA
10	Yeni bir kültür üremesi olmadı			
11	22.11.2021	12.12.2021	KK	AB
12	Yeni bir kültür üremesi olmadı			
13	16.11.2021	28.12.2021	TAK	KP
		28.12.2021	İK	AB
14	Yeni bir kültür üremesi olmadı			
15	03.12.2021	22.12.2021	TAK	AB
16	Yeni bir kültür üremesi olmadı			
17	17.12.2021	30.12.2021	TAK	KP
18	Yeni bir kültür üremesi olmadı			
19	Yeni bir kültür üremesi olmadı			
20	28.11.2021	27.12.2021	TAK	AB
		29.12.2021	İK	CA
21	20.11.2021	21.12.2021	İK	Cİ
		22.12.2021	TAK	AB
		24.12.2021	KK	AB
22	07.12.2021	28.12.2021	TAK	AB

TARİH: 05.01.2021-04.02.2022 (sisleme dönemi)				
Hasta No	**Yatış Tarihi**	**Örnek Tarihi**	**Kültür Adı**	**Patojen**
1	Yeni bir kültür üremesi olmadı			
2	Yeni bir kültür üremesi olmadı			
3	Yeni bir kültür üremesi olmadı			
4	Yeni bir kültür üremesi olmadı			
5	Yeni bir kültür üremesi olmadı			
6	30.01.2022	02.02.2022	TAK	AB
7	Yeni bir kültür üremesi olmadı			
8	Yeni bir kültür üremesi olmadı			
9	Yeni bir kültür üremesi olmadı			
10	Yeni bir kültür üremesi olmadı			
11	Yeni bir kültür üremesi olmadı			
12	Yeni bir kültür üremesi olmadı			
13	Yeni bir kültür üremesi olmadı			
14	Yeni bir kültür üremesi olmadı			
15	Yeni bir kültür üremesi olmadı			
16	Yeni bir kültür üremesi olmadı			
17	05.01.2022	12.01.2022	TAK	AB
18	28.11.2021	17.01.2022	KK	CP
19	17.12.2021	12.01.2022	KK	SM
		14.01.2022	TAK	AB
20	Yeni bir kültür üremesi olmadı			
21	Yeni bir kültür üremesi olmadı			
22	16.01.2022	29.01.2022	TAK	AB
		29.01.2022	İK	AB
23	Yeni bir kültür üremesi olmadı			
24	05.01.2022	06.01.2022	İK	CA
		11.01.2022	TAK	KP
25	Yeni bir kültür üremesi olmadı			
26	Yeni bir kültür üremesi olmadı			
27	20.11.2021	14.01.2022	İK	CA
28	Yeni bir kültür üremesi olmadı			
29	09.01.2022	11.01.2022	TAK	AP
		12.01.2022	İK	CA
30	Yeni bir kültür üremesi olmadı			
31	Yeni bir kültür üremesi olmadı			
32	14.01.2022	18.01.2022	TAK	SH

TAK: trakeal aspirat kültürü, İK: idrar kültürü, KK: kan kültürü.
RP: *Raoultella planticola*, CA: *Candida albicans*, AB: *Acinetobacter baumannii*, CT: *Candida tropicalis*, CP: *Candida parapsilosis*, KP: *Klebsiella pneumonia*, Cİ: *Candida inconspicua*, SM: *Stenotrophomonas maltophilia*, AP: *Acinetobacter piti*, SH: *Staphylococcus haemolyticus*

Tablo 3. Kültür Üremelerinin ve Sağlık Hizmeti İlişkili Enfeksiyon Hızının Sisleme Uygulanan ve Uygulanmayan Yoğun Bakımlarda Karşılaştırılması

Yoğun bakım adı	Tarih aralığı	Üreme olan hastalar	Pozitif kültür sayısı	SHİE	SHİE hızı	SHİE hızı
Sisleme uygulanan YBÜ	Sisleme dönemi öncesi	12 (%54,5)	17	4	4/22x100	18,2
	Sisleme dönem sonrası	9 (%28,1)	13	1	1/32x100	3,1
Sisleme uygulanmayan YBÜ	Sisleme dönemi öncesi	8 (%36,4)	15	1	1/22x100	4,5
	Sisleme dönem sonrası	9 (%29)	19	4	4/31x100	12,9

SHİE: Sağlık hizmeti ilişkili enfeksiyon, YBÜ: Yoğun bakım ünitesi
SHİE hızı =(enfeksiyon sayısı/yatan hasta sayısı) x 100 (1)

Tartışma

Hastanemizde 2021 yılının Kasım ayında YBÜ'lerde yatan hastaların alınan kültürlerinde *Acinetobacter* başta olmak üzere birçok patojenin normalden daha fazla ürediği fark edildi. Özellikle *Acinetobacter* üreyen vaka sayısının beklenen vaka sayısından yüksek olması sebebi ile "*Acinetobacter* salgını" düşünülerek acil eylem planı yapıldı (8). Üremeler incelendiğinde, üremelerin komşu yataklar arasında olması sebebiyle bulaş kaynağının öncelikli olarak dolaylı temas ve eller olduğu düşünüldü. Ayrıntılı çevre kültürleri alındı. Hasta yataklarında, hasta başlarındaki distile suda, hasta bakıcı eldivenin alınan örnekte ve hasta etejerinde *Acinetobacter* üremeleri tespit edildi. Acil eylem planı doğrultusunda 6 kişilik özel bir temizlik ekibi oluşturuldu. Bu ekibe yeniden temizlik, izolasyon ve el hijyeni eğitimi verildi. Eğitimlerin ardından bu ekip hafta sonları YBÜ'lerine genel mekanik ve terminal temizlik işlemleri uyguladı. Hastane geneline SHİE, el hijyeni ve hastane temizliği eğitimleri tekrar verildi. Tüm bu çabalara rağmen YBÜ'lerindeki üreme sayımızda bir azalma gözlenmedi. *Acinetobacter* salgını ve SARS-Cov-2 salgını birlikteliği

ve YBÜ ihtiyacının fazla olması sebebi ile, YBÜ kapatma ve terminal dezenfeksiyon yapma şansımız yoktu, mevcut temizlik ve dezenfeksiyon işlemlerinin hasta bakımı olduğu anda yapılması gerekmekte idi. Bu sebeple hastaların ve sağlık çalışanlarının YBÜ'de olduğu saatlerde uygulandığında, insan sağlığı için risk oluşturmayan bir dezenfektan kullanmamız gerekiyordu. Biz de enfeksiyon kontrol komitesi olarak ilave bir önlem amacıyla etkili bir dezenfektan olduğu bilinen hipokloröz asitin kullanılmasına karar verdik.

Hipokloröz çözeltinin güvenliği ile ilgili yapılan çalışmalarda, diş tedavisinde güvenle gargara olarak kullanılabileceği, yutulsa bile zararlı olmadığı saptanmıştır, ayrıca blefarit tedavisinde de göze zararlı etkisi olmadan güvenli kullanılabileceği, perioküler cilt florasındaki bakteri yükünü azalttığı belirlenmiştir (9, 10). Hipokloröz çözeltinin peroperatif kullanımlarında biyofilm etkisi için implantlara uygulanabileceği ve hatta yara yıkaması amaçlı intraperitoneal lavaj yapılabileceği belirtilmiştir (11, 12). Özellikle yara bakımında sık kullanılan hipoloröz çözeltinin *Acinetobacter* başta olmak üzere yara yüzeyindeki bakteri yükünü azaltmakta başarılı olduğu saptanmıştır (13). Yine hipokloröz çözeltilerin insan ve hayvanların olduğu ortamlarda püskürtülerek kullanımının etkinlik ve güvenilirliğinin test edildiği çalışmalarda havadaki virüsleri birkaç saniye içinde inaktive ederken, ortamdaki canlı hayvanlarda enfeksiyon belirtisi ya da dezenfektana karşı herhangi bir reaksiyon geliştirmediği gösterilmiştir (14, 15). Ayrıca hipokloröz çözeltinin diğer dezenfektanlarla karşılaştırıldığı çalışmalarda hipokloröz asitin, yüzey temizliğinde virüslere sadece 1 dakikalık temas süresinde bile dekontaminasyon sağlayabildiği, hatta tıbbi cihazlardaki dirençli ve biyofilm üreten bakterilere karşı bile etkili olduğu gösterilmiştir (16, 17). Overholt ve ark. hipokloröz çözeltiyi standart dezenfektanlarla karşılaştırdıkları çalışmalarında bakteri yükünü diğer dezenfektanlardan daha çok azalttığı ortaya koymuşlardır (18).

Hastane temizliği ve dezenfeksiyonu sonrasında hızla yeniden dekontamine olma ihtimali sebebi ile yeni teknolojilerin geliştirilmesi gerekmektedir (19). Bu yeni teknolojiler içinde dezenfektan maddelerin sisleme ile uygulanması da sayılmaktadır. Amerika Hastalık Kontrol ve Önleme Merkezleri (Centers for Disease Control and Prevention: CDC) rehberleri dezenfeksiyon için sisleme tekniklerini enfeksiyon kontrolünde yetersiz olması sebebi ve hem hasta hem de sağlık çalışanlarının üzerine olumsuz etkileri olduğu için önermemekte idi. Ancak bu öneriler formaldehit, fenol bazlı ajanlar veya kuaterner amonyum bileşikleri için geçerli önerilerdi. 2009 yılında yapılan son güncellemede, ozon sisleri, buharlaştırılmış hidrojen peroksit gibi yeni teknolojilerin bu önerilerden sonra geliştiğinden bahsedilmekte ancak hidrojen peroksitin monitörlerdeki metal ve plastiklere zarar verme riski, klor dioksitin güneş ışığında kararsız olması ve patlayıcı olması gibi sıkıntılar sebebi ile bu konuda ek çalışma gerektiğinden bahsedilmektedir (4). Ancak 2009 güncellemesinden daha sonra gündeme gelen hipokloröz asit, ökaryotik hücreler için minimal toksisiteye sahip etkili bir anti-bakteriyel ajan olan iyi bilinen bir bileşiktir ve hipokloröz asitin ultrasonik sisleme aparatı kullanılarak sentezlenmesi ve uygulanması kolaydır (20). Henüz CDC rehberlerinde hipokloröz asit ile sisleme ile ilgili bir güncelleme yapılmamıştır.

Hipokloröz asit ile sisleme üzerine birçok güncel çalışma bulmak mümkündür. Bu çalışmalarda hipokloröz çözelti ile sisleme öncesi ve sonrası yapılan ölçümlerde, yüksek temaslı yüzeylerde ATP (adenozin trifosfat) puanlarında önemli bir azalma sağlandığı, sisleme ile hem dikey yüzeylerde ve hem de yatay yüzeylerde virüslerin sayısını ve patojenitesini azalttığı tespit edilmiştir (16, 18). Hipokloröz çözelti ile sisleme virüs, bakteri, spor ve mantar sayısında azalmaya neden olurken, tıbbi cihaz ve elektronik sistemlerin içine nüfus etmemekte ve onlara zarar vermemektedir (21). Hipokloröz çözelti ile sisleme işlemi, sisleme makinesinin elle taşınabilir bir alet olması sebebi ile kullanımı kolay, su ve sodyum klorür hidrolizi ile üretildiği için ucuz, hasta ve sağlık çalışanı için güvenli, bakteriosidal, virüsidal ve sisleme ile aerosol olarak yayılabildiği için geniş alanlarda hızlı-etkili bir uygulamadır (16). Çalışmamızda hem sisleme uygulanan ve hem de sisleme uygulanmayan YBÜ'lerin sisleme öncesi dönemde ve sisleme süresince alınan kültür sonuçları ve enfeksiyon hızları karşılaştırılmıştır. Sisleme uygulanmayan YBÜ'de üreme olan hasta oranı %7,4 azalırken, sisleme uygulanan YBÜ'de bu oran %26,4 azalmıştır. Pozitif kültür sayısı sisleme uygulanmayan YBÜ'de 15'ten 19'a çıkarken, aksine sisleme uygulanan YBÜ'de pozitif kültür sayısı azalmıştır (17'den 13'e). Çalışmamız retrospektif bir çalışma olduğu için kültürlerin koloni sayılarına ulaşılamamış ve ortam kültürü alınamamıştır. Yine de sisleme yapılan YBÜ'de sisleme süresince alınan kültürlerde üreme olan pozitif kültür sayılarının hem sisleme öncesi dönemden daha az olması ve hem de sisleme yapılmayan YBÜ ile karşılaştırıldığında daha az pozitiflik olduğu saptanmıştır. Çalışmalarda hipokloröz çözeltinin virüslerin ve bakterilerin sayısını ve patojenitesini azalttığı dikkate alındığında, çalışmamızın sonucunda da bakteri kolonizasyonda ve bakteri yükünde azalma olduğunu düşündürebilir. Bunun yanı sıra SHİE sayılarındaki azalma, bakterilerin hastalık yapma yeteneğinde azalma olduğunu düşündürebilir (16, 18). SHİE hızlarına bakıldığında, sisleme uygulanmayan YBÜ'de SHİE hızının 4,5'tan 12,9'a çıkarken, sisleme uygulanan YBÜ'de 18,2'den 3,1'e gerilemiş olması bu hipotezimizi güçlendirmektedir. Ayrıca uygulama sonrası hastalar ve sağlık personelinden hipokloröz asit uygulamasına bağlı olarak herhangi bir yan etki bildirilmemiş, ayrıca tıbbi aletlerde herhangi bir istenmeyen etkiye yol açmamıştır.

Sonuç olarak el hijyeni ve rutin ortam dezenfeksiyon önlemlerine ek olarak hipokloröz çözelti ile sislemenin, kültür pozitifliğinde ve SHİE hızında azalma ile ilişkili olabileceği ve hastalar, sağlık personeli ve tıbbi aletler açısından herhangi bir olumsuz duruma yol açmadığı sonucuna varılmıştır. Lakin konu hakkında kesin kanaate varmak için ortam kültürlerinin de ele alındığı, ortamdaki koloni sayılarının kantitatif olarak ortaya konduğu, kültür alma kriterlerinin uygulama öncesi ve sonrası dönemde standardize edilmiş olduğu prospektif di-

zayn edilmiş çalışmalarla sonuçlarımızın desteklenmesine ihtiyaç olduğu değerlendirilmektedir.

Teşekkür

Yoğun bakım salgınları sırasında hipokloröz çözeltiyi uygulama kısmında yardımlarını esirgemeyen Dr. İnşa Gül EKİZ İŞCANLI ve Hemşire Elvan KUTKAN'a teşekkürü borç bilirim.

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Research Article / Araştırma Makalesi

Relationship Between Core and Respiratory Muscle Endurance in Elite Handball Players

Elit Hentbol Oyuncularında Kor ve Solunum Kas Enduransı Arasındaki İlişki

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Abstract

Background: Postural and respiratory control cooperation is crucial in handball, which requires high levels of postural control, strength, aerobic and respiratory endurance. In the literature, no study has been found that examines the relationship between respiratory and core endurance in handball players. This study aims to investigate the correlation between core muscle endurance and respiratory muscle function in elite handball players.
Materials and Methods: Twenty-four female handball players were (22.17±3.42 years) included in the study. Core endurance, pulmonary functions including Forced Vital Capacity (FVC), Forced Expiratory Volume in First Second (FEV_1), FEV_1/FVC, Peak Expiratory Flow (PEF), respiratory muscle endurance and strength (Maximal Inspiratory Pressure; MIP, Maximal Expiratory Pressure; MEP) were evaluated in players.
Results: There were positive significant correlations between dominant wall sit hold test duration (s) and respiratory muscle performance, including respiratory muscle endurance (cmH_2Oxs) (r=0.536) and duration (T_{max}) (r=0.441), MIP (r=0.446; r=0.439), MEP (r=0.482;r=0.546) ($cmH_2O/\%$). The positive significant correlations were observed between non-dominant wall sit hold duration and MIP (r=0.534; r=0.548) ($cmH_2O/\%$), MEP (r=0.442) (%) (p≤0.05). The respiratory muscle endurance and expiratory muscle strength values (53.4%, p=0.001; r=0.764) have a significant influence on core muscle endurance.
Conclusions: Trainings that include core-respiratory muscle cooperation should be developed for better postural control, strength and endurance in handball players. The contribution of a comprehensive training program to improve postural stability and respiratory function on athletic performance should be investigated.

Keywords: Endurance, Maximal Inspiratory Pressure, Maximal Expiratory Pressure, Handball, Diaphragm

Öz

Amaç: Yüksek düzeyde postüral kontrol, kuvvet, aerobik ve solunum kas enduransı gerektiren hentbolda postüral kontrol ve solunum iş birliği çok önemlidir. Literatürde hentbol oyuncularında solunum-kor endurans ilişkisini inceleyen çalışmaya rastlanmamıştır. Bu çalışma elit hentbol oyuncularında gövde kas dayanıklılığı ile solunum kas fonksiyonu arasındaki ilişkiyi incelemeyi amaçlamaktadır.
Materyal ve Metod: Çalışmaya 24 (22.17±3.42 yıl) kadın hentbol oyuncusu dahil edildi. Sporcularda kor endurans, Zorlu Vital Kapasite (FVC), 1. saniyedeki Zorlu Ekspirasyon Hacmi (FEV_1), FEV_1/FVC, Zirve Ekspiratuar Akım Hızı (PEF)'nı içeren pulmoner fonksiyonlar, solunum kas kuvveti (Maksimal İnspirasyon Basıncı; MIP, Maksimal Ekspirasyon Basıncı; MEP) ve enduransı değerlendirildi.
Bulgular: Baskın ekstremite duvar destekli oturma tutma testi süresi (s) ile solunum kas performansını içeren solunum kası enduransı (cmH_2Oxs) (r=0,536) ve süresi (Tmax) (r=0,441), MIP (r=0,446; r=0,439), MEP (r=0,482; r=0,546) ($cmH_2O/\%$) arasında pozitif yönde anlamlı ilişki vardı. Baskın olmayan ekstremite duvar destekli oturma süresi ile MIP (r=0,534; r=0,548) (cmH2O/%), MEP (r=0,442) (%) arasında pozitif yönde anlamlı ilişki gözlemlendi (p≤0,05). Solunum kas enduransı ve ekspiratuar kas kuvveti değerleri (%53,4, p=0,001; r=0,764) kor kas enduransı üzerinde önemli bir etkiye sahiptir.
Sonuç: Hentbol oyuncularında daha iyi postüral kontrol, kuvvet ve dayanıklılık için kor-solunum kası iş birliği içeren antrenmanlar geliştirilmelidir. Postüral stabiliteyi ve solunum fonksiyonunu iyileştirmeye yönelik kapsamlı bir eğitim programının atletik performansa katkısı araştırılmalıdır.

Anahtar Kelimeler: Endurans, Maksimal İnspirasyon Basıncı, Maksimal Ekspirasyon Basıncı, Hentbol, Diyafram

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Introduction

Respiratory muscle performance is important in ensuring adequate gas exchange and pulmonary ventilation during activities that require endurance (1). Reduced respiratory muscle function related to respiratory muscle fatigue activates the metaboreflex mechanism, increasing blood flow to respiratory muscles and decreasing blood flow to locomotor muscles. Respiratory muscle fatigue results in a decline in sports performance (2). Respiratory muscle strength and endurance are components of respiratory muscle function (3). The diaphragm plays a key role in maintaining respiratory muscle function. In addition, the diaphragm is a respiratory muscle and a postural stability muscle. The diaphragm mechanically supports the trunk by maintaining intra-abdominal pressure at a high level (4). Breathing and postural control are inevitably related and have a mechanism that supports each other (5). No studies have been found to evaluate the connection between core and respiratory muscle endurance in athletes so far.

Handball is a sport including multi-functional components that requires a high level of strength, power, and endurance (6). A study emphasized that better core endurance is connected with improved extremity stability, performance, and throwing ball velocity in handball players (7). A significant relationship has been found between core muscle endurance, to which the diaphragm also contributes, and extremity injury risk in athletes. Athletes with poor lumbopelvic-hip core muscle endurance are especially vulnerable to injury. Therefore, it is essential to evaluate core muscle endurance, which significantly impacts individuals' participation in sports and maintenance of their performance (8, 9). In the literature, unilateral wall sit hold, trunk flexion hold, and horizontal trunk hold tests were performed to assess lumbopelvic-hip endurance screening in athletes (8). However, the literature lacks information on the association between core muscle endurance and respiratory muscle function in athletes. The study focused on the correlation between core muscle endurance, respiratory muscle endurance, and strength by performing unilateral wall sit hold, trunk flexion hold, and horizontal trunk hold tests in elite handball players. We tested the hypothesis that elite female handball players who have better lumbopelvic-hip endurance have better respiratory strength and endurance.

Materials and Methods

In total, 25 elite female handball players came to the clinic for routine control. Because one player was unable to complete the tests due to dental braces, 24 players (22.17 ± 3.42 years) were included in this prospective, correlational study. The inclusion criteria were individuals who were playing handball and who had the same training program. Exclusion criteria were athletes with a history of any chronic lung disease, who could not comply with the test, who had an active infection that could affect the evaluation, and who were unwilling to participate in the study. Gazi University Ethics Committee approved (No: 2023-1199) this study. All players signed an informed consent form. The assessments were applied following the Declaration of Helsinki. Core and respiratory muscle endurance, respiratory muscle strength, pulmonary functions, and body compositions were evaluated in elite female handball players. Respiratory performance and core endurance tests were performed one hour apart. The demographic characteristics, including age, weight, height, sports age, and smoking exposure were noted.

Core muscle endurance was assessed with unilateral wall sit hold, trunk flexion hold, and horizontal trunk hold tests. The unilateral wall sit hold test was conducted on both dominant and non-dominant extremity. The players were asked to stand leaning against the wall and cross their arms across their chests. The players were instructed to squat in a 90-degree position with their hips and knees while maintaining this position and lift (3-5°) their dominant feet. The players were expected to maintain this position for as long as possible. The test was repeated for non-dominant extremities following rest. The rest period between tests was 5 minutes. The maximum time the players could endure was recorded. To perform the trunk flexion hold test, the players sat on the floor. The players were asked to lift their feet off the ground while the angle of the trunk with the ground was 60 degrees, the angle of the knees was 90 degrees, and the shoulder was in a horizontal abduction position of 90 degrees. The maximum reached time without changing position was recorded. The players were instructed to perform shoulder horizontal abduction with the thumbs pointed up while the hip and knee were in the 90-degree position in the crawling position to conduct the horizontal trunk hold test. The longest time in this position was recorded (10).

The respiratory muscle endurance was evaluated with a constant load inspiratory muscle endurance test using Powerbreathe® (POWERbreathe International Ltd., England). The players sat in an upright position and took the device into their mouths, keeping the device parallel to the ground. The test was applied at a load equivalent to 70% of MIP for 10 minutes. The metronome was adjusted to allow players to take 20 breaths per minute. It was stated that the test would be finished if the athletes could not take two correct breaths in a row or felt breathlessness that could not continue. The maximum time (Tmax) and percentage of maximal load (%) were recorded. Standard respiratory muscle endurance values were calculated by multiplying the 70% of maximum peak pressure and T_{max} for each player (11).

The respiratory muscle strength (maximal inspiratory/expiratory pressure) and pulmonary functions (Forced Vital Capacity (FVC), Forced Expiratory Volume in First Second (FEV_1), Forced Expiratory Volume in First Second/Forced Vi-

tal Capacity (FEV_1/FVC), Peak Expiratory Flow (PEF)) of players were assessed using spirometer (Pony FX, COSMED Inc., Italy). To measure MIP and MEP values, at least five repetitions were performed, and the highest value was recorded for analysis. The reference values were used for calculating the percentage of expected MIP and MEP values (12). The dynamic lung volumes, including FVC, FEV_1, FEV_1/FVC, and PEF were evaluated at least three repetitions and expressed as percentages of the predicted values. The pressure-time curve was interpreted to determine the best measurement (13).

To evaluate the body composition, including weight, fat mass, fat mass percent, fat-free mass, and body mass index, TANITA bioelectrical impedance analysis (BC418-MA, TANITA Corporation, Tokyo, Japan) was used (14).

The statistical analyses were applied with the Windows-based Statistical Package for Social Sciences version 20 (SPSS-20) statistical analysis program. The suitability of the data for normal distribution was evaluated with the Shapiro-Wilk test. Percentage, mean, and standard deviation were used in the interpretation of descriptive data. Two-tailed Pearson's correlation analysis was used to evaluate the association between core endurance tests and respiratory performance variables. The correlation between core muscle endurance tests and respiratory muscle performance tests is expressed with Pearson correlation coefficient (strong relationship; $0.5 \leq r \leq 1.0$, moderate relationship; $0.3 \leq r < 0.5$, weak relationship; $r < 0.3$). The level of significance was determined as $p<0.05$ (15). After residual and goodness of fit statistics, the multiple linear regression forward model was performed for significant values to show how the MIP, MEP, and respiratory endurance influenced core endurance (wall sit hold-D test).

Model selection was performed by checking whether the variables known to be effective on the dependent variable meet the necessary assumptions for multiple regression analysis. The post-hoc power (1-β=0.80) analysis was performed according to the correlation between core and respiratory muscle endurance outcomes using the G-Power program 3.0.10 system (Franz Faul, Universität Kiel, Germany) (16).

Results

The twenty-four elite female handball players were included in this study. The demographic characteristics of handball players are given in Table 1. The results of respiratory muscle performance and core endurance tests in handball players are given in Table 2.

There were positive moderate-strong correlations between wall sit hold-D endurance test duration (s) and respiratory muscle performance, including respiratory muscle endurance (r=0.536) (cmH_2Oxs) and endurance test duration (r=0.441) (s), MIP (r=0.446; r=0.439), and MEP (r=0.482;r=0.546) (cmH_2O, %).

Table 1. Demographic Characteristics of Handball Players

Characteristics	M (SD)/n/% (n=24)
Age, y	22.17 (3.42)
Weight, kg	66.22 (10.57)
Height, cm	172.29 (6.34)
BMI, kg/m²	22.26 (3.11)
Fat mass, kg	13.92 (5.99)
Fat mass percent, %	20.29 (5.34)
Fat-free mass, kg	52.30 (5.15)
Smoking (current; non-smoker, n/%)	6/25%; 18/75%
Smoking exposure	2.70 (1.44)
Sports age, y	9.82 (3.40)

kg, kilogram; cm, centimeter; m, meter; y, year; M, mean, SD, standard deviation

Table 2. The Results of Respiratory Performance and Core Endurance Tests in Handball Players

Variables	M (SD)
Core endurance	
Wall sit hold-dominant, s	39.56 (24.74)
Wall sit hold-nondominant, s	45.21 (30.68)
Trunk flexion, s	101.24 (44.07)
Horizontal trunk hold, s	85.23 (58.88)
Respiratory muscle endurance	
T_{max}, s	236.84 (217.18)
Endurance, cmH_2Oxs	17791.30 (16623.81)
Respiratory muscle strength	
MIP, cmH_2O	114.74 (24.77)
MEP, cmH_2O	96.21 (18.45)
MIP, %	109.25 (21.89)
MEP, %	68.47 (12.65)
Pulmonary functions, %	
FVC	107.83 (11.90)
FEV_1	102.58 (12.79)
FEV_1/FVC	98.79 (9.16)
PEF	92.04 (17.46)

s, second; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; FEV_1/FVC, Forced expiratory volume in the first second/forced vital capacity; PEF, Peak expiratory flow; FEF_{25-75}%, Forced expiratory flow from 25% to 75%; cmH2O, centimeter water

In addition, positive moderate-strong correlations were observed between wall sit hold-ND endurance test duration and MIP (r=0.534; r=0.548) (cmH_2O, %) and MEP (r=0.442) (%) (p≤0.05; Table 3). No significant correlations were revealed between other core endurance tests and respiratory muscle performance. There were no significant correlations between core endurance tests, dynamic lung volumes, and body composition values (p>0.05; Table 3). The Model 1, including MEP value, explained 31.4% of the variance test (p=0.006; r=0.592; Table 4). and the Model 2, including respiratory muscle endurance and MEP values, explained 53.4% of the variance in core endurance (wall sit hold-D) test (p=0.001; r=0.764; Table 4).

Table 3. The Correlation Between Core Endurance Tests, Respiratory Functions and Anthropometric Features

Variables	Wall sit hold-D	Wall sit hold-ND	Trunk flexion	Horizontal trunk hold
	r	r	r	r
Respiratory muscle endurance				
Endurance, cmH_2Oxs	**0.536****	0.254	0.035	0.187
T_{max}, s	**0.441***	0.155	0.039	0.202
Respiratory muscle strength				
MIP, cmH_2O	**0.446***	**0.534****	0.367	0.010
MEP, cmH_2O	**0.482***	0.387	0.317	0.307
MIP, %	**0.439***	**0.548****	0.339	0.030
MEP, %	**0.546****	**0.442***	0.349	0.369
BMI, kg/m^2	-0.024	-0.100	-0.062	-0.133
Fat mass, kg	-0.049	-0.206	-0.175	-0.209
Fat mass percent, %	-0.170	0.016	-0.108	-0.222
Fat free mass, kg	-0.272	-0.145	-0.147	-0.199
Pulmonary functions, %				
FVC	0.140	0.127	0.086	-0.043
FEV_1	0.165	0.335	0.032	-0.091
PEF	0.037	0.060	0.069	-0.211

MIP, Maximal inspiratory pressure; MEP, Maximal expiratory pressure; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; FEV_1/FVC, Forced expiratory volume in the first second/forced vital capacity; PEF, Peak expiratory flow; FEF_{25-75}%, Forced expiratory flow from 25% to 75%; cmH_2O, centimeter water; D, Dominant; ND, Non-Dominant; s, sec

**p≤0.05,*

***p≤0.01*

Table 4. The Results Of Linear Regression Analysis

Model	Model		B	β	P
	R(Adjusted R^2)	R^2 significance (p)			
Model 1	0.592 (0.314)	0.006*			
MEP			0.720	0.592	0.006*
Model 2	0.764 (0.534)	0.001*			
MEP			0.619	0.509	0.005*
Endurance, cmH_2Oxs			0.001	0.490	0.007*

MIP, Maximal inspiratory pressure; MEP, Maximal expiratory pressure; cmH_2O, centimeter water; s, sec

Discussion

This study first revealed the association between core muscle endurance and respiratory muscle function in handball players. Consistent with our hypothesis, our results showed that the wall sit hold core endurance test (D), which is an effective test to especially demonstrate fatigue of lumbopelvic, hip, and lower extremities significantly related to inspiratory and expiratory muscle strength and respiratory muscle endurance. In addition, the respiratory muscle endurance and expiratory muscle strength values (53.4%, p=0.001) have a significant influence on core muscle endurance.

Handball is a known sport containing high-level aerobic and anaerobic components and requiring various motor abilities such as endurance, strength, substantial throwing velocity and power, and speed (6). It is critical for handball players to have an elevated level of endurance capacity during prolonged training and competitions (17). In addition, better aerobic endurance and athletic performance are related to improved core muscle endurance (7). On the other hand, respiratory muscle fatigue also mutually affects performance in athletes (1). Diaphragm, one of the core stability muscles, provides postural stability by modulating intra-abdominal pressure and is also a respiratory muscle that has a pivotal role in maintaining respiratory function (18). The intra-abdominal pressure modulation supports the connection of breathing-postural control and maintaining extremity movement in a controlled manner (5). The respiratory function and core muscle endurance have important effects in enhancing performance in athle-

tes; therefore, there is a need to better explain the cooperation of core-respiratory muscle endurance due to insufficient data. In our study, core endurance tests, including unilateral wall sit hold, trunk flexion, and horizontal trunk hold tests, which are frequently used in athletes for injury risk monitoring, were performed (10, 19). According to the results of the wall sit hold test (D), there was positive moderate-strong relationship between core muscle endurance and respiratory muscle endurance and strength in the current study. It was also observed that respiratory performance including respiratory muscle endurance and expiratory muscle endurance had a high impact on core muscle endurance (53.4%). However, core endurance test results for non-dominant extremity were related only to respiratory muscle strength. Considering other core endurance test results, there was no relationship between core endurance and respiratory performance in this study.

The wall sit test was commonly used to evaluate the lumbopelvic-hip and lower extremity stability in previous studies (10, 19). In addition, Chimera et al. (19) found that decreased wall sit hold test duration is related to reduced trunk stability, core endurance, and performance. Given that our respiratory performance test results are related to the results of the wall sit test, it was thought that the possibility of more functional effort of the diaphragm may be required to provide better lower pelvic and limb stabilization. Beales et al. (20) emphasized that functional load transfer is achieved between the trunk and pelvis in the "Active Straight Leg Raise" test, thanks to the internal stability provided by intra-abdominal pressure. Based on this study, a possible explanation for the relationship between core and respiratory endurance in our study, the role of the diaphragm in maintaining the balance between intra-abdominal and thoracic pressure may be increasing to provide better lower extremity stabilization. However, large-scale studies are needed to reach more definitive inferences.

Yuksel et al. (21) found a relationship between trunk muscle endurance, dynamic lung volumes, and respiratory muscle strength in healthy individuals. Our study has similar and different aspects to this study. Unlike this study, no significant relationship between dynamic lung volumes, body compositions, and core muscle endurance in our research. A possible explanation for the difference could be that the included sample and the methods, especially core endurance tests applied in the mentioned study, are different from our study. In addition, pulmonary functions may be affected by individual differences such as age and gender. On the other hand, both studies emphasize the association between respiratory muscle strength and core muscle endurance.

Our study additionally reveals the positive relationship between respiratory and core muscle endurance with effective results in players. Respiratory-core endurance cooperation was also emphasized in a recent study (22) that evaluated the relationship between respiratory and trunk muscle endurance in healthy individuals with different assessment tools and methods than our study. Although there are not enough studies examining the respiratory-core connection in athletes, intervention studies are proving that inspiratory and core muscle training improves athletic performance. Tong et al. (23) focused on the effects of functional inspiratory and core muscle training to enhance running performance. Mackala et al. (24) found the positive effect of inspiratory muscle training using inspiratory muscle trainers on aerobic endurance in young soccer players. Saeterbakken et al. (25) emphasized that core stability training improves throwing velocity in handball players. Furthermore, some previous studies found that decreased diaphragm function causes deteriorated movement control and ability, postural control, and balance (26-28). Given the clear contribution of respiratory and core muscle training on athletic performance, increasing interventions to improve diaphragm function in athletes' training programs is vital. On the other hand, Hubscher et al. (29) emphasized that core and lower extremity neuromuscular control which enhances balance, strength, and endurance, contributes to reducing injury rates. Future studies should focus on the effect of better respiratory-core cooperation on injury rates.

The limitation of this study is that more athletes could not be included to reach over 80 percent power because only one elite female handball team with the same training level and program could be reached.

Conclusion

This study reveals the relationship between core endurance and respiratory performance in elite female handball players. Because of the interrelation between respiratory-core muscle endurance and both contributions to athletic performance, we think that the evaluation of respiratory muscle functions and inclusion of respiratory and core muscle training will enrich the athlete training program.

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Araştırma Makalesi / Research Article

Ultrason Eşliğinde Yapılan Popliteal Arter ve Diz Kapsülü Arası İnfiltrasyon Bloğu (IPACK) için Hangi Pozisyon En İdealdir?

Which USG Guided Position is The Most Ideal For The Infiltration Block Between The Popliteal Artery and Capsule of Knee (IPACK) ?

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Öz

Amaç: IPACK blok diz arka kapsülü ile popliteal arter arasına lokal anestezik enjeksiyon yöntemi ile siyatik sinirin derin diz dallarını etkilemeyi amaçlar. Bu blokla dizin motor fonksiyonları korunarak ağrı azaltılır. Çalışmamızda prone, supine ve kurbağa bacağı (fleksiyon, abduksiyon) pozisyonunda usg ile ölçümler yaparak blok için en ideal pozisyonu tespit etmek ve bu pozisyonlarda görüntü kalitesini tespit etmeyi amaçladık. Çalışmamızda farklı hasta pozisyonlarının IPACK blok uygulamasındaki etkinliği ve görüntü kalitesine etkisi araştırılmıştır.
Materyal ve metod: Gönüllülere prone, supine ve kurbağa bacağı (fleksiyon, abduksiyon) pozisyonu verildi ve USG ile popliteal arter ve diz kapsülü mesafelerinin cilde olan uzaklığı ölçüldü, kayıt edildi. Görüntü kaliteleri çok kötü, kötü, vasat, iyi, çok iyi olmak üzere beş kategoriye ayrıldı ve kayıt edildi.
Bulgular: Çalışmamızda popliteal arter mesafe ölçümümüz prone pozisyonda cilde en yakındı (p<0,01). Diz kapsülü mesafe ölçümlerimizde kurbağa bacağı pozisyonu cilde en yakın olarak ölçüldü (p<0,01). En kaliteli görüntü prone pozisyonda tespit edildi (p<0,01). Vücut kitle indeksi (VKİ) ile görüntü kalitesi arasında negatif yönlü zayıf ilişki tespit ettik (VKİ arttıkça görüntü kalitesi düşen) (p<0,05).
Sonuç: IPACK blok için prone pozisyonun popliteal arter mesafesi ve görüntü kalitesi açısından en uygun pozisyon olduğunu tespit ettik. Hastaya özel durumlar ve ek blok uygulama ihtiyacı nedeniyle farklı pozisyonlar da tercih edilebilir. Farklı USG prob ve pozisyonlarda geniş ve ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ipack blok, Postoperatif Analjezi, USG, Sinir Bloğu

Abstract

Background: IPACK block aims to affect the deep knee branches of the sciatic nevre by local anesthetic injection between the posterior knee capsule and the popliteal artery. With this block, pain is reduced by preserving the motor functions of the knee. In our study, we aimed to determine the most ideal position for the block by making USG measurements in prone, supine and frogleg (flexion, abduction) positions and to determine the image quality in these positions. In our study, the effectiveness of different patient positions in IPACK block applying and their effects on image quality were investigated.
Materials and Methods: Volunteers were given prone, supine and frog-leg (flexion, abduction) positions, and the distance of the popliteal artery and knee capsule to the skin was measured and recorded using USG. Image quality was divided into five categories: verybad, bad, mediocre, good and very good and recorded.
Results: In our study, our popliteal artery distance measurement was closest to the skin in the prone position (p<0,01). In our knee capsule distance measurements, the frog-leg position was measured closest to the skin (p<0,01). The best quality image was detected in the prone position (p<0,01). We detected a weak negative relationship between body mass index (BMI) and image quality (p<0,05).
Conclusions: We found that the prone position for IPACK block is the mosta ppropriate position in terms of popliteal artery distance and image quality. Different positions may be preferred due to patient-specific conditions and the need for additional block application. Large and further studies are needed with different USG probes and positions.

Keywords: Ipack block, postoperative analgesia, USG, nerve block

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Giriş

Diz operasyonları kronik eklem dejenerasyonları ya da travma sonucu olan patolojileri gidererek diz eklemine tekrar eski fonksiyonunu kazandırmayı amaçlar. Bu tür operasyonlarda, ağrı kontrolü için çeşitli yöntemler kullanılmaktadır, bunlar arasında oral ve sistemik ilaçlar, eklemin içine ilaç enjeksiyonu, periferik sinir bloğu teknikleri bulunmaktadır.

Femoral sinir bloğu, siyatik sinir bloğu ve lomber pleksus bloğu gibi çeşitli seçenekler bulunmaktadır. Femoral sinir, dizin ön yüzünün duyusunu ileten en büyük lomber pleksus dalıdır, siyatik sinir ise dizin arka yüzünün duyusunu sağlar. Bu nedenle, dizdeki ağrı kontrolü için femoral sinir bloğuyla birlikte siyatik sinir bloğu uygulanmaktadır (1).

Femoral sinir bloğu, kuadriseps adı verilen ön bacak kaslarına etki edebilirken, siyatik sinir bloğu ise alt bacakta derin kas güçsüzlüğüne yol açabilir. Femoral sinirin ön dalı diz eklemine duyu salları gönderse de dizin arka yüzündeki postoperatif ağrıyı femoral veya adduktor kanal bloğu ile engellemek mümkün değildir. Bu nedenle, siyatik sinir bloğu, bu bölgenin büyük bölümünün analjezisini sağlarken aynı zamanda alt bacak ve ayakta derin motor duyuyu da engelleyebilir. Adduktor kanal bloğu (ACB), femoral üçgenin tepesinden addüktör açıklığa kadar uzanan bir musküloapenörotik kanalı hedefler. ACB anestetize edilebilecek tek motor sinir vastus medialis siniridir. Bu nedenle ACB, minimal motor blokaj ile daha çok duysal blokaj sağlar. ACB, femoral sinir bloğu (FNB) ile kıyaslandığında daha az quadriseps zayıflığına neden olur. Ayrıca ACB, erken mobilizasyon ve hastanın daha erken taburcu olabilmesine katkı sağlar(2).

IPACK (interspace between the popliteal artery and the capsule of the posterior knee) blok, postoperatif diz ağrısını kontrol etmek için kullanılan bir tekniktir. İlk olarak 2012 yılında MD Sanjay Sinha tarafından tanıtılan bu blok, popliteal arter ile dizin arka kapsülü arasına lokal anestezik enjeksiyonunu içerir (3). Bu teknik, derin geniküler sinirleri bloke etmeyi amaçlar. Bu nedenle motor blok yapmaz ve kas gücünü kaybetmez. Bu da hastaların daha erken iyileşmesine ve rehabilitasyonuna olanak tanır (4).

İğne, popliteal arter ile femoral şaft arasında doğru bir düzlemde yerleştirilir ve popliteal arteri 2 cm kadar geçecek şekilde ileri doğru yönlendirilir. Son olarak, lokal anestezik popliteal arter ile femur arasına eşit bir şekilde ve yavaşça enjekte edilir.

Çalışmamızda farklı hasta pozisyonlarının IPACK blok uygulamasındaki etkinliği ve görüntü kalitesine etkisi araştırılmıştır. USG rehberliğinde hastalara verilen farklı pozisyonlarla ve mesafe ölçümleri en güvenilir ve en kolay IPACK blok uygulama şeklini tespit etmeyi ve en iyi görüntü kalitesine ulaşmayı amaçladık.

Materyal ve Metod

Çalışmamıza Harran Üniversitesi Tıp Fakültesi 09.01.2023 tarih 01 sayı 23.01.12 numaralı etik kurulu' nun kararı ile onay alınarak başlanmıştır. Çalışma katılımcılarına araştırmanın amacı ve yöntemi hakkında detaylı bilgi verilmiş olup, yazılı ve sözlü olarak bilgilendirilmiş onam alınmıştır. Çalışma, evrensel etik kurallara ve Helsinki Deklarasyonu'na uygun olarak yürütülmüştür.

Bu çalışmaya alt ekstremitede hareket kısıtlılığı olmayan, çalışma yapılacak bölgede travma, cerrahi işlem, yanık skarı olmayan ve aktif enfeksiyonu olmayan, Body Mass İndeks (BMI)<35 olan 18 – 65 yaş arası sağlıklı gönüllüler ve çalışmaya katılmayı kabul eden hastalardan 100 kişi dahil edildi. Hastaların demografik özellikleri kaydedildi ve Ultrason cihazının (Esaote My Lab 30 Gold (ABD)] yüksek frekanslı doğrusal probu ile görüntülemeler yapıldı. Hastalara sedye üzerinde prone, supine (diz 45 derece fleksiyon), kurbağa bacağı (fleksiyon, abduksiyon) pozisyon verilerek popliteal arter ve diz kapsülü görüntülendi. Popliteal arter saat 6 hizası ile diz kapsülü mesafesinin cilde olan uzaklıkların ölçümleri yapılıp kayıt edildi.

Ölçüm alınan bölgelerdeki görüntü kalitesi; Çok kötü: 1, Kötü: 2, Vasat: 3, İyi: 4, Çok iyi: 5 olarak kaydedildi. Mesafe ölçümlerini etkilememek adına cilde aynı ölçüde baskı uygulanmaya çalışıldı, ölçümler ve görüntü kalitesi değerlendirmeleri aynı araştırmacı tarafından yapıldı.

İstatistiksel analizler için SPSS 26 programı kullanıldı. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel metodlar kullanıldı. Nicel verilerin normal dağılıma uygunlukları Kolmogorov-Smirnov ve Shapiro-Wilk testi ve grafiksel incelemeler ile sınanmıştır. Normal dağılım gösteren üç ve üzeri sayıdaki bağımlı nicel değişkenin karşılaştırmalarında tekrarlı ölçümler varyans analizi ve ikili karşılaştırmaların değerlendirmelerinde Bonferroni düzeltmeli ikili değerlendirmeler kullanıldı. Normal dağılım göstermeyen iki bağımlı nicel değişkenin karşılaştırmalarında Wilcoxonsigned-ranks test kullanıldı. Normal dağılım göstermeyen üç ve üzeri sayıdaki bağımlı nicel değişkenin grup içi karşılaştırmalarında Friedman Test ve ikili karşılaştırmaların değerlendirilmesinde Bonferroni düzeltmeli Dunn test kullanıldı. Nicel değişkenler arası ilişkilerin değerlendirilmesinde Pearsonkorelasyon analizi ve Spearman korelasyon analizi kullanıldı. İstatistiksel anlamlılık $p<0,05$ olarak kabul edildi.

Bulgular

Çalışma Ocak-Aralık 2023 tarihleri arasında Üniversitemiz Tıp Fakültesi Hastanesinde %41'i (n=41) kadın, %59'u (n=59) erkek toplam 100 olguyla yapılmıştır. Çalışmaya katılan olguların yaşları 18 ile 65 arasında değişmekte olup, ortalama 38,58±12,53 yaş olarak saptanmıştır (Tablo 1).

Olguların vücut kitle indeksi ölçümleri 18,1 ile 35 kg/m^2 arasında değişmekte olup, ortalama 27,18±4,55 kg/m^2 olarak saptanmıştır. VKİ 18-24,9 kg/m^2 arası normal kilolu, 25-29,9 kg/m^2 arası fazla kilolu, 30-35 kg/m^2 arası obez olarak kategorize edildi. Olguların %34'ünün (n=34) kilosunun normal olduğu gözlenirken, %36'sının (n=36) fazla kilolu, %30'unun (n=30) ise obez olduğu gözlenmiştir (Tablo 1).

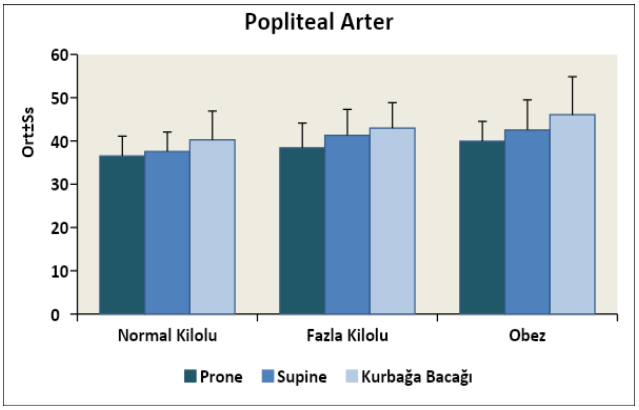
Tablo 1. Demografik Özelliklerin Dağılımı

Yaş	*Ort±Ss*	38,58±12,53
	Medyan (Min-Maks)	36,5 (18-65)
Cinsiyet	**Kadın**	41 (41,0)
	Erkek	59 (59,0)
VKİ	*Ort±Ss*	27,18±4,55
	Medyan (Min-Maks)	26,9 (18,1-35,2)
	Normal Kilolu	34 (34,0)
	Fazla Kilolu	36 (36,0)
	Obez	30 (30,0)

Pozisyonlara göre olguların popliteal arter mesafe ölçümleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır (p<0,01). Cilde olan uzaklık prone pozisyonda en kısa, kurbağa bacağı pozisyonunda en uzun olarak tespit edildi (p<0,01). Pozisyonlara göre olguların diz kapsülü mesafe ölçümleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır (p<0,01). Cilde olan uzaklık en kısa Kurbağa bacağı(p<0,01), en uzun supine pozisyonda tespit edildi(p<0,05), (Tablo 2).

Kurbağa bacağı pozisyonundaki olguların görüntü kalitesi, prone ve supine pozisyonundaki olgulara göre anlamlı düzeyde düşük saptanmıştır (p<0,01).(Tablo 3)

Pozisyonlara göre normal kilolu, fazla kilolu ve obez BMI gruplarında da olguların popliteal arter mesafe ölçümleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır. Her üç grupta da cilde en yakın mesafe prone (p<0,01) en uzak mesafe kurbağa bacağı olarak tespit edilmiştir (p<0,05), (Tablo 3, Şekil 1).



Şekil 1. Vücut Kitle İndekslerine Göre Pozisyonlardaki Popliteal Arter Mesafe Dağılımı

Tablo 2. Pozisyonlara Göre Popliteal Arter ve Diz Kapsülü Mesafe Ölçümlerinin Değerlendirilmesi

		Prone	Supine	Kurbağa Bacağı	*p*
Popliteal Arter	*Ort±Ss*	38,23±5,39	40,41±6,21	42,97±7,21	***[a]0,001***
	Medyan (Min- Maks)	38,5 (22,1-55,6)	40,8 (26,5-59,1)	42,7 (22,9-74,1)	
Diz Kapsülü	*Ort±Ss*	49,62±7,05	51,91±7,39	41,06±9,49	***[a]0,001***
	Medyan (Min-Maks)	49,8 (33,2-72,4)	52,1 (33,9-70,7)	38,9 (25,2-71,3)	
Görüntü Kalitesi	**Çok Kötü**	0 (0,0)	0 (0,0)	1 (1,0)	
	Kötü	1 (1,0)	3 (3,0)	1 (1,0)	
	Vasat	7 (7,0)	6 (6,0)	16 (16,0)	
	İyi	34 (34,0)	41 (41,0)	51 (51,0)	
	Çok İyi	58 (58,0)	50 (50,0)	31 (31,0)	
	Medyan (Q1-Q3)	4,0 (3-4)	3,5 (3-4)	3,0 (3-4)	***[b]0,001***

*[a]RepeatedMeasure&Bonferroni Test [b]Friedman's Test **p<0,01*

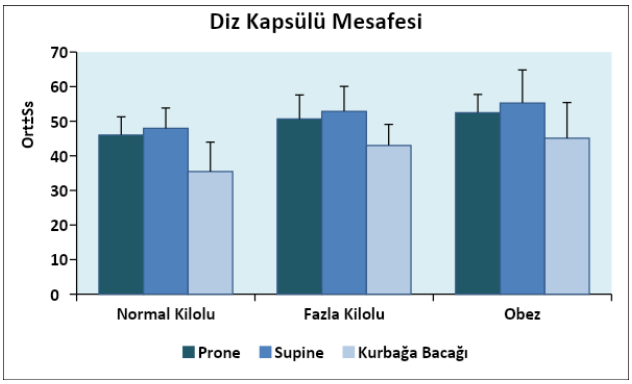
Pozisyonlara göre normal kilolu, fazla kilolu ve obez olguların diz kapsülü mesafe ölçümleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır (p<0,01). Kurbağa bacağı pozisyondaki olguların diz kapsülü mesafe değerinin cilde en yakın (p<0,01), supine pozisyonundaki olguların cilde en uzak olması anlamlı bulunmuştur (p<0,01), (Tablo 3, Şekil 2).

Pozisyonlara göre normal kilolu, fazla kilolu ve obez olguların görüntü kaliteleri arasında istatistiksel olarak anlamlı farklılık saptanmıştır (p<0,05). Kurbağa bacağı pozisyonundaki olguların görüntü kalitesi, prone ve supine pozisyonundaki olgulara göre anlamlı düzeyde düşük saptanmıştır (p<0,05), (Tablo 3, Şekil 3).

Olguların vücut kitle indeksi ile supine pozisyonda diz kapsülü mesafe ölçümleri arasında pozitif yönlü (VKİ arttıkça diz kapsülü değeri artan) 0,440'lık orta düzeydeki ilişki istatistiksel olarak anlamlı bulunmuştur (r=0,440; p<0,01), (Tablo 3).

Olguların vücut kitle indeksi ile prone ve kurbağa bacağı pozisyonlarında diz kapsülü mesafe ölçümleri arasında pozitif yönlü (VKİ arttıkça diz kapsülü değeri artan) zayıf ilişki istatistiksel olarak anlamlı bulunmuştur (r=0,395; p<0,01), (Tablo 3).

Olguların vücut kitle indeksleri ile prone (r=-0,276; p<0,01), supine (r=-0,389; p<0,01) ve kurbağa bacağı (r=-0,207; p<0,05) pozisyonlarındaki görüntü kalite düzeyleri arasında negatif yönlü (VKI arttıkça görüntü kalitesi düşen) zayıf ilişki istatistiksel olarak anlamlı bulunmuştur (Tablo 3, Şekil 3).



Şekil 2. Vücut Kitle İndekslerine Göre Pozisyonlardaki Diz Kapsülü Mesafesi Dağılımı

Tablo 3. BMI gruplarında; Pozisyonlara Göre Popliteal Arter ve Diz Kapsülü Mesafe Ölçümlerinin Değerlendirilmesi

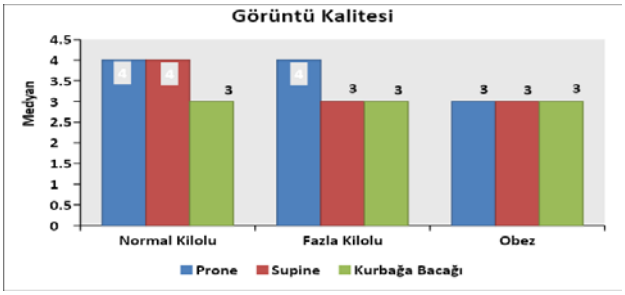
		Prone[1]	Supine[2]	Kurbağa Bacağı[3]	*p/Post Hoc*
Popliteal Arter					
Normal Kilolu	*Ort±Ss*	36,52±4,59	37,57±5,74	40,26±4,60	***[a]0,002***
	Medyan (Min-Maks)	36,1 (22,1-43,4)	36,9 (27,3-51)	40,3 (31-51)	***3>1-2***
Fazla Kilolu	*Ort±Ss*	38,41±4,48	41,30±6,02	42,95±6,92	***[a]0,001****
	Medyan (Min-Maks)	38,5 (30-52,4)	41,9 (26,5-51,7)	43 (25,3-55,6)	***1<2-3***
Obez	*Ort±Ss*	39,94±6,66	42,54±5,92	46,07±8,79	***[a]0,018****
	Medyan (Min-Maks)	39,1 (26,9-55,6)	41,7 (28-59,1)	45,6 (22,9-74,1)	***1<3***
Diz Kapsülü					
Normal Kilolu	*Ort±Ss*	46,03±5,24	47,95±6,95	35,44±5,24	***[a]0,001****
	Medyan (Min-Maks)	47,1 (34,3-57)	47,1 (33,9-63)	35,2 (26,7-50)	***3<1-2***
Fazla Kilolu	*Ort±Ss*	50,64±5,87	52,86±7,22	43,01±9,58	***[a]0,001****
	Medyan (Min-Maks)	50,1 (38,8-67,1)	53,6 (35,7-66,6)	41 (25,2-66,9)	***3<1-2***
Obez	*Ort±Ss*	52,47±8,49	55,27±6,10	45,08±10,35	***[a]0,001****
	Medyan (Min-Maks)	52,2 (33,2-72,4)	55,9 (43,8-70,7)	41,7 (33,3-71,3)	***3<1-2***
Görüntü Kalitesi					
Normal Kilolu	**Çok Kötü**	0	0	0	
	Kötü	0	0	0	
	Vasat	2 (5,9)	1 (2,9)	2 (5,9)	
	İyi	6 (17,6)	8 (23,5)	19 (55,9)	
	Çok İyi	26 (76,5)	25 (73,5)	13 (38,2)	
	Medyan (Q1-Q3)	4,0 (4,0-4,0)	4,0 (3,0-4,0)	3,0 (3,0-4,0)	***[b]0,001****
					3<1-2
Fazla Kilolu	**Çok Kötü**	0	0	0	
	Kötü	0	0	0	
	Vasat	1 (2,8)	4 (11,1)	7 (19,4)	
	İyi	16 (44,4)	19 (52,8)	20 (55,6)	
	Çok İyi	19 (52,8)	13 (36,1)	9 (25,0)	
	Medyan (Q1-Q3)	4,0 (3,0-4,0)	3,0 (3,0-4,0)	3,0 (3,0-3,5)	***[b]0,002****
					3<1
Obez	**Çok Kötü**	0	0	1 (3,3)	
	Kötü	1 (3,3)	3 (10,0)	1 (3,3)	
	Vasat	4 (13,3)	1 (3,3)	7 (23,3)	
	İyi	12 (40,0)	14 (46,7)	12 (40,0)	
	Çok İyi	13 (43,3)	12 (40,0)	9 (30,0)	
	Medyan (Q1-Q3)	3,0 (3,0-4,0)	3,0 (3,0-3,5)	3,0 (2,0-4,0)	***[b]0,023****
					3<1

*[a]RepeatedMeasure&Bonferroni Test [b]Friedman's Test **p<0,01*

Tablo 4. Pozisyon ve Bölgelere Göre Mesafe Ölçümlerinin Yaş ve VKI Ölçümleri Arasındaki İlişkinin Değerlendirilmesi

		Yaş		VKI	
		R	***P***	**R**	***p***
Popliteal Arter	**Prone**	0,120[c]	***0,233***	0,297[c]	***0,003****
	Supine	0,041[c]	***0,683***	0,385[c]	***0,001****
	Kurbağa Bacağı	0,277[c]	***0,005****	0,312[c]	***0,002****
Diz Kapsülü	**Prone**	0,241[c]	***0,016****	0,395[c]	***0,001****
	Supine	0,158[c]	***0,116***	0,440[c]	***0,001****
	Kurbağa Bacağı	0,214[c]	***0,032****	0,379[c]	***0,001****
Görüntü Kalitesi	**Prone**	-0,061[d]	***0,548***	-0,276[d]	***0,005****
	Supine	-0,054[d]	***0,591***	-0,389[d]	***0,001****
	Kurbağa Bacağı	0,026[d]	***0,800***	-0,207[d]	***0,039****

*[c]r=Pearson Korelasyon Katsayısı [d]r=Spearman's Korelasyon Katsayısı*p<0,05 **p<0,01*



Şekil 3. Vücut Kitle İndekslerine Göre Pozisyonlardaki Görüntü Kalitesi Düzeylerinin Dağılımı

Tartışma

Dünya üzerinde yaşlı nüfusun artmasıyla birlikte osteoartrit, insidansı artan bir hastalık haline gelmiştir. Osteoartrit, şiddetli diz ağrılarına yol açabilir ve hastaların günlük yaşamlarını kısıtlayabilir. Total Diz Replasmanı (TDR), bu hastalar için en sık tercih edilen cerrahi yöntemdir (5).

Postoperatif süreçte, etkili bir ağrı kontrolü için multimodal bir analjezik rejimi belirlenmelidir. Günümüzde ultrasonografi (USG) kullanımının artmasıyla, analjezik amaçla yapılan

lokalanestezik enjeksiyonlarının etkinliği ve güvenilirliği artmıştır. Bu nedenle, diz eklemi innervasyonunda birçok sinir ve terminal dalın rol alması sebebiyle, çeşitli periferik sinir blokları ve kombinasyonları analjezi ve etkinlik açısından karşılaştırılmıştır (6).Rejyonel anestezinin genel anesteziye kıyasla sistemik ve kardiyak fonksiyonları daha az etkilemesi, uzun süreli analjezik etkinlik göstermesi, minimum aspirasyon riski taşıması, yüksek hasta konforu sağlaması gibi avantajları nedeniyle rejyonel anestezinin popülerliği giderek artmaktadır (7).

MD Sanjay Sinha tarafından açıklanan IPACK (interspace between the popliteal arter and the capsule of the knee) blok, ultrason eşliğinde uygulanan bir sinir bloğu tekniğidir. Bu teknik, lokal anestezik infüzyonuyla arka diz ağrısını kontrol etmeyi amaçlar. IPACK bloğunun özelliği, siyatik sinirin sadece terminal dallarını etkileyerek, motor blok oluşturmadan, düşük ayak insidansını azaltarak ağrı kontrolü sağlamaktır (8).

Literatürde IPACK blokla ilgili bizim çalışmamıza benzer çalışma bulamadık farklı periferik sinir bloklarıyla ilgili az sayıda çalışma olduğunu gördük. Çalışmamızda yaş ve VKİ' nin farklı pozisyonlardaki mesafelere ve görüntü kalitesi üzerine etkilerini de inceledik.

USG ve sinir stimülatörlerinin kullanılmaya başlanmasıyla birlikte, periferik sinir blokları daha güvenli bir şekilde uygulanabilir hale gelmiştir. Bu yaklaşım, iğnenin gidiş yönünün görülmesini sağlar, daha düşük hacimde lokal anestezik kullanımına izin verir ve bu nedenle komplikasyon oranını düşürerek daha güvenli bir uygulama imkanı sunar (9).

Biehl ve arkadaşlarının gerçekleştirdiği retrospektif çalışmada, ameliyat günü ağrı skorları açısından addüktör kompartman bloğu (ACB) ve iPACK veya femoral sinir bloğu ve iPACK yapılan hastaların, ağrı skorları yapılmayanlara göre daha düşük olduğu bulunmuştur. (10).

Chan Edmund ve arkadaşlarının yaptığı çalışmada, diz operasyonu geçiren hastalarda iPACK bloğunun potansiyel olarak ACB'yi tamamlayıcı nitelikte olduğu ve motor fonksiyonu koruyucu bir teknik olarak tanımlandığı belirtilmiştir (11).

Sankineani ve arkadaşlarının yaptığı çalışmada, ACB'ye IPACK eklenen grupta IPACK uygulanmayan gruba göre total diz artroplastisi (TDA) sonrasında artmış hareket açıklığı, yürüme mesafesinde artış ve VAS skorlarında azalma tespit edilmiştir (12).

Thobhani ve arkadaşlarının yaptığı çalışmada, total diz artroplastisi (TDA) uygulanan hastalarda FNB (femoral sinir bloğu), IPACK ile FNB ve IPACK ile ACB tekniklerini karşılaştırmışlardır. Bu çalışmada, IPACK ile FNB bloğu uygulanan gurupta opioid tüketiminin anlamlı şekilde azaldığı sonucuna varılmıştır. IPACK ile ACB uygulanan gurupta fizik tedavi sırasında en uzun yürüyüş mesafeleri elde edilmiş ve yine bu gurupta hastanede kalış süresi en kısa olarak tespit edilmiştir (8).

Tran ve arkadaşları tarafından gerçekleştirilen kadavra çalışmasında, USG rehberliğinde IPACK bölgesine 10 ml metilen mavisi uygulanmıştır. Daha sonra, sinir boyaması gözlemlenmiştir. Elde edilen sonuçlar, enjekte edilen maddenin popliteal bölgedeki birçok artiküler sinir dalına yayılmasının yanı sıra, anterior yayılımı göstermiştir. Bu çalışmanın bulguları, IPACK bloğunun hem posterior hem de anterior dizde analjezik etkinliğini desteklemektedir (13).

IPACK blok ilk tanımlandığında prone pozisyon ve posterior akustik pencereden uygulanmış zamanla, IPACK enjeksiyonu tekniği hasta sırt üstü pozisyondayken ve posteromedial akustik pencereden tarama yaparak gerçekleştirmeye yönelik olarak değişim göstermiştir. IPACK genellikle addüktör kanal bloğu veya femoral sinir bloğu ile birleştirildiğinden, mevcut teknik farklı bloklar için birden fazla hazırlık veya örtme ve konum değişikliğini önlemektedir (3). Blok prone ya da supine pozisyonlarda başarıyla uygulanabilir ancak kombine edilecek bloğa göre pozisyon verilmesi hasta açısından ve sterilizasyon teknikleri açısından dikkate alınmalıdır.

Çalışmamıza benzer bir çalışma, Binici ve arkadaşları tarafından yapılmıştır (14). Bu çalışma, transversus abdominis plan (TAP) bloğu üzerinedir. Binici ve arkadaşları, hangi bölgeden TAP bloğunun uygulanması gerektiğini araştırmışlardır. Krista iliyaka seviyesinden yapılan ölçümlerde, ön aksiler hattan yapılan ölçümlerin orta aksiler hattan yapılan ölçümlere göre daha düşük çıktığını bulmuşlardır. Kosta altı bölgeden yapılan ölçümlerde ise internal oblik kası ve transversus abdominis fasyasının ölçümlerinin, yine orta aksiler hatta göre daha düşük seviyede olduğunu rapor etmişlerdir.

Duran ve arkadaşları femoral sinir bloğu için benzer bir çalışma yapmışlar alt ekstremiteyi nötral, 45 derece abduksiyon ve diz fleksiyonu olmak üzere üç farklı pozisyonda incelemişler ve supine diz fleksiyon pozisyonunu femoral blok için ideal olarak tespit etmişlerdir (15).

Benzer başka bir çalışma Zaragoza ve arkadaşları tarafından gerçekleştirilmiştir. Bu çalışmada, kola verilen açı ile ultrasonografi (USG) görüntüsünün kalitesi arasındaki ilişkiyi incelemişlerdir. Yaptıkları gözlemlere göre, kola verilen açı arttıkça (90 derecede), USG görüntü kalitesinin en iyi olduğunu belirtmişlerdir. Ayrıca, kol açısı 0 derece olduğunda ise USG görüntü kalitesinin en düşük olduğunu ifade etmişlerdir (16).

Biz çalışmamızda lineer probla en net görüntüyü prone pozisyonda elde ettik. Görüntü kalitemiz kurbağa bacağı pozisyonunda en düşük olarak tespit edildi (Tablo 2). Görüntü kalitemiz VKİ gruplarına göre değerlendirdiğimizde VKİ arttıkça görüntü kalitesinin negatif yönde etkilendiği zayıf bir ilişki tespit ettik bu nedenle ileri araştırma yapılmasına ihtiyaç vardır. (Tablo 3, Şekil 3) Yaş ile görüntü kalitesi arasında anlamlı bir ilişki tespit etmedik. Yaşın artması ya da azalmasının çalışmamıza bir etkisi olmadı (Tablo 4).

Başka bir çalışmada, Ruíz ve arkadaşları, infraklaviküler blok uyguladıkları hastalarda kola verdikleri abduksiyon açısını düşükten yükseğe doğru değiştirdiklerinde, brakial pleksusun cilde yakınlaştığını gözlemlemişlerdir (17). Bizde çalışmamızda popliteal arter mesafesinin cilde en yakın olduğu

pozisyonu prone pozisyon olarak tespit ettik. Sonra sırayla supine ve kurbağa bacağı pozisyonunu tespit ettik (Tablo 2). Çalışmamızda demografik verilerimizden olan yaş ile popliteal arter mesafelerimizde prone ve supine pozisyonda bir ilişki saptamadık. Kurbağa bacağı pozisyonunda yaşla beraber artan popliteal arter mesafesi arasında zayıf bir ilişki tespit ettik. Diz kapsülü mesafe ölçümlerimizde yaşla ilgili supine pozisyonda bir ilişki bulamazken prone ve kurbağa bacağı pozisyonunda yaşla artan zayıf ilişki tespit ettik (Tablo 4).

Çalışmamızda VKİ yi normal kilolu, fazla kilolu ve obez olarak sınıflara ayırdık ve mesafe ölçümlerimiz beklediğimiz üzere VKİ arttıkça referans noktalarının cilde olan uzaklığı arttı. Pozisyonlara göre baktığımızda tüm VKİ gruplarında popliteal arter mesafe ölçümlerimiz prone pozisyonda en düşük kurbağa bacağı pozisyonunda anlamlı derecede en yüksek olarak ölçüldü (Tablo 3, Şekil 1).

Diz kapsülü mesafemiz ise VKİ kategorilere göre her kategoride kurbağa bacağı pozisyonunda en düşük supine pozisyonunda en yüksek olarak tespit edildi. Biz kurbağa bacağı pozisyonunda ölçümümüzü blok tekniğine uygun olarak, postero-medial akustik pencereden yaptık usg probunu diğer pozisyonlarda popliteal fossaya yerleştirdik ve ölçümlerimizi posterior akustik pencereden yaptık. Bu nedenle diz kapsülü mesafemizi kurbağa bacağı pozisyonunda cilde daha yakın olarak tespit ettik (Tablo 3, Şekil 2).

Biz çalışmamızda ölçümlerde farklılıklar olmaması ve görüntü kalitesi etkilenmemesi için aynı pozisyonlar vermeye, dokulara aynı şiddette basınç uygulamaya ve farklılıkları engellemek adına tüm ölçümlerin aynı araştırmacı tarafından yapılmasına özen gösterdik.

Sonuç olarak araştırmalarımızda IPACK blok için bizim çalışmamıza benzer bir çalışmaya rastlamadık. Popliteal arter mesafelerimizin en yakın ve görüntü kalitesi en yüksek olması nedeniyle prone pozisyonun bu blok için en uygun pozisyon olduğu sonucuna vardık. Tamamlayıcı farklı bloklar (ACB, FNB) eklenecek ise tekrar pozisyon değiştirip sterilizasyon zorlukları ile uğraşmamak adına supine pozisyonda bu blok uygulanabilir. En uygun pozisyon tespiti ve en iyi görüntü kalitesi elde etmek için farklı usg problarıyla, daha geniş örneklem gruplarıyla daha fazla klinik araştırmaya gerek duyulmaktadır. Farklı bloklar için de benzer araştırmalar yapılabilir.

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Research Article / Araştırma Makalesi

Management of Gallbladder Perforation: A Single Center Clinical Experience

Safra Kesesi Perforasyonunun Yönetimi: Tek Merkez Klinik Deneyimi

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Abstract

Background: Cholelithiasis and cholecystitis are among the most common general surgery diseases. Gallbladder perforation (GBP) is a rare but potentially fatal complication of these conditions. GBP can present with varied clinical manifestations among patients. We present our clinical experience regarding the diagnosis and treatment of patients treated for GBP in our clinic.
Materials and Methods: This study included patients admitted to our clinic between January 2018 and January 2022, diagnosed with GBP either preoperatively or intraoperatively, and treated using medical or surgical methods. Demographic and clinical records were retrospectively collected from the patients' electronic records and analyzed.
Results: Eighteen patients (10 males and 8 females) were included in the study. The mean age of the patients was 68.1 ±18.1 years. Neimeier classification revealed that 2 patients had Type I, 14 had Type II, and 2 had Type III GBP. Laparoscopic cholecystectomy was performed on 6 patients, open cholecystectomy on 5, and 3 patients required conversion to open cholecystectomy. Percutaneous cholecystostomy was performed in 3 patients. One patient received medical treatment due to a self-limiting abscess, with cholecystectomy recommended electively. Ultrasonography (USG) and computed tomography (CT) were used together for diagnose in 12 patients. Diagnosis was made in 3 patients only by USG, in 1 patient only by CT, and in 2 patients using both CT and MRI. Sixteen of these patients had comorbidities, with diabetes mellitus (DM) and hypertension (HT) being the most common. The mean hospital stay was 14.4 ± 9.5 days, and mortality occurred in only one patient.
Conclusions: Although GBP is a rare but potentially fatal complication of cholecystitis, it is associated with high morbidity and mortality. Lacking specific pathognomonic features, GBP often leads to misdiagnosis or delayed diagnosis. Early diagnosis and prompt surgical intervention are essential for successful outcomes in GBP. Laparoscopic cholecystectomy may be challenging in these patients, necessitating open or partial cholecystectomy. Percutaneous cholecystostomy presents a viable option for elderly patients and those with comorbidities.

Keywords: Acute cholecystitis, Cholelithiasis, Gallbladder perforation

Öz

Amaç: Kolelitiyazis ve kolesistit en sık görülen genel cerrahi hastalıkları arasındadır. Safra kesesi perforasyonu (SKP), bu durumların nadir görülen ancak potansiyel olarak ölümcül bir komplikasyonudur. SKP, farklı klinik belirtilerle kendini gösterebilir. Kliniğimizde SKP nedeniyle tedavi edilen hastaların tanısı ve tedavisiyle ilgili klinik deneyimimizi sunuyoruz.
Materyal ve Metod: Bu çalışmaya Ocak 2018 ile Ocak 2022 arasında kliniğimize başvuran, ameliyattan önce veya ameliyat sırasında SKP tanısı konulan ve tıbbi veya cerrahi yöntemlerle tedavi edilen hastalar dahil edildi. Demografik ve klinik veriler, hastaların elektronik kayıtlarından retrospektif olarak toplandı ve analiz edildi.
Bulgular: Çalışmaya on sekiz hasta (10 erkek ve 8 kadın) dahil edildi. Ortalama yaş 68,1 yıl (yaş aralığı: 27-92) idi. SKP'nin Neimeier sınıflamasına göre dağılımı; 2 hastada Tip I, 14 hastada Tip II ve 2 hastadaTip III SKP şeklindeydi. Altı hastaya laparoskopik kolesistektomi, 5 hastaya açık kolesistektomi uygulandı ve 3 hastada laparoskopik kolesistektomiden açık kolesistektomiye dönüldü. 3 hastaya perkütan kolesistostomi uygulandı. Bir hastaya kendiliğinden sınırlanan apse nedeniyle tıbbi tedavi uygulandı ve elektif olarak kolesistektomi önerildi. On iki hastaya tanı koymak için ultrasonografi (USG) ve bilgisayarlı tomografi (BT) birlikte kullanıldı. Tanı, 3 hastada yalnızca USG ile, 1 hastada yalnızca BT ile ve 2 hastada ise hem BT hem de MRI ile konuldu. Bu hastaların 16'sında eşlik eden hastalıklar vardı ve en yaygın olanları diabetes mellitus (DM) ve hipertansiyon (HT) idi. Ortalama hastanede kalış süresi 14,4 gündü ve sadece bir hastada mortalite meydana geldi.
Sonuç: SKP, yüksek morbidite ve mortaliteye sahip kolesistitin nadir bir komplikasyonu olmasına rağmen, spesifik patognomonik özelliklerden yoksundur ve bu da sıklıkla yanlış tanıya veya geç tanıya yol açar. SKP'nin erken tanısı ve acil cerrahi tedavisi çok önemlidir. Laparoskopik kolesistektomi bu hastalarda zorlayıcı olabilir, açık veya kısmi kolesistektomi gerektirebilir. Perkütan kolesistostomi yaşlı hastalar ve eşlik eden hastalıkları olanlar için uygulanabilir bir seçenektir.

Anahtar Kelimeler: Akut kolesistit, Safra kesesi taşı, Safra kesesi perforasyonu

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Introduction

Gallbladder perforation (GBP) is a rare but potentially mortal complication of acute or chronic cholecystitis. It occurs following inflammation of the gallbladder due to both calculous and acalculous cholecystitis. Some gallbladder diseases can progress to GBP. The incidence of both cholecystitis and GBP increases with age (1). Due to its varied clinical presentations, GBP can diagnosed late or incorrectly. The clinical features of GBP can range from symptoms of acute cholecystitis limited to the right upper quadrant to generalized peritonitis. GBP can lead to various clinical conditions, including localized abscess formation around the gallbladder, generalized peritonitis, and cholecystoenteric fistula in chronic cases.

The Niemeier classification, introduced in 1934, is the most commonly used system for classifying GBP. It divides free gallbladder perforations into three types: Type I (acute) involves free perforation into the peritoneal cavity, leading to generalized peritonitis; Type II (subacute) is characterized by localized fluid collection, pericholecystic abscess, and localized peritonitis; and Type III (chronic) presents as a cholecystoenteric or cholecystocutaneous fistula (2, 3, 4).

Causes of GBP can be classified as traumatic, iatrogenic or idiopathic. Systemic diseases, such as infections, malignancies, diabetes mellitus, trauma, corticosteroid use and atherosclerotic heart disease are among the most common predisposing factors (3,5). In asymptomatic diabetic patients, gangrenous cholecystitis and perforation have been reported to due to gallbladder ischemia resulting from diabetic neuropathy or nerve denervation (4,6).

In the progression toward gallbladder perforation (GBP) and abscess formation, a stone obstructing the cystic duct triggers inflammation. This inflammation, combined with bile stasis, increases intraluminal pressure in the gallbladder, leading to ischemic necrosis and eventual perforation, most commonly in the fundus region (7,8). Depending on the location of the perforation, it may remain confined to adjacent organs, resulting in localized pericholecystic abscess formation. If GBP is not promptly diagnosed and managed, it can progress to generalized peritonitis, significantly increasing morbidity and mortality rates. Ultrasonography (USG) is the diagnostic modality of choice, and in cases where USG findings are inconclusive, computed tomography (CT) or magnetic resonance imaging (MRI) may be utilized (6).

GBP poses a significant challenge for surgeons due to its difficulty in early diagnosis, often only being identified intraoperatively. The mortality rate associated with GBP, a rare complication of acute cholecystitis, has been reported to range from 2% to 42% in previous reviews (9)(10). Patients with GBP typically present with abdominal pain, fever, and nausea and vomiting. However, these symptoms can also be indicative of other conditions such as acute cholecystitis, pancreatitis, cholangitis, or appendicitis, complicating the diagnosis.

The fundus of the gallbladder, where vascular supply is weakest, is the most common site for perforation (3, 9). Fundus perforations and Type I perforations usually present with widespread peritonitis rather than localized abscess or fistula formation. In these cases, standard abdominal CT plays a critical role in diagnosing GBP. For acute cholecystitis with pericholecystic fluid detected by ultrasonography, upper abdominal CT may enhance the rate of preoperative GBP diagnosis (5,11).

This study aims to evaluate 18 patients diagnosed with GBP before or intraoperatively at our clinic for the treatment of gallbladder diseases, alongside a review of existing literature, and to share our clinical experiences.

Materials and Methods

This retrospective study included patients diagnosed with GBP either before or during surgery who presented to the emergency department or general surgery clinic of Inonu University between January 2018 and January 2022. Ethics committee approval was obtained from the Inonu University Clinical Research Ethics Committee dated 14-05-2024 and numbered 2024/5972. Patient data were retrospectively collected from the hospital's information system. The included patients were classified according to Niemeier's GBP classification, based on both radiological and intraoperative findings. The following parameters were analyzed: age, gender, hospitalization diagnosis, laboratory values, radiological diagnostic tools, radiological findings, time of surgery, surgical techniques used, comorbidities, Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures, antibiotic treatments, management options for perforation, length of hospital stay, survival rates, and histopathological data (Table-1 and 2).

Results

A total of 18 patients were included in the study, consisting of 10 males (55.5%) and 8 females (44.5%). The mean age of the patients was 68.1 ± 18.1 years. According to the Niemeier classification, the distribution was as follows: Type I (2 patients, 11.1%), Type II (14 patients, 77.7%), and Type III (2 patients, 11.1%). The mean ages of these groups were 66.5, 66.2, and 82.5 years, respectively. Type II was the most common perforation type, with 14 patients. Type I GBP was diagnosed intraoperatively; one patient underwent laparoscopic cholecystectomy, and another underwent open cholecystectomy. Preoperative diagnosis for Type II GBP was made using radiological methods in 10 patients. In this group, 5 patients underwent laparoscopic cholecystectomy, 6 patients underwent open cholecystectomy, and 2 patients underwent percutaneous cholecystostomy. Patients who underwent percutaneous cholecystostomy did not undergo surgical cholecystostomy. One patient received medical treatment for a self-limiting abscess, with no clinical or laboratory findings necessitating urgent surgery.

Cholecystectomy was planned electively. Open cholecystectomy was performed on one patient with Type III GBP, while cholecystostomy was performed under local anesthesia for abscess drainage and biliary drainage in one patient with fistulization to the skin. Overall, 6 patients underwent laparoscopic cholecystectomy, 5 underwent open cholecystectomy, and 4 underwent conversion cholecystectomy (Table-1 and 2).

Table 1. Demographic, clinical characteristics and laboratory values of the patients.

Variables	Mean	SD	Median	IQR
Age	68.1	18.1	70.5	19
AST	32.8	25.4	21.5	26
ALT	44.6	85.2	20	23
CRP	15.8	15.7	11	20
T.BIL	1.54	2.06	0.8	0.28
ALP	207.3	295.4	109.5	100
GGT	108.9	127.7	66	90
WBC	18.4	23.4	10.5	10.5
HGB	8.8	4.6	9.5	8
PLT	334.4	134.6	286.5	109
Amylase	44.1	29.3	33	27.5
Hospital Stay (Day)	14.4	9.5	11.5	15.5
Cost (Dollar)	1815	1554	1293	1949

***Abbreviations** (**normal value ranges**) of the laboratory parameters: **Amylase:** (25-125 U/L), **AST:** Aspartate aminotransferase (1-40 IU/mL), **ALT:** Alanine aminotransferase (1-40 IU/mL), **CRP:** C-Reactive Protein (0-0,35 mg/dL) **T. Bil:** Total Bilirubin (<1.2 mg/dL), **ALP:** Alkaline Phosphatase (100-400 IU/mL), **GGT:** Gamma Glutamyl transferase (1-36 IU/mL), **WBC:** White Blood Cell (4,3-10,3 10^3 µl), **HGB:** Hemoglobin (13,6-17,2 g/dL), **PLT:** Platelet (156 – 373 10^3 µl)*

Table 2. Diagnosis, Treatment and clinical features of the patient.

	Count (n)	Percentage (%)
Gender (Male/Female)	10 / 8	55.5 / 44.5
Hospitalization Diagnosis (Acute Cholecystitis / Perforation / Other)	7 / 8 / 3	38.9 / 44.4 / 16.7
Radiological Imaging (USG / BT / MRG)	15 / 14 / 2	83.3 / 77.8 / 11.1
Gallstone	12	66.7
Medical Treatment (Yes / None)	12 / 6	66.7 / 33.3
Time of Diagnosis (Preop / Intraop)	13 / 5	72.2 / 27.8
Surgery Type (Open / Laparoscopic / Conversion)	5 / 6 / 3	35.7 / 42.9 / 21.4
Percutaneous Bile Drainage (Yes / None)	7 / 11	61.1 / 38.9
ERCP (Yes / None)	2 / 16	11.1 / 88.9
Pathology (Cholecystitis/ Adenocarcinoma / N/A)	11 / 2 / 5	61.1 / 11.1 / 27.8

GBP was diagnosed during follow-up examinations in 8 patients whose symptoms did not improve despite medical treatment for cholecystitis and cholelithiasis. One patient had perforation detected while being treated for a primary sclerosing cholangitis attack and underwent emergency surgery (Figure 1). Another patient had perforation identified during elective surgery for symptomatic cholelithiasis (Figure 2). In one patient with a previous history of stomach cancer who was being examined for a mass at the head of the pancreas, laparotomy was performed due to acute abdomen, revealing intraoperative GBP, and cholecystectomy was subsequently performed.

Seven patients (38.9%) underwent percutaneous cholecystostomy, and 5 patients underwent delayed cholecystectomy. In the other two patients, cholecystectomy was performed during the same hospitalization after percutaneous cholecystostomy proved ineffective.

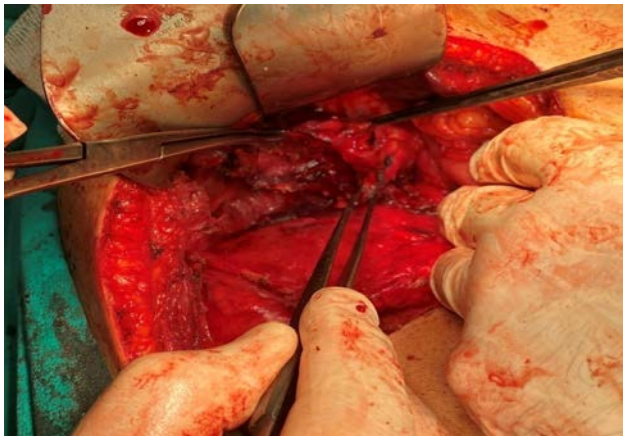

Figure 1. Type II perforation identified in a patient who underwent emergency surgery after being diagnosed with perforation while receiving treatment for an acute attack of primary sclerosing cholangitis.

During hospitalization, elevated parameters included a median CRP of 11 (Interquartile Range (IQR): 20), a median WBC of 10.5 (IQR: 10.5), a median total bilirubin of 0.8 (IQR: 0.28), a median ALP of 109.5 (IQR: 100), and a median GGT of 66 (IQR: 90). AST, ALT, amylase, and PLT levels were within normal ranges. The median hemoglobin value was below the reference range at 9.5 (IQR: 8) (Table-1).

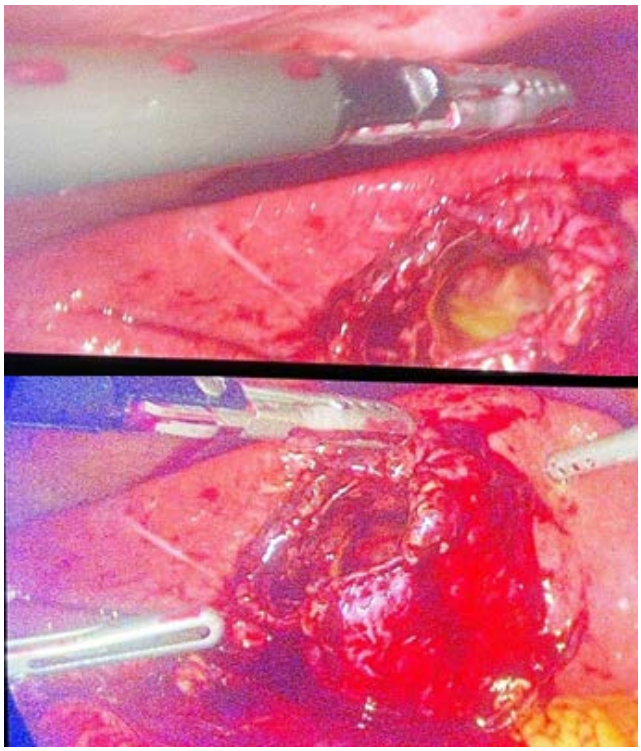

Figure 2. Type II perforation identified in a patient during elective surgery for symptomatic cholelithiasis.

Postoperatively, broad-spectrum antibiotics were initiated by the infectious diseases department in 11 patients, while 7 patients continued the antibiotics that had been started prophylactically. USG and CT were used together to diagnose of 12 patients. Three patients were diagnosed with only USG, one patient with only CT, and two patients with both CT and magnetic resonance imaging (MRI). Pathological examination revealed the following diagnoses: 5 patients with acute cholecystitis, 3 with chronic cholecystitis, 2 with xanthogranulomatous cholecystitis, 1 with adenocarcinoma, and 1 with gastric cancer metastasis. Fifteen of these patients had additional comorbidities, with the most common being diabetes mellitus (8 patients), hypertension (8 patients), and coronary artery disease (4 patients). A total of 7 patients had more than one comorbidity. Postoperatively, an abscess catheter was inserted radiologically in one patient due to the development of an intra-abdominal abscess. The mean hospital stay was 14.4 ±9.5 . One 90-year-old patient, with an ejection fraction of 35% and a pacemaker, died of postoperative cardiac arrest (mortality rate: 5.6%). Seventeen patients (94.4%) were discharged in recovery (Table-1 and 2).

Discussion

In two literature reviews involving 198 and 176 patients, Type II perforation was the most common, occurring in 46.2% and 45.5% of cases, respectively. The incidence of Type I perforation was 40.6% and 42.6%, and Type III perforation was reported at 10.1% and 11.9% (3,10). In our study, the distribution of perforation types was different, with Type II at 77.7%, Type I at 11.1%, and Type III at 11.1%. This shift is likely due to our center's high volume of liver transplant cases, which often involve Type II and III perforations, while Type I cases are generally treated at other centers. Our study's mean patient age and male percentage (55.5%) align with the literature, which reports an average age range of 55-77 years and a male proportion of 55%-60% (9).

Type III perforations are associated with significant complications, such as abscess formation and fistulization to adjacent structures (3,6). In our study, one patient developed skin fistulization, which was managed successfully with antibiotic therapy and drainage. Cholecystectomy was not performed due to the patient's advanced age (92) and comorbidities. Although GBP is more common in elderly patients, our study also included a 27-year-old male with acute calculous cholecystitis, underscoring that even younger patients can experience this condition, as documented in the literature (12,13).

The role of timely antimicrobial therapy is emphasized by guidelines from the Surgical Infection Society and Infectious Disease Society of America, particularly for secondary peritonitis, which requires coverage of both aerobic and anaerobic bacteria (14,15). In our study, patients were given third-generation cephalosporin and ornidazole preoperatively. Postoperatively, the antibiotic regimen was adjusted for 11 patients based on infectious disease consultations, and 7 patients continued prophylactic antibiotics. Only one patient developed an intra-abdominal abscess, which required percutaneous drainage.

Mortality rates for GBP vary widely, with reported figures ranging from 6.25% to 10.8% (5,6,7). In contrast, our study had a relatively low mortality rate of 5.6%, with the sole death attributed to cardiac causes rather than sepsis. The treatment of GBP remains controversial, with options such as open or laparoscopic cholecystectomy and percutaneous cholecystostomy. Cholecystectomy is considered the treatment of choice for Type I and III perforations, while the management of Type II perforations remains more complex. Laparoscopic cholecystectomy is preferred due to its minimally invasive nature, but conversion to open surgery may be necessary in cases with anatomical challenges (9,16). Additionally, many surgeons opt for percutaneous cholecystostomy in emergency settings for Type II perforations associated with subacute cholecystitis (10,17). Ultimately, the decision between surgical options should account for the patient's age, comorbidities, and the severity of the perforation, as mortality rates appear to be independent of perforation type.

Our study found a notable shift in perforation type distribution compared to the literature, with Type II accounting for 77.7%, compared to the 46.2% and 45.5% reported in other studies (3,10). This could be attributed to the high volume of liver transplant cases at our center, which often result in more complex cases involving Type II and III perforations. These patients are typically referred to our hospital, whereas less severe Type I perforations are often managed at other centers. This trend highlights the need to consider GBP as a differential diagnosis in a wide range of patients, including younger individuals and those with underlying comorbidities, who may present atypically.

The management of Type II perforations in our study included a variety of approaches, including preoperative radiological assessment, laparoscopic cholecystectomy, open cholecystectomy, and percutaneous cholecystostomy. While laparoscopic cholecystectomy remains the standard treatment for Type I and III perforations, the management of Type II perforations requires careful consideration of patient-specific factors. Percutaneous cholecystostomy serves as an important option in high-risk patients, especially those who are not surgical candidates due to age or comorbidities. Tailoring the treatment approach to the individual patient's condition is essential for optimizing outcomes and reducing the risk of complications.

Conclusion

Gallbladder perforation can lead to various clinical conditions, including peritonitis, abscess formation, fistulas, and sepsis. The impact of advanced age and comorbidities, and delays in diagnosis and treatment, must be considered. Early diagnosis and timely medical and surgical interventions are crucial for reducing morbidity and mortality in patients with complicated GBP. Percutaneous cholecystostomy is a valuable option for patients who are not surgical candidates.

Ethical Approval: *Ethics committee approval for the study was obtained from the Inonu University Non-Interventional Clinical Research Ethics Committee with the decision numbered 2024/5972 on 14-05-2024 in its 9th session.*

Author Contributions:
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Data acquisition: A.T., Z.O.
Analysis and interpretation: A.T., Z.O.
Writing manuscript: A.T., Z.O.
Critical revision of manuscript: A.T., Z.O., E.K.
Conflict of Interest: *The authors have no conflicts of interest to declare.*
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Research Article / Araştırma Makalesi

The Prevalence of Comorbid Psychiatric Disorders in Children and Adolescents with Asperger Syndrome

Asperger Sendromu Olan Çocuk ve Ergenlerde Komorbid Psikiyatrik Bozuklukların Yaygınlığı

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Abstract

Background: Most studies in the literature on comorbid psychiatric conditions in children and adolescents with Asperger syndrome (AS) either consist of individual case reports or have evaluated cases only in terms of a specific comorbid psychiatric diagnosis. Therefore, especially in recent years, there are few studies in the literature examining the comorbidity of all psychiatric disorders in patients with AS in a holistic manner. The present study aimed to determine the prevalence and types of comorbid psychiatric disorders in a clinic-based sample of 34 children and adolescents with AS.
Materials and Methods: Thirty-four children and adolescents with AS [31 males (91.2%), 3 females (8.8%) mean age 12.62±3.75 years] were gathered from clinical referrals between 2017 and 2024. Participants' sociodemographic characteristics, age at first diagnosis of AS, clinical features, comorbid psychiatric disorders, and treatment regimens were retrospectively reviewed from each hospital's records. AS diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria. Psychiatric comorbidity was assessed using DSM-5 criteria.
Results: Comorbid psychiatric disorders were present in 31 (91.2%) of the cases, with 5 (14.7%) having a single comorbid disorder and 26 (76.5%) having at least two. The most common comorbid diagnoses were anxiety disorders (67.6%, n=23), attention deficit hyperactive disorder (64.7%, n=22), obsessive-compulsive disorder (29.4%, n=10), and depression (29.4%, n=10). No cases were identified with post-traumatic stress disorder, panic disorder, eating disorders, alcohol or substance use, bipolar disorder, and psychotic disorders. In age-related comparisons, conduct disorder, specific phobia, separation anxiety disorder, and enuresis were more frequently observed in childhood, whereas social phobia, obsessive-compulsive disorder, and depression were more prevalent in adolescence.
Conclusions: Our findings highlight the high prevalence of psychiatric comorbidity in children and adolescents with AS, often involving multiple conditions. Routine assessment of psychiatric comorbidity should be an integral part of clinical evaluations for this population.

Keywords: Asperger syndrome, Autism spectrum disorder, Psychiatric comorbidity, Psychopathology, Child-adolescent

Öz

Amaç: Literatürdeki Asperger sendromu (AS) olan çocuk ve ergenlerde komorbid psikiyatrik durumlar üzerine yapılan çalışmaların çoğu ya bireysel vaka raporlarından oluşmaktadır ya da vakaları yalnızca belirli bir eşlik eden psikiyatrik tanı açısından değerlendirmiştir. Bu nedenle, özellikle son yıllarda literatürde AS hastalarında tüm psikiyatrik bozuklukların komorbiditesini bütüncül bir şekilde inceleyen az sayıda çalışma bulunmaktadır. Bu çalışmada, AS'li 34 çocuk ve ergenden oluşan klinik bir örneklemde komorbid psikiyatrik bozuklukların yaygınlığının ve türlerinin belirlenmesi amaçlanmıştır.
Materyal ve Metod: AS'li otuz dört çocuk ve ergen [31 erkek (%91,2), 3 kız (%8,8) ortalama yaş 12,62±3,75 yıl] 2017-2024 yılları arasındaki klinik başvurulardan toplandı. Katılımcıların sosyodemografik özellikleri, ilk AS tanı yaşı, klinik özellikler, komorbid psikiyatrik bozukluklar ve tedavi rejimleri her bir hastanenin kayıtlarından retrospektif olarak incelendi. AS tanısı, Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı 4. Baskı (DSM-IV) kriterlerine göre konuldu. Psikiyatrik komorbidite DSM-5 kriterlerine göre değerlendirildi.
Bulgular: Olguların 31'inde (%91,2) komorbid psikiyatrik bozukluk, 5'inde (%14,7) tek bir komorbid psikiyatrik bozukluk, 26'sında (%76,5) ise en az iki komorbid psikiyatrik bozukluk vardı. En sık komorbid tanılar anksiyete bozuklukları (%67,6, n=23), dikkat eksikliği hiperaktivite bozukluğu (%64,7, n=22), obsesif kompulsif bozukluk (%29,4, n=10) ve depresyondu (%29,4, n=10). Hiçbir olguda travma sonrası stres bozukluğu (TSSB), panik bozukluğu, yeme bozuklukları, alkol veya madde kullanımı, bipolar bozukluk ve psikotik bozukluklar saptanmadı. Yaşa göre karşılaştırmalarda çocukluk çağında davranım bozukluğu, özgül fobi, ayrılma kaygısı bozukluğu ve enürezis daha sık görülürken, ergenlikte sosyal fobi, obsesif kompulsif bozukluk ve depresyon daha sık görüldü.
Sonuç: Bulgularımız AS'li çocuk ve ergenlerde psikiyatrik komorbiditenin yüksek yaygınlığını vurgulamaktadır ve bu sıklıkla birden fazla durumu içermektedir. Psikiyatrik komorbiditenin rutin değerlendirmesi bu popülasyon için klinik değerlendirmelerin ayrılmaz bir parçası olmalıdır.

Anahtar Kelimeler: Asperger sendromu, Otizm spektrum bozukluğu, Psikiyatrik komorbidite, Psikopatoloji, Çocuk-ergen

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Introduction

Asperger syndrome (AS) is a disorder that falls under the large umbrella of autism spectrum disorders (ASDs) and is distinguished by social-communication impairment, overfocused, repetitive interests and behavior patterns, and lack of any substantial learning disability or language delay (1-3). AS was included in the psychiatric diagnostic system with the name Asperger Disorder in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) in 1994 and began to be included as a separate diagnosis, but it was removed from the diagnostic system in DSM-5 and included in the scope of ASD (3, 4). Even though classic autism and AS are both classified as ASDs, people with AS typically have a unique pattern of social impairment that appears to be less severe than that of people with classic autism (1,2), but, as with other types of autistic disorders, the main difficulty in AS is the deficit in social learning and social awareness (5).

Despite intact language and cognitive development, individuals with AS experience social difficulties due to significant deficiencies in nonverbal communication and pragmatic language skills, impairment in reciprocal social interaction, unusual, isolated special interests and preoccupations, low empathy, a lack of understanding of social norms, misinterpreting figurative and intended meanings, and difficulty in coping with their own emotions (1-7). These children have difficulty socializing with their peers, usually do not have close friends, avoid others, and are often lonely and solitary. Some researchers have identified three different types of AS: "withdrawn-aloof", "active-odd", and "passive-friendly" (7). Even though children with AS sometimes make an effort and are willing to engage in communication, others frequently reject or exclude them due to their inappropriate and clumsy social interaction approaches and their inability to accurately read the emotions, intentions, and subliminal cues of others (1, 2, 6, 7). They cannot look at events from the other person's perspective and empathize with the others, so they cannot give appropriate emotional responses, mutual emotional sharing, and long-term interpersonal relationships (5). Over time, most realize that they are different, strange, and unusual (1, 2, 5-7). Furthermore, they frequently lack passion for other facets of life due to their intensely focused unique hobbies, which hinders communication and connection with others (1, 2, 5-7). Previous studies have reported higher rates of psychiatric disorders in children and adolescents with AS compared to their healthy peers and that comorbid psychiatric disorders may contribute to functional impairments in these children (8-14). Although all types of psychiatric disorders can be seen in children and adolescents with AS, the most common comorbid conditions are attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, mood disorders, obsessive-compulsive disorder (OCD), eating behavior disorders, post-traumatic stress disorder (PTSD), tic disorders, learning disorders, and psychosis (8-16).

However, the rates of psychiatric comorbidity reported in studies vary widely (from 44% to 100%) (8-16). In conclusion, it is emphasized that the occurrence of psychiatric comorbidities in children and adolescents with AS is almost the rule rather than the exception. These conditions can cause significant distress for both the child and the family, contribute to functional impairments, and further impair quality of life (7, 9, 10, 12, 14-18).

Given this, it is essential to thoroughly assess psychiatric comorbidities in individuals with AS, and clinicians must be particularly vigilant in identifying them (6, 12). However, most existing studies on psychiatric comorbidities in AS are either limited to case reports or focus on specific psychiatric diagnoses. Therefore, especially in recent years, there is a notable lack of comprehensive research evaluating the full spectrum of psychiatric comorbidities in children and adolescents with AS (7, 9, 10, 12, 13). Thus, this study aimed to investigate the frequency and types of comorbid psychiatric disorders in a clinic-based sample of children and adolescents with AS.

Materials and Methods

***Participants*:** The study sample consisted of 34 children and adolescents [31 males (91.2%), 3 females (8.8%) mean age 12.62±3.75 years] diagnosed with AS who applied to three different Child and Adolescent Psychiatry outpatient clinics. Participants' sociodemographic characteristics, age at first diagnosis of AS, clinical features, comorbid psychiatric disorders, and treatment regimens were retrospectively reviewed from each hospital's records. AS diagnosis was made according to DSM-IV criteria, because AS is not included as a separate diagnostic category in DSM-5 (3). Psychiatric comorbidity was assessed using DSM-5 criteria (4); the Wechsler Intelligence Scale for Children (WISC) was administered to assess IQ (19, 20). Participants with missing data were not included in the study, and no further exclusion criteria were applied.

The local ethics committee approved the study protocol (Date: 17.05.2023, No: 2023-05/11) and conducted it according to the principles of the Helsinki Declaration and Good Clinical Practice for Biomedical Research.

Statistical Analysis: Statistical data were analyzed using IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD), and qualitative data were presented as number (n) and percentage (%) whenever appropriate. Descriptive statistics were used to summarize variables. The Shapiro-Wilk test was employed to assess the normality of continuous variables. Comparisons of the groups were performed using the chi-square test for categorical variables. The p-value of <0.05 was accepted as an indication of statistical significance.

Results

Descriptive and clinical characteristics of the sample

Thirty-one (91.2%) of the participants were male, three (8.8%) were female, and the mean age was 12.62±3.75 (min-max: 8-17) years. The mean age at AS diagnosis was 9.44±1.96 years. The total intelligence score mean was 108.53±8.40 (min-max: 96-129). When the cases were separated according to age groups, fourteen (41.2%) were children and twenty (58.8%) were adolescents. The mean age of the mothers was 40.71±4.62 years, fourteen (41.2%) were university graduates, and twelve (35.3%) were working in a regular job. The mean age of the fathers was 42.21±4.76 years, 25 (73.5%) were university graduates, and 31 (91.2%) were working in a regular job. 73.5% of the sample (n=25) had a family income above minimum wage. Sociodemographic characteristics of the participants are presented in Table 1.

Table 1. Sociodemographic characteristics of the sample

Variables	Number (%) or mean±SD
Age (mean-years±SD)	12.62±3.75
Age at first Asperger Syndrome diagnosis (mean-years±SD)	9.44±1.96
Age groups	
School-age group (<12 ages)	14 (41.2)
Adolescent group (≥12 ages)	20 (58.8)
Sex	
Male	31 (91.2)
Female	3 (8.8)
Total intelligence score (mean±SD)	108.53±8.40
Academic performance	
Average	13 (38.2)
Below average	11 (32.4)
Above average	10 (29.4)
Age of mother (mean-years±SD)	40.71±4.62
Level of education of the mother	
High school and lower	20 (58.8)
University	14 (41.2)
Regular job of the mother	
Yes	12 (35.3)
No	22 (64.7)
Age of father (mean-years±SD)	42.21±4.76
Level of education of the father	
High school and lower	9 (26.5)
University	25 (73.5)
Regular job of the father	
Yes	31 (91.2)
No	3 (8.8)
Family income level	
The minimum wage/less than minimum wage	9 (26.5)
Above the minimum wage	25 (73.5)

Abbreviations: AS: Asperger Syndrome; SD: Standard Deviation.

Upon analyzing the sample's past psychopathological status, it was found that 88.2% (n=30) of the participants had received a prior diagnosis of any comorbid psychiatric condition. When the number of past psychiatric comorbidities was examined, it was determined that 17.6% (n=6) of the cases had a single comorbid psychiatric disorder and 70.6% (n=24) had at least two comorbid psychiatric disorders. The most frequently diagnosed comorbid psychiatric disorders in the past were ADHD (64.7%, n=22), anxiety disorders (52.9%, n=18), and ODD (32.4%, n=11). Previously diagnosed comorbid psychiatric disorders were, in order of frequency, ADHD (64.7%, n=22), specific phobia (47.1%, n=16), separation anxiety disorder (38.2%, n=13), ODD (32.4%, n=11), OCD (23.5%, n=8), enuresis (23.5%, n=8), social phobia (14.7%, n=5), depression (11.8%, n=4), tic disorders (11.8%, n=4), CD (8.8%, n=3), encopresis (8.8%, n=3), generalized anxiety disorder (GAD) (5.9%, n=2), and PTSD (2.9%, n=1). Psychopharmacological agents used in the past, in decreasing order of frequency, were antipsychotics (61.8%, n=21), antidepressants (47.1%, n=16), methylphenidate (44.1%, n=15), and atomoxetine (29.4%, n=10). Alcohol or substance use, panic disorder, eating disorders, bipolar disorder, and psychotic disorders were not detected as past psychiatric disorders in the sample. The past psychopathological status and psychopharmacological drug use of the sample are shown in Table 2.

Table 2. Past psychopathological status and psychopharmacological drug use of the sample

Variables	Number (%)
Presence of a past diagnosis of a psychiatric disorder	30 (88.2)
Past psychopathology status	
No	4 (11.8)
A single comorbid psychiatric disorder	6 (17.6)
At least two comorbid psychiatric disorders	24 (70.6)
Previous history of ADHD	22 (64.7)
Previous history of CD	3 (8.8)
Previous history of ODD	11 (32.4)
Previous history of any anxiety disorder	18 (52.9)
Previous history of GAD	2 (5.9)
Previous history of specific phobia	16 (47.1)
Previous history of social phobia	5 (14.7)
Previous history of separation anxiety disorder	13 (38.2)
Previous history of OCD	8 (23.5)
Previous history of tic disorder	4 (11.8)
Previous history of PTSD	1 (2.9)
Previous history of depression	4 (11.8)
Previous history of enuresis	8 (23.5)
Previous history of encopresis	3 (8.8)
Previous history of antipsychotic use	21 (61.8)
Previous history of antidepressants use	16 (47.1)
Previous history of methylphenidate use	15 (44.1)
Previous history of atomoxetine use	10 (29.4)

Abbreviations: *ADHD: Attention Deficit Hyperactive Disorder; CD: Conduct disorder; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional Defiant Disorder, PTSD: Post-Traumatic Stress Disorder.*

When the reasons for the sample's current applications to psychiatric clinics were examined, it was seen that 8 (23.5%) applied with symptoms specific to AS only, 11

(32.4%) with other psychiatric symptoms not directly related to AS, and 15 (44.1%) with both symptoms specific to AS and other psychiatric symptoms not directly related to AS. Regarding the socialization status of the cases, it was learned that 9 (26.5%) were withdrawn-aloof, 19 (55.9%) were active-odd, and 6 (17.6%) were passive-friendly. It was found that 31 (91.2%) of the cases had comorbid psychiatric disorders, 5 (14.7%) had a single comorbid psychiatric disorder, and 26 (76.5%) had at least two psychiatric disorders. When current comorbid psychiatric disorders were examined, the most common diagnoses were anxiety disorders (67.6%, n=23), ADHD (64.7%, n=22), OCD (29.4%, n=10) and depression (29.4%, n=10). Current comorbid psychiatric disorders, in decreasing order of frequency, were ADHD (64.7%, n=22), social phobia (35.3%, n=12), OCD (29.4%, n=10), depression (29.4%, n=10), ODD (26.5%, n=9), specific phobia (23.5%, n=8), tic disorders (20.6%, n=7), GAD (14.7%, n=5), separation anxiety disorder (11.8%, n=4), CD (8.8%, n=3), enuresis (8.8%, n=3) and encopresis (2.9%, n=1). In the current psychopathology examination of the sample, PTSD, panic disorder, eating disorders, alcohol or substance use, bipolar disorder, and psychotic disorders were not detected in any case. Regarding current psychopharmacological agent use, the most frequently prescribed drugs, in decreasing order of frequency, were antidepressants (76.5%, n=26), antipsychotics (73.5%, n=25), methylphenidate (47.1%, n=16), and atomoxetine (29.4%, n=10). Current psychopathological status and psychopharmacological drug use in the sample are given in Table 3.

Table 3. Current psychopathological status and psychopharmacological drug use of the sample

Variables	Number (%)
Reason for applying to the psychiatric clinic	8 (23.5)
Symptoms specific to AS only	11 (32.4)
Other psychiatric symptoms not directly related to AS	15 (44.1)
Both AS-specific symptoms and psychiatric symptoms not directly related to AS	
Socialization status	
Withdrawn-aloof	9 (26.5)
Active-odd	19 (55.9)
Passive-friendly	6 (17.6)
Current diagnosis of a psychiatric disorder	31 (91.2)
Current psychopathology status	
No	3 (8.8)
A single comorbid psychiatric disorder	5 (14.7)
At least two comorbid psychiatric disorders	26 (76.5)
Presence of current ADHD diagnosis	22 (64.7)
Presence of current CD diagnosis	3 (8.8)
Presence of current ODD diagnosis	9 (26.5)
Presence of current any anxiety disorder diagnosis	23 (67.6)
Presence of current GAD diagnosis	5 (14.7)
Presence of current specific phobia diagnosis	8 (23.5)
Presence of current social phobia diagnosis	12 (35.3)
Presence of current separation anxiety disorder diagnosis	4 (11.8)
Presence of current OCD diagnosis	10 (29.4)
Presence of current tic disorders diagnosis	7 (20.6)
Presence of current PTSD diagnosis	0 (0)
Presence of current depression diagnosis	10 (29.4)
Presence of current enuresis diagnosis	3 (8.8)
Presence of current encopresis diagnosis	1 (2.9)
Current antipsychotic use	25 (73.5)
Current antidepressants use	26 (76.5)
Current methylphenidate use	16 (47.1)
Current atomoxetine use	10 (29.4)

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder; CD: Conduct Disorder; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional Defiant Disorder, PTSD: Post-Traumatic Stress Disorder.

When the existing comorbid psychopathologies were compared according to age groups, it was found that the frequency of having at least two comorbid psychiatric disorders was significantly higher in the adolescent group than in the child age group (p=0.036). There was no significant difference in the rates of comorbid ADHD, ODD, any anxiety disorder, GAD, tic disorders, and encopresis between age groups (p=0.275, p=0.435, p=0.793, p=0.379, p=0.410, p=0.412, respectively). However, comorbid CD, specific phobia, separation anxiety disorder, and enuresis were significantly higher in the childhood age group (p=0.030, p=0.004, p=0.022, p=0.030, respectively), while comorbid social phobia, OCD, and depression were significantly higher in the adolescent group (p<0.001, p=0.024, p=0.024,

respectively). Regarding the psychopharmacological agents used, the frequency of prescription of antipsychotics, methylphenidate, and atomoxetine was similar between the two groups (p=0.116, p=0.092, p=0.928, respectively), while the frequency of prescription of antidepressants was significantly higher in the adolescent group than in the childhood age group (p=0.004). The comparison of current comorbid psychopathologies according to age groups is shown in Table 4.

Table 4. Comparison of current comorbid psychopathologies according to age groups

	Children group (N=14)	Adolescent group (N=20)	p-value*
Current psychopathology status			
No	2 (14.3)	1 (5.0)	0.036
A single comorbid psychiatric disorder	4 (28.6)	1 (5.0)	
At least two comorbid psychiatric disorders	8 (57.1)	18 (90.0)	
Presence of current ADHD diagnosis	11 (78.6)	11 (55.0)	0.275
Presence of current CD diagnosis	3 (21.4)	0 (0)	0.030
Presence of current ODD diagnosis	5 (35.7)	4 (20.0)	0.435
Presence of current any anxiety disorder diagnosis	10 (71.4)	13 (65.0)	0.793
Presence of current GAD diagnosis	1 (7.1)	4 (20.0)	0.379
Presence of current specific phobia diagnosis	7 (50.0)	1 (5.0)	0.004
Presence of current social phobia diagnosis	0 (0)	12 (60.0)	<0.001
Presence of current separation anxiety disorder diagnosis	4 (28.6)	0 (0)	0.022
Presence of current OCD diagnosis	1 (7.1)	9 (45.0)	0.024
Presence of current tic disorders diagnosis	4 (28.6)	3 (15.0)	0.410
Presence of current depression diagnosis	1 (7.1)	9 (45.0)	0.024
Presence of current enuresis diagnosis	3 (21.4)	0 (0)	0.030
Presence of current encopresis diagnosis	1 (7.1)	0 (0)	0.412
Current antipsychotic use	8 (57.1)	17 (85.0)	0.116
Current antidepressants use	7 (50.0)	19 (95.0)	0.004
Current methylphenidate use	9 (64.3)	7 (35.0)	0.092
Current atomoxetine use	4 (28.6)	6 (30.0)	0.928

*The chi-square test for categorical variables was used to test group differences.
Abbreviations: ADHD: Attention Deficit Hyperactive Disorder; CD: Conduct disorder; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional Defiant Disorder, PTSD: Post-Traumatic Stress Disorder.

Discussion

In this study, the reasons for psychiatric referral and the frequency and distribution of psychiatric comorbidities in children and adolescents with AS were evaluated. It was revealed that 88.2% of the participants had at least one comorbid psychiatric disorder in the past and 91.2% had at least one current comorbid psychiatric disorder. Regarding psychopharmacological agent use, the most frequently prescribed drugs, in decreasing order of frequency, were antidepressants (76.5%), antipsychotics (73.5%), methylphenidate (47.1%), and atomoxetine (29.4%).

No large community studies show definitive incidence and prevalence rates regarding comorbid psychiatric conditions seen in AS, and existing studies vary in terms of diagnostic criteria, age of subjects, and sampling methods, making it difficult to generalize the data. Numerous studies examining comorbid psychopathology in children with AS have shown a wide range of psychiatric comorbidity rates, from 44% to 100%, probably due to methodological variations, such as very few samples, heterogeneity in study settings, data sources, case definitions, and included age ranges, highly variable exclusionary criteria, and possible clinical misinterpretation of symptoms (8-14).

However, it is known that children and adolescents with AS are at higher risk for psychiatric comorbidity when compared with a sample from the general population, and some researchers even report that the occurrence of psychiatric comorbidities in AS is almost the rule rather than the exception (7,9,10,12,14-18). The increased risk of comorbid psychopathology in children with AS has been linked to their greater likelihood of attending mainstream school, their disadvantages such as being bullied and having less social support than typically developing children, low-quality social relationships, and poor socialization skills; and these are often associated with increased psychiatric comorbidities such as conduct problems, anxiety and depression (8,12,21). Children and adolescents with AS may exhibit serious psychiatric breakdowns even in mild-stress situations and experience distress and anxiety as a result of even the slightest changes in their environment. In such cases, the likelihood of secondary psychological problems is high (8,12,21). In our study, we determined that 91.2% of the sample have comorbid psychiatric disorders, 14.7% of them have a single psychiatric disorder, and 76.5% have at least two psychiatric disorders.

The most common comorbid psychiatric diagnoses we found were anxiety disorders (67.6%), ADHD (64.7%), OCD (29.4%) and depression (29.4%). When the literature data on the subject is examined, it is seen that our findings are compatible with the results of previous studies. A study of children with high-functioning autism (HFA) and AS found that 44.2% of the sample had at least one comorbid psychiatric disorder, and the most common comorbid diagnosis was ADHD (12). Other comorbid psychiatric diagnoses are depression, bipolar disorder, generalized anxiety disorder (GAD), positive psychotic symptoms, learning disability, OCD, eating disorders, ODD, tics, and Tourette's syndrome (12). Another study screening for comorbid psychiatric disorders in children with ASD yielded that 70% of the sample had at least one comorbid disorder and 41% had two or more comorbid disorders (11). In the same study, the most common comorbid psychiatric diagnoses were found to be social phobia (29.2%), ADHD (28.2%), and ODD (28.1%), and a second comorbid diagnosis was found in 84% of those with ADHD comorbidity (11). Again, another study showed the rate of psychiatric comorbidity as 74% in children and adolescents with AS and HFA, and the rate of more than one comorbid psychiatric disorder was also high (14). The researchers revealed that 44% of the sample had behavioral disorders, 42% had anxiety disorders, and 26% had tic disorders (14). The same study showed that comorbidity of ODD, major depressive disorder, and anxiety disorders was associated with significantly worse levels of functioning and highlighted the importance of routinely assessing psychiatric comorbidity in these patients to target therapies (14). In a study examining the rate and type of comorbid psychiatric disorders in children and adolescents with HFA and AS, a very high rate of comorbid psychiatric disorders was found, 100% in the AS group and 93.3% in the HFA group, and the most common comorbid diagnosis was reported to be ADHD (13).

None of the participants in this study had PTSD, panic disorder, eating disorders, alcohol or substance use, bipolar disorder, or psychotic disorders. Bipolar disorder has also been reported as a comorbidity in ASD, especially in adolescence, although not as frequently as depression (8,9,12,22,23). However, it has been emphasized that the rates reported for bipolar disorder are very high and that the developmental characteristics of autism can be confused with symptoms of mania. It has been stated that the enthusiastic and long-winded conversations and mental preoccupations of individuals with ASD regarding their own special interests can be confused with symptoms of hypomania (22,23). As for psychotic disorders, although some studies have identified psychotic disorders as a comorbid diagnosis in children and adolescents with AS (24-26), some studies have not identified psychotic disorders as comorbidity, consistent with our results (27,28). Inconsistent results may be due to methodological differences across studies. In addition, considering that both bipolar disorder and psychotic disorders are often diagnosed in late adolescence or young adulthood, symptoms suggestive of bipolar disorder and psychotic disorders may not have started yet in our cases, and this finding may be related to the age group of our sample. There are also studies in the literature showing the association of eating disorders with AS (29,30), and the fact that eating disorders were not detected in our study may be related to the small sample size. None of our participants had panic disorder. This result is consistent with the studies that detected panic disorder in this population at least or not at all (28,31). Similarly, we did not detect alcohol or substance use in our sample, consistent with studies showing that alcohol or substance use is quite rare in individuals with AS (31) and this finding can also be attributed to the age group of our sample.

It is unclear what factors increase a child's chance of developing comorbid mental health disorders if they have Asperger syndrome. Nonetheless, previous studies have emphasized the importance of psychiatrists assessing psychiatric comorbidity in children and adolescents with AS, since in these children, additional psychiatric disorders can create significant distress for both the child and the family and further impair quality of life (7,9,10,12). These comorbid psychiatric conditions may also lead to loss of functionality and increased morbidity and mortality rates, decreased compliance with treatment, increased risk of drug interactions due to multiple drug use, increased likelihood of medical complications, and increased healthcare costs (7,9,10,12,14-16,32). However, the diagnosis of psychiatric comorbidity in AS patients can be very challenging, since these children may have difficulties processing and identifying their own emotions and feelings (6,8,10,32,33). Indeed, although AS children have better verbal expressions than children with ASD, their verbal expressions are still inadequate compared to their typically developing peers, their empathy skills are limited, and their ability to recognize and express their own emotions is weak (1-7). These difficulties make it difficult for children with AS to define and describe their own mental states and the situations they have difficulty with in daily life (1,8,12). Furthermore, comorbid psychiatric symptoms in children with AS may occur atypically compared to the general population and may be masked by the core symptoms of AS (12). Add to these difficulties the confusion regarding diagnostic criteria and the lack of diagnostic tools to assess comorbid psychiatric problems specific to these individuals, it is quite difficult to identify and recognize comorbid psychiatric problems in AS and they may be overlooked in the clinical setting (1,8,12). Despite self-report questionnaires, checklists, and clinical interviews being helpful diagnostic aids in clinical settings, they may not always be suitable for AS because most of these tools are geared toward identifying psychopathological symptoms in the general population (8). Therefore, just as the validity of these tools needs to be tested in individuals with AS, their application may also be problematic in individuals with AS due to their lack of ability

to maintain a reciprocal conversation, talk about themselves, convey events, and understand and empathize with other people's feelings. All these problems make it more difficult to evaluate responses correctly, which misinterprets the genuine nature of comorbidity symptoms (8,12). In addition, there is debate over whether comorbid psychiatric conditions are part of the basic symptoms of AS and overlap or whether they should be considered a separate disorder added to AS. Thus, one of the most common difficulties in assessing psychiatric comorbidity is deciding whether symptoms are a manifestation of AS itself or are symptoms representing a concomitant psychiatric disorder (8,12,21,33). The primary reason for this is that the core symptoms of AS frequently obscure the symptoms of the comorbid disorder(s) (8). Sometimes symptoms of comorbid psychiatric conditions are severe enough to be the main reason for clinical presentation and determine the main goals of treatment. On the other hand, it has also been suggested that the lines separating core AS symptoms from comorbid psychiatric symptoms may become blurred and that AS-specific symptoms may disguise signs of comorbid psychopathologies (8,12,21,33). Therefore, it is underlined that when diagnosing comorbid psychiatric conditions in children and adolescents with AS, it would be healthier to gather clinical information primarily from family members or by closely observing people in their social environment, rather than collecting it directly from children with AS (8,12,21,33).

On the other hand, it is also known that AS, which has milder core symptoms, is far less recognized and diagnosed. Therefore, children with AS may present to the clinic with other psychiatric symptoms that do not clearly suggest the presence of AS (21,34). In this situation, early detection of AS can often be difficult since AS symptoms can be masked or confused with those of other psychiatric disorders (12,21,34).

In this study, when we compared the existing comorbid psychopathologies according to age groups, we determined that the frequency of having at least two comorbid psychiatric disorders was significantly higher in the adolescent group than in the child age group. Consistent with our results, although certain types of comorbidities affect every age group in AS, it has been discovered that adolescence is the age group with the highest prevalence of psychiatric comorbidity, and the prevalence of multiple comorbidities increases in adolescence (7,12,14). Possible reasons for our result include increased social expectations during adolescence, individuals with AS becoming more aware of their own inadequacies, social withdrawal, and poor communication skills (7,35). Because adolescence is a period when peer relationships become increasingly important and social and emotional expectations rise, adolescents with AS may experience extreme distress and withdraw from the social world due to the expectation of complex social skills (35,36). Especially during this period, their awareness of being different from their peer increases (1,2,5-7). In addition, adolescents with AS will most likely have more negative social experiences, which will make the adolescents with AS more vulnerable, have lower self-esteem, and increase the risk of psychopathology (5,33). There was no significant difference in the rates of comorbid ADHD, ODD, any anxiety disorder, GAD, tic disorders, and encopresis between age groups, in our study. However, comorbid CD, specific phobia, separation anxiety disorder, and enuresis were significantly higher in the childhood age group, while comorbid social phobia, OCD, and depression were significantly higher in the adolescent group. Previous studies have also found that ADHD and disruptive behavior disorders are the most common comorbid diagnoses in the pre-pubertal period, while mood disorders are more common in adolescence (7,12). In the present study, among anxiety disorders, specific phobia and separation anxiety disorder were significantly more frequently comorbid diagnoses in the childhood age group, while social phobia was significantly more frequent in the adolescent group. This situation can be explained by the fact that specific phobia and separation anxiety disorder decrease developmentally with age, while social phobia becomes more evident in adolescence. A study of adolescents with AS/HFA revealed that social anxiety increases with age in the HFA/AS group, while behavioral avoidance decreases with age in the control group. Especially, those who were active-odd in childhood may develop social phobia in adolescence (35,37).

There are several limitations of this study. The important limitations of the study are the moderate sample size, the lack of a comparison group, the fact that psychiatric diagnoses were not made through a semi-structured diagnostic interview, and the retrospective nature of the study. These limitations prevent our results from being generalized and revealing a cause-effect relationship. Despite these limitations, the present study makes important contributions to expanding the literature by providing data on the frequency and type of comorbid psychiatric conditions in children and adolescents with AS. To enhance our understanding of psychiatric comorbidities in AS, future research should focus on: (1) Prospective Studies: Longitudinal studies with larger sample sizes are needed to monitor the development and progression of psychiatric comorbidities in individuals with AS over time; (2) Diagnostic Tools: Developing and validating assessment tools specifically designed for individuals with AS will improve the accuracy of diagnosing comorbid psychiatric conditions; (3) Intervention Efficacy: Evaluating the effectiveness of tailored intervention programs in reducing psychiatric comorbidities and enhancing functional outcomes in AS populations is crucial. Addressing these areas will contribute to more effective management strategies and better quality of life for individuals with AS.

Clinical Implications and Early Intervention

The high rate of psychiatric comorbidities in individuals with AS necessitates early identification and tailored interventions. Clinicians should conduct thorough assessments to detect comorbid conditions promptly, facilitating timely and appropriate treatment strategies. Intervention programs

should address basic social and communication skills (with a focus on pragmatic communication), adaptive functioning, and academic or vocational skills, while ensuring that learned skills generalize to naturalistic environments. Early intervention can mitigate the impact of comorbid psychiatric conditions, improving the overall quality of life for individuals with AS. Implementing appropriate interventions based on individual needs, considering social skills training, cognitive-behavioral therapy, and other evidence-based approaches, is essential.

Conclusion

Our findings indicated that comorbid psychiatric disorders are common and often multiple in children and adolescents with AS, and knowing this may provide targets for intervention and that psychiatric comorbidity should be routinely assessed in the clinical evaluation of this group. Routine screening for common psychiatric comorbidities such as anxiety disorders, ADHD, and depression should be included in regular evaluations of children and adolescents with AS. Utilizing standardized tools like the Child Behavior Checklist (CBCL) can aid in the early detection of these conditions. Early identification and intervention for these comorbid conditions are crucial, as they can significantly improve the child's daily functioning and overall quality of life. Research in this area will also be important for preventive mental health services. However, especially considering the relative decrease in interest in this topic in recent years, longitudinal studies are necessary to draw definitive conclusions about whether children with AS have an increased risk of developing psychiatric disorders or whether they have a constitutional predisposition in this regard.

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Research Article / Araştırma Makalesi

The Relationship Between Chronic Fatigue, Sleep quality, and Melatonin Levels in Sjogren's Syndrome

Sjögren Sendromu Tanılı Hastalarda Kronik Yorgunluğun Uyku Durumu ve Melatonin Düzeyi ile İlişkisi

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Abstract

Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease and majority of patients have fatigue and insomnia. Melatonin has many functions in addition to improving sleep quality and duration.The aim of this study was to explore the relationship between fatigue and insomnia, and the association of melatonin levels with fatigue and insomnia in patients with pSS.
Materials and Methods: This cross-sectional cohort study included 116 patients and 27 healthy controls. Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS) and SF-36 questionnaires were obtained from patients. Melatonin was measured by ELISA from the patients' serum.
Results: Patients with pSS exhibited greater fatigue compared to the control group, additionally, patients with somnolence exhibited higher levels of fatigue compared to those without somnolence. The median melatonin level was 239 ng/L (189-460) in patients with fatigue and 266 ng/L (219-552) in patients without fatigue (p=0.11). Patients with and without daytime sleepiness had similar melatonin levels, too. The median melatonin level was 429 ng/L (268-774) in healthy controls compared to 254 ng/L (197-491) in patients with PSS (p=0.0098) The quality of life, as measured by the SF-36, was significantly worse in patients with fatigue across all subgroups compared to those without fatigue. There was no correlation between melatonin levels and the subparameters of the SF-36.
Conclusions: Fatigue had a negative impact on both quality of life and sleepiness. Those who experienced sleepiness had a poorer quality of life. Early morning serum melatonin levels were lower in PSS patients. There was no significant difference in mean serum melatonin levels between patients with and without fatigue. No correlation was found between serum melatonin levels and quality of life.

Keywords: Sjogren's syndrome, Fatigue, Sleepiness, Melatonin, Quality of life

Öz

Amaç: Primer Sjögren sendromu (pSS), sistemik bir otoimmün hastalıktır ve hastaların çoğu yorgunluk ve uykusuzluk yaşamaktadır. Melatonin, uyku kalitesini ve süresini iyileştirmenin yanı sıra birçok farklı işlevi olan bir hormondur. Bu çalışmanın amacı, yorgunluk ve uykusuzluk arasındaki ilişkiyi ve melatonin seviyelerinin yorgunluk ve uykusuzluk ile olan bağlantısını pSS hastalarında araştırmaktır.
Materyal ve Metod: Bu kesitsel kohort çalışmasına 116 hasta ve 27 sağlıklı kontrol dahil edilmiştir. Epworth Uykululuk Ölçeği (ESS), Yorgunluk Şiddeti Ölçeği (FSS) ve SF-36 anketleri hastalardan elde edilmiştir. Hastaların serum melatonin seviyeleri ELISA yöntemiyle ölçülmüştür.
Bulgular: pSS hastaları kontrol grubuna kıyasla daha fazla yorgunluk göstermiştir. Ayrıca, gündüz aşırı uykululuğu olan hastalar, olmayanlara göre daha yüksek yorgunluk seviyelerine sahipti. Yorgunluğu olan hastalarda medyan melatonin seviyesi 239 ng/L (189-460) iken, yorgunluğu olmayan hastalarda 266 ng/L (219-552) olarak ölçülmüştür (p=0.11). Gündüz aşırı uykululuğu olan ve olmayan hastaların melatonin seviyeleri benzer bulunmuştur. Sağlıklı bireylerde medyan melatonin seviyesi 429 ng/L (268-774) iken, pSS hastalarında 254 ng/L (197-491) olarak ölçülmüştür (p=0.0098). SF-36 ile ölçülen yaşam kalitesi, yorgunluğu olan hastalarda tüm alt gruplarda yorgunluğu olmayanlara kıyasla anlamlı derecede daha kötüydü. Melatonin seviyeleri ile SF-36'nın alt parametreleri arasında bir korelasyon bulunmamıştır.
Sonuç: Yorgunluk, hem yaşam kalitesi hem de uyku hali üzerinde olumsuz etkiye sahiptir. Gündüz uykululuğu yaşayan hastalar daha düşük yaşam kalitesine sahiptir. pSS hastalarında sabah erken saatlerde ölçülen serum melatonin seviyeleri daha düşük bulunmuştur. Yorgunluğu olan ve olmayan hastalar arasında serum melatonin seviyeleri açısından anlamlı bir fark saptanmamıştır. Ayrıca, serum melatonin seviyeleri ile yaşam kalitesi arasında bir korelasyon bulunmamıştır.

Anahtar Kelimeler: Sjögren sendromu, Yorgunluk, Uykululuk, Melatonin, Yaşam kalitesi

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands (1). Besides sicca symptoms and arthralgia, nearly 70% of patients report fatigue, one of the most debilitating symptoms (2). Additionally, patients with pSS experience poorer sleep quality and insomnia (3, 4). Those with poor sleep quality exhibit higher levels of fatigue compared to those with good sleep quality (5). Quality of life (QoL) is significantly impaired in pSS patients compared to control groups (6). Fatigue is one of the primary predictors of poor QoL in pSS patients, regardless of other factors such as disease activity, age, and fibromyalgia (7) . Conflicting results have been reported regarding the relationship between serum cytokine levels and fatigue. While one study found no direct correlation between fatigue and serum cytokine levels (8), another study associated high levels of inflammatory cytokines with fatigue (9). A meta-analysis highlighted numerous discrepancies between fatigue and inflammatory markers in pSS patients (10).

Melatonin is the primary product of the pineal gland, secreted in a circadian manner, and has various physiological functions, including immune regulation, anti-infection, antioxidant, and anti-aging properties (11). External administration of melatonin regulates the immune response and ameliorates Sjögren's-like syndrome in rats (12). In a recent study, melatonin reduced lymphocytic infiltration, effectively prevented glandular damage, and maintained the functional integrity of the salivary glands in NOD mice by inhibiting IL-6/STAT3 (interleukin-6/signal transducer and activator of transcription 3 pathway) through receptor-dependent manner (13).

In addition, melatonin improves both the quality and duration of sleep (11). Melatonin levels are lower in patients with systemic lupus erythematosus (SLE) compared to controls, and this difference is related to disease activity (14). Similarly, serum melatonin levels are lower in pSS, which is associated with disease activity (15).

Unfortunately, there is still a lack of large-scale studies examining melatonin levels and their correlation with clinical features in patients with pSS. In this study, we aim to explore the relationship between fatigue and insomnia, and the association of melatonin levels with fatigue and insomnia in patients with pSS. Additionally, we seek to investigate the relationship between fatigue, sleep deprivation, and quality of life, as well as the correlation between serum melatonin levels and quality of life.

Materials and Methods

This is a cross-sectional cohort study was approved by the Ethics Committee of Akdeniz University (Approval no: 296; Date 18.06.2014). The study was conducted in accordance with the Declaration of Helsinki and informed consent forms were obtained from the patients whose data were used in the study, indicating their acceptance of the treatment. The study was conducted at the Department of Rheumatology, Akdeniz University Hospital. A total of 116 patients with PSS and 27 healthy controls were enrolled. Patients diagnosed with pSS over the age of 18 were included in the study. Individuals under the age of 18, those with pregnancy, and other rheumatological diseases, hepatitis C, sarcoidosis, malignancy, or a history of radiotherapy were excluded from the study.

All patients signed an informed consent form. Demographic data such as age, sex, main symptoms at the time of diagnosis, anti-nuclear antibody (ANA), romatoid factor (RF), anti-SSA, anti-SSB positivity, erythrocyte sedimentation rate and CRP levels were collected from the medical records. Patient blood samples were collected between 9:00 am and 10:00 am and stored at -80 °C until analysis. Melatonin was measured by ELISA test from patients serum. The study obtained ethical approval from the institutional review board.

The Epworth Sleepiness Scale (ESS) was used to measure participants' sleepiness state (ESS) (16). The ESS consists of 8 items in which the rate of the tendency to sleepy state ranges from zero to three for each of the items. The activities listed include sitting and reading, watching television, passive sitting in a public area, being a passenger in a vehicle for at least an hour without interruption, reclining for rest in the afternoon when possible, engaging in seated conversation, sitting quietly post-lunch without alcohol, and remaining in a stationary car during traffic for a few minutes. A higher score reflects an increased propensity for daytime sleepiness. A cumulative score of 10 or more suggests insufficient sleep

The severity of fatigue and its effect on daily activities were evaluated using the Fatigue Severity Scale (FSS) (17). This scale comprises nine items designed to assess fatigue symptoms by considering their influence on motivation, physical activity, functional capacity, and daily tasks. The FSS is scored by computing the mean of all nine items, with elevated scores reflecting greater fatigue severity. A total score of 36 or above indicates the presence of significant fatigue.

The health-related quality of life of the patients was evaluated utilizing the SF-36 instrument (18). The SF-36 consists of 8 domains representing physical functioning, physical role, bodily pain, mental health, emotional role, social functioning, vitality, and general health. Each of these domains has values between 0 and 100, with lower values indicating a lower quality of life.

Descriptive statistics were presented using mean, standard deviation, median, and interquartile range values. To compare continuous variables between two groups, the Student's t-test and Mann-Whitney U test were used for normally distributed and non-normally distributed data, respectively. The chi-square test was utilized to assess cate-

gorical variables between the two groups. Correla tion analysis was conducted using the Spearman correlation test for nonparametric data. Normality assumptions were evaluated using the Kolmogorov-Smirnov test, and significance was set at a p-value ≤ 0.005.

Results

This cross-sectional study included 116 patients diagnosed with pSS and 27 healthy controls. The majority of participants in both groups (109 out of 116 patients and 26 out of 27 healthy individuals) were female. The mean age of the patients was 48 years, compared to 47 years in the control group. At the time of diagnosis, half of the patients experienced arthralgia, 85.3% had xerostomia, and 78% presented with xerophthalmia. The main characteristics of the patients are outlined in Table 1.

Table 1. Main characteristics of patients at the time of diagnosis

		N (%)
RF	**positive**	24 (20.6)
ANA	**positive**	74 (63.8)
Schirmer	**sağ (≤5 mm)**	51 (43.9)
Schirmer	**sol (≤5 mm)**	51 (43.9)
BUT	**sağ (≤10 sn)**	53 (45.6)
BUT	**sol (≤10 sn)**	52 (44.8)
Anti SSA	**positive**	41 (35.3)
Anti SSB	**positive**	26 (22.4)
ESR*		31 (26.7)
CRP*		25 (21.5)

**Values of at the time of melatonin measurement*
ANA: Antinuclear antibody; BUT: Breakup time; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; mm: Millimeter; N: Number; RF: Rheumatoid factor; sec: Second

The relationship between fatigue and sleepiness

Patients with pSS exhibited greater fatigue compared to the control group, with 59.1% (n=68) of patients and 0% (n=0) of controls reporting fatigue (p=0.000). Patients with PSS experienced significantly higher daytime sleepiness than the control group, with a prevalence of 36.9% compared to 0% in healthy individuals. Moreover, those experiencing somnolence reported greater fatigue levels than those without. Among patients with sleepiness, fatigue prevalence was 79.5%, whereas it was 45.8% in those without sleepiness (*p*=0.001), as detailed in Table 2.

The median melatonin level was 239 ng/L (189-460) in patients with fatigue and 266 ng/L (219-552) in patients without fatigue (p=0.11). Patients with and without daytime sleepiness had similar melatonin levels, with a median of 234 ng/L (191-363) in those with daytime sleepiness and 270 ng/L (202-603) in those without daytime sleepiness (p=0.11). Healthy controls exhibited higher melatonin levels than patients with PSS. The median melatonin level was 429 ng/L (268-774) in healthy controls compared to 254 ng/L (197-491) in patients with PSS (p=0.0098). The quality of life, as measured by the SF-36, was significantly worse in patients with fatigue across all subgroups compared to those without fatigue Table 3.

Similarly, patients with daytime sleepiness demonstrated a lower quality of life across all subdomains of the SF-36 compared to those without daytime sleepiness (Table 4). The affected quality of life parameters included physical functioning, physical role functioning, pain, general health, vitality, social functioning, emotional role functioning, and mental health.

The relationship between melatonin levels and the subparameters of the SF-36 was examined. There was no correlation between physical functioning and melatonin levels (r=0.02, p=0.787). Similarly, no correlation was observed between physical role functioning and melatonin levels (r=0.07, p=0.44). All other subparameters also showed no significant correlations Table 5.

Table 2. The Relationship Between Sleepiness and Fatigue

Sleepiness* Fatigue		Fatigue		Total	P
		No	Yes		
Without sleepiness	N	39	33	72	0,001
	%	54,2%	45,8%	100,0%	
Sleepiness	N	9	35	44	
	%	20,5%	79,5%	100,0%	
Total	N	48	68	116	
	%	41,4%	58,6%	100,0%	

Table 3. Comparison of Quality of Life Between PSS Patients With Fatigue and Those Without Fatigue

	Fatigue Median (IQR)	Not fatigue Median (IQR)	P value
Physical functioning	45 (25-57.5)	67 (50-80)	P<0.0001
Physical role functioning	0 (0-50)	100 (12.5-100)	P<0.001
Pain	32 (21-44)	44 (40-64)	P<0.0001
General health	33 (29-37)	50 (45-58)	P<0.0001
Vitality	30 (20-40)	45 (30-60)	P=0.0007
Social functioning	50 (25-62,5)	75 (62,5-87,5)	P<0.0001
Emotional role functioning	0.5 (0-66)	100 (33-100)	P<0.0001
Mental health	40 (32-54)	52(44-64)	P=0.0001

IQR: Interquartile range

Table 4. Comparison of Quality of Life Between pSS Patients With Daytime Sleepiness and Those Without Daytime Sleepiness

	Patients with daytime sleepiness Median (IQR)	Patients without daytime sleepiness Median (IQR)	P value
Physical functioning	37.5 (25-50)	60 (40-75)	P=0.0002
Physical role functioning	0 (0-25)	75 (0-100)	P=0.0001
Pain	22 (20-44)	43 (30-54)	P=0.0003
General health	29 (16-39)	45 (37-58)	P<0.0001
Vitality	25 (20-35)	35 (30-55)	P=0.0007
Social functioning	50 (25-62.5)	62 (50-87.5)	P<0.0001
Emotional role functioning	0 (0-33)	66 (33-100)	P<0.0001
Mental health	40 828-52)	48 (36-60)	P=0.0192

Table-5. SF-36 subparameters and melatonin level

	r value	P value
Physical functioning and melatonin	0.02	P=0.787
Physical role functioning and melatonin	0.07	P=0.44
Pain and melatonin	0.07	P=0.42
General health and melatonin	0.11	P=0.23
Vitality and melatonin	0.03	P=0.71
Social functioning and melatonin	-0.006	P=0.95
Emotional role functioning and melatonin	0.10	P=0.29
Mental health and melatonin	0.02	P=0.76

Discussion

Fatigue is commonly associated with numerous rheumatologic diseases, including primary Sjögren's Syndrome (pSS). Nearly two-thirds of individuals with pSS experience fatigue (2). In our study, we found that 59.1% of patients reported fatigue, while none of the control group did. This finding aligns with existing literature indicating that fatigue is more prevalent in pSS patients compared to controls. Additionally, our study revealed that patients with pSS experienced more daytime sleepiness than the control group (36.9% vs. 0%). In a previous study (4), 55% of pSS patients reported excessive daytime sleepiness, though it included only 32 patients compared to our 116 patients, which may account for the discrepancy. Consistent with our findings, a meta-analysis also indicated that patients with pSS experience more sleep disturbances than controls (19).

In our study, we observed that patients with daytime sleepiness exhibited higher levels of fatigue compared to those without sleepiness. A study conducted in Brazil also identified a positive correlation between sleep disorders and fatigue (5). Additionally, another study found that patients with pSS experienced more sleep disturbances than the control group, and these disturbances may contribute to fatigue (20). These findings collectively suggest a strong relationship between sleepiness and fatigue.

Melatonin is a hormone secreted in a circadian rhythm, known for its diverse functions including antioxidant promotion, neural survival, circadian rhythm regulation, and sleep regulation (21). In the context of rheumatologic diseases, melatonin supplementation has shown positive effects in conditions such as fibromyalgia, osteoarthritis, and osteoporosis, but not in rheumatoid arthritis and lupus (22). Melatonin is thought to modulate T and B lymphocyte functions, inhibit inflammatory signals, downregulate apoptosis, and improve sleep, which has led to the hypothesis that melatonin could ameliorate symptoms of primary Sjögren's Syndrome (11).). For instance, melatonin administration has been found to alleviate Sjögren's-like symptoms in mice (12). In our study, we discovered that morning melatonin levels were significantly lower in patients with pSS compared to the control group. This result suggests that melatonin dysregulation may play a role in the etiology of pSS.

Interestingly, in our study, we found no statistically significant difference in melatonin levels between patients with and without sleep disturbance. The melatonin level was 234 ng/L (191-363) in patients with sleepiness and 270 ng/L (202-603) in patients without sleepiness. Similarly, in a study involving idiopathic Parkinson's disease, no correlation was observed between sleep quality and morning melatonin levels (23).). Since melatonin follows a circadian rhythm, serial measurements may be more appropriate than early morning measurements. Moreover, factors such as age, depression and anxiety, pain, and sicca symptoms may influence sleep quality in PSS (24).

Having established that patients with sleep disorders experience heightened fatigue, we aimed to investigate the correlation between fatigue and melatonin levels in patients with pSS. The etiology of fatigue in pSS has been extensively explored, with studies focusing on serum cytokine levels. For instance, one study revealed elevated levels of tumor necrosis factor-α (TNFα), interferon-α (IFNα), interferon-γ (IFN-γ), and lymphotoxin-α (LT-α) in patients with pSS compared to non-fatigued controls (9). Additionally, interleukin-6 levels were found to be higher in PSS patients with fatigue (25). In our study, we observed no disparity in melatonin levels between patients with and without fatigue.

Similarly, in another study, there was no significant variation in melatonin levels between patients with chronic fatigue syndrome and controls (26).

As expected, fatigue is one of the main predictors of poor quality of life in PSS (7, 27). In our investigation, patients experiencing fatigue exhibited lower quality of life across all domains assessed by the SF-36. This observation aligns with existing literature. Furthermore, our findings indicate that patients with daytime sleepiness also experience reduced quality of life across all aspects evaluated by the SF-36 test. Previous research has demonstrated a link between poor sleep quality and diminished quality of life (28), with another study among Chinese PSS patients highlighting a significant correlation between poor sleep quality and declining quality of life (29). In addition to the association between fatigue and sleepiness in PSS patients, our study reveals that both fatigue and sleepiness exert a negative impact on the quality of life among individuals with PSS.

Finally, our analysis revealed no significant correlation between melatonin levels and quality of life across all SF-36 domains, including physical functioning, physical role functioning, pain, general health, vitality, social functioning, emotional role functioning, and mental health**.** While melatonin administration has been shown to improve quality of life in patients with fibromyalgia (30), it did not have the same effect in cancer patients (31). Given melatonin's diverse functions, further research is warranted to explore the relationship between melatonin and quality of life.

Our study has some limitations. First, being a cross-sectional study, we measured melatonin levels at a single point in time. Considering melatonin's circadian rhythm, serial measurements may provide more accurate data. Second, we only measured serum melatonin levels, whereas salivary and urinary melatonin levels could also be informative. Finally, the potential effects of melatonin supplementation on sleep, fatigue, and quality of life were not assessed in our study, and our results did not include information on melatonin supplementation.

Conclusions

In patients with pSS, fatigue negatively impacted both quality of life and sleepiness, with those experiencing sleepiness having a poorer quality of life. Early morning serum melatonin levels were lower in pSS patients compared to controls. There was no significant difference in median serum melatonin levels between patients with and without fatigue, and no correlation was found between serum melatonin levels and quality of life. There is a need for both basic research and large-scale clinical trials with a larger patient cohort to explore the effects of melatonin on pSS-related chronic fatigue and sleep disorders, its influence on the consequent decline in quality of life, and its potential role in the treatment of primary sjögren's syndrome.

Ethical Approval: *This is a cross-sectional cohort study was approved by the Ethics Committee of Akdeniz University (Approval no: 296; Date 18.06.2014). The study was conducted in accordance with the Declaration of Helsinki and informed consent forms were obtained from the patients whose data were used in the study, indicating their acceptance of the treatment.*

Author Contributions:
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Research Article / Araştırma Makalesi

Serum Bilirubin Levels and Mortality Risk: Evaluation of Prognostic Use in a High-Risk Intensive Care Population

Serum Bilirubin Düzeyleri ve Mortalite Riski: Yüksek Riskli Yoğun Bakım Popülasyonunda Prognostik Kullanımının Değerlendirilmesi

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Abstract

Background: Serum bilirubin serves as a crucial biomarker for liver function and may reflect the severity of systemic inflammatory responses in critically ill patients. This study aims to assess the prognostic significance of serum bilirubin levels in predicting mortality among high-risk patients admitted to the emergency intensive care unit (EICU).
Materials and Methods: In this retrospective cohort study, an evaluation was conducted on high-risk patients admitted to the EICU between January 2020 and December 2022. The patients were grouped based on 28-day mortality outcomes. Serum bilirubin levels, along with other clinical and laboratory parameters, were recorded and examined using multivariable logistic regression and receiver operating characteristic (ROC) curve analysis.
Results: The most common comorbidities were Chronic Obstructive Pulmonary Disease (COPD) (80.2%) and sepsis (67.2%). Multivariate analyses identified hypertension (OR=4.165, p=0.004), sepsis (OR=8.459, p<0.001), chronic kidney disease (OR=3.910, p=0.009), and total bilirubin levels (OR=1.605, p=0.036) as independent risk factors for mortality. ROC curve analysis demonstrated that a total bilirubin cutoff value of 1.75 mg/dL provided 86.4% sensitivity and 60.0% specificity in predicting mortality. AUC was calculated to be 0.761, indicating that bilirubin levels possess significant power in distinguishing between surviving and died patients.
Conclusions: Elevated serum bilirubin levels have been identified as an independent predictor of mortality in critically ill patients. This finding suggests that bilirubin levels can serve as a reliable indicator in prognostic evaluations within the EICU setting, thereby contributing to more effective management of the patients' treatment process.

Keywords: Bilirubin, Mortality, Emergency intensive care unit, Prognostic marker, Sepsis

Öz

Amaç: Serum bilirubin, karaciğer fonksiyonunun önemli bir biyobelirteci olup, kritik hastalarda sistemik inflamatuar yanıtın şiddetini yansıtabilir. Bu çalışma, yoğun bakım ünitesine (YBÜ) kabul edilen yüksek riskli hastalarda serum bilirubin düzeylerinin mortaliteyi öngörmedeki prognostik önemini değerlendirmeyi amaçlamaktadır.
Materyal ve Metod: Bu retrospektif kohort çalışmasında, Ocak 2020 ile Aralık 2022 tarihleri arasında yoğun bakım ünitesine (YBÜ) kabul edilen yüksek riskli hastalar değerlendirilmiştir. Hastalar, 28 günlük mortalite sonuçlarına göre gruplandırılmıştır. Serum bilirubin düzeyleri ile diğer klinik ve laboratuvar parametreleri kaydedilmiş ve çok değişkenli lojistik regresyon ile alıcı işletim karakteristiği (ROC) eğrisi analizi kullanılarak incelenmiştir.
Bulgular: En sık görülen komorbiditeler Kronik Obstrüktif Akciğer Hastalığı (KOAH) (%80,2) ve sepsis (%67,2) olarak tespit edilmiştir. Çok değişkenli analizlerde hipertansiyon (OR=4,165, p=0,004), sepsis (OR=8,459, p<0.001), kronik böbrek hastalığı (OR=3,910, p=0,009) ve toplam bilirubin düzeyleri (OR=1,605, p=0,036) mortalite için bağımsız risk faktörleri olarak belirlenmiştir. ROC eğrisi analizi, 1,75 mg/dL'lik toplam bilirubin kesim değerinin mortaliteyi öngörmede %86,4 duyarlılık ve %60,0 özgüllük sağladığını göstermiştir. Eğri altında kalan alan (AUC) 0,761 olarak hesaplanmış ve bilirubin düzeylerinin sağ kalan ve ölen hastalar arasında anlamlı bir ayrım gücüne sahip olduğu gösterilmiştir.
Sonuç: Artmış serum bilirubin düzeyleri, kritik hastalarda mortalite için bağımsız bir öngördürücü olarak tanımlanmıştır. Bu bulgu, bilirubin düzeylerinin yoğun bakım ortamında prognostik değerlendirmelerde güvenilir bir gösterge olarak kullanılabileceğini ve hastaların tedavi sürecinin daha etkin yönetilmesine katkı sağlayabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Bilirubin, Mortalite, Yoğun bakım ünitesi, Prognostik belirteç, Sepsis

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Introduction

Bilirubin is a compound metabolized in the liver as a byproduct of heme catabolism and is excreted via bile. This pigment is an important biomarker that reflects the functional status of the liver, and elevated serum levels may indicate liver diseases as well as various systemic inflammatory processes (1,2). However, the prognostic value of bilirubin is not limited to liver diseases alone; it has been demonstrated that bilirubin can also be utilized to predict mortality risk, particularly among critically ill patients (3). A significant portion of patients admitted to intensive care units (ICUs) present with severe comorbidities such as sepsis, chronic kidney disease (CKD), and multiple organ failure, among which mortality rates have been found to be high. (4,5). Bilirubin levels rise as a result of inflammatory processes, oxidative stress, and cellular breakdown, and are therefore closely associated with overall mortality risk (6).

As clinical practice becomes increasingly complex, developing individualized approaches to patient treatment is becoming essential (7). Accurate prognostication in ICU patients is crucial not only for treatment planning but also for providing information to patients' families (8). The role of bilirubin levels in this context has been highlighted in numerous studies, repeatedly demonstrating that elevated levels are associated with poor prognosis (3,9). However, determining the independent impact of bilirubin levels on mortality requires new findings that would facilitate the integration of this biomarker into clinical decision-making processes (10,11).

This study aims to investigate the prognostic value of serum bilirubin levels on mortality among high-risk patients admitted to the ICU. We sought to determine whether bilirubin levels are an independent factor in predicting mortality when adjusted for other clinical and laboratory variables.

Materials and Methods

Patient Population and Study Design

This retrospective cohort study included high-risk patients admitted to the emergency intensive care unit (EICU) between January 2020 and December 2022. Our ICU is a tertiary care unit connected to the emergency department, comprising 23 intensive care beds and dedicated to the management of internal medicine and trauma patients. A total of 1,100 patients admitted to the ICU during the two-year period were reviewed. To ensure the homogeneity of the study, patients with pre-existing liver disease, those receiving hepatotoxic treatment, trauma patients, or those with incomplete medical records were excluded. A total of 116 patients aged 18 years and older, who had elevated bilirubin levels within the first 48 hours of ICU admission, were included in the study. Sepsis was diagnosed according to the Sepsis-3 criteria.

Accordingly, sepsis was defined as patients with a Quick SOFA (qSOFA) score of ≥2 or an increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score in response to infection. Septic shock was diagnosed based on the presence of vasopressor requirement and a lactate level exceeding 2 mmol/L (12). Chronic kidney disease (CKD) was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m² or albuminuria of ≥30 mg/g persisting for at least three months (13). Chronic obstructive pulmonary disease (COPD) was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, defined as a forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC) of <0.70, along with clinical evidence of persistent airflow limitation (14). Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication (15).

The study population was divided into two groups based on the 28-day mortality outcomes: survivors and non-survivors. Demographic characteristics such as age, gender, and comorbidities were recorded for each patient. In addition to bilirubin levels, other laboratory parameters such as albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and renal function tests were collected.

Statistical Analysis

Statistical analyses were performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) for data with a non-normal distribution. Categorical variables were summarized as frequencies and percentages. Normality of continuous data was assessed using the Shapiro-Wilk test. For comparisons between the survivor and deceased groups, the independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was applied for non-normally distributed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the context.

To identify independent predictors of mortality, multivariable logistic regression analysis was performed, including variables with a p-value < 0.05 in univariable analysis. Results from the logistic regression were reported as odds ratios (OR) with 95% confidence intervals (CI). The ability of serum bilirubin levels to predict mortality was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) calculated to assess discrimination. The Youden Index was applied to determine the optimal bilirubin cutoff value for mortality prediction, balancing sensitivity and specificity. Statistical significance was defined as a p-value < 0.05 for all tests.

Results

A total of 116 patients were included in this study, 71 of whom belonged to the surviving group. The mean age of the overall patient group was 68.3 ± 18.1 years, with an age range of 20 to 100 years. Regarding gender distribution, 61.2% of the patients were male. Among the comorbid conditions, sepsis was the most common, observed in 67.2% of the patients, followed by Chronic Obstructive Pulmonary Disease (COPD), seen in 80.2% of the cases. Diabetes (29.3%), hypertension (48.3%), and malignancy (44.0%) rates were also notable in Table 1.

Table 1. Demographic and Clinical Characteristics of The Study Population

Variables	n = 116
Age	68.3 ± 18.1
Gender (%)	
Male	45 (38.8)
Female	71 (61.2)
Diabetes (%)	34 (29.3)
Hypertension (%)	56 (48.3)
CHF (%)	47 (40.5)
Malignancy (%)	51 (44.0)
COPD (%)	23 (19.8)
CKD (%)	58 (50)
Sepsis (%)	78 (67.2)
Systolic Blood Pressure (mmHg)	119.9 ± 23.6
Diastolic Blood Pressure (mmHg)	70.0 ± 12.5
ALT (U/L)	46.1 (2.8-3418.5)
AST (U/L)	63.0 (6.1-9237.7)
Albumin (g/L)	2.4 (1.2-10.4)
GGT(U/L)	62.2 (6.1-784.0)
Blood Glucose (mg/dL)	124.3 (35.4-478.8)
WBC (10e3/uL)	14.5 ± 8.0
Total Bilirubin (mg/L)	1.9 (1.1-24.3)
HGB (g/dL)	10.1 ± 2.0

BP: Blood Pressure, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, WBC: White Blood Cell.

Table 2 shows the comparative analysis of the surviving and died groups. The died group was significantly older than the surviving group (p=0.005). Hypertension and Chronic Kidney Disease (CKD) (p=0.009) were significantly more prevalent in the died group. Sepsis was also significantly more common in the died group p<0.001. Liver function tests, including AST p<0.001, ALT p<0.001, and total bilirubin p<0.001, were found to be significantly higher in the died group. The albumin level was significantly lower in the died group p<0.001. *Table 3* and *Figure 1* evaluate the impact of variables on mortality between the died and surviving groups. Multivariate analysis demonstrated that hypertension (OR: 4.165, 95%CI: 1.562-11.108, P=0.004), sepsis (OR: 8.459, 95%CI: 2.828-25.305, P<0.001), chronic kidney disease (OR: 3.910, 95%CI: 1.399-10.925, P=0.009), and total bilirubin levels (OR: 1.605, 95%CI: 1.030-2.501, P=0.036) were independent predictors of mortality.

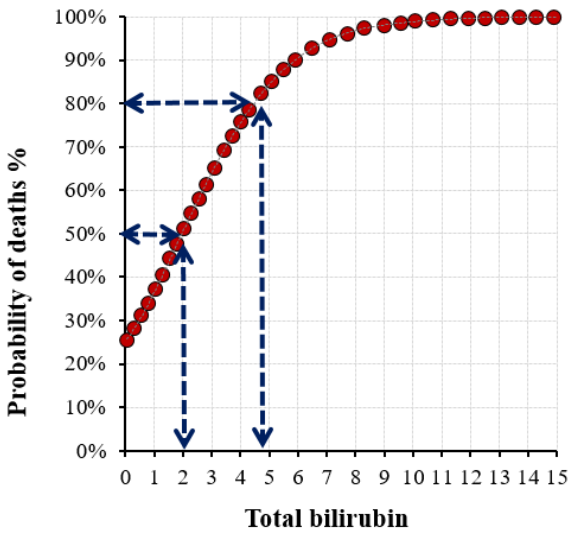

Figure 1. Probability of death based on total bilirubin levels

Table 4 and Figure 2 assess the effectiveness of total bilirubin levels in distinguishing between died and surviving patients using the area under the ROC curve. The effectiveness of total bilirubin in distinguishing between died and surviving patients was significant [Area under the curve 0.761 (0.674-0.849)]. A significant [Area under the curve 0.732 (0.635-0.828)] effectiveness was observed for a total bilirubin cutoff value of 1.75 in distinguishing between died and surviving patients. At a total bilirubin cutoff value of 1.75, the sensitivity in distinguishing between died and surviving patients was 86.4%, positive predictive value 74.0%, specificity 60.0%, and negative predictive value 76.9%.

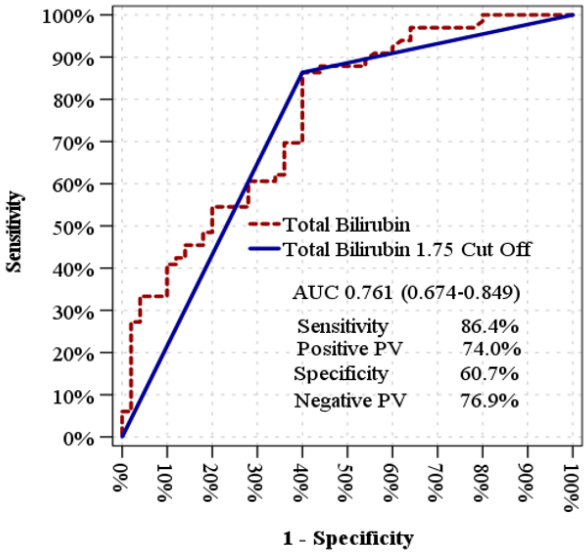

Figure 2. ROC curve analysis of total bilirubin and its 1.75 cut-off for predicting mortality

Table 2. Comparison of Demographic and Clinical Characteristics Between Surviving and Died Patients

		Surviving	Died		
Variables		**n=50**	**n=66**	p	
Age		62.1 ± 20.5	73.1 ± 14.5	***0.005***	m
Gender (%)	Female	22 (44.0)	23 (34.8)	0.316	X^2
	Male	28 (56.0)	43 (65.2)		
Diabetes (%)		18 (36.0)	16 (24.2)	0.168	X^2
Hypertension (%)		14 (28.0)	42 (63.6)	***0.001***	X^2
CHF (%)		15 (30.0)	32 (48.5)	***0.045***	X^2
Malignancy (%)		25 (50.0)	26 (39.4)	0.254	X^2
COPD(%)		8 (16.0)	15(22.7)	0.368	X^2
CKD (%)		18 (36.0)	40 (60.6)	***0.009***	X^2
Sepsis (%)		19 (38.0)	59 (89.4)	***0.001***	X^2
Systolic Blood Pressure (mmHg)		121.8±18.1	118.4±27.1	0.489	m
Diastolic Blood Pressure (mmHg)		70.0±10.1	69.9±14.1	0.686	m
ALT (U/L)		28.3	66.3	***0.001***	m
AST (U/L)		38.1	135.4	***0.001***	m
Albumin (g/L)		2.7	2.3	***0.001***	m
GGT (U/L)		62.2	61.8	0.971	m
Blood Glucose (mg/dL)		126.4	122.3	0.304	m
WBC (10e3/uL)		12.9	14.0	0.110	m
Total Bilirubin (mg/L)		1.7	2.4	***0.001***	m
HGB (g/dL)		10.2	9.1	0.092	m

m Mann-Whitney U Test , X^2 Chi-Square Test, SD: Standard Deviation.
BP: Blood Pressure, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, WBC: White Blood Cell.

Table 3. Univariate and Multivariate Logistic Regression Analysis of Factors Associated with Mortality

	Univariate Model						**Multivariate Model**				
	OR	**%95 CI**			**p**		**OR**	**%95 CI**			**p**
Age	1.037	1.013	-	1.061	*0.002*						
Hypertension	4.500	2.031	-	9.969	*0.001*		4.165	1.562	-	11.108	*0.004*
CHF	2.196	1.013	-	4.761	*0.046*						
CKD	2.735	1.279	-	5.847	*0.009*		3.910	1.399	-	10.925	*0.009*
Sepsis	13.752	5.216	-	36.260	*0.001*		8.459	2.828	-	25.305	*0.001*
ALT	1.001	1.000	-	1.002	0.132						
AST	1.003	1.000	-	1.006	*0.035*						
Albumin	0.995	0.965	-	1.026	0.734						
Total Bilirubin	1.752	1.164	-	2.637	*0.007*		1.605	1.030	-	2.501	*0.036*
Logistic Regression (Forward LR), OR: Odds Ratio, CI: Confidence Interval, SD: Standard Deviation											

BP: Blood Pressure, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, WBC: White Blood Cell.

Table 4. Receiver Operating Characteristic (ROC) Curve Analysis for Total Bilirubin and Its Predictive Value for Mortality

		Area Under the Curve			% 95 Confidence Interval			p
Total Bilirubin		0.761			0.674	-	0.849	***0.001***
Total Bilirubin 1.75 Cut Off		0.732			0.635	-	0.828	***0.001***
		Surviving	Died					%
Total Bilirubin	≤ 1.75	30	9		Sensitivity			86.4%
	> 1.75	20	57		Pozitive Predictive Value			74.0%
					Specificity			60.0%
					Negative Predictive Value			76.9%

ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval.

Discussion

This study demonstrated that elevated serum bilirubin levels are independently associated with mortality in critically ill patients admitted to the emergency intensive care unit. Additionally, hypertension, sepsis, and chronic kidney disease were identified as significant predictors of mortality. These findings suggest that bilirubin levels could be integrated into clinical prognostic models to enhance risk stratification. Age was found to be significantly associated with mortality, with older age strongly correlated with higher mortality rates, consistent with previous research conducted in intensive care settings. Elderly patients are more susceptible to the systemic effects of critical illnesses, and their physiological reserves are often inadequate to counteract the stress of severe conditions (16). This vulnerability is further exacerbated by the presence of comorbidities, which are more prevalent in older populations. Conversely, gender did not emerge as a significant predictor of mortality in our study, aligning with several studies suggesting that gender differences in ICU outcomes are generally negligible when other variables are controlled (17,18).

The significant association between high bilirubin levels and mortality observed in this study is consistent with previous research. Bilirubin, an indicator of oxidative stress and inflammation, has been linked to adverse outcomes in various patient populations, including those with sepsis and liver dysfunction (19). The mechanisms underlying this relationship are multifaceted, involving the role of bilirubin in modulating inflammatory responses and its potential as a surrogate marker of hepatic and extrahepatic injury (20). Prior studies have demonstrated that hyperbilirubinemia is associated with increased mortality in septic patients, supporting the notion that elevated bilirubin levels may reflect the severity of systemic inflammation and multiple organ failure (21). The role of total bilirubin levels in predicting mortality is particularly noteworthy when compared with comorbidities such as sepsis, chronic kidney disease (CKD), and hypertension. Our study demonstrated that elevated bilirubin levels remained significantly associated with mortality even after adjusting for these comorbidities (22). This finding suggests that bilirubin levels not only reflect liver function but also serve as an indicator of systemic inflammation and organ dysfunction (1,23).

When evaluated through ROC analysis, bilirubin levels were found to provide high sensitivity and acceptable specificity in predicting mortality, with a cutoff value of 1.75 mg/dL. This result supports the use of bilirubin levels as a prognostic marker in critically ill patients in the ICU (8,11). However, the predictive capability of bilirubin levels in forecasting mortality should be assessed in conjunction with other clinical markers. For instance, low albumin levels have also been associated with poor prognosis, and in our study, this was found to be an independent risk factor for mortality alongside bilirubin (9,24). The prognostic value of bilirubin may vary depending on the underlying cause of its elevation. For example, patients with pre-existing liver disease may have chronically elevated bilirubin levels, complicating its use as a mortality predictor (25,26). In contrast, acute elevations in bilirubin in the context of sepsis or multiple organ failure are more likely to reflect the severity of critical illness and may presage a poorer prognosis (1). Therefore, while bilirubin is a useful marker, its interpretation should be contextualized within the broader clinical picture.

When comparing our findings with similar studies, the prognostic utility of bilirubin in critically ill patients appears robust. For instance, the study by Shah et al. found that elevated bilirubin levels were associated with increased mortality in septic ICU patients, reinforcing our findings (27). Additionally, the results of our study are consistent with the research by Han et al., which suggested that bilirubin, when used alongside a broader panel of liver function tests, can effectively predict mortality in the ICU setting (11). These studies and our findings suggest that bilirubin should be routinely considered in prognostic assessments, particularly in critically ill patients with complex comorbidities.

Our study has important implications for clinical practice. Integrating bilirubin levels into the prognostic assessments of ICU patients may improve risk stratification and guide therapeutic decision-making. For instance, patients with elevated bilirubin levels may benefit from more aggressive monitoring and early interventions to prevent adverse out-

comes (28). Furthermore, our findings suggest that bilirubin could serve as a therapeutic target for interventions aimed at reducing oxidative stress and improving patient outcomes in the ICU (29). The use of bilirubin levels as a prognostic marker is also important for treatment planning. In patients with elevated bilirubin levels, closer monitoring and the implementation of aggressive treatment strategies may improve prognosis. However, an aggressive treatment approach is feasible only with a detailed assessment of the clinical condition in the intensive care unit and the creation of an individualized plan. For instance, elevated bilirubin levels in patients with sepsis may indicate liver dysfunction or multiple organ failure, necessitating early initiation of hemodynamic support or organ support therapies. In this context, bilirubin levels can serve not only as a prognostic marker but also as a guide in determining therapeutic strategies (30).

Limitations

This study has several limitations. Its retrospective design may introduce selection bias and limit the generalizability of the findings. Additionally, liver function was not assessed using advanced imaging or histopathological evaluation, which could have provided more detailed insights into bilirubin dynamics and its prognostic value.

Conclusion

This study highlights the independent association of bilirubin with mortality, emphasizing its importance as an indicator of disease severity, alongside factors such as age, sepsis, and chronic kidney disease (CKD). The findings suggest that bilirubin levels can serve as a reliable prognostic marker in critically ill patients, thereby contributing to improved risk stratification and guiding therapeutic decisions.

Ethical Approval: *The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (Approval Date: March 15, 2023; Approval Number: 86). The study was conducted in accordance with the principles of the Helsinki Declaration*

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Research Article / Araştırma Makalesi

A Unique Pathognomic Skin Manifestation of Familial Mediterranean Fever: Erysipelas-Like Erythema

Ailevi Akdeniz Ateşinin Eşsiz Patognomik Cilt Bulgusu: Erizipel Benzeri Eritem

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Abstract

Background: The present study aimed to describe the differences between patients with and without ELE in patients with Familial Mediterranean Fever (FMF) and to determine the relationship between erysipelas-like erythema (ELE) and demographic, clinical, genetic and treatment characteristics of the patients.
Materials and Methods: The medical files of patients who were followed up with a diagnosis of FMF in the Pediatric Rheumatology Department of Gaziantep City Hospital between October 2023 and October 2024 were retrospectively analysed.
Results: Of 409 patients with FMF, 205 (50.1%) were male. The median age at diagnosis was 6 (minimum:1-maximum:18) years. FMF attack was accompanied by fever in 325 (79.5%), abdominal pain in 302 (73.8%), arthralgia in 121 (29.6%), arthritis in 56 (13.7%), chest pain in 62 (15.6%) and ELE in 55 (13.4%) patients. When comparing patients with ELE to those without, the frequencies of chest pain, arthralgia, and arthritis were significantly higher in the ELE group (p=0.014, p<0.001, p<0.001, respectively).
Pathological mutations were significantly more common in FMF with ELE than those without one (p<0.001). Additionally, among FMF patients, the use of anti-interleukin-1 (anti-IL-1) treatment combinations due to colchicine resistance was significantly higher in those with ELE (p<0.001).
Conclusions: The present study showed that ELE may be associated with subclinical inflammation, arthritis, colchicine resistance, pathogenic mutations, and severe disease scores in FMF patients. Based on these findings and existing literature, we believe that the presence of ELE in FMF patients is significant in terms of diagnosis, prognosis, and predicting the course of the disease.

Keywords: Anti-interleukin-1, Colchicine resistance, Erysipelas-like erythema, Familial mediterranean fever

Öz

Amaç: Bu çalışmanın amacı erizipel benzeri eritemi olan ve olmayan Ailevi Akdeniz Ateşi (AAA) hastaları arasındaki farklılıkları tanımlamak ve erizipel benzeri eritem ile hastaların demografik, klinik, genetik ve tedavi özellikleri arasındaki ilişkiyi ortaya koymaktır.
Materyal ve Metod: Ekim 2023 ve Ekim 2024 tarihleri arasında Gaziantep Şehir Hastanesi Çocuk Romatoloji bölümünde AAA tanısıyla takip edilen hastaların dosyaları retrospektif olarak incelendi.
Bulgular: Ailevi Akdeniz Ateşi olan 409 hastanın 205'i (%50,1) erkekti. Hastaların tanı yaşı ortanca 6 (minimum:1-maksimum:18) yıldı. Hastaların 325'inde (%79,5) ateş, 302'sinde (%73,8) karın ağrısı, 121'inde (%29,6) artralji, 56'sında (%13,7) artrit, 62'sinde (%15,6) göğüs ağrısı ve 55'inde (%13,4) erizipel benzeri eritem FMF atağına eşlik ediyordu.
Erizipel benzeri eritemi olan hastalar olmayanlarla karşılaştırıldığında, göğüs ağrısı, artralji ve artrit sıklıkları erizipel benzeri eritemi olan grupta anlamlı olarak daha yüksekti (sırasıyla p=0.014, p<0.001, p<0.001).
Ailevi Akdeniz Ateşi hastalarında patolojik mutasyonlar ELE'si olanlarda ELE'si olmayanlardan daha yaygındı (p<0,001). Ayrıca AAA hastaları arasında kolşisin direnci nedeniyle anti-interlökin-1 tedavi kombinasyonlarının kullanımı erizipel benzeri eritemili hastalarda anlamlı derecede daha yüksekti (p<0.001).
Sonuç: Bu çalışma erizipel benzeri eritemin AAA hastalarında subklinik inflamasyon, artrit, kolşisin direnci, patojenik mutasyonlar ve ciddi hastalık skorları ile ilişkili olabileceğini göstermiştir. Bu bulgulara ve mevcut literatüre dayanarak AAA hastalarında erizipel benzeri eritem varlığının tanı, prognoz hem de hastalık seyrinin öngörülmesi açısından öneme sahip olduğana inanıyoruz.

Anahtar Kelimeler: Ailevi akdeniz ateşi, Anti-interlökin-1, Erizipel benzeri eritem, Kolşisin direnci

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Introduction

Familial Mediterranean Fever (FMF), an autoinflammatory disease characterized by fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema (ELE), is an autosomal recessive hereditary disease affecting ethnic groups, primarily those living in the Mediterranean region, such as Turkish, Armenian, Arab, and Jewish (1,2). Attacks are self-limiting and typically resolve within 1–3 days. FMF attacks usually begin in early childhood (3). Colchicine remains the mainstay of FMF treatment, aiming to prevent acute attacks and chronic inflammation (4). If left untreated, FMF patients are at risk of developing severe secondary amyloidosis, especially in the kidneys, and potentially renal failure.

Clinical manifestations of FMF are linked to mutations in the MEFV gene (2). More than 300 mutations of the MEFV gene that can lead to FMF have been identified (5). Detailed information about each mutation, including variant details, phenotype/genotype relationships, and pathogenicity, can be found in the InFevers database. M694V, M680I, V726A, and M694I are the most recognized and prevalent pathogenic mutations. While E148Q is a common mutation, its pathogenicity remains unknown (6).

The presence of mucocutaneous symptoms is clinically significant, as it may represent the first manifestation or the activation phase of autoinflammatory rheumatic diseases (7). Erysipelas-like erythema is a rare but essential and pathognomonic skin finding associated with FMF (7,8). The lesions are characterized by tender, erythematous plaques on the legs. These plaques can be triggered by physical exertion and usually resolve spontaneously after 48 to 72 hours of rest.

This study aimed to define the differences between FMF patients with and without ELE and to reveal the relationship between ELE and patients' demographic, clinical, genetic, and treatment characteristics.

Materials and Methods

Patients

The medical records of patients who were followed up with a diagnosis of FMF in the Pediatric Rheumatology Unit of Gaziantep City Hospital between October 2023 and October 2024 were retrospectively analyzed. Sixty-nine patients with incomplete file data, no regular follow-up, less than 6 months of follow-up, and eight patients with comorbid diseases were excluded from the study. The study included 409 patients who met Yalçınkaya and Özen's FMF diagnostic criteria (patients with at least three attacks lasting 6-72 hours; axillary fever above 38°C, abdominal pain, chest pain, arthritis, and at least two of the following criteria for FMF in the family) and re-evaluated by an expert (AT) and the diagnosis of FMF was confirmed (9,10).

Definitions

In this study, the PRAS disease severity score adapted to children (i.e., in terms of age and colchicine doses) by Özen and colleagues was used to determine the disease activity of FMF patients (11,12). For the calculation of the PRAS score, the age at presentation, the frequency of attacks in one month, arthritis, amyloidosis, and the dose of colchicine were recorded. ELE was removed from the score because it would affect the result. PRAS score was calculated as 2,3,4 points for 11 years, 6-10 years and under 6 years, respectively. 1 point for fewer than one attack per month, 2 points for 1-2 attacks per month, 3 points for more than two attacks per month, 2 points for acute arthritis, 3 points for chronic arthritis, and 3 points for amyloidosis. Colchicine dosage earns points: 1 point for less than 1 mg/day, 2 points for 1 to 1.5 mg/day, and 3 points for 2 mg/day.

All FMF patients included in the study were defined according to the International Study Group for Systemic Autoinflammatory Diseases (INSAID) classification criteria as MEFV variants a) pathogenic, b) likely pathogenic, c) variant of uncertain significance (VUS), d) likely benign, e) benign, f) unclassified (13).

One attack per month or persistence of subclinical inflammation despite colchicine use for at least 6 months was considered colchicine resistance (13-15). Elevated acute phase reactants in the absence of clinical symptoms were defined as subclinical inflammation (13).

Study Protocol

All FMF patients included in the study were analyzed by dividing them into two groups, those with and without ELE findings. It was investigated whether there were any differences between these two groups regarding demographic findings, clinical features, laboratory findings, genetic analyses, disease severity score, and treatments.

This study was evaluated and approved by the XXX ethics committee (Approval number/date: 94/2024-18.12.2024). All procedures performed during the study were fully compliant with ethical rules and the principles outlined in the Declaration of Helsinki.

Statistical Analysis

The data obtained were analyzed using version 22.0 of the Statistical Package for Social Sciences (SPSS). Chi-square (X^2) tests were conducted to compare categorical variables between groups. Categorical variables are presented as frequencies (n) and percentages, while continuous variables are presented as median values and minimum and maximum ranges. The Shapiro-Wilk test was employed to assess the normality of the data distribution. Independent-sample t-tests were used to compare two independent groups for normally distributed variables, whereas the Mann-Whitney U test was applied for non-normally distributed variables. The statistical significance level was accepted as $p < 0.05$.

Results

Of 409 patients with FMF, 205 (50.1%) were male. The median (minimum-maximum) age at disease onset was 5 (1-18) years, and the median age at diagnosis was 6 (1-18) years. The median delay in diagnosis was 1 year (0-13). FMF attack was accompanied by fever in 325 (79.5%), abdominal pain in 302 (73.8%), arthralgia in 121 (29.6%), arthritis in 56 (13.7%), chest pain in 62 (15.6%) and ELE in 55 (13.4%) patients (Table 1). Consanguinity was present in 102 (24.9%) patients. Family history of the patients: 97 patients had at least one history of FMF in their first, second, or third-degree relatives.

In the attack-free period, the mean ESR was 7.2 ± 5.3 mm/hour, and the mean CRP was 3 ± 2.5 mg/L. In the attack, the mean ESR was 28.1 ± 22.7 mm/hour, and the mean CRP was 41.1 ± 34.4 mg/L.

The most common MEFV mutation was M694V homozygous mutation detected in 73 (17.8%) patients.

During the last visit, 320 (78.2%) had mild disease activity (PRAS <6), 69 (16.9%) had moderate disease activity (PRAS= 6-8) and 20 (4.9%) had severe disease activity (PRAS ≥ 9). 382 (93.4%) patients were treated with colchicine only. Colchicine treatment was discontinued in 27 (2.3%) patients during follow-up. Colchicine resistance was present in 12 (2.9%) patients whose attacks could not be controlled despite colchicine treatment, and anti-interleukin-1 (Anti-IL-1) treatment was added to these patients in addition to colchicine treatment. Of the patients receiving anti-IL-1 treatment, 10 (83.3%) used canakinumab and 2 (16.7%) used anakinra.

Table 1. Demographic, clinical and laboratory characteristics of FMF

	All FMF n= 409	**FMF with ELE n= 55**	**FMF without ELE n= 354**	***p value***
Age at diagnosis, years, median (min-max)	6 (1-18)	7 (2-15)	6 (1-16)	0.426
Gender, n (%)				
Male	205 (50.3)	18 (32.7)	187 (52.8)	**0.004**
Female	204 (49.7)	37 (67.3)	167 (47.2)	
Fever, n (%)	325 (79.5)	39 (70.9)	286 (80.8)	0.320
Abdominal pain, n (%)	302 (73.8)	37 (67.24)	265 (74.9)	0.250
Chest pain, (%)	62 (15.6)	15 (27.2)	47 (13.3)	**0.014**
Arthralgia, n (%)	121 (29.6)	29 (52.7)	92 (26)	**<0.001**
Arthritis, n (%)	56 (13.7)	23 (41.8)	33 (9.3)	**<0.001**
WBC count, x10^9/L Median (min-max)	10.4 (5.9-15.9)	10.8 (5.9-15.9)	9.7 (6.1-14)	0.530
Hemoglobin, g/dL Median (min-max)	12.1 (10.1-16.4)	12.8 (10.1-15.3	11.8 (10.5-16.4)	0.860
Thrombocyte, x10^9/L Median (min-max)	383 (236-564)	386 (252-334)	363 (236-564)	0.617
PRAS score**,** mean±sd	6.3±0.5	9.2±18	5.9±1.1	**<0.001**
Anti-IL-1	12 (2.9)	8 (14.5)	4 (1.1)	**<0.001**

Anti-IL-1: anti-interleukin-1; ELE: erysipelas-like erythema; FMF: familial mediterranean fever; WBC: white blood cell; Bold values are p <0.05 is statistically significant.

Analysis of patients with and without ELE

Of the 55 patients with ELE, 37 (67.3%) were female, and it was found to be significantly more frequent in females (p=0.004).

Among these 55 patients, the following symptoms were observed: 39 patients (70.9%) experienced fever, 37 patients (67.2%) had abdominal pain, 15 patients (27.2%) reported chest pain, 29 patients (52.7%) experienced arthralgia, and 23 patients (41.8%) showed signs of arthritis. Out of the patients with arthritis accompanying ELE, 15 (65.2%) had arthritis in the ankle, 6 (26.1%) in the knee, and 2 (8.7%) had sacroiliitis.

When comparing patients with ELE to those without, the frequencies of chest pain, arthralgia, and arthritis were significantly higher in the ELE group (p=0.014, p< 0.001, p< 0.001, respectively). However, there were no significant differences in fever and abdominal pain (p =0.320, p =0.250, respectively).

FMF patients with ELE exhibited significantly higher frequent subclinical inflammation and/or attacks and higher PRAS scores at the last follow-up (p<0.001 for both).

The most frequently detected MEFV gene mutation in FMF patients with ELE was the homozygous M694V mutation, found in 30 (54.5%) patients. Pathological mutations were significantly more common in FMF patients with ELE than those without one (p<0.001). However, no significant differences were observed regarding the frequencies of possible pathological, benign, or clinically unknown mutations (p=0.230, p=0.560, p=0.220, respectively). In addition, among FMF patients, the use of anti-IL-1 treatment combinations due to colchicine resistance was significantly more common in ELE patients (p < 0.001).

Discussion

Familial Mediterranean fever, the most common hereditary periodic fever syndrome, is characterized by attacks of inflammation, although subclinical inflammation may persist during attack-free periods (16). The presence of mucocutaneous symptoms is of clinical importance as it may be part of the activation phase and a clue of autoinflammatory rheumatic diseases (8). ELE is a rare but pathognomonic finding of FMF and has been associated with subclinical inflammation and high disease activity (17,18). This study demonstrated that ELE is linked to a higher frequency of pathogenic mutations, increased subclinical inflammation, more severe disease, and a greater likelihood of colchicine resistance and anti-IL-1 treatment requirements in FMF patients. This study showed that the presentation of ELE in FMF is not only pathognomonic for the diagnosis but also an important and noteworthy finding for the course of the disease.

Mutations in the MEFV gene, which encodes the pyrin protein, cause the clinical picture in FMF patients (2). In a study evaluating pediatric FMF patients, Yildirim et al. reported that the M694V homozygous mutation was more frequent in FMF with pediatric FMF in whom there is ELE (7). In another study, Çakmak et al. reported that homozygous M694V mutation was statistically significantly more common in the FMF group with ELE (19). Similarly, Öztürk et al. reported that the frequency of ELE was significantly higher in patients with M694V homozygous mutations compared to other patients (20). Moradian et al. reported that exon 10 mutations, especially the M694V mutation, were more common in FMF patients with ELE (21). In contrast to these studies, Arpaci et al. reported that the mutation E148Q was the more frequent MEFV mutation in FMF patients with ELE (2). In the present study, the most common mutation in FMF patients with ELE was the homozygous M694V mutation, and pathological mutations were more common in the ELE group.

Subclinical inflammation is an important indicator, as it impacts the treatment and monitoring of FMF. Many studies have demonstrated that ELE is a key finding indicating subclinical inflammation.

Bayram et al. reported in their study evaluating pediatric FMF patients that ELE is an independent risk factor for subclinical inflammation in FMF patients (18). Yıldırım et al. reported in their study evaluating pediatric FMF patients that ELE may predict persistent inflammation in FMF patients (17). Avar-Aydın et al. reported that ELE indicates severe disease course and subclinical inflammation in pediatric FMF patients (22). Another study reported that FMF patients with ELE tend to have a more severe disease course (23). In this study, subclinical inflammation was found to be more common in patients with ELE than those without ELE, which is consistent with the literature.

Arthritis in children with FMF is usually monoarticular and affects primarily the lower extremities (hip, knee, ankle) (24). Yıldırım et al. reported that arthritis was more common in patients with ELE in their study evaluating pediatric FMF patients (7). In a similar study, Avar-Aydın et al. reported that arthritis was more common in patients with ELE (22). In this study, in agreement with the authors, more arthritis was observed in FMF with ELE than in FMF without ELE.

It was reported that colchicine could potentially prevent FMF attacks (25). Biologic agents such as anakinra, rilonacept, canakinumab, tocilizumab, etanercept, infliximab, or adalimumab may be helpful for individuals resistant or intolerant to colchicine (2). Mosa et al. reported that ELE was more common in colchicine-resistant patients in a study including pediatric FMF patients (26). Yıldırım et al. reported that higher doses of colchicine were required in pediatric FMF patients due to the severe disease course in patients with ELE (7). Batu et al. reported that ELE may be a clue for less colchicine response in a study evaluating pediatric FMF patients (27). Avar-Aydın et al. reported that anti-IL-1 therapy was used more frequently in pediatric FMF patients with ELE (28). In addition, Aktay Ayaz et al. developed a scoring system containing ELE to predict colchicine resistance in a study involving pediatric FMF patients (29). In this study, colchicine and colchicine resistance-associated anti-IL-1 use was more common in FMF patients with ELE than in the group without ELE.

The most important limitations of this study are the retrospective design and the single-center patients. Another limitation is the short follow-up period, which makes it impossible to observe whether patients will have ELE at follow-up. Despite this, a large number of patients from a single center were evaluated.

In conclusion, the present study showed that ELE may be associated with subclinical inflammation, arthritis, colchicine resistance, pathogenic mutations, and severe disease scores in FMF patients. Based on these findings and the existing literature, we believe that the presence of ELE in FMF is important not only for diagnosis but also for prognosis and prediction of disease course.

Ethical Approval: *The study was approved by the Gaziantep City Hospital, ethics committee before the study. (Approval number/date: 94/24-18.12.2024). Due to the retrospective design of the study, no patient consent was obtained.*

Author Contributions:
Concept: S.C.
Literature Review: S.C, A.T.
Design : S.C., A.T.
Data acquisition: S.C., A.T.
Analysis and interpretation: S.C.
Writing manuscript: S.C., A.T.
Critical revision of manuscript: S.C.

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Araştırma Makalesi / Research Article

Sağlık Çalışanlarında HIV ile Yaşayan Bireylere Yönelik Damgalama

Stigmatization of People Living with HIV in Healthcare Workers

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Öz

Amaç: Günümüzde insan immün yetmezlik virüsü (Human Immunodeficiency Virus - HIV) enfeksiyonu tedavi edilebilir kronik bir hastalık olup görülme sıklığı artmaktadır. Bu enfeksiyona sahip olan hastaların karşılaştığı en büyük zorluklardan biri damgalanma ve ayrımcılıktır. Damgalanan kişi, hastalığı nedeniyle başkaları tarafından ön yargıya ve itibarsızlaştırmaya maruz kalmaktadır. Ayrımcılıkta ise bu ön yargı, kişiye karşı olumsuz bir eyleme dönüşmektedir. Sağlık çalışanları arasında HIV ile yaşayan bireylere (HİYB) yönelik damgalama ve ayrımcılık, sağlık hizmetlerinde aksamalara neden olmaktadır**.** Bu çalışmada, bir eğitim ve araştırma hastanesindeki sağlık çalışanlarının HIV enfeksiyonu hakkındaki bilgi düzeyi ve HİYB'lere yönelik damgalanmanın boyutu incelenmiştir.
Materyal ve metod: Hastanemizde çalışan asistan ve uzman doktorlar, hemşire ve laborantlar ile temizlik personeli ve hasta bakıcılardan oluşan toplam 304 kişi, gönüllülük esasına dayalı olarak 18-25 Mart 2022 tarihleri arasında çalışmaya dahil edilmiştir. Katılımcılardan internet üzerinden 12 soruluk bir anket doldurmaları istenmiştir. Katılımcıların HİYB'lere karşı sosyal ve mesleki hayatlarındaki yaklaşımları, HIV/edinsel immün yetmezlik sendromu (Acquired Immunodeficiency Syndrome - AIDS) ve kanda belirlenemeyen HIV viral yükü olanların cinsel yolla hastalığı bulaştırmadığını belirten "Belirlenemeyen=Bulaştırmayan" (B=B) hakkındaki bilgi düzeyleri değerlendirilmiştir.
Bulgular: Ankete katılanların %63,9'u kadın, %36,5'i erkektir. Katılımcıların %43,4'ü doktor, %29,9'u hemşire/laborant ve %26,6'sı hasta bakıcı/temizlik personeli olup toplamda %45,4'ü 20-29, %33,6'sı 30-49, %13,2'si 40-49, %7,9'u 50-65 yaş aralığındadır. HIV ile enfekte bir sağlık çalışanının yakınına sağlık hizmeti vermesi, HİYB ile yemeğini paylaşmak veya aynı tuvaleti kullanmak sağlık çalışanları arasında belirgin bir tutum farklılığı oluşturmamıştır. HIV ile enfekte kişilerin ameliyatında bulunmak doktorlar ile hemşireler ve laborantlar için daha büyük bir endişe kaynağı olmuştur. Temizlik personelleri ve hasta bakıcılar ise non-invaziv işlemler konusunda daha çekingen yaklaşmaktadır. HIV ile ilgili temel bilgilere en az temizlik personelleri ve hasta bakıcılar sahiptir. Belirlenemeyen=Bulaştırmayan kavramı en çok doktorlar tarafından bilinmektedir ($p<0,001$). Daha önce B=B kavramını duymayan katılımcıların bilgilendirme metni sonrasındaki tutumlarında sağlık çalışanları arasında istatistiksel olarak anlamlı bir fark bulunmamıştır ($p=0,226$).
Sonuç: Sağlık çalışanlarının eğitim düzeyinin düşük olması ve HIV hakkındaki bilgilerinin yetersizliği, enfekte olma korkusuna yol açarak damgalamaya ve sağlık hizmetlerinde aksamaya neden olmaktadır. Bu nedenle, sağlık çalışanlarına yönelik HIV ile ilgili bilgilendirme eğitimlerinin meslek hayatına başlanmadan önce öğrencilik yıllarında verilmesi ve hastane içinde belirli periyotlarla tekrar edilmesi, damgalamayı azaltabilecektir.

Anahtar Kelimeler: Damgalama, HIV/AIDS, Sağlık çalışanı

Abstract

Background: Human Immunodeficiency Virus (HIV) infection is a chronic disease and increasing today. Stigma and discrimination are among the biggest challenges facing by people living with HIV (PLWH). A stigmatized person is subject to prejudice and discredit by others due to their illness. In discrimination, this prejudice turns into a negative action against the person. Stigmatization and discrimination against PLWH among healthcare professionals cause disruptions in healthcare services. This study aimed to show the level of knowledge of the healthcare workers in a training and research hospital about HIV and the extent of the stigmatization of PLWH.
Materials and Methods: A total of 304 volunteers from assistant and specialist doctors, nurses/laboratory workers, cleaning staff/caregivers in our hospital were included in the study between 18-25 March 2022. They were asked to fill out a 12-question questionnaire online. The approaches to healthcare workers in their social and professional lives, their knowledge levels about HIV/Acquired Immunodeficiency Syndrome (AIDS) and an undetectable level of HIV viral load in the blood does not transmit HIV infection to his/her sexual partner "Undetectable=Untransmittable" (U=U) were questioned.
Results: Of the participants, 63.9% were female and 36.5% were men. In total, 43.4% people were doctors, 29.9% people were nurses/laboratory workers and 26.6% people were cleaning staff/caregivers and 33.6% of those who answered the questions are between the ages of 20-29, 13.2% are between the ages of 40-49, and 7.9% are between the ages of 50-65. HIV infected healthcare worker providing health care to their relative, sharing food with a PLWH and using the same toilet did not create a significant difference in attitudes among healthcare workers. While performing surgery on PLWH caused hesitation among doctors and nurses/laboratory workers, non-invasive procedures caused hesitation among auxiliary health personnel. Staff and caregivers had the least basic knowledge of HIV. The concept of U=U was best known to doctors ($p<0.001$). There was no significant difference in the post-informing attitudes among healthcare workers who had not heard of the concept U=U before ($p=0.226$).
Conclusions: The low level of education and insufficient knowledge of healthcare workers about HIV cause the fear of being infected, which leads to stigma and disruption in health services. The lack of change in the dripping attitude despite education suggested that other factors caused stigma. However, starting information training during the student years and repeating it at regular intervals within the hospital will reduce stigma among healthcare professionals.

Keywords: Healthcare workers, HIV/AIDS, Stigma

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Giriş

Edinsel immün yetmezlik sendromu (Acquired Immunodeficiency Syndrome -AIDS) ilk kez 1981 yılında tanımlanmış, 1983 yılında bu sendroma yol açan virüs izole edilmiş ve insan immün yetmezlik virüsü (Human Immunodeficiency Virus - HIV) olarak isimlendirilmiştir. Virüs bulaştıktan sonra tedavi edilmezse hastalık ölümle sonuçlanmaktadır (1). Antiretroviral tedavi (ART) ile HIV ilişkili morbidite ve mortalite önemli ölçüde azalmış ve HIV ile yaşayan bireylerin (HİYB) yaşam süresi uzamıştır (2).

Birleşmiş Milletler HIV/AIDS programı (Joint United Nations Programme on HIV/AIDS - UNAIDS) verilerine göre 2024 yılı itibarıyla dünyada 39,9 milyon HİYB bulunmaktadır. Küresel olarak yeni tanı alan HİYB'lerin azalmasına rağmen, AIDS'e bağlı ölümlerde yıllar içinde belirgin bir azalma olduğu için HİYB'lerin sayısı artmaktadır (3). Ülkemizde ise yeni tanı alan HİYB'lerin sayısında artışın devam ettiği görülmektedir (4).

Günümüzde HİYB'lerin karşılaştığı en büyük zorluklardan biri damgalanma ve ayrımcılıktır. HIV ile ilgili damgalama, HİYB'lere karşı ön yargı, küçümseme, itibarsızlaştırma ve ayrımcılık olarak tanımlanmıştır (5). Sağlık çalışanlarının HIV enfeksiyonu hakkındaki yetersiz bilgi düzeyi, damgalamaya ve ayrımcılığa neden olmaktadır (6,7). Çalışmalar, sağlık hizmeti sunumunda HİYB'lere yönelik ayrımcılığın, sağlık çalışanları tarafından bakımın reddi, mahremiyet ihlalleri, olumsuz tutumlar ve küçük düşürücü uygulamalar olarak ortaya çıktığını bildirmiştir (8).

Bu çalışmada sağlık çalışanlarının HIV enfeksiyonu hakkındaki bilgi düzeyi ve HİYB'lere yönelik damgalanmanın boyutunu göstermek amaçlanmıştır.

Materyal ve Metod

Bir eğitim ve araştırma hastanesinde çalışan asistan ve uzman doktorlar, hemşireler ve laborantlar ile temizlik personeli ve hasta bakıcılardan gönüllülük esasına göre toplamda 304 kişi 18-25 Mart 2022 tarihleri arasında kesitsel bir anket çalışmasına dahil edilmiştir. Hastane geneli dolaşılarak ankete katılmak için gönüllülerin e-posta adreslerine 12 soruluk anket linki gönderilmiştir. Anket, katılımcılar tarafından gözlem altında olmadan doldurulmuştur. Katılımcıların HİYB'lere karşı yaklaşımları, HIV/AIDS ve Belirlenemeyen=Bulaştırmayan (B=B) kavramı hakkındaki bilgi düzeyleri sorgulanmıştır.

Ankete katılanlara, son sorudan önce B=B ile ilgili bilgilendirme metni sunulmuş ve okunması istenmiştir. Bu metnin açıklaması şu şekildedir: "HPTN 052 klinik çalışmasına 10 yıl boyunca 1,600'den fazla heteroseksüel çift dahil edilmiş olup en az 6 ay boyunca HIV viral yükü kanda belirlenemeyen HİYB'nin cinsel yolla HIV enfeksiyonunu partnerine bulaştırmadığı kabul edilmiştir. Daha sonrasında yapılan PARTNER ve Opposites Attract çalışmaları da HPTN 052 çalışmasının sonucunu güçlendirmiştir.

PARTNER çalışmasının ikinci aşaması olan PARTNER2 çalışmasından elde edilen bulgular, B=B kavramının yalnızca heteroseksüel çiftlerde değil, aynı zamanda biseksüel ve erkekle seks yapan erkeklerde (men who have sex with men - MSM) de geçerli olduğuna dair kesin kanıtlar sağladığını göstermiştir" (9). Açıklama metni sonrası HİYB'lere karşı tutumlarında değişiklik olup olmadığı tek bir soru ile sorgulanmıştır.

Çalışma için 01.03.2023 tarihinde İstanbul Haseki Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan (Karar No: 41-2023) onay alınmıştır.

İstatistiksel analiz için SPSS 15.0 Windows programı kullanılmıştır. Tanımlayıcı istatistikler; Kategorik değişkenler için sayı ve yüzde olarak hesaplanmış, gruplar arasındaki oranlar Ki-Kare testi ile karşılaştırılmıştır. Alfa anlamlılık seviyesi p<0,05 olarak kabul edilmiştir.

Bulgular

Ankete katılanların 193'ü (%63,9) kadın, 111'i (%36,5) erkektir. Katılımcıların 132'si (%43,4) doktor, 91'i (%29,9) hemşire/laborant ve 81'i (%26,6) hasta bakıcı/temizlik personelidir. Soruları yanıtlayanlardan 138'i (%45,4) 20-29 yaş, 102'si (%33,6) 30-39 yaş, 40'ı (%13,2) 40-49 yaş, 24'ü (%7,4) 50-65 yaş aralığındadır. Ankete, ilkokul mezunu 22 (%7,2), lise mezunu 49 (%16,1), en az lisans seviyesinde mezun olan 233 (%76,6) kişi katılmıştır. Demografik özellikler Tablo 1'de gösterilmektedir.

Tablo 1. Demografik veriler

		n	%
Hastanede çalıştığı pozisyon	Doktor	132	%43,4
	Hemşire/Laborant	91	%29,9
	Hasta Bakıcı/Temizlik Personeli	81	%26,6
Öğrenim durumu	İlkokul	22	%7,2
	Lise	49	%16,1
	Lisans	101	%33,2
	Yüksek Lisans	132	%43,4
Yaş	20-29	138	%45,4
	30-39	102	%33,6
	40-49	40	%13,2
	50-65	24	%7,9
Cinsiyet	Erkek	111	%36,5
	Kadın	193	%63,5

HIV ile enfekte olduğunu bildiği biriyle aynı ortamda çalışmak (p<0,001), tokalaşmak veya sarılmak (p<0,001), sağlık çalışanları arasında en çok temizlik personeli ve hasta bakıcılar için sorun oluşturuyordu. HIV ile enfekte bir sağlık çalışanının kendi yakınına sağlık hizmeti vermesi (p=0,063), HİYB'le yemeğini paylaşmak (p=0,297) ve aynı tuvaleti kullanmak (p=0,076), sağlık çalışanları arasında belirgin bir tutum farklılığı oluşturmamıştır. HIV ile enfekte hastanın ameliyatında bulunmak, en çok doktorlar ile hemşireler ve laborantlar açısından çekince oluşturan bir durumdu (p=0,041). HIV ile enfekte hastaya invaziv olmayan işlemlerde bulunmak ise temizlik personeli ve hasta bakıcılar için daha fazla endişe kaynağıydı (p<0,001). HIV enfeksiyonunun tedavisinin olup olmadığı hakkındaki bilgiye en az hemşire ve laborantlar sahipti (p<0,001). HIV ve AIDS kavramlarının aynı şeyi ifade edip etmediği hakkındaki bilgiye ise en az hasta bakıcı ve temizlik personeli sahipti (p<0,001). Katılımcıların hastanede çalıştığı pozisyona göre HIV hakkındaki bilgileri ve HİYB'lere karşı tutumları Tablo 2'de gösterilmiştir.

Belirlenemeyen=Bulaştırmayan kavramı daha önceden en çok doktorlar tarafından bilinmekteydi (p<0,001). Bu kavramı daha önce bilmeyen katılımcıların bilgilendirme metni sonrasında, B=B anlamını biliyor olsalardı HİYB'lere karşı tutumlarındaki değişiklik sorgulandığında sağlık çalışanları arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p=0,226). Katılımcıların B=B kavramına karşı bilgi ve yaklaşımları, Tablo 3'te gösterilmiştir.

Tablo 2. Katılımcıların hastanede çalıştığı pozisyona göre HIV enfeksiyonu bilgileri ve HIV ile yaşayan bireylere karşı tutumlarının ilişkisi

		Hastanede çalıştığı pozisyon						
		Doktor		Hemşire/ Laborant		Hasta Bakıcı/ Temizlik Personeli		
		n	%	n	%	n	%	p
HIV (+) olduğunu bildiğiniz biriyle aynı ortamda beraber çalışmak sizin için bir sorun oluşturur mu?	Evet	14	%10,6	15	%16,5	36	%44,4	**<0,001**
	Hayır	94	%71,2	54	%59,3	39	%48,1	
	Kararsızım	24	%18,2	22	%24,2	6	%7,4	
Aynı ortamda beraber çalıştığınız HIV (+) olduğunu bildiğiniz bir arkadaşınızın yemeğini paylaşır mısınız?	Evet	28	%21,2	21	%23,1	22	%27,2	0,297
	Hayır	78	%59,1	55	%60,4	52	%64,2	
	Kararsızım	26	%19,7	15	%16,5	7	%8,6	
HIV(+) olduğunu bildiğiniz arkadaşınızla aynı tuvaleti kullanmak sizin için bir sorun oluşturur mu?	Evet	48	%36,6	48	%52,7	43	%53,1	0,076
	Hayır	49	%37,4	27	%29,7	25	%30,9	
	Kararsızım	35	%26,0	16	%17,6	13	%16,0	
HIV(+) olduğunu bildiğiniz bir arkadaşınızla tokalaşırken veya sarılırken bir çekinceniz olur mu?	Evet	27	%20,5	23	%25,3	43	%53,1	**< 0,001**
	Hayır	94	%71,2	56	%61,5	26	%32,1	
	Kararsızım	11	%8,3	12	%13,2	12	%14,8	
HIV (+) olduğunu bildiğiniz bir sağlık çalışanının yakınınıza veya size sağlık hizmeti vermesi sizi tedirgin eder mi?	Evet	49	%37,1	38	%41,8	46	%56,8	0,063
	Hayır	54	%40,9	35	%38,4	26	%32,1	
	Kararsızım	29	%22,0	18	%19,8	9	%11,1	
HIV(+) olduğunu bildiğiniz bir hastanın ameliyatında bulunmak sizi tedirgin eder mi?	Evet	91	%68,9	58	%64,4	39	%48,1	**0,041**
	Hayır	28	%21,2	21	%23,3	26	%32,1	
	Kararsızım	13	%9,8	12	%12,2	16	%19,8	
HIV (+) olduğunu bildiğiniz bir kişiyi muayene etmek veya transportunu sağlamak gibi invaziv olmayan işlemler sizi tedirgin eder mi?	Evet	16	%12,1	20	%22,0	28	%35,0	**<0,001**
	Hayır	111	%84,1	65	%71,4	36	%45,0	
	Kararsızım	5	%3,8	6	%6,6	17	%20,0	
HIV enfeksiyonunun bir tedavisi var mıdır?	Evet	107	%81,1	36	%40,0	45	%55,6	**<0,001**
	Hayır	14	%10,6	35	%38,9	13	%16,0	
	Kararsızım	11	%8,3	20	%21,1	23	%28,4	
HIV ile AIDS aynı şeyi mi ifade etmektedir?	Evet	10	%7,6	48	%52,7	57	%70,4	**<0,001**
	Hayır	121	%91,6	37	%40,7	10	%12,3	
	Kararsızım	1	%0,8	6	%6,6	14	%17,3	
Belirlenemeyen= Bulaştırmayan (B=B) kavramını daha önce duydunuz mu?	Evet	62	%47,0	24	%26,3	16	%19,8	**<0,001**
	Hayır	67	%50,8	61	%67,0	55	%67,9	
	Kararsızım	3	%2,2	6	%6,6	10	%12,3	
HIV ile yaşayan bireyler düzenli antiretroviral tedavi aldıklarında kanda HIV RNA belirlenemez ise bulaştırmayan (B=B) kabul edilir mi?	Evet	73	%55,3	22	%24,2	10	%12,3	**<0,001**
	Hayır	13	%9,8	20	%22,0	28	%34,6	
	Kararsızım	46	%34,8	49	%53,8	43	%53,1	

Tablo 3. Katılımcıların Belirlenemeyen=Bulaştırmayan (B=B) kavramına yaklaşımları

		Belirlenemeyen= Bulaştırmayan (B=B) kavramını daha önce duydunuz mu?				
		Evet		Hayır-Kararsızım		
		n	%	n	%	p
HIV ile yaşayan bireyler düzenli antiretroviral tedavi aldıklarında kanda HIV RNA belirlenemez ise bulaştırmayan (B=B) kabul edilir mi?	Evet	59	%57,8	46	%22,8	**<0,001**
	Hayır	19	%18,6	42	%20,8	
	Kararsızım	24	%23,5	114	%56,4	
HIV ile yaşayan bireylerin düzenli tedavi aldıkları takdirde kanda HIV RNA belirlenemez olduğunda bulaştırmayan (B=B) olduğunu biliyor olsaydınız HIV(+) olduğunu bildiğiniz ve düzenli tedavi alan bir kişiye karşı tutumunuz değişir miydi?	Evet	38	%37,3	76	%37,8	0,226
	Hayır	40	%39,2	65	%31,8	
	Kararsızım	24	%23,5	61	%30,3	

Tartışma

Global olarak HIV enfeksiyonu tanısı alan hastaların sayısı azalmasına rağmen, ülkemizde yeni tanı alan kişi sayısında artış devam etmektedir. Sağlık Bakanlığı'nın Kasım 2023 verilerine göre ülkemizde 39.437 HİYB vardır (4). Önceden yalnızca belirli hastanelerde HİYB'lere hizmet verilirken, günümüzde HİYB'ler her koşulda tanıya ve sağlık hizmetine ulaşabilmeleri gerekmektedir. Antiretroviral tedavilerdeki ilerlemeler, HIV enfeksiyonunu ölümcül bir hastalık olmaktan çıkarmış ve kronik hastalıklar sınıfına almıştır. Sağlık sistemi ve bireysel sağlık hizmeti sağlayıcıları ile etkileşim, HİYB'lerin düzenli ART kullanımına uyum sağlamasında temel faktördür. Sağlık çalışanlarının, HİYB'lere karşı destekleyici ve cesaretlendirici olması beklenirken, zaman zaman damgalayıcı tutumlar sergiledikleri de görülmektedir (10). HIV ilişkili damgalama, HİYB'lerin tanı ve tedaviye erişiminde en büyük engellerden biri olarak kabul edilmektedir (11). Bazı sağlık çalışanları tarafından damgalama bilinçli bir tutum olarak algılanmasa da, HİYB'lerin dosyalarına özel işaretler koymak gibi uygulamalar damgalamanın bir örneği olarak değerlendirilebilir (12).

Sağlık çalışanlarının eğitim seviyesinin düşük ve HIV hakkındaki bilgilerinin yetersizliği, enfekte olma korkusuna yol açarak HİYB'lere yönelik damgalamaya ve sağlık hizmetlerinde aksamalara neden olmaktadır (7). "HIV/AIDS tedavi edilen bir hastalıktır" sorusuna hekim ve hemşirelerin katıldığı bir çalışmada %44 evet cevabı alınırken (13), başka bir çalışmada bu oran %59,4 olarak belirlenmiştir (14). Bizim çalışmamızda ise bu oran tüm meslek grupları içinde toplam %61,8 olarak bulunmuştur. Doktorlar, hemşireler ve laborantlar arasında bu oran %47 olarak saptanmıştır. Eğitim seviyesi daha düşük olan hasta bakıcı ve temizlik personeli grubunun %70,4'ü HIV ile AIDS kavramlarını aynı şeyler olarak değerlendirmiştir.

Çeşitli ülkelerde yapılan çalışmalar, sağlık çalışanlarının HİYB'lere bakım vermek istemediğini göstermektedir. Örneğin, Ürdün'de yapılan bir çalışmada hemşirelerin %84'ü, Mısır'da yapılan bir çalışmada ise hemşirelerin %72,3'ü HİYB'lere bakım vermek istemediğini ifade etmiştir (15,16). Dünya genelinde yapılan çok merkezli bir çalışmada, 1000'den fazla sağlık çalışanı değerlendirilmiş ve %25-30'unun HİYB'lere sağlık hizmeti sunmak konusunda isteksiz olduğu tespit edilmiştir (17). Buna karşın, İtalya'da yapılan bir çalışmada, hemşirelerin sadece %2'sinin HİYB'lere sağlık hizmeti sunmak konusunda çekinceleri olduğu belirlenmiştir. Bu düşük oranın, İtalya'daki hemşirelerin HIV konusunda iyi eğitim almalarına bağlı olduğu düşünülmektedir (18).

Vietnam'da tıp fakültesi öğrencileriyle yapılan bir çalışmada, HIV eğitiminin damgalamayı azalttığı gösterilmiştir (19). Ancak, Örnek ve Kocamış tarafından yapılan bir çalışmada, hastanelerde çalışan personelin HIV/AIDS eğitimi almış veya almamış olmasının damgalama davranışları açısından istatistiksel olarak anlamlı bir fark oluşturmadığı belirlenmiştir (20). Bu durum, eğitimin etkinliği ve içeriğinin daha ayrıntılı incelenmesi gerektiğini ortaya koymaktadır. Benzer bir çalışmada da doktorlar ve hemşirelerde HIV eğitimi almış olanlar ile almayanlar arasında HIV ilişkili damgalama açısından anlamlı bir fark tespit edilmemiştir (21). Eğitimin içeriği kadar, hangi aşamada verildiği de önemlidir. HIV ile ilgili bilgilendirme eğitimlerinin, meslek hayatına başlamadan önce verilmesi, bireylerde ön yargıların oluşmasını önleyebilir.

Bayrak ve arkadaşlarının yaptığı çalışmada, doktorların ve hemşirelerin %26'sı, HİYB'lerle aynı ortamda çalışmak istemediğini belirtmiştir (13). İnci ve arkadaşlarının çalışmasında ise doktorların %17'si, hemşirelerin %18'i ve yardımcı sağlık personelinin %60'ı HİYB'lerle aynı ortamda çalışmak istemediğini ifade etmiştir (22). Bizim çalışmamızda bu oran doktorlar için %10,6, hemşireler ve laborantlar için %16,5 ve yardımcı sağlık personeli için %44,4 olarak belirlenmiştir. Pakistan'da yapılan bir çalışmada, tıp ve diş hekimliği fakültesi öğrencilerinin %37,1'i HİYB'lere sağlık hizmeti sunmaktan rahatsız olacağını, %61,4'ü ise HİYB'lerle fiziksel temastan kaçınacağını belirtmiştir (23). Çalışmamızda doktorlar ve hemşireler HİYB'lerin ameliyatına girmekten daha çok çekinceli iken, hasta bakıcılar ve temizlik personelleri invaziv olmayan işlemler konusunda daha fazla tereddüt göstermiştir. Ancak, HİYB'lere sağlık hizmeti vermek konusunda tedirginlik varken, HİYB'lerden sağlık hizmeti almak katılımcılar için önemli bir sorun oluşturmamıştır.

Tayland'da yapılan bir çalışmada toplumun %52,1'inin HIV ile enfekte bir kişiden taze sebze veya meyve almayacağını belirtmiştir (24). Umman'daki sağlık çalışanlarıyla yapılan bir ankette bu oran %50 olarak saptanmıştır (25). Bizim çalışmamızda ise "Aynı ortamda beraber çalıştığınız ve HIV (+) olduğunu bildiğiniz bir arkadaşınızın yemeğini paylaşır mısınız?" sorusuna "Hayır" veya "Kararsızım" yanıtını verenlerin oranı %76,6 olarak belirlenmiştir.

Bayrak ve arkadaşlarının çalışmasında, ön yargı oluşumunda, HIV bilgi düzeyi haricinde başka faktörlerin de etkili olduğu saptanmıştır. En önemli faktör olarak toplumsal baskı nedeniyle bireylerin, toplum tarafından doğru kabul edilen seçeneği cevaplamaları gösterilmiştir (13). Amerika Birleşik Devletleri'nde yapılan bir çalışmada, hem doktorların hem de diğer sağlık çalışanlarının %66'sında HİYB'lere karşı damgalama görülmüştür. Damgalayıcı tutum sergileyen grup HİYB'lerin çocuk sahibi olmamaları gerektiğini de savunmuştur (26). Çalışmanın yapıldığı hastanedeki sağlık çalışanlarının periyodik olarak HIV ile ilgili eğitime tabi tutulmalarının zorunlu olmasına rağmen damgalama oranının yüksek olması dikkat çekicidir (26,27). Araştırmacılar, bu durumu HIV eğitimi verilse bile eğitimi alan kişilerin kendi takdirlerine göre karar verdikleri yönünde açıklamışlardır (28). Evlenmeyi seçmek ve/veya çocuk sahibi olmak temel bir insan hakkıdır. Umman'da yapılan bir çalışmada, sağlık çalışanlarının %47'sinin HİYB'lerin evlenmesine, %53'ünün ise çocuk sahibi olmalarına itiraz ettiği görülmüştür (24). Çok uluslu, 1000'den fazla sağlık çalışanını kapsayan bir çalışmada ise katılımcıların %40'ı HİYB'lerin üreme hakkına sahip olmasına karşı çıkmıştır (29). Bu sonuçlar, B=B kavramının hem sağlık çalışanlarına hem de topluma detaylı bir şekilde anlatılmasının önemini ortaya koymaktadır.

Sağlık çalışanları arasındaki damgalamayı azaltmak için alınması gereken önlemler, Gerbert ve arkadaşları tarafından, sağlık çalışanlarının HIV'in bulaşıcılığı konusunda eğitilmeleri ve HIV'in ahlak dışı davranışlarla bulaştığı yönündeki yanlış yargının ortadan kaldırılması şeklinde özetlenmiştir. Çevresel önlemler ise devlet düzeyinde alınması gereken ve mesleki bulaşmayı önleyecek önlemler olarak belirtilmiştir (30). Önceki bazı araştırmalar, HİYB'lerle daha fazla temasın, HIV ile ilgili damgalamada azalma ve HİYB'lere karşı daha olumlu tutumlarla ilişkili olduğunu öne sürmüştür (31). Sağlık hizmeti sağlayıcılarının HİYB'lere yönelik tutumlarını etkileyebilecek diğer özellikler arasında kırsal yerleşimde yaşama, bireyin HIV enfeksiyonunun seviyesi ve sağlık çalışanlarının HIV maruziyetinden korunmak için gerekli malzemelere ve maruziyet sonrası profilakside ilaçlara erişim olanakları yer almaktadır. Sağlık çalışanlarına, HIV enfeksiyonunun nasıl bulaştığını ve bundan korunma yollarını anlatan, HIV ile ilgili damgalamayı engellemeye odaklanan bir eğitimin, damgalama düzeylerini düşüreceği öngörülmektedir (31,32).

HIV ile yaşayan bireylere karşı tutumu gösteren bir meta-analizde dini inanışın damgalamayı belirleyen faktörlerden biri olduğu belirtilmiştir (33). Çalışmamızda, ankete katılanların dini görüşleri ve damgalama arasındaki ilişki incelenmemiştir; bu durum, çalışmamızın önemli bir kısıtlılığıdır. Sağlık çalışanlarının kişisel açıdan damgalamanın nedenlerine dair daha ayrıntılı soruların hazırlanması gerektiğini düşünmekteyiz.

Sonuç

HIV ile yaşayan bireylere yönelik damgalama toplumun her kesiminde olduğu gibi sağlık çalışanları arasında da yaygındır. Çalışmamızda, HIV ile ilgili genel bilgilerin en az temizlik personeli ve hasta bakıcılar tarafından bilindiği, buna bağlı olarak en çok ön yargının yine grupta olduğu belirlenmiştir. Eğitim seviyesi yüksek bireylerde hastalığın tedavi ile bulaştırıcılığının en aza indirildiği bilgisi mevcut olmasına rağmen, bu durum damgalamayı tamamen ortadan kaldırmamaktadır. Bu sonuç, damgalamanın eğitim ile değil, toplumsal normlar ve kültürel faktörlerle de ile ilişkili olabileceğini düşündürmektedir.

Damgalama, HİYB'lerin yaşam kalitesini, ruhsal ve fiziksel durumunu doğrudan etkilediği için sağlık çalışanlarına yönelik HIV eğitiminin daha kapsamlı ve sürekli hale getirilmesi gerekmektedir. Ayrıca, sağlık çalışanları arasındaki ön yargıların nedenlerini anlamaya yönelik daha fazla araştırma yapılması önem arz etmektedir.

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Research Article / Araştırma Makalesi

Impact of Massive Trauma on Brain Structures: MRI Volumetric Analysis Post-February 6 Earthquake

Masif Travmanın Beyin Yapıları Üzerindeki Etkisi: 6 Şubat Depremi Sonrası MR Volümetrik Analizi

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Abstract

Background: This study aims to investigate the impact of the February 6 earthquake on brain structures, particularly mood centers, using MRI volumetric analysis.
Materials and Methods: In this retrospective study, 20 neurology clinic patients who were treated at a neurology clinic and underwent brain MRI both before and after the earthquake (2022–2023). MRI scans were analyzed within one year prior to and after the disaster. Patient data included age, gender, MRI indications and medical history. Inclusion criteria required participants to have experienced headaches but excluded those with neurodegenerative diseases, head trauma, or other structural brain pathologies. The volBrain method was used to assess total brain, white and grey matter, cerebrospinal fluid, limbic system (hippocampus, parahippocampal gyrus, amygdala, hypothalamus, cingulate gyrus, entorhinal cortex), prefrontal cortex, cerebellum, and thalamus via 3T MRI T1 sequences. All participants had experienced first-degree relative loss or home destruction.
Results: The study group comprised 65% women and 35% men, with a mean age of 42.15 ± 8.41 years. Significant volumetric changes were observed in several brain regions post-earthquake. White matter volume decreased significantly (p=0.011), while CSF volume increased (p=0.017), and total brain volume showed a significant reduction (p=0.025). The cerebellum exhibited significant volume reductions, including total volume (p=0.023), as well as the right (p=0.021) and left hemispheres (p=0.029). Similarly, the thalamus demonstrated significant reductions in total volume (p=0.008), right hemisphere (p=0.009), and left hemisphere (p=0.010). Conversely, the posterior cingulate gyrus (PCgG) showed significant volume increases in total (p=0.007), right (p=0.023), and left hemispheres (p=0.012).
Conclusions: The findings reveal significant volumetric changes in specific brain regions suggesting neurobiological effects of acute stressor trauma caused by the earthquake. These changes highlight the need for further studies to understand the mechanisms underlying these alterations and to develop interventions aimed at mitigating the long-term effects of such traumatic events.

Keywords: Limbic system, Mrı volumetric analysis, Earthquake, Disaster, Massive trauma, Neuroimaging

Öz

Amaç: Bu çalışma, 6 Şubat depremi sonrası beyin yapıları üzerindeki etkileri, özellikle duygu durumla ilişkili merkezleri Manyetik Rezonans Görüntüleme (MRG) volümetrik analizi kullanarak incelemeyi amaçlamaktadır.
Materyal ve Metod: Bu retrospektif çalışma, nöroloji kliniğinde takip edilen ve beyin MRG'i hem deprem öncesinde hem de sonrasında çekilmiş 20 hastayı (2022-2023) içermektedir. MRG taramaları, felaketten önceki ve sonraki bir yıl içinde analiz edilmiştir. Çalışmaya dahil edilen hastaların yaşı, cinsiyeti, MRG endikasyonları ve tıbbi öyküsü kaydedilmiştir. Dahil edilme kriterleri baş ağrısı öyküsü bulunan bireyleri kapsarken, nörodejeneratif hastalıkları, kafa travması veya diğer yapısal beyin patolojileri olan hastalar çalışmadan dışlanmıştır. Beyin hacminin volümetrik analizi için volBrain yöntemi kullanılmıştır. 3T MRG T1-ağırlıklı sekanslar ile toplam beyin hacmi, beyaz madde, gri madde, beyin omurilik sıvısı (BOS) ve limbik sistem (hipokampus, parahipokampal girus, amigdala, hipotalamus, singulat girus, entorinal korteks), prefrontal korteks, beyincik ve talamus gibi belirli beyin bölgeleri değerlendirilmiştir. Çalışmaya katılan tüm hastalar deprem nedeniyle birinci derece yakın kaybı yaşamış veya evleri yıkılmış bireylerden oluşmaktadır.
Bulgular: Çalışma grubunun %65'i kadın, %35'i erkek olup, yaş ortalaması 42,15 ± 8,41 yıldır. Deprem sonrası birçok beyin bölgesinde anlamlı volümetrik değişiklikler gözlemlenmiştir. Beyaz madde hacmi belirgin şekilde azalırken (p=0,011), BOS hacmi artmıştır (p=0,017). Toplam beyin hacminde anlamlı bir azalma saptanmıştır (p=0,025). Beyincik toplam hacmi (p=0,023) ile sağ (p=0,021) ve sol hemisferleri (p=0,029) anlamlı küçülme göstermiştir. Benzer şekilde, talamus toplam hacmi (p=0,008), sağ (p=0,009) ve sol hemisferleri (p=0,010) anlamlı olarak azalmıştır. Buna karşın, posterior singulat girus (PCgG) toplam (p=0,007), sağ (p=0,023) ve sol (p=0,012) hemisferlerinde belirgin hacim artışı göstermiştir.
Sonuç: Elde edilen bulgular, akut stres veya travmanın nörobiyolojik etkilerini yansıtan belirgin beyin hacmi değişikliklerine işaret etmektedir. Bu değişimler, deprem gibi travmatik olayların uzun vadeli etkilerini anlamak ve bu etkileri azaltmaya yönelik müdahaleler geliştirmek için ileri çalışmalara duyulan ihtiyacı ortaya koymaktadır.

Anahtar Kelimeler: Deprem kaynaklı travma, MRG volümetrik analiz, Limbik sistem, Deprem, Nörogörüntüleme

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Introduction

Massive trauma lacks a universally accepted definition due to the diverse nature of traumatic events. However, it can be quantitatively characterized by the large-scale impact on individuals during catastrophic events such as earthquakes, wars, or major terrorist attacks (1). On February 6, 2023, two powerful earthquakes with magnitudes of 7.7 and 7.5 struck the Kahramanmaraş region of Turkey. These earthquakes caused extensive destruction, a significant loss of life, and numerous injuries, with Hatay experiencing the most severe devastation and casualties. The widespread trauma resulting from these events profoundly impacted the region.

Natural disasters like earthquakes are among the most severe and unpredictable stressors, significantly affecting individuals' mental and physical health (2, 3). Massive trauma has been shown to induce physiological changes in the brain, particularly in regions associated with memory, emotional regulation, and threat detection (4, 5). Acute stress from traumatic events has been linked to various neuropsychiatric outcomes, including post-traumatic stress disorder (PTSD), anxiety and depression (6, 7). Increasing evidence suggests that significant stressors can alter both brain structure and function, particularly in regions involved in mood regulation and cognitive processing, such as the limbic system, prefrontal cortex, cerebellum, and thalamus (8). These regions are known to be especially vulnerable to the effects of acute stress and trauma (8).

Recent advancements in neuroimaging, particularly magnetic resonance imaging (MRI) with volumetric analysis, have enabled researchers to quantify structural changes in these critical brain regions. These methods have provided valuable insights into the neural correlates of trauma (9-11). However, despite these advancements, the specific effects of large-scale disasters, such as earthquakes, on brain structures remain poorly understood.

The devastating February 6 earthquake, which caused significant loss of life and property, offers a unique opportunity to explore the neurological impacts of massive trauma. This study focuses on individuals who experienced severe stress, such as the loss of a first-degree relative or home destruction. Using MRI-based volumetric analysis, this study aims to evaluate structural alterations in the limbic system, prefrontal cortex, cerebellum, thalamus, and other related brain regions.

Materials and Methods

This cross-sectional study was conducted at a single center between 2022 and 2023. Ethical approval was obtained from the Mustafa Kemal University Local Ethics Committee (Approval No: 2024.07.09/10).

All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki. The study retrospectively included 20 patients followed up in the neurology clinic who underwent brain MRI examinations both before and after the February 6, 2023 earthquake. The data were retrieved from the archives of the Department of Radiology.

Patients aged 18 to 60 years who experienced significant trauma, such as first-degree relative loss or home destruction due to the earthquake, were included in the study. Exclusion criteria included a history of stroke, psychiatric illnesses such as psychosis, schizophrenia, or major depression, brain tumors, epilepsy, head trauma with loss of consciousness during the earthquake, or limb loss resulting from the disaster. Patients' demographic data, including age, gender, the reason for MRI request, and known medical history, were recorded. Written and verbal informed consent was obtained from all participants, explaining the purpose of the study and the use of MRI examinations.

MRI Acquisition

Conventional brain MRI examinations were performed using a GE-3 Tesla Signa Architect MRI device located in the Department of Radiodiagnostics. Structural MRI data were acquired using the T1-weighted brain volume sequence. The imaging parameters were set as follows: a repetition time (TR) of 2220 ms, an echo time (TE) of 2.8 ms, a field of view (FOV) of 22.4 mm, a flipangle of 8°, 220 slices, and a voxel size of 1.0 × 1.0 × 1.4 mm.

Segmental volumetric analysis of the brain structures was carried out using the volBrain algorithm, an open-access platform for MRI-based brain analysis. The volBrain platform (http://volbrain.upv.es) is an AI-powered system that processes brain MRI images to provide volumetric data for various brain regions (12). The process includes loading T1-weighted images, quality control, removal of non-brain structures, correction and normalization, automated tissue classification, segmentation and parcellation of brain regions, volume calculation and reporting (13). In this study, T1-weighted images were converted from DICOM to NIfTI format using MRI cron software. Anonymized and compressed NIfTI (nii.gz) files, alongwith the participants' age and gender, were uploaded to the volBrain platform, which provided volumetric measurements and normal reference values for each tissue or structure.

The analysis encompassed total brain volume, cerebrospinal fluid (CSF) volume, and specific brain region volumes such as the hippocampus, parahippocampal gyrus, amygdala, hypothalamus, posterior cingulate gyrus, entorhinal cortex, prefrontal cortex, thalamus and cerebellum. These volumes were calculated for both the left and right hemispheres, where applicable (Figure 1).

Statistical Analysis

Data analysis was conducted using SPSS software (version 25). Descriptive statistics, including frequencies and percentages for categorical variables and means with Standard deviations for continuous variables, were used to summarize the data. The Wilcoxon Signed-Rank Test was employed to compare volumetric measurements obtained before and after the earthquake. A p-value of less than 0.05 was considered statistically significant.

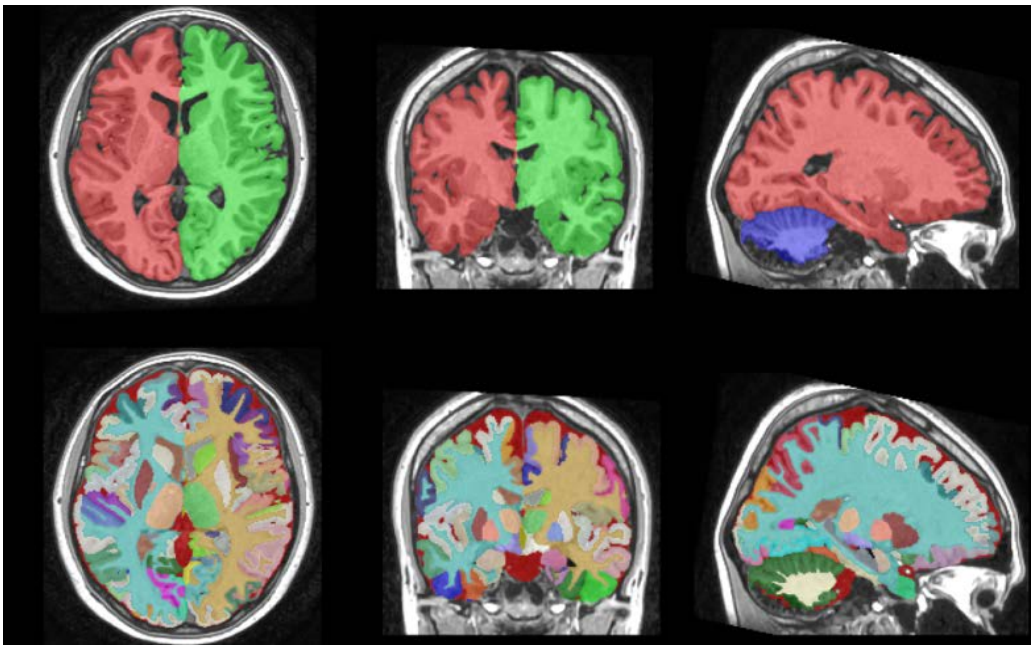

Figure 1. Structure segmentation and volumetric analysis of the brain using the volBrain pipeline.All the volumes are presented in absolute value (measured in cm3) and in relative value (measured in relation to the ICV).Segmentation images are located in the MNI space (neurological orientation).

Results

The study group consisted of 65% women and 35% men, with a mean age of 42.15 ± 8.41 years (range: 27–55 years). Volumetric measurements of various brain structures were obtained both before and after the earthquake. These measurements were statistically analyzed, including calculations of mean, Standard deviation, minimum and maximum values, and p-values. The findings provide critical insights into the potential impact of the earthquake on brain volumes. White matter volume (WM) showed a significant decrease after the earthquake (p=0.011). Similarly, cerebrospinal fluid (CSF) volume demonstrated a notable increase post-earthquake (p=0.017). Thalamic volumes, including total, right, and left thalamus, experienced significant reductions with p-values of 0.008, 0.009, and 0.010, respectively. Cerebellum volume, encompassing total, right, and left cerebellum, also decreased significantly, with p-values ranging from 0.021 to 0.029. The posterior cingulate gyrus (PCgG) exhibited a significant increase in total, right, and leftvolumes, with p-values of 0.007, 0.023, and 0.012, respectively (Table 1).

Table 1.Volumetric Analysis of Brain Regions with Statistically Significant Changes Before and After the February 6 Earthquake

Regions	Before Earthquake		Post Earthquake		P value
	Volume (cm^3)				
	Mean±SD	Min - Max	Mean±SD	Min - Max	
White Matter	491.2 ± 61.4	406.2 - 612.0	479.0 ± 52.9	403.3 - 582.5	0.011
Cerebrospinalfluid	168.5 ± 57.6	63.7 - 347.1	180.2 ± 60.4	129.1 - 386.4	0.017
Brain WMGM	1148.8 ± 93.3	993.5 - 1332.8	1136.3 ± 90.0	981.2 - 1296.2	0.025
Cerebellum total	121.7 ± 12.5	95.3 - 144.7	119.4 ± 13.5	87.0 - 145.4	0.023
Cerebellum right	60.9 ± 6.3	47.8 - 73.0	59.8 ± 6.9	43.4 - 73.9	0.021
Cerebellum left	60.7 ± 6.2	47.4 - 72.4	59.6 ± 6.7	43.6 - 71.5	0.029
Thalamus total	12.0 ± 1.2	10.1 - 14.4	11.9 ± 1.2	9.9 - 14.2	0.008
Thalamus right	6.0 ± 0.5	5.0 - 7.0	5.9 ± 0.6	4.9 - 7.0	0.009
Thalamus left	6.0 ± 0.6	5.0 - 7.3	6.0 ± 0.6	5.0 - 7.2	0.010
PCgG total	9.2 ± 0.7	7.9 - 10.2	9.5 ± 0.8	8.5 - 11.3	0.007
PCgG right	4.6 ± 0.4	3.7 - 5.3	4.8 ± 0.5	4.1 - 5.9	0.023
PCgG left	4.6 ± 0.3	3.7 - 5.2	4.7 ± 0.4	4.1 - 5.4	0.012

WMGM:White Matter and Gray Matter, PCgG: Posterior cingulate gyrus.

There were no statistically significant changes in grey matter volume (p = 0.940), indicating stability in grey matter over this period. The limbic system, including total, right, and left limbic volumes, did not exhibit statistically significant changes (p > 0.05). Similarly, the prefrontal cortex showed no significant alterations (p > 0.05). Other regions, such as the hippocampus, insular cortex, amygdala, basalforebrain, and entorhinal cortex, displayed no significant volumetric changes,

reflecting stability in these areas following the earthquake (Table 2).

Table 2. Volumetric Analysis of Brain Regions with Statistically Non-Significant Changes Before and After the February 6 Earthquake

Regions	Before Earthquake		Post Earthquake		p
	Volume (cm^3)				
	Mean±SD	Min - Max	Mean±SD	Min - Max	
Grey Matter	657.5 ± 46.0	586.3 - 790.2	657.303±45,94	45.94036	0.94
FRP total	61613.3 ± 25360.4	6613.0 - 91723.0	64931.85±22398,12	22398.128	0.60
FRP right	31796.1 ± 11164.2	3263.0 - 48327.0	32266.55±11407,19	11407.194	0.91
FRP left	34760.8 ± 8956.5	3871.0 - 44669.0	32776.00±11201,64	11201.645	0.27
GRe total	36673.1 ± 12228.3	4261.0 - 52371.0	31338.20±16723,90	16723.901	0.26
GRe right	15262.0 ± 9049.3	1497.0 - 25118.0	20517.05±2148,99	2148.997	0.20
GRe left	19075.3 ± 5175.2	2076.0 - 27253.0	20244.65±2996,82	2996.829	0.70
OpIFG total	50435.7 ± 24387.1	5404.0 - 75389.0	55048.65±18440,14	18440.146	0.37
OpIFG right	29498.6 ± 10061.7	1947.0 - 41441.0	31749.15±4677,17	4677.1764	0.91
OpIFG left	27544.9 ± 9835.1	2674.0 - 43056.0	30148.7±4802,75	4802.75	0.82
OrIFG total	22756.9 ± 8253.7	2984.0 - 34329.0	26010.90±6382,06	6382.063	0.62
TrIFG total	51899.7 ± 21607.9	5869.0 - 71697.0	55594.50±16139,81	16139.810	0.60
TrIFG right	27031.7 ± 10350.3	2363.0 - 39574.0	28040.10±8194,33	8194.333	0.57
TrIFG left	27424.5 ± 9115.8	3183.0 - 36351.0	26326.05±10751,003	10751.003	0.31
Amygdala total	1.9 ± 0.2	1.4 - 2.2	1.881±0,93	.193	0.42
Amygdala right	0.9 ± 0.1	0.7 - 1.2	.94±0,09	.096	0.54
Amygdala left	0.9 ± 0.1	0.7 - 1.1	.94±0,10	.100	0.17
Basal Forebrain total	0.8 ± 0.1	0.5 - 1.0	.77±0,09	.096	0.70
Basal Forebrain right	0.4 ± 0.1	0.3 - 0.6	.40±0,052	.058	0.40
Basal Forebrain left	0.4 ± 0.1	0.2 - 0.5	.37±0,05	.0530	0.71

FRP: Frontal Pole, GRe: Gyrus Rectus, OpIFG: Opercular Part of the Inferior Frontal Gyrus, TrIFG: Triangular Part of the Inferior Frontal Gyrus (These are parts of the prefrontal cortex)

Table 3. Volumetric Analysis of Brain Regions with Statistically Significant Changes Before and After the February 6 Earthquake According to Sex

Sex	Regions	Before Earthquake		Post Earthquake		p
		Volume (cm^3)				
		Mean±SD	Min - Max	Mean±SD	Min - Max	
Women=13	**GRe right**	13602.5±9599.1	1497.0-25118.0	20410.3±2381.1	14081.0-23316.0	**0.028**
	CO left thickness mm	27910.1±2381.1	200043.0-47150	23789.3±6978.6		**0.028**
	CerebroSpinal Fluid (CSF)	152.0±42.6	63.7-253.4	165.5±41.4	129.2-256.1	**0.019**
	Cerebellum right volume	58.5±5.6	47.8	57.2±6.2	67.7	**0.046**
	Amygdala total volume	1.7±0.2	1.43-1.99	1.8±0.2	1.61-2.19	**0.034**
	Amygdala right volume	0.8±0.1	0.73-0.99	0.9±0.1	0.81-1.08	**0.027**
	Amygdala left volume	0.8±0.8	0.70-1.00	0.9±0.8	0.80-1.11	**0.036**
	Basal Forebrain total volume	0.7±0.1	0.5-0.8	0.8±0.1	0.6-0.9	**0.049**
	Hippocampus left volume	3.7±0.4	3.21-4.29	3.8±0.3	3.2-4.4	**0.022**
	Thalamus total volume	12.0±1.2	10.12-13.91	11.8±1.1	13.8-9.9	**0.030**
	PCgG total volume	5.4±0.5	4.2-6.6	5.5±0.5	4.7-6.6	**0.016**
Men=7	**Amygdala right volume**	1.1±0.1	0.8-1.2	1.0±0.1	0.8-1.2	**0.027**
	Basal Forebrain total volume	0.9±0.1	0.7-1.0	0.8±0.1	0.8-0.9	**0.027**
	FRP left volume cm3	37688.0±5306.1	31183.0-43396.0	31905.8±13462.5	32860.0-43325.0	**0.018**
	OpIFG total	35229.5±29355.0	5404.0-73271.0	58137.1±190635.9	42156.0-72175.0	**0.043**
	Caudate total volume	7.4±0.9	6.0-9.1	7.2±0.8	6.1-8.6	**0.028**
	Caudate right volume	3.7±0.5	2.4-.6	3.6±0.4	2.9-4.3	**0.028**
	Thalamus right volume	6.1±0.6	5.6-7.1	6.0±0.6	5.4-7.1	**0.043**
	Limbic right volume	20.5±1.4	19.2-23.4	20.1±1.4	19.1-23.0	**0.028**
	Insular right volume	14.2±1.1	12.6-15.7	13.8±0.9	12.6-13.7	**0.018**

FRP: Frontal Pole, GRe: Gyrus Rectus, OpIFG: Opercular Part of the Inferior Frontal Gyrus

Discussion

This study provides critical insights into the volumetric changes observed in various brain regions following the February 6 earthquake. The findings reflect both the brain's vulnerability to acute stress and its adaptive capacity.

In our study, white matter volume showed a significant decrease after the earthquake, suggesting that this region is particularly vulnerable to acute stress. White matter plays a crucial role in facilitating communication between brain regions, and its disruption may impair cognitive and motor functions. Abraham et al. emphasized consistent reductions in white matter integrity in individuals experiencing stress and depression, attributing these changes to neuroinflammation and stress-induced demyelination (14). Similarly, Meng et al. Reported long-term white matter microstructural alterations in survivors of traumatic events, highlighting the susceptibility of white matter to acute and chronic stress (15).

In contrast to white matter, our study found no significant changes in grey matter volume, indicating structural resilience to acute stress. McEwen et al. proposed that grey matter exhibits greater resistance to short-term stress due to its robust synaptic and neuronal architecture, which helps maintain functionality under environmental challenges (16). However, longitudinal studies are needed to explore whether chronic stressors might induce observable changes in grey matter structure.

Our findings revealed a significant increase in cerebrospinal fluid volume post-earthquake, likely reflecting compensatory mechanisms. Romeo et al. described CSF as a reservoir for brain-derived proteins and cellular by-products, which can provide insights into brain injury or stress (17). Hladky et al. emphasized that increases in CSF volume may result from reductions in other brain regions, such as white matter, to maintain intracranial pressure equilibrium(18). This dynamic fluid redistribution underscores the brain's capacity to adapt to acute stress while preserving structural balance.

The thalamus exhibited significant volume reductions, highlighting its vulnerability to stress-induced damage in our study. As a key relay center for sensory and motor signals, the thalamus is integral to emotional regulation and cognitive functions. Batail et al. linked thalamic atrophy to emotional dysregulation in patients with depressive disorders, further demonstrating the susceptibility of this region to stress (19). Similarly, Hong et al. identified heterogeneous alterations in thalamic subfields among individuals experiencing chronic stress, which may explain its significant reduction in our study (20).

Our study showed significant reductions in total cerebellar volume, including both hemispheres. The cerebellum, traditionally associated with motor coordination, also plays a critical role in emotional regulation. Lange et al. identified cerebellar lobule VI as essential for processing fear-related stimuli and memory consolidation (21). The reductions observed in our study may contribute to both motor and emotional impairments, reflecting the cerebellum's involvement in stress responses (22).

In our study, no significant changes were observed in the volumes of the limbic system. Despite its critical role in emotion and memory, Pitman et al. suggested that the limbic system may exhibit structural alterations only in response to prolonged or chronic stress (23). This stability in acute stress scenarios aligns with our findings.

In our study, the posterior cingulate gyrus demonstrated significant volume increases. This region, a central hub in the default mode network, is associated with self-referential thought, memory, and emotional regulation. Zhang et al. reported increased white matter integrity in the posterior cingulate gyrus during post-traumatic stres disorder recovery, attributing this to neuroplasticity (24). Leech et al. emphasized the importance of this region in maintaining cognitive and emotional equilibrium, particularly during adaptation to stress (25, 26).

In volume analysis according to the sex showed some differences. Forexample women exhibit a significant increase in amygdala volumes, while men show a stabilization or slight reduction. This suggests women may have a heightened emotional response to trauma.

Divergent changes in basal forebrain between sexes suggest potential sex-specific adaptations in attention and arousal mechanisms post-trauma. The observed reduction in cortical thickness in women but not men suggests possible structural vulnerability in female participants.

In our study, no significant alterations were observed in the prefrontal cortex volumes (PFC). The PFC is pivotal for higher-order cognitive functions and emotional regulation. Anderson et al. highlighted its role in "top-down" regulation of limbic structures such as the amygdala and hippocampus, which may explain its stability in acute stress scenarios (26).

The structural changes identified in our study can be attributed to three primary mechanisms: stress-induced neurobiological effects, neuroplasticity, and fluid redistribution. Elevated glucocorticoid levels, a hallmark of acute stres responses, are known to cause neuro inflammation, disrupt neurotransmitter systems, and result in structural damage to stress-sensitive brain regions (27, 28). Sorrells et al. linked such glucocorticoid-induced inflammation to demyelination and decreased neural connectivity, particularly affecting white matter and the thalamus (29). The observed increase in posterior cingulate gyrus volume likely reflects neuroplastic adaptations to acute stress. Hermans et al. underscored that stres responses can promote structural and functional brain changes, facilitating recovery and enhancing resilience in the aftermath of trauma (30). Additionally, fluid redistribution mechanisms were evident in the significant increase in CSF volume. Hinson et al. demonstrated that brain injuries often result in blood-brain barrier dysfunction, leading to shifts in CSF volume as a compensatory response to maintain intracranial equilibrium (31). These

dynamic interactions highlight the brain's ability to adapt and respond to acute stress through a combination of biological, structural, and fluid-related mechanisms.

This study has limitations, including its retrospective design, small sample size, and lack of validated PTSD assessment scales. Future studies with larger cohorts and prospective designs are needed to validate these findings.

Future research should focus on longitudinal studies to evaluate the long-term persistence or reversibility of these changes and their implications for cognitive and emotional functions. Understanding the relationship between structural alterations and behavioral outcomes, as well as exploring hormonal and inflammatory mediators, will provide deeper insights into the neurobiological effects of natural disasters. Early diagnosis and targeted interventions are crucial to mitigate neurological damage and support recovery, ultimately enhancing the quality of life for individuals affected by such catastrophic events.

In conclusion, this study highlights the profound impact of acute stress caused by the February 6 earthquake on brain structure, revealing both vulnerabilities and adaptive mechanisms in various brain regions. Significant reductions in white matter, thalamus and cerebellum volumes indicate the brain's susceptibility to stress-related damage, while increases in CSF and posterior cingulate gyrus volumes reflect compensatory and neuroplastic responses. These findings underscore the brain's dynamic interplay between vulnerability and resilience in the face of acute trauma.

Ethical Approval: *Ethical approval was obtained from the Mustafa Kemal University Local Ethics Committee (Approval No: 2024.07.09/10), accordance with the principles stated in the Declaration of Helsinki.*

Author Contributions:
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Design : F.Ö., H.B.
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Writing manuscript: D.Y.D., F.Ö.
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Research Article / Araştırma Makalesi

Abdominal Complications After Ventriculoperitoneal Shunt placement in Pediatric Patients with Hydrocephalus

Hidrosefalili Çocuklarda Ventrikülöperitoneal Şant Yerleştirilmesi Sonrası Abdominal Komplikasyonlar

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Abstract

Background: The insertion of a ventriculoperitoneal shunt is a necessary neurosurgical procedure to treat hydrocephalus. However, the placement of shunts can be associated with rare but significant postoperative abdominal complications, which can subsequently lead to a range of problems.
Materials and Methods: In this study, we reviewed case histories of patients with abdominal complications who previously underwent ventriculoperitoneal shunt insertion for hydrocephalus between 2008 and 2023 at single - institution. Complications related to the abdomen were analysed.
Results: During the 15-years observation period, a total 475 patients had a ventriculoperitoneal shunt placement. 101 (21,19%) patients with abdominal complications after ventriculoperitoneal shunt insertion were examined. Twelve patients (2,52%) who had shunt insertion out of peritoneal cavity and 245 (70,81%) patients with non- abdomen related complications were excluded from the study.
Ninety seven patients (96,04%) required shunt revisions. Obstruction of abdominal end of the ventriculoperitoneal shunt occurred in 63 (62,38%) patients, cerebrospinal fluid pseudocyst of peritoneal cavity occurred in 27 (26,73%) patients. Twenty three patients (22,77%) had a large size of the pseudocyst with a cerebrospinal fluid volume more than 300 mL. Four patients (3,96%) had a pseudocyst with a cerebrospinal fluid volume less than 300 mL.
Four patients (3,96%) had a medical conservative treatment. Risk factors for abdominal cerebrospinal fluid pseudocyst complications were intestinal adhesion and peritoneal thickness, for mechanical dysfunction of ventriculoperitoneal shunt were obstructions of the distal end by fat tissues and for extrusions were long distal end of the shunt. The rates of other rare complications such a spontaneous extrusion of the peritoneal catheter through the anus, urethra, inguinal canal and migration through the abdominal wall were < 1 (0,22%).
Conclusions: All patients who will have treatment with ventriculoperitoneal shunts should be informed about the potential abdominal complications. If there is any suspicion to abdomen related complications after ventriculoperitoneal shunt surgery all patients should be verified through imaging, followed by appropriate treatment. Although these complications are rare, unrecognized and untreated cases can be fatal.

Keywords: Abdominal pseudocyst, Hydrocephalus, Ventriculoperitoneal shunt, Small-bowel obstruction

Öz

Amaç: Hidrosefali tedavisinde ventrikülöperitoneal şant takılması gerekli bir nöroşirürjik işlemdir. Ancak şant yerleştirilmesi sonrası postoperatif abdominal komplikasyonlar gelişebilir ve bu da önemli problemlere yol açabilir.
Materyal ve Metod: Bu çalışmada, 2008-2023 yıllar arasında tek merkezde hidrosefali nedeniyle ventrikülöperitoneal şant takılan hastaların, şantlarla ilgili abdominal komplikasyonlarını retrospektif olarak inceledik.
Bulgular: On beş yılda toplam 475 hastaya ventrikülöperitoneal şant takılmıştır. Ventrikülöperitoneal şant takılması sonrası 101 (%21,19) hasta da abdomen ile alakalı komplikasyonlar gelişmiştir. On iki (%2,52) hastaya şantlar periton dışı takılmıştı ve 245 (%70,81) hastanın şant sonrası gelişmiş komplikasyonları karın boşluğu ile alakalı değildi. Bu hastalar çalışmaya dahil edilmedi.
Doksan yedi (%96,04) hastada şant revizyonuna ihtiyaç duyuldu, Altmış üç (%62,38) hastada ventrikülöperitoneal şantın abdominal ucunda obstrüksiyon, yirmi yedi (%26,73) hastada periton boşluğunda beyin omurilik sıvısı psödokisti gelişmişti. Hastaların yirmi üçünde (%22,77) beyin omurilik sıvısı hacmi 300 mL'den fazlaydı ve dört (%3,96) hastada beyin omurilik sıvısı hacmi 300 mL'den daha azdı. İntestinal yapışıklık ve peritoneal kalınlık bulunması karın serebrospinal sıvı psödokist komplikasyonları için risk faktörlerin arasındaydı, ventrikülöperitoneal şantın mekanik disfonksiyonu için risk faktorler ise distal ucun yağ dokuları tarafından tıkanması veya şantın uzun distal ucuydu. Peritoneal kateterin anüs, üretra, inguinal kanaldan kendiliğinden ekstrüzyonu gibi diğer nadir komplikasyonların görülme oranları < 1 (%0,22) idi.
Sonuç: Ventrikülöperitoneal şant tedavisi görecek tüm hastalar olası abdominal komplikasyonlar hakkında bilgilendirilmelidir. Ventrikülöperitoneal şant ameliyatından sonra karınla ilgili komplikasyonlara dair herhangi bir şüphe varsa görüntüleme yoluyla doğrulanmalı ve ardından uygun tedavi uygulanmalıdır. Bu komplikasyonlar nadir olsa da, tanınmayan ve tedavi edilmeyen vakalarda ölümcül olabilir.

Anahtar Kelimeler: Abdominal psödokisti, Hidrosefali, Ventrikuloperitoneal şant, İntestinal obstrüksyon

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Introduction

Increasing cerebrospinal fluid (CSF) in the brain cavities increases intracranial pressure causing hydrocephalus. This condition may be primary as a congenital hydrocephalus due to brain malformation or spinal dysraphism. Secondary hydrocephalus occurs from post-inflammatory conditions, haemorrhages or brain injuries, leading to an imbalance in the production and absorption of cerebrospinal fluid. Brain tumours can block the circulation pathways of CSF at any location, leading to an increase in intracranial pressure. Ventriculoperitoneal shunt (VPS) surgery involves draining CSF from the ventricles into the intraperitoneal cavity, allowing its absorption. VPS placement steel is commonly used for the treatment of this condition, but shunt placement sometimes may cause various abdomen related problems such as shunt migration, extrusion, disconnection, infection, blockage, excessive drainage or abdominal pseudocyst as a result of intraperitoneal CSF accumulation (1-8).

In this manuscript, we present our experience with rare abdomen related complications of VPS such as abdominal pseudocyst, intestinal strangulation with distal end of VPS catheter, extrusion and disconnection, and our management of patients with these complications.

Materials and Methods

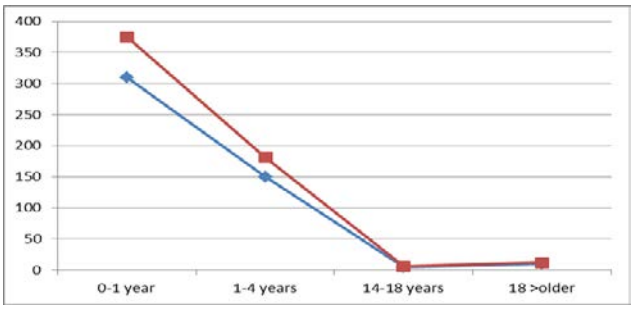
This is a retrospective a single-institution study in patients with hydrocephalus after VPS surgery with abdominal and bowel related complications between 2008 and 2023 at Harran University Hospital. The study was conducted at the departments of neurosurgery and paediatric surgery. Records of all the patients who had VPS insertion and revisions for VPS complications were reviewed. Written informed consent for publication of their details was obtained from the parents of the patients. Complications were categorized into two groups: abdominal and non-abdominal. Cases that were not associated with abdominal complications and where the distal end of the VPS was inserted outside the peritoneal cavity were excluded from this study.

The variables data were: age, sex, demographic details, aetiology of hydrocephalus and indication for VPS, clinical presentation for revisions surgery and outcome. All cases had computed tomography scan (CT) or abdominal shunt X-ray, laboratory tests at admission. We categorized the pseudocyst cases based on cerebrospinal fluid collection volumes more than 300 mL as a large, and cyst sizes of less than 300 mL were classified as a small after puncture. Those patients who had a VPS dysfunction, acute hydrocephalus symptoms and abdominal complaints underwent shunt revision surgery. Four patients without VPS dysfunction and acute hydrocephalus symptoms had a conservative medical treatment. The data was analysed using the statistical program IBM SPSS version 20.

Results

During the 2008 to 2023 surveillance period, a total of 475 patients were treated surgically for hydrocephalus. Indications for VPS placement were: 1) congenital hydrocephalus (CH) 419 (88,21%), 2) secondary hydrocephalus after intracerebral haemorrhage, atrophy of the brain parenchyma or non-communicant / obstructive hydrocephalus as a result of previous meningitis, surgery or tumour 56 (11,79%).

The distribution between the sex of the patients was approximately equal: boys 237 (49,89%) and girls 238 (50,11%). During the above period the majority of patients had a shunt placement procedure at age 0-1 years old 310 (65,26%), 150 (31,58%) at age 1-14 years old and 15 (3,16%) patients at age 15 or older. Figure 1 shows a distribution between the age groups of the patients who had VPS insertion.



Fugure 1. The distribution between different age groups: red line represents the number of female patients and blue line indicates the number of male patients.

Table1. A summary of the inclusion and exclusion criteria of the patients in this study.

Records between 2008-2023 screened total *n* = 475	
Congenital hydrocephalus *n* = 419 (88,21%)	
Secondary hydrocephalus *n* = 56 (11,79%)	
Patients included in the study	**Patients excluded from the study**
Intraperitoneal *n* = 463 (97, 48%)	Intrapleural *n* = 5 (1,05%) Intraatrial *n* = 6 (1,26%) Intravesical *n* = 1 (0,21%)
Abdomen related complications *n* = 101 (21,19%)	Non-abdominal complications *n* = 245 (70,81%)

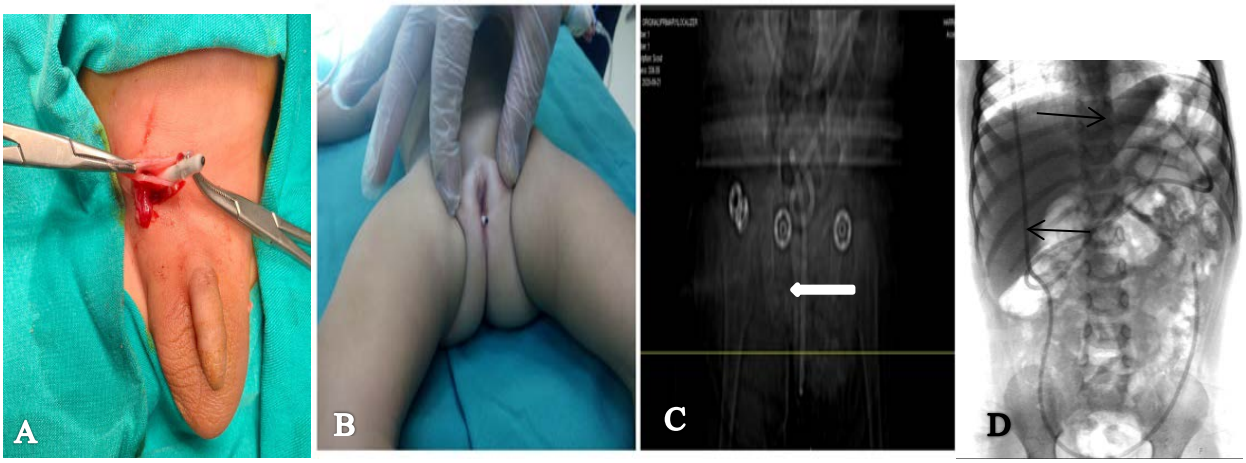


Figure 2. A-spontaneous extrusion of the distal end of the VPS through the inguinal canal, B- uretra, C- X-ray shows that the distal end (white arrow) has passed through the abdominal wall into the bladder, formed a knot, and protruded outward through the urethra, D- complete detachment of the distal end of the VPS within the peritoneal cavity (black arrow).

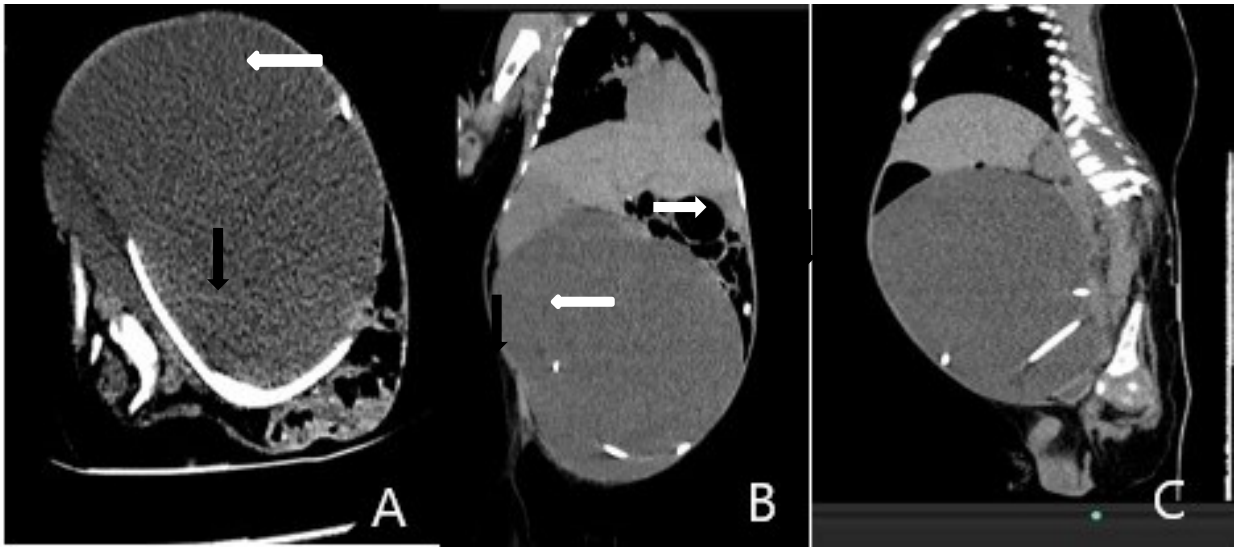


Figure 3. A-Axial, B-frontal and C-sagittal views of a large peritoneal pseudocyst (white arrow) and one of the silicone catheter of VPS was located inside the peritoneal pseudocyst (black arrow).

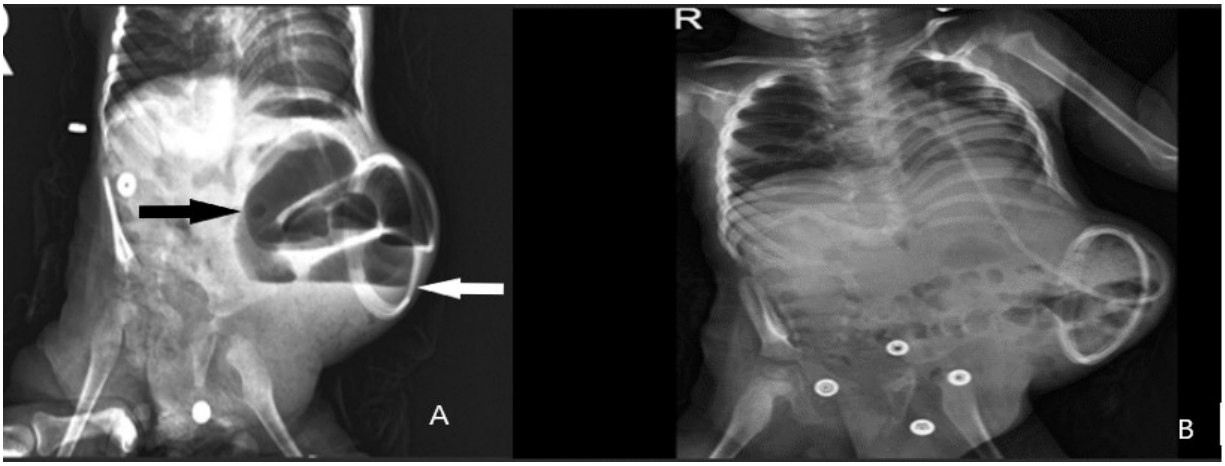


Figure 4. A- Direct abdominal radiography before treatment: mechanical obstruction of small bowel from distal peritoneal catheter (white arrow) wrapped around the loop of ileum. Abdominal distention, intestine dilatation, air-liquid levels (black arrow). B- Direct abdominal radiography after conservative treatment, obstruction was resolved.

Complications related to postoperative VPS insertion were experienced by 346 (100%) patients during the follow-up period. Twelve patients with a history of abdominal issues, were excluded from this study as they had undergone a procedure where the distal end of a VPS was inserted outside the peritoneal cavity. Two hundred forty five (70,81%) of the cases had non-abdominal issues such as a shunt infection or VPS dysfunction as a result of cranial end of VPS catheter or valve blockages. These patients were also excluded from this study, because we would like discuss only abdominal related complications in this article and these were presented in table 1.

Complications relating to the abdominal cavity were observed in 101 (21,19%) of patients. The complaints were evident within the 5-6 months after the VPS placement. The patients at admission had some various complaints such a sliding in the eyes, inability to feed, increased head circumference, nausea and vomiting, abdominal pain, absolute constipation and distention for 1 week. Clinical characteristics of complaints at admission of abdominal complications of VPS are detailed in table 2.

Table 2. Clinical characteristics of complaints of abdominal complications after VPS placement.

Complaints	*n*	Frequency
Sliding in the eyes	44	43,56
Inability to feed	95	93,07
Increased head circumference	28	27,72
Nausea and vomiting	96	95,05
Abdominal pain	37	36,63
Constipation	33	32,67
Distention	32	31,68

In the physical examination, all patients were conscious. The most of the patients had nausea with vomiting 96 (95,05%) followed by inability to feed 95 (93,07%). About half of patients with symptoms of intracranial hypertension (IHT) had a sliding in the eyes 44 (43,56%) and patients under 1 year of age were macrocephalic 28 (27,72%). Patients with bowel related complications such an abdominal CSF pseudocyst or volvulus had a big abdomens and intestinal sounds were not heard. The main presented symptoms with these patients were abdominal pain 37 (36,63%), constipation 33 (32,67%) and distention 32 (31,68%).

Approximate two-thirds of the patients with complications related to the abdominal cavity had an obstruction of the distal end of VPS by fat tissue. The amount of abdomen related complications after VPS insertion are presented in table 3.

Ninety seven (96,04%) patients required a VPS revision surgery. The majority of the patients had an obstruction of abdominal end of the VPS 63 (62,38%), followed by CSF pseudocyst of peritoneal cavity 27 (26,73%), and other each patient had different rare complications such a spontaneous extrusion of the peritoneal catheter of the VPS through the anus, urethra, inguinal canal, migration through the abdominal wall to the scrotal sac and total disconnection (Figure 2). The rate of this rare complications was < 1 (0,22%).

Table 3. Distribution of the patients with abdomen related complications after ventriculoperitoneal shunt placement *n*=101 (100%).

Complication	*n*	Frequency
CSF pseudocyst of peritoneal cavity	27	26,73
Trans-anal extrusion	3	2,97
Trans-inguinal extrusion	1	0,99
Trans-uretral extrusion	1	0,99
Migration to the scrotal sac	1	0,99
Total disconnection	1	0,99
Volvulus	4	3,96
Obstruction of distal end of VPS	63	62,38

Brain CT revealed that the cranial end of the VPS was in the ventricle in all patients and that in 31 (30,69%) of these patients were no signs of acute hydrocephalus or brain compression. There was no significant change in the blood tests, with the exception of hyponatremia, on average sodium count of 119 mEq/L in 23 (22,77%) patients with a large peritoneal pseudocyst. In patients with an abdominal pseudocyst containing less than 300 mL of CSF 4 (3,96%) no decrease in blood sodium levels was noted. Abdominal direct x-ray and abdominal non-contrast axial CT showed that intestines were shifted and we observed a large peritoneal pseudocyst filled with the fluid, and we also saw that one of the silicone catheter of VPS was located inside the peritoneal pseudocyst (Figure 3). Abdominal X-Ray examination in patients with volvulus demonstrated mechanical obstruction of small bowel by distal end of VPS catheter, abdominal distention, intestine dilatation, air-liquid levels (Figure 4 A).

Before the shunt revision in patients with a pseudocyst more than 300 mL of CSF, cyst was punctured and average of 500 mL light coloured liquid was taken from the cyst. The largest pseudocyst had 3500 mL of content while the smallest pseudocyst had 100 mL. When supraumbilical laparotomy was performed, we observed in these patients intestinal adhesion and peritoneal thickness. The peritoneal catheter was carefully freed from intestines and the peritoneal catheter was placed back. After the operation, patients did not have any problems; abdominal weakness and constipation decreased.

Four patients with partial small- bowel obstruction by long distal end of VPS had a conservative treatment. No decline in the overall condition or reported symptoms of these patients was noted during conservative treatment, which involved intravenous fluid and electrolyte replacement, gastrointestinal decompression, and prophylactic antibiotics. A follow-up was conducted using direct abdominal radiography, and no notable changes were detected in the blood tests. All of these patients recovered dramatically within 48 hours after conservative treatment (Figure 4 B). The management strategies for these cases with abdominal complications are depicted in figure 5.

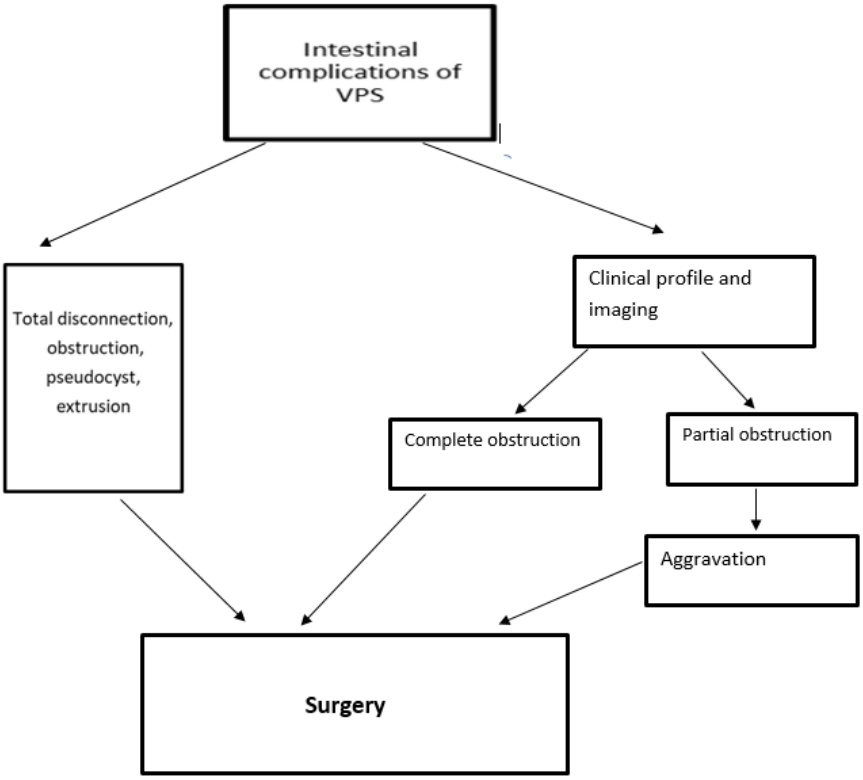


Figure 5. Algorithm of the treatment of the patients with an abdominal complication of VPS.

Discussion

VPS surgery is a common procedure to treat a congenital hydrocephalus as well as hydrocephalus associated after trauma, infection or tumour. Despite the development of new techniques in patients with hydrocephalus, VPS is still the most preferred treatment, because the peritoneal cavity provides a good absorptive surface for CSF, and VPS is easily chased by X-Ray. But complications of VPS have been frequently reported in the literature. All VPS complications can be classified into two groups: group A- abdomen related complications and group, B- others (dysfunction of ventricular catheter, shunt infection or intracranial complications). Also shunt complications may occur as a result of obstruction of proximal and distal ends of VPS or from pump malfunctions. Abdomen related complications were defined as shunt migration to the scrotal sac, extrusion trough anus or urethra, disconnection and completely fall into abdominal cavity, excessive drainage with abdominal pseudocyst, intestinal volvulus or perforation, intestinal adhesions.

The most common complications are shunt dysfunction and shunt tip, infection intracranial shunt migration, abdominal migration, extrusion through anus, urethral or scrotal extrusion, extrusion through chest wall, pneumothorax, abdominal pseudocyst, bowel perforation with subcutaneous emphysema, small bowel obstruction with abdominal end of VPS with secondary ischemia and necrosis (9-17).

There are limited cases of abdominal pseudocyst and intestinal obstruction as an intra-abdominal complications of VPS (19-22). Abdominal symptoms can develop at any time after the shunting procedure. In our study, abdominal complications developed in average in 5,5 months after VPS implementation. In the aetiology of abdominal pseudocyst formation, we believe that there are a few factors. First of all, intestinal adhesions may have been caused by sterile inflammation of cerebrospinal fluid (23). CSF pseudocyst infection usually associated with Staphylococcus epidermis, Staphylococcus aureus, and Streptococcus (24). Abdominal infection followed by fibrosis may have thickened peritoneum and reduced absorption of SCF. Secondly, adhesions and fibrosis may reduce peristaltic movements of the bowel. In our presentation bacteriological cultures of cyst collection were sterile. All 27 cases with pseudocyt collection had abdominal adhesions which decreased peritoneal absorption of CSF. Some pseudocysts may have been due to silicone allergy (25).

The size and volume of the abdominal pseudocysts may vary from 10 mL to 1000 mL and abdominal symptoms are related to their pressure on abdominal organs (8, 15, 16, 26). In our study of abdominal pseudocysts, the largest cyst had a volume of CSF 3500 mL, while the smallest were measured 100 mL. The literature review did not reveal any classification of SCF pseudocyst that occur after intraperitoneal shunt insertion based on their intra-abdominal size. The literature

review did not reveal any classification of SCF fistulas that occur after intraperitoneal shunt insertion based on their intra-abdominal size. In our cases, in large pseudocysts bigger than 300 mL, we observed hyponatremia. Consequently, if the cyst is large, it is important to consider the potential for hyponatremia, even if the shunt is functioning properly. In previously reported cases, hyponatremia was associated with ventricular drainage and CSF loss and huge pseudocyst accumulated CSF or the low of dietary daily sodium intake because of nausea and vomiting (27-29). This is similar to our patients who experienced abdominal issues, which may have contributed to sodium depletion. All of our cases had a cyst drainage followed by open laparotomy. An alternative approach is laparoscopic cyst drainage, which involves repositioning the abdominal catheter of the shunt (30).

Other cases had some factors to consider, such as twisting distal catheter of VPS around a bowel and causing mechanical obstruction in the intestine. The causes of aetiology are not clear but based on previously reported cases, long length abdominal catheter end and bowel movements may have caused spontaneous knotting between bowel and VPS (31). Spontaneous knotting of an agitated string experiments has shown that knots depend on agitation time and string length (32). The small bowel obstruction was due to adhesions at the VP shunt (20, 22).

There are different views in the treatment of abdominal pseudocyst and bowel strangulation, such as excision of the cyst by laparotomy or aspiration; change of VPS to lumboperitoneal (LP) or ventriculoarterial (VA) shunts (1, 14, 18, 20).

Selecting the type of treatment requires careful attention, taking into account the potential complications that could rise after the insertion of a VPS. Even if patients with obstructive hydrocephalus treated with endoscopic third ventriculostomy (ETV), recurrent shunting was required in 20% (33). In our study surgical intervention was required for 97 patients with rapidly progressing clinical course. Four patients with a partial bowel obstruction had a conservative treatment.

Conclusion

Due to the increasing incidence of abdominal complications after VPS surgery, it is important to classify complications such as abdominal pseudocysts based on the volume of CSF accumulation or the size of the cysts. In conclusion, abdominal pseudocyst and bowel strangulation with intestinal obstruction are rare but have serious potential complications of a VP shunt. Patients who had VP shunt placement may have nonspecific gastrointestinal complaints. Increased abdominal symptoms in addition to clinical symptoms must be carefully investigated and necessary treatment should be given.

Abbreviations

CSF - Cerebrospinal fluid
CH - Congenital hydrocephalus
ICH - Intracranial hypertension
EVT - Third ventriculostomy
LP - Lumboperitoneal shunt
VA - Ventriculoarterial shunt
VPS - Ventriculoperitoneal shunt

Ethical Approval: *Ethical approval for the study was obtained from the Harran University Ethics Committee (date: 16/10/2023, decision no: HRU/23.19.36). Our study was planned in accordance with the ethical standards stated in the Helsinki Declaration.*

Author Contributions:
Concept: G.C.
Literature Review: G.C., M.E.B.
Design : G.C., M.E.B.
Data acquisition: -
Analysis and interpretation: G.C.
Writing manuscript: G.C.
Critical revision of manuscript: M.E.B.

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Araştırma Makalesi / Research Article

Testis Torsiyonunda Organ Kaybını Öngörmede Sistemik İmmün İnflamasyon İndeksinin Etkinliğinin Değerlendirilmesi

Efficiency of Systemic Immune Inflammation Index in Predicting Organ Loss in Testicular Torsion

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Öz

Amaç: Bu çalışma, testis torsiyonu (TT) nedeniyle cerrahi müdahale yapılan hastalarda sistemik immün inflamasyon indeksinin (SII) testis kaybını öngörmedeki etkinliğini değerlendirmeyi amaçlamaktadır.
Materyal ve metod: Ocak 2012-Aralık 2023 tarihleri arasında TT tanısı ile cerrahi uygulanan hastaların verileri retrospektif olarak incelendi. Hastalar, cerrahi sonrası orşiopeksi ve orşiektomi yapılanlar olarak iki gruba ayrıldı. Demografik veriler, semptom süresi ve tam kan sayımı değerleri kaydedildi. Nötrofil-lenfosit oranı (NLO), platelet-lenfosit oranı (PLO) ve SII hesaplandı. İki grup arasında hematolojik ve klinik parametreler karşılaştırıldı.
Bulgular: Çalışmaya toplamda 107 hasta dahil edildi; 66'sına orşiopeksi, 41'ine orşiektomi uygulandı. Çok değişkenli analizlerde semptom süresi, WBC, PLO ve SII'nin organ kaybını öngörmede bağımsız ve anlamlı belirteçler olduğu saptandı($p<0,05$). Özellikle semptom süresi ve SII'nin testis kaybını öngörmede yüksek etkinlikte olduğu görüldü (AUC=0,942 ve 0,658).
Sonuç: SII, TT'da testis kaybını öngörmede etkili bir biyobelirteç olabilir. Hızlı ve düşük maliyetli bir yöntem olarak, özellikle görüntüleme yöntemlerine erişimin sınırlı olduğu durumlarda cerrahi karar süreçlerine rehberlik edebilir.

Anahtar Kelimeler: Testis torsiyonu, Orşiektomi, İmmün inflamasyon indeksi, Orşiepoksi, Platelet-lenfosit oranı

Abstract

Background: This study aims to evaluate the efficacy of the systemic immune-inflammation index (SII) in predicting testicular loss in patients undergoing surgical intervention for testicular torsion (TT).
Materials and Methods: The data of patients diagnosed with TT and treated surgically between January 2012 and December 2023 were retrospectively analyzed. Patients were divided into two groups based on the type of surgical intervention: orchiopexy and orchiectomy. Demographic data, symptom duration, and complete blood count parameters were recorded. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII were calculated. Hematological and clinical parameters were compared between the two groups.
Results: A total of 107 patients were included in the study, with 66 undergoing orchiopexy and 41 undergoing orchiectomy. Multivariate analyses revealed that symptom duration, white blood cell count (WBC), PLR, and SII were independent and significant predictors of organ loss ($p<0.05$). Specifically, symptom duration and SII demonstrated high efficacy in predicting testicular loss (AUC=0.942 and 0.658).
Conclusions: SII may serve as an effective biomarker in predicting testicular loss in TT. As a rapid and cost-effective method, it can guide surgical decision-making, particularly in settings with limited access to imaging modalities.

Keywords: Testicular torsion, Orchiectomy, Systemic immune-inflammation index, Orchiopexy, Platelet-to-lymphocyte ratio

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Giriş

Testis torsiyonu (TT), spermatik kordun dönmesi sonucu meydana gelir. Testise giden kan akımının azalması veya kesilmesine bağlı şiddetli ağrı ve şişlik oluşur (1). Tanı atlanır veya zamanında tedavi edilmezse testis kaybı ile sonuçlanır. Buna bağlı olarak hastalarda fertilitede azalma ve psikolojik etkiler görülebilir (2). Bu nedenle tedavi de testisin kurtarılması için hızlı tanı konulup detorsiyon yapılması amaçlanır (3). Semptom başlangıcından ilk 6 saat içinde detorsiyon yapılırsa testis nekrozunun önüne geçilebilir (4). Eğer intraoperative incelemede testis canlılığını kaybetmiş ise orşiektomi yapılmalıdır (5). Bu nedenle erken tanı ve tedavi organ kaybını önlemek için en önemli parametrelerden biridir.

Testis kaybına neden olabilecek yaş, ırk, sigorta durumu, bölge ve sosyodemografik faktörler gibi risk faktörleri bildirilse de preoperatif testis kaybını öngörecek marker son derece sınırlıdır (6). Son yıllarda testis kaybını öngörmede preoperatif hematolojik parametrelerin kullanılabileceği ile ilgili çalışmalar yer almaktadır (7). Sistemik immün inflamasyon indeksi (SII), nötrofil lenfosit oranı (NLO) ile platelet sayısının kombinasyonundan hesaplanan yeni bir inflamatuvar belirteçtir (8). Günümüzde immün durumu yansıtmak ve bazı hastalıkların prognozunu ve risk sınıflandırmasını belirlemek için yaygın olarak kullanılmaktadır (9). Literatürde TT ile SII ilişkisini inceleyen çalışma bulunmamaktadır. Bu çalışmada TT'de organ kaybını öngörmede SII'in ekinliğini araştırmayı amaçladık.

Materyal ve Metod

Lokal etik komiteden etik kurul onayı alındıktan (HRÜ/25.02.14) sonra Ocak 2012 ile Aralık 2023 tarihleri arasında testis torsiyonu tanısı ile cerrahi girişim yapılan hastaların dosyaları geriye dönük incelendi. Fizik muayene ve doppler ultrasonografi bulgularında TT şüphesi olan hastalar opere edildi. Hastalara skrotal eksplorasyon yapıldı ve TT düzeltildi. Tüm olgularda testis ılık spanca sarılıp bekletildikten sonra testislerin canlılığı tunika albuginea insizyonu ile test edildi. Kanlanma olmayan nekroze olan testislerde orşiektomi yapıldı. Hastaların demografik verileri, semptom süresi ve tam kan sayımı kaydedildi. Tam kan sayımından; NLO, platelet/lenfosit oranı (PLO) ve SII (Platelet X nötrofil / lenfosit) hesaplandı. Hastalar orşiopeksi grubu (Grup 1) ve orşiektomi grubu (Grup 2) olmak üzere iki gruba ayrıldı. Tüm parametreler iki grup arasında karşılaştırıldı.

Apendiks testis torsiyonu, karaciğer disfonksiyonu, böbrek yetmezliği, hematolojik hastalıklar, inflamatuar hastalıklar ve bilinen malignitesi olan hastalar çalışmaya alınmadı.

İstatistiksel analiz

Tanımlayıcı istatistiklerde ortalama, standart sapma, medyan, minimum, maksimum değer, frekans ve yüzde kullanıldı. Değişkenlerin dağılımı kolmogorov-simirnov testi ile kontrol edildi. Niceliksel verilerin karşılaştırılmasında Mann-Whitney U testi kullanıldı. Niteliksel verilerin karşılaştırılmasında Ki-Kare testi kullanıldı. Etki düzeyini göstermek için Lojistik Regresyon kullanıldı. Etki düzeyini göstermek için ROC analizi kullanıldı. İstatistiksel analizlerde SPSS 27.0 kullanıldı.

Bulgular

Çalışmaya katılan 107 hastanın 66'sına orşiopeksi yapılırken, 41'ine orşiektomi yapıldı. Orşiopeksi ve orşiektomi grubunda hastaların yaşları, mevsim dağılımı, lenfosit, MPV, NLO değeri anlamlı ($p > 0.05$) farklılık göstermemiştir. Orşiektomi grubunda semptom süresi, WBC değeri, nötrofil değeri, platelet değeri, CRP değeri, PLO, SII değeri orşiopeksi grubundan anlamlı ($p < 0.05$) olarak daha yüksekti (Tablo 1).

Tek değişkenli analizde orşiopeksi ve orşiektomi yapılanların ayrımında semptom süresi, WBC, nötrofil, platelet, CRP, PLO, SII'nin istatistiksel anlamlı olduğu görüldü ($p < 0.05$), (Tablo 2). Çok değişkenli anelizde ise orşiopeksi ve orşiektomi yapılanların ayrımında semptom süresi, WBC, PLO, SII değerinin anlamlı-bağımsız ($p < 0.05$) etkinliği gözlenmiştir. (Tablo 2). Orşiopeksi ve orşiektomi yapılanların ayrımında semptom süresi, WBC, nötrofil, platelet, CRP, PLO, SII değerlerinin anlamlı etkinliği, eğri altı alanı gözlenmiştir (Tablo 3).

Tartışma

Testis torsiyonu zamanında müdahale edilmediği takdirde organ kaybına yol açabilen cerrahi bir acil durumdur. TT, 25 yaş altı her 4.000 erkekten 1'inde görülür ve acil servis ortamında tanısında halen zorluklar yaşanmaktadır (10). TT'li hastalarda testisin kurtarılabilmesi için, zamanında hastaneye başvuru, hızlı tanı ve küratif müdahale gerekmektedir (11). Çalışmamızda, SII'in TT'de organ kaybını öngörmedeki etkinliği araştırılmış ve kayda değer veriler elde edilmiştir.

Semptom süresi, TT'de testis kaybını öngörmede en önemli faktörlerden biri olarak kabul edilmektedir. Literatürde, semptom başlangıcından itibaren ilk 6 saat içinde yapılan müdahalelerin testis kurtarma oranlarını %90'ın üzerine çıkardığı, ancak 12 saati aşan durumlarda bu oranın %50'nin altına düştüğü gösterilmiştir (1,4,5). Çalışmamızda da benzer şekilde, semptom süresinin uzamasıyla orşiektomi oranlarının anlamlı şekilde arttığı tespit edilmiştir (AUC = 0.942). Bu bulgu, hızlı tanı ve müdahalenin önemini bir kez daha vurgulamaktadır. Mevsimsel faktörler ve sosyodemografik özelliklerin de testis kaybı riskini etkileyebileceği literatürde rapor edilmiştir (6). Ancak çalışmamızda bu faktörler istatistiksel olarak anlamlı bulunmamıştır.

Testis torsiyonu ile hematolojik parametreler arasındaki ilişki, esasen inflamatuar yanıtın ve iskemi-reperfuzyon hasarının biyokimyasal belirteçlerine dayanır. NLO, PLO ve ortalama trombosit hacmi (MPV) gibi parametrelerin, iskemi süreci ve reperfüzyon hasarı ile ilişkili oldukları bilinmektedir. Önceki çalışmalarda artmış NLO ve PLO değerlerinin, testis torsiyonunun ciddiyetini öngörmede güvenilir birer

belirteç olduğunu öne sürülmüştür. Bu parametrelerin, inflamatuar yanıtın şiddetini yansıttığı ve iskemi sürecinde patofizyolojik etkilerle uyumlu olduğu belirtilmiştir (12-14). Jang ve arkadaşlarının yaptığı çalışmada testis torisyonu ile başvuran 60 hastanın 22'sinde testis nekrozu nedeniyle orşiektomi yapılmış. Orşiektomi yapılan hastalarda WBC ve NLO, anlamlı şekilde daha yüksek bulunmuş (11). Ancak Merder ve arkadaşlarının çalışmasında ise orşiekromi yapılan hastalar ile detorsiyon yapılan hastalarda WBC, NLO, PLO değerleri benzer bulunmuş. Bu çalışmada sadece monosit sayısı orşiektomi yapılan hastalarda detorsiyon yapılan hastalara göre istatistiksel olarak anlamlı derecede daha yüksek bulunmuş (7). Bizim çalışmamızda NLO iki grup arasında benzer bulunurken, WBC değeri, nötrofil ve CRP orşiektomi grubunda daha yüksek bulundu.

Tablo1. Grupların karşılaştırılması

		Orşiopeksi(n:66)				Orşiektomi(n:41)				p	
		Mean±sd/n-%			Median	Mean±sd/n-%			Median		
Yaş (yıl)		19,7	±	8,1	16,0	17,8	±	9,7	16,0	0,639	m
Taraf	**Sağ**	43		65,2%		31		75,6%		0,255	x^2
	Sol	23		34,8%		10		24,4%			
Mevsim	**Kış**	18		27,3%		13		31,7%		0,644	x^2
	İlkbahar	17		25,8%		10		24,4%			
	Yaz	17		25,8%		13		31,7%			
	Sonbahar	14		21,2%		5		12,2%			
Semptom süresi (h)		11,0	±	13,7	7,0	70,6	±	65,1	48,0	***0,000***	m
WBC (/µL)		11,1	±	2,7	10,5	12,6	±	3,4	12,9	***0,027***	m
Nötrofil		7,7	±	3,0	7,3	9,0	±	3,2	8,2	***0,046***	m
Lenfosit		2,4	±	1,0	2,3	2,2	±	1,4	1,9	0,140	m
Platelet		277,2	±	69,2	269,5	324,1	±	90,2	328,0	***0,006***	m
MPV		7,6	±	1,2	7,3	7,9	±	1,3	7,7	0,110	m
CRP		0,6	±	1,4	0,1	2,3	±	2,6	0,9	***0,000***	m
NLO		4,4	±	3,5	3,4	5,1	±	2,7	4,9	0,053	m
PLO		141,2	±	73,2	119,1	179,1	±	89,0	158,9	***0,013***	m
SII		1204,7	±	925,8	826,7	1577,4	±	818,6	1499,3	***0,006***	m

m Mann-whitney u test/ x^2 Chi-square test
WBC: White Blood Cells,MPV: Ortalama Platelet Hacmi, CRP:C Reaktif Protein,NLO: Nötrofil Lenfosit Oranı
PLO: Platelet Lenfosit Oranı, SII: Sistemik Immun Inflamasyon Indeksi

Tablo 2. Tek değişkenli ve çok değişkenli analizin özeti

	Univariate Analiz					Multivariate Analiz				
	OR	**% 95 CI**			**p**	**OR**	**% 95 CI**			**p**
Yaş	0,974	0,930	-	1,021	0,276					
Taraf	0,603	0,252	-	1,446	0,257					
Semptom süresi (h)	1,102	1,064	-	1,141	***0,000***	1,093	1,054	-	1,133	***0,000***
Mevsim	0,867	0,602	-	1,248	0,441					
WBC (/µL)	1,176	1,028	-	1,345	***0,018***	2,264	1,290	-	3,975	***0,004***
Nötrofil	1,140	1,003	-	1,296	***0,045***					
Lenfosit	0,879	0,616	-	1,255	0,479					
Platelet	1,008	1,002	-	1,013	***0,005***					
MPV	1,273	0,929	-	1,746	0,134					
CRP	1,640	1,217	-	2,211	***0,001***					
NLO	1,070	0,947	-	1,208	0,277					
PLO	1,006	1,001	-	1,011	***0,024***	1,053	1,017	-	1,090	***0,004***
SII	1,000	1,000	-	1,001	***0,040***	0,996	0,992	-	0,999	***0,008***

WBC: White Blood Cells,MPV: Ortalama Platelet Hacmi, CRP:C Reaktif Protein,NLO: Nötrofil Lenfosit Oranı
PLO: Platelet Lenfosit Oranı, SII: Sistemik Immun Inflamasyon Indeksi

Tablo 3. ROC analizi

	AUC	% 95 CI			p
Semptom süresi (h)	0,942	0,897	-	0,987	***0,000***
WBC (/µL)	0,628	0,518	-	0,738	***0,027***
Nötrofil	0,615	0,507	-	0,722	***0,046***
Platelet	0,659	0,548	-	0,769	***0,006***
CRP	0,813	0,730	-	0,896	***0,000***
PLO	0,643	0,534	-	0,751	***0,013***
SII	0,658	0,553	-	0,762	***0,006***

WBC: White Blood Cells,CRP:C Reaktif Protein, PLO: Platelet Lenfosit Oranı, SII: Sistemik Immun Inflamasyon Indeksi

Platelet sayısı ve PLO, inflamasyonun yanı sıra trombotik süreçlerin değerlendirilmesinde de kullanılan parametrelerdir. Vural ve ark. PLO'nın testis torsiyonunda inflamatuvar bir belirteç olarak önemini vurgulamış ve PLO'nın torsiyona bağlı testis kaybını öngörmede etkili bir parametre olduğunu göstermiştir (15). Bizim çalışmamızda da benzer şekilde platelet ve PLO'nı orşiektomi yapılanlarda istatistiksel anlamlı olarak yüksek bulundu.

Sistemik immün inflamasyon indeksi, nötrofil, lenfosit ve platelet seviyelerinin kombinasyonundan türetilen bir inflamasyon belirtecidir ve inflamasyonun sistemik etkilerini yansıtmada kapsamlı bir araç olarak öne çıkmaktadır. Bir çok onkolojik hastalıkta incelenmiş, hem tanısal hem de prognostik bir belirteç olduğu gösterilmiştir (8,9,16-19). Benzer şekilde iskemik inme, ARDS, böbrek yetmezliği gibi hastalıklarda SII'nin hem tanısal hem de prognostik bir araç olduğu ortaya konmuştur (20-22). Bizim çalışmamızda da orşiektomi yapılan hastalarda SII değerlerinin anlamlı şekilde daha yüksek olduğu görülmüştür (AUC = 0.658). SII'nin yüksek AUC değerine sahip olması, bu parametrenin testis torsiyonu prognozunda kullanılabilir bir biyobelirteç olabileceğini düşündürmektedir.

Çalışmamızın retrospektif olması elde edilen bulguların genellenebilirliğini sınırlamaktadır. Ayrıca, SII değerlerini etkileyebilecek inflamatuar hastalıkların ve komorbiditelerin tamamen dışlanamamış olması, sonuçlarımızı etkileyebilir. Bununla birlikte, SII'nin prognostik değerini ortaya koyan bulgularımız, bu parametrenin TT'de tanı ve tedavi karar süreçlerinde kullanılabilirliğini desteklemektedir.

Sonuç olarak TT'de testis kaybını öngörmede birden fazla faktör etkili olmakla birlikte, semptom süresi ve inflamatuvar belirteçlerin özellikle ön planda olduğu görülmektedir. SII'nin hızlı, invaziv olmayan ve düşük maliyetli bir yöntem olması, TT'nin yönetiminde önemli avantajlar sunmaktadır. Doppler ultrasonografi gibi görüntüleme yöntemlerine erişimin sınırlı olduğu durumlarda, SII değerleri, cerrahi müdahale gerekliliği hakkında hızlı kararlar alınmasına yardımcı olabilir. Bununla birlikte, SII'nin klinik uygulamalarda yaygın olarak kullanılabilmesi için farklı popülasyonlarda ve klinik senaryolarda daha geniş kapsamlı çalışmalar gerekmektedir. Özellikle, SII'nin eşik değerlerinin standardizasyonu ve diğer biyobelirteçlerle birlikte kullanımı gelecekteki çalışmalar için önemli bir araştırma alanı sunmaktadır.

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Research Article / Araştırma Makalesi

Management and Outcomes of Displaced Fractures of the Acetabulum

Deplase Asetabulum Kırıklarının Yönetimi ve Klinik Sonuçları

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Abstract

Background: Surgical management of displaced acetabular fractures represents a challenge for orthopedic surgeons due to their biomechanical complexity. An open reduction with anatomical correction can provide good to excellent clinical results for these patients. However, this depends on several determinants, such as the center experience, surgical approach, patient age, and fracture mechanism. The purpose of this study was to evaluate the anatomical, radiologic and functional results of the acetabular fracture treatments in a level 1 trauma center of a university hospital.
Materials and Methods: This single-center retrospective clinical study was conducted between January 2011 and June 2015 at Harran University Medical School, Department of orthopedics, and traumatology. Patients who presented to the emergency department with acetabular fractures and managed surgically were included in the study. Demographic variables, mechanisms of injury, surgical approach, complications, radiographic and functional outcomes were recorded from patient charts. Anatomical results were examined on standard x rays of the pelvis and Judet`s oblique radiographs. Clinical results were analyzed according to the Postel-Merle d'Aubigne criteria.
Results: Forty-eight patients presented to our emergency department with acetabular fractures. Seventeen of these patients were treated surgically, whereas 31 were managed conservatively. The most common type of injury was motor vehicle accidents. In the surgical reduction of these fractures, mostly the Kocher-Langenbeck approach was preferred by the surgeons. The mean follow-up of patients was mean 4.2 years. According to Matta's criteria, the reduction was considered anatomical in 5 patients, acceptable in 10 patients, and poor in 2 patients. During the last postoperative follow-up of these patients, eight were evaluated as excellent, four good, two fair, and three poor according to Matta`s radiologic criteria. Overall, twelve patients in the study cohort presented good or excellent clinical and functional results (70.5%).
Conclusions: This study adds additional data to the growing body of clinical research and validates open reduction as the treatment of choice in selected high energy injuries of the acetabulum. Additionally, in the long-term follow-up, this strategy has shown satisfactory clinical and functional results.

Keywords: Acetabulum fracture, Kocher Langenback, Pelvis fracture

Öz

Amaç: Yer değiştirmiş asetabular kırıkların cerrahi yönetimi, biyomekanik karmaşıklıkları nedeniyle ortopedik cerrahlar için bir zorluk teşkil etmektedir. Anatomik düzeltme ile açık redüksiyon bu hastalar için iyi ila mükemmel klinik sonuçlar sağlayabilir. Ancak, bu durum merkez deneyimi, cerrahi yaklaşım, hasta yaşı ve kırık mekanizması gibi çeşitli belirleyicilere bağlıdır. Bu çalışmanın amacı, bir üniversite hastanesinin 1. seviye travma merkezinde asetabulum kırığı tedavilerinin anatomik, radyolojik ve fonksiyonel sonuçlarını değerlendirmektir.
Materyal ve Metod: Bu tek merkezli retrospektif klinik çalışma Ocak 2011 ile Haziran 2015 tarihleri arasında Harran Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Anabilim Dalı'nda gerçekleştirildi. Acil servise asetabulum kırığı ile başvuran ve cerrahi olarak tedavi edilen 48 hasta çalışmaya dahil edildi. Demografik değişkenler, yaralanma mekanizmaları, cerrahi yaklaşım, komplikasyonlar, radyografik ve fonksiyonel sonuçlar hasta dosyalarından kaydedildi. Anatomik sonuçlar standart pelvis grafileri ve Judet'in oblik grafileri ile incelendi. Klinik sonuçlar Postel-Merle d'Aubigne kriterlerine göre analiz edildi.
Bulgular: Araştırmaya dahil edilen 48 hasta acil servisimize asetabulum kırığı ile başvurdu. Bu hastaların 17'si cerrahi olarak tedavi edilirken, 31'i konservatif olarak tedavi edildi. En sık görülen yaralanma tipi motorlu araç kazalarıydı. Bu kırıkların cerrahi redüksiyonunda cerrahlar tarafından çoğunlukla Kocher-Langenbeck yaklaşımı tercih edildi. Hastaların ortalama takip süresi 4,2 yıldı. Matta'nın kriterlerine göre redüksiyon 5 hastada anatomik, 10 hastada kabul edilebilir ve 2 hastada kötü olarak değerlendirildi. Bu hastaların ameliyat sonrası son takiplerinde Matta'nın radyolojik kriterlerine göre sekizi mükemmel, dördü iyi, ikisi orta ve üçü kötü olarak değerlendirildi. Genel olarak, çalışma kohortundaki on iki hasta iyi veya mükemmel klinik ve fonksiyonel sonuçlar sundu (%70,5).
Sonuç: Bu çalışma, artan klinik araştırmalara ek veriler eklemekte ve asetabulumun seçilmiş yüksek enerjili yaralanmalarında tercih edilen tedavi olarak açık redüksiyonu doğrulamaktadır. Ayrıca, uzun dönem takipte, bu strateji tatmin edici klinik ve fonksiyonel sonuçlar göstermiştir.

Anahtar Kelimeler: Asetabulum kırığı, Kocher Langenback, Pelvis kırığı

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Introduction

Acetabular fractures are among the most complex fractures in orthopedic surgical practice (1). Anatomic reduction of these fractures was shown to provide excellent functional outcomes. In 1964, Robert Judet and Emile Letournel described an anatomical reduction technique for these fractures (2). Subsequently, Matta worked on the reduction and fixation techniques and emphasized the force distribution on the acetabulum and its specific arcs (3). The measurements described in this report were used as a guide to decide for an open versus closed management (3). In the short-term, the anatomical and functional results of surgical management were reported as satisfactory by several trauma centers (4-6). However, the risk of inadequate reduction, nerve injury, and heterotrophic ossification continued to be a primary cause of morbidity after surgery (7). Besides, long-term follow-up results are yet to be shared by some centers with a relatively high caseload.

The purpose of this study was to evaluate the long-term anatomical and functional results of the acetabular fractures treated with surgery in a level 1 regional trauma center of a University Hospital in Turkey.

Materials and Methods

This retrospective clinical study was conducted between January 2011 and June 2015 at Harran University Medical Faculty, Department of Orthopedics and Traumatology. It was approved by the local Ethical Review Committee of the same university. All patients were previously asked to sign a consent form to use their medical and surgical data in the context of this study. The data of the patients who signed these forms were reviewed. Patients who presented with acetabular fractures to the emergency department and underwent surgeries for acetabular reduction were included in this study. Patients younger than 15 and those with recoil time less than 36 months were excluded. Additionally, patients with incomplete data or those who were lost to follow-up were omitted.

Patients suspected of having an acetabular trauma at the emergency department were evaluated with the plain anteroposterior pelvis and Judet oblique radiographs. This evaluation was followed by three-dimensional computed tomography (CT) scans in case of a fracture. These radiological images and their reports were recorded in PACS (Picture Archiving and Communication System). Fracture patterns were classified according to Judet and Letournel (2). Indications for surgical treatment comprised of fractures presenting with more than 3mm of displacement, joint instability, and marginal articular impaction with loose bodies. Surgical interventions were initiated as soon as the patients` general condition permitted, and diagnostic evaluations were completed. The primary determinant of the surgical approach was the fracture pattern.

General endotracheal anesthesia was performed for all surgical interventions. When possible, a urinary catheter and a gastric tube were placed. Prophylactic second-generation cephalosporin antibiotics were administered intravenously 30 minutes before the skin incision, and prophylactic antibiotherapy continued until the surgical drains were removed. Compression stockings were used by all patients preoperatively for deep vein thrombosis (DVT) prophylaxis. Additionally, 0.6 ml of low molecular weight heparin was administered subcutaneously daily until the patients were fully mobilized. The patients were mobilized from bed to chair on postoperative day 2. Limited weight-bearing on the involved leg (toe-touch 10 kg) was maintained for 8-12 weeks, depending on the injury pattern. Weight-bearing of the body weight was allowed on postoperative 14th week. The patients were evaluated clinically and radiologically in the early postoperative period, and the quality of fracture reduction was assessed by measuring the residual displacement. The maximum residual displacement was measured to grade the quality of reduction according to Matta's criteria as anatomical (i.e., displacement less than 2 millimeters), imperfect (i.e., a displacement between 2 and 3 mm), or poor (i.e., displacement more than 3 mm) (3). Postoperative complications such as surgical site infection, deep vein thrombosis (DVT), heterotrophic ossification, and nerve palsies were recorded from the patient charts. On postoperative 12th month and once a year afterward, patients were evaluated radiologically as per Matta's criteria and clinically according to Postel-Merle d'Aubigne criteria (Tables 1 and 2) (1, 3). Overall functional outcome was assessed based on pain, range of motion of the joint, and ambulation status of the patient.

Statistical Analysis

Descriptive statistics were used to present the data. As a measure of central tendency, mean values were calculated. Standard deviation and minimum-maximum values were displayed as measures of variability.

Results

Forty-eight patients presented to our emergency department with an acetabular fracture within the study period. Seventeen (35.4%) of these patients were treated surgically, whereas 31 (64.6%) were managed conservatively. Thirteen patients were injured due to motor vehicle collisions, 10 were inside the vehicle, and 3 were pedestrians (Table 3). The other causes of trauma were gunshot, motorcycle accident, and accidental high fall. Nine (52%) of the surgically treated patients had one or more additional injuries, and six of them underwent concomitant surgical interventions other than acetabular fixation.

The majority of these patients were male (n=12, 70%), while only five were female (30%). The mean age of these patients was 36.3 [15-78]. Nine (53%) patients had right-sided and 8 (47%) patients had left-sided acetabular fractures. Fracture types, classified according to Judet, are shown in Table 3. Nine of the fractures were classified as simple fractures of the acetabulum (53%), while complex fractures were encountered in 8 (47%) of these patients (Table 4).

Table 1. Radiological outcome according to Matta.

Grade	Osteophytes	Joint Space Narrowing	Sclerosis	Femoral Head Subluxation
Excellent	None	Normal	None	None
Good	Small	> 1mm	Minimal	None
Fair	Moderate	< 50%	Moderate	Minimal
Poor	Large	>50%	Severe	Moderate to Severe

mm: Milimeter

Table 2. Clinical outcome scoring system according to Postel-Merle d'Aubigne criteria

Score	Pain	Mobility	Ability to Walk
0	Intense and permanent	Ankylosis abnormal position	Impossible
1	Severe, disturbing sleep	Ankylosis normal position	Only with crutches
2	Severe, when walking	Flexion <40˚	Only with two canes
3	Severe, with limited activity	Flexion <40˚- 60˚	With one cane
4	Only with walking	Flexion <60˚- 80˚	Limited without a cane
5	Intermittent, normal activity	Flexion <80˚- 90˚, limited abduction	No cane with slight limp
6	None	Flexion >90˚, abduction	Normal

Table 3. Patient characteristics.

Patient no.	Gender	Age	Injury	Fracture type	Surgical Approach	Radiologic Score	Clinical Score
1	Male	15	High Fall	Complex	Extended Iliofemoral + Kocher Langenbeck	Fair	Excellent
2	Male	35	Gun Shot	Simple	Kocher Langenbeck	Good	Excellent
3	Female	40	MVA	Simple	Kocher Langenbeck	Excellent	Excellent
4	Female	32	MVA	Complex	Kocher Langenbeck	Fair	Fair
5	Female	34	MVA	Complex	Ilioinguinal + Kocher-Langenbeck	Poor	Good
6	Male	28	MVA	Complex	Ilioinguinal + Kocher-Langenbeck	Fair	Fair
7	Male	41	MVA	Simple	Kocher Langenbeck	Excellent	Excellent
8	Female	52	MVA	Complex	Ilioinguinal + Kocher-Langenbeck	Poor	Fair
9	Male	20	MVA	Simple	Kocher Langenbeck	Excellent	Excellent
10	Male	28	MVA	Simple	Ilioinguinal	Poor	Good
11	Male	78	MVA	Simple	Kocher Langenbeck	Excellent	Fair
12	Male	56	MVA	Complex	Kocher Langenbeck	Fair	Poor
13	Male	18	MC	Simple	Kocher Langenbeck	Good	Excellent
14	Male	73	MVA	Simple	Kocher Langenbeck	Excellent	Good
15	Female	24	MVA	Simple	Ilioinguinal	Excellent	Excellent
16	Male	28	MVA	Complex	Kocher Langenbeck	Good	Good
17	Male	15	MC	Complex	Kocher Langenbeck	Good	Excellent

MVA: Motor Vehicle Accident, MC: Motorcycle Crash

Seven of the patients had posterior hip dislocation at the time of admission, and reduction of the hip dislocations was performed under sedation at the emergency department. Skeletal traction was applied to these patients using a Schanz nail until the definitive surgical procedure. The mean interval between conclusive surgery and admission to hospital was 4. 9 [2-12] days. The most frequently used surgical approach was Kocher-Langenbeck, followed by the simultaneous ilioinguinal and Kocher-Langenbeck approach (Table 5).

The minimum and mean follow-up durations were 3 and 4.2 years. Radiographic fracture union was attained in all patients within a mean period of 3.5 months postoperatively. In the early postoperative period, the assessment revealed that the reduction was anatomical in 5, fair in 10, and poor in 2 patients as per Matta's criteria. During the last postoperative follow-up visit of these patients, 8 were evaluated as excellent, 4 as good, 2 as fair, and 3 as poor according to Matta`s radiological criteria.

Clinically, according to Postel-Merle d'Aubigne criteria, 8 (47%) of our patients had 'excellent' and 4 (23.5%) of our patients had 'good' clinical scores. On the other hand, 4 (23.5%) had fair, and 1 (6%) had poor scores. Overall, 12patients in the study cohort presented excellent or good clinical results (70.5%.) During the follow-up period, sciatic nerve paralysis was not encountered in any patients. Surgical site infections were detected in 4 (23.5%) of the 17 surgically treated patients. Three were superficial infections managed with daily wound care. One deep surgical site infection required systemic antibiotic treatment. This patient was eventually taken back to the operating room for washout and debridement. The infection improved with continued wound care and the use of antibiotics effective against the cultured bacteria. Deep vein thrombosis and heterotopic ossification were not detected in any study patients.

Table 4. Fracture types according to Judet classification.

Fracture Type	Number of Patients
Complex Fractures	8 (47%)
• T Shaped and Posterior Wall	2
• Posterior Wall and Anterior Colon	2
• Posterior Wall and Posterior Colon	1
• Posterior Column and Hemi- transverse	1
• Transverse and Posterior Wall	1
• Anterior and Posterior Wall	1
Simple Fractures	9 (53%)
• Posterior Column	4
• Posterior Wall	3
• Transverse	2

Table 5. Frequency of surgical approaches used for management of acetabular fractures.

Surgical Procedure	Number of Patients
Kocher-Langenbeck	11 (64.7%)
Ilioinguinal	2 (11.7%)
Extended Iliofemoral + Kocher-Langenbeck	1 (6%)
Ilioinguinal + Kocher-Langenbeck	3 (17.6%)

Discussion

With the advancements in technology and industry, the number and severity of traffic and work accidents increased (8). These accidents usually involve complicated high-energy injuries, and by its very nature, they can affect multiple organ systems (9). Since acetabular fractures may occur during these injuries, these fractures' rates increased over the last 15 years (10). However, since these cases are shared between different centers, the number of centers with comprehensive experience regarding complex acetabular fractures remains insufficient. These centers' clinical and radiological results are also highly variable, and mostly their long-term outcomes are lacking in the literature. One of the primary reasons for this variability and underrepresentation is the discrepancy among the acetabular fracture classifications (11, 12). Since the Judet-Letournel classification is most widely used in the literature, we used this classification in our study (11). We routinely obtain anteroposterior, Judet's 45˚ iliac, and obturator radiographs preoperatively in our clinical practice. This approach was useful for classifying the acetabular fractures as per the Judet-Letournel classification system.

Matta and Letournel, who are the leading advocates of surgical management in acetabular fractures, reported satisfactory clinical results in more than 80% of their patients (12, 13). Subsequently, Ridder and Ruesch shared their own experiences on the surgical treatment of acetabular fractures, which were consistent with Letournel and Matta's results. In this study, we obtained 'excellent' or 'good' clinical results in 70.5% of our patients. This finding is compatible with the literature (12, 13).

It is widely accepted that these patients' clinical results were correlated with the quality of the articular reduction and radiologic correction (14). In 2012, Matta published the most extensive single surgeon series of patients surgical treated for acetabular fractures (3). This study demonstrated that the postoperative radiographic findings were strong indicators of the long-term clinical outcomes. The radiological classification system proposed in this report has been accepted as established evaluation criteria for articular reductions. In a meta-analysis including 3249 patients with acetabular fractures, only 6.9% of patients demonstrated poor radiological results according to the Matta classification (15). In this study, poor radiological results were encountered in only 3 patients according to the Matta criteria, and a total of 15 patients had satisfactory radiological results.

Anatomical reduction of these fractures is necessary to obtain optimal radiologic outcomes. However, the achievement of anatomical reduction depends on the surgical exposure, and surgical exposure is directly affected by the surgical technique (16). The ideal surgical technique is the one that provides adequate exposure and permits anatomical reduction of the fracture with good control over the fracture fragments. It also has low complication rates. The Kocher-Langenbeck approach was widely used to fix acetabular fractures with relatively low complication rates (16, 17). The reliability of this approach was proven by Letournel and Matta (2, 3). In our center, the most frequently performed technique was Kocher-Langenbeck; 11 of the 17 surgically treated patients underwent this procedure.

Complications that may occur during the treatment of acetabular fractures may significantly impact clinical outcomes (18, 19). Inadequate anatomical reduction, intraarticular implant, heterotopic ossification, vascular nerve injuries are the most frequent complications encountered after the surgery of acetabular fractures. Deep venous thrombosis, heterotopic ossification, infection, chondrolysis, avascular necrosis of the femoral head, and posttraumatic osteoarthritis are the other complications reported in the literature

(20, 21). In our study, we did not encounter DVT or heterotopic ossification in any of our patients. However, we detected infection in 4 patients (23.5%). The underrepresentation of possible complications in this study may be due to its small sample size.

Additionally, since this is a retrospective study, there might have been an information bias leading to inaccurate data analysis regarding complications. However, it must also be considered that our refined surgical technique, paying close attention to anatomical planes during surgery, and insight into acetabular injury's mechanism might have a significant impact on these positive clinical outcomes. The mean patient age was 36.3 years in our study, indicating that our patients were younger than those reported in other series. This fact might also have contributed to the favorable clinical outcomes of our study population.

Conclusion

This study adds data to the growing body of clinical research and validates open reduction as the treatment of choice in selected high-energy injuries of the acetabulum. Additionally, in the long-term follow-up, this strategy has shown satisfactory clinical and functional results.

***Ethical* Approval:** For the study, approval dated 12/12/2014 and numbered HRU/14.12.05 was obtained from the Research Ethics Committee of Harran University and the article was produced from the thesis (master's/doctoral) study. Our study was planned in accordance with the ethical standards specified in the Declaration of Helsinki.

Author Contributions:
Concept: M.Y., B.S., C.E.
Literature Review: M.Y., B.S.
Design : A.L.
Data acquisition: M.Y.
Analysis and interpretation: M.Y., A.L., E.V.
Writing manuscript: M.Y.
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Derleme Makalesi / Review Article

Alzheimer Hastalığının Patogenezinde Sideritis L. (Dağçayı) Türlerinin Biyokimyasal ve Moleküler Etkileri

Biochemical and Molecular Effects of Sideritis L. (Dağçayı) Species in the Pathogenesis of Alzheimer's Disease

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Öz

İlerleyici bir nörodejeneratif hastalık olan Alzheimer hastalığı, kolinerjik sistemdeki eksiklikler, nörofibriler yumak ve amiloid plaklar şeklinde beta amiloid birikimi ile karakterizedir. Alzheimer hastalığını tanımlamak için kullanılan beta amiloid beyin proteinlerinin aynı zamanda hastalığın patogenezinde de rol aldığına yönelik kanıtlar amiloid-β hipotezini ortaya çıkarmıştır. Bu hipotez, serebral beta amiloid birikiminin tau patolojisine, nöroinflamasyona, nöronal kayba ve bilişsel bozukluğa yol açtığını ileri sürmektedir. Kolinerjik sistem öğrenme ve hafıza süreçlerinin düzenlenmesinde önemli bir rol oynamaktadır. Kolinerjik hipoteze göre, Alzheimer hastalığında kolinerjik fonksiyonlardaki bozulma neokorteks ve hipokampüsü içeren beyin bölgelerinde kritik öneme sahiptir. Ayrıca asetilkolinesteraz ve bütilkolinesterazın senil plak oluşumunun erken evrelerinde beta amiloid agregasyonunda önemli bir rol oynadığı bilinmektedir. Gama aminobütirik asit merkezi sinir sisteminde görev yapan en önemli inhibitör nörotransmitterdir ve disfonksiyonu Alzheimer hastalığı ile ilişkilendirilmektedir. Lamiaceae familyasından olan Sideritis cinsine ait bitkiler ülkemizde çoğunlukla Marmara, Ege ve Akdeniz bölgelerinde yetişmektedir. Sideritis bitkileri çok eski çağlardan bu yana folklorik tıpta çoğunlukla aromatik bitki çayı şeklinde kullanılmaktadır. Uçucu yağlarının Akdeniz tıbbında akciğer dezenfektanları, diüretikler, mide ilaçları ve sinir gevşetici maddeler olarak kullanımı birçok etnofarmakolojik makalede rapor edilmiştir. Son yıllarda yapılan çalışmalarda *Sideritis L.* türlerinin nörodejeneratif hastalıklarda da koruyucu ve iyileştirici etkiye sahip olabileceğine işaret edildiğinden, Alzheimer hastalığındaki biyokimyasal ve moleküler etkilerinin derlenmesi amaçlanmıştır.

Anahtar Kelimeler: Alzheimer Hastalığı, Sideritis, Asetilkolin esteraz, beta Amiloid

Abstract

Alzheimer's disease, a progressive neurodegenerative disease, is characterized by deficiencies in the cholinergic system and beta amyloid deposition in the form of neurofibrillary tangles and amyloid plaques. Evidence that beta amyloid brain proteins used to define Alzheimer's disease also play a role in the pathogenesis of the disease has led to the amyloid-β hypothesis. This hypothesis proposes that cerebral beta amyloid deposition leads to tau pathology, neuroinflammation, neuronal loss, and cognitive impairment. The cholinergic system plays an important role in the regulation of learning and memory processes. According to the cholinergic hypothesis, the impairment of cholinergic functions in Alzheimer's disease is of critical importance in brain regions including the neocortex and hippocampus. It is also known that acetylcholinesterase and butylcholinesterase play an important role in beta amyloid aggregation in the early stages of senile plaque formation. Gamma aminobutyric acid is the most important inhibitory neurotransmitter in the central nervous system and its dysfunction is associated with Alzheimer's disease. Plants belonging to the Sideritis genus, which is from the Lamiaceae family, grow mostly in the Marmara, Aegean and Mediterranean regions of our country. Sideritis plants have been used in folkloric medicine since ancient times, mostly in the form of aromatic herbal tea. The use of essential oils in Mediterranean medicine as lung disinfectants, diuretics, stomachic drugs and neurorelaxants has been reported in many ethnopharmacological articles. Since recent studies have indicated that Sideritis L. species may have protective and healing effects in neurodegenerative diseases, it was aimed to compile their biochemical and molecular effects.

Keywords: Alzheimer's Disease, Sideritis, Acetylcholine esterase, beta Amyloid

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Giriş

Nörodejeneratif Demans

Nörodejeneratif demanslar, özellikle ileri yaşlarda olmak üzere dünya çapında yaygın ve giderek artan bir ölüm ve sakatlık nedenidir (1). Dünya çapında nörodejeneratif demansın en yaygın şekli Alzheimer tipi demanstır. Daha az görülen tipler ise frontotemporal demans (FTD) (%5-7) ve Lewy cisimcikli demanstır (LCD) (%7) (2). Bu nörodejeneratif demanslar, örtüşen özellikleri paylaşsalar da, klinik görünümleri ve altta yatan patofizyolojileri açısından heterojendir (3). Alzheimer hastalığı (AH), FTD, LCD ve Huntington hastalığı dahil olmak üzere birçok nörodejeneratif bozukluğun, günümüzde yanlış katlanmış proteinlerin toplanması ve birikmesiyle ilişkili proteinopatiler olduğu düşünülmektedir. AH biyobelirteçlerinin geliştirilmesinden önce, klinik tanı mümkün veya olası olarak tanımlanıyordu ve kesin tanının ölüm sonrası beyin dokusu histopatolojisi ile doğrulanması gerekiyordu (4). AH biyobelirteçlerinin keşfi, dejeneratif demanslarla ilgili yeni bir paradigmanın ortaya çıkmasına neden oldu. Biyobelirteçler, nörolojik hastalıkların spektrumunu en erken belirtilerden son aşamalara kadar tanımlayarak anlamak için güçlü bir yaklaşım sağlar (5). Biyobelirteçler, patofizyolojik hastalık özelliklerinin in vivo değerlendirilmesine olanak sağlayan objektif ve ölçülebilir parametreler olarak tanımlanmaktadır. AH için güncel biyobelirteçler: 1) Beyin omurilik sıvısında (BOS) Aβ1-42, toplam tau ve fosforile tau testi; 2) beyin manyetik rezonans görüntüleme (MRI) ve hipokampal hacim analizi gibi yapısal nörogörüntüleme çalışmaları; 3) 18F florodeoksiglukoz (FDG) positron emisyon tomografisi (PET) gibi metabolik aktivitenin fonksiyonel nörogörüntülemesi ve amiloid PET ve tau PET gibi protein tanımlayıcı nörogörüntülemedir (6). AH'daki klinik semptomların mutlaka amiloid birikintileri sonrasında görülmesi gerekmez. Birikim seviyeleri veya bölgeleri ile ilişkili değildirler. Ancak nörofibriler dejenerasyon sonrasında nöronal hasar oluşmaktadır. Amiloid birikimi frontal lob ve precuneus bölgelerinde başlar ve hipokampustaki tau patolojisi parieto temporal asosiasyon alanlarına doğru ilerler. Günümüzde tau birikiminin nöronal yolakları izlediği bilinmektedir (7).

Sideritis L. Türleri

Sideritis cinsi, dağlık bölgelerde doğal olarak yetişen yıllık veya çok yıllık kserofitik ve termofitik bitkilerin 150'den fazla türünü içerir. Türlerin çoğu esas olarak Kanarya Adaları ve Madeira'dan Kafkasya'ya kadar Akdeniz bölgesinde bulunur; İspanya ve Türkiye en fazla sayıda farklı türe sahiptir. İspanya'da İber Yarımadası'nın Güneydoğusu ve Kanarya Adaları'nda görülürken, Türkiye'de ise çoğunlukla Marmara ve Ege bölgelerinde yetişmektedir (8-10). Sideritis L. cins adı, demirden yapılan silahların neden olduğu yaraları iyileştirmek için eski çağlardan beri bu bitkilerin kullanıldığına atıfla Yunanca "sideros" (demir) kelimesinden türemiştir. Antik çağlardan beri Sideritis bitkileri halk hekimliğinde çoğunlukla aromatik bitki çayı şeklinde kullanılmaktadır (11-13). Sideritis türlerinin geleneksel Akdeniz tıbbında yaygın ve önemli kullanımı birçok etnofarmakolojik makalede rapor edilmiştir. Yıllar içerisinde Sideritis taksonları kimyasal çeşitlilikleri açısından araştırılmış ve uçucu (uçucu yağ; monoterpenler, seskiterpenler, vb.) ve uçucu olmayan bileşikler (örneğin terpenoidler, flavonoidler, feniletanoid glikozitler ve fenolik asitler) dahil olmak üzere çeşitlendirilmiş özel ürünlerden oluşan zengin bir rezervuar ortaya çıkarılmıştır. Sideritis esansiyel yağlarının verimi genel olarak düşük olup, kozmetik ve parfüm endüstrisinde kullanımı sınırlıdır. Sideritis türleri uçucu yağ açısından fakir olmasına rağmen infüzyonları hoş karakteristik bir aromaya sahiptir. Sideritis uçucu yağları akciğer dezenfektanları, diüretikler, mide ilaçları ve sinir gevşetici maddeler olarak kullanılmıştır (14,15). Son yıllarda yapılan çalışmalar Sideritis L. türlerinin ekstreleri ve sekonder metabolitlerinin nörodejeneratif hastalıklarda da koruyucu ve iyileştirici etkiye sahip olabileceğine işaret etmektedir.

Amiloid β proteini toksisitesine karşı aktivite

AH'nı tanımlamak için kullanılan beyin proteinlerinin aynı zamanda patogenezinde nedensel bir rol oynadığını öne süren amiloid beta (Aβ) hipotezi, bu mekanistik yaklaşımın ön saflarında yer almaktadır (16). Hastalığın etiyopatogenezi tam olarak anlaşılmamış olsa da, amiloid kaskad hipotezi AH'yi anlamak için en çok kabul gören modellerden biri olmaya devam etmektedir. Bu hipotez, serebral Aβ birikiminin AH'da merkezi bir olay olduğunu ve tau patolojisine, nöroinflamasyona, nöronal kayba ve nihayetinde bilişsel bozukluğa yol açtığını ileri sürmektedir. Aβ üretimi ile temizlenmesi arasındaki dengesizliğin, hastaların beyninde bu peptidin anormal birikimine yol açtığı düşünülmektedir (17). Aβ patolojisinin ilerlemesinin, beyin bölgelerinde doğal olarak katlanmış proteinlerin yanlış katlanmasını ve toplanmasını şablonlayan yanlış katlanmış Aβ kümelerinin veya "tohumların" kendi kendine yayılmasıyla aracılık edildiğine inanılmaktadır. Aβ'lar yanlış katlandığında sulu ortamlarda çözünmezlik, proteoliz ve denatürasyona direnç ve toksisite dahil olmak üzere yeni biyokimyasal ve biyolojik özellikler kazanır (18). Aβ peptidi, amiloid öncü proteini adı verilen daha büyük bir transmembran proteinin proteolitik ürünüdür. Aβ öncelikle hücre dışı boşluğa salınır ve beyinde ve beyin-omurilik sıvısı (BOS) ve plazma gibi birçok vücut sıvısında bulunabilir. Beyin düzeyinde Aβ, neprilisin, plazmin, endotelin dönüştürücü enzimler, insülin parçalayıcı enzim ve diğerleri gibi çok sayıda proteaz tarafından parçalanır. Aβ ayrıca periferik bozunma için beyinden dışarı atılabilir. Bu olaylar, ileri glikozilasyon son ürün spesifik reseptörü, apolipoproteinler ve aquaporin-4 gibi çok sayıda ve karmaşık mekanizma aracılığıyla gerçekleşir. Beyindeki Aβ bozunmasının yukarıda belirtilen mekanizmalarına rağmen, çeşitli kanıtlar Aβ peptitlerinin çoğunun periferik dokularda da bozunduğunu göstermektedir (17). Mevcut ilaçlarla ortaya çıkan olumsuz yan etkilerin olasılığını azaltmak amacıyla AH'nı önlemek, yavaşlatmak ve hatta tedavi etmek için yeni ajanların tanımlanmasına yönelik çok fazla araştırma yürütülmektedir. Doğal ürünler, antioksidan ve/veya antiinflamatuvar aktiviteler ve Aβ üretimine ve toplanmasına karşı

inhibitör aktiviteyi de içeren pleiotropik nöroprotektif aktivite potansiyelleri nedeniyle ayrıcalıklı adaylardır. *Sideritis scardica (S. Scardica)* ekstraktlarının, çeşitli nörolojik bozukluklarda yer alan bazı nörotransmiterlerin alımının inhibitörleri olarak görev yapmakta veya α-amino-3-hidroksi-5-metil-4-izoksazolpropiyonik asit (AMPA) reseptörüne bağımlı nörotransmisyonu modüle etmektedir (19,20). Tau hiperfosforilasyonunun, amiloidojenik ve nörofibriler yumakların oluşumunu ve nihayetinde sinir kaybını teşvik ederek AH patogenezinde çok önemli rolü olduğu düşünülmektedir. PC12-htau hücrelerinde glikojen sentaz kinaz 3 (GSK3) ve hücre dışı sinyalle düzenlenen kinaz (ERK1/2) gibi tau kinazlar, tauyu Thr231 ve Ser199/Ser202'de fosforile ederek pThr231-tau ve pSer199/Ser202-tau oluşturmaktadır. S. scardica ekstraktının toplam tauyu (%45), tau fosforilasyonunu (pThr231 %75 ve pSer199/Ser202 %66), ERK2'yi (%35) ve pERK2'yi (%85) azalttığı ve inaktif pSer9-GSK3 (%150) ve ERK1 (%24) seviyelerini arttırdığı gösterilmiştir (21). $A\beta_{25-35}$ peptitleri, $A\beta_{1-42}$'ya benzer şekilde sitotoksisite yapan daha kısa Aβ formlarıdır. Bu nedenle nörotoksik Aβ peptitlerinin aktif bölgesi olarak kabul edilmektedirler ve SH-SY5Y insan nöroblastoma hücrelerinde AH hücre hattı modeli oluşturmak amacıyla kullanılan ideal bir araçtır. Ververis ve ark. bu modeli kullanarak yaptıkları çalışmada S. scardica ekstraktının $A\beta_{25-35}$ sebepli sitotoksisiteyi azalttığını, başka bir deyişle nöroprotektif etki gösterdiğini tespit etmişlerdir (22). *S. scardica* ekstraktları, çeşitli AH Caenorhabditis elegans modellerinde Aβ agregatlarında bir azalma sağlamış ve buna önemli ölçüde gecikmiş bir felç oranı eşlik etmiştir (23). Çözünür Aβ peptidleri oldukça nörotoksiktir. Kümelenmiş formlar distrofik nöritlere sebep olur ve aksonal taşıma bozulur. Sadece bununla kalmayıp, özellikle çözünür Aβ konsantrasyonu sinaptik değişimin ve bilişsel gerilemenin bir göstergesi olabilir ve nörodejenerasyon ve hafıza bozulmasının şiddetini belirler. AH'de mikroglianın senil plaklara verdiği yanıt tam olarak anlaşılmamıştır. Akut inflamatuar uyarılar doku onarım süreçleri ve Aβ fagositozu gibi yararlı etkilere neden olsa da, kontrolsüz ve kronik inflamasyon altta yatan hastalık durumlarını güçlendiren ve nöronal ölüme yol açan nörotoksik faktörlerin üretimine neden olabilir. Artan mikroglial aktiviteye öncelikle Aβ üretimini azaltan, aynı zamanda mikroglia aracılı nöroproteksiyonda önemli bir rol oynayan fraktalkin (CX3CL1) için ana dağıtıcı enzim olan bir disintegrin ve metalloproteinaz alanı içeren protein 10 (ADAM10)'un artan ekspresyonu yardımcı olur. ADAM10 nakavt fareler öğrenme yeteneğinde azalma, sinaptik kusurlar ve ağ aktivitesinde değişiklik göstermektedir. Mutant amiloid prekürsör protein (APP) eksprese eden transgenik farelere (APP-tg) gavaj yoluyla *S. scardica* ve *S. euboea* ekstraktlarının ayrı ayrı ve kombine olarak uygulandığı çalışmada özellikle kombine uygulama yapılan gruplarda hem plak oluşumunun azaldığı hem de ADAM10 ekspresyonunun artarak hafızanın düzeldiği görülmüştür (24). Gioran ve ark. *Sideritis clandestina* türlerinden *Sideritis clandestina* (Bory and Chaub.) Hayek subsp. *peloponnesiaca* (Boiss.and Heldr.) Baden (SCP)'nin Aβ toksisitesi ve agregasyonuna karşı etkili olduğunu göstermişlerdir (25).

Kolinesteraz enzim inhibisyonu

Nörofibriler yumaklar ve amiloid plaklar formundaki Aβ'nın yanı sıra kolinesteraz (ChE) enzim ailesi aracılığıyla bilişsel işlevlerle ilgili kolinerjik sistem, AH'nın patogenezinde kritik bir rol oynamaktadır (26,27). ChE inhibitörlerinin AH tedavisinde birinci basamak semptomatik ilaçlar olduğu düşünülmektedir (28-32). AH'nın patolojisi kolinerjik hipotez ve amiloid hipotezi olmak üzere iki ana mekanizma ile açıklanan, ilerleyici karaktere sahip nörodejeneratif bir hastalık olduğu bilinmektedir (33). Kolinerjik hipotez, "kardeş" enzimlerin serin proteaz tipi, yani asetilkolinesteraz (AChE) ve butirilkolinesteraz (BChE), nöronlar arasındaki kolinerjik iletimin düzenlenmesiyle bağlantılıdır (34). Kolinerjik hipoteze göre, Alzheimer hastalığında kolinerjik fonksiyonlardaki bozulma özellikle öğrenme, hafıza, davranış ve duygusal tepkilerden sorumlu neokorteks ve hipokampüsü içeren beyin bölgelerinde kritik öneme sahiptir. Beyin atrofisi, bir sinir hücresinden diğer bir sinir hücresine elektriksel uyarıların iletilmesinden sorumlu bir nörotransmitter olan asetilkolinin (ACh) AChE tarafından hızlı hidrolizi nedeniyle düzeylerinin azaldığı AH'nın en belirgin klinik bulgusudur. Amiloid hipotezine göre AChE, etkilenen bireylerin beyninde senil plaklar/nörofibriler yumakları şeklinde Aβ birikiminin teşvikini içeren ikincil kolinerjik olmayan işlevler üretir. Aβ birikiminin AH'nın hem başlangıcında hem de ilerlemesinde önemli bir rol oynadığı düşünülmektedir. BuChE, AChE ile yakın ilişkili bir enzimdir ve ACh'yi hidrolize ederek kolinerjik nörotransmisyonun yardımcı düzenleyicisi olarak görev yapar. Çalışmalar, AH gelişimi sırasında temporal korteks ve hipokampüs gibi beynin en çok etkilenen bölgelerinde BuChE aktivitesinin (%40-90) arttığını göstermiştir. Artan BuChE aktivitesi, senil plak oluşumunun erken evrelerinde Aβ agregasyonunda da önemli bir rol oynar. Bu nedenle AChE ve BuChE inhibisyonunun, beyin bölgelerinde ACh kullanılabilirliğinde bir artış ve Aβ birikiminde azalma yoluyla AH'nın etkili yönetimi için kritik hedefler olduğunu göstermektedir (35,36). Skopolamin, Alzheimer tipi demansın *in vivo* deneysel modellerinin geliştirilmesinde sıklıkla kullanılan bir farmakolojik araçtır. Temel bir muskarinik kolinerjik reseptör antagonisti olarak, ACh bağlanma bölgelerini bloke ederek ACh konsantrasyonlarını artırır ve hipokampal sinirlere zarar verir. Bu kolinerjik sistem bozukluğu, skopolaminin neden olduğu beyin oksidatif durumundaki değişikliklerle birlikte bilişsel ve hafıza eksikliklerine yol açan bazı ilişkili nörokimyasal kaskadları da etkiler. Lazarova ve ark. yaptığı çalışmada *S. scardica* ekstraktının AChE inhibisyonuna sebep olmadığı halde skopolaminle indüklenen demanslı farelerde hafıza bozukluğunun derecesinde ve anksiyete benzeri davranışlarda azalmaya neden olduğunu ortaya konulmuştur (37). *Sideritis albiflora (S. albifora)* ve *Sideiritis leptoclada (S. leptoclada)* uçucu yağlarının antikolinesteraz aktivitesine yönelik yapılan çalışmada; *S. albiflora*'nın uçucu yağının (%22,1 ± 0,4), *S. leptoclada*'nın uçucu yağından (%4,3 ± 0,3) beş kat daha yüksek asetilkolinesteraz aktivitesi sergilediği gösterilmiştir. Ayrıca BChE enzimine karşı, *S. albiflora* ve *S. leptoclada*'nın esansiyel yağları,

sırasıyla 157,2 ± 0,9 µg/mL ve 199,0 ± 1,0 µg/mL IC50 değerleriyle orta düzeyde inhibitör aktivite göstermiştir (38). Zengin ve ark. farklı solventlerle elde ettiği *Sideritis galatica* ekstrelerinden etil asetat ekstresinin antikolinesteraz aktivitesinin en yüksek olduğunu tespit etmişlerdir (39).

Gama aminobütirik asit reseptör modülasyonu

Gama aminobütirik asit (GABA), merkezi sinir sistemindeki en önemli inhibitör nörotransmitterdir. GABA'nın iyonotropik gama aminobütirik asit tip A reseptörlerini (GABAAR) aktive etmesi, yetişkin beyinde postsinaptik nörona Cl^- iyonlarının akışı nedeniyle membranın hiperpolarizasyonuna yol açar. GABAAR'lar sadece korteks, hipokampüs ve serebellum gibi beyin bölgelerindeki çok çeşitli nöronlarda değil, aynı zamanda nöronal olmayan hücrelerde ve periferik dokularda da eksprese edilir. Tanımlanmış alt birimlerin geniş bir repertuvara sahip olması nedeniyle, pentamerik GABAAR komplekslerini oluşturan alt birim kombinasyonları değişkenlik gösterebilir. Heteromerik reseptörlerin çoğu, beyindeki en bol reseptör izoformunu (tüm GABAAR'ların yaklaşık %60'ı) temsil eden α1β2γ2 kompozisyonuna sahip alt birimler içerir (40). GABAAR'lar, nikotinik asetilkolin reseptörlerini (nAChR), glisin reseptörlerini ve serotonin reseptörlerini (5HT3R) de içeren Cys-loop reseptör süper ailesinin üyeleridir. Bunların hepsi, isimsiz Cys döngüsünü oluşturan korunmuş bir disülfid köprüsünü barındıran büyük bir hücre dışı N-terminusuna sahip benzer bir topolojik organizasyonu paylaşırlar. N-terminus, Ig benzeri yapısal bir organizasyonda 10β tabaka taşır ve pentamerik reseptör komplekslerinin bitişik alt birimleri arasında bulunan ortosterik bağlanma bölgesini oluşturur (41). Bölgeye yönelik mutajenez çalışmaları, bu bağlanma bölgesinin yanı sıra bu reseptörlerin fonksiyonunu modüle edebilen birçok ajanın bağlanma bölgeleri hakkında da çok fazla bilgi sağlamıştır (42). GABA'nın ana işlevi hücrelerde Cl^- iyon taşınmasını kontrol etmek ve uzun vadeli potansiyalizasyon ile uzun vadeli depresyon arasındaki dengeyi korumaktır. Normal GABA fonksiyonu birçok nörolojik ve nöropsikiyatrik bozuklukta önemlidir. GABA disfonksiyonunun AH ile ilişkisi bilinmektedir. GABA'nın alfa alt birimi, GABA nöronlarının düzgün çalışması için çok önemlidir. GABA alt birimlerinin düzeylerinin AH beyninde azaldığı bilinmektedir (43). Kessler ve ark. GABAAR'ın *Sideritis* ekstraktlarından elde edilen terpenoidlerle modüle edilebileceğini göstermişlerdir (44). Pinenler, *Sideritis* ekstraktlarındaki uçucu aroma bileşenlerinin en yaygın olanlarıdır ve pinen metabolitleri olan mirtenol ve verbenol, α1β2 ve α1β2γ2 alt ünitelerinden oluşan sinaptik GABAAR'ın en güçlü pozitif allosterik modülatörleri olarak tanımlanmıştır. Mirtenol ve verbenol, sinaptik ve ekstrasinaptik GABAAR'larda pozitif allosterik modülatörler olarak etki ederek, fazik ve tonik GABAerjik inhibisyonu arttırdığı gösterilmiştir (45).

Sonuç ve Öneriler

Alzheimer hastalığı, yaşa bağlı ve en yaygın ilerleyici nörodejeneratif hastalıklardan biridir. Yıllar geçtikçe bu hastalık hafızayı giderek bozar, konuşmayı etkiler ve hastaların kişilik ve davranışlarında anormalliklere yol açar. 2050 yılına kadar 59 yaş üstü insanların dünya nüfusunun yaklaşık %22'sini oluşturacağı tahmin edilmektedir. Demanslı birey sayısı 2010 yılında dünya genelinde 35,5 milyon iken hasta sayısının her 20 yılda yaklaşık iki katına çıkarak 2030 yılında 65,7 milyona ve 2050 yılında 115,4 milyona ulaşması beklenmektedir. Günümüzde hastalığın tedavisi için donepezil, galantamin, rivastigmin gibi kolinesteraz inhibitörleri ve N-metil-D-aspartat reseptör antagonisti memantin yer almaktadır. Ayrıca amiloid plaklarını hedef alarak amiloid fibrillerine bağlanıp beyinden temizlenmesini sağlayan amiloid karşıtı bir antikor olan Lecanemab yakın zamanda kullanıma sunulmuştur. Türkiye'de Salvia L. ve Stachys L. çok sayıda türe sahip iki Lamiaceae cinsidir ve diğeri Sideritis ise yüksek endemizm oranına sahiptir (%79). Sideritis türünün ana yayılış alanı Akdeniz havzasıdır; ancak Bahamalar ve Kanarya Adaları'ndan Çin'e kadar uzanan yaklaşık 150 türü ve 42 melezi bulunmaktadır. İspanya 75 Sideritis türüyle dünyada ilk sırada yer alırken, Türkiye dünyada ikinci sırada yer almaktadır; her ikisi de cinsin en fazla türüne sahip gen merkezleridir. Lamiaceae familyası bitkileri, diğer ikincil metabolitlerden ziyade terpenik bileşenleri ve flavonoidleri ve diğer fenolikleri nedeniyle iyi bilinir. Lamiaceae bitkilerinin çoğu, uçucu yağlarını oluşturan mono ve seskiterpenlerden oluşan aromatik ve uçucu terpenler açısından zengindir. Ancak Sideritis türlerinin uçucu yağları üzerine yapılan çalışmalarda verimin düşük olduğu belirtilmiştir. Sideritis bitkilerine ve bileşenlerine olan ilgi son yıllarda artmış olup, bunların farklı aktivitelerini araştıran çok sayıda çalışma yayınlanmıştır. Anadolu Sideritis türleri, özellikle üst solunum sistemlerinin tedavisinde ve anti-inflamatuar/anti-ülser rahatsızlıkları ve hastalıklarında çeşitli in vitro ve in vivo aktiviteler sergilemiştir. Bunlar arasında *S. congesta, S. condensata, S. trojana, S. perfoliata ve S. stricta* çay olarak tüketilmekte ve tıbbi amaçlarla kullanılmaktadır. Son yıllarda yapılan çalışmalarda Sideritis türlerinin tau proteinlerinin hiperfosforilasyonunu engellediği, Aβ proteinlerinin agregasyonunu ve toksisitesini azalttığı, kolinesteraz enzim ve GABAerjik inhibisyonu arttırdığı, bunların sonucunda da bilişsel fonksiyonları düzelttiği gösterilmiştir. Bu nedenle Sideritis türleri Alzheimer hastalığının tedavisi için umut vadeden doğal kaynaklar olarak öne çıkmaktadırlar.

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Case Report / Olgu Sunumu

Rare Side Effect of Immune Checkpoint Inhibitors: Adrenal Insufficiency

İmmün Checkpoint İnhibitörlerinin Nadir Yan Etkisi: Adrenal Yetmezlik

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Abstract

Background: Immune checkpoint inhibitors are cell membrane proteins that regulate the immune response. They are used in the treatment of non-small cell lung cancer, renal cell carcinoma, melanoma, and other tumor types. They affect dermatological, gastrointestinal, hepatic, endocrine and other systems. We present a case of adrenal insufficiency caused by nivolumab in a patient who presented with fatigue, weakness, nausea, and vomiting.

Keywords: Adrenal insufficiency, Immune checkpoint inhibitors, Nivolumab

Öz

Amaç: İmmün kontrol noktası inhibitörleri immun yanıtı düzenleyen hücre zar proteinleridir. Küçük hücreli dışı akciğer kanseri, renal hücreli karsinom, melanom ve diğer bazı tümör tiplerinin tedavisinde kullanılmaktadır. Dermatolojik, gastrointestinal, hepatik, endokrin ve diğer sistemleri etkilerler. Halsizlik, yorgunluk, bulantı ve kusma şikâyetleri ile başvuran bir hastada nivolumabın neden olduğu adrenal yetmezlik olgusunu sunuyoruz.

Anahtar Kelimeler: Adrenal yetmezlik, İmmün kontrol noktası inhibitörleri, Nivolumab

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Introduction

Immune checkpoints inhibit co-stimulatory signaling, thereby suppressing the immune response of T cells against tumour cells, functioning as an immune evasion mechanism for the tumour cells. To overcome this immune suppression, monoclonal antibodies targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are used in clinical practice. These immune-modulating monoclonal antibodies enhance immune system activity, thus improving the prognosis in patients with advanced malignancies (1,2). Ipilimumab, by blocking CTLA-4, is used in malignant melanoma, while cemiplimab, which blocks PD-1, is used in cutaneous squamous cell carcinoma. Pembrolizumab and nivolumab are utilized in malignancies such as melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, colorectal cancer, and urothelial carcinoma. Atezolizumab, durvalumab, and avelumab, which block PD-L1, are employed in urothelial carcinoma (3-5). With the introduction of immune checkpoint inhibitors (ICIs) in clinical practice, immune-related side effects, as opposed to conventional chemotherapy agents, have been reported. These side effects are often associated with better cancer survival. The most common adverse effects are dermatological, gastrointestinal, and endocrine, while neurological, cardiac, and rheumatological side effects are rarer (6-8). Management of these side effects includes strategies such as dose reduction, interruption of the drug, and steroid treatment. In severe cases, infliximab, mycophenolate mofetil, anti-thymocyte globulin, methotrexate, calcineurin inhibitors, intravenous immunoglobulin, and plasmapheresis can be used (9).

Case

A 70-year-old female patient, followed by the department of medical oncology for malignant melanoma, was admitted to our clinic with complaints of fatigue, weakness, nausea, and vomiting for the past two months. Additionally, she had a history of hypertension and had experienced a weight loss of 15 kg over the past 2 months. The patient had received a total of 14 cycles of nivolumab therapy for her malignant melanoma. The first 12 cycles were administered biweekly, and the last two cycles were given monthly due to her current symptoms. Her family history was unremarkable. She had no history of smoking or alcohol consumption. Physical examination revealed only pallor. Laboratory investigations revealed normal complete blood counts, but her biochemistry showed a glucose level of 58 mg/dL (normal range: 74-106 mg/dL), while other biochemical tests were normal. The patient's biochemical data at diagnosis and during follow-up are presented in Table 1.Serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and
prolactin were within normal limits. Serum cortisol was <0.5 µg/dL (normal range: 4.3-22.4 µg/dL), and adrenocorticotropic hormone (ACTH) was <5 pg/mL (normal range: 5-46 pg/mL).

Thyroid-stimulating hormone (TSH) was 9.67 mIU/L (normal range: 0.35-5.5), free triiodothyronine (FT3) was 3.76 pmol/L (normal range: 2.3-4.2), and free thyroxine (FT4) was 0.81 ng/dL (normal range: 0.89-1.76). An upper gastrointestinal endoscopy performed due to her nausea and vomiting symptoms was unremarkable. A dynamic abdominal tomography scan revealed normal bilateral adrenal glands. A pituitary magnetic resonance imaging (MRI) was also normal. The patient was not using steroids for her condition or any other reason. Given the low levels of ACTH and cortisol, the normal pituitary MRI, and the absence of exogenous steroid use, secondary adrenal insufficiency induced by nivolumab was diagnosed. Nivolumab was discontinued, and intravenous methylprednisolone 40 mg/day was administered for 2 days. The patient's symptoms improved, and she was discharged on the third day with oral prednisolone.

Table 1. Patient's Biochemical Data

	At diagnosis	One month after treatment
ACTH	<5 pg/mL	6,99 pg/mL
Cortisol	< 0,5 µg/dL	9,25 µg/dL
Glucose	58 mg/dL	83 mg/dL
Urea	15 mg/dL	27 mg/dL
Creatinine	0,32 mg/dL	0,52 mg/dL
Albumin	3,19 g/dL	3,86 g/dL
ALT	19 U/L	14 U/L
AST	43 U/L	21 U/L
Sodium	136 mmol/L	138 mmol/L
Potassium	3,75 mmol/L	3,75 mmol/L
Calcium	10,5 mg/dL	9 mg/dL
TSH	9,67 µIU/mL	8,77 µIU/mL
fT4	0,81 ng/dL	1,08 ng/dL
fT3	3,76 pg/mL	3,03 pg/mL

ACTH: Adrenocorticotropic hormone (normal value 1,3-16,7 pmol/L), AST: Aspartate aminotransferase (normal value 10-35 U / L), ALT: Alanine aminotransferase (normal value 10-40 U / L), TSH: Thyroid-stimulating hormone (normal value 0,27–4,2 µIU/mL) T4:Thyroxine (normal value 0.8-1.8 ng/dL), T3: Triiodothyronine (normal value 2.3-4.1 pg/mL))

Discussion

Immune checkpoint inhibitors (ICIs) are among the most successful immunotherapies used extensively in recent years. These agents enhance T cells' ability to kill tumor cells and exhibit antitumor activity, resulting in significant improvements across multiple cancer types (10). However, ICIs, unlike traditional chemotherapy, radiation, and other cancer treatments, can cause a variety of autoimmune adverse events. Among these, endocrinopathies are the most frequently reported autoimmune adverse events associated with the use of these agents. While thyroiditis and hypophysitis are the most commonly reported endocrinopathies, type 1 diabetes mellitus and adrenal insufficiency are reported less frequently (11). The incidence of endocrinopathies varies depending on the type of ICIs used. Symptoms generally emerge within six months of initiating ICIs, although the onset time remains unpredictable. Endocrinopathies may develop at any point after treatment initiation or even a few months after discontinuation (12). The nonspecific nature of the symptoms, the unpredictable timing of onset, and the potential for mortality—albeit rarely—highlight the critical importance of early detection and effective management of endocrinopathies, as these factors significantly impact patients' quality of life.

Nivolumab is a novel ICI that exerts its effect by enhancing T cell-mediated immune responses against tumor cells in the treatment of various cancers (10). The T cell activation caused by the blockade of the PD-1 pathway by nivolumab increases antitumor immunity while potentially triggering dysregulated immune responses against normal endocrine tissues. Adrenal insufficiency associated with ICIs is believed to result from autoimmune-mediated damage to the hypothalamic-pituitary-adrenal (HPA) axis. This autoimmune attack can lead to hypophysitis, resulting in impaired ACTH secretion and subsequent secondary adrenal insufficiency, as observed in our patient (13). Adrenal insufficiency is a rare side effect of ICIs, occurring in less than 1% of treated patients. This adverse effect typically emerges about two months after treatment initiation (14).

The diagnosis of adrenal insufficiency requires an integrated assessment of clinical findings, laboratory tests, and imaging studies. A low morning cortisol level (<5 µg/dL) is a strong indicator of adrenal insufficiency. While elevated ACTH levels suggest primary adrenal insufficiency, low or normal ACTH levels indicate secondary adrenal insufficiency (15). Our patient presented with common clinical features of adrenal insufficiency, including fatigue, weakness, nausea, and vomiting. The patient's low morning cortisol level (<0.5 µg/dL) and ACTH level (<5 pg/mL) were indicative of secondary adrenal insufficiency, obviating the need for confirmatory cosyntropin stimulation testing. The absence of electrolyte imbalances, such as hyponatremia and hyperkalemia, commonly observed in primary adrenal insufficiency, and a normal pituitary MRI, along with no history of exogenous steroid use or recent radiation therapy, led us to attribute the findings to nivolumab use.

Adrenal insufficiency may be overlooked due to its low incidence and nonspecific symptoms. Furthermore, the absence of routine endocrine screening contributes to delays in diagnosis, which can lead to severe consequences. Endocrine dysfunction should be considered in patients undergoing immunotherapy, and these patients should be frequently monitored for endocrine complications. Clinicians must remain vigilant about the potential for adrenal insufficiency as a possible side effect of ICIs in cancer patients receiving immunotherapy. In cases of suspected adrenal insufficiency, serum cortisol and ACTH levels should be promptly evaluated.

In conclusion, adrenal insufficiency, as a side effect of nivolumab, can have serious consequences if not identified and treated early. As ICIs are increasingly used across various conditions, patients are presenting more frequently to emergency departments and outpatient clinics with adverse effects associated with these new drugs. Therefore, the side effects of these medications must be well-understood, and all physicians—not just oncologists—should be knowledgeable about how to manage these complications effectively.

Ethical Approval: *There is an informed consent form for the patient.*

Author Contributions:
Concept: R.Y.
Literature Review: R.Y., B.K.
Design : R.Y., M.K.
Data acquisition : B.K., A.Ü., Ü.K.
Analysis and interpretation: F.U., M.K.
Writing manuscript: R.Y., B.K.
Critical revision of manuscript: M.K., F.U.

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Olgu Sunumu / Case Report

Çocuk Gelişiminde Babanın Rolüne Yönelik Psikodinamik Bakış Açısı: Bir Olgu Sunumu ve Gözden Geçirme

The Psychodynamic Perspective on the Father's Role in Child Development: A Case Presentation and Review

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Öz

Çocuk-ebeveyn/bakım veren ilişkisi, bebek tarafından oluşturulan ilk önemli ilişkidir. Çocuklar ve ergenler ebeveynlerinin tutumlarını, inançlarını, dünya görüşlerini ve değerlerini gözlemleyerek, model alarak veya doğrudan öğrenerek kendi değerlerini oluşturmaktadırlar. Çok sayıda çalışma çocuğun iyi bir duygu düzenleme becerisinin gelişiminde ebeveynin etkisinin önemli olduğunu öne sürse de babanın rolü henüz tam olarak anlaşılmamıştır. Babanın koruyucu ve güç kaynağı olduğu algısı onunla özdeşleşmeyi, güvenlik ve hayatta kalma vaadini beslerken, baba figürünün varlığı olmadan çocuğun süperego yapılanması olumsuz etkilenebilmektedir. Bu makalede, babası ile sağlıklı bir ilişki kuramayan ve babasının evden ayrılmasının ardından kendisini polis-özel koruma rolünde gören, çevresindekileri aşırı koruma davranışları sergileyerek gerçeği değerlendirme sınırlarını zorlayan bir rol üstlenen bir olgu sunulacaktır ve psikodinamik kuram çerçevesinde tartışılacaktır.

Anahtar Kelimeler: Baba-Çocuk İlişkileri, Çocuk Gelişimi, Savunma Mekanizmaları, Süperego

Abstract

The child-parent relationship is the first important relationship formed by the child. Children and adolescents form their own values by observing, modelling or directly learning their parents' attitudes, beliefs, worldviews and values. Although numerous studies suggest that parental influence is important in the development of good emotion regulation skills, the role of the father is not yet fully understood. While the perception of the father as a protector and source of power promotes identification with him and the promise of security and survival, the child's superego structuring may be negatively affected in the absence of the father figure. In this article, a case will be presented of an individual who was unable to establish a healthy relationship with their father and, following the father's departure from the household, assumed a role in which they saw themselves as a police-like private protector. This role was characterized by exhibiting overly protective behaviors toward those around them, pushing the boundaries of reality testing. The case will be discussed within the framework of psychodynamic theory.

Keywords: Father-Child Relations, Child Development, Defense Mechanisms, Superego

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Giriş

Çocuk- ebeveyn/bakım veren ilişkisi, bebek tarafından oluşturulan ilk önemli ilişkidir. Çocuklar ve ergenler ebeveynlerinin tutumlarını, inançlarını, dünya görüşlerini ve değerlerini gözlemleyerek, model alarak veya doğrudan öğrenerek kazanmaktadırlar. Çok sayıda çalışma çocuğun iyi bir duygu düzenleme becerisi gelişiminde ebeveyn etkisinin önemli olduğunu öne sürse de babanın rolü henüz tam olarak anlaşılamamıştır (1). Yapılan güncel bir çalışmanın bulguları baba-çocuk ilişkisinin kalitesinin de çocuğun duygu düzenleme becerisinin gelişiminde rol oynayabileceğini göstermektedir (2). Bu yazıda, polikliniğimize babasının evden ayrılması sonrası polis-özel koruma rolü davranışları ile başvuran, bilinen ek tanısı olmayan, 13 yaş bir erkek olgu sunulmakta ve psikodinamik kuram yönünden tartışılmaktadır.

Olgu

13 yaşındaki erkek olgu, 2023 yılında "ileride polis olmakla ilgili yoğun meşguliyet, okulda güvenliği sağlamaya çalışma ve sevdiği insanların koruması olarak evlerine kadar takip etme" nedeniyle kliniğimize öğretmenleri tarafından yönlendirilmiştir.

Olgunun geçmiş psikiyatrik öyküsünden edinilen bilgilere göre başvuru şikayetleri 6 yaşında iken kendi isteği ile polis rolü ile sınıfta güvenliği ve disiplini sağlama davranışları şeklinde başlamıştır. Sürekli polis kıyafetleri giydiği, telsiz-kulaklık gibi eşyalar taşıdığı, odasını makam odası kabul ettiği, annesinin sekreteri olduğunu söylediği, toplantısı olduğunu söyleyerek ders yapmadığı öğrenilmiştir. Bu dönemde İl Emniyet Müdürü ile tanışmış ve sık sık Emniyet Müdürlüğü'ne ziyarete gidiyormuş. Ailesi, olgunun etrafındaki insanlara güvenmek ve başkalarına kendisiyle ilgili bilgiler vermekle ilgili zorluklar yaşadığını, tehlikelere karşı sürekli tetikte olması gerektiğini düşündüğünü ifade etmiştir. Şikayetlerin devam etmesi üzerine 4. sınıfa giderken öğretmenlerin yönlendirmesi ile dış merkezde ailesi tarafından Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Bölümüne götürülmüş, herhangi bir psikopatoloji saptanmadığı bildirilmiş. 1 sene önce eğitimi nedeniyle zorunlu okul üniforması giymesi gerektiği için polis kıyafetlerini giymeyi bırakmış. Sonrasında protokole (emniyet müdürü, milletvekili gibi) daha yakın olabilmek için sivil giyimli özel koruma olmaya karar vermiş. Protokoldekilerin yapacakları ziyaretlerin duyurusunu internet sitelerinden öğrenir ve ziyaret gününde onların koruması olduğunu düşünüp bisikletle arabalarını takip edermiş. Özel koruma olduğunda protokole yakın olmakla kendini ayrıcalıklı hisseder ve bununla mutlu olurmuş. Son 1 senedir sevdiği insanları korumakla görevli olduğunu düşünür ve onları evlerine kadar takip edermiş. Annesini evden çıktığında takip eder, kardeşinin kendisinin yardımcısı olduğunu söylermiş. Koruma olmanın kendisine ait bir görev olduğunu, bu görevi yapmazsa etrafındakilerin ona güvenmeyeceğini ve kendisini gördüklerinde sevmedikleri kişilerin akıllarına geleceğini düşünürmüş. Ebeveynleri ayrılmadan önceki dönemde de kreşe giderken kendisinin cumhurbaşkanı olduğunu söylermiş. Olgu 7. sınıfa devam ederken ailesi tarafından dış merkezde bir Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Bölümü'ne götürülmüş, tanısı tarafımızca bilinmemekle birlikte bir tedavi düzenlendiği öğrenilmiştir. Ancak aile, önerilen tedaviye başlamadan önce tarafımıza başvurmuştur.

Olgunun anne ve babası 7 yıl önce ayrılmış. Annesiyle ilişkisi şefkat dolu, babasıyla ilişkisi ise mesafeliymiş. Anneden alınan bilgiye göre olgumuzun babasının paranoid örüntülerinin olduğu, eşini ve kendi annesini sadakatsizlikle suçladığı, eşini evden tek çıkarmadığı öğrenilmiştir. Sık sık ev içinde tartışmalar olduğu, babasının annesine şiddet uygulamasına şahit olduğu, 6 yaşındayken annesi ve kardeşiyle beraber babası tarafından evden kovulduğu öğrenilmiştir. Olgumuz, babasının talebi olduğu zamanlarda birkaç ayda bir telefonda görüşüyormuş. Kendisi babasının ilgisiz ve evde öfkeli davranışları olduğunu ifade etmiştir. Annesinden öğrenilen bilgiye göre anne-babası ayrıldıktan sonra sık sık bir babasının olmasını istediğini söylemektedir. Babasıyla ilgili anıları hatırlamadığını anlatmaktadır. Annesinin verdiği bilgiye göre, babasının da bulunduğu ailecek geçirilen zamanlarla ilgili olarak, olgumuz babasını hatırlamadığını ifade etmektedir.

Gelişim öyküsünde annenin 1. gebeliğinden, hastanede, normal spontan vajinal doğumla, 2500 gr ağırlığında, miadında dünyaya geldiği; gebelik dönemi süresince, doğum sırasında ve sonrasında herhangi bir sorun yaşanmadığı; annenin gebelik döneminde evliliğiyle ilgili stresörlere maruz kaldığı; olgunun gelişim basamaklarını zamanında tamamladığı; herhangi bir ilaç tedavisi kullanmadığı saptanmıştır. Annenin verdiği bilgiler doğrultusunda, olgunun çocukluk döneminde yaşıtlarıyla sınırlı etkileşim kurduğu, daha çok yetişkinlerle vakit geçirmeyi tercih ettiği öğrenilmiştir. İlkokul döneminde ise, aile gözlemleri, olgunun belirgin bir sosyal izolasyon yaşamadığını ancak sosyal etkileşimlerde kendi ilgi alanlarına odaklanma eğilimi gösterdiğini ortaya koymuştur. Yaşıtlarıyla zaman zaman oyunlara katılmakla birlikte, bu ilişkilerin yüzeysel ve kısa süreli olduğu belirtilmiştir. Bu durum, sosyal becerilerinde belirgin bir eksiklikten ziyade bireysel tercihlerle ilişkili görülmüştür. Soygeçmişinde, anne-babanın sağ ve 7 yıldır ayrı olduğu, olgunun anne ile kaldığı, ailede akrabalık öyküsü olmadığı, anneden alınan öyküde olgunun babasında paranoid örüntüler tariflendiği, olgunun 8 yaşında bir sağlıklı kız kardeşi olduğu öğrenilmiştir.

Ruhsal Durum Muayenesinde:

Genel görünüm yaşına uygun, öz bakım yeterli, görüşme sırasında tetikte olma hali gözlendi. Duygulanım ve duygudurumu hafif anksiyöz, ancak belirgin bir duygudurum bozukluğu bulgusu saptanmadı. Düşünce süreci ve içeriğinde polis/özel koruma rolüyle ilişkilendirdiği aşırı değer verilmiş düşünceler mevcuttu. Sanrı veya obsesyon ile uyumlu düşünce içeriği gözlemlenmedi. Herhangi bir algı bozukluğu saptanmadı. Olgunun içgörüsünün kısmen korunmuş olduğu düşünüldü. Kendi davranışlarının alışılmadık olduğunu kabul etmekle birlikte bu davranışları "görev" olarak nitelendirmekteydi. Bilişsel işlevleri klinik gözlem doğrultusunda yaşına uygun bulundu.

Ön Tanılar:

Olguda başlangıçta şizotipal kişilik özellikleri ve paranoid düşünce yapısının varlığı değerlendirilmeye alınmıştır. Ancak sanrısal bir yapı olmaması ve çevresindekilerden zarar görmeye dair sürekli bir şüphe geliştirmemesi nedeniyle paranoid düşünce yapısından ziyade güvenlik arayışı ve aşırı tetikte olma davranışı olarak yorumlanmıştır. Olgu, sosyal ilişkilerde zorluklar yaşasa da bu zorluklar şizotipal kişilik özellikleri için tipik olan derecede belirgin veya sürekli bulunmamıştır.

Olgumuzun, babasının evden ayrılmasından sonra geliştirdiği "koruyucu olma" rolü ve buna eşlik eden polis/özel koruma davranışları, "aşırı değer verilmiş düşünce" olarak yorumlanmıştır. DSM-5 kriterlerine göre bir sanrı olarak nitelendirilmemiştir; çünkü sanrılara özgü sistematik bir yapı taşımamaktadır. Bu inançlar, olgunun gerçeği değerlendirme yetisini kısmen zorlasa da içgörüsünün korunmuş olması ve sosyal işlevselliğini tamamen bozacak düzeyde olmaması nedeniyle sanrıdan ayrılmıştır.

Tekrarlayıcı düşünce ve davranışlar, obsesyon veya kompülsiyon yerine, "koruma" rolüne yönelik aşırı değer verilmiş bir düşünce biçimiyle ilişkilendirilmiştir. Bu düşünce biçiminin, baba figürünün yokluğu ile ilişkilendirilebileceği düşünülmektedir. Olgu, kendisi ile yapılan görüşmede tetikte ve aşırı dikkatli bir tutum sergilemiştir. Klinik görüşme sırasında olgunun dikkat, bellek ve muhakeme yetilerinin yaşına uygun olduğu gözlemlenmiştir. Soyut düşünme becerileri de yeterli seviyede bulunmuştur. Dolayısıyla, bilişsel kapasite açısından belirgin bir patoloji düşünülmemiştir.

Tipik obsesyon veya kompulsiyonlar da klinik olarak gözlemlenmediği için bir obsesif-kompülsif bozukluk tanısı uygun bulunmamıştır. Olgunun sosyal iletişim ve empati becerilerinde belirgin bir eksiklik olmaması, tekrarlayıcı motor davranışların veya ritüelistik yapıların gözlenmemesi, dil kullanımının işlevsel ve akıcı olması ve başvuru öncesinde aile tarafından arkadaş ilişkilerinde belirgin bir güçlük ve dışlanmanın tarif edilmemesi nedeniyle Otizm Spektrum Bozukluğu düşünülmemiştir.

Tanı: Olgu, DSM 5 tanı ölçütlerine göre herhangi bir tanı almamıştır, ancak baba figürünün yokluğu ve buna bağlı olarak oluşan psikodinamik çatışmalar ile ilişkili aşırı değer verilmiş düşüncelere sahip olduğu düşünülmüştür.

Tartışma

Bu olguda, babası ile sağlıklı bir ilişkisi olmayan ve gerçeği değerlendirme sınırını aşacak düzeyde aşırı koruyuculuk rolü üstlenmiş bir ergen olgu sunulmuştur. Psikanalitik açıdan babanın rolü ilk kez babanın çocuk gelişiminin hem ödipal öncesi hem de ödipal evrelerinde önemli bir rol oynadığını düşünen Sigmund Freud tarafından tanımlanmıştır. Freud, özellikle erkek çocuklar için babaya sevgi dolu bir bağlanmanın geliştirilmesinin hem sağlıklı gelişim hem de ödipus evresinin çözümü için çok önemli olduğunu öne sürmüştür. Freud, erkek çocuklarının babalarını ensest cinsel dürtülerin rakibi ve yasaklayıcısı, kıskançlık ve nefret nesnesi, suçluluk ve korkuyu kışkırtan biri olarak deneyimledikleri görüşünü ortaya atmıştır (3). Babanın yokluğuna ilişkin psikanalitik literatür, kaybın etkilerine gelişimsel bir çerçeve içerisinde ve dört ana psikoloji kuramının perspektifinden bakma eğiliminde olmuştur. Bunlar; dürtü kuramı, ego kuramı, nesne ilişkileri kuramı ve kendilik psikolojisidir (4). Freud süperegoyu ödipus kompleksinin mirasçısı olarak görmektedir ve süperego gelişimini şu şekilde açıklamaktadır; fallik dönemde ödipus kompleksinin neden olduğu yoğun bunaltıdan kurtulmak isteyen ego, aynı cinsten ebeveyni ile özdeşim yoluna girmekte ve aynı cinsten ebeveynin etik kurallarını, ülkülerini, vicdani değerlerini içselleştiren ego bölmesinden süperego gelişmektedir (5). Baba figürünün yokluğunda çocuğun süperego yapılanması bozulabilir; çünkü baba, koruyucu ve güç kaynağı olarak algılandığında, bu algı çocuğun onunla özdeşleşmesini ve güvenlik ile hayatta kalma duygusunu güçlendirmektedir. Eğer baba tarafından terk edilme gibi travmatik bir durum meydana gelirse, çocukta savunmacı bir şekilde kendisiyle ilgili hak sahibi olma duyguları oluşabilmektedir. Bu bireyler, yeterince acı çektiklerine inanmakta ve yaşamın zorluklarından muaf olmaları gerektiğini hissetmektedirler. Baba, içselleştirilmiş bir öteki ve kendilik nesnesi olarak ayrışma-bireyleşme sürecinin kendi başına kolaylaştırıcısı olan bir bağlanma figürü olarak görülmektedir (6). Buna ek olarak baba, çocuğun anneyle ortak yaşamdan intrapsişik olarak ayrılmasına yardım etme gibi önemli bir işleve de hizmet etmektedir (6). İnsan gelişimsel olarak, hayata kendisini çevresinden ayıramayan, farklılaşmamış bir durumda başlamaktadır. Ebeveynleri ile kurduğu ilişkilerle kim olduğunu yavaş yavaş öğrenmektedir. Freud'un 'Yas ve Melankoli' adlı makalesinde; ölüm, terk edilme veya duygusal olarak erişilemezlik yoluyla meydana gelen önemli bir diğerinin kaybına, güçlü bir kararsızlık duygusunun eşlik ettiğini, kayıp nesneye yönelik olumsuz duygularla ilgili suçluluğun inkar edilerek, ötekine ilişkin olumlu bir imajı korumak için, terk eden nesnenin benimsenip onunla özdeşleşildiğini ve ardından öfke ve hayal kırıklığı duygularının kendiliğe yöneltildiğini belirtmiştir. Freud 1917'de, 'Böylece nesnenin gölgesi egonun üzerine düşer.' sözüyle nesne ile ilişkisinin psişik yapısının doğasını etkilediği şeklindeki fikrini beyan etmiştir (7). Winnicott bağlanma durumuyla birlikte ayrı olma durumunu uzlaştırma çabasında çocukların 'geçiş nesnelerini' kullandıklarını gözlemlemiştir. Çocuk henüz içsel tasarımlarını oluşturmak için yeterli kapasiteye sahip olmadığında, ayrılık bir yok olma, kalıcı bir boşluk olarak yaşanabilmektedir. Bu durumda geçiş nesnesi, kişi yok olsa bile varlığını sürdürme olasılığına giden bir köprü görevi görmektedir (8). Kernberg, bir çocuğun erken ego gelişiminin sağlanması için kendilik tasarımlarının nesne tasarımlarından farklılaşması ve olumlu-olumsuz kendilik tasarımlarının birleşik bir kendilik tasarımı ile bütünleştirilmesi gerektiğini düşünmektedir (9). Bahsedilen dört alanla ilgili olarak, olgunun babasının yokluğu kendilik ve nesne ilişkilerinin oluşumunu olumsuz yönde etkilemiş olabilir. Bu yoksunluk durumunda çocuk, babasının ilgisizliğinden kendisinin sorumlu olduğuna ve dolayısıyla kusurlu, istenmeyen ve

sevilmeyen biri olduğuna inanmaya yönelik içsel bir baskı hissedebilir. Dolayısıyla babanın empati ve ilgisinin kaybından kaynaklanan bu utanç duygusu, art arda gelen kızgınlık ve hak sahibi olma duygularının temelini oluşturabilir. Ödipal rekabetin doruğa ulaştığı yaşamın üçüncü ve altıncı yılları arasını kaplayan fallik dönemde olgunun babasının ortadan kaybolması, süperego gelişimi henüz tamamlanmadığı için çocuğu suçluluk duygusuyla baş başa bırakmış olabilir. Kızgın, potansiyel olarak misilleme yapan bir babanın içe atılması, çocuğu yoğun kaygıya karşı savunmasız bırakabilir. Bu olguda bulunan çatışma id ve süperego arasındadır. İd dürtüleriyle ego sahasına baskı uygularken ego ise süperegonun katı ahlaki değerlerini gözeterek çeşitli savunma mekanizmaları ile dürtüye doyum yolları arar veya dürtüyü, doyurulmasına izin vermeden ide geri gönderir. Doyum sağlanmadan geri gönderilen dürtü egoda bunaltıya neden olur. Ego bu bunaltıya karşı kendini korumak için savunma yöntemleri kullanır. Olguda babasıyla ilgili anıların hatırlanmaması kullanılan savunma mekanizmalarından bastırma ile ilişkili olabilir. Diğer bir savunma mekanizması olan yansıtmalı özdeşim ile babasının kuşkucu özelliklerini egosunun bir parçası haline getirmiş olabilir (10). Olgunun babanın terki döneminde henüz içsel tasarımlarını oluşturmak için yeterli kapasiteye sahip olmadığı düşünüldüğünde varlığının devamlılığı için geçiş nesnesi olarak kendisini polis olarak tanımlıyor olabilir. Herzog yaptığı çalışmalarında babası olmayan çocuklarda, potansiyel baba figürlerini taklit etme ve onları memnun etme çabasından bahsetmektedir (11). Bu durum bizim olgumuzda da olgunun daha çok güvenlik alanlarıyla uğraşmasını açıklayabilir. Babasının ortadan kaybolması, çocuğun bu adaletsizliğin telafisinin yapılmasının hakkı olduğunu düşündürdüğü için polis kıyafetleri giyerek emniyet amirliği rolünü almasına neden olmuş olabilir. Böylece hak sahibi olmayı, utanç, suçluluk ve öfke duygularına karşı bir savunma olarak kullanıyor olabilir. Olgumuzun babasıyla ilgili anıları hatırlayamıyor olması güvensiz bağlanmayla ilişkili olabilir. Bu konuda yapılan bir çalışmada güvenli bağlanması yüksek olan çocuklarda daha az hafıza hatası olurken; daha az güvenli bağlanan çocuklar daha fazla hafıza hatası yapmakta olduğu ve bunun nedeni belki de bu tür anıları zayıflatan savunma süreçleri ya da sosyo-duygusal faktörler olabileceği söylenmiştir (12). Yapılan başka bir çalışmada çocuklukta kişilerarası travma ile paranoya arasındaki ilişkiye, düzensiz bağlanma ve başkaları hakkındaki olumsuz şematik inançların aracılık ettiğini göstermektedir (13). Bu çalışma olgumuzda olan kuşkuculuk, kendini üstün görme, kendisine kötülük yapıldığını düşünme, sürekli tetikte olma, kimseye güvenmeme gibi paranoid özelliklerin güvensiz bağlanma ile ilişkili olabileceğini düşündürmektedir. Sunduğumuz vakada DSM-5 tanı kriterlerine göre sanrı, varsanı, dezorganize konuşma ve davranış, negatif belirtilerinin olmaması, içgörünün bulunması nedeniyle paranoid bulgular şizofreni, sanrılı bozukluk tanı kriterlerini karşılamamaktadır (14). Çocuk-ebeveyn ilişkisi ile ilgili araştırmalarda daha çok anneler çalışılmıştır. Bu olgu sunumunda baba figürünün çocuğun gelişimindeki rolü ile ilgili kanıtlar sunulmaktadır. Çocukların gelişiminde baba figürünün etkisini gösteren çalışmalar artırılmalıdır.

Etik onam: *Hastadan aydınlatılmış onam alınmıştır.*

Yazar Katkıları:
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The Importance of Psychological Resilience in Earthquake Survivors' Mental Health

Depremzedelerin Ruh Sağlığında Psikolojik Sağlamlığın Önemi

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Dear Editor,

I read with interest the article titled "Investigation of Suicide Attempt, Impulsivity, Psychological Pain and Depression in Earthquake Survivors Affected by the February 6, 2023 Kahramanmaraş Centered Earthquake" published in the latest issue of your journal and written by Sehlikoğlu and her colleagues (1). Accordingly, Sehlikoğlu et al. reported that the levels of psychological pain in earthquake survivors who were affected by the February 6, 2023 Kahramanmaraş centered earthquake and attempted suicide after these earthquakes were related to depressive and anxious symptoms. I congratulate the authors for this research that draws attention to the important psychological problems of earthquake survivors.

I would like to contribute to the findings of the research article titled "Investigation of Suicide Attempt, Impulsivity, Psychological Pain and Depression in Earthquake Survivors Affected by the February 6, 2023 Kahramanmaraş Centered Earthquake" through the effects of psychological resilience on earthquake-related mental and psychosocial outcomes. "Psychological resilience" is defined as the totality of characteristics that enable adaptation to stressful life events, and is affected by factors such as an individual's character traits, coping strategies, the individual's social support network, and level of education. Individuals with high levels of psychological resilience have an easier time adapting to traumatic life events and are less likely to have trauma-related psychological disturbances (2).

The most common mental and psychological disturbances in earthquake survivors are acute stress reactions, acute stress disorder, post-traumatic stress disorder, depression, anxiety disorders, substance use disorders, domestic violence, anger management problems, and burnout. These disturbances in earthquake survivors can be affected by many factors. The personality traits of earthquake survivors, psychosocial support, previous traumatic experiences, the time it takes to reach professional support, and the status of meeting needs such as shelter are among the most important factors affecting trauma-related consequences that can be seen in earthquake survivors (3).

Psychological resilience defined is also defined as an important factor that can affect trauma-related problems in earthquake survivors. The findings of the study I conducted on the academicians affected by the earthquakes on February 6, 2023 showed that a high level of psychological resilience was related to low post-traumatic stress and low burnout levels (4). Namely, as the psychological resilience of earthquake-affected academicians increased, post-traumatic stress and burnout levels decreased. The findings of other studies conducted on earthquake survivors on February 6, 2023 also showed that earthquake survivors with higher levels of psychological resilience had higher mental health levels and lower earthquake-related anxiety levels (5). Considering that psychological resilience is a concept that can be improved, psychological resilience can be assumed as a factor that can be intervened in to prevent mental problems that may arise in earthquake survivors.

In conclusion, the fact that our country is located in an earthquake geography reveals the possibility of encountering earthquake-related psychological consequences. Therefore, psychosocial intervention programs aimed at improving psychological resilience can be disseminated in earthquake survivors to prevent psychological problems such as suicide, depression, post-traumatic stress disorder, and burnout.

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