e-ISSN: 2687-4717

7 cilt volume
2 sayı issue
2025 haziran june

HİTİT MEDICAL JOURNAL

HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

HİTİT ÜNİVERSİTESİ YAYINLARI

HMJ

HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025
Periyot: Yılda 3 Sayı (Şubat & Haziran & Ekim) | Period: 3 Issues per Year (February & June & October)

YAYIN DİLİ | LANGUAGE OF PUBLICATION

Türkçe & İngilizce | Turkish & English

YAZIŞMA ADRESİ | CONTACT ADDRESS

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YAYINCI | PUBLISHER

Hitit Üniversitesi Yayınları | Hitit University Press

HAKEM KURULU | REFEREE BOARD

Hitit Medical Journal Dergisi, çift taraflı kör hakemlik sistemi kullanmaktadır. Hakem isimleri gizli tutulmakta ve yayımlanmamaktadır.

Hitit Medical Journal uses a double-blind review. Referee names are kept strictly confidential.

LOCKSS: https://dergipark.org.tr/tr/pub/hititmedj/lockss-manifest

OAI: https://dergipark.org.tr/api/public/oai/hititmedj/

Editörden

Değerli Bilim İnsanları, Kıymetli Meslektaşlarımız ve Saygıdeğer Okurlarımız,

Sağlık bilimleri alanındaki güncel gelişmeleri takip etmek, yeni verileri değerlendirmek ve bilimsel bilgi birikimine katkıda bulunmak amacıyla sürdürdüğümüz yayıncılık serüvenimizde, Hitit Tıp Dergisi'nin Haziran 2025 sayısını sizlerle buluşturmanın mutluluğunu yaşıyoruz.

Her yeni sayıda, yalnızca günceli yakalamayı değil, aynı zamanda bilimin evrensel diline nitelikli katkı sunmayı da hedefliyoruz. Bu hedef doğrultusunda hazırlanan Haziran sayımızda; akademik çeşitliliği ve yayın kalitesini önceleyen bir anlayışla, farklı disiplinlerden derlenen 15 özgün araştırma makalesi, 1 derleme, 2 olgu sunumu ve 2 editöre mektup olmak üzere toplam 20 bilimsel eser yer almaktadır.

Bu sayımızda yer alan çalışmalar, hem temel bilimler hem de klinik uygulamalar açısından dikkate değer akademik çabaların ürünüdür. Araştırma makalelerimiz, çağdaş yöntemlerle üretilmiş ve titiz hakem sürecinden geçmiş bilimsel verileri içermekte olup, multidisipliner yaklaşımların bir yansıması olarak değerlendirilmelidir. Derleme makalemiz, mevcut literatürü güncel bilgilerle harmanlayan değerli bir katkı niteliği taşırken; olgu sunumlarımız nadir klinik karşılaşmaların deneyime dayalı yansımalarını içermektedir. Editöre mektuplar ise alanın uzmanları tarafından kaleme alınmış, eleştirel düşünceyi ve bilimsel tartışmayı teşvik eden nitelikli yazılardır.

Hitit Tıp Dergisi olarak amacımız; yalnızca bir yayın platformu olmak değil, aynı zamanda bilimsel düşüncenin gelişimine katkı sunan, eleştirel aklı teşvik eden ve disiplinler arası iletişimi destekleyen bir ortak akıl zemini oluşturmaktır. Bu doğrultuda, her geçen gün daha fazla sayıda araştırmacının dergimize gösterdiği ilgi, bizler için hem bir mutluluk kaynağı hem de daha iyisini üretme yönünde bir sorumluluktur. Yayın kurulumuz, hakemlerimiz ve teknik ekibimizle birlikte, başvuru sürecinden yayına kabul aşamasına dek geçen her adımda şeffaflığı, bilimsel etiği ve yayıncılık ilkelerini esas almaktayız. Özellikle genç araştırmacıların desteklenmesi, bilimsel yazım kültürünün yaygınlaştırılması ve akademik gelişimin teşvik edilmesi dergimizin öncelikleri arasındadır.

Bu vesileyle, dergimize değerli katkılarını sunan tüm yazarlarımıza, titiz ve özverili değerlendirmeleriyle yayın sürecinin bilimsel kalitesini güvence altına alan hakemlerimize ve yayın kurulu üyelerimize içtenlikle teşekkür ederiz. Ayrıca dergimizi takip eden ve geri bildirimleriyle gelişimimize katkıda bulunan siz değerli okuyucularımıza da en içten saygılarımızı sunarız.

Bilimin yol göstericiliğinde, daha nice sayıda buluşmak ümidiyle...

Doç. Dr. Abdulkerim YILDIZ
HMJ Editöryal Kurul adına

From the Editor

Dear Esteemed Readers, Colleagues, and Contributors,

It is with great pleasure that we present to you the June 2025 issue of the Hitit Medical Journal. As in every issue, we remain committed to our mission of disseminating high-quality scientific knowledge across all fields of health sciences, bridging the gap between clinical practice and academic research.

In this issue, we are proud to share a total of 20 scientific contributions, consisting of 15 original research articles, 1 review, 2 case reports, and 2 letters to the editor. This broad spectrum of submissions reflects the interdisciplinary scope of our journal and its growing relevance within the scientific community.

Our original articles represent rigorous and methodologically sound research efforts, spanning diverse domains within medicine and health sciences. The review offers a timely synthesis of the current literature on a focused topic, while the case reports provide insightful documentation of rare or instructive clinical encounters. The letters to the editor contribute to the scholarly discourse, offering critical reflections and professional perspectives that enrich the scientific conversation.

Hitit Medical Journal is not only a platform for scientific publication, but also a forum for intellectual collaboration, academic mentorship, and the promotion of ethical scholarship. As editors, we are fully committed to upholding the highest standards of peer review, editorial integrity, and transparency at every stage of the publication process. We take particular pride in supporting young researchers, fostering a culture of scientific writing, and cultivating critical inquiry.

The increasing volume and quality of submissions we receive from diverse institutions both nationally and internationally is a testament to the growing trust in our journal. We are deeply grateful to all authors for their contributions, to our peer reviewers for their meticulous evaluations, and to our editorial board for their unwavering dedication.

We extend our sincere thanks to all who continue to support the mission of the Hitit Medical Journal. May this issue inspire new ideas, spark meaningful research, and foster continued collaboration in the service of science and public health.

With our warmest regards,

Doç. Dr. Abdulkerim YILDIZ
On behalf of the HMJ Editorial Board

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HMJ

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HAZİRAN - 2025
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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Evaluation of GSTP1 Inhibition Potentials and Pharmacokinetic Properties of Stigmasterol, Sesamin, and Pinosylvin

Stigmasterol, Sesamin ve Pinosilvin'in GSTP1 İnhibisyon Potansiyellerinin ve Farmakokinetik Özelliklerinin Değerlendirilmesi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1599510
Geliş Tarihi | Received: 10.12.2024
Kabul Tarihi | Accepted: 11.01.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Küçük N, Özcan M. Evaluation of GSTP1 Inhibition Potentials and Pharmacokinetic Properties of Stigmasterol, Sesamin, and Pinosylvin. Hitit Medical Journal 2025;7(2):154-163. https://doi.org/10.52827/hititmedj.1599510

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: NK Tasarım: NK, MO Veri Toplama/Veri İşleme: NK Veri Analizi: NK, MO Makalenin Hazırlanması: NK.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: NK Design: NK, MO Data Collection/Data Processing: NK Data Analysis: NK, MO Manuscript Preparation: NK.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Evaluation of GSTP1 Inhibition Potentials and Pharmacokinetic Properties of Stigmasterol, Sesamin, and Pinosylvin

ABSTRACT

Objective: Glutathione S-transferase P1 (GSTP1), an important target affecting drug resistance in cancer treatment, is a critical issue due to its role in detoxifying and regulating reactive oxygen species. This study evaluated the inhibitory potentials of natural compounds (bakuchiol, sesamin, hydroxytyrosol, stigmasterol, and pinosylvin) against Glutathione S-transferase P1 and their absorption, metabolism, distribution, and elimination (ADME) profiles.

Material and Method: The inhibitory activities of these compounds were compared with those of the reference inhibitor, etacrynic acid, using molecular docking simulations and absorption, metabolism, distribution, and elimination profiling.

Results: Docking simulations showed that stigmasterol (-9.2 kcal/mol) and sesamin (-8.2 kcal/mol) exhibited the most potent binding affinities, followed by pinosylvin (-7.1 kcal/mol), surpassing etacrynic acid (-6.7 kcal/mol) in inhibition potential. Although the absorption, metabolism, distribution, and elimination analysis indicated risks related to solubility and enzyme interactions, it highlighted favorable pharmacokinetic properties for sesamin and pinosylvin.

Conclusion: This study emphasizes the potential of plant-derived compounds by targeting Glutathione S-transferase P1-mediated drug resistance. Such approaches may enable the development of new and effective strategies in cancer treatment.

Keywords: ADME profiling, cancer therapy, drug resistance, GSTP1, molecular docking, phytochemicals.

ÖZET

Amaç: Kanser tedavisinde ilaç direncini etkileyen önemli bir hedef olan Glutatyon S-transferaz P1 (GSTP1), detoksifikasyon ve reaktif oksijen türlerinin regülasyonundaki rolü nedeniyle kritik bir konudur. Bu çalışmada, doğal bileşiklerin (bakuchiol, sesamin, hidroksitirosol, stigmasterol ve pinosilvin) GSTP1'e karşı inhibitör potansiyelleri ve ADME (Absorpsiyon, metabolizma, dağılım, eliminasyon) profilleri değerlendirilmiştir.

Gereç ve Yöntem: Moleküler kenetleme simülasyonları ve absorpsiyon, metabolizma, dağılım, eliminasyon profillemesi kullanılarak, bu bileşiklerin inhibitör etkinlikleri referans inhibitör olan etakrinik asit ile karşılaştırılmıştır.

Bulgular: Kenetleme simülasyonları, stigmasterol (-9,2 kcal/mol) ve sesaminin (-8,2 kcal/mol) en güçlü bağlanma afinitelerini sergilediğini, ardından pinosilvin'in (-7,1 kcal/mol) inhibisyon potansiyelinde etakrinik asidi (-6,7 kcal/mol) geride bıraktığını gösterdi. Absorpsiyon, metabolizma, dağılım ve eliminasyon analizi, çözünürlük ve enzim etkileşimi riskleri belirtmiş olsa da sesamin ve pinosylvin için olumlu farmakokinetik özellikleri vurguladı.

Sonuç: Bu çalışma, Glutatyon S-transferaz P1 aracılı ilaç direncini hedef alarak, bitki kaynaklı bileşiklerin potansiyelini vurgulamaktadır. Bu tür yaklaşımlar, kanser tedavisinde yeni ve etkili stratejiler geliştirilmesine olanak sağlayabilir.

Anahtar Sözcükler: ADME profillemesi, fitokimyasallar, GSTP1, ilaç direnci, kanser tedavisi, moleküler yerleştirme.

Introduction

Cancer remains a leading cause of death globally, driving the need for innovative therapeutic approaches to overcome its challenges, particularly drug resistance. The glutathione detoxification pathway plays a significant role among the cellular defense mechanisms implicated in drug resistance. A central enzyme in this pathway, Glutathione S-transferase P1 (GSTP1), is known for its ability to neutralize reactive oxygen species (ROS) and detoxify harmful agents, including many chemotherapeutic drugs. GSTP1 is known to be overexpressed in a variety of malignancies, including breast, lung, and colorectal. This overexpression plays a key role in promoting tumor survival and resistance to therapies (1,2). As a result, GSTP1 has emerged as an important molecular target in cancer treatment, aiming to overcome resistance mechanisms and improve therapeutic outcomes.

Ethacrynic acid, initially developed as a diuretic, was one of the first compounds identified to inhibit GSTP1. It works by binding covalently to the enzyme's active site, effectively blocking its detoxification function (3). Despite its potential, its clinical use is restricted by unwanted side effects and less-than-ideal pharmacokinetic characteristics. These limitations highlight the need for alternative GSTP1 inhibitors that are not only effective but also associated with fewer adverse reactions. In this regard, natural compounds have gained attention as a promising option due to their diverse structures, broad biological activities, and generally favorable safety profiles.

A range of natural compounds, such as bakuchiol, sesamin, hydroxytyrosol, stigmasterol, and pinosylvin, have demonstrated considerable therapeutic potential. Bakuchiol, a meroterpene phenol obtained from Psoralea corylifolia, has been extensively researched for its antioxidant, anti-inflammatory, and anticancer effects. Notably, it has shown the ability to regulate oxidative stress and trigger apoptosis in cancer cells (4,5). Similarly, sesamin, a lignan derived from sesame seeds (Sesamum indicum), has shown significant anticancer properties, mainly by reducing ROS production and blocking inflammatory pathways (6,7). Hydroxytyrosol, a significant phenolic compound in olive oil, has attracted interest for its ability to protect cells from oxidative stress and promote apoptosis in cancer models (8).

Stigmasterol, a phytosterol found in several plant oils, has demonstrated anticancer effects by modulating cellular cholesterol metabolism and inhibiting the proliferation and migration of tumor cells (9,10). Pinosylvin, a stilbenoid present in pine wood, is another promising compound that has demonstrated significant anti-inflammatory and antiproliferative properties. These effects are partly attributed to its ability to induce cell cycle arrest and enhance apoptotic pathways in cancer cells (11,12). The wide range of biological activities and pharmacokinetic properties of these compounds make them promising candidates for inhibiting GSTP1 in cancer treatment.

Recent advancements in computational methods, especially molecular docking and ADME (Absorption, distribution, metabolism, and excretion) analysis, have significantly transformed the drug discovery process. Molecular docking allows for the prediction of interactions between small molecules and target proteins, while ADME profiling evaluates the pharmacokinetic properties of a compound, ensuring its effectiveness in biological systems. These techniques are essential for screening extensive natural compound libraries and identifying promising candidates for further experimental testing (13,14).

In this study, ethacrynic acid was used as a reference inhibitor to assess the binding affinities and docking performance of selected natural compounds. Although ethacrynic acid is a recognized GSTP1 inhibitor, its limitations emphasize the need for alternatives that offer enhanced safety and efficacy (15,16). This study compares ethacrynic acid with compounds like bakuchiol, sesamin, hydroxytyrosol, stigmasterol, and pinosylvin to explore their potential as GSTP1 inhibitors. By combining molecular docking and ADME profiling, it aims to identify natural compounds that could address the limitations of current inhibitors. The findings could lead to safer and more effective GSTP1-targeted cancer therapies and highlight the untapped potential of plant-derived compounds in drug discovery.

Material and Method

Preparation of Ligands

In this study, the molecular structures of several natural compounds, along with the GSTP1 inhibitor

ethacrynic acid, were retrieved from the PubChem database for docking analysis (17). The compounds selected for the study included bakuchiol (PubChem ID: 5468522), sesamin (ID: 72307), hydroxytyrosol (ID: 82755), stigmasterol (ID: 5280794), pinosylvin (ID: 5280457), and ethacrynic acid (ID: 3278). Prior to docking simulations, these molecular structures were energy-minimized using Avogadro software to ensure they adopted energetically favorable conformations, thereby improving the accuracy of the docking process (18).

Docking Procedure

The crystal structure of the Glutathione S-transferase P1 (GSTP1) enzyme was obtained from the Protein Data Bank (PDB) with the ID 2GSS. The structure has a resolution of 1.9 Å and *R-factor and R-free values* of *0.209 and 0.229,* respectively (19). Water molecules and other non-protein components were removed to prepare the structure for docking. Hydrogen atoms were then added, and Gasteiger charges were assigned to the protein to ensure precise docking results. The active site of GSTP1 was determined by examining the binding pocket of ethacrynic acid, a known GSTP1 inhibitor. The coordinates for the active site were defined as follows: x = 9.07595, y = 1.00542, and z = 26.9067. A cubic grid of 15 Å × 15 Å × 15 Å was created around this region to guide the docking simulations. The docking was performed using AutoDock Vina (version 1.2.5), utilizing the Lamarckian Genetic Algorithm with its default settings to compute the binding affinities of each ligand (20,21).

Analysis of Molecular Interactions

After the docking simulations were finished, the binding interactions between GSTP1 and the compounds were analyzed to identify the key interaction types. Using Discovery Studio software, hydrogen bonds, hydrophobic interactions, and other relevant binding interactions were visualized and thoroughly examined (22). These analyses offered valuable insights into the binding mechanisms that govern the interaction between GSTP1 and the selected compounds.

ADME analysis

The pharmacokinetic profiles of the selected compounds and ethacrynic acid were assessed using the SwissADME online tool (http://www.swissadme.ch/), which provides insights into essential ADME parameters for drug development. Molecular structures of the compounds were obtained from the PubChem database in SMILES format and entered into the SwissADME platform. The tool generated predictions for key factors such as absorption (e.g., gastrointestinal absorption and skin permeability), distribution (e.g., blood-brain barrier permeability and P-glycoprotein interaction), metabolism (e.g., cytochrome P450 enzyme interactions), and excretion (e.g., water solubility). Additionally, lipophilicity (LogP and LogD), bioavailability, and adherence to drug-likeness criteria like Lipinski's Rule of Five were assessed. The results, including bioavailability radar plots and medicinal chemistry features, were analyzed to identify compounds with favorable pharmacokinetic profiles, focusing on those with optimal absorption, solubility, and metabolic stability for further investigation.

Statistical Analysis

Energy minimization of the compounds was performed using Avogadro, which employs the default MMFF94 force field to optimize molecular geometries, ensuring stable conformations prior to docking. This step includes default statistical methods to assess the stability and energy profiles of the minimized structures. Docking simulations were carried out with AutoDock Vina, utilizing its standard Lamarckian Genetic Algorithm to calculate binding affinities based on both energy and geometric complementarity. The docking process also incorporated default statistical approaches to evaluate the reliability and significance of the calculated binding affinities. The docking results were visualized using Discovery Studio, which provides standard features to assess binding affinities and interaction frequencies. This software enables the identification of critical interactions, such as hydrogen bonds and hydrophobic contacts, while applying default statistical analyses to offer insights into the distribution and significance of these interactions.

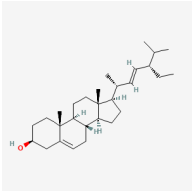
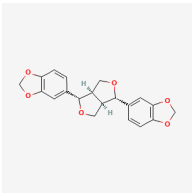
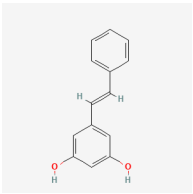
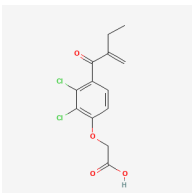
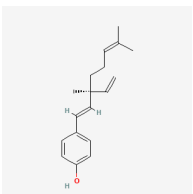
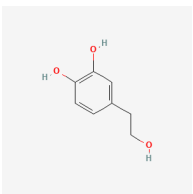
Results

Evaluation of Molecular Docking Analysis

The molecular docking study demonstrated that the natural compounds interact with the GSTP1 protein at varying strengths, as detailed in Table I.

Binding energies, measured in kcal/mol, indicate the interaction strength, with more negative values corresponding to stronger binding affinities. The inhibition constant (Ki) serves as a key parameter to evaluate the compounds' ability to inhibit GSTP1 activity, with lower Ki values indicating higher potency and stronger affinity for the target protein. The Ki values were derived from the binding energy (ΔG) using the formula Ki = eΔG/RT, where R is the universal gas constant (1.985×10^{-3} kcal mol^{-1} K^{-1}), and the temperature (T) was set at 298.15 K.

Table I. Binding Energies of Photosensitizer Compounds and Ethacrynic Acid to GSTP1

Compounds	Molecular structure	Binding energy (kcal/mol)	Calculated *Ki* (μM)
Stigmasterol		-9.2	0.18
Sesamin		-8.2	0.96
Pinosylvin		-7.1	6.16
Ethacrynic acid		-6.7	12.12
Bakuchiol		-6.5	16.99
Hydroxytyrosol		-4.9	253.68

The molecular docking analysis identified stigmasterol and sesamin as the most effective GSTP1 inhibitors among the compounds tested. Stigmasterol exhibited the most potent binding affinity (-9.2 kcal/mol) and the lowest inhibition constant (0.18 μM), followed closely by sesamin (-8.2 kcal/mol, Ki: 0.96 μM). Pinosylvin also displayed moderate inhibitory potential (-7.1 kcal/mol, Ki: 6.16 μM). These results suggest that these natural compounds may offer advantages over ethacrynic acid, a known GSTP1 inhibitor (-6.7 kcal/mol, Ki: 12.12 μM). In comparison, bakuchiol and hydroxytyrosol showed weaker interactions, with hydroxytyrosol being the least effective. These findings highlight stigmasterol and sesamin as promising candidates for further research into GSTP1-targeted therapies.

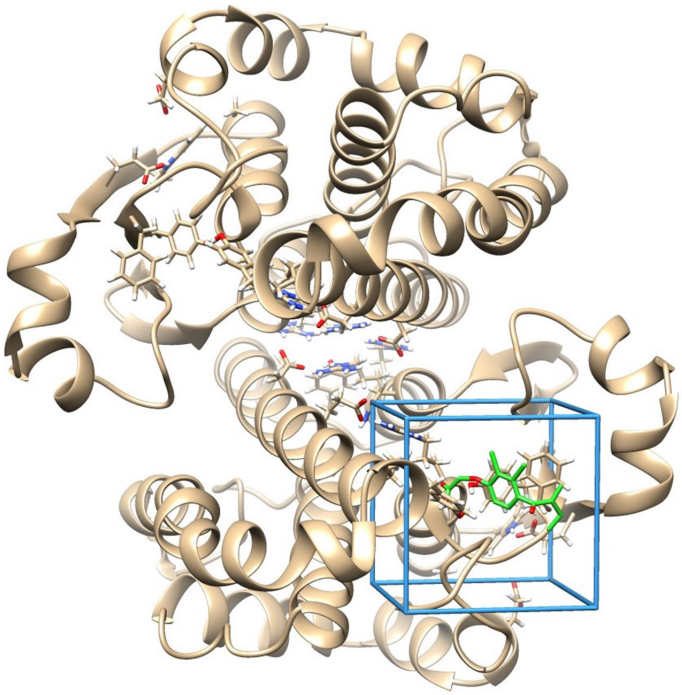


Figure I. 3D Binding pose of ethacrynic acid within the active site of GSTP-1 with a 15 Å cubic grid box. The GSTP1 protein structure is depicted in brown while the structure of ethacrynic acid is shown in green.

Spatial Arrangement of Compounds

The docking process of GSTP-1 with ethacrynic acid was performed using a grid box containing the active site of GSTP1 (H-site), as shown in Fig. I. The grid box was positioned around the site where the crystal structure of ethacrynic acid was previously identified in a complex with GSTP-1. A cubic grid box of 15 Å was created around this site, accommodating

the molecular size of the compounds. Subsequently, all compounds were docked within this grid box.

Furthermore, the spatial arrangement of each compound within the active site of GSTP1 is illustrated in Fig. II. This figure provides a visual overview of the docking results, highlighting how each compound is positioned in relation to the active site. These binding patterns provide insight into how each compound may interact with GSTP1, impacting their potential efficacy in cancer therapy applications targeting this enzyme.

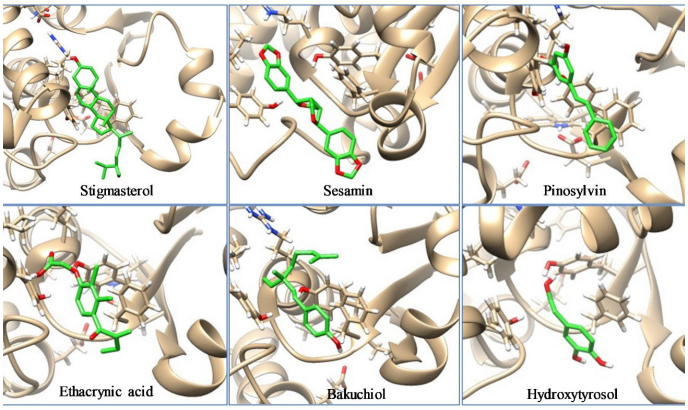


Figure II. The spatial positioning of compounds within the active site of GSTP1. The GSTP1 protein structure is depicted in brown, while the structures of the compounds are shown in green.

Interaction Profiles

The interaction profiles of the compounds with the active site of GSTP1 provide valuable insights into their binding mechanisms and potential as inhibitors (Fig. III). The 2D interaction diagrams illustrate the binding interactions between GSTP1 and four compounds: Stigmasterol (a), Sesamin (b), Pinosylvin (c), and Ethacrynic acid (d). In panel (a), Stigmasterol forms significant van der Waals interactions with residues such as VAL A35 and TYR A7, as well as a pi-alkyl interaction with PHE A3. Additionally, there is an unfavorable donor-donor interaction between ARG A13 and the compound. In panel (b), Sesamin exhibits similar van der Waals interactions with key residues like VAL A10 and TYR A8, and forms a pi-pi stacked interaction with PHE A8. Conventional hydrogen bonds are also observed with residues such as TYR A108. Panel (c) shows Pinosylvin interacting with TYR A7 through a conventional hydrogen bond, while also forming pi-anion interactions with PHE A8 and additional van der Waals contacts. Lastly, in panel (d), Ethacrynic acid demonstrates a range of interactions, including multiple van der Waals contacts with residues such as ARG A19 and ILE A104, as well as pi-anion interactions with the aromatic ring of PHE A8. These interaction profiles highlight the specific binding modes and affinities of each compound with GSTP1, which can contribute to their inhibitory potential.

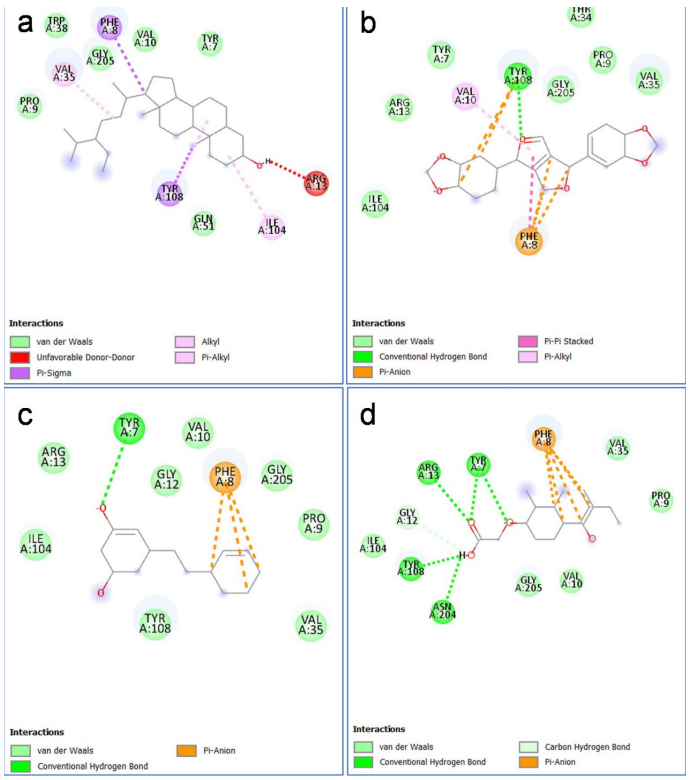


Figure III. 2D Interaction diagrams of top hits and reference compound with GSTP1 protein: (a) Stigmasterol (b) Sesamin (c) Pinosylvin and (d) Ethacrynic acid.

Evaluation of Physicochemical Properties and Pharmacokinetic Profiles

The properties of the compounds with the highest binding energies to GSTP1 were evaluated to gain a better understanding of their potential as inhibitors. This analysis focused on key factors such as molecular size, hydrophobicity, and functional group interactions, which are crucial for determining their binding affinity and overall drug-likeness. By examining these characteristics, we can determine the most promising candidates for further investigation and optimize their potential as therapeutic agents targeting GSTP1

Figure IV presents radar plots and pharmacokinetic data for three compounds: Stigmasterol, Sesamin,

and Pinosylvin. In the radar plots, the red lines represent the compounds' profiles, while the pink shaded areas denote optimal ranges for drug-likeness. Stigmasterol exhibits favorable lipophilicity (LIPO) but shows deficiencies in solubility (INSOLU), suggesting challenges in its bioavailability. Its gastrointestinal (GI) absorption is low, and it does not cross the blood-brain barrier (BBB). Sesamin, on the other hand, demonstrates balanced properties with high GI absorption and BBB permeability, aligning well within the optimal zones for most parameters except solubility. Pinosylvin shows strong flexibility (FLEX) and size (SIZE) attributes but struggles significantly in solubility and saturation (INSATU), despite high GI absorption and BBB permeability. The pharmacokinetics table highlights that none of the compounds act as P-glycoprotein (P-gp) substrates, but Sesamin and Pinosylvin have notable inhibitory effects on CYP450 enzymes (e.g., CYP2C19 and CYP2D6), indicating potential drug-drug interaction risks. Pinosylvin has the highest skin permeability (Log Kp: -5.12 cm/s), followed by Sesamin (-6.56 cm/s) and Stigmasterol (-2.74 cm/s), emphasizing variability in dermal absorption potential. These findings suggest that while each compound has distinct advantages, solubility and enzyme interaction risks remain key considerations in their development as drug candidates.

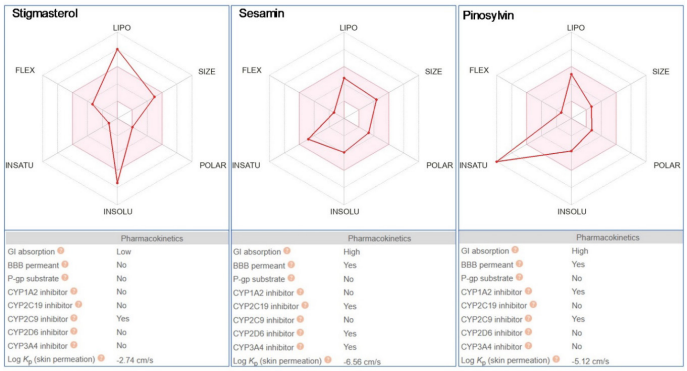


Figure IV. Comparative analysis of physicochemical properties and pharmacokinetics of stigmasterol, sesamin, and pinosylvin

Table II presents the analysis of three natural compounds based on Lipinski's Rule of Five, which evaluates their potential for good oral bioavailability by examining specific molecular properties. Stigmasterol, with a molecular weight of 412.69 g/mol, a LogP of 6.62, one hydrogen bond donor (HBD), and one hydrogen bond acceptor (HBA), has five rotatable bonds and violates one rule due to its high LogP value exceeding the threshold of 5. Sesamin, with a molecular weight of 354.35 g/mol, a LogP of 1.98, no HBDs, six HBAs, and two rotatable bonds, meets all criteria with no violations. Similarly, Pinosilvin complies fully with the rules, featuring a molecular weight of 212.24 g/mol, a LogP of 2.87, two HBDs, two HBAs, and two rotatable bonds. This analysis highlights that while Sesamin and Pinosilvin align with Lipinski's criteria, Stigmasterol may face limitations due to its higher lipophilicity.

Table II. Lipinski's Rule of Five Analysis of Natural Compounds

Compound	MW (g/mol)	LogP	HBD	HBA	Rotatable Bonds	Rule Violations
Stigmasterol	412.69	6.62	1	1	5	1 (LogP>5)
Sesamin	354.35	1.98	0	6	2	0
Pinosilvin	212.24	2.87	2	2	2	0

Abbreviations: MW, Molecular Weight (≤500 g/mol); LogP, Partition coefficient (≤5); HBD, Hydrogen Bond Donors (≤5); HBA, Hydrogen Bond Acceptors (≤10); RB, Rotatable Bonds (≤10).

Discussion

This study has provided valuable insights into the potential of natural compounds as GSTP1 inhibitors, highlighting their role in combating drug resistance, a major challenge in cancer therapy. Through molecular docking and ADME profiling, stigmasterol and sesamin emerged as the most promising candidates, demonstrating superior binding affinities and inhibition constants compared to the reference compound ethacrynic acid. These findings underscore the growing interest in leveraging plant-derived molecules for targeted cancer treatment.

GSTP1, as a key enzyme in detoxification pathways, plays a critical role in neutralizing reactive oxygen species (ROS) and conjugating glutathione to toxic substrates, thereby reducing chemotherapy efficacy in cancer cells (23,24). The docking studies revealed that stigmasterol binds strongly to the active site of GSTP1, with a binding energy of -9.2 kcal/mol and an inhibition constant (Ki) of 0.18 µM. This potency can be attributed to its steroidal structure, which facilitates optimal spatial orientation and robust interactions

with key residues such as VAL A35 and TYR A7. These findings suggest that stigmasterol is not only a potent inhibitor but also an adaptable molecule capable of engaging GSTP1's active site through multiple binding modes. Stigmasterol exhibits a single Lipinski violation due to its high lipophilicity, which may affect its aqueous solubility while enhancing membrane permeability. Despite its relatively low oral bioavailability, stigmasterol's therapeutic potential remains promising, particularly when paired with optimized pharmaceutical formulations. Its flexible molecular structure, characterized by a higher number of rotatable bonds, may enable diverse binding modes with target proteins. Research by Rolta et al. highlights stigmasterol's inhibitory effect on HPV proteins, suggesting its potential as an anticancer agent, especially for localized applications or with enhanced bioavailability (25). Strategies such as nano-carrier systems, liposomes, or solubility-enhancing complexes could further improve its clinical utility (26).

Sesamin demonstrated promising potential with a binding energy of -8.2 kcal/mol and stable hydrogen bond interactions, such as with TYR A108. Its lignan structure supports these interactions, underscoring the role of molecular features in enhancing affinity for target proteins. Sesamin complies with Lipinski's parameters, indicating favorable drug-like properties and a balanced lipophilicity/hydrophilicity profile. However, its poor water solubility and rapid hepatic metabolism significantly limit its oral bioavailability (27). Despite this, studies have shown that sesamin meets key drug-likeness criteria, including favorable ADME properties, making it a promising therapeutic candidate (28). Potential interactions with CYP3A4 and CYP2D6 enzymes highlight the need for careful consideration of drug-drug interactions in clinical use. To address its bioavailability challenges, innovative delivery systems like SNEDDS have proven effective, paving the way for its optimized therapeutic application (27).

Pinosylvin demonstrated moderate inhibition potential based on its binding energy and Ki value, likely influenced by the phenolic groups in its stilbene structure interacting with GSTP1. Its LogP value indicates moderate lipophilicity, is suitable for passive diffusion across cell membranes, and supports oral absorption. The compound's small size and lack of rule violations further enhance its absorption potential. Additionally, its limited number of rotatable bonds suggests a stable metabolic profile, which is beneficial for maintaining bioavailability (29,30). In contrast, bakuchiol and hydroxytyrosol showed lower inhibition potential. The relatively weak affinity of hydroxytyrosol suggests that the presence of phenolic groups alone is insufficient for strong inhibition.

Ethacrynic acid has long served as a benchmark GSTP1 inhibitor. However, its clinical use is limited due to suboptimal pharmacokinetics and significant side effects (31). The comparatively weaker binding affinity (-6.7 kcal/mol) and higher Ki value (12.12 µM) observed in this study emphasize its inferiority to stigmasterol and sesamin. This discrepancy demonstrates that natural compounds not only match but exceed the inhibitory capacity of synthetic inhibitors. Moreover, the reduced toxicity and multifunctional therapeutic effects of natural molecules further elevate their appeal as candidates for clinical application.

Advancing natural compounds as GSTP1 inhibitors necessitates strategic research efforts. Optimizing formulations through innovative delivery systems like SNEDDS or liposomal methods could enhance the bioavailability and stability of stigmasterol and sesamin, addressing solubility challenges. Molecular dynamics simulations may offer deeper insights into binding stability, while structural modifications of lead compounds could improve their potency and pharmacokinetic properties. Preclinical studies are essential to assess anticancer efficacy, toxicity, and biodistribution, with subsequent clinical trials validating therapeutic potential. Additionally, exploring synergistic combinations with standard therapies could enhance effectiveness, reduce drug resistance, and minimize adverse effects, positioning these compounds as promising candidates for resistant cancer treatments.

This study has some limitations, including the fact that the findings are based on in silico analyses, which provide predictive insights but may require further experimental validation. Additionally, factors such as solubility and potential enzyme interactions, especially for compounds like stigmasterol and sesamin, could influence their practical applicability. Future studies

incorporating experimental approaches could help confirm and extend these results.

Conclusion

This study highlights the promising role of natural compounds like stigmasterol and sesamin as GSTP1 inhibitors, offering a novel avenue for tackling drug resistance in cancer treatment. Their unique biochemical properties and the potential for enhancement through modern pharmaceutical strategies position them as valuable candidates in the fight against resistant malignancies. Beyond their direct therapeutic applications, these compounds underscore the broader significance of nature-derived molecules in innovative drug development. With continued focus on refining their efficacy, safety, and delivery, these agents could significantly impact cancer treatment paradigms, bridging the gap between traditional and advanced therapeutic approaches.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Upper Gastrointestinal Bleeding in Geriatric and Young Patients: Evaluation of Clinical and Endoscopic Findings

Geriatrik ve Genç Hastalarda Üst Gastrointestinal Kanama: Klinik ve Endoskopik Bulguların Değerlendirilmesi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1575890
Geliş Tarihi | Received: 30.10.2024
Kabul Tarihi | Accepted: 10.02.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Ergin M, Kıvrakoğlu F, Cindoruk M. Upper Gastrointestinal Bleeding in Geriatric and Young Patients: Evaluation of Clinical and Endoscopic Findings. Hitit Medical Journal 2025;7(2):164-172. https://doi.org/10.52827/hititmedj.1575890

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışmaya ilişkin onay Aksaray Üniversitesi Klinik Araştırma Etik Kurulu'ndan alınmıştır. (Karar no: 2023/23-34, Tarih: 07.12.2023, Sayı: 153-SBKAEK)
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: ME, FK, MC Tasarım: ME, FK, MC Veri Toplama/Veri İşleme: ME, FK, MC Veri Analizi: ME, FK, MC Makalenin Hazırlanması: ME, FK, MC
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Clinical Research Ethics Committee of Aksaray University. (Decision no: 2023/23-34, Date: 07.12.2023, Number: 153-SBKAEK)
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ME, FK, MC Design: ME, FK, MC Data Collection/Data Processing: ME, FK, MC Data Analysis: ME, FK, MC Manuscript Preparation: ME, FK, MC.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Upper Gastrointestinal Bleeding in Geriatric and Young Patients: Evaluation of Clinical and Endoscopic Findings

ABSTRACT

Objective: Acute upper gastrointestinal (GI) bleeding causes significant mortality and morbidity and can be life-threatening. This study aimed to compare the clinical-endoscopic characteristics and outcomes of patients aged <65 and ≥65 years who presented with upper GI bleeding.

Material and Method: A total of 412 patients who underwent endoscopic procedures for GI bleeding were included. The clinical and endoscopic characteristics, treatments, and hospital stays of the patients were retrospectively reviewed from the hospital system and recorded. The results were compared by dividing the patients into two groups: those aged <65 years and those aged ≥65 years.

Results: There were 244 patients aged ≥65 years and 168 patients aged <65 years. Male sex was predominant in both groups. Comorbidities were significantly more common in geriatric patients. Nonsteroidal anti-inflammatory drugs (NSAID) use was similar between the two groups. The etiologies of bleeding were similar in both groups, with peptic ulcers being the most common cause. The need for erythrocyte transfusion was increased in the geriatric group, and the length of hospital stay was significantly longer in the ≥65 years age group. There was no statistically significant difference in in-hospital mortality rates between the two groups.

Conclusion: Peptic ulcer was the most common etiology in both the groups. NSAID use was recognized as an important risk factor for bleeding in both the groups. Older age and the presence of comorbid diseases were thought to be the main factors affecting length of hospital stay and erythrocyte transfusion needs. Age alone was not considered a factor that increased in-hospital mortality.

Keywords: Age, comorbidity, mortality, upper gastrointestinal bleeding.

ÖZET

Amaç: Akut üst gastrointestinal (Gİ) kanama, önemli oranda mortalite ve morbiditeye neden olur ve potansiyel olarak yaşamı tehdit edebilir. Bu çalışmada üst Gİ kanama nedeniyle başvuran <65 yaş ve ≥65 yaş hastalarda klinik-endoskopik özellikler ve sonuçların karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Gİ kanama nedeniyle endoskopik işlem yapılan 412 hasta alındı. Hastaların klinik ve endoskopik özellikleri, tedavileri ve yatış süreleri retrospektif olarak hastane sisteminden taranarak kaydedildi. <65 yaş ve ≥65 yaş hastalar olarak iki gruba ayrılarak sonuçlar karşılaştırıldı.

Bulgular: Toplamda ≥65 yaş 244 hasta, <65 yaş 168 hasta mevcuttu. Her iki grupta da erkek cinsiyet baskındı. Komorbid hastalıklar geriatrik grupta anlamlı şekilde daha fazlaydı. Nonsteroidal anti-inflamatuvar ilaç (NSAİİ) kullanımı iki grupta benzerdi. Kanama etiyolojileri iki grupta benzerdi, en sık sebep peptik ülser idi. Eritrosit transfüzyon ihtiyacı geriatrik grupta daha fazla idi, hastanede yatış süresi ≥65 yaş grubunda istatistiksel anlamlı şekilde daha uzundu. İki grup arasında hastane içi mortalite oranları arasında istatistiksel olarak anlamlı fark yoktu.

Sonuç: Hastalarımızda her iki grupta da en sık üst Gİ kanama sebebi peptik ülser olarak bulunmuştur. NSAİİ kullanım öyküsü, iki grupta da kanamada önemli bir risk faktörü olarak saptandı. Hastaların hastanede yatış süresini ve eritrosit transfüzyon ihtiyacını etkileyen faktörlerin başında, ileri yaş ve komorbid hastalık varlığı geldiği düşünüldü. Yaşın tek başına hastane içi mortaliteyi artıran bir faktör olmadığı düşünüldü.

Anahtar Sözcükler: Komorbidite, mortalite, üst gastrointestinal kanama, yaş.

Introduction

Upper gastrointestinal (GI) bleeding is a common, potentially life-threatening condition. It originates in the esophagus, stomach, or duodenum, proximal to the ligament of Trietz. It may present with hematemesis and melena, or hematochezia may also be present in cases of severe bleeding (1). It can be acute, occult, or obstructive. In addition to bleeding, patients may also experience symptoms of blood and fluid loss, such as syncope, weakness, and dyspnea (2).

Upper GI bleeding constitutes approximately 75% of all acute GI bleeding cases. Although its incidence varies globally and regionally, it is approximately 80-150 per 100,000 annually, with estimated mortality rates ranging between 2-15% (3). Mortality is associated with age, and studies have reported higher mortality in individuals over 60 years of age (4). Various studies have shown that factors other than age, such as hemodynamic instability, hypotension, low hematocrit, and low albumin levels, are independent predictors of mortality (5,6).

Among the causes of upper GI bleeding, peptic ulcer disease accounts for 40-50% of cases. Most (30%) of these patients had duodenal ulcers. It is usually associated with nonsteroidal anti-inflammatory drugs (NSAIDs), Helicobacter pylori (H. pylori), and stress-related mucosal diseases (7). In addition to peptic ulcers, erosive esophagitis (11%), duodenitis (10%), varices (5-30%) (depending on whether the population included in the study had chronic liver disease), Mallory-Weiss lesions (5-15%), and vascular malformations (5%) are other common causes of upper GI bleeding (3).

In approximately 80-85% of patients with upper GI bleeding, bleeding resolves spontaneously without complications (8). However, recurrent and life-threatening bleeding can occur in the remaining cases, requiring additional endoscopic interventions or, if uncontrolled, interventional radiological and surgical treatment.

Approximately 70% of acute upper GI bleeding cases occur in individuals > 60 years of age, and the incidence increases with age. Older age is identified as a risk factor for mortality in patients presenting with upper GI bleeding, likely due to the higher prevalence of comorbidities, such as pulmonary and cardiovascular diseases, in older patients than in younger patients (9).

This study aimed to compare the clinical, laboratory, and endoscopic characteristics of patients presenting with acute upper gastrointestinal (GI) bleeding based on age groups (≥65 years and <65 years) and to evaluate how these differences influence the management of bleeding. Considering that peptic ulcer is the most common cause in both age groups, this study sought to understand the impact of age-related comorbidities and medications on bleeding. Additionally, the length of hospital stay and erythrocyte transfusion requirements were evaluated to investigate how these findings can be integrated into clinical management strategies. This study aimed to determine whether older age and associated comorbidities are critical factors in determining bleeding outcomes. In this context, the findings are expected to contribute significantly to optimizing age-specific management approaches and improving health care delivery.

Material and Method

This study included patients aged ≥ 18 years who presented with symptoms of upper gastrointestinal bleeding and underwent endoscopy at Aksaray Training and Research Hospital between February 2022 and October 2023. Endoscopy was performed in patients with hematemesis, melena, or hematochezia, after hemodynamic stabilization. Three patients with missing data in their files, 17 patients who did not undergo endoscopy, and five patients who were discharged at their own request were excluded from the study (Figure I). Approval for the study was obtained from the Clinical Research Ethics Committee of University (Decision no: 2023/23-34, Date: 07.12.2023, Number: 153-SBKAEK) and was conducted in accordance with the principles of the Declaration of Helsinki. Patient files were retrospectively scanned. Demographic characteristics, laboratory values, comorbid diseases, medications used, and endoscopy reports of the 412 patients included in the study were examined. The length of the hospital stay and mortality due to bleeding were also recorded.

Figure I. Flowchart of the study

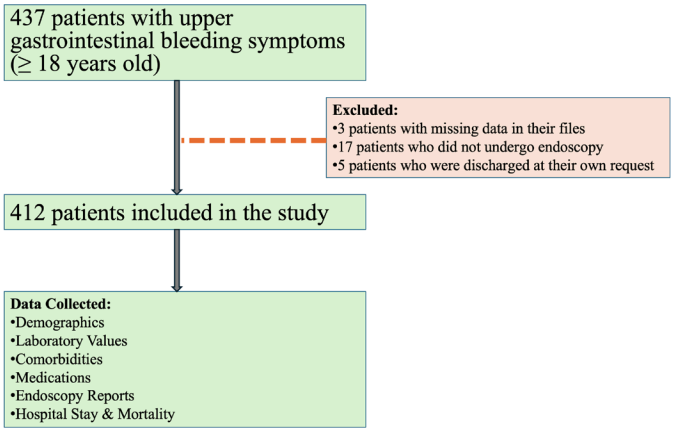
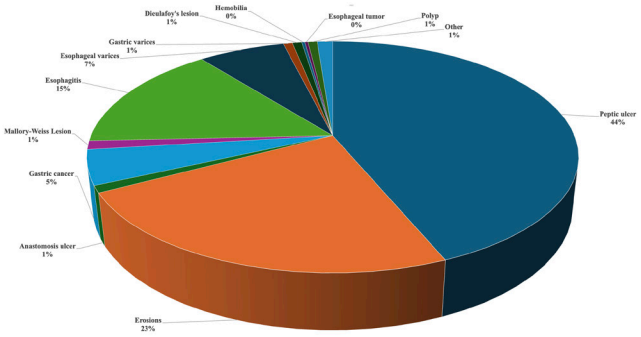


Figure II. Etiologies of Upper Gastrointestinal Bleeding



SPSS version 29.0 was used for statistical analyses. Descriptive statistics were presented as numbers (n) and percentages (%). For quantitative data, mean and standard deviation were given for normally distributed data, and median and minimum-maximum values were given for non-normally distributed data. Comparisons of categorical variables between the groups were performed using the Chi-square or Fisher's exact test. To compare continuous variables in two independent groups, Student's t-test was used when the assumption of normal distribution was met, and the Mann-Whitney U test was used when the assumption of normal distribution was not met. Type 1 error margin (alpha) was accepted as 0.05 for all statistics.

Results

This study included 412 patients, 157 females and 255 males, with an average age of 69 years. Of these, 244 were aged ≥65 years, and 168 were aged <65 years. Most patients presented with melena. The percentage of patients who smoked and consumed alcohol was 18.4% and 3.6%, respectively. Erythrocyte transfusion was administered to 44.7% of the patients. Comorbid conditions were present in 76.9% of patients, with hypertension, cardiovascular diseases, and diabetes mellitus being the most common. Among the medications that increased the bleeding risk, NSAID use was the most common. Table I presents the demographic and laboratory characteristics of the patients.

Peptic ulcer was the most common cause of upper GI bleeding, followed by erosion, esophagitis, and esophageal variceal bleeding (Figure II).

Table I. Demographic Characteristics of Patients

Variable	n (%) or median (min-max)
Age (years)	69 (18-96)
≥65 years	244 (59.2)
<65 years	168 (40.8)
Sex	
Female	157 (38.1)
Male	255 (61.9)
Smoking use	76 (18.4)
Alcohol use	15 (3.6)
Presentation	
Melena	262 (63.6)
Hematemesis	148 (35.9)
Hematochezia	2 (0.5)
Hemoglobin (on admission) (g/dL)	10 (3.8-17.9)
Urea (on admission) (mg/dL)	58 (8-478)
Number of Patients Receiving Erythrocyte Transfusion	184 (44.7)
Presence of Comorbidities	317 (76.9)
Cardiovascular Disease	137 (33.3)
HT	187 (45.4)
DM	112 (27.2)
Liver cirrhosis	31 (7.5)
Atrial Fibrillation/Heart Valve Replacement	60 (14.6)
COPD/Asthma	51 (12.4)
CKD	51 (12.4)
Stroke	25 (6.1)
Other	76 (18.4)
Medication use	281 (68.2)
NSAIDs	145 (35.2)
Aspirin	124 (30.1)
Other antiplatelets	36 (8.7)
NOAC	38 (9.2)
Warfarin	27 (6.6)
Steroids	2 (0.5)

Abbreviations: CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; HT, Hypertension; NOAC, New Oral Anticoagulants; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs

Table II. Comparison of Geriatric and Young Populations

Variable	n (%)[a] or mean ±SD/ median (min-max)		*p-value*
	<65 years (n=168)	≥65 years (n=244)	
Sex			*0.002*[b]
Female	49 (29.2)	108 (44.3)	
Male	119 (70.8)	136 (55.7)	
Smoking use	65 (38.7)	11 (4.5)	*<0.001*[b]
Alcohol use	15 (8.9)	-	*<0.001*[b]
Presentation			*0.001*[c]
Melena	92 (54.8)	170 (69.7)	
Hematemesis	76 (45.2)	72 (29.5)	
Hematochezia	-	2 (0.8)	
Hemoglobin mean±SD	11.5±3.2	9.4±2.8	*<0.001*[d]
Urea median (min-max)	45 (8-321)	91.6 (13-478)	*<0.001*[e]
Erythrocyte transfusion	48 (28.6)	136 (55.7)	*<0.001*[b]
Presence of Comorbidities	86 (51.2)	231 (94.7)	*<0.001*[b]
Cardiovascular Disease	25 (14.9)	112 (45.9)	*<0.001*[b]
HT	32 (19.0)	155 (63.5)	*<0.001*[b]
DM	31 (18.5)	81 (33.2)	*<0.001*[b]
Liver cirrhosis	17 (10.1)	14 (5.7)	*0.098*[b]
Atrial Fibrillation/Heart Valve Replacement	2 (1.2)	58 (23.8)	*<0.001*[b]
COPD/Asthma	9 (5.4)	42 (17.2)	*<0.001*[b]
CKD	10 (6.0)	41 (16.8)	*0.001*[b]
Stroke	4 (2.4)	21 (8.6)	*0.009*[b]
Other	23 (13.7)	53 (21.7)	*0.039*[b]
Medication use	85 (50.6)	196 (80.3)	*<0.001*[b]
NSAIDs	62 (36.9)	83 (34.0)	*0.546*[b]
Aspirin	28 (16.7)	96 (39.3)	*<0.001*[b]
Other antiplatelets	14 (8.3)	22 (9.0)	*0809*[b]
NOAC	-	38 (15.6)	*<0.001*[b]
Warfarin	3 (1.8)	24 (9.8)	*0.001*[b]
Steroids	-	2 (0.8)	*0.516*[c]
Etiology			*0.224*[c]
Peptic ulcer	66 (39.3)	114 (46.7)	
Erosive gastritis	40 (23.8)	57 (23.4)	
Anastomotic ulcer	2 (1.2)	2 (0.8)	
Gastric cancer	9 (5.4)	11 (4.5)	
Mallory-Weiss tear	2 (1.2)	3 (1.2)	
Esophagitis	24 (14.3)	38 (15.6)	
Esophageal varices	16 (9.5)	12 (4.9)	
Gastric varices	2 (1.2)	1 (0.4)	
Dieulafoy lesion	3 (1.8)	-	
Hemobilia	1 (0.6)	-	
Esophageal tumor	-	1 (0.4)	
Polyp	-	3 (1.2)	
Other	3 (1.8)	2 (0.8)	
Ulcer location			*0.002*[b]
Duodenal ulcer	51 (77.3)	62 (54.4)	
Gastric ulcer	15 (22.7)	52 (45.6)	
Forrest Classification (n=180)			*0.089*[c]
Forrest 1A	1 (1.5)	1 (0.9)	
Forrest 1B	1 (1.5)	4 (3.5)	

Forrest 2A	3 (4.5)	1 (0.9)	
Forrest 2B	-	6 (5.3)	
Forrest 2C	25 (37.9)	53 (46.5)	
Forrest 3	36 (54.5)	49 (43.0)	
Endoscopic Treatment	21 (12.5)	23 (9.4)	*0.321*[b]
Sclerotherapy	7 (4.2)	9 (3.7)	*0.805*[b]
Hemoclip	11 (6.5)	12 (4.9)	*0.479*[c]
Band ligation	9 (5.4)	6 (2.5)	*0.123*[b]
Argon/Heater	2 (1.2)	2 (0.8)	*1.000*[c]
Sclerotherapy+Hemoclip	7 (4.2)	6 (2.5)	*0.330*[b]
Sclerotherapy+Argon/Heater	1 (0.6)	2 (0.8)	*1.000*[c]
Interventional Radiology	-	3 (1.2)	*0.274*[c]
Surgery	3 (1.8)	-	*0.067*[c]
Other	4 (2.4)	4 (1.6)	*0.721*[c]
Length of Hospital Stay Median (min-max)	2 (0-12)	3 (0-22)	*<0.001*[e]
Mortality	2 (1.2)	7 (2.9)	*0.320*[c]

Abbreviations: CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; HT, Hypertension; NOAC, New Oral Anticoagulants; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs
[a] Column percentage [b] Pearson Chi-square test [c] Fisher Exact test [d] Student T test [e] Mann-Whitney U test

In both groups, males were dominant in the geriatric and young populations. Smoking and alcohol consumption were significantly higher in the younger population (*p<0.001*). In both groups, the presentation type was melena, which was significantly more obvious, especially in the geriatric population, than other bleeding presentations. Hemoglobin levels were significantly lower, and urea levels were higher in the geriatric population, and the need for erythrocyte transfusion was more obvious in the geriatric population. Comorbid diseases were significantly more common in the geriatric group. Although NSAID use was similar in both groups, aspirin, new oral anticoagulants, and warfarin were more frequently used in the geriatric population. The etiologies of bleeding were similar in both groups. There was no difference between the groups in terms of the Forrest classification in patients with upper GI bleeding due to peptic ulcers. The endoscopic hemostatic treatments applied to the patients were similar in both groups. The length of the hospital stay was longer in the geriatric population. Mortality rates were similar in both the groups. Information regarding the comparison of geriatric and youth population data is presented in Table II.

Discussion

Despite advances in diagnostic and therapeutic approaches, GI bleeding remains a significant cause of morbidity and mortality. In the United States, although the mortality rate from upper GI bleeding has decreased, it still leads to 300,000 hospital admissions annually and an economic burden of 3.3 billion dollars (10, 11). Therefore, it is crucial to investigate and mitigate the factors that increase the risk of bleeding.

Upper GI bleeding is most commonly observed in the geriatric population. In our study, bleeding frequency was also higher in patients aged ≥65 years. This prevalence in the geriatric population is thought to be due to factors such as the increased use of NSAIDs and other toxic medications with age and the higher incidence of H. pylori and gastroesophageal reflux disease in older adults (12).

Endoscopy is the best method for diagnosing and treating upper GI bleeding. Early (≤24 hours) GI endoscopy following hemodynamic resuscitation is recommended for suspected cases of bleeding (13). The most common cause of upper GI bleeding identified on endoscopy is peptic ulcer disease, which accounts for approximately 40% of all hospitalizations (14). Other common causes include esophagitis (24%), gastritis or gastric erosions (18-22%), duodenitis (13%), and variceal bleeding (11%). Additionally, malignancies, Dieulafoy's lesions, and Mallory-Weiss lesions are among the most frequent causes (15). The frequency ranking may vary based on region and geography. Studies from Türkiye have also reported peptic ulcers as the most common cause of upper GI bleeding (16-20). In our study, peptic ulcers (44%)

were the most common cause of bleeding in all patients, consistent with the literature, followed by erosions (23%), esophagitis (15%), and esophageal varices (7%). Duodenal ulcers were more common than gastric ulcers. Western sources indicate that gastric ulcers are more common than duodenal ulcers, which may be explained by the higher prevalence of H. pylori in our country and its stronger association with duodenal ulcers (21).

In both groups, the causes of bleeding were similar. Peptic ulcer was the most common cause of bleeding in both the groups. According to the localization of peptic ulcers, duodenal ulcers were more common than gastric ulcers in both the groups. Duodenal ulcers were significantly more common in the young group than in the geriatric group. Disruption of the balance between aggressive factors affecting the mucosa and defensive mechanisms protecting the mucosa plays a role in the development of peptic ulcers (22). An increase in aggressive factors often leads to the development of duodenal ulcers, while a decrease in defensive mechanisms frequently leads to the development of gastric ulcers (23). In our study, smoking and alcohol use, which are known to negatively affect both defensive and aggressive factors and primarily lead to the development of gastric ulcers in the young population (23), were significantly more common than in the geriatric population. However, duodenal ulcers were more common in contrast. The presence of H. pylori was not evaluated in this study. This situation may be interpreted as the possibility that H. pylori is more prevalent in the younger group. H. pylori infection frequently causes duodenal ulcer development (24). In addition, although the use of NSAIDs, which are the most common agents causing peptic ulcers, was similar in both groups, comorbid diseases were more common in the geriatric group. The use of aspirin, warfarin, and new oral anticoagulants was more common in the geriatric group. All these factors may lead to ulcer development by affecting the aggressive and defensive factors of the mucosa in various ways and may have affected ulcer localization.

The literature suggests that upper GI bleeding is generally more common in males (25). In our study, bleeding was more frequent in men than in women in both the <65 and ≥65 years age groups, particularly in the younger population. This difference may be due to higher estrogen levels in women, which are thought to increase vascularization and proliferation of the gastric mucosa (26). In the geriatric population, estrogen levels decrease after menopause, bringing the male-to-female ratio closer together, thus supporting this information.

The most common presentation in patients with upper GI bleeding was melena. Especially in the geriatric population, melena was observed at a significantly higher rate than hematemesis. In the laboratory, it was observed that the mean hemoglobin levels were lower and urea levels were higher in the geriatric population than in the young group. The need for erythrocyte transfusion was also significantly higher in the geriatric group than that in the young group. The use of risky drugs and the higher presence of comorbid diseases in the elderly population, which led to the need for earlier erythrocyte transfusion, may have contributed to this. Guidelines also recommend a restrictive transfusion strategy in hemodynamically stable patients with acute upper GI bleeding and no history of cardiovascular disease, and it is recommended to consider replacement if the hemoglobin level is ≤7 g/dL. In contrast, in hemodynamically stable patients with a history of cardiovascular disease, the hemoglobin threshold was determined to be 8 g/dL, and the target hemoglobin concentration was ≥ 10 g/dL (13). The patients in our study received erythrocyte transfusions in accordance with literature. Endoscopic treatments applied in both groups were similar, regardless of the patient's age. Approximately 10% of patients in both the young and geriatric groups underwent endoscopic treatment. The most commonly applied treatments included sclerotherapy, hemoclips, and their combinations, which were similarly frequent in both the groups. In addition, treatments such as band ligation, argon/heater, interventional radiological, and surgical procedures applied according to bleeding etiology were similar, regardless of age. The literature emphasizes the necessity of selecting and applying endoscopic hemostasis methods based on patient indications (27). Koruk et al. compared endoscopic treatments in patients with non-variceal upper GI bleeding and, similar to our study, found that sclerotherapy,

thermal treatments, and hemoclips, either alone or in combination, were the most commonly applied treatments (28). Köseoğlu et al. demonstrated the effectiveness of clip methods in controlling bleeding in patients with nonvariceal upper GI bleeding (29). We believe that endoscopic treatment selection for bleeding control should prioritize the etiology over age, and that the most appropriate endoscopic hemostasis technique should be chosen and used according to local resources. In our study, age did not influence selection.

The literature provides conflicting results on the mortality rates from acute upper GI bleeding in geriatric and young populations. Data from one study showed that patients over 70 years of age had a 20-30 times higher incidence of GI bleeding than those under 30 years of age. Additionally, mortality rates were 12-25% in patients over 60 years of age and less than 10% in patients under 60 years of age (5). In a study by Nahon et al., which examined 3,287 patients with upper GI bleeding, patients aged > 75 years were compared, and the in-hospital mortality rates were found to be similar regardless of etiology (30). In a study by Özveren et al., the mortality rate for upper GI bleeding in patients aged ≥ 65 years was 8.4%. When examined according to age groups, mortality rates were 5% in those aged 65-74, 6.5% in those aged 75-84, and 29.6% in those aged ≥ 85 years (31). In a study by Segal et al., patients aged ≥ 60 years did not show significant differences from those aged < 60 years in terms of intensive care needs, transfusion requirements, hospital stay duration, and mortality (32). In another study by Kır et al., age alone was not found to be an independent risk factor for mortality (33). In our study, the total mortality rate was approximately 2.2%, and there was no significant difference in mortality between the young and geriatric groups. Based on these data, it can be concluded that age alone is not a factor affecting mortality. However, the length of hospital stay was significantly longer in the geriatric population than in the younger group. This may be because of the higher prevalence of comorbid diseases in the geriatric group. The need for transfusion was also significantly higher in the geriatric population than that in the younger population.

This study evaluated 412 patients with upper gastrointestinal bleeding and compared clinical, laboratory, and endoscopic differences between geriatric (≥65 years) and young (<65 years) patients. The large sample size and multidimensional analysis of the data based on age groups are among its key strengths. This study highlights that peptic ulcer is the most common cause of bleeding in both age groups and that age-related comorbidities play a critical role in the management of bleeding. However, the retrospective design and lack of data on H. pylori infection are notable limitations.

Conclusion

In conclusion, GI bleeding remains a significant cause of mortality and morbidity in all age groups. The causes of upper GI bleeding were similar in both geriatric and young populations. While hospital stays were longer and erythrocyte transfusion needs were higher in the geriatric group, mortality rates were similar between the two groups.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Outcomes of Partial Intracapsular Bizact™ Versus Bipolar Electrocautery Tonsillectomy in Pediatric Patients: A Prospective Analysis

Pediatrik Hastalarda Parsiyel İntrakapsüler Bizact™ ve Bipolar Elektrokoter Tonsillektominin Sonuçları: Prospektif Bir Değerlendirme

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1581528
Geliş Tarihi | Received: 08.11.2024
Kabul Tarihi | Accepted: 20.02.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Alaskarov E, Özçelik N. Outcomes of Partial Intracapsular Bizact™ Versus Bipolar Electrocautery Tonsillectomy in Pediatric Patients: A Prospective Analysis. Hitit Medical Journal 2025;7(2):173-180. https://doi.org/10.52827/hititmedj.1581528

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Medipol Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan çalışma için etik onay alınmıştır. (Tarih: 03/06/2020; Karar numarası:E-10840098-202.3.02-3329)
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: EA, NÖ Tasarım: EA Veri Toplama/Veri İşleme: EA, NÖ Veri Analizi: EA, NÖ Makalenin Hazırlanması: EA, NÖ
Hasta Onamı: Hastalardan bilg onam alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Ethical approval for the study was obtained from the Medipol University Clinical Research Ethics Committee (Date: 03/06/2020; Decision No: E-10840098-202.3.02-3329).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: EA, NO; Design: EA, NO; Data Collection/Data Processing: EA, NO; Data Analysis: EA, NO; Manuscript Preparation: EA, NO.
Informed Consent: Informed consents were obtained from the patients.
Financial Disclosure: There are no financial funds for this article.

Outcomes of Partial Intracapsular Bizact™ Versus Bipolar Electrocautery Tonsillectomy in Pediatric Patients: A Prospective Analysis

ABSTRACT

Objective: : This study aimed to compare the intraoperative and postoperative outcomes of Partial Intracapsular Bizact™ Tonsillectomy (PIBT) and Bipolar Electrocautery Tonsillectomy (BET) in pediatric patients.

Material and Method: We conducted a single-center, prospective, randomized study involving 260 pediatric patients who underwent tonsillectomy under general anesthesia. Patients were randomly assigned to either the PIBT group or the BET group. Demographic and clinical data were collected, and the measured outcomes included operation time, intraoperative bleeding, postoperative pain scores, time to resume a normal diet, and the incidence of secondary bleeding.

Results: The mean age of patients was similar between the PIBT and BET groups. The PIBT group demonstrated a significantly shorter operation time (11 ± 3.3 minutes) compared to the BET group (18 ± 3.7 minutes, $p<0.05$). Intraoperative bleeding was significantly lower in the PIBT group (PIBT: 11 ± 2.7 ml; ET: 13 ± 2.3 ml, $p<0.05$). Postoperative pain scores were significantly lower in the PIBT group on days 3 and 7. Patients in the PIBT group resumed a normal diet significantly earlier (7.3±1.5 days) than those in the BET group. The incidence of secondary bleeding was slightly lower in the PIBT group (3.6%) compared to the BET group (4.7%).

Conclusion: Partial Intracapsular Bizact™ Tonsillectomy offers significant advantages over electrocautery tonsillectomy, including shorter operation time, reduced intraoperative blood loss, decreased postoperative pain, and a faster return to a normal diet. These findings suggest that PIBT may be a preferred technique for pediatric tonsillectomy.

Keywords: Bizact™, intraoperative bleeding, postoperative pain, tonsillectomy.

ÖZET

Amaç: Bu çalışmanın amacı, pediatrik hastalarda Parsiyel Intrakapsüler Bizact™ Tonsillektomi (PIBT) ve Bipolar Elektrokoter Tonsillektomi (BET) tekniklerinin intraoperatif ve postoperatif sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Genel anestezi altında tonsillektomi yapılan 260 pediatrik hasta dahil edildi. Tek merkezli, prospektif ve randomize bir çalışma gerçekleştirildi. Hastalar rastgele olarak PIBT grubuna veya BET grubuna atandı. Demografik ve klinik veriler toplandı; değerlendirme ölçütleri arasında ameliyat süresi, intraoperatif kanama, postoperatif ağrı skorları, normal diyete dönüş süresi ve sekonder kanama insidansı yer almaktaydı.

Bulgular: Hastaların yaş ortalaması PIBT ve BET grupları arasında benzerdi. PIBT grubunda ameliyat süresi (11 ± 3,3 dakika), BET grubuna göre anlamlı olarak daha kısaydı (18 ± 3,7 dakika, $p<0,05$). İntraoperatif kanama miktarı PIBT grubunda diğer guruba göre azdı. (PIBT: 11 ± 2,7 ml; BET: 13 ± 2,3 ml, $p<0,05$). PIBT grubunda postoperatif ağrı skorları 3. ve 7. günlerde anlamlı derecede düşüktü. PIBT grubundaki hastalar, BET grubuna kıyasla normal diyete daha erken döndü (7,3±1,5 gün). İkincil kanama insidansı PIBT grubunda (%3,6) BET grubuna (%4,7) göre istatistiksel anlamlı olmasa da düşük olarak gözlendi.

Sonuç: Parsiyel İntrakapsüler Bizact™ Tonsillektomi, elektrokoter tonsillektomiye kıyasla daha kısa ameliyat süresi, azalmış intraoperatif kanama, düşük postoperatif ağrı ve normal diyete erken dönüş gibi önemli avantajlar sunmaktadır. Bu bulgular, PIBT'nin pediatrik tonsillektomide tercih edilen bir teknik olabileceğini göstermektedir.

Anahtar Sözcükler: Bizact™, intraoperatif kanama, postoperatif ağrı, tonsillektomi.

Introduction

Tonsillar hypertrophy and recurrent tonsillitis are common childhood conditions that significantly impact a child's quality of life. Tonsillectomy, either alone or in combination with adenoidectomy, is a commonly performed surgery in ENT practice for these reasons (1).

Conventional tonsillectomy is a well-known and widely performed technique. However, new surgical techniques such as monopolar or bipolar electrocautery, cryosurgery, laser, and coblation tonsillectomy have also been described. Despite the availability of these new techniques, there is no standardized optimal technique or device (2).

Several different surgical techniques have been described in the literature, particularly concerning the risk of postoperative pain and bleeding. Therefore, the optimal tonsillectomy technique should ensure fast recovery, acceptable levels of pain, and a low complication risk (3).

One of the new tonsillectomy devices, Bizact™, produced by Medtronic (Minneapolis, MN, USA), has been frequently used in recent times. Previous studies have reported its advantages, such as reduced bleeding and tissue damage (4).

In our study, we used Bizact™ devices in one of the groups during the operation. We aimed to compare the intraoperative and postoperative parameters of Partial Intracapsular Bizact™ Tonsillectomy (PIBT) and Bipolar Electrocautery Tonsillectomy (BET).

Material and Method

Study Design

We conducted a single-center prospective randomized study at the Ear, Nose, and Throat (ENT) Department of Medipol University, Istanbul, Turkiye. The study included 260 pediatric patients who underwent tonsillectomy under general anesthesia between March 1st, 2020, and November 1st, 2022. The study was designed as a single-blind prospective study.

Patient Selection

Patient selection was based on history and physical examination results obtained from the children's families. Preoperative data, including age, gender, vital signs, tonsil size, tonsillectomy indication, and medical history, were documented. Children aged 4 to 8 with a history of recurrent tonsillitis or symptoms of upper airway obstruction, such as open-mouth breathing during sleep, snoring, and sleep apnea, were included. Patients with systemic diseases such as coagulopathies, craniofacial disorders, or genetic variants were excluded. Physical examination included evaluating tonsil hypertrophy using the Brodsky grading system (Grade 1-4) (5).

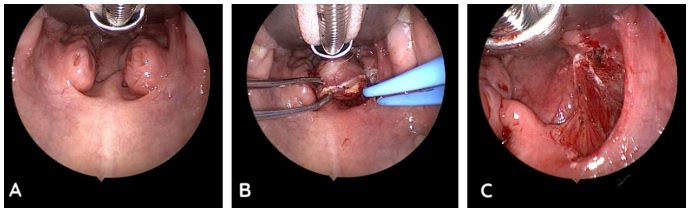
The surgical technique, intraoperative, and postoperative medications used for general anesthesia were standardized across all patients. Patients were randomly divided into two groups: those who underwent Bipolar Electrocautery Tonsillectomy (BET) and those who underwent Partial Intracapsular Bizact™ Tonsillectomy (PIBT). Families unaware of the surgical technique recorded pain scores, daily activities, and diet for 7 days.

Surgical Technique

All surgeries were performed by a single operator who holds a proficiency certificate. The operation began after placing the mouth gag and was recorded until the mouth gag was removed. Preoperative preparation and anesthesia processes were not included in the operation time.

In the BET group, bipolar electrocautery (Valleylab Force 2 ESU, USA) was utilized for both dissection and cauterization, with the device set at a power level of 35 watts. During the procedure, the tonsil was grasped with one hand while electrocautery was used with the other hand to dissect and excise the tonsil tissue along with its capsule. Hemostasis was then ensured in the surgical field (Figure I).

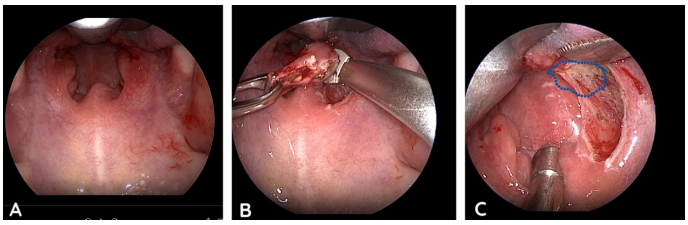
Figure I. A- Preoperative endoscopic examination reveals bilateral tonsils, B- The tonsil was grasped and retracted from the tonsillar fossa, followed by the dissection using bipolar electrocautery, C- Post-tonsillectomy surgical field appearance



In the PIBT group, the Bizact™ device (Medtronic, Minneapolis, MN, USA) was utilized for surgical dissection, incision, and hemostasis. Dissection was performed using an extracapsular approach for the

superior and middle poles of the tonsil. For the inferior pole, the dissection continued in an intracapsular plane, ensuring the complete excision of the tonsillar tissue. Great care was taken to ensure that no visible residual tonsil tissue was left. In both inferior tonsillar fossae, the white capsule was observed to be intact (Figure II).

Figure II. A- Preoperative endoscopic examination reveals bilateral tonsils, B- Extracapsular dissection of the tonsil tissue using the Bizact™ device at the superior and middle poles, followed by transitioning to an intracapsular dissection plane at the inferior pole, C- Post-tonsillectomy appearance of the surgical field, showing the preserved tonsil capsule at the marked area on the inferior pole.



Intraoperative bleeding during tonsillectomy was quantified using a vacuum aspirator bottle that collected all blood and fluids. The total volume of bleeding was calculated by substracting the volume of irrigation fluid administered from the total volume of fluid collected in the aspirator container at the end of the procedure.

Postoperative Period

All patients were monitored in the hospital for one day after the surgery. A single dose of intravenous cefazolin sodium was administered at a dosage of 30 mg/kg. All children received regular oral non-steroidal anti-inflammatory drugs (5 mg/kg-100 mg ibuprofen and 1 mg chlorpheniramine maleate) every 6 hours to relieve postoperative pain. Oral amoxicillin-clavulanate was prescribed at a dose of 50 mg/kg and continued for seven days postoperatively. Patients were discharged on the first day postoperatively. All patients were provided with a one-week dietary plan. They were instructed to follow a liquid-based diet for the first three days, transitioning to soft solid foods for the following four days.

Upon discharge, families were provided with instructions on postoperative pain management and oral intake, along with detailed guidance on completing notes. All patients were seen and examined on the 7th day postoperatively. Postoperative pain was assessed using the Wong–Baker FACES® Pain Rating Scale on postoperative days 1, 3, and 7. Early (within 24 hours post-operation) (6) and late postoperative complications, such as bleeding, infection, difficulty in oral feeding, rehospitalization, or reoperation, were recorded. All patients were followed up for an average of two years postoperatively.

Ethics Statement and Statistical Analysis

Ethics approval was obtained from the Institutional Ethics Committee of Our University before the study commenced, in accordance with the Helsinki Declaration (Date: 03/06/2020; Decision No: E-10840098-202.3.02-3329). Detailed information about the surgical procedure and postoperative care was provided to the families, and informed consent forms were obtained from the parents. Statistical analyses were performed using SPSS software (version 20.0; IBM, Armonk, NY). Mann-Whitney U-test and independent t-test were used for between-group evaluation of quantitative data. The chi-square test was used to compare qualitative data. A *p-value* of less than *0.05* was considered significant.

Results

The mean age of the 150 patients in the BET group was 4.5 ± 2.6 years. According to gender distribution, 78 of these patients were male and 72 were female. Among them, 26 patients were diagnosed with recurrent tonsillitis, 69 with tonsil hypertrophy, and 55 with both conditions. Both tonsillectomy and adenoidectomy were performed on 98 patients, while only tonsillectomy was performed on 52 patients. The mean age of the 110 patients in the PIBT group was 4.2 ± 2.3 years. According to gender distribution, 59 were male and 51 were female. In this group, 12 patients were diagnosed with recurrent tonsillitis, 55 with tonsil hypertrophy, and 43 with both conditions. Both adenoidectomy and tonsillectomy were performed on 76 patients, while only tonsillectomy was performed on 34 patients.

The demographic and clinical characteristics of the patients were compared in Table I. There was no statistical difference in the mean age and gender distribution between the two groups.

Table I. Demographic and Clinical Characteristics of Each Group of Patients

	BET n=150	PIBT n=110	*p value**
Sex,n(%) **Male** **Female**	 78(52) 72(48)	 59(53.6) 51(46.4)	*0.415*
Age,years **Mean ± SD**	4.5±2.6	4.2±2.3	*0.335*
Indications for tonsillectomy,n **Tonsillar hypertrophy** **Hypertrophy and Recurrent tonsilitis** **Recurrent tonsilltis**	 69 55 26	 55 43 12	*0.295*
Surgical preformed,n **Tonsillectomy+Adenoidectomy** **Tonsillectomy only**	 98 52	 76 34	*0.452*

BET=Bipolar Electrocautery Tonsillectomy;PIBT= Partial Intracapsular Bizact™ Tonsillectomy;SD=Standart deviation

* P-values were derived using the Chi-square test, as deemed appropriate for the data type and distribution.

The operation time was 18 ± 3.7 minutes in the BET group and 11 ± 3.3 minutes in the PIBT group. The operation time was shorter in the BiZact™ tonsillectomy group, and this difference was statistically significant (*p<0.05*).

Intraoperative blood loss was also significantly lower in the PIBT group (11 ± 2.7 ml) compared to the BET group (13 ± 2.3 ml, *p=0.004*).

Postoperative pain scores were compared in both groups. The average pain scores on days 3 and 7 were significantly lower in the PIBT group(Figure III). Additionally, in the PIBT group, the average time to return to a normal diet was 7.3 ± 1.5 days. This duration was found to be significantly shorter compared to the BET group (Table II).

Figure III. Comparison of postoperative visual analog scale (VAS) pain scores between the two groups. P-values at postoperative day (POD) 1, 3, and 7 are 0.31, 0.03, and 0.05 each. BET=Bipolar Electrocautery Tonsillectomy;PIBT= Partial Intracapsular Bizact™ Tonsillectomy;SD=Standart Deviation

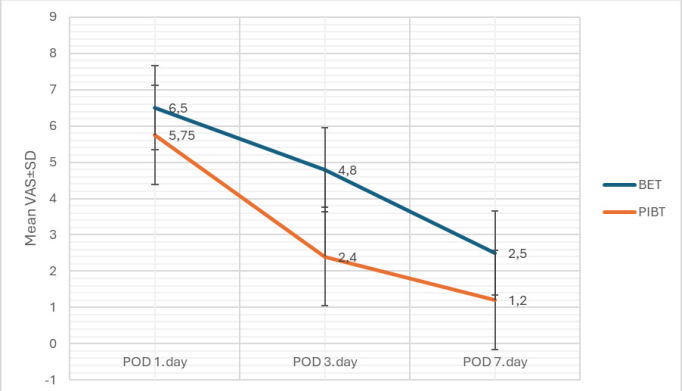


Table II. Comparison of the Intraoperative and Postoperative Parameters of Each Group of Patients

	BET n=150	PIBT n=110	*p value**
Mean operative time, minutes(±SD)	18 ±3.7	11 ±3.3	*<0.001*
Intra-operative blood loss, ml (± SD)	13 ±2.3	11 ±2.7	*0.004*
PPS mean (± SD) 1.day 3.day 7.day	 6.5 ±1.5 4.8±1.2 2.9±1.5	 5.75±1.4 2.4±1.1 1.2±0.4	 *0.046* *<0.001* *<0.001*
Day to normal diet mean (± SD)	9.7±2.4	7.3±1.5	*<0.001*

BET=Bipolar Electrocautery Tonsillectomy; PIBT= Partial Intracapsular Bizact™ Tonsillectomy;SD=Standart deviation; PPS=Postoperative pain score.

*- independent samples t-test

Post-tonsillectomy secondary hemorrhage was graded according to the Stammberger classification (7). Postoperative secondary hemorrhage was observed in 7 (4.7%) patients in the BET group and 4 (3.6%) patients in the PIBT group. In the BET group, one patient underwent bleeding control under general anesthesia on the 7th day due to active bleeding. The days, sites, and severity of bleeding in both groups are recorded in Table III. There was no significant difference in bleeding rates between the two groups. In both groups, no recurrent tonsillitis or regrowth of tonsil tissue was observed during the 2-year follow-up period.

Table III. Comparison of Secondary Hemorrhage Data According to Group

	BET n=7(4.7%)	PIBT n=4(3.6%)
Day of POB, n <1 1-3 4-6 >7	 1 1 3 2	 0 2 1 1
POB site,n Superior pole Middle pole Inferior pole	 2 2 3	 1 1 2
POB severity*, n Grade A1 Grade A2 Grade B1 Grade B2 Grade C	 2 2 1 1 1	 2 1 1 0 0

BET=Bipolar Electrocautery Tonsillectomy;PIBT= Partial Intracapsular Bizact™ Tonsillectomy;POB=Post-Operative Bleeding,

*Severity of bleeding according to the Stammberger classification system.

Discussion

Postoperative pain management following tonsillectomy can be challenging and frequently insufficient. Pediatric patients often experience prolonged painful recoveries with symptoms such

as odynophagia, otalgia, dehydration, and poor oral intake, which significantly impact both the patients and their caregivers (8).

The use of the Wong-Baker FACES® scale for postoperative pain assessment has certain limitations, particularly within the pediatric population, due to subjectivity and communication challenges. Children's inability to accurately express pain or the potential biases in parental observations necessitate caution when interpreting the data (9). To mitigate this limitation, parents were thoroughly educated about pain scoring, and assessments were conducted under the supervision of a nurse on postoperative day 1. In our study, pain scores were significantly lower in the PIBT group on the 3rd and 7th days. Additionally, the shorter time required to resume a normal diet in this group (7.3 ± 1.5 days) can be considered a concrete indicator supporting the reduction in pain scores.
New surgical techniques and instruments aim to reduce morbidity and enable patients to return to their normal lives quickly. The extent and depth of dissection during tonsillectomy, along with tissue damage and necrosis, can increase postoperative pain, infection, and bleeding risk (10,11).

One such technique is intracapsular tonsillectomy, which has gained popularity in recent years. This technique is particularly common in cases involving obstructive symptoms and offers advantages over classical extracapsular tonsillectomy, such as faster postoperative recovery and reduced pain. However, there is a risk that residual tonsil tissue may cause recurrent tonsillitis in the long term following intracapsular tonsillectomy (12,13). In our study, patients were followed up for an average of 2 years postoperatively. No residual or recurrent tonsil tissue was observed in either group.

Koltai and colleagues observed a reduction in postoperative morbidity with intracapsular tonsillectomy in cases of hypertrophic tonsils. They attributed this to the small diameter of vessels in the intracapsular area, suggesting that the preserved tonsil capsule acts as a biological dressing (14). In our study, the PIBT group had the inferior tonsillar capsule left intact, and it was observed that patients in this group were able to resume a normal diet in a shorter period.

Bipolar electrocautery tonsillectomy is commonly used for its ease of use and reduced intraoperative bleeding. However, a study comparing blunt dissection and bipolar electrocautery dissection found that the latter group experienced increased postoperative pain and delayed oral intake resumption, possibly due to thermal tissue damage from frequent cauterization (15,16). Our study found significant difference in intraoperative bleeding between the BET and PIBT groups. Higher pain scores were observed in the BET group on days 3 and 6. This outcome is attributed to dermal tissue damage caused by extracapsular dissection and cauterization.

Coblation tonsillectomy has emerged as an alternative with advantages such as less pain and shorter operation time due to its low-temperature coagulation that minimizes tissue damage. However, it has a higher risk of secondary bleeding compared to conventional tonsillectomy (17).

A study by Lowe D. et al. found that tonsillectomies performed with diathermy (an electric cutting tool) for removal and bleeding control had higher rates of bleeding compared to those using traditional cold steel instruments and ties to stop bleeding (18). The secondary hemorrhage rates in both of our groups were observed to be consistent with the data reported in the literature.

Preserving the tonsil capsule in the inferior pole during tonsillectomy, as described in the Tonsillectomy with Inferior Pole Capsule Preservation technique, has been shown to reduce postoperative pain and bleeding risk. This is due to the short distance between the tonsil capsule and the superior pharyngeal constrictor muscle, as well as the presence of important vessels supplying the tonsil in this area (19,20). In our study, there was no statistically significant difference in the risk of postoperative bleeding in the group where the tonsil capsule was preserved at the inferior pole. In a retrospective study conducted by Falz H and colleagues, the intraoperative and postoperative parameters of BiZact™ tonsillectomy were compared with cold steel dissection with bipolar hemostasis in adults. The study found that BiZact™ tonsillectomy offers advantages such as shorter operative time and reduced intraoperative bleeding. However, there was no significant difference in terms of post-hemorrhagic bleeding and pain between the two techniques (21).

The Ligasure group, which included BiZact tonsillectomy, performed simultaneous dissection and hemostasis. This technique offers advantages such as a clear surgical field and a shorter operation time, ultimately reducing patients' exposure to anesthesia (22). Our finding of a shorter operation time is consistent with the literature.

In a study conducted by Mao et al., the primary bleeding rate among 1,717 patients who underwent BiZact™ tonsillectomy was reported to be low. The secondary bleeding rate of 5.9% was found to be comparable to other techniques (23). In our series, the PIBT group demonstrated a secondary bleeding rate of 3.6%. When compared to the rates reported in the literature, this lower bleeding rate can be attributed to the intracapsular dissection performed at the inferior tonsillar pole.

A systematic review and meta-analysis evaluated the intraoperative outcomes and morbidity associated with BiZact™ tonsillectomy. A total of 12 studies involving 1,452 patients were analyzed, revealing that BiZact™ resulted in less intraoperative bleeding, lower postoperative pain scores, and shorter recovery times compared to traditional techniques, including bipolar electrocautery, coblation, and cold dissection (24). In our study, intraoperative blood loss was significantly lower in the PIBT group. This finding can be attributed to the design of the BiZact™ device, which allows simultaneous dissection and hemostasis. Additionally, the low tissue temperature during hemostasis minimizes tissue necrosis at the surgical site, thereby reducing postoperative pain and promoting a faster return to a normal diet.
Tierney et al. conducted a randomized controlled trial comparing the outcomes of extracapsular tonsillectomy performed using Coblation and BiZact™ in adult patients. Although the rates of secondary bleeding were similar between the two techniques, BiZact™ demonstrated superior results in terms of shorter operative time and reduced postoperative pain. The study concluded that BiZact™ is an effective and safe alternative for adult tonsillectomy (25).

Another study compared the intraoperative and postoperative outcomes of BiZact™ and Bipolar Electrocautery Tonsillectomy techniques in pediatric patients. Tonsillectomy performed with BiZact™ was associated with a shorter operative time, reduced bleeding (16 ml), lower postoperative pain, and faster recovery compared to the bipolar electrocautery technique (26). In contrast to our study, the intraoperative blood loss was lower (11 ml) in our PIBT group. Although the irrigation fluid used was included in the calculation of blood loss, the influence of bodily fluids should also be taken into account. Furthermore, in our PIBT group, intracapsular dissection at the inferior pole may have contributed to reduced intraoperative bleeding compared to total extracapsular dissection.

In the PIBT group, we hypothesized that intracapsular dissection at the inferior pole of the tonsil would reduce postoperative pain and secondary bleeding rates. Comparing this technique with the other group, it is too early to conclude whether the quicker return to normal activities and significantly lower postoperative pain are attributable to this specific technique or to BiZact™ tonsillectomy itself. Future studies comparing intracapsular and extracapsular BiZact™ tonsillectomy outcomes will be necessary to address this question.

Despite its single-center nature, limited case number, and lack of long-term follow-up, our study prospectively evaluated two different groups, providing unique insights. Future research should aim for an adequate number of patients and a double-blind, randomized prospective design comparing different techniques.

Conclusion

Partial Intracapsular Bizact™ Tonsillectomy (PIBT) demonstrates significant clinical advantages over bipolar electrocautery tonsillectomy (BET) in pediatric patients. The PIBT technique achieved a shorter operative time, reduced intraoperative blood loss, and lower postoperative pain scores. These findings position PIBT as a preferred surgical approach for pediatric tonsillectomy, balancing efficacy, safety, and enhanced patient outcomes.

Acknowledgements

We extend our heartfelt gratitude to all participants and their families for dedicating their valuable time to this research program.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

A Fatal Complication in Intensive Care Units: Tracheoesophageal Fistulas

Yoğun Bakım Ünitesinde Ölümcül Bir Komplikasyon: Trakea-özofageal Fistül

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1572393
Geliş Tarihi | Received: 23.10.2024
Kabul Tarihi | Accepted: 26.02.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Şahin F, Kocayiğit H. A Fatal Complication in Intensive Care Units: Tracheoesophageal Fistula. Hitit Medical Journal 2025;7(2):181-187. https://doi.org/10.52827/hititmedj.1572393

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 24/05/2024 tarihinde Sakarya Üniversitesi Girişimsel Olmayan Etik Kurulu'ndan onay alınmıştır. Karar no: E-71522473-050.04-364001-139.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: FŞ, HK Tasarım: FŞ, HK Veri Toplama/Veri İşleme: FŞ Veri Analizi: FŞ, HK Makalenin Hazırlanması: FŞ, HK
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Sakarya University Faculty of Medicine Non-Interventional Research Ethics Committee on 24/05/2024. Decision no: E-71522473-050.04-364001-139.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: FŞ, HK Design: FŞ, HK Data Collection/Data Processing: FŞ Data Analysis: FŞ, HK Manuscript Preparation: FŞ, HK
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

A Fatal Complication in Intensive Care Units: Tracheoesophageal Fistulasis

ABSTRACT

Objective: Tracheoesophageal fistula is an abnormal connection between the posterior wall of the trachea and the anterior wall of the adjacent esophagus. Its etiology includes trauma related to endotracheal cuff, damage to the posterior wall during tracheostomy procedure, poor health status, respiratory infections, and steroid treatments. This study aims to investigate the demographic characteristics of patients with tracheoesophageal fistula, the timing of tracheostomy, duration of intubation, and the characteristics of microorganisms isolated from these patients.

Material and Method: The study included patients who developed tracheoesophageal fistula while receiving mechanical ventilation through orotracheal intubation or tracheostomy in the intensive care unit. Data collected included age, sex, reason for intensive care unit admission, day of tracheoesophageal fistula occurrence, tracheostomy status, mortality, medication usage, and microorganisms isolated from tracheal aspirate cultures.

Results: Thirty patients were included. The mean duration of mechanical ventilation before tracheoesophageal fistula development was 41.3 days, with 27 patients (90%) having tracheostomies. The average day of tracheostomy application was 21.7 days. The mean duration of mechanical ventilation was 68.5 days, and the average intensive care unit stay was 71.2 days. Of 65 deep tracheal aspirate cultures samples, 24 patients (80%) exhibited growth, predominantly Klebsiella pneumoniae (26.1%). Mortality occurred in 86.7% of patients, while 13.3% were discharged in healty.

Conclusion: In conclusion, tracheoesophageal fistula, which can be observed in intensive care units, is a highly mortal complication. The majority of these patients exhibited prolonged mechanical ventilation, microorganism growth in tracheal aspirate cultures, steroid use, hypoalbuminemia, use of neuromuscular agents, and high SAPS III and APACHE II scores.

Keywords: Intensive care unit, mechanic ventilation, tracheostomy, Tracheoesophageal Fistula..

ÖZET

Amaç: Trakea-özofageal fistül, trakeanın posterior duvarı ile komşu özofagusun anterior duvarı arasında gelişen anormal yoldur ve etiyolojisinde endotrakeal balon ilişkili travma, trakeostomi uygulaması sırasında arka duvar hasarı, kötü genel sağlık durumu, solunum yolu enfeksiyonları ve steroid tedavileri bildirilmiştir. Bizim bu çalışmadaki amacımız trakea-özofageal fistül gelişen hastaların demografik özelliklerini, trakeostomi uygulanma zamanını ve hastaların trakeal aspirasyon kültürlerinde üreyen mikroorganizmaların özelliklerini araştırmaktır.

Gereç ve Yöntem: Çalışmaya herhangi bir sebeple yoğun bakım ünitesinde orotrakeal entübasyon tüpü veya trakeostomi kanülü aracılığıyla mekanik ventilasyon ile takip edilirken trakea-özofageal fistül gelişen tüm hastalar dahil edilmiştir. Hastaların yaş, cinsiyet, yoğun bakım ünitesi kabul nedeni, trakea-özofageal fistülün kaçıncı günde gerçekleştiği, trakeostomi uygulaması, mortalite durumu, ilaç kullanımı, trakeal aspirasyon kültüründe üreyen mikroorganizmalar kaydedildi.

Bulgular: Toplam 30 hasta çalışmaya dahil edildi. Hastalarda trakea-özofageal fistül geliştiğinde mekanik ventilasyon günü 41,3 gün idi. Trakea-özofageal fistül geliştiğinde 27 hasta (%90) trakeostomili iken 3 hastada (%10) endotrakeal tüp mevcuttu. Trakeostomi uygulanma günü ise ortalama 21,7 gün idi. Hastaların mekanik ventilasyon süresi ortalama 68,5 gün iken yoğun bakım ünitesi yatış gün sayısı 71,2 gündü. Hastalardan toplam 65 derin trakeal aspirasyon kültürü örneği alındı. 24 hastada (%80) trakea-özofageal fistül gelişimi öncesinde trakeal aspirasyon kültüründe üreme varken en sık üreme %26,1 ile klebsiella pneumoniae idi. Hastaların %86,7'sinde mortalite gelişirken %13,3 hastanın sıhhat ile taburcu olduğu saptandı.

Sonuç: Sonuç olarak yoğun bakım ünitelerinde gelişen trakea-özofageal fistül oldukça mortal seyreden bir komplikasyon olup, bu hastaların büyük çoğunluğunda uzamış mekanik ventilasyon, trakeal aspirasyon kültüründe üreme, steroid kullanımı, hipoalbuminemi, nöromüsküler ilaç kullanımı, yüksek SAPS 3 ve APACHE II skorları olduğunu görmekteyiz.

Anahtar Sözcükler: Mekanik ventilasyon, trakea-özofageal fistül, trakeostomi, oğun bakım ünitesi.

Giriş

Trakea-özofageal fistül (TÖF), trakeanın posterior duvarı ile komşu özofagusun anterior duvarı arasında bir veya daha fazla noktada ortaya çıkan anormal bir yoldur. TÖF oluşumunun çeşitli sebepleri vardır. Literatürde TÖF gelişen hastaların %75'inden fazlasının, uzun süreli MV'a maruz kalan hastalarda endotrakeal balon ilişkili travmanın sonucu olduğu bildirilmiştir (1). TÖF etiyolojisinde diğer risk faktörleri arasında trakeostomi uygulaması sırasında arka duvar hasarı, kötü genel sağlık durumu, solunum yolu enfeksiyonları ve steroid tedavileri bildirilmiştir (1-3). Uzun süreli entübasyon veya trakeostomili takip sonrasında trakeal dokuda iskemi, trakea dokusunda skarlaşma ve stenoz da görülebilmektedir (4). Daha önce yapılan çalışmalarda TÖF gelişiminin MV başlamasından ortalama 43 gün içinde ortaya çıkabileceği ancak nadir de olsa kısa süreli entübasyonlarda da görülebileceği bildirilmiştir (5,6). Bu kısa bir sürede TÖF oluşumuna, genellikle cerrahi faktörler ve travmatik yaralanmalar neden olabilmektedir (7).

TÖF oluşumu çok eski yıllardan beri iyi bilinen bir komplikasyondur ve gelişen teknoloji ile birlikte birçok yenilik TÖF gelişimini azaltmayı ve tedavi etmeyi amaçlamaktadır. Fakat artan nüfus ve insan ömrünün uzamasıyla birlikte YBÜ hasta sayısındaki artışa paralel olarak MV ile takip edilen hasta sayısı ve trakeostomi uygulanan hasta sayısı artmaktadır. Bunun sonucunda TÖF günümüzde hala YBÜ'lerinde önemli bir komplikasyon olarak karşımıza çıkmaya devam etmektedir. Bizim bu çalışmadaki amacımız YBÜ'de MV tedavisi uygulanırken TÖF gelişen hastaların demografik özelliklerini, trakeostomi uygulanma zamanı, yoğun bakım ünitesi ve hastane yatış gün sayıları, mortalite oranları ve hastalarda üreyen mikroorganizmaların özelliklerini araştırmaktır.

Gereç ve Yöntemler

Bu çalışma, Sakarya Üniversitesi Girişimsel Olmayan Etik Kurulu tarafından (E-71522473-050.04-364001-139) onaylanarak Helsinki Bildirgesi'ne uygun bir şekilde retrospektif olarak üçüncü basamak anestezi YBÜ'nde gerçekleştirilmiştir. Ocak 2016 ile Mayıs 2024 arasında üçüncü basamak anestezi YBÜ'de takip edilen tüm hastalar taranarak hasta bilgileri elektronik hasta bilgi sisteminden alındı. Çalışmaya herhangi bir sebeple anestezi YBÜ'nde orotrekeal entübasyon tüpü veya trakeostomi kanülü aracılığıyla MV ile takip edilen tüm hastalar hasta grubu ayırt edilmeksizin dahil edildi. Supraglottik hava yolu aracılığıyla MV tedavisi uygulanan ve MV uygulanmayan tüm hastalar çalışma dışında bırakıldı. YBÜ tedavisi sürecinde orotrekeal entübasyon tüpü veya trakeostomi kanülü aracılığıyla MV uygulanan ve takibi yapılan toplam 32 hastada TÖF geliştiği tespit edilirken 30 hasta çalışmaya dahil edildi. 2 hasta verilerindeki eksiklikler ve tutarsızlıklardan dolayı çalışma dışında bırakıldı. Hastaların yaş, cinsiyet, YBÜ kabul nedenleri kaydedildi. YBÜ yatış nedenleri; cerrahi sonrası uzamış MV hastaları, travmatik beyin hasarı hastaları, resüsitasyon sonrası bakım hastaları, kardiyak nedenli hastalar ve pulmoner nedenli hastalar olarak gruplandırıldı. TÖF gelişiminin YBÜ yatışının kaçıncı gününde gerçekleştiği, trakeostomi uygulanma durumu, trakeostomi uygulandı ise kaç gün sonrasında TÖF geliştiği, hasta eksitus oldu ise TÖF gelişiminden kaç gün sonra geliştiği kaydedildi. Sedo-analjezide kullanılan ilaçlar midazolam, propofol, fentanil, deksmetotimidin olarak kaydedildi. TÖF öncesi yeniden entübasyon ve nöromuskuler bloke edici ajan kullanımı kaydedildi. Nöromuskuler bloke edici ajan olarak rokuronyum bromür kullanılmıştı. TÖF öncesi steroid ilaç kullanımı kaydedildi. Kullanılan inotroplar ilaçlar dopamin, dobutamin ve noradrenalin olarak kaydedildi. Hastaların yatışı sırasında SAPS 3 skoru, APACHE II, beklenen ölüm oranları kaydedildi. TÖF gelişimi öncesinde trakeal aspirasyon kültürü (TAK)'nde üreyen mikroorganizmalar kaydedildi.

İstatistiksel Analiz

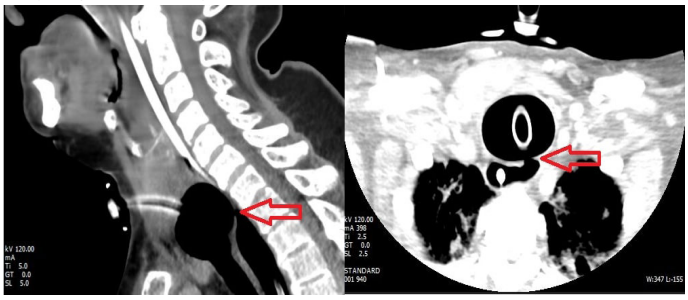
Verilerin istatistiksel analizinde SPSS 20 paket programı kullanıldı. Niteliksel veriler sayı ve yüzde olarak, nicel veriler ortalama ± standart sapma olarak belirtildi.

Bulgular

Toplam 30 hasta çalışmaya dahil edildi. Bu hastalarda TÖF tanısı fiberoptik bronkoskopi ve boyun bilgisayarlı tomografi görüntülemesi ile göğüs cerrahisi konsültasyonu sonrasında konuldu (Şekil I). Hastaların yaş ortalaması 65,8 idi. Hastaların %53,3'ü erkek hasta iken %46,7'si kadın hasta idi. En sık yatış nedeni %30 ile başarılı kardiyopulmoner resüsitasyon sonrası bakım, %26,7 travmatik beyin

hasarı, %16,7 ile cerrahi sonrası uzamış entübasyon idi. Sedasyon için en sık kullanılan ilaç %96,7 ile midazolam, %90 ile fentanil, %60 ile propofol idi. Hastaların %76,7'sinde hipoalbuminemi nedeniyle human albümin kullanılmıştı. Hastaların %80'ninde nöromuskuler ilaç kullanımı mevcuttu. 25 hasta steroid kullanırken hastaların %56,7'sinde metilprednizolon, %26,7'sinde ise deksametazon kullanımı mevcuttu. Hastaların %80'ininde inotrop kullanımı mevcut olup en sık kullanılan ilaç %56,7 ile noradrenalin idi. Hastaların YBÜ'ne yatışında ortalama SAPS 3 skoru 80,2, APACHE II skoru ortalaması 28,4, beklenen ölüm oranı ise 64,2 idi (Tablo I).

Şekil I. Trakea-Özofageal Fistül Gelişen Hastanın Boyun Bilgisayarlı Tomografi Görüntüsü



Tablo I. Demografik Veriler, İlaçlar ve Skorlamalar

	Tüm hastalar, n=30
Yaş	65,8 ± 15,6
Cinsiyet, n (%)	
Kadın	14 (46,7)
Erkek	16 (53,3)
YBÜ kabul nedeni, n (%)	
Resüsitasyon sonrası bakım hastası	9 (30)
Travmatik beyin hasarı	8 (26,7)
Cerrahi sonrası uzamış MV	5 (16,7)
Pulmoner hastalık	4 (13,3)
Kardiyak hastalık	4 (13,3)
Sedasyon, analjezik ilaçlar, n (%)	
Midazolam	29 (96,7)
Propofol	18 (60)
Fentanil	27 (90)
Deksmedetomidin	5 (16,7)
Kas gevşetici ilaç, n (%)	24 (80)
Steroidler, n (%)	
Yok	5 (16,7)
Metilprednizolon	17 (56,7)
Deksametazon	8 (26,7)
İnotrop, n (%)	
Yok	6 (20)
Norepinefrin	17 (56,7)
Dopamin	10 (33,3)
Dobutamin	4 (13,3)
Yeniden entübasyon, n (%)	15 (50)
SAPS 3 skoru	80,2 ± 7,5
APACHE II skoru	28,4 ± 4,5
Beklenen ölüm oranı	64,2 ± 14,1

Hastalardan toplam 65 TAK örneği alındı. 24 hastada (%80) TÖF gelişimi öncesinde TAK'nde üreme saptandı. Alınan örneklerde en sık görülen mikroorganizma %26,2 ile *klebsiella pneumoniae*, %21,6 ile *pseudomonas aeruginosa*, % 10,8 ile ise *escherichia coli* idi (Tablo II). TAK'nde üreme olan ve üreme olmayan hastalar karşılaştırıldığında mortalite ve TÖF gelişim günü arasında anlamlı fark bulunamadı (sırasıyla; *p=0,169, p=0,295*).

Tablo II. Trakeal Aspirat Kültüründe Üreyen Mikroorganizmalar

	Toplam trakeal aspirat kültür sayısı, n=65
Klebsiella pneumoniae, n (%)	17 (26,2)
Pseudomonas aeruginosa, n (%)	14 (21,5)
Escherichia coli, n (%)	7 (10,8)
Staphylococcus aureus, n (%)	6 (9,2)
Acinetobacter baumannii, n (%)	5 (7, 7)
Cornybacterium striatum, n (%)	4 (6,2)
Staphylococcus epidermidis, n (%)	3 (4,6)
Enterobacter cloacae, n (%)	2 (3,1)
Moraxella nonliquefaciens, n (%)	1 (1,5)
Stenotrophomonas maltophilia, n (%)	1 (1,5)
Moraxella catarrhalis, n (%)	1 (1,5)
Delftia acidovorans, n (%)	1 (1,5)
Proteus mirabilis, n (%)	1 (1,5)
Candida spp., n (%)	1 (1,5)
Serratia marcescens, n (%)	1 (1,5)

TÖF geliştiğinde MV altında tedavi süresi ortalama 41,3 gün idi. TÖF tespit edildiğinde 27 hasta (%90) trakeostomili vaziyette iken 3 hastada (% 10) endotrakeal tüp mevcuttu. Hastaların % 76,7'sına perkütan dilatosyonel teknikle trakeostomi uygulanırken, % 13,3 hastaya cerrahi yöntemle trakeostomi uygulanmıştı. Trakeostomi uygulanma günü ise ortalama 21,7±9,6 gün idi. TÖF gelişimi sonrasında hastaların % 16,7'sine tedavi edici müdahale uygulanmıştı. Bu hastalardan iki hastaya primer trakeal onarım, 2 hastaya trakeal stent, 1 hastaya ise özofagus stenti uygulanmıştı. Bu hastalardan %60'ı sıhhatle taburcu olurken %40'ında eksitus gerçekleşti. Hastaların MV süresi ortalama 68,5±43 gün, YBÜ yatışı ise ortalama 71,2±43 gündü. TÖF gelişen tüm hastalar değerlendirildiğinde hastaların %86,7'ında mortalite gelişirken hastaların %13,3'nün sıhhat ile taburcu olduğu saptandı (Tablo III). Cerrahi yöntem trakeostomi ve perkütan dilatasyonel yöntemle trakeostomi uygulanan hastalar karşılaştırıldığında ise mortalite arasında anlamlı fark bulunamamıştır

(*p=0,377*).

Tablo III. Çalışmanın Sonuçlar

TÖF gelişim günü	41.7 ± 27,3
Trakeostomi uygulanma günü	21,7 ± 9,6
Trakeostomi tekniği, n (%) Perkütan dilatasyonel trakeostomi Cerrahi trakeostomi	 23 (76,7) 4 (13,3)
Cerrahi tedavi, n (%)	5 (16,7)
Mekanik ventilasyon gün sayısı	68,5 ± 43
YBÜ yatış gün sayısı	71,2 ± 43
Mevcut durum, n (%) Taburculuk Eksitus	 4 (13,3) 26 (86,7)

TÖF: Trakea-özofageal fistül, YBÜ: Yoğun bakım ünitesi

Tartışma

Entübasyon tüpü veya trakeostomi kanülü aracılığıyla uzamış MV tedavisi TÖF oluşumunda en önemli sebeplerden biridir (1). Bizim çalışmamızda YBÜ'de MV altında uzun süredir takip ettiğimiz hastalardan TÖF gelişenlerin büyük çoğunluğunda trakeostomi sonrasında TÖF geliştiği ve bu hastalarda mortalitenin yüksek olduğu sonucuna varılmıştır.

Posterior membranöz duvarda genellikle sert bir nazogastrik tüpe karşı fazla şişirilmiş endotrakeal tüp balonundan kaynaklanan basınç iskemik nekroza yol açar ve bu durum özofagus duvarını etkiler. Sonuç olarak trakea ve özefagus arasında anormal bir yol oluşur. TÖF gelişimine sebep olan faktörler; MV sırasında yüksek hava yolu basıncı, endotrakeal tüpün hareketliliği, uzun süreli entübasyon, steroid tedavisi, kötü beslenme durumu, kronik hipoksi, uzun süreli hipotansiyon atakları, kronik anemi, sepsis, gastroözofageal reflü, kadın cinsiyet ve yaşlılıktır (2,3). Entübasyon sonrası gelişen fistülün lokalizasyonu genellikle trakeanın üst kısmında olup, endotrakeal tüp balonunun olduğu bölgede görülür. Birçok durumda meydana gelen fistül oluşumu, aynı iskemik nekroz mekanizması tarafından meydana gelen trakea çevresindeki tahribat ile ilişkilidir (8). Trakea yaralanmaları ve erozyonları, MV uygulanan hastaların yaklaşık %0,3 ile %3'ü arasında görülebilmektedir (9). Trakeada balonla ilişkili yaralanmalara bağlı TÖF'ler ise genellikle 4 hafta içinde semptomatik hale gelir (1). Marzelle ve ark. TÖF gelişen hastalarda ortalama yaşın 43 olduğunu bildirmişlerdir. Bu hastalarda TÖF gelişiminin %62,9'unda trakeostomili vaziyette, %29,6'sında entübasyon tüpüne bağlı vaziyette, %7,4'ünün ise trakeostomi uygulanırken yaralanma sonucunda oluştuğu bildirilmiştir (5). Toplam 32 hastanın değerlendirildiği başka bir çalışma da ise TÖF gelişen hastaların yaş ortalamasının 51 olduğu bildirilmiştir. Bu hastalarda TÖF, MV uygulamasının 30. gününde gelişirken hastaların %62,5'inde trakeostomili iken TÖF geliştiği gösterilmiştir (10). Bizim çalışmamızda da TÖF gelişen hastalarda yaş ortalaması 65,8 yaş iken MV tedavisi başladıktan 41,7 gün sonra TÖF gelişmişti. Bu hastaların %90'ında trakeostomili vaziyette TÖF geliştiği saptanmıştır. Diğer çalışmalardan farklı olarak, TÖF gelişen hastaların büyük kısmının trakeostomili hastalardan oluştuğunu gözlemledik fakat bu durum erken trakeostominin uygulanmasına engel bir durum oluşturmamaktadır. Tam aksine ekstübasyona uygun olmayan hastalarda trakeostominin olabildiğince erken dönemde yapıldığını göstermektedir.

Trakeostomi sonrası ortaya çıkan TÖF, trakeostomi yapılan hastaların %1'inden daha azında görülen nadir bir komplikasyondur (11). 1989 yılında Amerikan Göğüs Hastalıkları Uzmanları Koleji yapay hava yolları konsensüs konferansında, 21 günden uzun süre MV tedavisi alan hastalarda trakeostomi uygulamasının değerlendirilmesini önermiştir (12). Daha güncel bazı çalışmalarda ise entübasyon sonrası 7 ile 15 gün arasında trakeostomi uygulanması gerekliliği vurgulanmıştır (13-15). Bizim çalışmamızdaki hastalarda ortalama trakeostomi açılma günü 21,7 gün iken bu hastalardan %16,7'sinde 14 gün altında, %56,67'sinde ise 14-21 gün arasında trakeostomi uygulandığı görülmüştür. Rutin YBÜ prosedürümüzde trakeostomi uygulamaları YBÜ yatışın ilk 7 ile 14 günü arasında gerçekleştirilmektedir. Trakeostomi uygulanmasını geciktiren en önemli neden, anestezi YBÜ'ne dış YBÜ'lerinden devralınan hastalar iken, ikinci en önemli neden hastaların spontan solunumları geri kazanım ihtimalinden dolayı trakeostomi kararının geç verilebilmesi idi. Aynı zamanda hastaların %50'sinde kas gevşetici kullanımı vardı. Kas gevşetici kullanım nedeni ise başarısız ekstübasyon denemeleri sonrasında tekrarlayan entübasyon uygulamalarıydı ve bu hastalarda buna bağlı olarak trakeostomi uygulama gününde gecikmeler olduğu saptandı.

TÖF gelişen hastalarda tedavi edici müdahale uygulanmadan spontan iyileşme ihtimali çok düşüktür. Bu işlemler direk cerrahi veya son zamanlarda

kullanımı yaygınlaşan özofagus ve/veya trakeal stentleme ile fistülün kapatılmasıdır. Bu yöntemler sayesinde fistül gelişen alandan sıvı ya da gaz kaçağı engellenmektedir (16). Wang ve ark. 344 hasta üzerinde yaptıkları çalışmada stent tedavisi uygulanan hastaların konservatif tedavi uyguladıkları hastalara göre anlamlı düzeyde iyileşme gösterdiğini bildirilmiştir (17). Macchiarini ve ark. 32 hastaya cerrahi tedavi uygulamış ve bu hastaların sadece %3'ünde mortalite geliştiğini bildirmişlerdir (10). Mathisen ve ark. ise cerrahi yapılan 38 hastada %10,5 mortalite geliştiğini bildirirken (18), Foroulis ve ark. cerrahi yaptıkları hastalarda %23,1 oranında mortalite geliştiğini bildirmişlerdir (19). Bizim hastalarımızda ise TÖF gelişen hastaların %86,7'sinde mortalite gelişmiştir. Bu hastaların hepsi göğüs cerrahisine konsülte edilirken sadece 5 hasta tedavi edici müdahalelere uygun görülmüştür. Tedavi edici müdahale uygulanan hastalardan 2 hasta postoperatif dönemde sepsis nedeniyle exitus olurken %60 hastada iyileşme gerçekleşmiştir. Literatür bilgilerinden anlaşılacağı üzere trakea ve özefagus arasındaki ilişki kesilmediği sürece iyileşme olmayacağından dolayı ve bizim hasta grubumuzda TÖF tedavisi için onarıcı müdahale uygulanan hasta sayısı az olması sebebiyle TÖF gelişen hastalardaki mortalite oranının çok yüksek olduğunu düşünüyoruz. Aynı zamanda bu hastalarda SAPS 3, APACHE II skorları ve beklenen mortalite oranlarının da yüksek olduğunu görmekteyiz.

Bağışıklığın baskılanması, kortikosteroid kullanımı gibi enfeksiyon sıklığını artıran sebepler veya daha önce solunum yolu enfeksiyonları olması TÖF gelişimi için risk faktörleri olarak kabul edilmektedir (20,21). Vedhapoodi ve ark. gerçekleştirdikleri çalışmada trakeostomi uygulandığında trakeal örnek alınan hastalarda 1. gün %87 hastada, 8. gün ise %93 hastada mikrobiyolojik üreme olduğu saptamıştır. En sık üreyen bakterinin *pseudomonas aeruginosa* olduğunu, trekeostomi süresi uzadıkça antibiyotik duyarlılığının azaldığını ve bu durumun hastane kökenli enfeksiyon gelişimi ile ilişkili olduğunu bildirmişlerdir (22). Lepainteur ve ark. ise 77 trakeostomili hastadaki trakeal kolonizasyonu inceledikleri çalışmada hastaların %90'ında patojenik bakterilerde üreme geliştiğini, %41 *pseudomonas aeruginosa*, %44 *staphylococcus aureus*, %38 *serratia marcescens* üremesi olduğunu bildirilmiştir (23). Scibik ve ark. trakeostomili hastalardan aldıkları örneklerin bakteri kültürlerinde % 35.5 *staphlycocus aureus*, %23.8 *klebsiella pneumonia* ürediğini tespit etmişlerdir (24). Teshon ve ark. yakın tarihli bir çalışmada *candida albicans* ve *actinomyces* üremelerinin TÖF gelişimine neden olduğunu bildirmişlerdir (25). Macchiarini ve ark. ise önceki hava yolu enfeksiyonlarının TÖF gelişiminde etken olduğunu bildirmişlerdir (10). Bu hastaların cerrahi tedavilerinin yanında antibiyotik kullanımı da tedavilerinde oldukça önemlidir (16). Bizim çalışmamızda hastaların %80'ninde steroid kullanımı mevcuttu. Bununla birlikte TÖF gelişmeden önce 24 hastanın (%80) TAK'nde mikrobiyolojik üreme varken, bu hastalardan toplam 65 TAK'ü alındığı tespit edildi. En sık üreyen mikroorganizmalar %26,15 ile *klebsiella pneumonia* ve %21,54 ile ***pseudomanas aeruginosa*** idi. Literatürden farklı olarak TÖF öncesi en sık üreyen mikroorganizma *klebsiella pneumonia*, ikinci en sık üreyen mikroorganizma ise *pseudomans auregenosa* olarak bulunmuştur. Bu farklılığının nedeninin hastanelerin YBÜ'lerinde üreyen mikroorganizmaların farklılık göstermesinden kaynaklı olduğunu düşünmekteyiz.

Sonuç olarak YBÜ'lerinde MV uygulanan hastalarda görülebilen TÖF oldukça mortal seyreden bir komplikasyon olup, TÖF gelişen hastaların büyük çoğunluğunda uzamış MV, TAK'nde üreme, steroid kullanımı, hipoalbuminemi, nöromuskuler ilaç kullanımı, yüksek SAPS 3 ve APACHE II skorları olduğunu görmekteyiz. Her ne kadar tedavi edici müdahaleler ile bu komplikasyonlara bağlı mortalite oranları azaltılsa da bununla birlikte TÖF gelişimine zemin hazırlayan sebeplerin engellenmesinin MV tedavisi alan hastalarda bu komplikasyona bağlı mortalite oranlarını azaltabileceği düşüncesindeyiz.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Contribution to Diagnosis of Microflow Imaging in Breast Lesions

Meme Lezyonlarında Mikroakım Görüntülemenin Tanıya Katkısı

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1580731
Geliş Tarihi | Received: 06.11.2024
Kabul Tarihi | Accepted: 04.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Sarman S, Beyhan M. Contribution to Diagnosis of Microflow Imaging in Breast Lesions. Hitit Medical Journal 2025;7(2):188-197. https://doi.org/10.52827/hititmedj.1580731

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 23/09/2021 tarihinde Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 21-KAEK-203.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: MB Tasarım: SS, MB Veri Toplama/Veri İşleme: SS, MB Veri Analizi: SS, MB Makalenin Hazırlanması: SS, MB.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma Tokat Gaziosmanpaşa Üniversitesi Bilimsel Araştırma Projelerinden 2020/71 no'lu "Radyoloji Anabilim Dalı Ultrasonografi Ünitesine Üst Düzey Dopplerli Ultrasonografi Alımı" projesi sonucu alınan cihazda yapılmıştır.

Teşekkür: Yazarlar, bu makalenin istatistiksel analiz değerlendirmeleri için Dr. Osman Demir'e (MD, Tokat Gaziosmanpaşa Üniversitesi, Tıp Fakültesi, Biyoistatistik AD) teşekkürlerini sunarlar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Tokat Gaziosmanpaşa University Faculty of Medicine Research Ethics Committee on 23/09/2021. Decision no: 21-KAEK-203
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MB Design: SS, MB Data Collection/Data Processing: SS, MB Data Analysis: SS, MB Manuscript Preparation: SS, MB.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: This study was conducted on the device purchased as a result of the project titled "Acquisition of High-Level Doppler Ultrasonography to the Ultrasonography Unit of the Radiology Department" from Tokat Gaziosmanpaşa University Scientific Research Projects numbered 2020/71.

Acknowledgement: The authors would like to thank Dr. Osman Demir (MD, Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Biostatistics) for his statistical analysis evaluations of this article.

The Contribution of Microflow Imaging to Diagnosis in Breast Lesions

ABSTRACT

Objective: In recent years, the cancer detection rate in breast biopsies varies between 10-31%. Appropriate classification is required to prevent unnecessary biopsies in breast lesions. The aim of our study is to investigate the contribution of microflow imaging to the diagnosis of benign and malignant breast lesions.

Material and Method: After local ethics committee approval, 109 lesions of 104 patients older than 18 years were prospectively included in the study. B-mode ultrasonography, color Doppler ultrasonography, power Doppler ultrasonography and microflow imaging were performed on all patients. B-mode ultrasonography findings were classified according to the BI-RADS category, color Doppler ultrasonography, power Doppler ultrasonography and microflow imaging findings were classified according to the ADLER method. Sensitivity, specificity, negative predictive values and positive predictive values of Doppler ultrasonographic methods were calculated.

Results: Histopathologically, 68 of the breast lesions were benign and 41 were malignant. There was a statistically significant difference between benign and malignant lesions on power Doppler ultrasonography and microflow imaging. Negative predictive values were higher than positive predictive values on Doppler ultrasonography examination methods. Doppler ultrasonography examinations were found to be more likely to identify malignant lesions.

Conclusion: Vascular findings on power Doppler ultrasonography and microflow imaging can be used as criteria to differentiate benign from malignant breast lesions. Thus, benign breast lesions can be monitored and unnecessary biopsies can be prevented.

Keywords: Breast cancer, color Doppler ultrasonography, microflow imaging, power Doppler ultrasonography.

ÖZET

Amaç: Son yıllarda yapılan meme biyopsilerinde kanser saptama oranı %10-31 arasında değişmektedir. Meme lezyonlarında gereksiz biyopsilerin önlenmesi için uygun sınıflandırma gerekmektedir. Çalışmamızın amacı benign ve malign meme lezyonlarında mikroakım görüntülemenin tanıya katkısını araştırmaktır.

Gereç ve Yöntem: Çalışmaya yerel etik kurul onayı alındıktan sonra prospektif olarak 18 yaşından büyük 104 hastanın 109 lezyonu dahil edildi. Hastaların hepsine B-mod ultrasonografi, renkli Doppler ultrasonografi, power Doppler ultrasonografi ve mikroakım görüntüleme yapıldı. B-mod ultrasonografi bulguları BI-RADS kategorisine göre, renkli Doppler ultrasonografi, power Doppler ultrasonografi ve mikroakım görüntüleme bulguları ise ADLER metoduna göre sınıflandırıldı. Doppler ultrasonografik yöntemlerin duyarlılık, özgüllük, negatif prediktif değerleri ve pozitif prediktif değerleri hesaplandı.

Bulgular: Toplam 30 hasta çalışmaya dahil edildi. Hastalarda trakea-özofageal fistül geliştiğinde mekanik ventilasyonHistopatolojik olarak meme lezyonlarının 68'i benign, 41'i maligndi. Power Doppler ultrasonografi ve mikroakım görüntülemede benign ve malign lezyonlar arasında istatistiksel olarak anlamlı farklılık mevcuttu. Doppler ultrasonografi inceleme yöntemlerinde negatif prediktif değerler pozitif prediktif değerlerden daha yüksekti. Doppler ultrasonografi incelemelerinin malign lezyonları tanımlama olasılığı daha yüksek bulundu.

Sonuç: Power Doppler ultrasonografi ve mikroakım görüntülemelerdeki vasküler bulgular benign ve malign meme lezyonlarının ayrımında bir kriter olarak kullanılabilir. Bu sayede benign meme lezyonları takip edilerek gereksiz biyopsiler önlenebilir.

Anahtar Sözcükler: Meme kanseri, mikroakım görüntüleme, renkli Doppler ultrasonografi, power Doppler ultrasonografi.

Introduction

Breast cancer, which is the most commonly diagnosed cancer in women, is the second most frequently diagnosed cancer worldwide after lung cancer without gender difference. However, due to its higher prevalence in developed countries and the high survival rates, it ranks fifth among cancer-related deaths (1).

Breast ultrasonography (US), a component of the examination of breast lesions, is more frequently used in diagnosis and screening than other screening techniques due to its low cost and the absence of ionizing radiation. It is widely used in patients with dense breast tissue, high-risk patients, young women (<30 years), the characterization of lesions that are not defined by mammography, the evaluation of palpable mass lesions, and for guiding interventional procedures (2, 3). At the present time, due to the importance of early diagnosis in breast cancer, the necessity not to miss early-stage lesions and the anxiety created by judicial processes, core needle biopsies or excisional biopsies are performed. This approach causes anxiety in the patient, prolongs the recovery period of the patient, and increases the treatment cost. The positivity rate for cancer in biopsies performed by the core needle biopsy approach varies between 10-31%. In other words, 70-90% of the biopsies are performed on benign lesions (4). Therefore, correct classification of breast lesions and avoiding unnecessary biopsies are essential.

Breast cancer requires microvascular angiogenesis for growth, spread, and survival of cancer cells. Tumor vascularity is important in such cases as tumor volume and cell cycle (5, 6). Based on angiogenesis, contrast-enhanced mammography is reported to be a promising technology for the diagnosis of breast cancer and determination of tumor size as a new method (7). However, the currently used color Doppler US (CDUS) and power Doppler US (PDUS) methods focus on the macrovascular structure of the tissue and do not provide sufficient information about small and slow-flowing microvascular structures due to artifacts and low vascular sensitivity (5, 6). Therefore, slow-flow imaging techniques, another new method developed recently, that does not involve radiation, are used. Advanced Doppler techniques are now commercially available in many high-end US systems [e.g., Superb Microvascular Imaging (SMI), Canon Medical; Slow Flow, Siemens Healthineers; Microvascular Imaging (MVI), GE Healthcare; MicroFlow Imaging (MFI), Philips; and MV-flow, Samsung] (8). In these techniques, smart wall filter systems separate low-velocity vascular flow signals originating from small vascular structures from motion signals originating from patient movement, pulse and respiration and signals from vascular structures are not suppressed. Therefore, microvessels (up to 0.1 mm) that cannot be visualized on conventional Doppler methods due to filter systems are visualized (5, 9, 10). The aim of our study is to evaluate whether the new method, microflow imaging (MFI), contributes to the differential diagnosis of benign and malignant breast lesions and to compare its diagnostic efficacy with other methods used to investigate vascularity, such as CDUS and PDUS.

Material and Method

Patients who applied to Tokat Gaziosmanpaşa University Hospital Interventional Radiology Clinic for breast biopsy between November 2021 and November 2023 were evaluated ultrasonography before biopsy. Patients with a history of previous cancer and surgery in the same breast and patients with a history of chemoradiotherapy were excluded. Our study was conducted prospectively with the approval of the local ethics committee (21-KAEK-203). The study adhered to the principles of the World Medical Association Declaration of Helsinki and good clinical practice guidelines, and informed consent forms were obtained from all patients. The study was performed with an 18-4 MHz probe on the Philips Epiq Elite (obtained as a result of the project "Acquisition of High-Level Doppler Ultrasonography to the Ultrasonography Unit of the Radiology Department" from our University Scientific Research Projects numbered 2020/71), and all lesions were examined by the same radiology research assistant doctor with at least 3 years of experience in B-mode US, CDUS, PDUS, and MFI.

B-mode US findings were evaluated according to the BI-RADS 2013 atlas, and the dimensions of the lesions, localization 1 (right, left), localization 2 (upper outer, upper inner, lower outer, lower inner,

and retroareolar), orientation features (parallel, nonparallel), echo pattern (hypoechoic, hyperechoic, complex, and anechoic), margin characteristics (well-defined, ill-defined, spiculated, and microlobulated) and, if any posterior acoustic features (acoustic shadowing, acoustic enhancement) were evaluated. While measuring the lesion dimensions, the longest single dimension was recorded.

For CDUS, PDUS, and MFI applications, probe pressure was not applied, and the device filter and gain settings were adjusted to optimal Doppler parameters. CDUS, PDUS, and MFI findings were classified according to the ADLER method, and all results were recorded. According to the ADLER method, in an imaging area, if no vascular structure was observed, it was classified as grade 0; if one or two small vessels (<1 mm) were observed, classified as grade 1; if one large vessel and/or more than two small vessels were visible, classified as grade 2; and if four or more vascular structures were detected, classified as grade 3 (11). Statistical analyses were first conducted using this classification, and then, ADLER grades 0 and 1 were named as Group 1 and ADLER grades 2 and 3 were named as Group 2. Statistical analyses were conducted for these two groups, which were coded as CDUS_2, PDUS_2, and MFI_2.

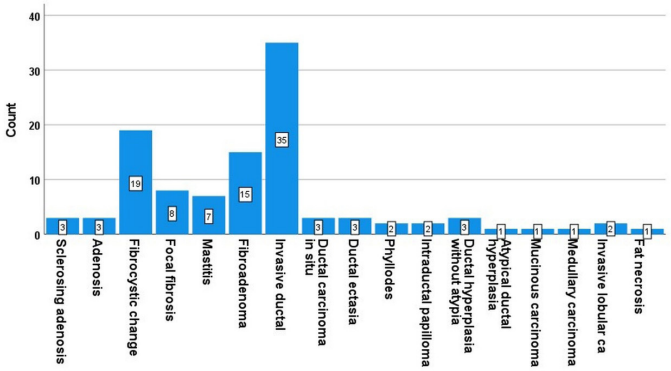
Statistical Analysis

Descriptive analyses were performed to provide information about the general characteristics of the study groups. Data for continuous variables are presented as mean ± standard deviation, and categorical variables as n (%). The normality of continuous variables were tested using the Shapiro-Wilk test. The significance of the difference in means between groups for quantitative variables was assessed using the Two-Sample t-test. To evaluate the relationship between qualitative variables, cross-tabulations and chi-square tests were used. Sensitivity, specificity, positive predictive, and negative predictive values were used for the variables associated with malignancy classification. ROC analysis was conducted to calculate the area under the curve. A *p-value* of less than *0.05* was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp).

Results

A total of 109 lesions from 104 female patients included in the study were evaluated and the age range of the patients ranged from 18 to 76 years. The mean age of patients with benign lesions was 41.3 ± 12.4, and the mean age of patients with malignant lesions was 54.8 ± 12.2, and the mean age in malignant lesions was statistically significantly higher (*p<0.001*). The mean size of malignant lesions was 22.7 mm, while the mean size of benign lesions was measured as 18.9 mm. The mean lesion size was higher in malignant lesions, but there was not a statistically significant difference (*p=0.123*). 68 benign (62.4%) and 41 malignant (37.6%) lesions were detected in the study. The graph describing the pathology results of the breast lesions in the study is shown in Figure I.

Figure I. Graph Describing Pathology Results of Breast Lesions



On the preoperative Doppler examination of the lesions; while CDUS, PDUS, MFI examinations were categorized as ADLER grade 0, 1, 2, 3 and comparison between benign and malignant lesions were made, there was no statistically significant difference (*p=0.067*; *p=0.074*; *p=0.079*, respectively). However, when ADLER 0 and ADLER 1 were classified as group 1, and ADLER 2 and ADLER 3 were classified as group 2, the lesions evaluated in group 1 with the PDUS examination were statistically significantly benign, while the lesions classified in group 2 were statistically significantly malignant (*p=0.013*). Similarly, with MFI imaging, the lesions evaluated as

group 1 were statistically significantly detected as benign (Figures II, III), while the lesions classified as group 2 were statistically significantly detected as malignant (*p=0.013*) (Table I) (Figure IV).

Table I. Distribution of Qualitative Variables on Color and Power Doppler Ultrasonography and Microflow Imaging According to Benign and Malignant Biopsy Group

Variables		Biopsy Pathology		X^2	*p*
		Benign	Malign		
		n (%)	n (%)		
CDUS_2	1	43 (63.2)	19 (46.3)	2.976	*0.084*
	2	25 (36.8)	22 (53.7)		
PDUS_2	1	40 (58.8)a	14 (34.1)b	6.231	*0.013*
	2	28 (41.2)a	27 (65.9)b		
MFI_2	1	31 (45.6)a	9 (22)b	6.152	*0.013*
	2	37 (54.4)a	32 (78)b		
CDUS	Adler 0	38 (55.9)	13 (31.7)	7.153	*0.067*
	Adler 1	5 (7.4)	6 (14.6)		
	Adler 2	18 (26.5)	13 (31.7)		
	Adler 3	7 (10.3)	9 (22)		
PDUS	Adler 0	35 (51.5)	11 (26.8)	6.922	*0.074*
	Adler 1	5 (7.4)	3 (7.3)		
	Adler 2	19 (27.9)	17 (41.5)		
	Adler 3	9 (13.2)	10 (24.4)		
MFI	Adler 0	15 (22.1)	4 (9.8)	6.794	*0.079*
	Adler 1	16 (23.5)	5 (12.2)		
	Adler 2	14 (20.6)	15 (36.6)		
	Adler 3	23 (33.8)	17 (41.5)		

Pearson chi-square test was used. (ab): The common letter in the row indicates statistical insignificance

CDUS: Color Doppler Ultrasonography; PDUS: Power Doppler Ultrasonography, MFI: Microflow imaging

The localization, border features, echo pattern, orientation and posterior acoustic features of the lesions were compared between malignant and benign groups by using Pearson chi-square test. As a result, no statistically significant difference was determined between malignant and benign groups with respect to localization 1, localization 2 and echo pattern (*p=0.145*; *p=0.738*; *p=0.286*, respectively). However, four lesions showing hyperechoic features were all reported as benign. When the border features were compared, well-defined border features were significantly higher in benign lesions than malignant lesions. Ill-defined and spiculated border feature were significantly higher in malignant lesions than benign lesions (*p<0.001*). Microlobulated border feature was present in four lesions and these lesions described as malignant. When the orientation features were compared, parallel orientation was significantly higher in benign lesions than in malignant lesions. The nonparallel orientation feature was significantly higher in malignant lesions than in benign lesions (*p<0.001*). In lesions which did not perform posterior acoustic features and showed posterior enhancement, there was no statistically significant difference between benign and malignant groups. However, all twelve lesions showing posterior enhancement were diagnosed as benign. The characteristic of posterior acoustic shadowing, on the other hand, was significantly higher in malignant lesions compared to benign lesions (*p<0.001*). Lesions categorized as BI-RADS 3 and BI-RADS 4a were statistically significantly resulted to be benign (Figures II, III). Statistically significant malignant pathology results were obtained in lesions categorized as BI-RADS 4b (*p<0.001*). Preoperative sonographic BI-RADS categories of the lesions were compared between malignant and benign groups and all 18 lesions categorized as BI-RADS 4c and BI-RADS 5 were diagnosed as malignant (Table II) (Figure IV).

Figure II. A 32-year-old female patient's well-circumscribed, oval-shaped lesion in the upper outer quadrant of the left breast was evaluated as BI-RADS 3 (a). Pathological diagnosis was reported as fibrocystic change. Color Doppler (b) and power Doppler (c) ultrasonography examinations of the patient did not reveal any significant vascularization in the lesion, while microflow imaging (d) shows 2 punctate vascular structures within the lesion (arrows).

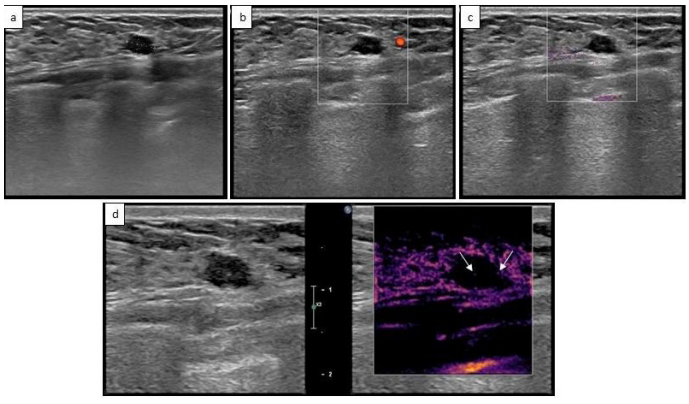


Table II. Distribution of Qualitative Variables According to Localization, Border, Orientation, Echogenicity, Posterior Acoustic Feature and BI-RADS Classification of Breast Lesions by Benign and Malignant Biopsy Group

Variables		Biopsy Pathology		X^2	*p*
		Benign	Malign		
		n (%)	n (%)		
Localization 1	Right	38 (55.9)	17 (41.5)	2.127	*0.145*
	Left	30 (44.1)	24 (58.5)		
Localization 2	Upper outer	36 (52.9)	24 (58.5)	1.99	*0.738*
	Upper inner	10 (14.7)	8 (19.5)		
	Lower outer	8 (11.8)	4 (9.8)		
	Lower inner	8 (11.8)	2 (4.9)		
	Retroareolar	6 (8.8)	3 (7.3)		
Margin features	Well-defined	50 (73.5)a	2 (4.9)b	52.562	*<0.001*
	Ill-defined	17 (25)a	27(65.9)b		
	Spiculated	1 (1.5)a	8 (19.5)b		
	Microlobulated	0 (0)	4 (9.8)		
Orientation	Parallel	45 (66.2)a	6 (14.6)b	27.293	*<0.001*
	Nonparallel	23 (33.8)a	35(85.4)b		
Echogenicity	Hypoechoic	56 (82.4)	36 (87.8)	2.506	*0.286*
	Hyperechoic	4 (5.9)	0 (0)		
	Complex	8 (11.8)	5 (12.2)		
	Anechoic	0 (0)	0 (0)		
Posterior acoustic features	None	51 (75)	30 (73.2)	13.857	*<0.001*
	Enhancement	12 (17.6)	0 (0)		
	Shadowing	5 (7.4)a	11(26.8)b		
BI-RADS	BI-RADS 3	40 (58.8)a	1 (2.4)b	74.566	*<0.001*
	BI-RADS 4a	27 (39.7)a	8 (19.5)b		
	BI-RADS 4b	1 (1.5)a	14(34.1)b		
	BI-RADS 4c	0 (0)	3 (7.3)		
	BI-RADS 5	0 (0)	15 (36.6)		

Pearson chi-square test was used. (ab): The common letter in the row indicates statistical insignificance,
BI-RADS: Breast imaging reporting and data system

When the ROC analysis results were examined in evaluating the diagnostic performance of Doppler tests; The area under the curve for CDUS is calculated as 0.584 and is not statistically significant (*p=0.141*). On PDUS examination, the area under the curve was 0.623 and is statistically significant (*p=0.031)*. On the MFI examination, the value under the curve is 0.618 and is statistically significant (*p=0.039*). The sensitivity values of CDUS, PDUS and MFI examinations are 0.53, 0.65, 0.78, respectively. The probabilities of diagnosing a malignant lesion as malignant are 53%, 65% and 78%, respectively. The specificity values of CDUS, PDUS and MFI examinations are 0.63, 0.58, 0.45, respectively. The probabilities of diagnosing a benign lesion as benign are 63%, 58%, and 45%, respectively. The positive predictive values of CDUS, PDUS, and MFI examinations are 0.46, 0.49, and 0.46, respectively. The probabilities of lesions evaluated as malignant by these tests to be truly malignant are 46%, 49%, and 46%, respectively. The negative predictive values of CDUS, PDUS, and MFI examinations are 0.69, 0.74, and 0.77, respectively. The probabilities of lesions evaluated as benign by these tests to be truly benign are 69%, 74%, and 77%, respectively (Table III). When the positive and negative predictive values are examined, the negative predictive values are higher on Doppler examination methods than the positive predictive values. These examination methods were found to have a higher possibility for diagnosing malignant lesions (Figure V).

Table III. ROC Analysis Results for Malignant Classification

Variables	AUC (95% GA)	Se	Sp	PPV	NPV	*p*
CDUS_2	0.584	0.537	0.632	0.468	0.693	*0.141*
PDUS_2	0.623	0.658	0.588	0.491	0.741	*0.031*
MFI_2	0.618	0.781	0.456	0.464	0.775	*0.039*

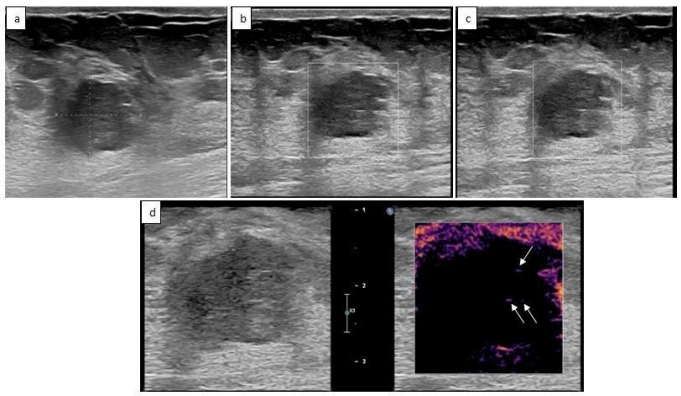
AUC: Area under the curve; Se: Sensitivity, Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value

Discussion

In Mao et al.'s study, 57 malignant and 66 benign lesions were examined, and the mean lesion size was found to be 2.1 cm in benign lesions and 2.4 cm in malignant lesions. Similar to our study, no statistically significant difference was detected in lesion size between benign and malignant lesions. While no significant difference was found between SMI and CDUS in detecting blood flow in benign lesions, they showed that SMI was more sensitive in malignant lesions. They used ROC analyses to evaluate the diagnostic performance of distinguishing malignant lesions from benign lesions in their study

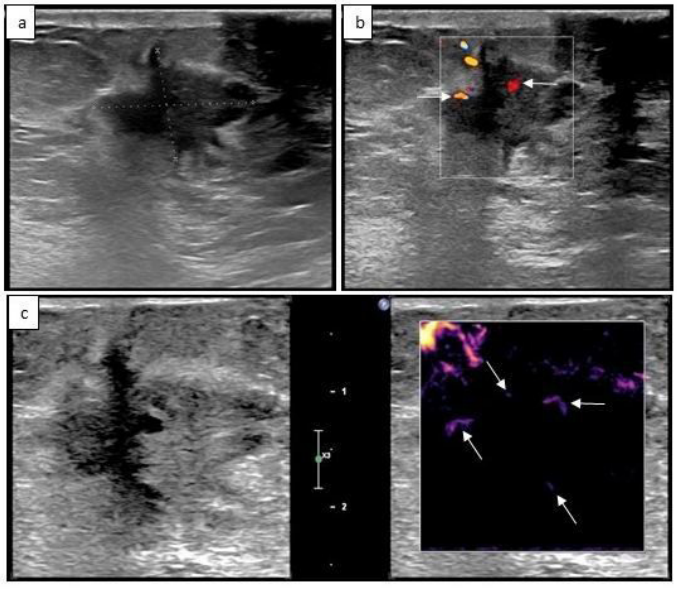
and outcomes were as following AUC: 0.73, sensitivity 66.7%, specificity 68.2% for CDUS, and AUC: 0.81, sensitivity 73.7%, specificity 80.3% for SMI (5). In our study, AUC values were lower for CDUS and MFI (0.584; 0.618, respectively), but similarly, AUC values were found to be higher for MFI. While sensitivity was higher for MFI in our study, specificity was higher for CDUS than MFI. For the study in the literature, SMI technique was used and the evaluation was performed by 3 radiologists. It was thought that the difference between the statistical datas were because of the use of a different brand of device in our study and the evaluation being performed by a single radiologist.

Figure III. A 36-year-old female patient's ill-defined lesion in the upper inner quadrant of the right breast, with occasionally angled edges, was evaluated as BI-RADS 4 (a). Pathological diagnosis was reported as benign phyllodes tumor. No significant vascularization was detected in the patient's color Doppler (b) and power Doppler (c) ultrasonography examinations, while microflow imaging (d) shows 3 point vascular structures in the lesion (arrows).



Similar to our study, in which the mean age was statistically significantly higher in the malignant group, Yongfeng et al. compared the diagnostic efficacy of PDUS and SMI with a total of 135 lesions, 94 of which were benign and 41 of which were malignant, and the mean age was found to be 46 in the malignant group and 36 in the benign group. They found no statistically significant difference in the evaluation of lesion size and location in the malignant and benign groups, similar to our study. In their study, the number of blood vessels and their distribution pattern were evaluated, and it was reported that benign lesions were in avascular or hypovascular character, while most of malignant lesions were hypervascular character. When hypervascularity was used as a criterion, the sensitivity and negative predictive value of SMI were found to be higher than PDUS. When the existence of penetrating vessels was used as a criterion, the sensitivity and negative predictive value of SMI were found to be higher than PDUS. When branching vascularization was used as a criterion, the sensitivity, specificity, positive and negative predictive values of SMI were found to be higher than PDUS (12). In our study, the sensitivity and negative predictive value of MFI were found to be higher than PDUS. Also, negative predictive value was found to be higher than positive predictive value in all three Doppler methods.

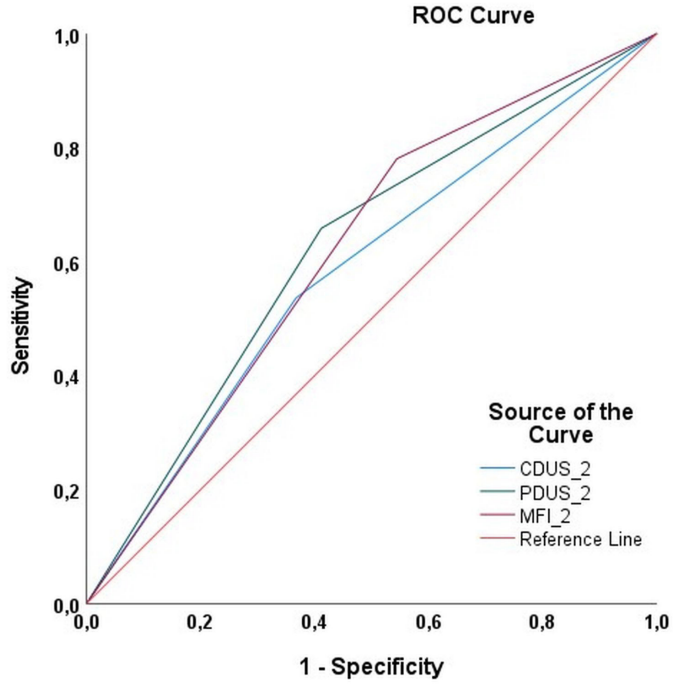
Figure IV. The ill-defined, lobulated contoured lesion in the upper outer quadrant of the right breast of a 45-year-old female patient was evaluated as BI-RADS 5 (a). Pathological diagnosis was reported as invasive ductal carcinoma. On the patient's color Doppler examination (b), two large vascular structures (arrows) were detected in the lesion, while on microflow imaging (c), two large and two small (arrows) punctate vascular structures were shown within the lesion.



In their study comparing the diagnostic efficacy of PDUS, RDUS and SMI in detecting penetrating vessels, Zhan et al. evaluated 82 avascular lesions, 45 of which were benign and 37 were malignant, and showed that SMI detected more penetrating vessels than RDUS and PDUS and was helpful in the differential diagnosis of malignant and benign lesions, especially in BI-RADS 4 lesions (10). In our study, it was shown that PDUS and MFI methods can be used in the differential diagnosis of benign-malignant

breast lesions and their diagnostic performances are similar.

Figure V. In the ROC curve, the curves of CDUS, PDUS and MFI diagnostic tests are on the reference curve, and PDUS and MFI methods can be used in the differential diagnosis of benign-malignant breast lesions.



Xiao et al. evaluated 132 breast lesions in which they compared the diagnostic performance of contrast-enhanced US (CEUS) and super-B microvascular imaging (SMI) Doppler and 58 of the lesions were diagnosed as malignant and 74 were diagnosed as benign. The number of blood vessels were less than 3 in benign lesions and more than 3 in malignant lesions. In their study, the morphological features and distribution characteristics of the vessels were also found to be different between benign and malignant lesions. It was found out that large, tortuous, radial and penetrating vessels were more frequent in malignant lesions, while annular vessels were frequent in benign lesions. The vascular microarchitecture is also different in benign lesions. Avascularity, linear and curvilinear patterns and branching patterns were found in benign lesions, and root hair-like and crab claw-like patterns were found in malignant lesions, and no significant difference in diagnostic performance was detected between CEUS and SMI Doppler (2). In our study, it was shown that PDUS and MFI methods can be used in the differential diagnosis of benign-malignant breast lesions and their diagnostic performances are close.

In another study evaluating the diagnostic performance of SMI Doppler, 85 breast lesions, 47 of which were benign and 38 were malignant, were examined and more penetrating vascular structures were detected in malignant lesions than in benign lesions using SMI and CEUS. The number of penetrating vascular structures detected with SMI and CEUS in malignant lesions was found to be significantly higher than the number of penetrating vascular structures detected with CDUS and PDUS. However, no significant difference was found between SMI and CEUS. In statistical evaluations using penetrating vascular structures as a criterion for the diagnosis of malignancy, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy values of SMI and CEUS were found to be higher than CDUS and PDUS. When classifying the vascular features of breast tumors in 5 different ways (avascular, linear shaped, branched shaped, root hair-like branching and crab claw-like shaped); Diao et al. reported that benign lesions showed mostly avascular, linear and branched patterns, malignant lesions mostly showed root hair-like branching and crab claw-like shaped patterns. When root hair-like branching patterns and crab claw-like shaped patterns were used as diagnostic criteria for malignancy; SMI and CEUS were found to be superior to CDUS and PDUS in terms of sensitivity and negative predictive value in the diagnosis of malignancy, however, no significant difference was observed between vascular distribution, internal vascularity, and internal vascular features in SMI and CEUS (13). In our study, MFI was shown to have a higher probability to identify malignant lesions than the other two Doppler US methods.

When a total of 210 benign and malignant breast lesions were evaluated in which the contribution of shearwave elastography and microvascular Doppler ultrasound methods to diagnosis was investigated, lesion size and patient age were found to be higher in the malignant group and were statistically significant (14). In our study, there was a significant difference between the malignant and benign groups with patient age, but no significant difference was found

with lesion size. The diagnostic performance of SMI Doppler in breast lesions, 30 of which were reported as malignant and 116 of which were reported as BI-RADS 4 according to the ADLER classification, was evaluated by Zhu et al. The AUC values for US+RDUS and US+SMI were found to be 0.760 and 0.852, respectively, and the difference between the AUC values between US+RDUS and US+SMI was evaluated as statistically significant (15). In our study, it was shown that statistically significant diagnostic evaluations could be made when the AUC values of PDUS and MFI were examined.

When CDUS and SMI Doppler were compared in malignant-benign groups; a statistically significant difference was found between the malignant-benign groups with CDUS and SMI Doppler variables, and grade 0 group on CDUS and SMI Doppler, benign lesion numbers were shown in significantly higher than malignant lesions. Detected benign lesion numbers were significantly lower than malignant lesions in grade 3 on CDUS, and in grades 2 and 3 on SMI Doppler (16). In our study, lesions with vascularity grade 2-3 on PDUS and MFI were statistically significantly malignant. When evaluated in general, according to our study, the differential diagnosis of benign-malignant breast lesions can be made with the use of MFI. MFI can contribute to the clinical management of cases with breast lesions, prevent additional radiological examination methods and unnecessary biopsies, reduce patient anxiety, shorten treatment times, and reduce treatment costs. In addition, since Doppler US does not contain radiation, it can be used safely in follow-up examinations.

There are some limitations to our study. Firstly, the number of patients included in the study was relatively small. Secondly, all patients were evaluated by a single radiologist, and interobserver variability could not be assessed. Thirdly, grading was assessed according to the number of vessels rather than morphological features such as penetration and branching patterns, which are reported to be highly suggestive of malignancy. Fourth, ultrasonographic images were evaluated using the MFI technique, which is less commonly used in the literature. Lastly, ultrasonographic contrast material could not be used.

Conclusion

In patients with breast lesions, in addition to B-mode US findings, PDUS and especially MFI methods used to investigate vascularity can contribute to the differential diagnosis of benign and malignant lesions. MFI will reduce additional radiological examination methods by contributing to the clinical management of cases with breast lesions, and can be used safely in follow-up examinations since it does not contain radiation. For these reasons, by following benign breast lesions; unnecessary biopsies will be prevented, treatment costs and patient treatment times will be limited and patient concerns can be reduced.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Evaluation of Desmoid-type Chest Wall Tumors: A Single Center Experience

Göğüs Duvarının Desmoid Tip Tümörlerin İncelenmesi: Tek Merkez Deneyimi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1610954
Geliş Tarihi | Received: 31.12.2024
Kabul Tarihi | Accepted: 18.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Ceberut K, Hasgül B. Evaluation of GSTP1 Inhibition Potentials and Pharmacokinetic Properties of Stigmasterol, Sesamin, and Pinosylvin. Hitit Medical Journal 2025;7(2):198-204. https://doi.org/10.52827/hititmedj.1610954

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu çalışma Tokat Gaziosmanpaşa Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylandı (Onay No: 22-Kaek-096).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: KC, BH Tasarım: BH Veri Toplama/Veri İşleme: KC Veri Analizi: KC,BH Makalenin Hazırlanması: KC.
Hasta Onamı: Hastalardan bilgilendirilmiş onam alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This study was approved by Tokat Gaziosmanpaşa University Faculty of Medicine, Clinical Research Ethics Committee (Approval No. 22-Kaek-096).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: KC, BH Design: BH Data Collection/Data Processing: KC Data Analysis: KC, BH Manuscript Preparation: KC.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Evaluation of Desmoid-type Chest Wall Tumors: A Single Center Experience

ABSTRACT

Objective: While chest wall desmoid-type tumors are rare, they do pose significant challenges in their management due to their high rate of recurrence. The purpose of this study is to evaluate our clinical experience of these tumors while reviewing the relevant literature.

Material and Methods: A retrospective study was conducted of patients diagnosed with desmoid-type chest wall tumors who underwent surgery at Gaziosmanpasa University Faculty of Medicine between 2007 and 2022. While all patients underwent surgical management, two patients received radiotherapy after their second recurrence. Demographic findings, clinical features, operative methods, local recurrences, and follow-up criteria were recorded as part of the study. Gastroscopies and colonoscopies were performed on all patients to exclude Gardner syndrome.

Results: Five of the patients in our study were female and one was male, which represented 16.6% of the group. The age range of the study group was between 14 and 76 years old. The recurrence rate was 33.3%, with two patients experiencing three tumor recurrences who received radiotherapy between the second and third recurrences. One patient, who still had a tumor, died due to a myocardial infarction. We did not observe any major complications in the other patients. All of the patients under follow-up are still alive.

Conclusion: While the primary goal of the treatment should be to perform as wide a resection as possible, this is insufficient for the prediction or prevention of recurrences, and close follow-up is necessary for the management of locally invasive tumors.

Keywords: Aggressive fibromatosis, desmoid tumors, epidemiology, soft-tissue tumor, thoracic surgery

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ÖZET

Amaç: Göğüs duvarı desmoid tipi tümörleri nadir görülür ve yüksek nüks oranları nedeniyle yönetimlerinde önemli zorluklar oluşturur. Bu çalışmanın amacı, bu tümörlerle ilgili klinik deneyimlerimizi aktarmak ve ilgili literatürü gözden geçirmektir.

Gereç ve Yöntem: Gaziosmanpaşa Üniversitesi Tıp Fakültesi' nde 2007-2022 yılları arasında ameliyat edilen ve histopatolojik olarak desmoid tipi göğüs duvarı tümörü tanısı almış hastalar retrospektif olarak incelendi. Tedavide tüm hastalara cerrahi uygulandı ve iki hastaya ikinci nüksünden sonra radyoterapi verildi. Demografik bulgular, klinik özellikler, cerrahi yöntemler, lokal nüksler ve takip kriterleri kaydedildi. Gardner sendromunu dışlamak için tüm hastalara gastroskopi ve kolonoskopi yapıldı.

Bulgular: Çalışmamızdaki hastaların beşi kadın ve biri erkekti. Çalışma grubunun yaş aralığı 14 ile 76 yaş aralığındaydı. Nüks oranı %33,3 olarak hesaplandı. İki hastada üçer kez tümör nüksü görüldü. Bu hastalara ikinci ve üçüncü nüksleri arasında radyoterapi uygulandı. Bir hasta, tedavi ve takip sürecinde miyokard enfarktüsü nedeniyle hayatını kaybetti. Diğer hastalarda herhangi bir major komplikasyon izlenmedi, tüm hastalar sağ olarak halen takiptedir.

Sonuç: Tedavideki birincil hedef mümkün olduğunca geniş bir rezeksiyon yapılması olmalıdır. Ancak bu tek başına nüksleri öngörmek veya önlemek için yeterli değildir. Desmoid tip tümörlerin yönetimi için hastaların yakın takibi önemlidir.

Anahtar Sözcükler: Agresif fibromatozis, desmoid tümörler, epidemiyoloji, torasik cerrahi, yumuşak doku tümörü.

Introduction

Desmoid tumors (DTs), which are soft-tissue tumors characterized by a proliferation of fibroblasts and myofibroblast-type spindle cells, infiltrate musculoaponeurotic tissue. They are rare pathological entities, representing 3.5% of fibrous tumors and 0.03% of all neoplasms (1). DTs are low-grade malignancies belonging to the sarcoma group and have microscopic features similar to, or even indistinguishable from, fibromas or fibrosarcomas (1, 2). Histopathologically, DTs are benign, locally aggressive tumors that do not tend to metastasize. DTs of the chest wall are uncommon and their etiology remains uncertain, although it is thought that trauma, hormonal factors, and genetic causes may all play a role in their development (2, 3). A common approach to primary treatment for DTs is wide surgical resection and RT or a combination of surgical resection and RT, although adjuvant treatments are also recommended in the postoperative period to reduce the risk of recurrence (2, 4). Recent alternative adjuvant therapies include tyrosine kinase inhibitors, gamma-secretase inhibitors, chemotherapy agents, estrogen receptor inhibitors, and cryoablation. Nirogacestat, a gamma-secretase inhibitor, is the preferred systemic therapy option. Tyrosine kinase inhibitors are also reasonable alternatives. Cytotoxic chemotherapy may be preferred for patients who require a more rapid response. Cryoablation, a percutaneous ablation technique, has recently been described in a few prospective reports as a newer treatment option. (5, 6). The unpredictable course of tumor requires as close and as long-term follow-up as possible. As the possibility of long-term recurrences must always be considered, the importance of long-term and close follow-up is emphasized. The primary treatment for DTs is wide surgical resection, although adjuvant treatments are also recommended in the postoperative period to reduce the risk of recurrence (2, 4). The unpredictable course of tumor requires as close and as long-term follow-up as possible. As the possibility of long-term recurrences must always be considered, the importance of long-term and close follow-up is emphasized. The purpose of this study is to evaluate our clinical experience with these tumors while reviewing the relevant literature.

Material and Methods

This study was approved by the local ethics committee (Approval No. 22-Kaek-096) and was conducted in accordance with the Declaration of Helsinki. This cross-sectional descriptive study included six patients who were diagnosed with chest wall DTs and underwent surgery between 2007 and 2022 at the Faculty of Medicine, Gaziosmanpasa University. Demographic data, clinical features, operative methods, local recurrences, and follow-up criteria were collected. All patients had gastroscopies and colonoscopies to rule out Gardner syndrome. Preoperatively, patients were evaluated with conventional radiological imaging using Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). During surgery, all patients underwent a wide resection, including skin and musculature structures, at least 2 cm away from the tumor lesion, as well as rib resections at least one rib above and below the tumor site. Frozen sections and surgical margins were studied in all patients whenever possible. Chest wall defects greater than 5 cm were closed by grafting, especially when defects occurred in the anterior region. None of the patients had a preoperative needle biopsy and electromyography was used to evaluate any neurological disorder. Recurrences were detected using computed tomography and magnetic resonance imaging. Two patients received radiotherapy after the second recurrence, and postoperative follow-ups were conducted using CT and MRI every six months for the first five years, then followed by annual check-ups.

Results

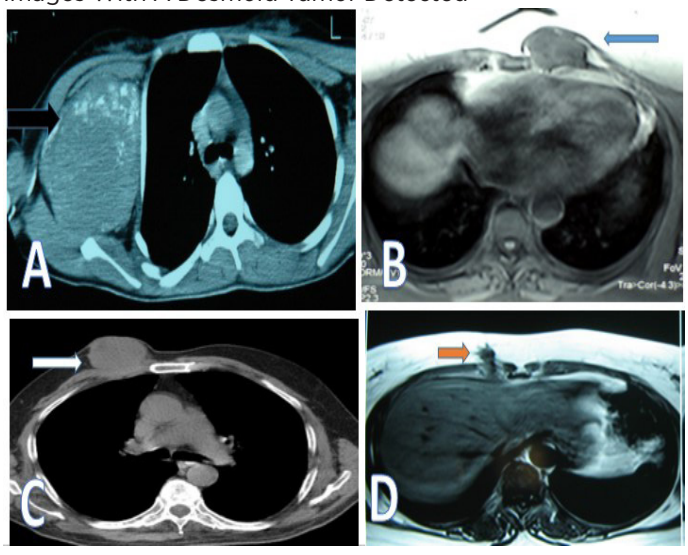
Our study included six patients, five of whom were female and one male, representing 16.6% of the group. The ages of the patients ranged from 14 to 76 years. The patients were evaluated preoperatively using conventional radiological imaging using Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) (Figure I A, B, C, D). During the surgery, all of the patients underwent a wide resection. This included skin and musculature structures at least 2 cm away from the tumor lesion, as well as rib resections at least one rib above and below the tumor site (Figure II A, B, C). All patients underwent surgical removal of the tumor, along with the surrounding tissue, and

Table I. The Clinical Features Of Patients With Desmoid-Type Tumors

Case	Age/Gender	Clinical Presentation	Tumor size	Surgery –surgical margins	Follow-up-recurrences	Progression
1	14/Female	Right axillo-thoracic	12 cm	Complete Inappropriate for surgical margins	Three recurrences 24+12+RT+36 months Still annual check-ups	Free of tumor
2	54/Female	Left parasternal 2.-3. costal cartilage	3 cm	Complete Negative surgical margins	24 months Out of follow-up	Free of tumor
3	36/Female	Inframammarial 6.-7. costal cartilage	2 cm	Complete Negative surgical margins	36 months Still annual check-ups	Free of tumor
4	76/Male	Right anterior chest wall right 3.-5. rib	7 cm	Complete Negative surgical margins	Three recurrences 36 months 12+18+RT-6 months	(Transition to sarcomatoid form. Died due to myocardial infarction with tumor)
5	53/Female	Right parasternal 8.-9. costal cartilage	3 cm	Complete Negative surgical margins	36 months Still annual check-ups	Free of tumor
6	41/Female	Left midaxillary 6.-7. Rib	3 cm	Complete Negative surgical margins	36 months Still annual check-ups	Free of tumor

the median follow-up was 36 months. Two patients, Case 1 and Case 4, had three tumor recurrences and received radiotherapy between the second and third recurrences, making the recurrence rate 33.3%. (Figure III A, B) Despite radiotherapy, the third recurrences occurred in both patients at the sixth month and in three years. Right-sided intermediate ulnar paresis, due to brachial plexus involvement, was detected in Case 1 before surgery, and the condition persisted after the surgery. Pathological analyses confirmed desmoid-type histologic features in all patients, and the Case 4 showed sarcomatoid transition in his recurrent tumor (Figure IV A, B). While preparing for surgery, this patient died in the hospital due to a myocardial infarction. One patient, Case 2, whose surgical margins were positive on permanent section surgery, was offered re-operative resection, but this was refused by the patient, and the patient also opted out of future follow-ups after the second year (Table I). At the time of writing, four patients are still attending annual check-up examinations and have had no signs of recurrent tumors.

Figure I. Computed Tomography and Magnetic Resonance Images With A Desmoid Tumor Detected



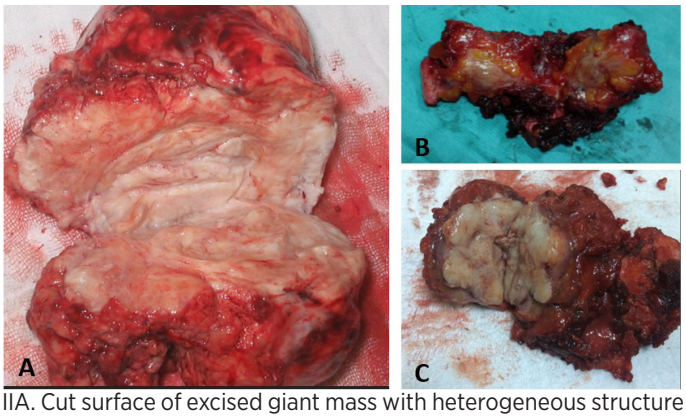
IA. Axial computed tomography image (black arrow shows calcifications), which demonstrates the huge tumor dwelling in the right axillo-thoracic area (Case 1)

IB. T1-weighted axial magnetic resonance image of the desmoid tumor with heterogeneous enhancement, low signal bands on the left side of the sternum (blue arrow) (Case 2)

IC. Computed tomography imaging of well-bounded desmoid tumor (white arrow) with subcutaneous placement just left side of the sternum (Case 4)

ID. Desmoid tumor formation with an irregular contour that penetrates the chest wall (orange arrow) (Case 3)

Figure II. Images of Desmoid Tumor Removed Through Surgery (Case 1)



IIA. Cut surface of excised giant mass with heterogeneous structure (white and fibrous appearance) (Case 1)
IIB. Excised chest wall desmoid tumor with intercostal muscle and costal cartilage (Case 3)
IIC. Excised chest wall desmoid tumor with skin and surrounding musculature structure (Case 4)

Figure III. Images of recurrences of Desmoid Tumor Cases

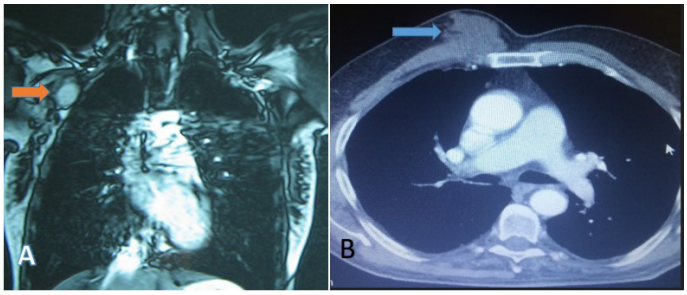


Fig. IIIA Case 1 Coronal Magnetic Resonance image showing well-circumscribed nodular lesion in the axillary fossa adjacent to the axillary artery (red arrow)
Fig. IIIB Case 4 Computed Tomography image showing a mass lesion with irregular borders and soft tissue density located subcutaneously in the right sterno-costal area in the mid-thoracic section image (blue arrow)

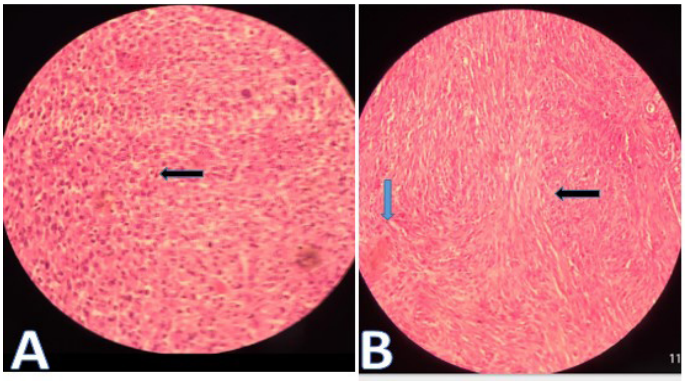
Discussion

DTs were first described by John MacFarlane in 1832 as abdominal wall tumors, with extra-abdominal types being later identified, particularly in the shoulder girdle and lower limbs (1). 10%–20% of tumors are located on the chest wall and an intrathoracic tumors is extremely rare (2). DTs are sometimes referred to as low-grade sarcomas or aggressive fibromatosis, as these synonyms more accurately describe their natural behavior. Chest wall DTs are rare and, due to their high recurrence rates, pose significant challenges in their management, surgical treatment, and follow-up. The exact pathological mechanisms behind these tumors are not yet fully understood, although there have been suggestions that hormonal factors, particularly estrogen, trauma to the chest wall, and previous thoracic operations, including breast implants, muscular transplants, and even intramuscular injections, may all play a role in their etiopathogenesis (2). None of the patients in our study had a history of trauma or a previous operation. Genetic predisposition, carried by the Y chromosome, or the long arm of the fifth chromosome in Gardner syndrome, which is frequently associated with women, results in 15% of patients possibly developing DTs. Our findings were consistent with previous reports, with women being slightly more susceptible to DTs than men (3, 4).

The majority of patients complain of chest pain and firm masses on their chest wall, which they have detected themselves. The sizes of tumors are typically large upon hospital examination due to their asymptomatic nature (3). Symptomatology varies due to tumor involvement of adjacent structures, and the involvement of brachial plexus, as with Case 1, has also been previously reported (7). As DTs in the mammary region may be misdiagnosed as breast tumors, meticulous screening methods are required to obtain an accurate differential diagnosis (8). CT and MRI studies are helpful for diagnosing and delineating tumor margins in preparation for surgery, and MRI is preferable in cases where bone involvement is suspected. Radiologic features of DTs are similar to those of soft tissue malignant tumors, with well-circumscribed masses that are predominantly homogeneous or heterogeneous. A preoperative incisional biopsy or needle biopsy may suggest certain diagnoses and provide helpful information regarding surgical margins and the determination of the tumor differentiation, which may be needed before surgery. However, tumor spillage or contamination is also possible (2, 3). The use of preoperative biopsies was not preferred. During surgery, the primary objective is to achieve a wide resection 2–4 cm from the tumor and rib resections above and below the tumor site with negative surgical margins. Chest defects can be closed with a muscle flap, autologous bone grafts, polytetrafluoroethylene (PTFE), or other similar synthetic tissues. Histological examinations have

demonstrated long fascicles of spindle cells of variable cell-density with few mitoses and the absence of atypical nuclear separations. Characteristically, there is a diffuse cell infiltration of adjacent tissue structures. Immunohistochemically, the spindle cells are positive for vimentin, smooth muscle actin, and muscle-specific actin, which reflects a fibroblastic-myofibroblastic differentiation. The possibility of transition to a sarcomatoid form of tumor during the follow-up period must be considered (8).

Figure IV. Histological Features of Operational Materials from Case 4



IVA. Spindle fibroblastic cells (black arrow) with elongated nuclei in a collagen-rich stroma

IVB. Microhemorrhages (blue arrow) and slender, spindle-shaped tumor cells arranged with ill-defined parallel fascicles (black arrow) that are loculated by abundant interstitial collagen without increased mitotic activity. (Hematoxylin-eosin, ×20). The same patient with a sarcomatoid transition.

(Permission was obtained from the pathology department for histopathological images)

Recurrence rate after surgery for DTs is high and has been reported to range between 25% and 75% in different series (3). The recurrence rate of this study is 33.3%. Some of the predictive parameters for recurrence suggested by authors include age, sex, incomplete resection, positive surgical margins, multiple recurrences, and the absence of radiotherapy (2). While recurrences after surgery are unpredictable, it is essential to aim for a wide resection with negative surgical margins during the first surgery (10). However, obtaining negative surgical margins may not be the only predictive key for recurrences. Furthermore, providing negative surgical margins may be difficult, particularly in the axillary and cervicothoracic regions. As occurred with Case 2, histopathologically negative frozen sections may become positive in permanent sections (3, 10). There is no difference in overall recurrences between microscopic negative and positive margins. In some cases, the main objective of management may be to preserve vital organs and a patient's quality of life (9, 11). Although the efficacy of radiotherapy after surgery in preventing recurrences is uncertain, it may be beneficial in delaying the onset of recurrences (12, 13). Radiotherapy is most suitable for unresectable or partially resectable residual tumors or in positive surgical margins, although some authors may prefer radiotherapy despite negative surgical margins (14, 15). A complete response after radiotherapy is difficult, but radiotherapy is recommended if the tumor is in the upper thorax and neck adjacent to the airway and major vessels (16). After the primary surgery, we preferred surgical resection for the first recurrence. Two patients, Case 1 and Case 4, received radiotherapy after second recurrences. However, tumor recurrences were detected again six months and three years after radiotherapy. Sarcomatoid transition, as with Case 4, and also spontaneous remission, have been reported in cases of DTs with no therapy or after a partial resection (1, 8). A protracted follow-up period is recommended because late recurrences have been reported (17). DTs have a five-year survival rate of nearly 93%, and since they rarely metastasize, death due to DTs has seldom been reported (16, 18). For unresectable cases, therapeutic agents such as estrogen receptor blockers, antifibrinolytic agents, nonsteroidal anti-inflammatory drugs, chemotherapy, tyrosine kinase inhibitors, or a combination of the above, have been applied with some promising outcomes (19). However, despite these successfully sporadic case reports, extensive success has not been reported (3).

Conclusion

Based on the collective data, it appears that standardized management still seems to be deficient, likely due to the varying development of these cases. The number of patients in our study group is low. Our own limited experience has taught us that each patient must be assessed on an individual basis, and if possible, a comprehensive resection with

negative surgical margins remains the mainstay of the treatment. Furthermore, a thorough and prolonged follow-up period may aid in the management of these locally aggressive tumors.

Acknowledgements

We thank the hospital staff and consultants who provided feedback on our initial interview guide, who participated in the pilot interviews, and who participated in the study.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data

TP53 Mutasyonlu Akut Myeloid Lösemiye Genel Bakış: Tek Merkez, Gerçek Yaşam Verisi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1628279
Geliş Tarihi | Received: 29.01.2025
Kabul Tarihi | Accepted: 05.04.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Küçükyurt Kaya S, Afacan Öztürk HB, Aydın Kaynar L, et al. Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data. Hitit Medical Journal 2025;7(2):205-213. https://doi.org/10.52827/hititmedj.1628279

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 31/07/2024 tarihinde Ankara Etlik Şehir Hastanesi Bilimsel Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: AEŞH-BADEK-2024-592.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: SKK, AKG Tasarım: SKK, HBAÖ, LA, HBE, AKG Veri Toplama/Veri İşleme: JY, BAK, MA, MKÇ, ŞZA Veri Analizi: SKK, HBAÖ, LAK, HBE, AKG Makalenin Hazırlanması: SKK, AKG.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Ankara Etlik City Hospital Scientific Research Ethics Committee on 31/07/2024. Decision no: AEŞH-BADEK-2024-592.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: SKK, AKG Design: SKK, HBAÖ, LA, HBE, AKG Data Collection/Data Processing: JY, BAK, MA, MKÇ, ŞZA Data Analysis: SKK, HBAÖ, LAK, HBE, AKG Manuscript Preparation: SKK, AKG.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Overview of Acute Myeloid Leukemia with TP53 Mutation: Single Center, Real-Life Data

ABSTRACT

Objective: Acute myeloid leukemia (AML) with TP53 mutations represents a distinct and high-risk molecular subgroup characterized by aggressive disease progression, chemoresistance, and poor survival outcomes. This study provides a single-center analysis of clinical characteristics, treatment responses, and survival outcomes in a real-world cohort of patients with TP53-mutated AML.

Material and Method: A retrospective observational study was conducted at Ankara Etlik City Hospital, analyzing nine patients diagnosed with TP53-mutated AML between January 2023 and January 2024. Patients were treated with intensive or less intensive induction regimens based on patient-related factors. Cytogenetic and molecular abnormalities were recorded, alongside treatment responses were assessed per the European Leukemia Net 2022 guidelines. The primary endpoint was overall survival.

Results: The median age at diagnosis was 65 years, with 55.5% female patients. Complex karyotypes were observed in 66.7% of cases, and multi-hit TP53 mutations were identified in two patients. A complete response was achieved in 75% of patients treated with intensive induction therapy (7+3), while a complete or partial response was achieved in 60% of patients receiving the azacitidine-venetoclax regimen. Six patients died within 12 months, predominantly due to infection, while the three surviving patients underwent for allogeneic hematopoietic stem cell transplantation (allo-HSCT). The median overall survival (OS) of the entire cohort was 9 months. Patients with TP53-mutated AML who underwent allo-HSCT exhibited significantly prolonged OS (*p=0.01*).

Conclusion: The prognosisof TP53-mutated AML remains particularly poor, highlighting an urgent need for the development of novel therapeutic approaches to improve patient outcomes. While allo-HSCT offers a potential survival benefit, effective bridging therapies and post-transplant management are critical for improving outcomes in this high-risk population

Keywords: Acute myeloid leukemia, stem cell transplantation, survival, TP53 mutation, treatment.

ÖZET

Amaç: TP53 mutasyonlu akut myeloid lösemi (AML), agresif hastalık seyri, kemoterapi direnci ve kötü sağkalım sonuçlarıyla karakterize, yüksek riskli ve farklı bir moleküler alt grup olarak tanımlanır. Bu çalışma, TP53 mutasyonlu AML hastalarının klinik özelliklerini, tedavi yanıtlarını ve sağkalım sonuçlarını tek merkezden bir gerçek yaşam kohortunun analiziyle sunmaktadır.

Gereç ve Yöntem: Ocak 2023 ile Ocak 2024 tarihleri arasında Ankara Etlik Şehir Hastanesi'nde TP53 mutasyonlu AML tanısı alan dokuz hastanın verileri retrospektif gözlemsel bir çalışmayla incelendi. Hastalar, hasta ile ilgili faktörlere bağlı olarak yoğun veya yoğun olmayan indüksiyon rejimleriyle tedavi edildi. Sitogenetik ve moleküler anomaliler kaydedildi ve tedavi yanıtları Avrupa Lösemi Ağı (ELN) 2022 kılavuzuna göre değerlendirildi. Birincil sonlanım noktası genel sağkalım idi.

Bulgular: Tanı anındaki medyan yaş 65 olup, hastaların %55,5'i kadındı. Olguların %66,7'sinde kompleks karyotip gözlendi ve iki hastada çoklu-vuruş TP53 mutasyonları tespit edildi. Yoğun indüksiyon tedavisi (7+3) ile tedavi edilen hastaların %75'inde tam yanıta ulaşılırken, azasitidin-venetoklaks rejimi alan hastaların %60'ında tam veya kısmi yanıt elde edildi. Tanıdan sonraki 12 ay içinde altı hasta, çoğunlukla enfeksiyon nedeniyle hayatını kaybederken, hayatta kalan üç hasta allojeneik hematopoetik kök hücre nakli (AHKHN) yapılan hastalardı. Tüm kohortun ortanca genel sağkalımı 9 ay idi. AHKHN yapılan hastalarda genel sağkalım anlamlı şekilde daha uzundu (*p=0,01*).

Sonuç: TP53 mutasyonlu AML'nin prognozu halen son derece kötü olmaya devam etmektedir ve bu durum hasta sonuçlarını iyileştirmek için yeni tedavi yaklaşımlarının geliştirilmesine acil ihtiyaç duyulduğunu göstermektedir. AHKHN potansiyel bir sağkalım faydası sunsa da, etkili köprüleme tedavileri ve nakil sonrası yönetim, bu yüksek riskli popülasyonda sonuçların iyileştirilmesinde kritiktir.

Anahtar Sözcükler: Akut myeloid lösemi, kök hücre nakli, sağkalım, tedavi, TP53 mutasyonu.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, defined by the heterogeneous and uncontrolled clonal expansion of myeloid blasts, which suppresses normal hematopoiesis. Despite significant advancements in our understanding of AML pathophysiology and the development of targeted therapies, the prognosis for patients with specific molecular abnormalities remains poor. TP53 mutations have emerged as a critical biomarker associated with high-risk disease, chemoresistance, and inferior survival outcomes (1).

The TP53 gene, often as called the "guardian of the genome," plays a central role in maintaining genomic stability by regulating cell cycle arrest, apoptosis, and DNA repair. Mutations in TP53 are detected in approximately 5–10% of newly diagnosed AML cases and are more prevalent in therapy-related AML, secondary AML, and AML with complex karyotypes. These mutations confer aggressive disease behavior and resistance to conventional cytotoxic chemotherapy and hypomethylating agents, highlighting the need for novel therapeutic strategies tailored to this patient population (1-3).

Managing TP53-mutated AML remains challenging, with limited data guiding clinical decision-making. Existing evidence is primarily derived from small, retrospective cohorts or clinical trials that often exclude patients with this mutation due to their poor prognosis. There is a growing recognition that TP53 mutations represent a distinct biological and clinical entity within AML, necessitating specialized management approaches that integrate molecular, cytogenetic, and clinical risk factors (4).

This study aims to provide a comprehensive overview of TP53-mutated AML through a single-center analysis of real-world data. By exploring the clinical characteristics, treatment paradigms, and preliminary outcomes of patients with this high-risk molecular subtype, our findings aim to enhance understanding and inform future therapeutic approaches.

Material and Method

This is a retrospective, single-center, observational study carried out at Ankara Etlik City Hospital. Our study enrolled 86 patients aged 18 years or older who were diagnosed with AML according to the WHO/ICC 2022 classification (5,6). Of these, 9 patients with pathogenic TP53 mutations who received first-line treatment at our center were analyzed between January 2023 and January 2024. Patients diagnosed with acute promyelocytic leukemia were not included in the study. The primary endpoint of our study was overall survival (OS). Per the principles outlined in the Declaration of Helsinki, the Institutional Review Board of the Ankara Etlik City Hospital reviewed and approved the study protocol (Date: 31-07-2024, Number: AEŞK-BADEK-2024-592). Informed consent for publication was obtained from the patients.

Patients' demographic characteristics, clinical features, comorbidities, and laboratory data were gathered from both manual and electronic medical records. These data included age, sex, date of diagnosis, disease subtype, values of complete blood count (CBC) at diagnosis, accompanying cytogenetic and molecular abnormalities, treatments received and treatment responses, and treatment-related toxicities (if any).

TP53 mutation analysis was conducted via Sanger sequencing for 8 patients and next-generation sequencing (NGS) for 1 patient. Any variants detected within the limitations of the Sanger method were reported (Table I). The presence of a pathogenic TP53 mutation was defined as AML with TP53 mutations that are mutated at variant allele frequency (VAF) of at least 10% (Table I). All cases underwent a comprehensive diagnostic workup that included conventional G-banding analyses, FISH testing (to detect 5q, 7q, 8, 20q deletions, t(8,21), t(15,17), inversion 16, t(9,22), KMT2A, DEK/NUP 214, inversion 3), as well as molecular studies (to detect inversion 16, t(8,21), t(9,22), t(15,17), NPM1, WT1, FLT3, C-KIT, CEBPA).

The induction regimens were classified into two categories: intensive and less intensive. Intensive induction treatments consisted of infusional cytarabine with idarubicin (7+3) and fludarabine with cytarabine, G-CSF, and idarubicin (FLAG-IDA), sometimes in combination with venetoclax (VEN). Less intensive induction regimens consisted of hypomethylating agents (HMA, azacitidine) with or without VEN (VEN-HMA or HMA).

The risk classification of AML and assessment of

treatment response were performed by the 2022 European Leukemia Net (ELN) guideline (7). Complete remission (CR) is defined as bone marrow blasts less than 5%, absence of circulating blasts, absence of extramedullary disease, absolute neutrophil count (ANC) less than 1.0 x 109/L (1000/mL), and platelet count less than 100 x 109/L (100.000/mL). CR with incomplete hematologic recovery (CRi) is defined as meeting all criteria for CR, except for residual neutropenia with an ANC of 1.0 x 109/L (1000/mL) or less, or residual thrombocytopenia with a platelet count of 100 x 109/L (100.000/mL) or less. Partial response is defined as meeting all hematologic criteria for CR, and achieving a reduction in bone marrow blast percentage to between 5% and 25%, with a decrease of at least 50% from pre-treatment levels. Refractory disease is defined as failure to achieve CR, CR with partial hematologic recovery (CRh), or CRi after two courses of intensive induction treatment, or within 180 days of starting less intensive therapy (7).

All data were analyzed by using IBM SPSS Statistics 25.0. Nominal variables were presented as frequency and percentages. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test, as appropriate. For variables not normally distributed, median with variables range (minimum to maximum) were used. Mann–Whitney U test was used for continuous variables that did show non-normal distribution to test whether there were any differences between the two groups. All tests were two-sided, and $p<0.05$ was considered statistically significant. Survival probabilities were calculated and plotted using the Kaplan-Meier method. Overall survival (OS) was determined by calculating the time between the date of AML diagnosis and the date of death from any cause or the date of the last follow-up (for patients who were still alive). Duration of follow-up were also documented.

Results

Nine patients with TP53-mutated AML followed in our center were included in the study. Table I provides a comprehensive overview of the patients' demographic and clinical profiles, including treatment regimens, therapeutic responses, comorbidities, and detailed follow-up and survival data. Also, demographic and clinical characteristics of the patients were grouped and summarized in Table II.

The median age at diagnosis was 65 years (range 34–78), and 55.5% of cases were female (n=5) (Table II). At least one comorbidity was present in 66.7% of patients (n=6), most commonly hypertension (n=4, 44.4%). Myelodysplastic syndrome-related cytogenetic or bone marrow dysplasia findings were observed in 88.9% of cases (n=8) (except Patient #6). Secondary AML developed in two patients with myeloproliferative neoplasm (Patient #8 and #9), and one patient had therapy-related AML (Patient #5) (Table I). No neoplasia was reported in other members of the families of all patients.

Only one patient (Patient #4) presented with leukocytosis, and while the hemoglobin (Hb) level exceeded 10 g/dL in this case, all patients exhibited anemia. At the time of admission, thrombocytopenia with a platelet (PLT) count below 50,000/µL was observed in five patients (Table I). Median Hb, white blood cell (WBC), PLT counts at diagnosis for both the entire cohort and transplanted and non-transplanted patients were shown in Table II.

All patients were classified as high-risk according to the 2022 ELN risk stratification. TP53 mutations were accompanied by WT1 mutation in five patients, while six patients (66.7%) presented with a complex karyotype (Table I, II). Additionally, multi-hit TP53 mutations were identified in two patients (Patients #3 and #7).

Of the patients included, 55.5% (n=5) were aged 65 years or younger. Four patients received standard 7+3 induction chemotherapy as their first-line treatment, achieving a CR in three cases (Table II). Five patients were treated with an azacitidine-venetoclax (Aza-Ven) regimen; of these, two of them achieved CR (Patient #8 and #9), one of them had a partial response (Patient #1), and the remaining two patients were refractory to this treatment (Patient #4 and #7) (Table II). Progression was observed during follow-up in both patients who initially responded to Aza-Ven (Patients #1 and #8). Among the nine patients, six patients died within the first 12 months following diagnosis, with infection being the leading cause of mortality. Of the three surviving patients, two of them underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) at our center

(Patients #2 and #6), while the remaining patient was referred to another facility for transplantation (Patient #3).

Patient 2 underwent a haploidentical transplant from her nephew while in CR for AML. Also, patient 6 received an allotransplant from a fully compatible donor through the TURKOK (Turkey's National Stem Cell Coordination Center) registry on May 31th, 2024. Patient #3 initially planned a haploidentical transplant from his brother but ultimately chose to proceed with transplantation at another center (Table I).

Table I. Patients Demographics, Comorbidities, Genetic Features, Treatment Responses, and Clinical Outcomes

Pts	Sex	Date of diagnosis	Age at diagnosis	Hematologic parameters at diagnosis	*TP53* pathogenic variants	Accompanying cytogenetic abnormalities	Accompanying molecular abnormalities	Treatments And Treatment Responses	Comorbidities	OS
1	M	May 2023	66	Hb 3.7 g/dl WBC 1320 /µl PLT 11000 /µl	c.406delC (exon5) c.742C>T (exon 7)	complex karyotype 5q,7q, 20q deletion Trisomy 8, DEK/ NUP214 CBFB (16q22) deletion	*WT1 +*	Aza-Ven → PR at the end of the 3rd cycle, disease progression at the end of the 6th cycle	CHD COPD Pulmonary HT BPH	8 mo
2	F	Jan 2024	59	Hb 8.1 g/dl WBC 1380 /µl PLT 121000 /µl	c.821T>A (exon 8)	5q deletion CBFB (16q22) monosomy	*WT1 +*	7+3 → CR Then, 2 cycles of IDAC →CR Then, 5/10 haploidentical transplant from nephew (4th June 2024)	None	NR
3	F	Jan 2024	34	Hb 7.5 g/dl WBC 3900 /µl PLT 24000 /µl	c.814G>A (exon 8)	complex karyotype Trisomy 8 7q, 20q deletion CBFB (16q22) and MYH11 (16p13.1) monosomy ETO (8q21.3) trisomy		7+3 → CR (long-term ICU follow up) Then, one course Aza → CR Then, haploidentical transplant from a 36-year-old brother in an external center	None	NR
4	M	Apr 2023	68	Hb 12.3 g/dl WBC 24540 /µl PLT 95000 /µl	c.797G>T (exon 8)	complex karyotype 5q, 7q deletion inversion 3	*WT1 +*	4 courses of Aza-Ven → refractory disease 1 cycle of Etoposide - ARA-C → refractory 1 course of FLAG-Ven → refractory disease	DM HT HL Arrhythmia	9 mo
5	F	Sept 2023	61	Hb 5.7 g/dl WBC 3570 /µl PLT 42000 /µl	c.427G>A (exon 5)	complex karyotype 5q, 7q deletion inversion 3	*WT1 +*	7+3 --> refractory disease Transplant ineligible patient Then, received 1 cycle of Aza-Ven	Metastatic breast cancer (chemotherapy history)	3 mo
6	F	Dec 2023	60	Hb 7.1 g/dl WBC 2070 /µl PLT 26000 /µl	c.524G>A (exon 5) c.375G>A (exon 4) VAF %40-41	complex karyotype		7+3 → CR Then, 3 cycles of IDAC →CR Then, allotransplantation from a fully compatible TURKOK donor on 31st May 2024	None	NR
7	M	Jan 2023	65	Hb 8.2 g/dl WBC 4180 /µl PLT 33000 /µl	c.797G>A (exon 8)	46, XY [10]		2 courses of Aza-Ven → refractory disease 7+3 → refractory disease FLAG-Ida refractory disease	HT HL CHD (CABG +)	8 mo
8	F	May 2023	78	Hb 8.7 g/dl WBC 890 /µl PLT 76000 /µl	c.517G>A (exon 5)	5q, 7q deletion Trisomy 8 ETO (8q21.3) trisomy CBFB (16q22) deletion	*WT1 +*	Aza-Ven → iCR at first, obvious relapse at the end of the 7th cycle	ET (hydroxyurea +) HT Osteoporosis Asthma Hypothyroidism	12 mo
9	M	Sept 2023	78	Hb 8.3 g/dl WBC 2770 /µl PLT 242000 /µl	c.716A>G (exon 7)	complex karyotype 5q, 20q deletion Monosomy 7	*JAK2 V617F +*	Aza-Ven → CR at the end of the 4th cycle, febrile neutropenia and septic shock developed in the 5th cycle	PV (hydroxyurea +) HT HL DM	6 mo

Apr; april, ARA-C; cytarabine, Aza-Ven; Azacitidine-Venetoclax, BPH; benign prostatic hyperplasia, CR; complete response, CABG; coronary artery bypass graft, CHD; coronary heart disease, COPD; chronic obstructive pulmonary disease, Dec; december, DM; diabetes mellitus, ET; essential thrombocythemia, F; female, FLAG-Ven; fludarabine with cytarabine, G-CSF-Venetoclax, ICU; intensive care unit, Hb; hemoglobin, HL; hyperlipidemia HT; hypertension, IDAC; intermediate-dose cytarabine, iCR; Complete Remission with Incomplete Count Recovery, Jan; january; M; male, mo; months, NR; not reached, OS; overall survival, PLT; platelet, PR; partial response, Pts; patients, PV; polycythemia vera, Sept; september, TURKOK; Turkey's National Stem Cell Coordination Center, VAF; variant allele frequency, WBC; white blood cell, WT-1; wilms tumor gene-1, 7+3; cytarabine with idarubicin

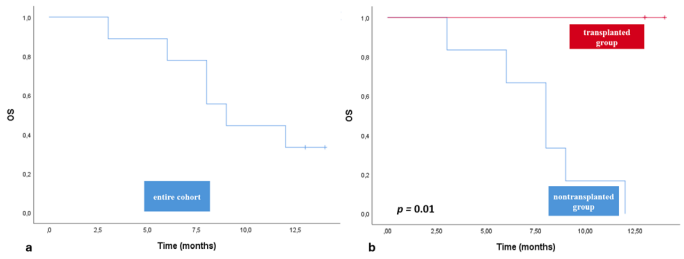
Table II. Demographic Features and Characteristics of the Patients

Characteristics	**Entire Cohort (n=9)**	**Transplanted Group (n=3)**	**Nontransplanted Group (n=6)**	*p*
Age at diagnosis, years Median (Range)	65 (34 – 78)	59 (34 – 60)	67 (61 – 78)	*0.024*
Sex, n (%) Female Male	5 (55.5) 4 (44.4)	3 (100) 0 (0)	2 (33.3) 4 (66.7)	*0.119*
Median Hb count at diagnosis (g/L) (range)	8.1 (3.7 – 12.3)	7.5 (7.1 – 8.1)	8.25 (3.7 – 12.3)	*0.548*
Median WBC count at diagnosis (k/mm³) (range)	2.77 (0.89 – 24.54)	2.07 (1.388 – 3.9)	3.17 (0.89 – 24.54)	*0.905*
Median PLT count at diagnosis (k/mm³) (range)	42 (11 – 242)	26 (24 – 121)	59 (11 – 242)	*0.714*
Co-mutation, n (%) WT1 mut JAK2 V617F	5 (55.5) 1 (11.1)	1 (33.3) 0 (0)	4 (66.7) 1 (16.7)	*0.548*
Complex karyotype, n (%)	6 (66.7)	2 (66.7)	4 (66.7)	*0.762*
First line therapy, n (%) Intensive Less intensive	4 (44.4) 5 (55.6)	3 (100) 0 (0)	1 (16.7) 5 (83.3)	*0.048*
Initial response following intensive therapy, n (%)(n: 4) CR + CRi PR Refractory	3 (75) 0 (0) 1 (25)	3 (100) 0 (0) 0 (0)	0 (0) 0 (0) 1 (16.7)	
Initial response following less intensive therapy, n (%) (n: 5) CR + CRi PR Refractory	2 (40) 1 (20) 2 (40)	0 (0) 0 (0) 0 (0)	2 (33.3) 1 (16.7) 2 (33.3)	
Median follow-up (months) (range)	9 (3 – 14)	13 (13 – 14)	8 (3 – 12)	*0.024*

CR, complete remission; CRi, CR with incomplete hematologic recovery; Hb, hemoglobin; PLT, platelet; PR, partial response; WBC, white blood cell

In May 2024, Patient #6 underwent an allo-HSCT using a fully HLA-matched donor identified through the TURKOK registry. The procedure utilized a myeloablative conditioning regimen consisting of fludarabine and busulfan (Flu-Bu). Graft-versus-host disease (GvHD) prophylaxis was managed with post-transplant cyclophosphamide (post-Cy), tacrolimus, and mycophenolate mofetil, ensuring a balanced approach to minimize GvHD while supporting successful engraftment. Also, Patient 2 underwent a haploidentical transplant from his nephew using myeloablative conditioning regimen with fludarabine-busulfan (Flu-Bu) using post-Cy, tacrolimus and mycophenolate mofetil as graft-versus-host disease (GvHD) prophylaxis o June 4, 2024.

Figure I. Overall survival of the entire cohort in patients with TP53-mutated acute myeloid leukemia (a) Overall survival of the transplanted and non-transplanted arms (b) (OS, overall survival)



Upon comparing TP53-mutated AML patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) with those who did not, it was observed that the median age at diagnosis was significantly younger in the transplanted group (p=0.024). Additionally, a higher proportion of patients in the allotransplanted cohort received intensive induction therapy as their first-line treatment (p=0.048). The median follow-up duration was longer in the transplanted group compared to the non-transplanted group. Other demographic and clinical characteristics were comparable between the two groups (Table II).

The median OS of the entire cohort was 9 months with a total follow-up duration of 14 months. The OS of the entire cohort was presented in Figure 1a. Patients with TP53-mutated AML who underwent allo-HSCT exhibited significantly prolonged OS (p=0.01) (Figure 1b).

Discussion

In our clinic, supported by a robust genetic laboratory and high-quality care infrastructure in

Turkey, we analyzed TP53-mutated AML patients during our inaugural year. Patients were treated with either intensive or less intensive induction regimens based on their age, performance status, comorbidities and patients' preferences. Among the four patients with TP53-mutated AML who received intensive induction therapy, three of them achieved first remission and subsequently underwent allo-HSCT; currently, only those bridged with transplantation have survived (Table I). The remaining five patients received less intensive induction therapy. Although two patients initially responded, their responses were not durable, and the disease subsequently relapsed; the remaining three patients were refractory to initial treatment. Efforts to intensify treatment in patients who did not respond to less intensive regimens with more aggressive therapies were ultimately unsuccessful. These findings emphasize the critical importance of selecting appropriate first-line therapy and employing allo-HSCT in eligible patients who achieve remission.

Myelodysplastic syndromes (MDS) and MDS/AML originate from clonal hematopoiesis driven by somatic mutations, but the presence of a TP53 mutation alone is insufficient to trigger leukemogenesis. The 2022 ELN guideline classifies TP53 mutations as a marker of unfavorable prognosis, correlating with median OS rates of less than two years. Patients with TP53-mutated AML or MDS with excess blasts-2 (MDS-EB-2) demonstrate overlapping biological and clinical characteristics, including aggressive disease progression, high relapse rates, and complex karyotypic abnormalities. Complex or monosomal karyotypes, observed in 80–90% of cases, frequently involve deletions or structural abnormalities in chromosomes 5, 7, and 17. These mutations typically originate in DNA-damage-resistant progenitor cells, which expand in response to cytotoxic therapies. Such mutations confer resistance to standard treatments, further complicating disease management and underscoring the necessity for novel therapeutic approaches tailored to this high-risk population (1,8,9). In our cohort, all but one patient exhibited the genetic abnormalities commonly associated with TP53 mutations, consistent with findings reported in the literature (Table I).

A retrospective study compared post-allo-HSCT outcomes between AML patients with WT1 and TP53 mutations, two groups with distinct genetic profiles. None had concurrent WT1 mutation and TP53 mutation. WT-1 mutated AML patients were significantly younger and less likely to have therapy-related disease and complex, or monosomal karyotypes compared to TP53-mutated AML. Despite these more favorable features, WT-1 mutated AML patients had similar 2-year OS (38.7% vs. 39.4%), relapse incidence, and non-relapse mortality compared to TP53-mutated AML patients. The findings suggest that WT1 mutations confer high-risk characteristics akin to TP53 mutations (10). In our cohort of nine patients with TP53-mutated AML, five also harbored concurrent WT1 mutations. Investigating the potential impact of this co-occurrence on treatment responses and survival outcomes is essential. Among these five patients with WT1 mutations, all exhibited a coexisting 5q deletion. Treatment outcomes varied, with two patients responding to Aza-Ven, one of them achieving a response with the 7+3 regimen, and the remaining two patients showing refractory disease despite therapy. Only one patient underwent allo-HSCT. By day +100 post-transplantation, her disease was in remission (Patient #2).

TP53 mutations are highly heterogeneous, the complex landscape in terms of co-mutation and gene expression profiles makes it difficult to develop effective treatment strategies targeting all TP53 mutated cancer clones, and the optimal treatment strategy in this subgroup of the disease is unknown (1, 4). Therefore, enrolling these patients in clinical trials should be strongly encouraged if available. This approach would allow access to innovative treatments or new drug combinations with the potential to improve outcomes, as the current median OS remains limited to about 10 months despite available therapies (1,3,11). There is no ongoing clinical trial on the treatment of TP53-mutated AML in Turkey. Also, unfortunately, in our cohort, the median OS was 9 months.

In elderly patients with AML, poor-risk cytogenetic abnormalities, including abnormalities of chromosomes 5 or 7 and the presence of complex or monosomal karyotypes, are more prevalent and are strongly associated with inadequate therapeutic responses, increased relapse rates, and dismal OS. The TP53

gene plays a critical role in maintaining genomic stability by activating DNA repair and inducing cell-cycle arrest. TP53 mutations, often linked to poor-risk cytogenetics, represent a major resistance mechanism to DNA-damaging chemotherapy, further contributing to poor outcomes (1,8,12).

The molecular subgroup analysis of the VIALE-A trial revealed that azacitidine combined with venetoclax achieved a significantly higher composite complete remission (CRc) rate compared to azacitidine alone in older patients with TP53-mutated AML. Specifically, the CRc rate was 55.3% (95% CI, 38.3–71.4) with the combination therapy, compared to 0% with azacitidine monotherapy (P<0.001) (12). While the combination therapy demonstrated an improvement in remission rates compared to AZA monotherapy, it did not significantly enhance the duration of response or OS, particularly in patients with low-risk cytogenetics and TP53 mutations. These findings highlight the ongoing challenges in improving outcomes for this high-risk patient population, despite advancements in combination therapies (13). If we look from another perspective, in our study, the response rates to the azacitidine and venetoclax combination in TP53-mutated AML patients were lower compared to those reported in the VIALE-A trial. This discrepancy may be attributed to our limited sample size and the stringent inclusion criteria of clinical trials, which often do not fully account for factors such as patients' comorbid conditions, concomitant medications, and potential drug interactions, thereby not always reflecting real-world scenarios. Additionally, ethnic and genetic factors can influence treatment responses. Therefore, our findings highlight the challenges faced in treating TP53-mutated AML patients in real-life settings and emphasize the need for larger, multicenter studies to better understand and address these issues.

On the other hand, a retrospective, single-center study analyzed 88 patients with TP53-mutated AML focusing on clinical and treatment outcomes. The median age was 67 years, with a male predominance, and most patients exhibited a high VAF with ASXL1 as the most frequent co-mutation, followed by KRAS and NRAS. Among the cohort, 17.1% had therapy-related AML, and 45.5% presented with secondary AML. Intensive therapies demonstrated superior outcomes, with higher CR rates (51.6% vs. 25.7%) and improved 2-year OS (13% vs. 3%) compared to ess intensive regimens. Among intensive regimens, 7+3 showed better OS than CPX-351. Patients who underwent allogeneic transplantation had significantly better survival (2-year OS: 21% vs. 4%). The findings suggest intensive treatment and transplantation confer a survival benefit in TP53-mutated AML, though patient fitness may influence outcomes (14). A multicenter real-world study evaluated treatment outcomes of patients with TP53-mutated AML. The median OS was 8.5 months, and no significant differences observed among patients receiving intensive, less-intensive, or venetoclax-based induction therapies. Notably, only 16% of patients proceeded to allo-HSCT, which was the sole factor independently associated with improved survival in multivariate analysis. These findings highlight the critical role of allo-HSCT in enhancing survival outcomes for patients with TP53-mutated AML, despite the challenges in making this treatment accessible to all eligible patients (15). Despite the persistently poor survival rates in this highly adverse AML subgroup, all patients in our cohort who survived approximately one year of follow-up had undergone allo-HSCT, highlighting its potential as a critical therapeutic intervention for these patients.

The limitations of our study include its retrospective nature, the small cohort size, and the fact that TP53 mutations were assessed using NGS method in only one patient, while Sanger sequencing was employed for the remaining cases. Therefore, we could not evaluate some important co-mutations like ASXL1, TET2, DNMT3a, etc. except for 1 patient, and could not measure VAF. In AML, TP53 mutations are considered pathogenic when the VAF is at least 10% (7). The TP53 VAF burden has prognostic significance and it is inversely correlated with OS. TP53 VAF clearance is a biomarker for the assessment of response to treatment and may provide valuable information for follow-up in patients undergoing allo-HSCT (1). We are currently using the NGS method in our center and will report more comprehensive data in future studies.

Conclusion

In conclusion, patients with TP53-mutated MDS/AML represent a distinct and highly aggressive

disease subgroup with dismal outcomes and limited therapeutic success to date. Extensive recent efforts to evaluate novel therapies for this challenging molecular subgroup have yet to yield success in pivotal trials. Clinicians often prefer less intensive strategies for this patient group due to the historically poor outcomes with intensive chemotherapy. To our knowledge, this is the first report from Turkey specifically addressing patients with TP53-mutated AML. Regardless of whether intensive or less intensive induction is used, facilitating allo-HSCT in eligible patients and optimizing post-transplant care could enhance treatment efficacy and improve survival outcomes. Future therapeutic strategies should focus on developing more effective agents, further investigating the role of transplantation, and determining whether specific patient subsets (e.g., those with a single TP53 mutation and low variant allele frequency) may benefit from existing treatments. Additionally, prioritizing prolonged maintenance therapy may be essential in improving outcomes in this high-risk population.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Comparison of Lateral and Cross Pinning Results in Pediatric Supracondylar Humerus Fractures

Çocuk Suprakondiler Humerus Kırıklarında Lateral ve Çapraz Pinleme Sonuçlarının Karşılaştırılması

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1572482
Geliş Tarihi | Received: 23.10.2024
Kabul Tarihi | Accepted: 15.04.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Ekici M, Melez M, Ozan F. Comparison of Lateral and Cross Pinning Results in Pediatric Supracondylar Humerus Fractures. Hitit Medical Journal 2025;7(2):214-220. https://doi.org/10.52827/hititmedj.1572482

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 12/12/2023 tarihinde Kayseri Şehir Hastanesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 977/2023.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: ME, MM, FO Tasarım: ME, MM, FO Veri Toplama/Veri İşleme: ME, MM, FO Veri Analizi: ME, MM, FO Makalenin Hazırlanması: ME, MM, FO
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Kayseri City Hospital Clinical Research Ethics Committee on 12/12/2023. Decision no: 977/2023.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ME, MM, FO Design: ME, MM, FO Data Collection/Data Processing: ME, MM, FO Data Analysis: ME, MM, FO Manuscript Preparation: ME, MM, FO
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: There are no financial funds for this article.

Comparison of Lateral and Cross Pinning Results in Pediatric Supracondylar Humerus Fractures

ABSTRACT

Objective: Supracondylar humerus fractures (SHF) occur in the immature skeleton. They account for 60-65% of elbow fractures in children, with the most common age group being 4-7 years. The aim of this study is to compare the radiological and functional outcomes of lateral and cross pinning methods used in the closed surgery of pediatric SHF.

Material and Method: This study was conducted on 46 patients with Gartland type 2 and 3 fractures. Group 1 who underwent only lateral pinning, and Group 2 patients who underwent both lateral and medial pinning. Anteroposterior and lateral elbow radiographs were taken postoperatively, at 3 weeks, and at 12 weeks, and radiological angles were measured and recorded. Elbow joint ROM was measured one year after the operation.

Results: The mean age of the patients was 6.28 ± 0.44 years. The decrease in Baumann angle was 2.61 ± 0.36° in Group 1 and 2.64 ± 0.38° in Group 2. The decrease in carrying angle was 0.80 ± 0.14° in Group 1 and 1.36 ± 0.26° in Group 2. The increase in The lateral capitellohumeral angle (LCHA) was 5 ± 0.74° in Group 1 and 6.72 ± 0.93° in Group 2. The elbow joint range of motion (ROM) was 132.85 ± 0.76° in Group 1 and 132 ± 1.01° in Group 2. Based on the measurements, there was no statistically significant difference in radiological and clinical outcomes between lateral and cross pin configurations.

Conclusion: Considering the possibility of iatrogenic ulnar nerve injury, lateral pinning may be considered a safer method.

Keywords: Cross pinning, pediatric trauma, percutaneous pinning, supracondylar humerus.

ÖZET

Amaç: Suprakondiler humerus kırıkları (SHK), gelişimini tamamlamamış iskelette meydana gelir. Çocuklarda görülen dirsek kırıklarının %60-65'ini oluştururlar ve en sık 4-7 yaş grubunda görülürler. Bu çalışmanın amacı, pediatrik SHK'ların kapalı cerrahisinde kullanılan lateral ve çapraz pinleme yöntemlerinin radyolojik ve fonksiyonel sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Bu çalışma, Gartland tip 2 ve 3 kırığı olan 46 hasta üzerinde yürütülmüştür. Sadece lateral pinleme uygulanan hastalar Grup 1'i, hem lateral hem de medial pinleme (çapraz pinleme) uygulanan hastalar ise Grup 2'yi oluşturmuştur. Ameliyat sonrası, 3. haftada ve 12. haftada anteroposterior ve lateral dirsek grafileri çekilmiş ve radyolojik açılar ölçülerek kaydedilmiştir. Dirsek eklemi hareket açıklığı (EHA) ameliyattan bir yıl sonra ölçülmüştür.

Bulgular: Hastaların yaş ortalaması 6,28 ± 0,44 yıldı. Baumann açısındaki azalma Grup 1'de 2,61 ± 0,36° ve Grup 2'de 2,64 ± 0,38° idi. Taşıyıcı açıda azalma Grup 1'de 0,80 ± 0,14° ve Grup 2'de 1,36 ± 0,26° idi. Lateral kapitellohumeral açıdaki (LKHA) artış Grup 1'de 5 ± 0,74° ve Grup 2'de 6,72 ± 0,93° idi. Dirsek eklemi hareket açıklığı (EHA) Grup 1'de 132,85 ± 0,76° ve Grup 2'de 132 ± 1,01° idi. Yapılan ölçümlere göre, lateral ve çapraz pin konfigürasyonları arasında radyolojik ve klinik sonuçlar açısından istatistiksel olarak anlamlı bir fark bulunmamıştır.

Sonuç: İyatrojenik ulnar sinir hasarı olasılığı göz önüne alındığında, lateral pinleme daha güvenli bir yöntem olarak değerlendirilebilir.

Anahtar Sözcükler: Çapraz pinleme, pediatrik travma, perkütan pinleme, suprakondiler humerus

Introduction

SHF frequently occurs in the immature skeleton. In children, the incidence of elbow fractures is around 60-65%. The most common age range for these fractures is between 4-7 years old (1). The Gartland classification is generally used to describe these fractures (2). Closed reduction and percutaneous pinning are the most commonly preferred treatment modalities for extension-type supracondylar humerus fractures (1). The most commonly used methods for pinning are medial-lateral crossed pinning or lateral pinning alone (3). Both of these methods have advantages and disadvantages. Crossed pinning provides a biomechanically more stable fixation. However, it can lead to iatrogenic ulnar nerve injury (4,5). Nevertheless, there is still debate regarding which pinning method is more advantageous. The aim of this study is to compare the radiological and functional outcomes of crossed pinning and lateral pinning techniques used in the closed surgery of pediatric SHF (Gartland types 2 and 3).

Material and Method

This study was performed after obtaining approval from the local ethics committee (977/2023). This study was designed retrospectively. Patients who presented to our emergency department between March 1, 2019, and March 1, 2020, and underwent surgery for supracondylar humerus fractures were included in the study. Inclusion criteria for the study were as follows: Gartland type 2 and type 3 SHF, patients who underwent closed reduction and percutaneous pinning, patients between the ages of four and fourteen, and those who sought medical attention within one week after the injury. Exclusion criteria included open fractures, patients who underwent open reduction, and patients with preoperative neurovascular deficits. Out of the total 55 patients who met these criteria, 9 were excluded due to loss of follow-up, and 46 patients were included in the study.

Study Group

Patients who underwent closed reduction and percutaneous pinning due to SHF were divided into two groups: Group 1 consisted of 21 patients who underwent only lateral pinning, and Group 2 included 25 patients who underwent both lateral and medial pinning. Of the patients included in the study, 15 had type 2 and 31 had type 3 SHF. The number of type 2/type 3 SHF in group 1 and group 2 was 10/11 and 6/19, respectively.

Surgery

Patients underwent closed reduction under general anesthesia. Patients who required open surgical procedures due to inability to achieve closed reduction were not included in the study. The closed reduction was evaluated with fluoroscopy. In Group 1, patients with an acceptable reduction were fixed with 2 Kirschner wires inserted in a divergent manner from the lateral side. In Group 2, after lateral pinning, medial fixation was performed with the ulnar nerve identification.

Follow-Up

Postoperative two-view elbow radiographs were taken at the third, sixth, and twelfth weeks. Baumann, carrying angle, and lateral capitellohumeral angle were measured. Elbow joint range of motion was recorded at least one year postoperatively. Changes in the Baumann angle between postoperative and twelfth-week radiographs were evaluated using the method described by Skaggs et al. (6)there is controversy about the optimal placement of the pins. A crossed-pin configuration is believed to be mechanically more stable than lateral pins alone; however, the ulnar nerve can be injured with the use of a medial pin. It has not been proved that the added stability of a medial pin is clinically necessary since, in young children, pin fixation is always augmented with immobilization in a splint or cast.\nMETHODS: We retrospectively reviewed the results of reduction and Kirschner wire fixation of 345 extension-type supracondylar fractures in children. Maintenance of fracture reduction and evidence of ulnar nerve injury were evaluated in relation to pin configuration and fracture pattern. Of 141 children who had a Gartland type-2 fracture (a partially intact posterior cortex: 1- no displacement, 2- mild displacement (6°-12°), 3- extensive displacement (greater than 12°).

Postoperative Care

Patients were discharged on the second day after surgery. Daily dressing changes were performed at the pin site. Patients were splinted for 3 weeks postoperatively. In the third week, Kirschner wires were removed in the outpatient clinic setting. Passive and

active elbow movements were initiated. Two-way elbow radiographs were taken at the postoperative third, sixth, and twelfth weeks. Incidences of postoperative pin site infection and any neurovascular damage occurring during or after surgery were recorded.

Statistical analysis

As a statistical method, the normal distribution of the data was evaluated by Shapiro-Wilk test and comparisons between the two groups were made by Chi-square, Mann Whitney-U and t-test. In the intergroup statistical analysis, $p<0.05$ was considered significant.

Results

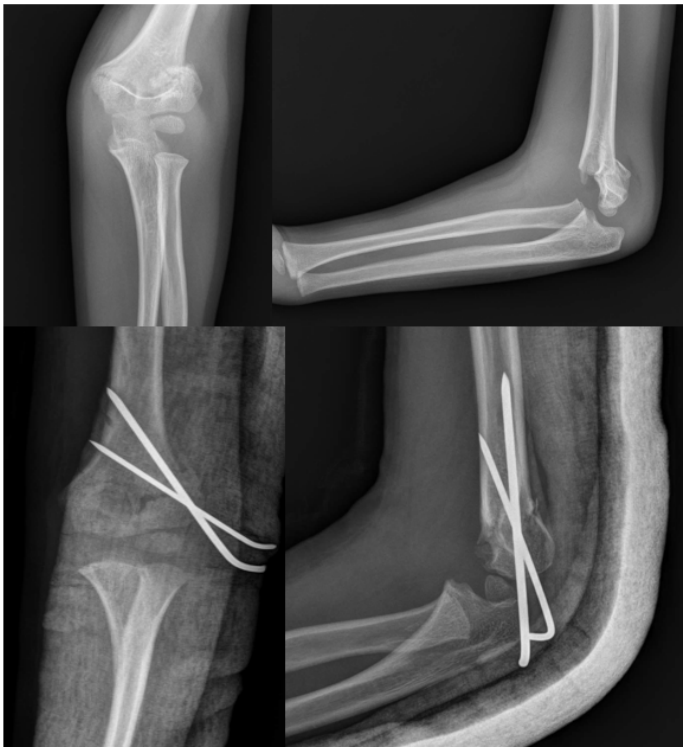
The mean age of the patients was 6.28 ± 0.44 years (ranging from 2 to 14 years). In Group 1, the mean age was 6.71 ± 0.61 years (ranging from 2 to 11 years), while in Group 2, it was 5.92 ± 0.65 years (ranging from 2 to 14 years). Among the patients, 24 had right elbow SHF, and 22 had left elbow fractures. In Group 1, the gender distribution was 11 females and 10 males, while in Group 2, it was 14 females and 11 males. There were 16 patients with Gartland type 2 fractures and 30 patients with Gartland type 3 fractures. The distribution of type 2 and type 3 fracture numbers in Group 1 and Group 2 was statistically no different ($p=0.094$).

Table I. Patients' Data

	Group 1 (n=21)	Group 2 (n=25)	*p*
Age (years)	6.71±0.61	5.92±0.65	*0.229*
Gender (Female/Male)	11/10	14/11	*1.000*
Side (Right/Left)	12/9	12/13	*0.568*
Displacement			
Posterolateral	15	16	*0.754*
Posteromedial	6	9	
Vascular Injury	0	0	
Compartment Syndrome	0	0	
Ulnar Nerve Injury	0	1 (temporary)	*0.359*
Infection	1	1	*0.901*
Hospitalization (day)	2.14±0.15	2.08±0.12	*0.740*

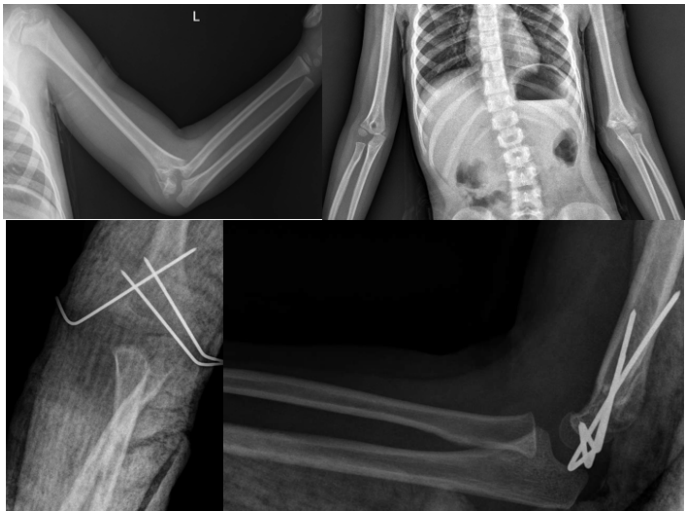
Upon evaluation of the initial radiographs of the patients, it was observed that 15 patients had posteromedial displacement, and 31 patients had posterolateral displacement. The average length of hospital stay for the patients was 2.10 ± 0.67 days. In Group 1, the length of stay was 2.14 ± 0.15 days, and in Group 2, it was 2.08 ± 0.12 days (Table I).

Figure I. Supracondylar Humerus Fracture in a 6-Year-Old Boy due to a Simple Fall (Group-1)



On the postoperative first-day radiographs of the patients, Baumann angles were measured as an average of 75.90 ± 0.44 degrees in Group 1 and 77.32 ± 0.58 degrees in Group 2. The lateral capitellohumeral angle (LKH) measured on the lateral radiograph was 41.66 ± 0.95 degrees in Group 1 and 39.24 ± 1.05 degrees in Group 2.

Figure II. Supracondylar Humerus Fracture in a 4-Year-Old Girl due to a Simple Fall (Group-2)



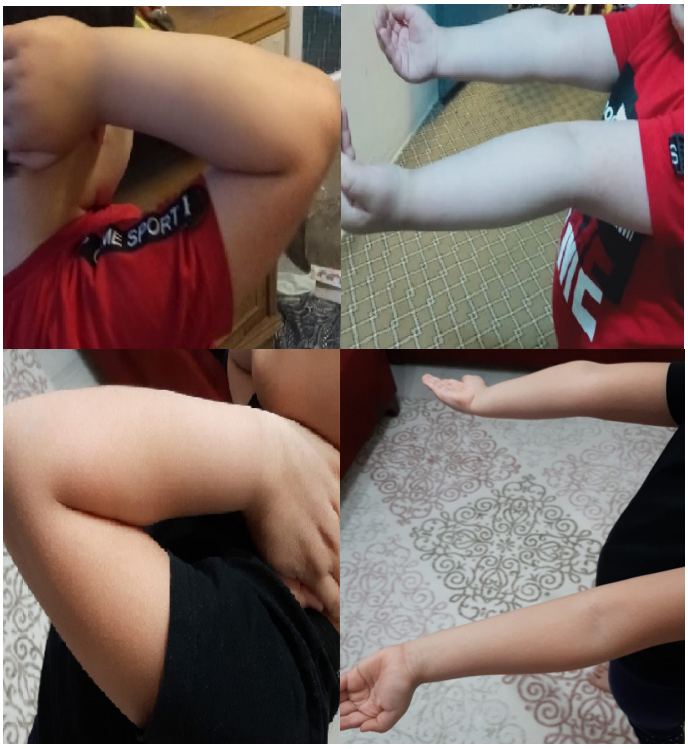
On the postoperative third-week radiographs, Baumann angles were measured as an average of 74.23 ± 0.51 degrees in Group 1 and 75.44 ± 0.61

degrees in Group 2. The LCHA measured on the lateral radiograph was 42.28 ± 0.98 degrees in Group 1 and 40.60 ± 1.06 degrees in Group 2. The carrying angle between the humerus shaft and ulna's long axis on anteroposterior radiographs was 9.57 ± 0.49 degrees in Group 1 and 10.20 ± 0.62 degrees in Group 2 (Figure I and II).

Table II. Radiological and Clinical Measurements of Patients

	Grup 1 (n=21)	Grup 2 (n=25)	*p*
Baumannn post-op	75.90±0.44	77.32±0.58	*0.117*
Baumannn 3rd week	74.23±0.51	75.44±0.61	*0.158*
Baumannn 12th week	73.19±0.55	74.68±0.59	*0.107*
LKH post-op	41.66±0.95	39.24±1.05	*0.504*
LKH 3rd week	42.28±0.98	40.60±1.06	*0.991*
LKH 12th week	43.61±1.27	42.96±1.10	*0.078*
Carrying angle 3rd week	9.57±0.49	10.20±0.62	*0.237*
Carrying angle 12th week	8.80±0.45	8.84±0.57	*0.596*
Joint Range of Motion	132.85±0.76	132±1.01	*0.535*

Figure III. Joint Range of Motion at One Year Postoperative (patient with lateral pinning above, patient with crossed pinning below)



On the postoperative twelfth-week radiographs, Baumann angles were measured as an average of 73.19 ± 0.55 degrees in Group 1 and 74.68 ± 0.59 degrees in Group 2. The LCHA measured on the lateral radiograph was 43.61 ± 1.27 degrees in Group 1 and 42.96 ± 1.10 degrees in Group 2. The carrying angle was 8.80 ± 0.45 degrees in Group 1 and 8.84 ± 0.57 degrees in Group 2. According to the Skaggs method, all patients in Group 1 were classified as having mild displacement, whereas in Group 2, two patients were considered to have mild displacement due to a 7° angle change (Table II).

The joint ROM, measured earliest at one year postoperatively, was 132.85 ± 0.76 degrees in Group 1 and 132 ± 1.01 degrees in Group 2 (Figure III).

Discussion

According to the results of our study, no statistically significant difference was observed between cross pinning and lateral pinning clinically and radiologically. This situation reveals that medial pinning, which puts the ulnar nerve at risk, does not actually contribute to the clinic. Avoiding this risk may be advantageous for clinicians.

Although there are many configurations discussed in the literature, the two most commonly used methods are lateral and crossed pinning (7,8). Both methods have their disadvantages. In the crossed pinning technique, the possibility of ulnar nerve injury has been found to be higher compared to lateral pinning (9). Iatrogenic ulnar nerve injury has been reported to range from 1.4% to 15.6% in medial pinning (10,11). Ayaş et al. found no difference between cross and lateral pinning in terms of nerve injury (12). However, unlike this study, in the meta-analysis including 22 RCTs, 20 studies showed that the probability of ulnar nerve injury was lower in the lateral pinning technique. No statistically significant difference was noted for other clinical outcomes (13). In our study, only one patient had temporary ulnar nerve injury due to neuropraxia. No statistically significant difference was found between the two groups. Previous studies have found that lateral pinning is biomechanically less stable and has a higher risk of reduction loss (14). However, unlike biomechanical studies, clinical studies reveal that there is no difference in the possibility of reduction loss for both groups (12,15–17).

Both methods share the disadvantage of pin-site infections related to closed pinning. The risk of pin-site infection, which depends on many factors during the preoperative, perioperative, and postoperative periods, is independent of pin configuration. The rates of pin-site infection in pediatric SHF range from

1% to 21% (18–20). In the study conducted by Zhao et al, it was stated that there was no statistically significant difference in terms of postoperative infection between cross-pinning and lateral pinning (16). In our study, pin-site infections were observed in one patient from each group. No statistically significant difference was found between the two groups. The overall infection rate was calculated as 3.57%, which is similar to the literature.

A study reported a higher probability of cubitus varus only in patients treated with lateral pinning (21). In other studies, a decrease in the carrying angle was found to be 4.12°-4.4° for lateral pinning and 3.8°-4.6° for crossed pinning (4,17). In our study, the carrying angle for Group 1 patients was measured as 9.57±0.49° at the third week and 8.80±0.45° at the third month. For Group 2 patients, the carrying angle was 10.20±0.62° at the third week and 8.84±0.57° at the third month. In Group 1, the angle change was 0.80±0.14°, while in Group 2, it was 1.36±0.26°. These values indicate that there was no significant difference between the two groups regarding cubitus varus.

Prashant et al. calculated a decrease in Baumann's angle of 4.74±1.29° for lateral pinning and 4.99±0.87° for crossed pinning (22). Afaque et al. calculated a decrease in Baumann's angle of 2.0±0.7° for lateral pinning and 2.1±0.8° for crossed pinning (4). In our study, Baumann's angle for Group 1 was 75.90±0.44° postoperatively and 73.19±0.55° at the third month, while for Group 2, it was 77.32±0.58° postoperatively and 74.68±0.59° at the third month. The decrease in Group 1 was 2.61±0.36°, while in Group 2, it was 2.64±0.38°. Consistent with previous studies, there was no statistically significant difference between the two groups in terms of the decrease in Baumann's angle (12,16). In the study by Pavone et al., radiographic measurements of the Baumann angle between the injured limb and the normal limb were as follows: Group 1: 5.3° ± 2.12° difference (range 4°–6.6°) and Group 2: 4.9° ± 2.82° difference (range 3.1°–6.7°) (17). According to the Skaggs method based on the decrease in Baumann's angle, two patients in Group 2 were classified as having mild displacement due to a 7° angle loss, while in Group 1, all patients had no displacement with less than 6° angle loss. However, this difference was not statistically significant.

LCHA measured on the lateral radiograph is not commonly used in standard follow-ups. Kiyota et al. calculated LCHA as 47.1° (27°-63°) in normal populations aged 0-11 years (23). In the study conducted by Karagöz et al., it was shown that the lateral capitellohumeral angle increased by 3.20 ±0.56° after lateral pinning (24). A decrease in this angle is natural due to an extension-type fracture of the supracondylar humerus. In our study, LCHA was 41.66±0.95° for Group 1 and 39.24±1.05° for Group 2 postoperatively. Over time, both groups showed an increase in this angle due to remodeling and active-passive flexion exercises. In Group 1, the angle increased by 5±0.74°, while in Group 2, it increased by 6.72±0.93°. However, there was no statistically significant difference between the two groups in terms of the increase in LCHA.

Joint range of motion measurements were 132.85±0.76° for Group 1 and 132±1.01° for Group 2. This difference was not statistically significant. In the study conducted by He et al., ROM in SHF fixed with K-wire was calculated as 141.75 ± 6.03 degrees (25). In another study, at the final follow-up examination after cross-pinning, the range of motion in the treated arm resulted in values of 103° ± 12.05° for flexion-extension. After lateral pinning, ROM was reported as 110.27° ± 14.39° (17).

One limiting factor of the study is that these measurements were made digitally by calculating from photographs taken after digital meetings with families due to pandemic conditions. According to the data obtained in our study, there was no statistically significant difference between using only lateral or crossed pin configurations in terms of radiological or clinical outcomes.

However, considering the possibility of ulnar nerve injury, lateral pinning may be preferred as a safer method. When making the choice, the structure of the fracture and the surgeon's experience should be taken into account. This study should be supported by larger studies conducted on a wider population.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Comparison of Analgesic Efficacy of Ultrasound Guided Ilioinguinal/iliohypogastric Nerve Block and Transversus Abdominis Plane Block in Pediatric Unilateral Lower Abdominal Surgery

Pediatrik Tek Taraflı Alt Batın Cerrahisinde Ultrasonografi Eşliğinde Yapılan İlioinguinal/ iliohipogastrik Sinir Bloğu ile Transversus Abdominis Plan Bloğunun Postoperatif Analjezik Etkinliğinin Karşılaştırılması

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1606905
Geliş Tarihi | Received: 24.12.2024
Kabul Tarihi | Accepted: 27.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Turhan Ö, Türk HŞ, Sayın P, Oba S. Comparison of Analgesic Efficacy of Ultrasound Guided Ilioinguinal/iliohypogastric Nerve Block and Transversus Abdominis Plane Block in Pediatric Unilateral Lower Abdominal Surgery. Hitit Medical Journal 2025;7(2):221-226. https://doi.org/10.52827/hititmedj.1606905

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 03/03/2015 tarihinde Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 422.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HŞT, SO Tasarım: HŞT, SO Veri Toplama/Veri İşleme: ÖT, PS Veri Analizi: ÖT, HŞT, PS Makalenin Hazırlanması: ÖT, HŞT, PS, SO.
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar. Bu çalışma Özlem Turhan'ın Tıpta Uzmanlık tezinden üretilmiştir ve tez.yok.gov.tr içerisinde 10621385 numarası ile tüm teze ulaşılabilir.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Şişli Hamidiye Etfal Training and Research Hospital Research Ethics Committee on 03/03/2015. Decision no: 422.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HŞT, SO Design: HŞT, SO Data Collection/Data Processing: ÖT, PS Data Analysis: ÖT, HŞT, PS Manuscript Preparation: ÖT, HŞT, PS, SO.
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: There are no financial funds for this article.

This study was Özlem Turhan's specialization thesis in medicine and was recorded at tez.yok.gov.tr with a registration number: 10621385.

Comparison of Analgesic Efficacy of Ultrasound Guided Ilioinguinal/iliohypogastric Nerve Block and Transversus Abdominis Plane Block in Pediatric Unilateral Lower Abdominal Surgery

ABSTRACT

Objective: Regional techniques providing effective postoperative analgesia in pediatrics are controversial. We compared analgesic efficacy of ilioinguinal/iliohypogastric nerve and transversus abdominis plane blocks in children underwent abdominal surgery.

Material and Method: In this retrospectively designed study, a total of 60 patients aged between 2 and 12 years who underwent abdominal surgery were divided into two groups: Group I (n=30), which received an ilioinguinal/iliohypogastric nerve block, and Group II (n=30), which received a transversus abdominis plane block. Demographics, intraoperative heart rate, fentanyl consumption, duration of anesthesia and surgery, postoperative pain scores and time to first additional analgesic, number of patients requiring additional analgesia, and complications were recorded.

Results: The time to first postoperative analgesia requirement was similar between Group I and Group II (258 ± 135 min and 193 ± 94 min, respectively *p=0.369*). Demographics, intraoperative fentanyl consumption, duration of anesthesia and surgery were similar in both groups. Intraoperative heart rate and postoperative pain scores at 0th, 1st, and 2nd hours were comparable between the groups. Heart rate decreased significantly from baseline at 15 and 30 minutes within each group. Pain scores decreased significantly at 1st and 2nd hours compared to 0th hour within each group. The number of patients requiring additional analgesia in the first 24 hours postoperatively was similar between the groups. No patients experienced any complications.

Conclusion: Ilioinguinal/iliohypogastric nerve and transversus abdominis plane blocks provided similar analgesic efficacy in pain management after pediatric lower abdominal surgery. Both techniques could be preferable regional analgesia methods as part of a multimodal approach in this population.

Keywords: Acute postoperative pain, nerve block, pediatrics, regional anesthesia.

ÖZET

Amaç: Pediatrik hastalarda etkin postoperatif analjezide rejyonal analjezi yöntemleri tartışmalıdır. Çocuklarda uyguladığımız ilioinguinal/iliohipogastrik sinir ve transversus abdominis plan bloklarının analjezik etkinliklerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif olarak planlanan çalışmada abdominal cerrahi geçiren 2-12 yaş arası toplam 60 hasta ilioinguinal/iliohipogastrik sinir bloğu uygulananlar Grup I (n=30), transversus abdominis plan bloğu uygulananlar Grup II (n=30) olmak üzere iki gruba ayrıldı. Demografik veriler, intraoperatif kalp tepe atımı, fentanil miktarı, anestezi ve cerrahi süreleri, hastaların postoperatif ağrı skorları ile ilk analjezi ihtiyacına kadar geçen süre, ek analjezik ihtiyacı olan hasta sayısı ve komplikasyonlar kaydedildi.

Bulgular: Postoperatif ilk analjezi gereksinimi Grup I ve Grup II arasında benzerdi (sırasıyla 258 ± 135 dakika ve 193 ± 94 dakika *p=0.369*). Demografik veriler, intraoperatif fentanil tüketimi, anestezi ve cerrahi süreleri iki grupta benzerdi. İntraoperatif kalp atım hızı ve postoperatif 0., 1. ve 2. saatlerdeki ağrı skorları gruplar arasında benzer bulundu. Grup içi analizlerinde her bir grupta kalp atım hızında 15. ve 30. dakikalarda başlangıç değerlerine göre anlamlı düşüş görüldü. Postoperatif ağrı skorları grup içi karşılaştırıldığında 1. ve 2. saatlerde 0. saate göre azalma gözlendi. Grup içi kalp atım hızı ve ağrı skorlarının zaman içerisinde gösterdiği değişimler gruplar arasında benzerdi. Postoperatif ilk 24 saatte ek analjezi ihtiyacı olan hasta sayısı gruplar arasında farklılık göstermedi. Hastalarda herhangi bir komplikasyona rastlanmadı.

Sonuç: İlioinguinal/iliohipogastrik sinir ve transversus abdominis düzlem blokları, pediatrik alt batın cerrahisi sonrası ağrı yönetiminde benzer analjezik etkinlik sağlamıştır. Çocuk popülasyonunun multimodal analjezi yaklaşımında her iki teknik de tercih edilebilir bölgesel analjezi yöntemleri olabilir.

Anahtar Sözcükler: Akut postoperatif ağrı, pediatri, rejyonal anestezi, sinir blok.

Introduction

Pain is a common clinical complaint during the postoperative period. The inability of pediatric patients to express pain, particularly in younger populations, is challenging. Postoperative pain must be managed properly, as it affects not only the child who experiences pain after surgery, but also the parent, surgeon, and anesthesiologist. Moreover, effective pain control has a positive impact on recovery, hospital stay, and patient comfort (1,2).

Multimodal treatment, including regional methods, can be used in pediatric postoperative analgesia (1). The method of regional analgesia commonly used in children undergoing lower abdominal surgery is caudal epidural block (3). However, over the years, the known complications of neuraxial anesthesia have increased the tendency of clinicians to use peripheral blocks (4,5). Transversus abdominis plane (TAP) and ilioinguinal/iliohypogastric nerve (IL/IH) blocks are regional analgesia techniques that have become widespread with the increasing use of ultrasound (US) in the management of pain after abdominal surgery in children (6,7). The use of regional analgesia methods that reduce intraoperative anesthetic consumption, surgical stress, and pain is recommended for improved recovery after surgery in the pediatric population (8). There is no agreement on the appropriate regional analgesia technique owing to conflicting results regarding the analgesic efficacy of regional methods in pediatrics.

In our study, we investigated the analgesic efficacy of TAP and IL/IH blocks performed as regional analgesia methods in pediatric patients who underwent lower abdominal surgery. We aimed to compare the analgesic efficacy of these blocks with the time to first analgesia requirement as our primary outcome. In addition, we examined pain scores, intraoperative opioid consumption, hemodynamic effects, and the number of patients requiring additional analgesics as secondary outcomes.

Material and Method

This study was conducted after obtaining approval from the Ethics Committee of the Şişli Hamidiye Etfal Training and Research Hospital (422/2015). Patients aged between 2 and 12 years with ASA I status, who underwent elective unilateral lower abdominal surgery between March 2013 and February 2014 were retrospectively examined. Written informed consent was obtained from all the parents. The patients were divided into two groups according to the regional analgesia method. Patients who underwent IL/IH block were defined as Group I, and those who underwent TAP block were defined as Group II.

The laryngeal mask airway (LMA) was placed in patients and US-guided IL/IH or TAP blocks were applied using 0.3 mL/kg 0.25% bupivacaine following standard anesthesia induction. Demographics, intraoperative heart rate (HR), total fentanyl consumption, duration of anesthesia, and surgery were noted from medical records.

In our institute, we evaluated the pain and analgesic needs of pediatric patients in the post-anesthesia care unit using the face, leg, activity, cry, consolability (FLACC) scale, which results in a total score between 0-10 (0: no pain, 10: very severe pain), as shown in Table I (9). Patients routinely received 10 mg/kg paracetamol at the end of surgery. Patients whose FLACC scores were 4 and above at 0th, 1st, and 2nd hours postoperatively were administered additional analgesics.

The time that patients needed the first additional analgesic, the number of patients who required additional analgesia in the first postoperative two hours with FLACC score of >4, the number of patients who required analgesia between the second and 24th hours postoperatively, and complications were recorded.

Statistical Analysis

The distribution of data was evaluated using the Kolmogorov-Smirnov test. Normally distributed quantitative data were analyzed using the Student t-test, and non-normally distributed quantitative data were analyzed using the Mann-Whitney U test. The chi-square test was used to analyze categorical data. Repeated measurements were evaluated using the paired t-test and Wilcoxon test. Statistical significance was accepted as $p<0.05$.

Results

Data from 60 patients were included in the statistical analysis: 30 in Group I and 30 in Group II. Demographics, intraoperative fentanyl consumption,

duration of anesthesia, and surgery were similar in both groups. (Table II)

Table I. Face Legs Activity Cry Consolability Scale

Categories	0	1	2
Face	No expression or smile	Occasional grimace, withdrawn or disinterest	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rijid or jerking
Cry	No crying (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Intraoperative HR values in Group I and Group II before induction (initial), after insertion of the LMA, and at the 15th and 30th minutes were statistically similar. When the timewise change in HR within the group was examined, there was a statistically significant decrease after LMA at the 15th and 30th minutes in both groups compared to the initial HR values. Deceleration in HR did not show a statistically significant difference between the groups. (Table III)

Table II. Demographic and Operative Data

	Group I (n=30)	Group II (n=30)	*p value*
Age (years)	4.4±2.2	4.1±2.1	*0.546*
Gender (female/ male)	11 (36.7%) / 19 (63.3%)	10 (33.3%) / 20 (66.7%)	*0.787*
Weight (kg)	17.4±4.9	16.3±4.7	*0.366*
Duration of anesthesia (min)	51±13.9	51.1±5.7	*0.971*
Duration of surgery (min)	34.8±14.8	31.7±6.9	*0.299*
Total fentanyl amount(mcg)	18.8±5.8	21.2±5.7	*0.063*

Data were expressed as mean ± standard deviation or number (percentage).
Group I: patients with ilioinguinal / iliohypogastric nerve block
Group II: patients with transversus abdominis plane block.

The FLACC scores at 0th, 1st, and 2nd hours were comparable between the groups. The timewise change of the FLACC scores within the group showed a statistically significant decrease at the 1st and 2nd hour compared to the 0th hour in both groups. This decrease in the pain score was not statistically different between the groups. (Table IV)

Table III. Intraoperative Heart Rate Variations

		Group I (n=30)		Group II (n=30)		*p value*
		mean±sd	median (min/max)	mean±sd	median (min/max)	
HR	Initial	116.6±11.4	117 (94-135)	115.2±9.3	115 (99-135)	*0.613*
	After LMA	112.8±12.3	115 (82-130)	113.2±8.3	113 (99-135)	*0.903*
	15th min	111.8±14	114 (84-141)	114±8.7	114 (97-135)	*0.475*
	30th min	106.3±11.3	106 (85-138)	108.3±8.9	109 (90-129)	*0.435*
Variations in HR According to Initial Value Within Groups						
After LMA		-3.7±12.2	-2 (-28/-15)	-2±6.4	-3 (-20/-14)	*0.502*
15th min		-4.7±16.8	-3 (-35/-34)	-1.2±9.3	-3(-19/-22)	*0.318*
p value of timewise variations		*<0.001*		*<0.001*		
30th min		-10.3±14.7	-10 (-48/-13)	-6.9±10	-7 (-26/-16)	*0.295*
p value of timewise variations		*<0.001*		*<0.001*		

HR, heart rate; LMA, laryngeal mask.
Group I: patients with ilioinguinal / iliohypogastric nerve block.
Group II: patients with transversus abdominis plane block.

The time to first additional analgesic requirement was 258 ± 135 min in Group I and 193 ± 94 min in Group II, and there was no statistically significant difference between the groups (*p=0.369*). The number of patients who required additional analgesia in the first 2 hours postoperatively was similar between the groups: 5 (17%) patients in Group I and 7 (23%) patients in Group II (*p=0.519*). Patients who needed additional analgesia between the 2nd and 24th hours were 5 (17%) patients in Group I and 6 (20%) patients in Group II, which was not statistically different between groups (*p=0.739*). No postoperative complications were observed in the patients.

Table IV. Postoperative Pain Scores

		Group I (n=30)	Group II (n=30)	*p value*
		median(min-max)	median(min-max)	
FLACC score	**0th hour**	1 (0-5)	1 (0-5)	*0.981*
	1st hour	0 (0-4)	1 (0-4)	*0.929*
	2nd hour	1 (0-3)	0 (0-5)	*0.344*
Variations in FLACC Score According to Initial Value Within Groups				
1st hour		0 (-4/-3)	0 (-3/-1)	*0.848*
p value of timewise variations		*<0.001*	*<0.001*	
2nd hour		0 (-5/-3)	0 (-5/-3)	*1*
p value of timewise variations		*<0.001*	*<0.001*	

FLACC score, Face Legs Activity Cry Consolability score.
Group I: patients with ilioinguinal/iliohypogastric block.
Group II: patients with transversus abdominis plane block.

Discussion

Postoperative pain management is particularly important in the pediatric patient population. Pain can cause stress response, negatively affect recovery, deteriorate the child's comfort, and lead to anxiety in parents (1,2,10). The use of regional anesthesia techniques has become a significant part of multimodal pain management in children. This can be attributed to advancements in US technology, the safety and efficacy of US guidance in block performance, and the accustomed use of US (11). The Pain Committee of the European Society for Pediatric Anesthesiology has recommended US-guided peripheral blocks performed by experienced clinicians for postoperative pain treatment of children in lower abdominal surgeries (e.g., inguinal hernia and appendectomy) (12). Ilioinguinal/iliohypogastric and TAP blocks are frequently used regional analgesia methods in these surgeries. However, studies investigating these blocks in pediatric patient populations are scarce. Our study is one of the few studies to compare the postoperative analgesic efficacy of IL/IH and TAP blocks in pediatric patients.

A randomized controlled study concluded that the IL/IH block was more suitable than wound infiltration, as it provided better postoperative analgesia (13). In a similar study comparing TAP block with wound infiltration, children with TAP block had lower postoperative pain scores, and fewer patients needed additional analgesia (14).

In our study, we investigated the efficacy of US-guided IL/IH and TAP blocks in the pediatric population. We found that the time to first analgesic requirement, which was our primary outcome (258 min in IL/IH and 193 min in TAP), the pain scores, and the number of patients requiring additional analgesia were comparable. Similarly, Priyadarshini et al. reported no difference in the time to first analgesic requirement and additional analgesia need in their study, which examined these blocks in children undergoing open inguinal surgery (15).

Caudal epidural block is applicable in a wide range of surgeries as a traditional regional analgesia technique because it is efficacious and easy to learn (16). In a meta-analysis consisting of 1399 patients, which compared IL/IH and TAP blocks with caudal block, similarly to our study, the pain scores at 0th and 2nd hours and additional analgesic requirement were close between IL/IH and TAP blocks (17). The authors stated that IL/IH and TAP blocks could be non-invasive alternative methods to caudal analgesia in pediatric genitourinary surgery because of the lower incidence of postoperative motor block and shorter time to first micturition compared to caudal analgesia (17).

In a large meta-analysis that reviewed various regional techniques in pediatric inguinal hernia repair (4636 patients), it was observed that the longest initial rescue analgesia time and the least need for rescue analgesics were achieved with TAP and quadratus lumborum blocks (18). We think that using anatomical landmark technique for IL/IH block performance may be one of the reasons for lower analgesic efficacy than US-guided TAP block. Failure rates of 28-45% were reported in IL/IH block applications with the traditional method, even performed by experienced clinicians (19). The study of Aveline et al., which showed that US-guided TAP block provided better analgesia in adult inguinal hernia repairs than conventional IL/IH block, also supports our opinion (20).

In our study, HR showed a decrease at the intraoperative 15th and 30th minutes compared to the initial values prior to induction in both blocks. Likewise, Karnik et al. observed a significant decrease in HR in the TAP block compared to local infiltration at the same follow-up times (21). Intraoperative fentanyl consumption was also similar between the groups, consistent with another pediatric study comparing these two blocks (22).

The primary limitation of our study was its retrospective design. As a result, pain assessments were limited to the data available patients' records, specifically the initial evaluations performed in the post-anesthesia care unit (PACU) during the first 2 hours postoperatively and the final pain scores recorded prior to discharge, approximately 24 hours after surgery. Intermediate time points could not be assessed due to lack of documented data. The third limitation was the absence of satisfaction questionnaires from surgeons and parents.

In conclusion, we observed that the IL/IH and TAP blocks had similar analgesic efficacy in pain management after pediatric lower abdominal surgery.

It appears that both IL/IH and TAP blocks are effective and could be preferable analgesia methods among regional techniques as part of multimodal analgesia in pediatric patients.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Relationship Between Atherogenic Indices and Cardiovascular Thromboembolic Events in Patients with Covid-19 Pneumonia

COVID-19 Pnömonili Hastalarda Aterojenik İndeksler ile Kardiyovasküler Tromboembolik Olaylar Arasındaki İlişki

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1594744
Geliş Tarihi | Received: 17.12.2024
Kabul Tarihi | Accepted: 21.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Kilci H, Melekoğlu A, Doğan GM, Sümerkan MÇ, Ser ÖS, Altınbilek E. Relationship Between Atherogenic Indices and Cardiovascular Thromboembolic Events in Patients with Covid-19 Pneumonia. Hitit Medical Journal 2025;7(2):227-234. https://doi.org/10.52827/hititmedj.1594744

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu çalışma Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi yerel etik kurulu tarafından 3227 numaralı protokolle onaylandı.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HK, AM Tasarım: HK, AM Data Collection/Data Processing: HK, GMD, ÖSS Veri Analizi: HK, AM, MÇS Makalenin Hazırlanması: HK, EA
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.
Bilgi: Bu çalışma 2021 Kardiyovasküler Akademi Kongresi'nde sözlü bildiri olarak sunulmuştur.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This study was approved by the local ethics committee of Sisli Hamidiye Etfal Training and Research Hospital with protocol No. 3227.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HK, AM Design: HK, AM Data Collection/Data Processing: HK, GMD, ÖSS Data Analysis: HK, AM, MÇS Manuscript Preparation: HK, EA
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

İnformation: This study was presented as an oral presentation in Cardiovascular Academy Congress 2021.

Relationship Between Atherogenic Indices and Cardiovascular Thromboembolic Events in Patients with COVID-19 Pneumonia

ABSTRACT

Objective: COVID-19, caused by coronavirus SARS-CoV-2, is a pandemic viral respiratory infection in which venous and arterial thromboembolic events are often observed. This study aimed to investigate the relationship between atherogenic indices and cardiovascular thromboembolic events in patients with COVID-19 pneumonia.

Material and Method: In this retrospective study, a total of 805 inpatients (median age 63 [IQR: 52-74] years; 45.1% female) who were diagnosed with COVID-19 pneumonia between March 2020 and December 2020 were evaluated. Patients were divided into two groups based on cardiovascular thromboembolic events with cardiovascular thromboembolic events (n=96) and without-cardiovascular thromboembolic events (n=709). All clinical and demographic data and laboratory results were analyzed. Atherogenic Index of Plasma (AIP (log10 (triglyceride/ HDL)), Atherogenic Coefficient (AC (HDL/ non-HDL)), Risk Index of Castelli-I (CRI-I (Total cholesterol/ HDL)), and Risk Index of Castelli-II (CRI-II (LDL/ HDL)) were calculated.

Results: Atherogenic Coefficient, CRI-I, and CRI-II values were significantly higher in the cardiovascular thromboembolic event group (*p=0.001*, *p=0.001*, *p=0.007*, respectively). AIP values were higher in the cardiovascular thromboembolic events group but were not statistically significant (*p=0.051*). In the cardiovascular thromboembolic events group, HDL values were found to be significantly lower (*p=0.001*), but CRP and D-dimer values were found to be significantly higher (*p<0.001*, *p=0.006*, respectively). In the multivariable analysis, Atherogenic Coefficient (OR: 1.294, 95% CI: 1.089-1.1537, *p=0.003*), D-dimer, Hypertension, and current smoking were found to be independent predictors of cardiovascular thromboembolic events in patients with COVID-19 pneumonia.

Conclusion: Atherogenic indices could be used to predict cardiovascular thromboembolic events in patients with COVID-19 pneumonia.

Keywords: Atherogenic indices, cardiovascular events, COVID-19 pneumonia.

ÖZET

Amaç: Koronavirüs SARS-CoV 2'nin neden olduğu COVID-19, venöz ve arteriyel tromboembolik olayların sıklıkla görüldüğü pandemik bir viral solunum yolu enfeksiyonudur. Bu çalışma COVID-19 pnömonili hastalarda aterojenik indeksler ile kardiyovasküler tromboembolik olaylar arasındaki ilişkiyi araştırmayı amaçlamıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Mart 2020 ile Aralık 2020 arasında COVID-19 pnömonisi tanısı alan toplam 805 yatan hasta (ortanca yaş 63 [IQR: 52-74] yıl; %45,1 kadın) dahil edildi. Hastalar kardiyovasküler tromboembolik olaylara göre kardiyovasküler tromboembolik olay olanlar (n=96) ve kardiyovasküler tromboembolik olay olmayanlar (n=709) olarak iki gruba ayrıldı. Tüm klinik ve demografik veriler ve laboratuvar sonuçları analiz edildi. Çalışmaya dahil edilen hastalarda Plazmanın Aterojenik İndeksi (AIP (Log10 (trigliserit / HDL)), Aterojenik Coefficient (AC (HDL / HDL olmayan)) Castelli-I Risk İndeksi (CRI-I (Total kolesterol / HDL)), Castelli-II Risk İndeksi (CRI-II (LDL / HDL)) hesaplanmıştır.

Bulgular: Aterojenik Coefficient, CRI-I ve CRI-II değerleri kardiyovasküler tromboembolik olay grubunda istatistiksel anlamlı derecede yüksek saptandı (sırasıyla *p=0,001*, *p=0,001*, *p=0,007*). Kardiyovasküler tromboembolik olaylar grubunda AIP değerleri daha yüksekti ancak istatistiksel olarak anlamlı değildi (*p=0,051*). Kardiyovasküler tromboembolik olaylar grubunda HDL değerleri istatiksel olarak anlamlı derecede düşük bulundu (*p=0,001*), CRP ve D-dimer değerleri ise istatiksel olarak anlamlı olarak yüksek bulundu (sırasıyla *p<0,001*, *p=0,006*). Çok değişkenli analizde COVID-19 pnömonili hastalarda Aterojenik Coefficient (OR: 1,294, %95 CI: 1,089-1,1537, *p= 0,003*), D-dimer, Hipertansiyon ve mevcut sigara içiminin kardiyovasküler tromboembolik olayların bağımsız öngördürücüleri olduğu saptandı.

Sonuç: Bu çalışmanın sonuçları COVID-19 pnömonili hastalarda kardiyovasküler tromboembolik olayları tahmin etmek için aterojenik indeksler kullanılabileceğini göstermektedir.

Anahtar Sözcükler: Aterojenik indeksler, COVID-19 pnömonisi, kardiyovasküler olaylar

Introduction

In recent years, a new coronavirus infection called COVID-19, caused by the coronavirus SARS-CoV-2, has created a pandemic and caused severe morbidity and mortality all over the world. Clinical findings of the infection may be asymptomatic, mild upper respiratory disease, mild pneumonia, or severe pneumonia, which causes respiratory insufficiency syndrome. Coagulation disorders and related complications are also frequently observed both in the autopsy studies performed and in the patients who were hospitalized and followed up due to COVID-19 (1–3). It has been reported that D-dimer values, a marker of hypercoagulation, are often increased in this infection and are associated with poor outcomes, especially in those with severe disease (4,5).

The association of adverse complications with the severity of the disease was also found at a high rate. Inflammation also plays a vital role in the pathogenesis of atherosclerosis and thrombosis. Due to severe inflammation of COVID-19 infection, endovascular damage might play a crucial role in the occurrence of acute myocardial infarction, stroke, pulmonary embolism, and venous thrombosis. It has been reported that pulmonary embolism, myocardial infarction, and stroke, which are fatal thromboembolic events, are frequently observed during the disease and are associated with a large majority of deaths due to COVID-19 in inpatient and outpatient patients (6–9). So, many societies have made notifications recommending antithrombotic agents in appropriate patient groups (10,11).

Some studies suggested that cardiovascular disease, hypertension, diabetes mellitus, and other cardiovascular risk factors are associated with the severity of the COVID-19 infection and related mortality and morbidities (9,12). Dyslipidemia is one of the significant risk factors for cardiovascular diseases such as myocardial infarction, stroke, peripheral vascular disease, etc. Increasing serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG) values, and a decrease in high-density level (HDL-c) cholesterol values are well-known associated with cardiovascular disease (13,14). Recent studies suggested that some atherogenic indices, such as the atherogenic index of plasma (AIP), atherogenic coefficient (AC), and risk index of Castelli-I and II (CRI-I and II), could be used for identifying cardiovascular disease and thromboembolic events (15,16).

In this study, we aimed to investigate the link between atherogenic indices and cardiovascular thromboembolic events in patients with COVID-19 pneumonia.

Material and Method

In this retrospective study, hospitalized patients diagnosed with COVID-19 pneumonia by laboratory and thoracic computed tomography in the emergency department between March 2020 and December 2020 were included. Patients older than 18 years who did not receive lipid-lowering therapy and whose lipid profile was studied at hospitalization were determined as the inclusion criteria.

After the criteria for inclusion in the study, the data of a total of 805 patients were analyzed. Patients were divided into two groups: those who had cardiovascular thromboembolic events during in-hospital follow-up and those who did not have cardiovascular thromboembolic events. Cardiovascular thromboembolic events were defined as acute coronary syndrome, stroke, pulmonary embolism, and/or deep vein thrombosis.

All biochemical and hematological parameters and demographic characteristics of the patients during hospitalization were recorded from the hospital database. Demographic characteristics of the patients, comorbid diseases, and biochemical tests, which were the measurements of C-reactive protein (CRP), D-dimer, and standard lipid profile, were also recorded. The lipid profiles included triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). The atherogenic coefficient (AC; non-HDL-c/HDL-c), risk index of Castelli-I (CRI-I; TG/HDL-c), risk index of Castelli-II (CRI-II; LDL-c/HDL-c), and atherogenic index of plasma (AIP; logarithm TG/HDL-c) were calculated by utilizing lipid parameters.

This study was approved by the local ethics committee on 27/04/2021 with protocol No. 3227.

Statistical Analysis

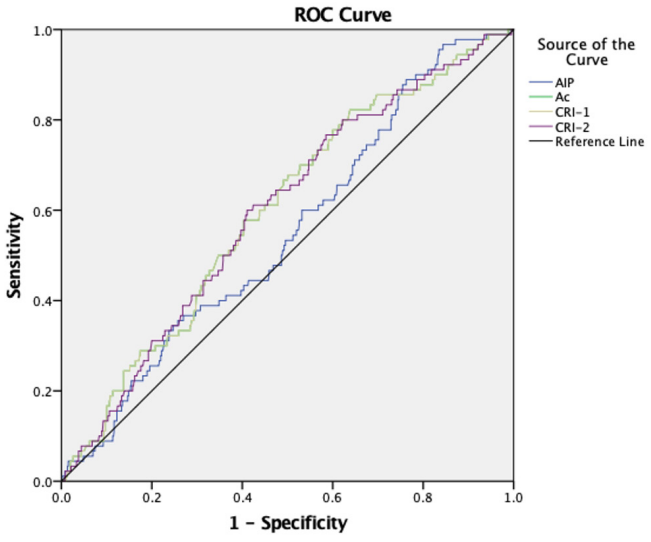
Statistical analysis of the data was performed in

SPSS program, version 22.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to check the normal distribution of continuous variables. Mean (±SD) and median (IQR) were used for quantitative variables, and the number of patients (percentage) was used for qualitative variables. Continuous variables were compared between groups using an independent-sample T-test or the Mann–Whitney U test, as appropriate. Categorical data were compared using the Chi-square or Fisher's Exact test. The univariable and multivariable logistic regression analyses were used to determine the risk factors affecting cardiovascular thromboembolic events. The evaluation of atherogenic indices as a predictive factor for cardiovascular thromboembolic events was performed using predicted probability curves and diagnostic accuracy assessments based on receiver operating characteristic (ROC) analysis. A value of *p<0.05* was considered statistically significant.

Results

A total of 805 patients (363 female, 45.1%) diagnosed with COVID-19 pneumonia were analyzed. The baseline demographic, clinical, and laboratory characteristics of the study population are listed in Table I. The median age of the patients was 63 [IQR: 52-74 years]. A total of 76 patients were identified with cardiovascular thromboembolic events (acute coronary syndrome, stroke, pulmonary emboli, and/or VTE) in-hospital follow-up. The distribution of patients who experienced a cardiovascular thromboembolic event is as follows: 23 patients had acute coronary syndrome, two patients had both acute coronary syndrome and stroke, three patients had deep vein thrombosis, four patients had both deep vein thrombosis and pulmonary embolism, six patients had pulmonary embolism, two patients had both stroke and pulmonary embolism, 36 patients had strokes. No significant difference was observed among patients with and without cardiovascular thromboembolic events group in terms of diabetes mellitus, sex, eGFR, previous history of coronary artery disease, chronic renal failure, and malignancy. Patients in the cardiovascular thromboembolic events group were older than the without-cardiovascular thromboembolic events group (63 (51-74) vs. 68 (57-80), *p=0.012*). Hypertension, atrial fibrillation, current smoking, chronic obstructive pulmonary disease (COPD), and previous history of stroke were significantly higher in the cardiovascular thromboembolic events group. In lipid parameters, HDL-c values were significantly low in the cardiovascular thromboembolic events group (*p=0.001*), but total cholesterol, LDL-c, and TG values were similar between the two groups. AC, CRI-I and CRI-II were found statistically significant when comparing cardiovascular thromboembolic events and without-cardiovascular thromboembolic events groups (4.00 (3.18-4.88) vs.3.47 (2.62-4.43), *p=0.001*; 5.00 (4.18-5.88) vs. 4.48 (3.62-5.43), *p=0.001*; 3.09± 0.96 vs. 2.78 ±1.03, *p=0.007*, respectively). However, AIP was higher in the cardiovascular thromboembolic events group than in the non-cardiovascular thromboembolic events group (0.23±0.24 vs. 0.17±0.25), but the p-value was found to be *0.051*. In addition, the CRP and D-dimer were also found to be statistically significant in patients who developed cardiovascular thromboembolic events (102 (28-183) vs. 150 (64-229), *p=0.002*; 869 (494-1627) vs. 1290 (585-2803), *p=0.006*, respectively).

Figure I. Receiver operating characteristic graphic to detect the best cut-off values of AC, CRI-I, CRI-II, and AIP for cardiovascular thromboembolic events development.



In the univariable logistic regression analysis (Table II), AC, age, D-dimer, current smoking, hypertension, CRP, CRI-I, and CRI-II were associated with cardiovascular thromboembolic events (*p=0.001; p=0.03; p=0.018; p<0.001; p=0.007; p=0.005; p=0.002; p=0.008,* respectively). Multivariable logistic regression analysis (Table 2) showed that AC was an independent predictor of cardiovascular

thromboembolic events (OR: 1.294, 95% CI: 1.089-1.1537, *p=0.003*). Current smoking, hypertension, and D-Dimer were also independent predictors of cardiovascular thromboembolic events (OR:6.113, 95% CI: 3.510-10.649, *p< 0.001;* OR:1.852, 95% CI: 1.078-3.179, *p=0.026*, and OR: 1.000077, 95% CI: 1.000013-1.000140, *p=0.018*, respectively).

Table I. Clinical, Demographic, and Laboratory Characteristics of the Study Group According to Cardiovascular Thromboembolic Events in Patients with COVID-19 Pneumonia

Variables	Total n=805	Without-cardiovascular thromboembolic events n=709	Cardiovascular thromboembolic events n=96	*p value*
Age, years	63 (52-74)	63 (51-74)	68 (57-80)	*0.012*
Female, n (%)	363 (45.1)	325 (45.8)	38 (39.6)	*0.248*
Diabetes Mellitus, n (%)	300 (37.3)	260 (36.7)	40 (41.7)	*0.342*
Hypertension, n (%)	406 (50.4)	345 (48.7)	61 (63.5)	*0.006*
Current smoking, n (%)	102 (12.7)	70 (9.9)	32 (33.3)	*<0.001*
Coranary artery diseases, n (%)	173 (21.5)	149 (21)	24 (25)	*0.372*
COPD/Asthma, n (%)	82 (10.2)	62 (8.7)	20 (20.8)	*<0.001*
Chronic renal failure, n (%)	120 (14.9)	112 (15.8)	8 (8.3)	*0.054*
Cerebrovascular diseases, n (%)	62 (7.7)	45 (6.3)	17 (17.7)	*<0.001*
Atrial fibrillation, n (%)	65 (8.1)	52 (7.3)	13 (13.5)	*0.036*
Malignancy, n (%)	104 (12.9)	93 (13.1)	11 (11.5)	*0.649*
eGFR ml/ min/1.73 m^2	77.6± 40.3	76.8 ±40.1	83.9 ±40.9	*0.106*
Total cholesterol, mg/dL	169 (137-204)	169 (137-204)	165 (139-205)	*0.883*
LDL cholesterol, mg/dL	101 (77-131)	102 (77-131)	100 (76-136)	*0.878*
HDL cholesterol, mg/dL	37 (30-46)	38 (31-47)	35 (28-40)	*0.001*
Triglyceride, mg/dL	129 (95-174)	129 (94-174)	125 (95-174)	*0.869*
C-Reactive Protein, mg/L	106 (31-190)	102 (28-183)	150 (64-229)	*0.002*
D-dimer, ng/ml	893 (500-1803)	869 (494-1627)	1290 (585-2803)	*0.006*
Creatinine, mg/dl	0.93 (0.73-1.29)	0.94 (0.74-1.29)	0.86 (0.67-1.30)	*0.156*
Atherogenic index of plasma (AIP)	0.18 ±0.26	0.17 ±0.25	0.23±0.24	*0.051*
Atherogenic coefficient (AC)	3.54 (2.66-4.46)	3.47 (2.62-4.43)	4.00 (3.18-4.88)	*0.001*
Risk Index of Castelli-I	4.55 (3.67-5.46)	4.48 (3.62-5.43)	5.00 (4.18-5.88)	*0.001*
Risk Index of Castelli-II	2.82 ±1.03	2.78 ±1.03	3.09± 0.96	*0.007*

COPD; Chronic obstructive pulmonary disease, eGFR; estimated glomerular filtration rate. HDL-C; High-density lipoprotein-cholesterol, LDL-C; Low-density lipoprotein-cholesterol,

a Data are presented as mean + SD, median (inter-quarter range) or n (%).

ROC analysis showed that the AC value for predicting the development of cardiovascular thromboembolic events was 3.78, with 59.4 % sensitivity and 41 % specificity (area under the ROC curve [AUC] =0.604; 95 % CI: 0.546-0.661; *p=0.001*, figure 1). Regarding ROC assessment, the AUC of the CR-I values was 0.603 (95 % CI: 0.545-0.660; *p=0.001*), and the AUC of the CR-II values was 0.597 (95 % CI: 0.537-0.657; *p=0.003*) (Figure I).

Table II. Univariable and Multivariable Logistic Regression Analysis to Detect The İndependent Predictors Of Cardiovascular Thromboembolic Events in Patients with COVID-19 Pneumonia

Variables	Univariable Analysis			Multivariable Analysis		
	OR	**(95% CI)**	***p value***	**OR**	**(95% CI)**	***p value***
Atherogenic coefficient (AC)	1.286	1.103-1.499	***0.001***	1.294	1.089-1.1537	*0.003*
Age	1.015	1.001-1.029	***0.030***	1.010	0.993-1.027	*0.262*
Gender	0.774	0.501-1.196	*0.249*	1.042	0.635-1.709	*0.872*
D-Dimer	1.000076	1.000013-1.000138	***0.018***	1.000077	1.000013-1.000140	***0.018***
Diabetes Mellitus	1.234	0.800-1.903	*0.343*	0.977	0.595-1.602	*0.925*
Current Smoking	4.564	2.794-7.457	***<0.001***	6.113	3.510-10.649	***<0.001***
Hypertension	1.839	1.183-2.858	***0.007***	1.852	1.078-3.179	***0.026***
C-Reactive protein	1.003	1.001-1.004	***0.005***	1.001	0.999-1.003	*0.189*
Atherogenic index of plasma (AIP)	2.270	0.994-5.186	*0.052*			
Castelli Risk Index I (CRI-I)	1.283	1.100-1497	***0.002***			
Castelli Risk Index II (CRI-II)	1.319	1.075-1617	***0.008***			

Discussion

In this study, we evaluated the association between lipid parameters and cardiovascular thromboembolic events in patients with COVID-19 pneumonia. AC, CRI-I, and CRI-II were independent predictors of the development of cardiovascular thromboembolic events in these patients. We also found that current smoking, hypertension, and D-dimer are independent risk factors for developing cardiovascular thromboembolic events in patients with COVID-19 pneumonia.

COVID-19 pneumonia is a severe viral infection that progresses to acute respiratory failure syndrome and is accompanied by severe inflammation (17,18). It is also well known that severe inflammation

triggers plaque rupture and erosion, especially in atherosclerotic patients with sensitive plaque, triggering fatal diseases such as acute myocardial infarction. It has been reported that early and late follow-up of patients suffering from COVID-19 infection develops conditions that cause severe mortality and morbidity, such as acute myocardial infection, stroke, and arterial and venous thromboembolism (6,9,19,20)the most significant medical challenge in the last century. COVID-19 is associated with notable increases in morbidity and death worldwide. Preexisting conditions, like cardiovascular disease (CVD. Our study found that thromboembolic events developed in about 12% of the patients we followed up with COVID-19 pneumonia. CRP values were statistically significantly higher in patients with an event. Similarly, we found that events occurred at a statistically high rate in those with underlying COPD. These findings suggest that the severity of COVID-19 infection plays a crucial role in the development of cardiovascular thromboembolic events.

In some studies conducted with COVID-19, it has been found that atherosclerotic risk factors are associated with poor outcomes (21,22). Although there was no difference between the groups regarding coronary artery disease in our study, it was found that the patients who had an event were older, hypertensive, and smokers, similar to the recent studies. It has been shown that hypertension and smoking are powerful predictors that independently predict the development of events. This supports the hypothesis of underlying silent atherosclerosis and the development of arterial and venous thromboembolism after the rupture and erosion of existing vulnerable plaques in patients with COVID-19 pneumonia.

COVID-19 infection is usually associated with thrombotic complications in both arterial and venous circulations. Thromboembolism is a common complication in hospitalized patients due to COVID-19 disease and is monitored in about 25-40% (23,24). Abnormal clotting parameters, such as high D-dimer levels, are often encountered in COVID-19 infection, even in patients who do not have apparent signs of thrombus (25). Some studies have also suggested a dynamic relationship between the level of D-dimer and the prognosis of COVID-19 patients and the need for anticoagulation (4,5,26). Potential mechanisms for increased D-Dimer levels in patients with COVID-19 include pulmonary endothelial damage with inflammation-induced intra-alveolar fibrin deposits, systemic endothelial damage with diffuse thrombosis of smaller vessels or larger vessels, and coagulopathy (27).

Some studies have shown that interleukin (IL), CRP, and D-dimer are associated with the severity of COVID-19 disease, and high CRP and D-dimer values are associated with mortality (26,28,29). Again, similarly, high D-dimer and CRP values have been shown to be associated with severe complications in the course of this disease, and it is thought that they can be used as biomarkers to detect hostile terminations in these patient groups (18). In our study, it was also found that CRP and D-dimer levels were significantly higher in the thromboembolic event group that occurred in the patient groups that had COVID-19 pneumonia, which supports the hypothesis.

The endothelium, which plays a fundamental role in ensuring hemostasis, regulating vascular permeability, and regulating the response of blood cells and immunomodulators, might become the target of viral infections that cause severe infection, such as the coronavirus (30). Histopathological studies have shown direct infection of the endothelium with the virus in both arterial and venous circulation, diffuse endothelial infection, and micro- and macrovascular thrombosis. Cytokine storms (IL-6, IL-2, TNF-α), also shown in COVID-19 infections, can also contribute to endothelial dysfunction and leukocyte uptake into the microvascular system. It is also known that endothelial dysfunction plays a significant role in organ dysfunction during viral infections, as it causes an anticoagulant state, microvascular leakage, and organ ischemia (31,32). The leading cause of thrombus formation in the vascular lumen in acute coronary syndrome and stroke is erosion or rupture of vulnerable plaque. The histopathological description of vulnerable plaque includes a lesion rich in lipid content, with a necrotic nucleus with signs of inflammation, including infiltration by macrophages and lymphocytes, with features such as a thin fibrous cap and neovascularization. Endothelial dysfunction is not only the first step of the atherosclerotic process that causes plaque

formation, but it also causes the plaque to grow, crack, and trigger thrombogenic events. As a result of the rupture of the thin fibrous cap on vulnerable plaques, direct contact of circulating blood with the thrombogenic content of the lipid-rich nucleus can lead to rapid activation of the coagulation cascade and acute thrombosis.

Although endothelial dysfunction is one of the most basic mechanisms in the atherosclerotic process, all known atherosclerotic risk factors, such as Dyslipidemia, cause chronic damage to the endothelium, leading to a decrease in vasodilatory response. Dyslipidemia is one of the most critical factors involved in the pathogenesis of atherosclerosis. Epidemiology studies show that increased serum cholesterol levels alone are sufficient for the development of atherosclerosis, even in the absence of other known risk factors.

Various lipoprotein ratios, which are also called atherogenic indices, have been defined in order to optimize the role of the lipid profile on atherosclerosis. Some studies have suggested that atherogenic indicators calculated from the lipid profile predict cardiovascular risk better than lipid parameters alone (33). The atherogenic indices consist of non-HDL cholesterol (NHC), AIP, CRI-I, CRI-II, and AC, which have been shown to be known independent risk factors for cardiovascular risk. Günay et al. suggested that atherogenic indices (AC, AIP, CRI-I, CRI-II) may be helpful in predicting the risk of atherosclerosis and cardiovascular diseases in stable patients with COPD (34). Another study suggested that atherogenic lipid indices were significantly higher in stroke patients compared to controls. NHC, AC, and CRI-I have been shown to contribute considerably to stroke risk (35). Turgay et al. showed that high AIP levels can predict in-hospital mortality for COVID-19 patients. It has also been suggested that AIP can be used as an early biomarker to predict pneumonia, intubation, and intensive care needs (36). Given the results of the above studies, it is not surprising that atherogenic indicators were found to be significantly higher in patients with COVID-19 pneumonia and cardiovascular thromboembolic events in our study.

In conclusion, COVID-19 pneumonia is a type of viral pneumonia that is accompanied by severe inflammation. It is highly likely that severe inflammation triggers thromboembolic events, especially in cardiovascular risk conditions that trigger endothelial dysfunction, such as Dyslipidemia. Early recognition and close monitoring of COVID-19 pneumonia patients with high cardiovascular is essential for preventing thromboembolic events and timely intervention. In our study, it was found that there is a significant association between atherogenic indices and cardiovascular thromboembolic events in patients with COVID-19 pneumonia. According to the results of this study, atherogenic indices such as AC, CRI-I, CRI-II, and AIP can be used for risk assessment in patients with COVID-19 pneumonia. Further studies may be useful both in terms of this relationship between atherogenic indices with cardiovascular thromboembolic events and treatment planning.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

The Effect of Serum and Follicular Fluid Fetuin-B Levels on In Vitro Fertilization Treatment

Serum ve Folikül Sıvısı Fetuin-B Düzeylerinin Tüp Bebek Tedavisi Üzerine Etkisi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1585893
Geliş Tarihi | Received: 15.11.2024
Kabul Tarihi | Accepted: 29.04.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Ay O, Toğrul C, Görkem Ü, Ayaz E, Taşkıran D. The Effect of Serum and Follicular Fluid Fetuin-B Levels on IVF Success in Patients with Polycystic Ovary Syndrome, Unexplained Infertility, and Poor Ovarian Response in IVF Treatment. Hitit Medical Journal 2025;7(2):235-243. https://doi.org/10.52827/hititmedj.1585893

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 08/09/2021 tarihinde Hitit Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 490.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: OA, CT Tasarım: OA, CT Veri Toplama/Veri İşleme: CT, ÜG, EA, DT Veri Analizi: OA Makalenin Hazırlanması: OA, CT
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Hitit University Clinical Research Ethics Committee on 08/09/2021. Decision no: 490.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: OA, CT Design: OA, CT Data Collection/Data Processing: CT, ÜG, EA, DT Data Analysis: OA Manuscript Preparation: OA, CT
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

The Effect of Serum and Follicular Fluid Fetuin-B Levels on In Vitro Fertilization Treatment

ABSTRACT

Objective: The aim of this study was to investigate the difference between fetuin-B levels in serum and follicular fluid of patients with unexplained infertility, polycystic ovary syndrome (PCOS) and poor ovarian response undergoing In vitro fertilization (IVF) treatment and to investigate the effect of fetuin-B levels on oocyte quality, embryo number and clinical pregnancy.

Material and Method: In this prospective study, women with unexplained infertility (n=25), women with polycystic ovary syndrome (n=25), and women with poor ovarian response (n=25) who were diagnosed with infertility and started IVF treatment were included. Fetuin-B levels in serum and follicular fluid of the groups were tested using the ELISA method. In addition, the effect of the difference in fetuin-B levels between the groups on reproductive success was investigated.

Results: The differences between the distributions of fetuin-B levels measured in follicular fluid were not statistically significant in all three groups ($p>0.05$). On the other hand, the fetuin-B level measured in serum was statistically significantly higher in the PCOS group than in the bad ovary group ($p<0.05$). According to the results of the Mann-Whitney U test performed as post-hoc, only the differences in serum fetuin-B levels between the PCOS group and the bad ovary group were statistically significant ($p<0.05$).

Conclusion: No statistically significant correlation was found between serum fetuin-B and fetuin-B in follicular fluid in the PCOS group. However, in the unexplained infertility group, there was a statistically significant and negative correlation between the level of fetuin-B in the follicular fluid and the number of biochemical pregnancies as well as the number of clinical pregnancies. In this respect, fetuin-B level may have predictive value in predicting the outcome of in vitro fertilization (IVF) in the unexplained infertility group.

Keywords: Fetuin-B, follicular fluid, in vitro fertilization, PCOS, unexplained infertility.

ÖZET

Amaç: İnfertilite tanısı olan ve tüp bebek tedavisi gören açıklanamayan infertilite, polikistik over sendromu ve kötü over yanıtlı hasta gruplarında serum ve folikül sıvılarındaki fetuin-B düzeyleri arasındaki farkı araştırmak ve fetuin -B düzeyinin oosit kalitesi, embriyo sayısı ve klinik gebelik üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Bu prospektif çalışmaya, infertilite tanılı ve tüp bebek tedavisine başlayan açıklanamayan infertilitesi olan kadınlar (n=25), polikistik over sendromlu kadınlar (n=25) ve kötü over yanıtı olan kadınlar (n=25) dahil edildi. Grupların serum ve foliküler sıvısındaki fetuin-B düzeyleri ELIZA yöntemi kullanılarak test edildi. Ayrıca gruplar arasındaki fetuin-B düzeyi farklılığının üreme başarısına etkisi araştırıldı.

Bulgular: Her üç grupta da folikül sıvısından ölçülen fetuin-B değerinin dağılımları arasındaki farklar istatistiksel olarak anlamlı değildi ($p>0.05$). Öte yandan serumda bakılan fetuin-B düzeyi istatistiksel olarak anlamlı şekilde PCOS grubunda kötü over grubundan daha yüksekti ($p<0.05$). Post Hoc olarak yapılan Mann Whitney U testi sonuçlarına göre, sadece PKOS grubu ile kötü over grubu arasındaki serum fetuin-B düzeyi arasındaki farklar istatistiksel olarak anlamlıydı ($p<0.05$).

Sonuç: PKOS grubunda serum fetuin-B ve folikül sıvısındaki fetuin-B arasında istatistiksel olarak anlamlı bir ilişki bulunamadı. Ancak açıklanamayan infertilite grubunda folikül sıvısındaki fetuin-B seviyesi ile biyokimyasal gebelik ve aynı zamanda klinik gebelik sayısı arasında istatistiksel olarak anlamlı ve negatif yönde ilişki bulundu. Fetuin-B düzeyi bu bakımdan açıklanamayan infertilite grubunda in vitro fertilizasyon (IVF) sürecinin sonuçlarını tahmin etmede prediktif değere sahip olabilir.

Anahtar Sözcükler: Açıklanamayan kısırlık, Fetuin-B, foliküler sıvı, PKOS, tüp bebek tedavisi.

Introduction

Infertility is the inability of a couple to conceive despite 12 months of regular unprotected intercourse under the age of 35 and 6 months of regular unprotected intercourse over the age of 35 (1). In 85 per cent of infertile couples, a cause can be found, while in about 15 percent no cause can be found. The patient group within this 15% is defined as unexplained infertility (2). Polycystic ovary syndrome, one of the common causes of infertility, is a metabolic disease with heterogeneous metabolic processes such as insulin resistance, with a prevalence of approximately 4-8% in reproductive age (1). Approximately 40% of patients with polycystic ovary syndrome (PCOS) present with infertility.

Poor ovarian response is when the ovaries do not respond or respond poorly. In recent years, especially pregnancies postponed for economic and social reasons or the increase in the childbearing age have increased the poor ovarian reserve (3). Ovarian reserve and oocyte quality are especially important in expectant mothers who want to conceive in their late 30s and early 40s and in patients undergoing in vitro fertilization (IVF) (4). Oocytes are surrounded by a layer of extracellular matrix called zona pellucida (ZP). Studies in the literature have reported that the thickness of the ZP, which is one of the morphological characteristics of oocytes, is effective on fertilization (5). In a recent study, it was found that serum fetuin-B level was associated with fertilization rate in IVF and may be a predictive marker of fertilization in IVF treatment (6)

Fetuin-B is a serum protein produced from the liver that is required for fertilization. Fertilization triggers proteolytic cleavage of the glycoproteins of the zona pellucida, resulting in a hardened state of the zona pellucida (7). Hardening of the zona pellucida prevents further sperm binding, further sperm penetration and protects the embryo before implantation. Ovastacin mediates hardening of the zona pellucida (8).

Fetuin-B is a potent ovastacin inhibitor that prevents early zona pellucida hardening. Thus, fetuin-B prevents premature zona pellucida hardening before fertilization and thus keeps the oocytes in a fertilizable state (7). Studies have shown that female mice lacking fetuin-B are infertile because their oocytes have prematurely hardened zona pellucida (9). The condition of the zona pellucida is essential for the success of in vitro fertilization in both humans and animals. Although the important effects of Fetuin-B protein on fertilization are known, the underlying mechanisms have not yet been fully elucidated.

This study aimed to investigate whether fetuin-B molecule levels in serum and follicular fluid of patients presenting with infertility differ between patients with PCOS, unexplained infertile patients, and infertile patients with poor ovarian response, and to investigate the effect on fertility.

Material and Method

The study included 75 infertile women admitted to the IVF center of a university hospital between November 2021 and November 2022. The Hitit University Faculty of Medicine Clinical Research Ethics Committee authorized this study according to the Declaration of Helsinki (approval number: 409). The study included patients who completed written informed consent forms after receiving comprehensive oral and written information. This study was conducted in accordance with the Declaration of Helsinki.

A total of 75 patients were divided into three groups. Infertile patients with PCOS (n=25), unexplained infertile patients (n=25), and patients with poor ovarian response (n=25) were included in the study. Unexplained infertility was diagnosed in women who met the infertility criteria and could not find the cause of their infertility. Patients' oligo-anovulation status, polycystic ovarian morphology (PCOM) on transvaginal ultrasonography and Ferriman-Gallwey scoring, which are clinical indications for hirsutism, were used for the diagnosis of PCOS. Bologna Criteria were used for indication of poor ovarian response. Bologna Diagnostic Criteria: age ≥40 years or presence of other risk factors for poor ovarian response, previously ≤3 oocytes with conventional stimulation, presence of abnormal ovarian reserve test (antral follicle count <5-7 or AMH<0.5-1.1 N-ng/ml).

Name, surname, age, weight, height, BMI, menstrual cycle, number of menstrual days, duration of unprotected sexual intercourse, acne status, and previous pregnancies were recorded. Hirsutism

was assessed using the modified Ferriman Gallwey scoring method. The results of a baseline ultrasound performed routinely throughout the evaluation were recorded. In addition, routinely requested basal hormones (FSH, LH, E2, Prolactin and AMH) were recorded. Chronic diseases, drug use, smoking and alcohol use were questioned.

The exclusion criteria for patients are as follows: women with a body mass index >30 kg/m^2, the patient did not consent to the study, alcohol use in the last 6 months, smoking more than 20 cigarettes a day, heavy exercise up to 1 month before the procedure, known chronic disease, chronic drug use.

Patient Blood Serum and Follicular Fluid Collection Since there were 3 different infertility groups in our study, the most appropriate ovarian stimulation protocol was applied to each patient individually. Oocyte collection was standardised and performed at 35 hours (between 10:00 and 12:00) after hCG treatment when sufficient follicular development was observed on serial transvaginal ultrasonography. Five cc of the remaining follicular fluid was placed in a dry tube and the oocytes were separated from the follicular fluid and stored at -20 °C. Approximately 8 cc of patient blood was placed in a 10 cc empty dry tube at the same time as routine blood tests were performed during the patient's hospitalization. Within 15 minutes, the blood sample was centrifuged at 4000 rpm for 10 minutes. The supernatants obtained were kept in Eppendorf test tube (1.5 ml, FIRADMED, polypropylene) at -20°C. The collected samples were stored at -20°C for 3 months. After the number of patients was completed, the samples were delivered to the laboratory according to the cold chain rule.

Fetuin-B levels were determined using the Enzyme Linked Immunosorbent Assay Fetuin- B Kit. After washing with Human brand, Combi Wash model washing device and reading with Next Level brand. Pregnancy and Oocyte Quality Monitoring

The embryologist noted the number of oocytes, their morphologic parameters (MII, PNII, etc.) and the number of embryos after oocyte collection. On day 14 after embryo transfer, patients were checked for hCG. hCG positive patients were monitored until fetal heartbeat was detected. The patient was considered clinically pregnant when a fetal heartbeat was detected. The study took approximately five months to complete.

Statistical analysis

In the analysis of the data, nominal and ordinal parameters, which are categorical variables, were defined by frequency analysis, and measurement data were defined by mean and standard deviation values. The chi-square test was used in the difference analysis of nominal and ordinal data. Before the difference analysis, the Kolmogorov-Smirnov Test was performed for normality analysis of the measurement data. One-way ANOVA test was used in the difference analysis of the parameters that fit the normal distribution between groups, and the Kruskal-Wallis test was used in the difference analysis of the parameters that did not fit the normal distribution. Spearman's rho analysis was used for correlational screening analysis. ROC analysis was performed for the prognostic value of Fetuin-B level. All analyses were performed in SPSS 17.0 for Windows package program with 95% confidence interval. We used the G*Power programme to calculate the sample size. We estimate that a sample size of 75 women (25 per treatment group) would have 90% power to compare serum and follicular fetuin-B levels in PCOS, unexplained infertility and poor ovarian response patient groups using an effect size of 0.25.

Results

Age and body mass index (BMI) were higher in the group with poor ovarian response, height in the unexplained group and weight in the PCOS group. The differences in age, height, weight and BMI between the patient groups were not statistically significant (*p>0.05*). Table I shows descriptive statistics.

Table I. Distribution of Age, Height, Weight and BMI Values of Patient Groups and Results of Difference Analysis

Mean±SD	**Unexplained infertility (n=25)**	**PCOS (n=25)**	**Poor ovarian response (n=25)**	*p value**
Age(year)	30.96±4.57	29.84±4.34	32.84±5.05	*0.078*
Height (cm)	162.64±5.45	162.44±5.97	159.56±4.77	*0.087*
Weight (kg)	64.08±7.25	67.72±10.20	64.84±6.43	*0.349*
BMI (kg/m^2)	24.14±2.60	25.64±3.53	25.66±2.86	*0.134*

*One-way ANOVA Test, *p<0.05* was considered statistically significant.

The total number of oocytes, M2 oocytes, G6 oocytes, PN2 oocytes and day 2 embryos were statistically significantly higher in the PCOS group (*p<0.05*). The difference in transfer data between the groups was not statistically significant (*p>0.05*) (Table II).

Table II. In Vitro Fertilization Parameters of Groups and Results of Difference Analysis

Mean±SD	Unexplained infertility (n=25)	PCOS (n=25)	Poor ovarian response (n=25)	*p value*
Total oocyte count	5.68±3.47	**10.12±4.92**	3.80±3.14	0.000*
M2 oocyte count	5.28±3.63	**9.76±4.64**	3.48±3.16	*0.000***
G6 oocyte count	3.84±3.21	**6.36±4.36**	1.56±2.14	*0.000**
PN2 oocyte count	3.44±2.45	**5.08±3.99**	1.68±1.44	*0.000**
Day 2 embryo counts	3.00±1.89	**3.96±3.75**	1.64±1.41	0.013*
Number of patients undergoing embryo transfer	1.00±0.65	0.72±0.61	0.84±0.69	*0.316**

*Kruskal Wallis Test, **One-way ANOVA, *p<0.05* was considered statistically significant.

The differences between the distributions of fetuin-B levels measured in follicular fluid were not statistically significant in all three groups (*p>0.05*). On the other hand, the fetuin-B level measured in serum was statistically significantly higher in the PCOS group (*p<0.05*). According to the results of the Mann-Whitney U test performed as post hoc, the differences in serum fetuin-B levels were statistically significant only between PCOS and the bad ovary (*p<0.05*). The differences in serum fetuin-B between the unexplained infertility group and the bad ovary group or between the unexplained infertility group and the PCOS groups were not statistically significant (*p>0.05*) (Table III).

Table III. Distribution of Fetuin B Values of Patient Groups and Results of Difference Analysis

Mean±SD	Unexplained infertility (n=25)	PCOS (n=25)	**Poor ovarian response (n=25)**	*p value*
Fetuin-B Follicul* (pg/mL)	240.50±59.60	270.72±85.80	301.15±117.04	0.067*
Fetuin-B Serum* (pg/mL)	184.22±93.47	**221.81±182.64**	136.51±60.67	0.035**

*One Way ANOVA Test, ** Kruskal Wallis Test, SD: Standard Deviation, *x1/500000.

There were statistically significant and positive correlations between PCOS group and menstrual cycle duration (*r=0.675; p<0.01*), menstrual pattern (*r=0.762; p<0.01*), Ferriman-Gallwey score (*r=0.818; p<0.01*), AMH (*r=0.655; p<0.01*). Among infertility outcomes, there were statistically significant and positive correlations between PCOS and total oocytes (*r=0.549; p<0.01*), M2 (*r=0.564; p<0.01*), G6 (*r=0.414; p<0.01*) and pN2 (*r=0.344; p<0.01*) (Table IV).

Table IV. Spearman's Rho Correlation Analysis Results for the Relationship between PCOS and Variables with Significant Differences

Group	**r**	**p**
Age	*-0.211*	*<0.01*
Menstrual cycle duration	*0.675*	*<0.01*
Menstrual pattern	*0.762*	*<0.01*
FGW Score	*0.818*	*<0.01*
AMH (ng/ml)	*0.655*	*<0.01*
Total oocyte count	*0.549*	*<0.01*
M2 oocyte count	*0.564*	*<0.01*
G6 oocyte count	*0.414*	*<0.01*
PN2 oocyte count	*0.344*	*<0.01*
Day 2 embryo count	*0.201*	*0.084*

In the unexplained infertility group, there was a statistically significant and negative correlation between the number of biochemical pregnancies and follicular fetuin-B level (*r=-0.562; p<0.01*) and between serum fetuin-B level and number of clinical pregnancies (*r=-0.409; p<0.05*) (Table V).

Figure I. ROC Analysis Results for the Diagnostic Value of Fetuin-B Serum Levels on PCOS

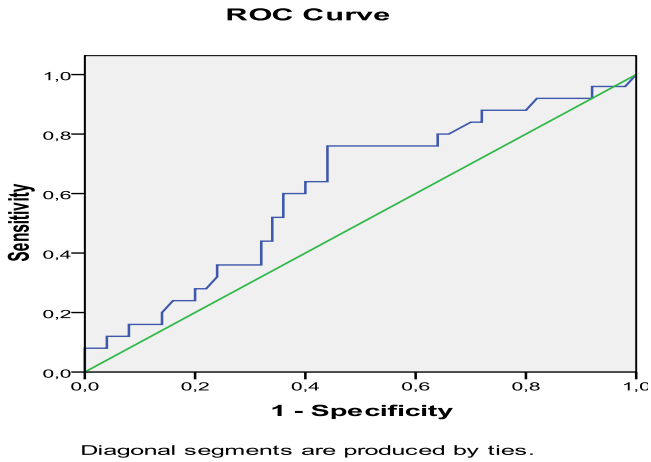

Table V. The Relationship Between Follicular Fluid Fetuin-B and Serum Fetuin-B Levels and Biochemical Pregnancy, Clinical Pregnancy, and Oocyte Quality in Unexplained Infertility Group

		Correlation coefficient	*p*
Number of biochemical pregnancy	Fetuin-B (Follicul)	-0.562**	*0.003*
	Fetuin-B (Serum)	-0.111	*0.597*
Number of clinical pregnancies	Fetuin-B (Follicul)	-0.205	*0.327*
	Fetuin-B (Serum)	-0.409*	*0.042*
Total oocyte count	Fetuin-B (Follicul)	-0.296	*0.151*
	Fetuin-B (Serum)	-0.050	*0.811*
M2 oocyte count	Fetuin-B (Follicul)	-0.221	*0.288*
	Fetuin-B (Serum)	-0.125	*0.551*
Day 2 embryo count	Fetuin-B (Follicul)	-0.162	*0.438*
	Fetuin-B (Serum)	-0.217	*0.297*
PN2 oocyte count	Fetuin-B (Follicul)	-0.246	*0.237*
	Fetuin-B (Serum)	-0.335	*0.101*
G6 oocyte count	Fetuin-B (Follicul)	-0.031	*0.881*
	Fetuin-B (Serum)	-0.281	*0.174*
Number of patients undergoing embryo transfer	Fetuin-B (Follicul)	-0.018	*0.934*
	Fetuin-B (Serum)	-0.026	0.901

**p<0.05 **p <0.01*

In the PCOS group, no statistically significant correlation was found between follicular fluid fetuin-B and serum fetuin-B levels and biochemical pregnancy number, clinical pregnancy number and oocyte quality (*p>0.05*) (Table VI).

Table VI. The Relationship Between Follicular Fluid Fetuin-B and Serum Fetuin-B Levels and Biochemical Pregnancy, Clinical Pregnancy, and Oocyte Quality in PCOS Group

		Correlation oefficient	*p*
Number of biochemical pregnancies	Fetuin-B (Follicul)	0.305	*0.138*
	Fetuin-B (Serum)	0.236	*0.257*
Number of clinical pregnancies	Fetuin-B (Follicul)	-	*>0.05*
	Fetuin-B (Serum)	-0.020	*0.923*
Total oocyte count	Fetuin-B (Follicul)	-0.059	*0.781*
	Fetuin-B (Serum)	0.047	*0.822*
M2 oocyte count	Fetuin-B (Follicul)	-0.086	*0.684*
	Fetuin-B (Serum)	0.083	*0.693*
Day 2 embryo count	Fetuin-B (Follicul)	-0.001	*0.996*
	Fetuin-B (Serum)	-0.280	*0.175*
PN2 oocyte count	Fetuin-B (Follicul)	0.012	*0.956*
	Fetuin-B (Serum)	-0.063	*0.765*
G6 oocyte count	Fetuin-B (Follicul)	0.197	*0.345*
	Fetuin-B (Serum)	0.043	*0.839*
Number of patients undergoing embryo transfer	Fetuin-B (Follicul)	0.111	*0.599*
	Fetuin-B (Serum)	-0.203	*0.330*

No statistically significant correlation was found between follicular fluid fetuin-B and serum fetuin-B levels and biochemical pregnancy number, clinical pregnancy number and oocyte quality in the poor ovarian response group (*p>0.05*) (Table VII).

Table VII. The Relationship Between Follicular Fluid Fetuin-B and Serum Fetuin-B Levels and Biochemical Pregnancy, Clinical Pregnancy and Oocyte Quality in Patients with Poor Ovarian Response

		Correlation coefficient	*p*
Number of biochemical pregnancies	Fetuin-B (Follicul)	0.184	*0.378*
	Fetuin-B (Serum)	0.020	*0.923*
Number of clinical pregnancies	Fetuin-B (Follicul)	0.184	*0.378*
	Fetuin-B (Serum)	0.020	*0.923*
Total oocyte count	Fetuin-B (Follicul)	-0.382	*0.059*
	Fetuin-B (Serum)	0.143	*0.495*
M2 oocyte count	Fetuin-B (Follicul)	-0.338	*0.099*
	Fetuin-B (Serum)	0.137	*0.515*
Day 2 embryo count	Fetuin-B (Follicul)	-0.130	*0.536*
	Fetuin-B (Serum)	0.156	*0.456*
PN2 oocyte count	Fetuin-B (Follicul)	-0.167	*0.424*
	Fetuin-B (Serum)	0.182	*0.385*
G6 oocyte count	Fetuin-B (Follicul)	-0.024	*0.910*
	Fetuin-B (Serum)	0.000	*0.999*
Number of patients undergoing embryo transfer	Fetuin-B (Follicul)	0.011	*0.957*
	Fetuin-B (Serum)	0.140	*0.504*

There was a statistically significant and negative correlation between fetuin-B level in follicular fluid and total oocytes (*r=-0.286; p<0.05*) and M2 (*r=-0.264; p<0.05*) in all patients (Table VIII).

Although the difference in serum fetuin-B level was significant between the PCOS group and other groups, the diagnostic value of serum fetuin-B level on PCOS was not statistically significant (AUC: 0.616; *p>0.05*) (Figure I).

Table VIII. Relationship Between Follicular Fluid Fetuin-B and Serum Fetuin-B Levels and Biochemical Pregnancy, Clinical Pregnancy and Oocyte Quality in All Patients

		Correlation coefficient	*p*
Number of biochemical pregnancies	Fetuin-B (Follicul)	-0.094	*0.422*
	Fetuin-B (Serum)	0.074	*0.526*
Number of clinical pregnancies	Fetuin-B (Follicul)	-0.003	*0.977*
	Fetuin-B (Serum)	-0.148	*0.206*
Total oocyte count	Fetuin-B (Follicul)	-0.286	*0.013*
	Fetuin-B (Serum)	0.148	*0.204*
M2 oocyte count	Fetuin-B (Follicul)	-0.264	*0.022*
	Fetuin-B (Serum)	0.129	*0.271*
Day 2 embryo count	Fetuin-B (Follicul)	-0.154	*0.189*
	Fetuin-B (Serum)	-0.046	*0.698*
PN2 oocyte count	Fetuin-B (Follicul)	-0.191	*0.102*
	Fetuin-B (Serum)	0.022	*0.854*
G6 oocyte count	Fetuin-B (Follicul)	-0.034	*0.769*
	Fetuin-B (Serum)	0.063	*0.591*
Number of patients undergoing embryo transfer	Fetuin-B (Follicul)	-0.024	*0.838*
	Fetuin-B (Serum)	-0.029	*0.807*

Discussion

The aim of this study was to investigate the relationship between the difference in serum and follicular fetuin-B levels and biochemical pregnancy number, clinical pregnancy number and oocyte quality in unexplained infertile patients, patients with polycystic ovary syndrome (PCOS) and patients with poor ovarian response during in vitro fertilization treatment. In the study, 25 samples were taken from each patient group and fetuin-B levels were obtained from the follicular fluid and blood obtained after ovulation induction.

IVF methods are increasing and improving every day. Studies and clinical applications range from oocyte quality to embryo transfer process and are planned to increase the efficiency of IVF (10). In order for the IVF process to be successful, the number of oocytes must be sufficient, the culture and spermatozoa obtained must be appropriate, the transfer process must be safe and post-implantation care is required. IVF procedures that are carried out successfully within this process have a very high success rate today (11, 12).

Fetuin-B is a pluripotent peptide hormone secreted by various tissues such as liver and adipose tissue. Fetuin-B, an inhibitor of papain-like cysteine proteinases, is an important inhibitor of ovastacin, a metalloproteinase (9, 13). In addition, studies on fetuin-B in serum and follicle fluid in the IVF process and oocyte quality and pregnancy process are becoming more prominent. Although limited today, the expansion of studies in this field and the demonstration of the predictive value of fetuin-B levels in unexplained infertility, PCOS and poor ovarian conditions may provide important clues for further studies and clinical applications.

The type of infertility is one of the important variables in both the occurrence and the process of pregnancy. In primary infertility, genetic and biological causes are more prominent, while in secondary infertility, it is possible to state that subsequent causes are also effective (14). In our study, the type of infertility (primary-secondary), biochemical pregnancy and clinical pregnancy rates were similar in all three groups and the differences between the groups were not statistically significant. In this respect, it is possible to state that the type of infertility has no effect on the relationships between the parameters examined in the study and on the outcomes of the IVF process. Again, the fact that the biochemical and clinical pregnancy rates were similar for the three groups and the difference was not statistically significant indicates that the effect of infertility type (unexplained, PCOS and bad ovary) was not significant.

Undoubtedly, oocyte quality is one of the most important parameters for pregnancy success in both normal pregnancies and IVF processes (15). Although it is not possible to link all parameters to oocyte quality until the last stage of pregnancy, it has been reported in many studies that low oocyte quality has a significant effect both in normal pregnancy and IVF process. In our study, total oocyte count, M2 oocyte count, G6 oocyte count, PN2 oocyte count and day 2 embryo count values, which are indicators of oocyte quality, were all higher in the PCOS group. From this point of view, it can be expected that the

IVF process was higher in the PCOS group than in the unexplained and bad ovary group. However, the fact that the difference in both biochemical pregnancy and clinical pregnancy rates between the groups was not statistically significant indicates that oocyte quality cannot be directly associated with pregnancy outcome and other predictive values are needed.

In the IVF process, many predictive markers are being studied to predict pregnancy success. Follicle and serum fetuin-B levels may have important value in this regard (7). However, there are not enough studies in the literature showing the difference between fetuin-B and IVF and our groups. The studies were mainly concerned with fertilization rates.

In a study investigating the success of serum and follicular fluid fetuin-B levels in predicting IVF outcomes, serum and follicular fluid fetuin-B levels were positively correlated (r=0.675, p<0.01). Serum and follicular fetuin-B levels were also lower in women with low fertility rates than in women with normal fertility rates [(6.09±1.31) µg/mL vs. (7.13±1.47) µg/mL, t=3.050, p<0.05; (5.13±0.96) µg/mL vs. (6.22±1.33) µg/mL, t=3.755, *p<0.01*] (16).

In a study comparing 78 cycles with a low fertilization rate with 104 cycles with a high fertilization rate, it was found that fetuin-B levels in both serum (5.81 ± 1.53 vs. 7.19 ± 1.42, *p<0.001*) and follicular fluid (5.06 ± 1.29 vs. 6.16 ± 1.52, *p<0.001*) were lower in the group with a low fertilization rate than in the group with a high fertilization rate. However, serum fetuin-B levels were not associated with preimplantation embryo development or clinical pregnancy (6).

In our study, although the differences between follicle fetuin-B levels were not statistically significant, serum fetuin-B levels were statistically significant and the highest value was in the PCOS group, followed by the unexplained infertility group and the poor ovarian response group, respectively.

According to the results of correlation analysis, there were statistically significant and negative correlations between the number of biochemical pregnancies and follicle fetuin-B levels and between serum fetuin-B levels and clinical pregnancy in the unexplained infertility group. In other words, in the unexplained group, follicle fetuin-B levels had predictive value for biochemical pregnancy rate and serum fetuin-B levels had predictive value for clinical pregnancy rate. In PCOS and poor ovarian groups, no statistically significant correlation was found between fetuin-B follicle and serum levels and biochemical pregnancy rate, clinical pregnancy rate and oocyte quality in PCOS group.

These results indicate that fetuin-B levels do not have a significant diagnostic value in PCOS and bad ovary groups, but can be used as an important parameter to indicate biochemical pregnancy and clinical pregnancy levels in the unexplained group. According to the results obtained in the study, oocyte quality was lower in the unexplained group and in the bad ovary group compared to the PCOS group. In this respect, the results of the study indicate that fetuin-B level may have a significant role in predicting biochemical pregnancy and clinical pregnancy rates even in the case of low oocyte quality in the unexplained infertility group. This makes the study valuable in terms of guiding further research and studies and clinical applications.

One of the limitations of our study is that since there were 3 different infertility groups, the most appropriate ovarian stimulation protocol was applied to each patient individually. Not applying the same standardised protocol to all groups is an important limitation of the study. Another limitation is that the study was conducted in a single centre. However, these limitations do not reduce the value of the study and constitute a source for further research. In this respect, our study may be a source for research on the estimation of biochemical pregnancy and clinical pregnancy rates, especially in the unexplained infertility group.

Conclusion

According to the results obtained in the study, there was no significant difference between the biochemical pregnancy and clinical pregnancy rates indicating IVF results and infertility types in the unexplained infertility, PCOS, and poor ovarian groups. In this respect, the findings obtained are consistent with the literature, but there is no clear finding on which group will have better results in terms of predicting IVF outcomes. Therefore, parameters that may have

predictive value such as fetuin-B are needed. This shows the originality of the study and its contribution to the literature. Although there are many studies showing the relationship between oocyte quality and pregnancy rate, at the last stage, it can be stated that there is no harmony and completeness in the studies on infertility in terms of the groups in our study. Therefore, more studies are needed. However, the results of our study can guide further research and studies. Although there are some indicators that measure success at intermediate stages in the IVF process, in general, biochemical pregnancy rates and clinical pregnancy rates can be shown as important indicators of a pregnancy achievement process. When these two rates are considered as outputs of the IVF process, oocyte quality is also an important factor in showing the success of the process. In conclusion, no statistically significant correlation was found between serum fetuin-B and fetuin-B in follicular fluid and PCOS. However, in the unexplained infertility group, there was a statistically significant and negative correlation between the number of biochemical pregnancies and follicular fetuin-B and between serum fetuin-B and clinical pregnancy. Fetuin-B level may thus have predictive value in predicting outcomes of the IVF process in unexplained pregnancies.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Clinical Impact of Incidental Findings on Surgical Planning in Coronary Artery Bypass Surgery

Koroner Arter Bypass Cerrahisinde İnsidental Bulguların Cerrahi Planlama Üzerindeki Klinik Etkisi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1675587
Geliş Tarihi | Received: 15.04.2025
Kabul Tarihi | Accepted: 29.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Türkmen U, Yiğit G, Çelikten AE, Yalvaç M. Clinical Impact of Incidental Findings on Surgical Planning in Coronary Artery Bypass Surgery. Hitit Medical Journal 2025;7(2):244-254. https://doi.org/10.52827/hititmedj.1675587

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 12/03/2025 tarihinde Hitit Üniversitesi Tıp Fakültesi Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2025/54.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: UT Tasarım: UT, AEÇ Veri Toplama/Veri İşleme: GY, AEÇ, MY Veri Analizi: UT Makalenin Hazırlanması: UT, AEÇ, MY.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Ethics Committee of Hitit University Faculty of Medicine on 12/03/2025. Decision no: 2025/54.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: UT Design: UT, AEÇ Data Collection/Data Processing: GY, AEÇ, MY Data Analysis: UT Manuscript Preparation: UT, AEÇ, MY.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Clinical Impact of Incidental Findings on Surgical Planning in Coronary Artery Bypass Surgery

ABSTRACT

Objective: To determine the frequency of incidental findings detected by preoperative non-contrast thoracoabdominal computed tomography (CT) in patients undergoing elective isolated coronary artery bypass grafting (CABG) and to assess their impact on surgical planning.

Material and Method: This retrospective study included 534 patients who underwent elective CABG between January 2021 and December 2024. As part of the routine preoperative assessment protocol, all patients received a non-contrast thoracoabdominal CT scan. Incidental findings were classified by clinical significance. Patients were grouped based on whether surgical planning was altered (Group 1), unchanged with incidental findings (Group 2), or unchanged without findings (Group 3). Demographic, intraoperative, and postoperative data were compared across groups.

Results: At least one incidentaloma was detected in 70.8% of patients. Of these, 12% led to changes in surgical strategy, most commonly off-pump surgery or graft modification. Surgery was canceled in six patients due to high-risk findings. Group 1 patients were older and had lower left ventricular function. Thirty-day mortality did not differ significantly between groups.

Conclusion: Preoperative non-contrast thoracoabdominal CT in elective CABG candidates contributes significantly to both surgical planning and systemic evaluation, enhancing patient safety. Given its accessibility and cost-effectiveness, this method represents a valuable tool in routine preoperative assessment.

Keywords: Coronary artery bypass grafting, Incidentaloma, non-contrast computed tomography, preoperative evaluation, surgical planning.

ÖZET

Amaç: Bu çalışmanın amacı, elektif izole koroner arter bypass greftleme (KABG) cerrahisi planlanan hastalarda, preoperatif dönemde uygulanan kontrastsız torakoabdominal bilgisayarlı tomografi (BT) ile saptanan insidentalomaların sıklığını belirlemek ve bu bulguların cerrahi planlama üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Ocak 2021 – Aralık 2024 tarihleri arasında elektif KABG uygulanan 534 hasta retrospektif olarak incelendi. Tüm hastalara, rutin preoperatif değerlendirme protokolü kapsamında kontrastsız torakoabdominal BT çekildi. Saptanan insidentalomalar klinik anlamlılıklarına göre sınıflandırıldı. Cerrahi plan değişikliği olan hastalar Grup 1, değişiklik olmayanlar insidentaloma varlığına göre Grup 2 ve 3 olarak gruplandırıldı. Demografik veriler, intraoperatif ve postoperatif sonuçlar karşılaştırıldı.

Bulgular: Hastaların %70.8'inde en az bir insidentaloma saptandı. Bu bulguların %12'si cerrahi planlamayı etkiledi. En sık değişiklik off-pump cerrahiye yönelim ve greft planlamasında oldu. Altı hastada operasyon iptal edilerek ileri merkeze yönlendirme yapıldı. Cerrahi plan değişikliği yapılan hastalar daha yaşlı ve sol ventrikül fonksiyonu daha düşük olan grubu oluşturuyordu. 30 günlük mortalite oranı gruplar arasında anlamlı fark göstermedi.

Sonuç: Elektif KABG hastalarında preoperatif kontrastsız torakoabdominal BT, hem cerrahi planlamaya hem de sistemik taramaya katkı sağlayarak hasta güvenliğini artırmaktadır. Uygun maliyeti ve yaygın erişilebilirliği ile bu yaklaşım, klinik uygulamada değerli bir araç olabilir.

Anahtar Sözcükler: Cerrahi planlama, İnsidentaloma, kontrastsız bilgisayarlı tomografi, koroner arter bypass greftleme, preoperatif değerlendirme.

Introduction

Coronary artery disease (CAD) remains one of the leading causes of cardiovascular morbidity and mortality worldwide and continues to be a major public health concern in both developed and developing countries. In cases such as left main coronary artery involvement, multivessel disease, or left ventricular dysfunction, coronary artery bypass grafting (CABG) surgery stands out as an effective treatment option for prolonging survival and improving symptom control (1).

In recent years, the role of imaging modalities in the preoperative planning process of CABG surgery has gained increasing importance. In this context, thoracoabdominal computed tomography (CT) has become a valuable tool not only for evaluating aortic calcifications but also for identifying extracardiac incidental findings (incidentalomas). Particularly in elderly patients, CT scans frequently reveal lesions in the adrenal, renal, pulmonary, and gastrointestinal systems, which may significantly influence both surgical planning and patient management (2–7). In the literature, large-scale studies involving transcatheter aortic valve implantation (TAVI) candidates have clearly demonstrated the clinical impact of incidental findings detected via CT on surgical decisions and overall patient care (8–14). However, there is a paucity of data regarding the impact of systematic non-contrast thoracoabdominal CT screening in patients scheduled for elective isolated CABG.

Moreover, as emphasized in the 2023 AHA/ACC guideline on coronary artery disease, the management of CAD requires a personalized and multidisciplinary approach. The guideline highlights the importance of integrating concomitant systemic conditions identified during the preoperative period into the clinical decision-making process. It further suggests that early detection of asymptomatic but high-risk findings may improve surgical success and long-term survival outcomes (1).

This study aims to evaluate the prevalence of unexpected findings detected by preoperative non-contrast thoracoabdominal CT in patients scheduled for elective isolated CABG and to assess the impact of these findings on surgical planning. In this regard, the study seeks to contribute to clinical practice and fill a gap in the current literature while laying the groundwork for future research.

Material and Method

Study Design and Patient Selection

This retrospective study included 534 patients who underwent elective CABG between January 2021 and December 2024. The study was approved by the Ethics Committee of Hitit University Faculty of Medicine, in accordance with the principles of the Declaration of Helsinki (Approval No: 2025/54). Written informed consent was obtained from all patients prior to treatment.

Patient data were retrospectively analyzed from electronic medical records and hospital files. As part of the standard institutional protocol, all patients scheduled for elective open-heart surgery undergo non-contrast thoracoabdominal CT scanning including the neck, thorax, and abdomen for the evaluation of additional pathologies. These CT scans are reviewed to identify unexpected findings (incidentalomas). Incidentalomas assessed in this study included aortic pathologies (such as calcifications and aneurysms), pulmonary nodules, renal/adrenal masses, and other thoracoabdominal lesions that may affect morbidity or mortality. All CT scans were evaluated by at least two cardiovascular surgeons in collaboration with a board-certified radiologist. Any discrepancies were resolved by consensus to ensure accuracy in identifying and classifying incidental findings.

In terms of surgical planning, it is determined whether these incidentalomas require further preoperative investigations and/or necessitate changes in surgical strategy. Examples of surgical modifications include alterations in cannulation sites, changes in graft selection, or even the complete cancellation of surgery.

Patients were divided into three groups: Group 1: Patients in whom incidentalomas were identified and who underwent further preoperative evaluation and/or surgical plan modification. Group 2: Patients in whom incidentalomas were identified but no additional investigations were performed, and no changes were made to the surgical plan. Group 3: Patients with no incidentalomas detected and no modifications in the surgical plan.

Study Definitions

All patients were monitored for postoperative complications, and this study evaluated only outcomes occurring within the first 30 days after surgery.

Benign incidental findings were defined as lesions detected on preoperative radiological evaluations that were not suspicious for malignancy, did not affect the surgical plan, and did not require further diagnostic work-up. These included simple renal cysts, benign adrenal lesions, benign pulmonary nodules, atheromatous plaques, and mild organomegaly findings considered to have low clinical significance.

Malignant incidental findings were defined as lesions identified on preoperative imaging that were considered suspicious for malignancy, required additional diagnostic evaluation or close follow-up, or necessitated changes in the surgical plan. These included solid pulmonary nodules, adrenal masses with mass-like features, hyper vascular organ lesions, large or irregular renal masses, and suspicious lymph nodes. Additionally, severely calcified aortic pathologies (e.g., porcelain aorta, extensive ascending or aortic arch calcification), significant atherosclerotic plaques, and vascular anomalies likely to complicate surgical intervention were also considered malignant incidental findings.

The new stroke was defined as a permanent brain injury occurring after surgery and confirmed by radiological evaluation. TIA (Transient Ischemic Attack) was defined as a focal neurological deficit due to ischemia of the brain, spinal cord, or retina that resolved completely within 24 hours and showed no signs of acute infarction in imaging studies. Acute renal failure (ARF) refers specifically to patients who require hemodialysis in the postoperative period. Chronic renal failure was defined as an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 or the need for maintenance dialysis. Prolonged ventilation was defined as the need for invasive mechanical ventilation exceeding 24 hours postoperatively. Rehospitalization was defined as readmission to the hospital within 30 days after discharge due to a complication related to the surgical procedure or the same diagnosis. This included readmissions due to postoperative complications, infections, heart failure, arrhythmias, chest pain, or other cardiovascular causes.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients undergoing elective CABG surgery, patients aged 20 years or older, and patients operated via median sternotomy.

Exclusion criteria: Patients with more than 50% occlusion or stenosis in the carotid arteries or those undergoing simultaneous carotid surgery, patients undergoing emergency coronary bypass surgery, patients undergoing additional cardiac procedures alongside CABG, patients with chronic renal failure, patients with a history of previous cardiac surgery or prior surgery involving the descending thoracic or abdominal aorta were excluded to ensure homogeneity of the study population, patients previously diagnosed with cancer, even if complete remission was achieved. These criteria were defined to ensure the homogeneity of the study content and the patient population.

Surgical Protocol and Technique

All patients were operated under general anesthesia via median sternotomy. A central venous catheter was inserted through the jugular vein for central venous access, and arterial blood pressure was monitored through the radial or brachial artery.

All patients received 300 IU/kg of heparin, and after achieving an activated clotting time (ACT)> 400 seconds, aorto-single venous cannulation was performed in patients undergoing cardiopulmonary bypass (CPB), and systemic cooling to 32°C was applied. Cardiac arrest was achieved after cross-clamping using Del Nido cardioplegia along with the application of cold saline slush. Cardioplegia was administered via the antegrade route. Cases operated on a beating heart were not included in this protocol.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Inc., Chicago, IL, USA). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Variables with normal distribution were reported as mean ± standard deviation (mean ± SD), while non-normally distributed variables were expressed as median (IQR: 25th–75th percentiles). Categorical variables were expressed as frequency and percentage (%) and compared using the Chi-square test or Fisher's exact test.

For comparisons among the three groups, one-way

analysis of variance (ANOVA) was used for normally distributed continuous variables, and the Kruskal-Wallis test was used for non-normally distributed continuous variables and ordinal variables. Post-hoc analyses were conducted for variables with statistically significant differences. Tukey's HSD test was used for post-hoc comparisons of normally distributed variables, while Dunn's test with Bonferroni correction was used for non-normally distributed variables. For categorical variables, pairwise comparisons were performed using the Chi-square test or Fisher's exact test with Bonferroni correction. A *p-value* of *<0.05* was considered statistically significant.

Results

A total of 534 patients were included in the analysis. Based on the presence of incidentalomas and whether surgical planning was altered, patients were categorized into three groups: Group 1 (n=64), Group 2 (n=314), and Group 3 (n=156). The demographic and preoperative clinical characteristics of the patients are summarized in Table I.

Table I. Demographic Characteristics of the Patients

Variable	Group 1 (n:64)	Group 2 (n:314)	Group 3 (n:156)	*p-value*
Sex (male)	47 (73.4%)	255 (81.2%)	118 (75.6%)	*0.211*[a]
Diabetes Mellitus	26 (40.6%)	163 (51.9%)	55 (35.3%)	*0.002*[b]
Chronic Obstructive Pulmonary Disease	10 (15.6%)	51 (16.2%)	8 (5.1%)	0.002[b]
Hypertension	47 (73.4%)	210 (66.9%)	122 (78.2%)	*0.035*[b]
Hypercholesterolemia	41 (64.1%)	212 (67.5%)	83 (53.2%)	*0.010*[b]
Smoking	37 (57.8%)	229 (72.9%)	101 (64.7%)	*0.0262*[b]
Previous Stroke	2 (3.1%)	10 (3.2%)	5 (3.2%)	0.999[a]
Vascular Pathologies	26 (40.6%)	157 (50.0%)	0 (0.0%)	*<0.001*[b]
Urological Pathologies	10 (15.6%)	100 (31.8%)	0 (0.0%)	*<0.001*[b]
Intra-abdominal Pathologies	22 (34.4%)	38 (12.1%)	0 (0.0%)	*<0.001*[b]
Pulmonary Pathologies	25 (39.1%)	19 (6.1%)	0 (0.0%)	<0.001[b]
Cervical Pathologies	6 (9.4%)	6 (1.9%)	0 (0.0%)	*<0.001*[b]
Age	69.00 (60.75-73.25)	64.00 (59.00-69.00)	59.00 (53.00-65.00)	*<0.001*[c]
Body Mass Index	27.26 (24.95-31.34)	29.46 (26.22-32.81)	27.93 (25.61-30.93)	*0.007*[c]
Ejection Fraction (%)	50.00 (40.00-60.00)	60.00 (50.00-60.00)	60.00 (53.75-60.00)	<0.001[c]
Number of total incidentalomas	2.00 (1.00-3.00)	1.00 (1.00-2.00)	0.00 (0.00-0.00)	*<0.001*[c]
Number of benign incidentalomas	1.00 (1.00-2.00)	1.00 (1.00-2.00)	0.00 (0.00-0.00)	*<0.001*[c]
Number of malignant incidentalomas	1.00 (1.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	*<0.001*[c]

COPD: Chronic Obstructive Pulmonary Disease

[a]: Chi-Square test (number, percentage), [b]:Fisher's Exact Test (number, percentage), [c]: Kruskal-Wallis test (IQR: 25th–75th percentile).

In terms of age, the median age of Group 1 was 69 years (60.75–73.25), which was significantly higher compared to the other groups (*p<0.001*). Post-hoc analysis revealed significant differences between Group 1 and Group 2 (*p=0.003*), Group 1 and Group 3 (*p<0.001*), and Group 2 and Group 3 (*p<0.001*). The distribution of male sex was similar across all groups, with no statistically significant difference observed (*p=0.211*). Regarding body mass index (BMI), patients in Group 2 had significantly higher BMI values compared to the other groups (*p = 0.007*). Post-hoc analysis showed significant differences between Group 1 and Group 2 (*p=0.031*), and between Group 2 and Group 3 (*p=0.007*).

There was a statistically significant difference in the prevalence of diabetes mellitus among the groups (*p=0.002*), with a significant difference observed between Group 2 and Group 3 in post-hoc analysis (*p=0.001*). For chronic obstructive pulmonary disease (COPD), a significant difference was found between groups (*p=0.002*), and post-hoc analysis revealed significant differences between Group 1 and Group 3 (*p=0.021*), and between Group 2 and Group 3 (*p=0.001*). A significant difference was observed among groups in terms of hypertension (*p=0.035*), with a post-hoc difference between Group 2 and Group 3 (*p=0.015*). Hypercholesterolemia also differed significantly among groups (*p=0.010*), with a significant difference between Group 2 and Group 3 (*p=0.003*). A statistically significant difference was observed in smoking history (*p = 0.026*), with a significant post-hoc difference between Group 1 and Group 2 (*p=0.024*).

Left ventricular ejection fraction (EF) was significantly lower in Group 1 compared to other groups (*p<0.001*). Post-hoc analysis confirmed significant differences between Group 1 and Group 2 (*p<0.001*), and between Group 1 and Group 3 (*p<0.001*).

There was a significant difference in the number of unexpected findings among the groups (*p<0.001*). Additionally, other preoperative findings such as vascular, retroperitoneal, intra-abdominal, pulmonary, and cervical pathologies showed significant differences between some of the groups (*p<0.001*).

Table II. Intraoperative and Postoperative Variables

Variable	Group 1 (n:58)	Group 2 (n:314)	Group3 (n:156)	*p-value*
Beating Heart Surgery	34 (58.6%)	15 (4.8%)	18 (11.5%)	*<0.001*[b]
Stroke	1 (1.7%)	4 (1.3%)	2 (1.3%)	*0.961*[a]
TIA	2 (3.4%)	6 (1.9%)	4 (2.6%)	*0.738*[a]
Prolonged ventilation	1 (1.7%)	17 (5.4%)	5 (3.2%)	*0.316*[a]
Pneumonia	3 (5.2%)	20 (6.4%)	9 (5.8%)	*0.924*[a]
Acute renal failure	1 (1.7%)	3 (1.9%)	1 (0.6%)	*0.564*[a]
Mediastinitis	1 (1.7%)	4 (1.3%)	4 (2.6%)	*0.595*[a]
Sepsis	1 (1.7%)	2 (0.6%)	3 (1.9%)	*0.420*[a]
Reoperation	2 (3.4%)	16 (5.1%)	6 (3.8%)	*0.757*[a]
Inotrope use	9 (15.5%)	43 (13.7%)	17 (10.9%)	*0.588*[a]
Pleural effusion	4 (6.9%)	15 (4.8%)	8 (5.1%)	*0.797*[a]
POAF	8 (13.8%)	35 (11.1%)	13 (8.3%)	*0.456*[a]
IABP	3 (5.2%)	10 (3.2%)	4 (2.6%)	*0.629*[a]
Rehospitalization	7 (12.1%)	16 (5.1%)	9 (5.8%)	*0.121*[a]
Mortality	1 (1.7%)	5 (1.6%)	2 (1.3%)	*0.957*[a]
CPB time (minute)	0.00 (0.00-74.50)	84.00 (67.00-103.00)	82.50 (60.00-100.00)	*<0.001*[c]
Cross-clamp time (minute)	0.00 (0.00-62.00)	64.00 (49.00-81.00)	61.50 (44.25-80.00)	*<0.001*[c]
ICU stay (days)	2.00 (2.00-2.00)	2.00 (2.00-2.00)	2.00 (2.00-2.00)	*0.013*[c]
Ward stay after ICU (days)	5.00 (5.00-6.00)	5.00 (5.00-6.00)	5.00 (5.00-6.00)	*0.375*[c]
Total hospital stay (days)	7.00 (7.00-8.00)	7.00 (7.00-8.00)	7.00 (7.00-8.00)	*0.398*[c]
Number of bypass grafts	2.00 (1.00-3.00)	3.00 (2.00-3.00)	3.00 (2.00-3.00)	*<0.001*[c]

TIA = Transient Ischemic Attack; POAF = Postoperative Atrial Fibrillation; IABP = Intra-Aortic Balloon Pump; CPB = Cardiopulmonary Bypass; ICU = Intensive Care Unit.

[a]: Chi-Square test (number, percentage), [b]:Fisher's Exact Test (number, percentage), [c]: Kruskal-Wallis test (IQR: 25th–75th percentile).

Of the 64 patients in Group 1, six were discharged without undergoing surgery due to changes in the surgical plan based on incidentaloma findings. Therefore, postoperative analyses in Group 1 were performed on 58 patients. Analyses in Group 2 and Group 3 included 314 and 156 patients, respectively.

Intraoperative Findings

There were statistically significant differences among the groups regarding CPB time and cross-clamp time (*p<0.001*). Post-hoc analyses revealed that these differences were significant between Group 1 and Group 2 (*p<0.001*), and between Group 1 and Group 3 (*p<0.001*) for both CPB and cross-clamp durations.

Regarding the use of the beating heart surgical technique (off-pump surgery), there were significant differences between groups (*p<0.001*). Post-hoc analysis showed significant differences between Group 1 and Group 2 (*p<0.001*), Group 1 and Group 3 (*p<0.001*), and Group 2 and Group 3 (*p=0.012*). The number of bypass grafts performed also differed significantly among groups (*p<0.001*). Post-hoc analysis indicated significant differences between Group 1 and Group 2 (*p<0.001*), and between Group 1 and Group 3 (*p<0.001*).

Postoperative Findings

There was a statistically significant difference among the groups in terms of intensive care unit (ICU) stay duration (*p=0.013*). Post-hoc analysis showed significant differences between Group 1 and Group 3 (*p=0.011*), and between Group 2 and Group 3 (*p=0.016*).

No statistically significant differences were observed among the groups in terms of stroke, TIA, prolonged ventilation, pneumonia, ARF, mediastinitis, sepsis, reoperation, inotropic support, pleural effusion, postoperative atrial fibrillation (POAF), intra-aortic balloon pump (IABP) usage, total length of hospital stay, rehospitalization, or mortality (*p>0.05*).

In this study, at least one incidentaloma was detected in 70.8% (n=378) of the 534 patients, and in 16.9% of these patients (n=64), the findings led to a change in the surgical strategy. This corresponds to a 12.0% surgical impact rate across the entire population.

Table III. Incidental Findings Detected on Thoracoabdominal CT and Their Distribution Across Groups

			Requiring Additional Diagnostic Workup (Group 1)	Not Requiring Additional Diagnostic Workup (Group 2)
Neck Pathologies 12 (2.24%)	Lymphadenopathy	2 (0.37%)	2 (0.37%)	0 (0%)
	Thyroid pathology	10 (1.87%)	4 (0.74%)	6 (1.12%)
Pulmonary Pathologies 44 (8.23%)	Tracheal Stenosis	1 (0.19%)	1 (0.19%)	0 (0%)
	Benign/Malignant Nodules	14 (2.62%)	14 (2.62%)	0 (0%)
	Emphysema	10 (1.87%)	10 (1.87%)	0 (0%)
	Bronchiectasis	19 (3.55%)	0 (0%)	19 (3.55%)
Abdominal Pathologies 60 (11.23%)	Gastric Malignancy	3 (0.56%)	3 (0.56%)	0 (0%)
	Splenic Atrophy	1 (0.19%)	1 (0.19%)	0 (0%)
	Gallbladder Pathologies	31 (5.80%)	13 (2.43%)	18 (3.37%)
	Hiatal Hernia	2 (0.37%)	0 (0%)	2 (0.37%)
	Liver Pathologies	14 (2.62%)	5 (0.93%)	9 (1.68%)
	Umbilical Hernia	9 (1.68%)	0 (0%)	9 (1.68%)
Urological Pathologies 110 (20.60%)	Renal Cell Carcinoma	1 (0.19%)	1 (0.19%)	0 (0%)
	Adrenal Adenoma	2 (0.37%)	2 (0.37%)	0 (0%)
	Horseshoe Kidney	1(0.19%)	0 (0%)	1 (0.19%)
	Renal Agenesis	4 (0.74%)	4 (0.74%)	0 (0%)
	Renal Stones	24 (4.50%)	0 (0%)	24 (4.50%)
	Renal Cysts	52 (9.73%)	3 (0.56%)	49 (9.17%)
	Prostatic Hypertrophy	26 (4.86%)	0 (0%)	26 (4.86%)
Vascular Pathologies 183 (34.26%)	Aneurysms	32 (6.00%)	3 (0.56%)	29 (5.43%)
	Calcifications	151 (28.27%)	23 (4.30%)	128 (23.97)
	Porcelain Aorta	11 (2.05%)	11 (2.05%)	0 (0%)
	Subclavian Artery Calcifications	3 (0.56%)	3 (0.56%)	0 (0%)
	Iliac Artery Calcifications	9 (1.68%)	9 (1.68%)	0 (0%)

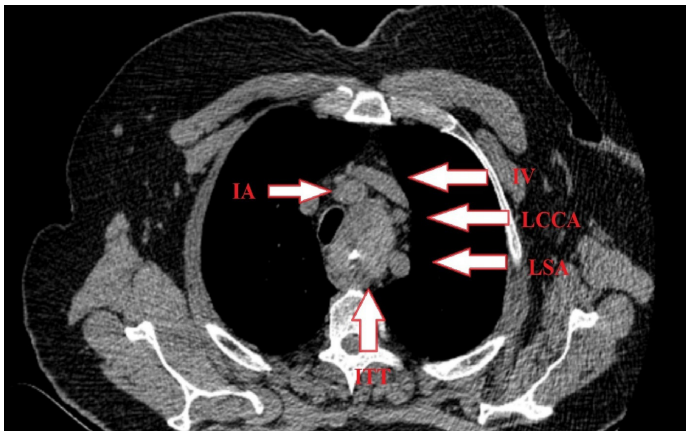
Neck Pathologies

Neck pathologies were identified in 12 patients (2.24%). Of these, 2 patients had lymphadenopathy and 10 had thyroid pathologies. Six patients (2 with lymphadenopathy and 4 with thyroid lesions) required further evaluation and were classified in Group 1, while the remaining 6 patients, who did not require additional assessment, were placed in Group 2. One patient underwent concomitant thyroidectomy during coronary bypass surgery due to a thyroid lesion located adjacent to the aorta (Figure I).

Pulmonary Pathologies

Preoperative CT evaluation revealed pulmonary pathologies in 44 patients (8.23%). One patient with tracheal stenosis was referred to a tertiary center. Fourteen patients had benign or malignant nodules; malignancy was confirmed in one patient following further evaluation, and the patient was discharged (Figure II). Emphysema was detected in ten patients, in whom the lungs were not deflated during surgery. As all of these cases necessitated a change in the surgical plan, they were classified in Group 1. Conversely, 19 patients with bronchiectasis did not require further evaluation and were classified in Group 2.

Figure I. Axial non-contrast thoracoabdominal CT image showing an intrathoracic thyroid lesion (ITT) located adjacent to the innominate artery (IA), innominate vein (IV), left common carotid artery (LCCA), and left subclavian artery (LSA). Due to its proximity to major vascular structures, the lesion was resected via concomitant thyroidectomy during CABG.

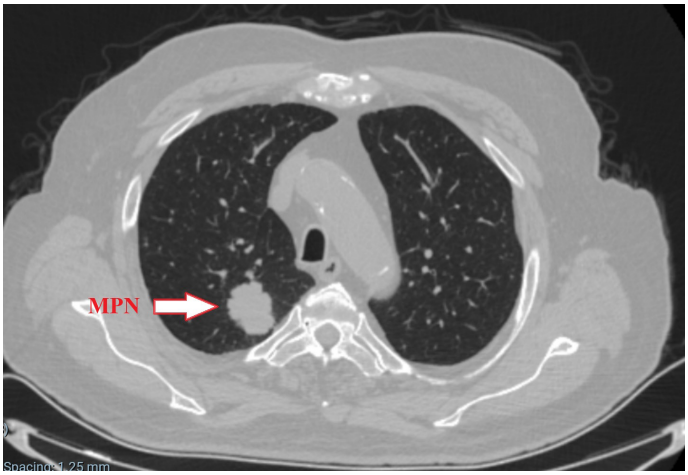


Abdominal Pathologies

Abdominal pathology was detected in 60 patients

(11.23%). Three patients were diagnosed with gastric malignancy, discharged, and referred for medical treatment. One patient with splenic atrophy required further evaluation and was included in Group 1. Gallbladder pathology was found in 31 patients; 13 of these required further investigation and were classified in Group 1, while 18 were classified in Group 2 due to the absence of need for additional evaluation. Hiatal hernia was detected in two patients and umbilical hernia in nine patients; these cases did not require surgical plan changes and were included in Group 2. Liver pathologies were identified in 14 patients; 5 were classified in Group 1 due to the need for further assessment, and 9 in Group 2.

Figure II. Axial non-contrast thoracoabdominal CT image showing a solitary pulmonary lesion (marked as MPN – malignant pulmonary nodule). Malignancy was confirmed through further evaluation, and the patient was discharged without undergoing coronary surgery.



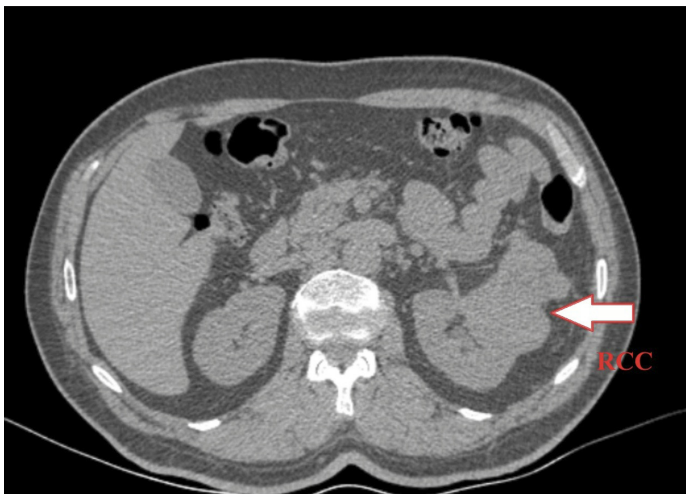
Urological Pathologies

Urological pathologies were found in 110 patients (20.60%). One patient was diagnosed with renal cell carcinoma (RCC) and referred to a tertiary center (Figure III). Two patients had adrenal adenomas, one had a horseshoe kidney, and four had renal agenesis; all were classified in Group 1 due to the need for further evaluation. Renal stones were detected in 24 patients and did not require changes to the surgical plan, so they were placed in Group 2. Renal cysts were found in 52 patients; 3 with multiple cysts requiring further evaluation were included in Group 1, and the remaining 49 were included in Group 2. Additionally, benign prostatic hyperplasia (BPH) was detected in 26 patients, all of whom were included in Group 2, as surgical planning was unaffected.

Vascular Pathologies

Vascular pathology was identified in 183 patients (34.26%). Aneurysmal dilatation was found in 32 patients, and in 3 of these cases, the findings required a change in the surgical plan, classifying them in Group 1. Additionally, vascular calcification was detected in 151 patients (28.27%), of which 23 cases (4.30%) required further evaluation and modifications in surgical strategy, thus classified in Group 1. Among these, porcelain aorta was detected in 11 patients, subclavian artery stenosis in 3, and iliac artery calcification in 9 patients.

Figure III. Axial non-contrast thoracoabdominal CT image showing a solid renal mass (RCC – renal cell carcinoma) in the left kidney. The patient was diagnosed with RCC and referred to a tertiary center for further management.



Discussion

In this study, at least one incidentaloma was detected in 70.8% (n=378) of patients scheduled for elective CABG. Of these findings, 12% (n=64) were considered clinically significant enough to warrant a change in the surgical strategy. The reported prevalence of incidentalomas in the literature varies widely. For example, in the study by Na et al. (86.7%), contrast-enhanced thoracoabdominal CT angiography was used, resulting in a high detection rate (2). In contrast, Park et al. reported a lower incidence (20.1%) using non-contrast chest CT (3). In our study, although non-contrast CT was also used, the scanning area was extended to cover the thoracoabdominal region, which may explain the differences in incidentaloma rates compared to both studies.

In some large series involving TAVI patients,

incidentaloma rates have been reported as high as 85% (8–14). However, these studies typically involve an older patient population and adopt a more extensive imaging approach covering multiple systems. Nevertheless, the use of non-contrast CT in our study may have contributed to a lower detection rate, particularly due to the potential for missing hypervascular lesions. Still, this imaging strategy stands out for its practical applicability and widespread accessibility in real-world clinical settings. Unlike the studies involving TAVI candidates, this study employed non-contrast CT in a younger and more selectively chosen patient population. This distinction may help explain the differences in incidentaloma prevalence.

The clinical impact of CT findings was most evident in the surgical planning process. In total, CT findings led to changes in the surgical plan in 64 patients (12.0%). The most frequent changes included switching to off-pump CABG and re-evaluating graft selection. Furthermore, surgery was canceled in six patients—five due to confirmed malignancies and one due to tracheal stenosis—and these patients were referred to tertiary centers. Similar scenarios have been reported in the literature. In the study by Aviram et al., surgical plans were altered in 6 out of 15 patients, and surgery was canceled in 2 cases (4). Park et al. reported that CT findings directly influenced surgical decisions in 142 patients (50%) (3). In studies involving TAVI patients, such as those by Goitein et al. and Trenkwalder et al., the rates of plan modifications were reported as 23.3% and 25%, respectively (9,11). The relatively lower rate of 12% in our study can be attributed to the more selective patient population and the exclusive use of non-contrast CT.

Extensive aortic calcifications and the presence of a porcelain aorta are significant risk factors in open-heart surgery (5,6,15). In our study, a porcelain aorta was identified in 11 patients, while severe vascular calcifications were observed in others; in the majority of these cases, the surgical approach was revised accordingly. Aviram et al. reported two patients with a porcelain aorta, and in one of them, surgery was canceled (4). Nishi et al. identified circumferential aortic calcification in 4.3% of their patients and noted that the cannulation site was changed in all such cases (5). In Sirin's review, the prevalence of porcelain aorta was reported to range between 2% and 9.3%, and off-pump, no-touch techniques were recommended in these scenarios (6). Similarly, in our study, patients with high-risk aortic pathology were directed toward off-pump surgery in an effort to prevent complications such as stroke.

Beating heart (off-pump) surgery was predominantly performed in patients with severe aortic calcification or porcelain aorta (Group 1). This approach was applied to minimize aortic manipulation and reduce embolic complications. Off-pump surgery was also conducted in other patients with suitable vascular anatomy, even when the surgical plan was not altered. In the study by Park et al., off-pump CABG was performed in 26 of 36 patients with severe aortic atherosclerosis (3). In the study by Na et al., anaortic off-pump CABG was performed in 64 of 66 patients with significant aortic calcification (2). These findings underscore the importance of preoperative CT in identifying high-risk patients and guiding the selection of an appropriate surgical technique.

Vascular calcification was not limited to the aorta but also provided critical information regarding peripheral arteries. In our study, significant calcification in the proximal segment of the left subclavian artery was observed in three patients, while diffuse iliac artery calcification was detected in nine. These findings directly influenced both graft selection and the need for potential postoperative support. In patients with subclavian artery calcification, the left internal thoracic artery (LITA) graft was generally used as a free graft or replaced with alternative grafting strategies. Furthermore, in cases of iliac artery calcification where IABP applicability was limited, preoperative assessment of peripheral arteries became a critical part of the surgical strategy. Similar findings in previous studies have also been shown to affect surgical planning (2,3). Sirin's review indicated that in cases of subclavian artery stenosis, the use of LITA grafts may still be feasible after preoperative stenting (6).

In our study, the 30-day mortality rate remained low, with no statistically significant differences observed between the groups. Even in the highest-risk group,

the mortality rate was comparable to that of the other groups. This finding suggests that CT-based risk assessment may be effective in anticipating and preventing complications. In the study by Park et al., the mortality rate reached up to 30% in patients with severe aortic atherosclerosis who did not undergo off-pump strategies (3). Similarly, Na et al. reported that a patient diagnosed with malignancy died without undergoing surgery (2). Other studies have indicated that excluding patients from surgery based on CT findings reduced the risk of stroke and mortality (5,15). TAVI-related studies further support this perspective; for instance, Trenkwalder et al. reported that clinically significant incidental findings could alter treatment planning without increasing mortality, while Markowiak et al. emphasized that certain CT findings might negatively affect long-term survival (11,12).

In our study, some patients with suspected malignancies were referred for further evaluation, including MRI, PET, or biopsy, and once the diagnosis was confirmed, five patients were not operated on and were referred to relevant specialties. Identified malignancies included lung cancer, gastric tumors, and renal cell carcinoma. Similar rates have been reported in the literature. In the study by Park et al., malignancy was detected in 8 patients (2.8%), and some underwent concurrent resections (3). Na et al. reported that one patient died due to advanced gastric cancer, while another underwent pulmonary lobectomy following CABG (2). TAVI studies have also reported substantial malignancy rates: Stachon et al. identified suspected malignancies in 18.7% of patients, while Bianchi et al. reported high-risk lesions in 15% of cases (8,14). Goitein et al. and Hussien et al. reported malignancy rates of 4.4% and 3.3%, respectively (9,10). In the study by Tobe et al., significant incidental findings were identified in 13.2% of Japanese TAVI candidates, and six patients were diagnosed with malignancies (13). These findings collectively indicate that preoperative CT can serve as an effective tool not only for anatomical assessment but also for systemic screening. In our study, early identification of suspicious lesions ensured patient safety and allowed for more predictable surgical planning.

This approach is also in line with the current recommendations of the 2023 AHA/ACC Guideline for Coronary Artery Disease. The guideline emphasizes the importance of comprehensive evaluation before surgical revascularization, considering comorbid conditions and balancing risks and benefits in surgical planning (1). The use of preoperative CT screening in our study provided results that are consistent with these principles in both surgical strategy and systemic assessment. Based on these findings, routine use of thoracoabdominal CT screening in elderly patients and those with comorbidities who are candidates for CABG should be considered.

This study has several limitations. First, all evaluations were based solely on non-contrast thoracoabdominal CT scans. This may have led to the omission of certain pathologies, especially hypervascular lesions that could be more clearly identified with contrast-enhanced imaging. However, the widespread availability, lower cost, and practical nature of non-contrast CT increase its applicability under real-world conditions. Second, the single-center, retrospective design of the study may limit the generalizability of the findings. Prospective studies conducted across multiple centers with diverse patient populations are needed to validate these results on a broader scale.

Third, the long-term clinical outcomes associated with incidental findings detected on CT were not assessed within the scope of this study. Further investigations are required to determine the potential effects of these findings on long-term mortality, morbidity, and quality of life. Additionally, some of the incidental pulmonary findings, such as ground-glass opacities, may have been related to prior COVID-19 infection, particularly since the study period overlaps with the pandemic years. Differentiating such post-infectious changes from other causes was beyond the scope of this retrospective analysis. Lastly, some incidental findings could not be pathologically confirmed, and assessments were based on clinical and radiological follow-up. This may have led to uncertainty in determining the true nature of certain lesions. Despite these limitations, our study clearly demonstrates the value of non-contrast thoracoabdominal CT in the preoperative assessment

of patients undergoing elective CABG.

Conclusion

This study demonstrated that preoperative non-contrast thoracoabdominal CT scanning provided significant contributions to surgical planning in patients scheduled for elective CABG. The early identification of high-risk conditions such as porcelain aorta, extensive vascular calcifications, and malignancies enabled strategic decisions, including the preference for off-pump surgery, appropriate graft selection, and, when necessary, cancellation of the operation. These measures contributed to the reduction of complications and resulted in low mortality rates. Non-contrast CT emerges as both a safe and accessible modality, offering not only anatomical but also systemic evaluation, thus serving as a valuable tool in surgical planning.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Evaluation of the Risk of Subclinical Atherosclerosis in Vitiligo Patients by Measuring Carotid Artery Intima Media Thickness via Ultrasonography

Vitiligo Hastalarında Ultrasonografi ile Karotis Arter İntima Media Kalınlığının Ölçülerek Subklinik Ateroskleroz Riskinin Değerlendirilmesi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1682097
Geliş Tarihi | Received: 23.04.2025
Kabul Tarihi | Accepted: 29.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Aydın ZB, Öztekin A. Evaluation of the Risk of Subclinical Atherosclerosis in Vitiligo Patients by Measuring Carotid Artery Intima Media Thickness via Ultrasonography. Hitit Medical Journal 2025;7(2):255-261. https://doi.org/10.52827/hititmedj.1682097

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 23/02/2022 tarihinde Hitit Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2022-13.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: ZBA, AÖ Tasarım: ZBA, AÖ Veri Toplama/Veri İşleme: ZBA, AÖ Veri Analizi: ZBA Makalenin Hazırlanması: ZBA, AÖ
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee on 23/02/2022. Decision no: 2022-13.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ZBA, AÖ Design: ZBA, AÖ Data Collection/Data Processing: ZBA, AÖ Data Analysis: ZBA Manuscript Preparation: ZBA, AÖ
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Evaluation of the Risk of Subclinical Atherosclerosis in Vitiligo Patients by Measuring Carotid Artery Intima Media Thickness via Ultrasonography

ABSTRACT

Objective: Vitiligo is an autoimmune disease characterized by the destruction of melanocytes. It is often associated with other autoimmune diseases and systemic metabolic disorders. This study aimed to evaluate the increased risk of subclinical atherosclerosis in vitiligo patients.

Material and Method: In this prospective study, 70 vitiligo patients and 70 healthy control subjects, who were over the age of 18 years and without cardiovascular disease risk factors, underwent carotid artery ultrasonography, between 2022 and 2023. Carotid artery intima-media thickness which is an indicator of subclinical atherosclerosis was measured bilaterally. Vitiligo patients were grouped according to the presence of vitiligo vulgaris, acrofacial disease, focal vitiligo, family history, duration of disease, and age of the patient at disease onset.

Results: The mean carotid artery intima-media thickness in vitiligo patients was significantly greater than healthy controls ($p<0.001$). In particular, intima-media thickness was greatest in vitiligo patients with a disease duration less than one year, but this difference was not statistically significant ($p>0.05$).

Conclusion: This study revealed the risk of subclinical atherosclerosis in vitiligo patients with the carotid artery ultrasonography, which is a radiation free, inexpensive imaging method. There are few studies on the risk of cardiovascular diseases in vitiligo patients. The main difference of our study is that we excluded the subjects with any risk factors for cardiovascular diseases to identify the vitiligo as an independent risk factor for subclinical atherosclerosis and therefore cardiovascular diseases. At this point, we think that our study makes an important contribution to the literature.

Keywords: Atherosclerosis, carotid artery, intima media, ultrasonography, vitiligo.

ÖZET

Amaç: Vitiligo, melanositlerin yıkımı ile karakterize otoimmün bir hastalıktır. Genellikle diğer otoimmün hastalıklar ve sistemik metabolik bozukluklarla birlikte görülür. Bu çalışmada vitiligoda artmış subklinik ateroskleroz riskinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif çalışmada, 18 yaş üstü, kardiyovasküler hastalık risk faktörü olmayan 70 vitiligo hastası ve 70 sağlıklı kontrole 2022-2023 yılları arasında karotis arter ultrasonografisi uygulandı. Subklinik aterosklerozun bir göstergesi olan karotis arter intima-media kalınlığı bilateral olarak ölçüldü. Vitiligo hastaları vitiligo vulgaris varlığı, akrofasiyal hastalık, fokal vitiligo, aile öyküsü, hastalık süresi ve hastalığın başlangıç yaşına göre gruplandırıldı.

Bulgular: Vitiligo hastalarında ortalama karotis arter intima-media kalınlığı sağlıklı kontrol grubu ile karşılaştırıldığında istatistiksel olarak anlamlı derecede yüksekti ($p<0.001$). Özellikle hastalık süresi bir yıldan az olan vitiligo hastalarında intima-media kalınlığı en yüksekti, ancak istatistiksel olarak anlamlı değildi ($p>0.05$).

Sonuç: Bu çalışma, radyasyon içermeyen düşük maliyetli bir görüntüleme yöntemi olan karotis arter ultrasonografisi ile vitiligo hastalarında subklinik ateroskleroz riskini ortaya koymaktadır. Vitiligoda kardiyovasküler hastalık riski ile ilgili az sayıda çalışma bulunmaktadır. Çalışmamızın temel farkı ise kardiyovasküler hastalıklar için risk faktörleri olan bireylerin çalışmaya dahil edilmeyerek, subklinik ateroskleroz ve dolayısıyla kardiyovasküler hastalıklar için vitiligonun bağımsız bir risk faktörü olarak ortaya konmasıdır. Bu noktada çalışmamızın literatüre önemli katkı sağladığını düşünmekteyiz.

Anahtar Sözcükler: Ateroskleroz, intima media, karotis arter, ultrasonografi, vitiligo.

Introduction

Vitiligo is a chronic skin disease which is characterized by acquired depigmentation disorder caused by the loss of melanocytes (1). The incidence of vitiligo is approximately 0.5-2% worldwide (2). Many conditions including genetic factors, neural factors, oxidative stress, and autoimmunity are thought to be responsible for the pathogenesis of vitiligo, which has not yet been confirmed (3-7).

Vitiligo is characterized by circumscribed white patches because of the destruction of melanocytes in the skin. Some areas containing melanocytes such as hair follicles, the eyes, the inner ear, and the brain are usually spared because of the immune context there (3,6). To determine the disease activity, the 'vitiligo disease activity score' (VIDA) and to evaluate the disease severity and treatment, the 'vitiligo area severity index' (VASI) scores are used by dermatologists (8). Patients with vitiligo are prone to complications, such as diabetes, obesity, hyperlipidemia, and hypertension (1). In particular, nonsegmental vitiligo, which is characterized by depigmented patches with a diameter of a few centimeters that are symmetrical and involve both sides of the body, is associated with autoimmune diseases, several systemic and metabolic disorders, insulin resistance, lipid abnormalities, and metabolic syndrome (9, 10).

Autoimmunity and oxidative stress which may cause skin findings with inflammatory and immunological responses in patients with vitiligo, can also cause certain systemic manifestations (10). Increased reactive oxygen species (ROS) and inefficiency in antioxidant mechanisms have been shown in vitiligo (11). Intracellular oxidative stress can cause melanocyte destruction as an immune response (12). Several observations have confirmed the systemic inflammatory process, and that IFNγ, in particular, demonstrates important contribution to the pathogenesis of the disease (13). Additionally, the chemokines CXCL9 and CXCL10 are biomarkers of disease activity (13). Inflammatory cytokines in the systemic circulation such as IL-1, IL-6 and TNF-α, which play a role in vitiligo, have been associated with atherosclerosis (13, 14). The expression of chemokines and cytokines, increased oxidative stress and inflammatory processes are the main pathways involved in the pathogenesis of atherosclerosis and vitiligo, in fact, atherosclerosis is the main cause of many cardiovascular diseases (9). Inflammation, oxidation, endothelial disfunction are considered to be functional triggers for atherosclerosis (15-17). Early phase of atherosclerosis can be quantified by the ultrasonographic measurement of carotid artery intima-media thickness (CIMT) (15-17).

Ultrasonography of the carotid artery is widely used for detailed evaluation arterial wall changes, for detecting subclinical atherosclerosis by measuring the intima-media thickness, and also for evaluating the atherosclerotic plaques (18). Many factors, such as sex, age, lifestyle, food habits, and ethnicity, etc. affect the CIMT (19). CIMT is an accepted predictor for future cardiovascular diseases (CVDs) (20). Ultrasonographic measurement of CIMT is an accurate and applicable method for subclinical atherosclerosis from childhood to early adulthood before carotid artery plaques occur (20).

Vitiligo is considered to be a systemic metabolic disorder, not just a skin disease, with accompanying comorbidities. There are currently very few studies on CVDs in individuals with vitiligo (9, 21, 22). The aim of the present study was to verify the presence of subclinical atherosclerosis in vitiligo patients via carotid artery ultrasonography, which is a noninvasive, radiation-free imaging method.

Material and Method

Study population

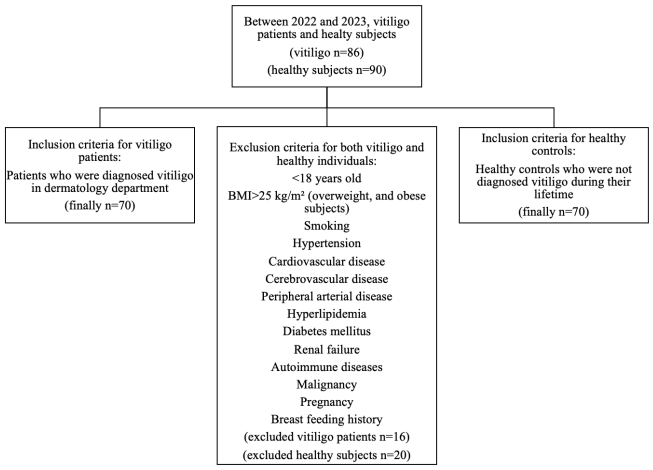
In this prospective study, between 2022 and 2023, 70 individuals with vitiligo, and 70 healthy subjects were included. The patients who were diagnosed with vitiligo were referred to the radiology department by the dermatologist with 15 years of experience. The control group included healthy subjects who applied to the dermatology department for other reasons (acne, bacterial skin infections, fungal nail infections, scabies, etc.). All of the vitiligo patients had nonsegmental vitiligo, and were divided into vitiligo vulgaris, acrofacial, and focal vitiligo groups. Additionally, family history, duration of the disease, and age of the patient at disease onset were added to the study. This study was carried out in accordance with the principles outlined in the latest version of the Declaration of Helsinki. This study was approved by

the local institutional ethics committee (Protocol no: 2022-13, approval date: 23 February 2022). Informed consent was obtained from the individuals included in the study.

Inclusion and exclusion criteria

The patients who were diagnosed with vitiligo, and for controls, subjects who were not diagnosed with vitiligo during their lifetime, were included in the study. In both the vitiligo and healthy control groups, the exclusion criteria were as follows: younger than 18 years, hyperlipidemia, and known history of CVD, cerebrovascular disease, renal failure, diabetes or hypertension, other autoimmune diseases, smoking, pregnancy, breast-feeding, and malignancy. Body mass index (BMI) was calculated for each group. Individuals who were overweight (BMI 25-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) were excluded. A flow chart is presented in Figure I.

Figure I. Flow chart (BMI: Body mass index)



Ultrasonography protocol

Carotid artery ultrasonography was performed by the radiologist with 10 years of experience who was blinded to the patient's clinical status with a linear transducer (3-12 MHz) in the B-mode, pulsed Doppler mode and color mode. The CIMT was measured when the patient was lying in the supine position. The transducer was positioned longitudinally 1 cm proximal to the carotid bifurcation, and CIMT measurements were obtained from three contiguous sites bilaterally. The mean values were used for statistical analysis (Figure II).

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 26 (SPSS Inc., Chicago, IL, USA). Ratio comparisons between categorical variables were analyzed via the chi-square test. The normality of the distribution of the data was evaluated with the Kolmogorov-Smirnov test. Student's t-test and the Mann Whitney U test were used for data normally distributed and nonnormally distributed data, respectively, to compare numerical variables between two independent groups. For comparisons between more than two groups, analysis of variance (ANOVA) test was used. A post-hoc test was used for multiple comparisons between groups to detect least significant differences when ANOVA test was used. Descriptive statistics of continuous variables were presented as the means±standard deviations (SDs). Categorical variables were reported as numbers (n) and percentages (%). The statistical significance was set at the *p<0.05* level.

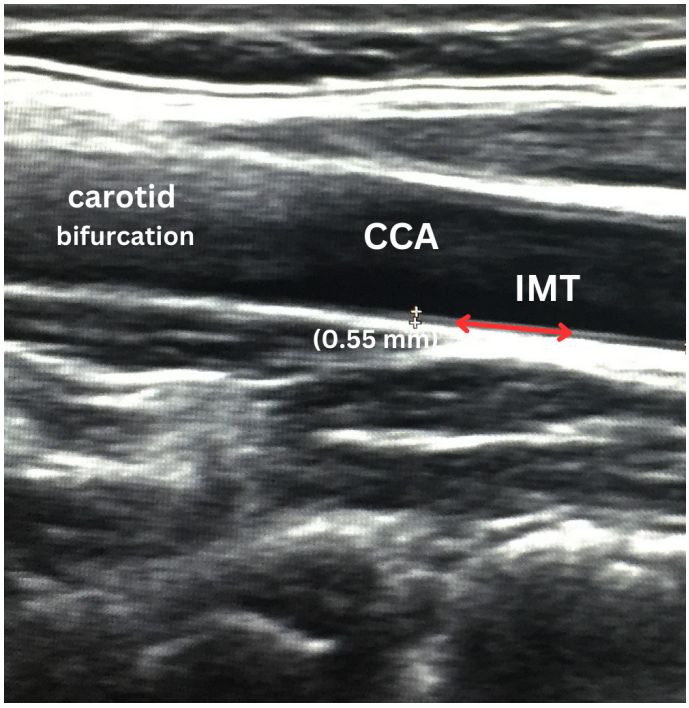


Figure II. Ultrasonographic measurement of carotid artery intima-media thickness (red line), the space between "(+) – (+)" (CCA: Common carotid artery, IMT: intima-media thickness)

Table I. Demographic Characteristics of the Participants

Variables (mean±SD)	Vitiligo (n=70)	Controls (n=70)	*p values*
Age (years)	32.74±9.275	30.16±8.196	*0.083*
Female [n (%)]	38 (54.3%)	35 (50%)	*0.612*
Male [n (%)]	32 (45.7%)	35 (50%)	*0.612*
BMI (kg/m^2)	24.51 ±3.46	24.62±3.17	*0.852*

(BMI: Body mass index, SD: Standard deviation)

Results

Seventy patients with vitiligo and 70 healthy

subjects were evaluated prospectively in the present study. The demographic data were presented in Table I. No significant differences in age, sex or BMI were observed between vitiligo patients and control subjects (*p>0.05*). All individuals underwent carotid ultrasonography. No atherosclerotic plaques were detected. CIMT values, both right and left, were significantly different between the vitiligo patients and control groups (*p<0.001*) (Table II). The patients with vitiligo had greater CIMT values than control group.

Table II. The Mean CIMT Among Vitiligo and Healthy Controls

Variables (mean±SD)	Vitiligo (n=70)	Controls (n=70)	*p values*
CIMT (right) (mm) CIMT (left) (mm)	0.571±0.084 0.592±0.092	0.517±0.046 0.518±0.046	*<0.001* *<0.001*

(CIMT: Carotid artery intima-media thickness, SD: Standard deviation)

Table III. The Mean CIMT between Vitiligo Subgroups

Vitiligo	CIMT (right) (mm) (mean±SD)	CIMT (left) (mm) (mean±SD)
Family history (yes) (n=20) Family history (no) (=50) *p value*	0.559±0.083 0.576±0.085 *0.524*	0.573±0.091 0.599±0.093 *0.201*
Duration of the disease Less than one year (n=9) 1-5 years (n=37) 6-10 years (n=12) More than 10 years (n=12) *p value*	 0.602±0.107 0.553±0.060 0.595±0.096 0.582±0.111 *>0.05*	 0.648±0.119 0.575±0.075 0.594±0.086 0.599±0.116 *>0.05*
Onset of the disease before the age of 18 Yes (n=19) No (n=51) *p value*	 0.581±0.109 0.568±0.074 *0.931*	 0.595±0.105 0.590±0.088 *0.878*
Focal disease (yes) (n=21) Focal disease (no) (n=49) *p value*	0.579±0.077 0.568±0.088 *0.688*	0.589±0.087 0.593±0.095 *0.928*
Acrofacial disease (yes) (n=25) Acrofacial disease (no) (n=45) *p value*	0.557±0.071 0.579±0.090 *0.771*	0.585±0.085 0.595±0.097 *0.862*
Vitiligovulgaris (yes) (n=22) Vitiligovulgaris (no) (n=48) *p value*	0.574±0.084 0.570±0.085 *0.803*	0.598±0.090 0.589±0.094 *0.653*

(CIMT: Carotid artery intima-media thickness, SD: Standard deviation)

Vitiligo patients were divided into subgroups according to their family history, duration of the disease, onset of the disease before the age of 18, focal disease, acrofacial disease, and vitiligo vulgaris. The results of the subgroup statistical analysis were presented in Table III. CIMT values were not significantly different between the vitiligo subgroups (*p>0.05*). The highest mean CIMT value was recorded in patients with a disease duration of less than one year (right: 0.602 mm, left: 0.648 mm). Patients who were diagnosed with vitiligo before 18 years of age at disease onset, patients with vitiligo vulgaris, patients without a family history had greater CIMT values.

Discussion

In this prospective study, CIMT was significantly greater in vitiligo patients than in healthy controls. The presented results indicate the risk of subclinical atherosclerosis in vitiligo patients. The relationships between vitiligo and CVDs have been reported in some literature reports (9, 21, 22). CVDs continue to increase due to the factors such as lifestyle habits, other concomitant diseases, and genetic factors, and they are responsible for approximately one-third of all deaths worldwide (23). It is important to identify possible risk factors and prevent them before the disease occurs.

High levels of inflammatory markers such as homocysteine, C-reactive protein, and the neutrophil/lymphocyte ratio have been reported in vitiligo patients (24, 25). Furthermore, some inflammatory cytokines: such as IL-1, IL-6, and TNF-α are associated with the pathogenesis of both vitiligo and atherosclerosis, insulin resistance, and other metabolic disorders (26). In the present study, the statistically significant increase in CIMT in vitiligo patients may be due to the presence of inflammatory chemicals in the systemic circulation. Additionally, a higher rate of metabolic syndrome was reported in vitiligo patients than in control groups in previous studies (8, 10, 21, 27). Sharma et al. reported a significant increase in the rates of metabolic syndrome, hypertriglyceridemia, low HDL levels, and impaired glucose tolerance in patients with vitiligo (27). Bathina et al. reported that metabolic syndrome was more common in vitiligo patients than in controls; in particular, the patients with vitiligo vulgaris had the highest ratio in their study (8). Metabolic syndrome is an independent risk factor for CVD, and the combination of these risk factors elevates the rates and severity of CVD (28). Therefore, the associations between metabolic syndrome and vitiligo reported by Bathina et al. and Sharma et al. were in concordance with our finding that the risk of subclinical atherosclerosis has been increased in vitiligo patients (8, 27).

Azzazi et al. investigated the association between vitiligo and atherosclerotic cardiovascular disease in Egyptian population (9). They reported that the mean CIMT for nonsegmental vitiligo patients was significantly greater than that for controls, which was consistent with our study. To explain this condition, they used the significantly high levels of malondialdehyde and hydrogen peroxide and significantly low level of total antioxidant capacity as indicators of oxidative stress in vitiligo patients. Namazi et al. reported that CIMT was greater and that subclinical atherosclerosis was more common in vitiligo patients than in controls (21). However, their results about CIMT values were not statistically significant. The mean age and BMI values in their study population were greater than those in our population. Additionally, total cholesterol and low-density lipoprotein (LDL) levels were high in their study population. For secondary analysis of CIMT values, they excluded all the subjects with metabolic syndrome from the vitiligo and control groups to eliminate their contribution to atherosclerosis. Compared with the healthy subjects, vitiligo patients in their study population had high CIMT values which was not statistically significant, and they had significantly more frequent subclinical atherosclerosis. In the present study, the patients and healthy controls with high lipid profiles were not included in the study. Therefore, our study may contribute to the literature in determining the effect of vitiligo as an independent factor for subclinical atherosclerosis without known risk factors such as hyperlipidemia.

We also evaluated the relationship between the disease duration and CIMT. CIMT was high in patients with a disease duration of less than one year and had the highest mean value among the vitiligo subgroups. In contrast, Namazi et al. reported a significant positive correlation between the duration of the disease and subclinical atherosclerosis; the mean duration of vitiligo was significantly longer in patients with subclinical atherosclerosis (21). This mismatch may be due to the small number of subjects in the study subgroups. The correlation between disease duration and the risk of subclinical atherosclerosis should be investigated by further studies with large sample sizes.

Fraczek et al. identified 94 cardiovascular diagnoses (cardiomyopathies, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, heart conduction disorders, heart valve diseases, heart failure, ischemic heart diseases, etc.) with a prevalence of ≥1% in patients with vitiligo in their retrospective study based on the basis of data from electronic health records (22). They reported that individuals with vitiligo were at increased risk of developing atherosclerosis as supported by the elevated CIMT values in our study. As a result, people with vitiligo may be prone to developing CVDs in the future.

The sample size of the study population was the main limitation of the study. While performing subgroup analysis, the small sample size limited the statistical analysis. The ultrasound, which we used during the study did not have an automatic measurement software program, so CIMT was measured manually. Measurements were performed by the same expert radiologist to exclude examiner bias. However, CIMT measurements could be performed by two or more radiologists to verify interobserver agreement in future studies.

Conclusion

The potential influence of other comorbidities might have an impact on the development of CVDs in vitiligo patients. This study focused on subjects, both controls and vitiligo patients, who do not have any risk factors for possible CVDs, such as smoking, obesity, hyperlipidemia, renal failure, cerebrovascular disease, other autoimmune diseases, etc. This was the main factor that distinguished our study from other studies in the literature. Therefore, the statistically significant increase in carotid artery intima-media thickness in vitiligo patients revealed by our study makes an important contribution to the literature in terms of vitiligo being a predisposing factor for subclinical atherosclerosis. Additionally, with the support of further large sample studies, a follow-up procedure should be performed in vitiligo patients for the prevention and treatment of cardiovascular diseases. To detect the risk of subclinical atherosclerosis, carotid artery ultrasonography which is a radiation-free, fast and inexpensive imaging method, can be used periodically in vitiligo patients.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

High-Intensity Laser Therapy for Hemiplegic Shoulder Pain: An Investigation of Efficacy

Hemiplejik Omuz Ağrısı için Yüksek Yoğunluklu Lazer Terapisi: Bir Etkinlik Araştırması

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1593963
Geliş Tarihi | Received: 22.01.2025
Kabul Tarihi | Accepted: 29.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Bilir EE, Kara O, Gümüş Atalay S, Tezen Ö, Uzun Ö, Karaköseoğlu İ. High-Intensity Laser Therapy for Hemiplegic Shoulder Pain: An Investigation of Efficacy. Hitit Medical Journal 2025;7(2):262-272. https://doi.org/10.52827/hititmedj.1593963

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 06/07/2022 tarihinde Ankara Şehir Hastanesi 2 Nolu Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: E2-22-1902.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: EEB, SGA Tasarım: EEB, SGA Veri Toplama/Veri İşleme: EEB, İK,OK,ÖT Veri Analizi: EEB, OK, ÖU Makalenin Hazırlanması: EEB, ÖU, İK
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Ankara City Hospital Clinical Research Ethics Committee on 06/07/2022. Decision no: E2-22-1902.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: EEB,SGA Design: EEB, SGA Data Collection/Data Processing: EEB, İK,OK,ÖT Data Analysis:EEB, OK, ÖU Manuscript Preparation:EEB, ÖU, İK
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

High-Intensity Laser Therapy for Hemiplegic Shoulder Pain: An Investigation of Efficacy

ABSTRACT

Objective: Hemiplegic shoulder pain is one of the most common complications after stroke. High-intensity laser therapy is a new treatment option between conventional treatment strategies. We aimed to compare the effectiveness of conventional physical therapy agents and high-intensive laser therapy in this study.

Material and Method: Randomized, case-control trial. Participants (n=43) were randomized into two groups. Group 1: high-intensive laser therapy (n=22), and group 2: conventional physical therapy (n=21), and additionally, therapeutic exercise programs were applied both groups. Patients were assessed before treatment and after treatment for clinical parameters with a visual analog scale, an arm motor ability test, functional independence measure scores, and modified ranking scores. Patients underwent sonographic diagnostic evaluation.

Results: Sociodemographic characteristics and clinical data and ultrasonographic findings were similar between groups (*p>0.05*). In both groups, within-group comparisons showed a significant decrease in activity and nocturnal pain scores and a significant increase in arm motor ability test function and movement scores and functional independence measure scores (*p<0.05*). Compared to the conventional physical therapy group, the HILT group showed a significantly greater improvement in the VAS night score (*p<0.05*).

Conclusion: Our study results indicate that both treatment interventions were efficacious in the management of hemiplegic shoulder pain. Therefore, high-intensity laser therapy presents as a potential alternative therapeutic modality for hemiplegic shoulder pain, demonstrating a comparable level of effectiveness.

Keywords: Hemiplegia, laser therapy, physical therapy modalities, shoulder pain, ultrasound therapy.

NIH Clinical Trials registration number: NCT06407596

ÖZET

Amaç: Hemiplejik omuz ağrısı, inme sonrası en sık görülen komplikasyonlardan biridir. Yüksek yoğunluklu lazer terapisi, konvansiyonel tedavi stratejileri arasında yeni bir tedavi seçeneğidir. Bu çalışmada, konvansiyonel fizik tedavi ajanları ile yüksek yoğunluklu lazer terapisinin etkinliğini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Randomize, vaka-kontrol çalışması. Katılımcılar (n = 43) iki gruba randomize edildi. Grup 1: yüksek yoğunluklu lazer tedavisi (n = 22) ve grup 2: geleneksel fizik tedavi (n = 21) ve ayrıca her iki gruba da terapötik egzersiz programları uygulandı. Hastalar tedavi öncesi ve tedavi sonrası görsel analog skala, kol motor yetenek testi, fonksiyonel bağımsızlık ölçüm puanları ve modifiye rankin puanları ile klinik parametreler açısından değerlendirildi. Hastalara ultrasonografik tanı değerlendirmesi yapıldı.

Bulgular: Sosyodemografik özellikler ve klinik veriler ve ultrasonografik bulgular gruplar arasında benzerdi (*p>0,05*). Her iki grupta da grup içi karşılaştırmalar aktivite ve gece ağrısı skorlarında anlamlı bir azalma ve kol motor yetenek testi fonksiyon ve hareket skorlarında ve fonksiyonel bağımsızlık ölçüsü skorlarında anlamlı bir artış gösterdi (*p<0,05*).

Sonuç: Çalışma sonuçlarımıza göre her iki tedavi uygulaması da hemiplejik omuz ağrısı için etkiliydi. Sonuç olarak, yüksek yoğunluklu lazer tedavisi hemiplejik omuz ağrısı için güncel bir tedavi seçeneği olabilir.

Anahtar Sözcükler: Ağrı, hemiplejik omuz ağrısı, inme, konvansiyonel fizik tedavi, lazer tedavisi.

Introduction

Hemiplegic shoulder pain (HSP) is one of the most common complications following stroke, negatively impacting rehabilitation outcomes and significantly reducing patients' quality of life (1,2). HSP can begin within the first week after stroke, but it is more frequently observed during the first 2–3 months and may become chronic, thereby delaying functional recovery.

The etiology of HSP is multifactorial and may involve conditions such as adhesive capsulitis, subacromial bursitis, shoulder subluxation, rotator cuff tears, complex regional pain syndrome, brachial plexus injuries, heterotopic ossification, and spasticity (3). Treatment of HSP is generally conservative and includes a wide range of physical therapy modalities such as analgesic medications, therapeutic exercises, proprioceptive training, kinesiology taping, thermotherapy, ultrasound (US), transcutaneous electrical nerve stimulation (TENS), extracorporeal shock wave therapy, pulsed electromagnetic fields, microwave diathermy, and low-level laser therapy (4,5).

TENS is a non-invasive modality that works on the basis of the gate control theory and primarily targets sensory nerve fibers (6). Therapeutic US physiologically induces increased blood flow, vascular permeability, and local metabolism, while also enhancing fibrous tissue extensibility and promoting muscle relaxation (7–9). Both modalities are commonly used in the treatment of shoulder pain, including HSP, within conventional physical therapy programs.

In recent years, high-intensity laser therapy (HILT) has emerged as a novel therapeutic approach for shoulder pain. HILT exerts photothermal, photomechanical, and biostimulator effects in deeper tissues, contributing to enhanced microcirculation, reduced inflammation and edema, and stimulation of tissue regeneration (10-12). While the literature includes studies investigating the effectiveness of High-Intensity Laser Therapy (HILT) in patients with hemiplegic shoulder pain, their number remains limited (13-15).

Musculoskeletal ultrasound is a non-invasive and dynamic imaging technique widely used for diagnosing hemiplegic shoulder pain. It is a valuable tool not only for structural evaluation but also for identifying prognostic factors before treatment. Compared to other imaging techniques, ultrasound offers several advantages including real-time visualization, absence of ionizing radiation, and cost-effectiveness (14,16). Generally sonographic evaluations in studies focusing on painful hemiplegic shoulder following stroke, common findings include effusion of the biceps tendon, tendinosis of the supraspinatus tendon, subacromial-subdeltoid (SA-SD) bursitis, partial-thickness tears of the rotator cuff, and full-thickness tears of the rotator cuff (17).

This study aims to compare the efficacy of high-intensity laser therapy (HILT) and conventional physical therapy (CPT) modalities (US, TENS) in the treatment of hemiplegic shoulder pain in post-stroke patients. Previous studies have investigated the effects of high-intensity laser therapy (HILT) on specific ultrasonographic changes in shoulder pathologies. In contrast, the present study broadly examined common ultrasonographic findings observed in hemiplegic shoulders and evaluated their potential impact on treatment response.

Specifically, this study aimed to investigate the relationship between clinical outcomes and sonographic findings and determine whether the presence of such sonographic abnormalities has predictive value in assessing the clinical efficacy therapeutic interventions and also , providing a comprehensive analysis of HILT's therapeutic potential in this specific patient population.

Material and Method

Trial design and Participants

This randomized, case control study was performed in the rehabilitation ward of a university hospital between June 2022 and February 2023. Ethical approval for the conduct of this research was acquired from the hospital's Institutional Review Board. The decision number is E2-22-1902. The study was executed in conformity with the principles of Declaration of Helsinki. Written informed consent was received from all patients participating in the study. Large Language Models (LLMs) were not used in our study.

Sixty eligible participants were initially recruited for this study. The inclusion criteria; patients have shoulder pain after stroke on hemiplegic side, male

or female between the ages of 18-75, first-ever unilateral stroke, pain visual analog scale (VAS) score ≥3cm, time since stroke ≥6 months, and time since last local intervention treatment >6 months.

The exclusion criteria were as follows: (1) a history of shoulder pain prior to stroke; (2) an unstable medical condition or uncontrolled systemic diseases (such as respiratory failure, congestive heart failure, liver and kidney dysfunction, or disorders affecting neuromuscular function); (3) bilateral hemiplegia; (4) those demanding cardiac pacemaker (5) administering any nonsteroidal anti-inflammatory drugs for shoulder pain prior to the study; (6) disturbance of awareness, severe visual, and cognitive impairment.

Baseline assessment and Randomization

Potentially qualified patients were eliminated through physical examination and clinical assessments. Patients were provided with comprehensive information about the aims and nature of the study, both verbally and in the form of an information sheet. The same physician performs all follow up assessments and interventions were performed by a physiotherapist. A total of 60 patients underwent assessment. Following the application of inclusion criteria and obtaining informed consent, 43 patients were enrolled in the study. Figure 1 demonstrates the study flow chart. The patients were randomly allocated to either the HILT group or the CPT group with a computer randomization programe. Computer generated random numbers were used for simple randomization of subjects.

Interventions

High Intensive Laser Therapy

Measurements before (at baseline) and after treatment (at the end of week 3) were evaluated by a single researcher. Group 1 (HILT group, n = 21) received HILT was administered three times per week for three weeks, resulting in a total of nine sessions. This was complemented by a therapeutic exercise program conducted five times per week for three weeks. A therapeutic exercise program for HSP, including passive, active-supported, and active range of motion exercises, stretching, and strengthening exercises were given both of group according to patient's motor recovery during follow up. Exercise program lasting 20-30 minutes, 3 sets of 10 repetitions, twice a day, was applied to both groups under the supervision of a physiotherapist.

Participants in Group 1 received HILT using a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser device (HIRO1.0, ASA). The physiatrist administered HILT beams longitudinally to the rotator cuff muscles, specifically targeting the supraspinatus and deltoid muscles. The pulsed Nd:YAG laser delivered ultrashort pulses, penetrating 3-4 cm into the tissue and providing a homogeneous distribution of light energy without excessive thermal effects. A standardized handpiece with fixed spacers ensured a consistent 90-degree angle and 3 cm distance between the laser source and the skin, with a 5 mm spot size as shown in Figure II. Each HILT session comprised three phases. Phase 1(Fast Scanning) rapid scanning of the upper trapezius, deltoid, and supraspinatus muscles at a frequency of 25 Hz, power of 8 W, and energy dose of 16 J/cm^2 for a total energy of 400 J over 2 minutes. Phase 2(Intermediate phase), direct application of the laser to trigger points at a frequency of 15 Hz and an energy dose of 6 J/cm^2 to 25cm2 area for a total energy of 150 J over 6 minutes, until a pain reduction of 70% to 80% was achieved with biostimulation effect. Phase 3; slow scanning of the previously treated areas at a frequency of 25 Hz/120 s until a total energy dose of 2,500 J was achieved. The time to apply all 3 stages of HILT was approximately 10 minutes (14). Protective goggles were utilized by both the practitioner and the patient during all laser applications

Conventional physical therapy

Group 2 (n=21) received conventional physical therapy by total of 15 sessions and a three-week therapeutic exercise program, consisting of five sessions per week, was implemented for individuals with HSP. Conventional physical therapy (TENS+US) were applied to group 2 by the same physiotherapist. TENS application was applied to the hemiplegic shoulder region with a Chattonoga brand device, using 4 adhesive electrodes of 5x5 cm in size, conventional current at a frequency of 80 Hz and 180ms current for 20 minutes. Ultrasound application, which is a deep heating method, was performed directly to the skin using a BTL brand device with a 3 MHz frequency and a dose of 1.5 Watt/cm^{2}intensity over 25 cm2 surface area for 5 minutes (18) with the help of ultrasound gel. The application was performed in

a 50% pulsed mode for 5 minutes by using gel and performing continuous circular motions. Furthermore, a comprehensive therapeutic exercise program for HSP was incorporated into the intervention, encompassing both passive and active supported and active range of motion exercises, stretching, strengthening, and mobilization exercises were performed to all patients by physiotherapists.

Clinical examination and the administration of patient-reported questionnaires were employed to assess adverse effects. These assessments were conducted immediately following the completion of the HILT and CPT procedures, as well as at all subsequent follow-up visits. Adverse events for HILT include temporary redness, skin irritation, a warm sensation during treatment, and a temporary increase in pain or discomfort. Adverse events for CPT include skin redness, tenderness, and increased pain and rare side effects include skin burns, heart rhythm disturbances, skin hypersensitivity, blood pressure changes, muscle-tendon damage-rupture during the release of joint restrictions, and bone fractures. No post-treatment complications were evident in any of the study participants

Clinical and Ultrasonographic Assessment

Demographic data including age, gender, marital and educational status, job, alcohol use, smoking and clinical features as stroke type, and hemiplegic side were recorded before treatment. The patients were assessed clinically at 0 (baseline) and at the end of week 3 after treatment. Pain intensity, measured using the Visual Analog Scale (VAS), served as the primary outcome measure. Secondary outcome measures included functional assessment as measured by the Functional Independence Measure (FIM) and the evaluation of upper extremity daily living activities. The shoulder of the patients on the painful side was evaluated with musculoskeletal ultrasonography at baseline. Shoulder ultrasonography examinations were conducted on all study participants by a physician possessing expertise in musculoskeletal ultrasonography. To ensure objectivity, the radiologist performing the examinations was blinded to the treatment group allocation of each participant. A 5-12 MHz linear-array transducer was employed for all examinations (LOGIC P5 Ultrasound System, used 11L liner prob). Ultrasonographic findings were recorded. Subacromial-subdeltoid (SA-SD) bursitis was diagnosed when ultrasonography revealed an effusion within the bursa exceeding 2 mm in thickness, accompanied by increased power Doppler signal. Rotator cuff tendinitis was identified by the presence of hypoechoic changes and a tendon thickness greater than 2 mm compared to the contralateral side. A full-thickness tear of the rotator cuff was diagnosed based on the following sonographic criteria: absence of the rotator cuff, exposed humeral tuberosity, focal areas of the cuff not visualized, discontinuity or a hypoechoic cleft within the cuff, herniation of the deltoid muscle or the subacromial-subdeltoid bursa into the cuff, or compression of the tendon (19). SA-SD bursitis, bicipital tendinosis, partial rupture, total rupture, calcific tendinitis findings were investigated with ultrasonographic assessment. And correlation analysis between ultrasonographic findings and improvements in pain and disability scales in the treatment groups were recorded.

The patients' movement and night pain were assessed through the use of Visual Analog Scale (VAS) to evaluate pain intencity and recovery. The VAS is used to measure pain on a 10-cm horizontal axis between a left endpoint of "no shoulder pain" and a right endpoint of "worst pain ever" (20).

The Modified Rankin Scale (MRS) is a widely used, ordinal scale designed to assess the level of disability or dependence commonly in stroke. It provides a standardized method for evaluating functional outcomes and is a critical tool in clinical practice. The mRS consists of seven ordinal levels, ranging from 0 (no symptoms) to 6 (death). Each level corresponds to a specific degree of disability, encompassing physical, cognitive, and social impairments (21).

FIM is a widely used tool that assesses patient's ability to perform daily activities after stroke. It covers basic self-care, moving around, managing toileting, communication, and social thinking. Scores range from 1 (needing total help) to 7 (completely independent). Higher scores mean the person is more independent in daily life (22).

Arm motor ability test (AMAT) assesses the disability and functional capacity of the upper extremity (UE) in activities of daily life. The measure requires clients to perform 13 common unilateral and bilateral UE tasks. The higher score means the

fewer activity limitations and the lower score means more activity limitations (23,24).

Statistical Analysis

The power analysis was performed using G-Power version 3.1.94, determining that a sample size of 40 patients (20 per group) was needed for an effect size of 0.925, a 0.05 margin of error, and 80% power in the study by Korkmaz et al. on shoulder pain after hemiplegia (14). Data were analyzed with SPSS version 25.0. Normality was assessed with the Shapiro-Wilk test. Continuous variables with normal distribution were reported as mean and standard deviation, while those without were reported as median and interquartile range (IQR). Categorical data were analyzed with Chi-square, Fisher's exact, or Yate's Continuity correction tests. Numerical variables were compared using independent samples t-tests or Mann-Whitney U tests, and within-group comparisons of repeated measurements were conducted with the Wilcoxon signed-rank test. Spearman correlation analysis assessed relationships between ultrasonographic findings and changes in pain, spasticity, and disability scales. A 95% confidence interval and 5% margin of error were used, with *P<0.05* considered statistically significant.

Results

In our study, total of 43 patients were allocated to the HILT group(n:22) and to the control group (n:21). Since 1 patient from the HILT group could not continue the treatment so the study was completed with 21 patients in the HILT group. Sociodemographic characteristics of the groups are summarized in Table I. There was no statistically significant difference between the groups. Treatment groups were similar in terms of clinical data and sonographic findings (Table II).

Figure I. Study Flow Chart

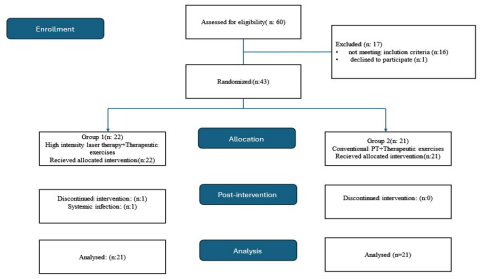


Figure 1: Study flow chat

In both groups, within group comparisons showed a significant decrease in VAS movement and night scores and a significant increase in AMAT-function, movement and FIM scores (*p<0.05*). On the other hand, there was no significant difference was found between the groups in terms of decrease in VAS movement scores, increase in AMAT-function and movement scores and FIM scores after treatment (*p>0.05*). Only the improvement in VAS night score was more significant in the HILT group compared to the conventional physical therapy group (*p=0.047*). No significant difference was found between the groups in pre-treatment, post-treatment MRS values and the difference of pre-treatment and post-treatment values (*p>0.05*). Table III shows the pre-treatment and post-treatment values of VAS, AMAT- function and movement, FIM scores differences between pre- treatment and post-treatment scores and MRS scores.

Table I. Sociodemographic Data of the Treatment Groups

	HILT group (n=21)	Conservative treatment group (n=21)	*p*
Age (median, IQR)	60.0 (17.0)	63.0 (9.0)	*0.571**
Gender (n/%) Female Male	 8 (38.1) 13 (61.9)	 10 (47.6) 11 (52.4)	*0.756*†
Marital status (n/%) Married Single Widow	 16 (76.2) 3 (14.3) 2 (9.5)	 18 (85.7) 1 (4.8) 2 (9.5)	
Educational status (n/%) Illiterate Primary-secondary Highschool License Postgraduate	 1 (4.8) 11 (52.4) 6 (28.6) 2 (9.5) 1 (4.8)	 1 (4.8) 12 (57.1) 5 (23.8) 3 (14.3) -	
Job (n/%) Housewife Deskwork Worker Retired	 7 (33.3) 3 (14.3) 4 (19.0) 7 (33.3)	 9 (42.9) 1 (4.8) 5 (23.8) 6 (28.6)	
Use of alcohol (n/%) Yes No	 1 (4.8) 20 (95.2)	 1 (4.8) 20 (95.2)	
Smoking (n/%) Smoker Non-smoker	 5 (23.8) 16 (76.2)	 5 (23.8) 16 (76.2)	*1.000*†

* Mann-Whitney U test, † Chi-square test,HILT: High-intensity laser treatment

The correlation analysis revealed that both the HILT and conservative treatment groups exhibited distinct relationships between USG findings and clinical outcomes. In HILT group, a strong negative correlation was observed between the presence

of Subacromial-Subdeltoid Bursitis condition and reductions in nighttime pain (VAS-night) (*Rho=-.626, p<0.01*), and functional movement (AMAT-movement) (*Rho=-.442, p=0.045*).

Table II. Clinical Features of the Treatment Groups

	HILT group (n=21)	Conservative treatment group (n=21)	*p*
	N/%		
Type of hemiplegia Ischemic Hemorrhagic	20 (95.2) 1 (4.8)	18 (85.7) 3 (14.3)	*0.599**
Side of hemiplegia Right Left	9 (42.9) 12 (57.1)	12 (57.1) 9 (42.9)	*0.538*†
Radiological findings SA-SD bursitis Bicipital tendinosis Partial rupture Total rupture ACJ joint degeneration	16 (76.2) 10 (47.6) 7 (33.3) 8 (38.1) 5 (23.8)	16 (76.2) 9 (42.9) 12 (57.1) 4 (19.0) 8 (38.1)	*1.000** *1.000** *0.215** *0.306** *0.505**
MAS score-Deltoid 0 1 1+ 2 3 4	13 (61.9) 4 (19.0) 2 (9.5) - 2 (9.5) -	17 (81.0) 2 (9.5) - 2 (9.5) - -	
MAS score-Biceps 0 1 1+ 2 3 4	8 (38.1) 3 (14.3) 7 (33.3) 2 (9.5) 1 (4.8) -	13 (61.9) 2 (9.59 1 (4.8) 4 (19.0) 1 (4.8) -	
MAS score-pronator 0 1 1+ 2 3 4	8 (38.1) 5 (23.8) 5 (23.8) 2 (9.5) 1 (4.8) -	14 (66.7) 4 (19.0) 2 (9.5) 1 (4.8) - -	
MAS score-wrist 0 1 1+ 2 3 4	8 (38.1) 6 (28.6) 4 (19.0) 1 (4.8) 2 (9.5) -	15 (71.4) - 2 (9.5) 4 (9.5) - -	
Brunnstrom-upper extremity 1 2 3 4 5	6 (28.6) 9 (42.9) 4 (19.0) 2(9.5) -	10 (47.6) 3 (14.3) 6 (28.6) 1 (4.8) 1 (4.8)	
Brunnstrom-lower extremity 1 2 3 4 5	5 (23.8) 4 (19.0) 7 (33.3) 4 (19.0) 1 (4.8)	4 (19.0) 10 (47.6) 2 (9.5) 4 (19.0) 1 (4.8)	
Brunnstrom-hand 1 2 3 4 5	8 (38.1) 7 (33.3) 3 (14.3) 2 (9.5) 1 (4.8)	9 (42.9) 6 (28.6) 4 (19.0) 1 (4.8) 1 (4.8)	

*Chi-square with Yate's correction, † Fischer exact test, HILT: High-intensity laser treatment

A strong negative correlation was found between bicipital tendinosis and reductions in nighttime pain (VAS-night) (*Rho=-.655, p<0.01*). This indicates that patients with tendinosis had significant improvements in nighttime pain relief after HILT. A moderate negative correlation was found between complete rupture and improvements in both functional and movement scores (AMAT-functional and AMAT-movement) (*Rho=-.480, p=0.028; Rho=-.540, p=0.012*) (Table IV). No significant correlations were found between USG findings and clinical outcomes in the conservative treatment group, indicating that the presence of specific shoulder pathologies did not influence the treatment response to conservative interventions. No correlation was found between USG findings and pain and disability scales in the conservative treatment group (*p>0.05*) (Table V).

Table III. Comparison of the Pre and Post-treatment Scores of Visual Analog Scales, Disability and Functional Independence Questionnaire scores between the Groups

	HILT (n=21)	CPT group (n=21)	*p*†
	Median (IQR)		
VAS-movement before treatment VAS-movement after treatment VAS-movement difference between before and after treatment p* (intra-group comparisons)	7.0 (1.0) 5.0 (3.0) 3.0 (2.0) ***<0.001***	7.0 (3.0) 5.0 (4.0) 2.0 (1.5) ***<0.001***	*0.158* *0.808* *0.192*
VAS-night before treatment VAS-night after treatment VAS-night difference between before and after treatment p* (intra-group comparisons)	5.0 (3.0) 2.0 (4.0) 2.0 (2.0) ***<0.001***	4.0 (5.0) 3.0 (4.0) 1.0 (2.0) ***<0.01***	*0.334* *0.889* *0.047*
FIM-before treatment FIM-after treatment FİM-difference between before and after treatment p* (intra-group comparisons)	47.0 (26.0) 58.0 (32.0) 2.0 (7.5) ***<0.001***	46.0 (19.0) 47.0 (20.0) 2.0 (2.5) ***<0.001***	*0.715* *0.308* *0.377*
MRS-before treatment	4.0(1.0)	4.0(1.0)	*0,693*
MRS -after treatment	4.0(1.0)	4.0(1.0)	*0,670*
MRS-difference between before and after treatment	0.0 (0.0)	0.0 (0.0)	*0.638*
p* (intra-group comparisons)	*0.083*	*0.157*	

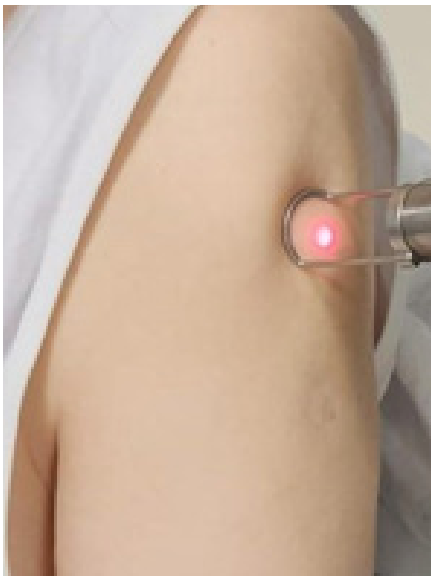
* Wilcoxon-signed ranks test, † Mann-Whitney U test,HILT: High-intensity laser treatment, CPT: Conventional physical therapy, VAS: Visual analog scale, FIM: Functional independence measurement,MRS: Modified rankin scale

Table IV. Spearman Correlation Analysis Between Ultrasonographic Findings and Improvements in Pain, Spasticity, and Disability Scales in the High-Intensity Laser Group

		Improvement in VAS-rest scores	Improvement in VAS-movement scores	Improvement in VAS-night scores	Improvement in MRS scores	Improvement in AMAT functional scores	Improvement in AMAT movement scores	Improvement in FIQ scores
Subacromial-subdeltoid bursitis	Rho	-.362	-.339	**-.626**	-.091	-.244	**-.442**	-.355
P	*0.107*	*0.133*	*0.002*	*0.694*	*0.286*	*0.045*	*0.114*	
N	21	21	21	21	21	21	21	
Bicipital tenosynovitis	Rho	-.179	-.313	**-.655**	.156	.233	-.049	.311
P	*0.438*	*0.167*	*0.001*	0.500	0.309	0.832	0.170	
N	21	21	21	21	21	21	21	
Tendinosis	Rho	.257	-.009	.057	.411	.098	.212	.420
P	*0.260*	*0.968*	*0.807*	*0.064*	*0.674*	*0.357*	*0.058*	
N	21	21	21	21	21	21	21	
Partial rupture of any rotator cuff muscles	Rho	.155	-.213	.009	-.289	.388	.313	.143
P	*0.502*	*0.355*	*0.971*	*0.204*	*0.082*	0.168	0.535	
N	21	21	21	21	21	21	21	
Complete rupture of any rotator cuff muscles	Rho	-.326	.066	-.150	-.040	-.480	-.540	-.410
P	*0.149*	*0.776*	*0.517*	*0.863*	*0.028*	*0.012*	*.065*	
N	21	21	21	21	21	21	21	

VAS: Visual analog scale, MRS: Modified ranking scale, AMAT: Arm motor ability test, FIQ: Functional independence questionnaire

Figure II. High Intensity Laser Application



Discussion

In this present study, we compared the results obtained after treatment with HILT and conventional physical therapy methods combined therapeutic exercise in subjects diagnosed with hemiplegic shoulder pain. Both the HILT and conventional therapy groups exhibited statistically significant improvements in pain and disability, and functional daily life activity in upper extremity immediately posttreatment compared to pre-treatment. Improvements in movement pain, disability and function were similar in two groups in the pre- and post-treatment evaluation. Only the HILT group demonstrated a greater improvement in nocturnal pain.

SA-SD bursitis, bicipital tendinosis and partial rupture were the most common pathologies that reported for hemiplegic shoulder pain as ultrasonographic finding by Lin in a study (17). Also, Wu et al. reported rotator cuff tears and subacromial-subdeltoid bursitis, conditions that can occur concurrently, are soft tissue injuries that may significantly contribute to the pathogenesis of HSP (25). We also detected similar pathologies in ultrasonographic assessment of our patients.

Recent clinical practice has witnessed the application of HILT across a spectrum of musculoskeletal conditions, including shoulder pain and hemiplegic shoulder pain (26). In a two-week study, Korkmaz et al. investigated the comparative efficacy of HILT and ultrasound therapy in patients with hemiplegic shoulder pain, a statistically significant reduction in pain intensity was observed. Furthermore, the HILT group demonstrated statistically significant intergroup differences in movement outcomes, functional scores, and muscle strength compared to the ultrasound therapy group after 10 treatment sessions. In this study the laser device produces a maximum of 12W power and emits wavelength of 1064 nm (Nd: YAG laser). used the device to the rotator cuff muscles area in two phases phase I and phase II. The pulse modality was used in phase I for

Table V. Spearman Correlation Analysis Between Ultrasonographic Findings and Improvements in Pain, Spasticity, and Disability Scales In The Conservative Treatment Group

		Improvement in VAS-rest scores	Improvement in VAS-movement scores	Improvement in VAS-night scores	Improvement in MRS scores	Improvement in AMAT functional scores	Improvement in AMAT movement scores	Improvement in FIQ scores
Subacromial-subdeltoid bursitis	Rho	.351	.259	.311	.181	-.127	-.399	-.105
	p	0.119	0.257	0.170	0.431	0.583	0.073	0.652
	N	21	21	21	21	21	21	21
Bicipital tenosynovitis	Rho	.035	-.198	-.234	.047	-.310	-.189	-.205
	p	0.882	0.389	0.307	0.840	0.172	0.412	0.374
	N	21	21	21	21	21	21	21
Tendinosis	Rho	.232	-.105	.012	.331	.258	.036	.174
	p	0.312	0.650	0.959	0.143	0.259	0.875	0.452
	N	21	21	21	21	21	21	21
Partial rupture of any rotator cuff muscles	Rho	.026	-.099	-.033	-.047	.310	.189	-.237
	p	0.911	0.669	0.885	0.840	0.172	0.412	0.300
	N	21	21	21	21	21	21	21
Complete rupture of any rotator cuff muscles	Rho	.348	-.094	.042	.256	-.367	-.433	-.165
	p	0.122	0.686	0.856	0.263	0.101	0.050	0.475

VAS: Visual Analog Scale, MRS: Modified Ranking Scale, FIM: Functional Independence Measurement; SS:subacromail subdeltoid,RCM: Rotator Cuff Muscle

the analgesic effect. A standard frequency of 25 Hz is applied. The first four therapy sessions were analgesic effect, using a power of 8 W, a dose of 12 J/cm^2, to 25 cm^2 area, for a total of 300 J of energy, for 2.5 min. The continuous wave modality was used in phase II for biostimulation effect. The subsequent five sessions were biostimulation effect, using a power of 7 W, a dose of 100 J/cm^2, to 25 cm^2 area, for a total of 2500 J of energy, for 5 min and 57 s (14). In another study, Santamanto et al. employed the following application dosages for HILT in three steps during the initial and final phases of treatment: 510, 610, and 710 mJ/cm^2, respectively. Consequently, the total administered energy in their study was approximately 2,050 J (27). In our study, although there was a significant improvement after treatment compared to before treatment in both groups, no significant difference in motor recovery, movement and functional activity was found in the analysis between HILT and CPT groups. Our HILT dosage was similar to Korkmaz et al. study with little differences. We added one more phase and applied three phases in accordance with the diagnostic specific program suggested by the device.

In another study Santamato et al. conducted a comparative study of HILT and ultrasound therapy in patients diagnosed with subacromial impingement syndrome, a significant reduction in pain and statistically significant intergroup differences favoring the HILT group in terms of movement, functional scores, and muscle strength compared to the ultrasound treatment group (11). Concurrent research examining the management of shoulder pain has indicated that HILT constitutes an effective therapeutic intervention, demonstrating significant reductions in pain and disability both post-treatment and during subsequent short-term follow-up periods (27). In our present study in both groups pain scores and functional scores were similary better after treatment according to baseline. Nevertheless, intergroup assessment in HILT group only VAS night score decreased more than conventional physical therapy group after treatment. In this study US therapy applied continuous US for 10 minutes with a frequency of 1 MHz, an intensity of 2 W/cm^2 (27). In another study, Ökmen et al. applied the ultrasound device at a frequency of 3 MHz and an intensity of 1.5 W/cm^2 over a surface area of 25 cm^2 (18). Our US therapy dosage was similar with this study.

HILT employs a multimodal approach, harnessing thermal, mechanical, and electrical energy to stimulate cellular and tissue responses. This stimulation is thought to induce beneficial effects, including increased blood flow and cellular activity, which may contribute to HILT's efficacy in reducing inflammation and edema (26, 28). In our study, we found that the HILT group experienced a significant decrease in nocturnal pain compared to the control group in the early period. Sonographic findings of subacromial-subdeltoid bursitis and bicipital tendinosis were

associated with increased nocturnal shoulder pain. Following HILT treatment, a significant reduction in night pain, as measured by VAS scores, was observed in this patient group. We believe that this is due to the anti-inflammatory and anti-edema effect of HILT therapy.

Unlike traditional laser therapy that uses concentrated light, HILT employs high-intensity laser radiation that scatters throughout the treated area. This diffused light penetrates deeper due to a slower absorption process, potentially making it more effective for treating larger areas. Studies suggest HILT offers a faster path to pain and inflammation relief 10. Additionally, we know from the recent literature HILT can induce photochemical and photothermic effects rapidly and thus increases blood flow, cell metabolism and vascular permeability (29). Our findings suggest that the lower nighttime VAS scores in the HILT group could be related to this mechanism of action.

The limitations of this present study are small sample size and the absence of a placebo control group and long-term follow-up results. Due to the limited sample size, the study may have lacked sufficient power to detect statistically significant effects. The absence of a control group prevents us from drawing conclusions about the comparative effectiveness of the two therapeutic methods. Ultrasonography findings were not evaluated after treatment due to the short follow-up period because no change was expected. A longer follow-up examination may be useful in determining ultrasonographic changes. Therefore, further large-scale, prospective, long-term outcomes, placebo-controlled studies are needed to confirm these findings.

Conclusion

In our study no significant superiority was observed between the two treatment options. However, a thorough assessment of HSP at the beginning of the rehabilitation program is crucial due to its potential negative impact on the rehabilitation process of existing shoulder pain in patients. Therefore, we believe that implementing HILT or CPT when necessary can be beneficial to accelerate the rehabilitation process. Long-term studies with a longer follow-up, including placebo groups, are needed. Moreover, there are still no guidelines on the dose, duration, and frequency of HILT in specific disorders.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Cryopreservation of CD34+ Hematopoietic Stem Cells Using Cryofit® DMSO and Its Outcomes

CD34+ Hematopoietik Kök Hücrelerin Cryofit® DMSO Kullanılarak Kriyoprezervasyonu ve Sonuçları

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1637294
Geliş Tarihi | Received: 17.02.2025
Kabul Tarihi | Accepted: 30.05.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Başcı S, Batgi H, Namdaroğlu S. Cryopreservation of CD34+ Hematopoietic Stem Cells Using Cryofit® DMSO and Its Outcomes. Hitit Medical Journal 2025;7(2):273-279. https://doi.org/10.52827/hititmedj.1637294

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 06/12/2023 tarihinde Dokuz Eylül Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2023/39-12.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: SB Tasarım: SB, HB Veri Toplama/Veri İşleme: HB, SN Veri Analizi: SB Makalenin Hazırlanması: SB, HB, SN
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu araştırma Gatamed (Ankara, Türkiye) tarafından desteklenmiştir. Finansman kuruluşunun çalışma tasarımı, veri toplama, analiz, yorumlama veya makale hazırlamada hiçbir rolü yoktur.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee on 06/12/2023. Decision no: 2023/39-12.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: SB Design: SB, HB Data Collection/Data Processing: HB, SN Data Analysis: SB Manuscript Preparation: SB, HB, SN
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: This research was supported by Gatamed (Ankara, Turkey). The funding body had no role in the study design, data collection, analysis, interpretation, or manuscript preparation.

Cryopreservation of CD34+ Hematopoietic Stem Cells Using Cryofit® DMSO and Its Outcomes

ABSTRACT

Objective: Autologous hematopoietic stem cell transplantation (auto-SCT) is a key treatment for hematological malignancies and immune disorders. Cryopreservation of CD34+ hematopoietic stem cells (HSCs) ensures transplant success. Dimethyl sulfoxide (DMSO) is a widely used cryoprotectant but can cause infusion-related toxicities. CryoFit® DMSO aims to enhance cell viability while reducing adverse effects. This study evaluates its efficacy and safety in auto-SCT.

Material and Method: A single-center, retrospective study was conducted on 80 patients who underwent auto-SCT with CD34+ HSCs cryopreserved using CryoFit® DMSO. Mobilization was performed using granulocyte colony-stimulating factor (G-CSF) ± chemotherapy and plerixafor when required. CD34+ cells were quantified via flow cytometry before cryopreservation. Post-transplant engraftment, transfusion needs, and infusion-related side effects were assessed. Data analysis was conducted using SPSS 26.0.

Results: The median patient age was 58.5 years (range: 19-75) and 53.8% (n=43) of the cohort sample was female. Multiple myeloma was the most common diagnosis (57.5%). The median collected CD34+ cell count was 5.8 x 106/kg (range: 3.2-14). Post-thaw viability was 98% (range: 90-99.5%). Neutrophil and platelet engraftment occurred at medians of 13 and 17 days, respectively. The median hospitalization duration was 24 days (range: 15-60). Infusion-related adverse effects occurred in 26.3% of patients, primarily nausea/vomiting (15%), all manageable.

Conclusion: CryoFit® DMSO effectively preserves CD34+ HSCs with high post-thaw viability and favorable engraftment. Mild infusion-related toxicities were observed but were transient. The results support its continued use in auto-SCT. Further multicenter studies are required to optimize cryopreservation protocols.

Keywords: Cryopreservation, dimethyl sulfoxide, engraftment, hematopoietic stem cell transplantation, mobilization.

ÖZET

Amaç: Otolog hematopoetik kök hücre nakli (OKHN), hematolojik maligniteler ve immün bozukluklar için önemli bir tedavi yöntemidir. CD34+ hematopoetik kök hücrelerin (HKH) kriyoprezervasyonu, nakil başarısını sağlamak için kritik bir adımdır. Dimetil sülfoksit (DMSO), yaygın olarak kullanılan bir kriyoprotektandır ancak infüzyona bağlı toksisiteler oluşturabilir. CryoFit® DMSO, hücre canlılığını artırmayı ve olumsuz etkileri azaltmayı amaçlamaktadır. Bu çalışma, DMSO ile kriyoprezervasyonun OKHN'de etkinliğini ve güvenliğini değerlendirmektedir.

Gereç ve Yöntem: Bu çalışma, tek merkezli retrospektif bir analiz olup daha önceden CryoFit® DMSO ile kriyoprezervasyon yapılmış kök hücrelerden OKHN olan 80 hasta dahil edildi. Kök hücre mobilizasyonu, granülosit koloni stimüle edici faktör (G-CSF) ± kemoterapi ve gerekli durumlarda plerixafor kullanılarak gerçekleştirilmiştir. CD34+ hücreleri kriyoprezervasyondan önce akış sitometrisi ile sayıldı. Nakil sonrası kök hücre yamanması (engraftment), transfüzyon ihtiyacı ve infüzyona bağlı yan etkiler değerlendirildi. Veri analizi SPSS 26.0 yazılımı ile yapıldı.

Bulgular: Hastaların medyan yaşı 58.5 (aralık: 19-75), ve kohortun %53,8'i kadındı. En yaygın tanı multipl miyelomdu (%57,5). Toplanan CD34+ hücrelerin medyan miktarı 5.8 x 106/kg (aralık: 3.2-14) idi. Çözündürme sonrası hücre canlılığı %98 (aralık: %90-99.5) olarak bulundu. Nötrofil ve trombosit engraftmanı sırasıyla medyan 13 ve 17 gün olarak izlendi. Medyan hastanede kalış süresi 24 gün (aralık: 15-60) idi. Hastaların %26,3'ünde infüzyona bağlı yan etkiler gözlendi, en yaygın olanı bulantı/kusmaydı (%15) ve tüm yan etkiler yönetilebilir düzeydeydi.

Sonuç: CryoFit® DMSO, CD34+ HKH'ların çözündürme sonrası yüksek canlılık oranları ile etkin bir şekilde korunmasını sağlamıştır. Hafif infüzyona bağlı toksisiteler gözlemlenmiş ancak geçici olmuştur. Bu sonuçlar, CryoFit® DMSO'nun OKHN'de kullanımını desteklemektedir. Kriyoprezervasyon protokollerini optimize etmek için çok merkezli ileri çalışmalar gereklidir.

Anahtar Sözcükler: Dimetil sülfoksit, hematopoetik kök hücre transplantasyonu, kriyoprezervasyon, dimetil sülfoksit, mobilizasyon, engrafman.

Introduction

Autologous transplantation of hematopoietic stem cells (auto-SCT) is a well-established treatment for numerous hematological and non-hematological malignancies, as well as immune disorders (1). The auto-SCT procedure involves multiple critical stages, including mobilization of stem cells into the peripheral bloodstream, CD34+ cell counting, apheresis, cryopreservation, and the re-infusion of thawed cells after intensive therapy (2).

Hematopoietic progenitor stem cells (HSCs) can be obtained from different sources such as peripheral blood, bone marrow, and umbilical cord blood (3). Peripheral blood stem cells (PBSCs) are often preferred due to the less invasive collection method compared to bone marrow. The mobilization process involves administering granulocyte colony-stimulating factor (G-CSF) alone or in combination with other agents over several days. Quantification of CD34+ cells is performed before collection to ensure sufficient cell doses (4).

Although auto-SCT is a well-standardized and relatively safe procedure, various elements influence the capacity of HSCs to efficiently reconstitute hematopoiesis. These include the quantity and viability of progenitor cells, cryopreservation methods, storage conditions, and thawing techniques (1,5). Freshly harvested HSCs require specific handling procedures, sterility, and temperature stability at 2-6°C (1,6,7). The duration between hematopoietic stem cell collection and infusion or cryopreservation can impact cell viability, with the preservation of fresh HSCs typically considered for 1 to 6 days, particularly at lower temperatures (8-10). In cases where myeloma and lymphoma patients planned autologous PBSC transplantation beyond 72 hours post-collection can result in up to 35% loss of stem cells (11,12). However, when immediate transplantation is unfeasible, cryopreservation is necessary. Dimethyl sulfoxide (DMSO) and diluted by substances like human albumin, plasma, or other clinically approved solutions, it is a common cryoprotectant to prevent ice crystal formation and cellular shock. These cryopreserved cells are stored in liquid nitrogen freezers at -140°C to -195°C for up to a decade (13-15). Furthermore, the freezing/thawing procedure can cause cell harm, as indicated by a substantial reduction in total nucleated cells (TNC), CD34+ cells, cell viability, and/or the number of colony-forming units (CFU) in post-thaw specimens compared to fresh PBSC (16-18). Studies have shown that the infusion of fresh PBSC leads to superior outcomes and fewer side effects (10,19). Furthermore, DMSO is thought to be the most hazardous component of the transplant material, causing adverse symptoms such nausea, vomiting, cramps, and headaches in some cases, cardiovascular or neurological reactions during infusion. These reactions may stem from factors like damaged cells post-cryopreservation or an excessively low infusion temperature (20-24).

The HSC cryopreservation is in widespread use among transplant centers, however there is a lack of standardized procedures. DMSO has been standard for a very long period. Now it is available in various forms of vials. These vials are accepted similarly in regular use, since DMSO is a chemical component and for pharmaceutical technology easy to produce. However, their production conditions and last product state are not identical. Here, we evaluated CryoFit® DMSO and its effect on outcomes.

Materials and Methods

Patient Selection

This retrospective, single-center study involved adult patients with hematological malignancies undergoing auto-SCT. Only patients whose HSCs were cryopreserved with CryoFit® DMSO were included. Ethical approval was obtained, and The Declaration of Helsinki was followed when conducting the study. (Approval No: 2023/39-12, Date: 06.12.2023).

Stem Cell Mobilization, Collection, and Cryopreservation

Patients received G-CSF alone or in combination with chemotherapy or plerixafor when required. CD34+ cells were quantified using flow cytometry before cryopreservation. Using flow cytometry, cell viability (7-aminoactinomycin D [7-AAD]) and viable CD45+ and CD34+ cells were measured in accordance with the ISHAGE recommendations (25). When the absolute number of CD34+ cells in the blood exceeded 10/µl, the collection process started. Apheresis was performed using a continuous flow blood cell separator, processing 2-2.5 times the total blood volume per session. The targeted CD34+ cell

dose was 2-4 × 10^6/kg. If the initial collection was insufficient, additional mobilization and apheresis were performed. Cryopreservation was performed using a cryoprotective solution containing 5% dimethyl sulfoxide (DMSO), hydroxyethyl starch (HES), and autologous plasma. Cell concentrations were adjusted to approximately 100–200 × 10^6 nucleated cells/mL in autologous plasma. Prior to the addition of DMSO, the cell suspension was cooled on ice to minimize thermal shock. DMSO was added slowly with gentle mixing to prevent localized overheating and osmotic injury. Depending on clinical workflow, products were either cryopreserved immediately or stored at 4°C for up to 24 hours before freezing. Freezing was performed using a controlled-rate freezing protocol, with an initial cooling rate of 1–2°C per minute to −40°C, followed by rapid descent to −80°C.

Conditioning Regimens, Engraftment, and Side Effects Monitoring

Conditioning regimens varied according to disease type, with BEAM (carmustine, etoposide, cytarabine, melphalan) used for lymphoma patients and melphalan for myeloma patients. Neutrophil engraftment was defined as the first day with an absolute neutrophil count (ANC) >500/mm^3 or 1000/mm^3 for three consecutive days without growth factor support. Platelet engraftment was achieved when platelet counts exceeded 20.000/mm^3 or 50.000/mm^3. G-CSF support was administered from day +4 post-transplantation. Blood transfusions were provided when necessary. Any adverse effects occurring within 24 hours of HSC infusion were recorded.

Statistical Analysis

Data analysis was performed using SPSS version 26.0. Categorical variables were presented in frequency tables, while numerical variables were expressed as mean ± standard deviation or median and range, depending on distribution.

Results

A total of 80 patients participated in the study. The median age was 58.5 years (range: 19–75), and 53.8% (n=43) of the cohort sample was female. The majority of patients (57.5%, n=46) were diagnosed with multiple myeloma, followed by non-Hodgkin lymphoma (31.3%, n=25) and Hodgkin lymphoma (11.3%, n=9). Most patients (60%, n=48) had received one line of chemotherapy prior to transplantation, while 30% (n=24) had two lines and 10% (n=8) had three or more. Radiotherapy was administered to 10% (n=8) of the patients. The median time of the stem collection to the transplant was 1 (1-6) months. The median time from diagnosis to transplantation was seven months (range: 3–25). Additional patient characteristics are presented in Table I.

Table I. Patient Characteristics

	All donors (n:80)
Median Patient Age	58.5 (19-75)
Gender (Male/Female)	37 (% 46.3) / 43 (%53.8)
Diagnosis	
Multiple Myeloma	46 (57.5%)
Non- Hodgkin Lymphoma	25 (31.3%)
Hodgkin Lymphoma	9 (11.3%)
Previous Treatments	
1 line chemotherapy	48 (60%)
2 lines chemotherapy	24 (30%)
≥ 3 lines chemotherapy	8 (10%)
RT	8 (10%)
Median Duration from Diagnosis to Transplant (months)	7 (3-25)

RT: Radiotherapy

All patients received a conditioning regimen prior to transplantation. The most commonly used regimen was melphalan (MEL) in 57.5% of cases (n=46), followed by BEAM (40%, n=32) and BEAC (2.5%, n=2). The median harvested CD34+ cell count was 5.8 × 10^6/kg (range: 3.2–14), with a high median viability of 98% (range: 90–99.5). The median duration of hospitalization was 24 days (range: 15–60). Neutrophil engraftment occurred at a median of 13 days (range: 7–19), while platelet engraftment occurred at a median of 17 days (range: 12–50). The median number of erythrocyte transfusions required was 0 units (range: 0–6), and the median platelet transfusion requirement was 2 units (up to 12). Further transplant characteristics are detailed in Table II.

Infusion-related side effects were observed in 26.3% (n=21) of patients. The most frequent complication was nausea and vomiting, affecting 15% (n=12) of the cohort. Other side effects included hypotension (5%, n=4), hypertension (3.8%, n=3), chills (2.5%, n=2), arrhythmia (2.5%, n=2), chest pain (1.3%, n=1), and various other mild symptoms in 6.3% (n=5). All side

effects were grade 1–2 in severity and manageable; no life-threatening adverse events were recorded. Complete side effect profiles are presented in Table III.

Table II. Transplant Characteristics

	All donors (n:80)
Conditioning Regimens	
MEL	46 (57.5%)
BEAM	32 (40%)
BEAC	2 (2.5%)
Median Duration from Diagnosis to Transplant (months)	7 (3-25)
Median Duration of Hospitalization (days)	24 (15-60)
Median Neutrophile Engraftment (days)	13 (7-19)
Median Platelet Engraftment (days)	17 (12-50)
Median Erythrocyte Transfusion (units)	0 (0-6)
Median Platelet Transfusion (units)	2 (12)
Median Viability	98 (90-99.5)
Median collected CD34+ cell count ($x10^6$/kg cell)	5.8 (3.2-14)

BEAM: Carmustine, Etoposide, Cytarabine, Melphalan, BEAC: Carmustine, Etoposide, Cytarabine, Cyclophosphamide, MEL: Melphalan.

Discussion

This study aimed to assess the outcomes of cryopreservation of CD34+ HSCs using CryoFit® DMSO and its associated clinical implications. The findings provide insights into the effectiveness and safety of this approach in the context of auto-SCT.

Table III. Side Effects

Infusion-related complications	All donors (n:80, 100%)
Nausea-Vomiting	12 (15)
Chills	2 (2.5)
Chest pain	1 (1.3)
Hypotension	4 (5)
Hypertension	3 (3.8)
Arrhythmia	2 (2.5)
Others	5 (6.3)
Any Side Effect	21 (26.3)

The overall success of auto-SCT relies heavily on the viability and functionality of the cryopreserved stem cells. In this study, the high post-thaw viability of CD34+ cells, with a median viability of 98%, suggests that the CryoFit® DMSO formulation maintains cellular integrity effectively during the freezing and thawing processes. This is consistent with earlier reports, which highlights the critical role of cryoprotectants like DMSO in preventing ice crystal formation and cellular damage during cryopreservation (26).

According to the American Society for Blood and Marrow Transplantation, a target dosage of 3–5×106 CD34+ cells/kg has been suggested (27). Moreover, the observed median CD34+ cell yield (5.8 x 106/kg) surpasses the recommended minimum threshold for successful engraftment, further underscoring the efficacy of the cryopreservation protocol used. Engraftment outcomes in the study were favorable, with a median neutrophil engraftment time of 13 days and platelet engraftment at 17 days. The transfusion requirements were also within acceptable range. These results align with previous reports on autologous transplants utilizing cryopreserved cells (5,12). The engraftment kinetics observed can be attributed to the high viability of CD34+ cells and the individualized conditioning regimens, which were tailored to optimize transplant success. However, as with most cryopreservation methods, the use of DMSO is not without its limitations. Side effects such as nausea, hypo-hypertension, and other infusion-related reactions were documented, although they were manageable and transient in most cases. These effects are consistent with known DMSO-associated toxicities reported in prior studies (28,29). This highlights the need for continued exploration of alternative cryopreservation agents or DMSO formulations that minimize toxicity without compromising cell viability.

An additional finding worth noting is the significant variability in engraftment times and transfusion requirements among patients. This variability could stem from differences in patient characteristics, underlying diseases, or prior treatment regimens. For instance, the myeloma patients in this cohort received Melphalan as the conditioning regimen, which might explain the relatively short time to engraftment compared to other conditioning regimens like BEAM used for lymphoma patients. Further subgroup analyses could help elucidate the impact of these factors on transplantation outcomes.

This study has some limitations. First, it was in a retrospective single-center setting which can limit the generalizability. Second, the lack of a comparator group using alternative cryopreservation methods

restricts the ability to directly assess the relative advantages of CryoFit® DMSO. Future multicenter, prospective studies are required to validate these results and further refine cryopreservation protocols to improve clinical outcomes.

In conclusion, CryoFit® DMSO demonstrated robust efficacy in preserving CD34+ HSCs with high post-thaw viability and favorable engraftment outcomes. While DMSO-related toxicities remain a concern, their transient nature and manageability suggest that CryoFit® DMSO is a reliable cryoprotectant for auto-SCT. Further advancements in cryopreservation techniques hold promise for enhancing the safety and efficacy of SCT.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Value of Aquaporins in the Eyes

Akuaporinlerin Gözdeki Değeri

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Derleme / Review
Doi: https://doi.org/10.52827/hititmedj.1532970
Geliş Tarihi | Received: 14.08.2024
Kabul Tarihi | Accepted: 03.04.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Karabacak E, Özelbaykal B. Value of Aquaporins in the Eyes. Hitit Medical Journal 2025;7(2):280-288. https://doi.org/10.52827/hititmedj.1532970

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: SB Tasarım: SB, HB Veri Toplama/Veri İşleme: HB, SN Veri Analizi: SB Makalenin Hazırlanması: SB, HB, SN
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: EK, BÖ Design: EK, BÖ Data Collection/Data Processing: EK, BÖ Data Analysis: EK, BÖ Manuscript Preparation: EK, BÖ
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Value of Aquaporins in the Eyes

ABSTRACT

Aquaporins (AQPs) are small integrated membrane proteins that enable water conduction across the plasma membranes of cells as a result of osmotic gradients. AQPs have been indicated to be involved in the molecular adjustment of many biological functions such as osmolarity, cell movement, junctional adhesion, management of surface protein expression, transepithelial water transport, energy metabolism, cellular proliferation, neuroexcitation, extracellular matrix stress regulation, cellular water adjustment. In addition to regulating aqueous humor balance, it also facilitates the removal of many residuals products of the cornea, lens, ciliary body and retina while preserving clarity in the optic compartments. Studies have ascertained the value of mammalian AQPs in both pathophysiological and physiological conditions. This suggests that pharmacological modulation of aquaporin expression and tasks may provide a novel therapy for the amelioration of various vision-related pathologies that may involve water and small solute transport. This review clarifies the physiological roles of AQPs in the eye and their involvement in pathological conditions in light of previous studies and highlights the development of selective pharmacological target strategies that may be beneficial for the treatment of related conditions, mobilization.

Keywords: Aquaporin, eye, osmolarity.

ÖZET

Akuaporinler (AQP'ler), ozmotik gradyanlara yanıt olarak hücrelerin plazma zarları boyunca su taşınmasını kolaylaştıran küçük, entegre zar proteinlerinin bir ailesidir. AQP'lerin; ozmolarite, hücre göçü, bağlantı adezyonu, yüzey proteini üretiminin düzenlenmesi, transepitelyal su transportu, hücresel proliferasyon, nöroeksitasyon, hücre dışı matris stres düzenlemesi, enerji metabolizması ve hücresel su düzenlemesi gibi birçok biyolojik fonksiyonun moleküler düzeyde düzenlemesinde yer aldığı belirtilmiştir. Göz yapılarının şeffaflığını korumasının yanında aköz hümör dengesinin düzenlenmesi, kornea, siliyer cisim, lens ve retina gibi dokuların metabolik ürünlerinin temizlenmesini de sağlamaktadır. Yapılan çalışmalar, memeli AQP'lerin hem fizyolojik hem de patofizyolojik ortamlardaki önemini ortaya çıkarmıştır. Bu, akuaporin ekspresyonunun ve aktivitesinin, farmakolojik modülasyonunun, su ve çözünebilen küçük maddelerin taşınmasının da dahil olabileceği çeşitli görme ile ilgili bozuklukların tedavisi için yeni araçlar sağlayabileceğini göstermektedir. Bu derleme, AQP'lerin göz organındaki fizyolojik rolünü ve patolojik durumlara katılımını yapılan çalışmalar ışığında açıklamakla birlikte ilgili durumların tedavileri için yararlı olabilecek hedefe yönelik farmakolojik stratejilerin geliştirilmesini vurgulamaktadır.

Anahtar Sözcükler: Akuaporin, göz, ozmolarite.

Giriş

Akuaporinler

Akuaporinler (AQP'ler), virüs dahil hemen hemen tüm türlerde bulunan, ozmotik ve hidrostatik kuvvetler tarafından yönlendirilen hızlı pasif su dengelemesine izin veren yaklaşık 28 kDa'lık geniş bir bütünleşik membran proteinleri ailesidir. Birçok dokuda eksprese edildiği ve esas olarak su dengesinin düzenlenmesinde rol aldığı belirtilmektedir (1-7). Bunlar, majör intrinsik protein (MIP) ailesinin içerisinde kabul edilmektedir (6). AQP ailesi, klasik akuaporinler (AQP 0, 1, 2, 4 ve 5), akuagliseroporinler (AQP 3, 7, 9 ve 10) ve alışılmışın dışında akuaporinler veya süper akuaporinler (AQP 6, 8, 11 ve 12) olarak sınıflandırılabilir. Tüm aile üyelerinin suya karşı geçirgen olmasının yanı sıra akuagliseroporinler gliserol, üre ve değişen ölçülerde nötral diğer küçük moleküllere karşı da geçirgendir (1-5,8).

AQP'lerin; ozmolarite, hücre göçü, bağlantı adezyonu, yüzey proteini ekspresyonunun düzenlenmesi, transepitelyal su transportu, adiposit metabolizması, hücresel proliferasyon, nöroeksitasyon, hücre dışı matris stres düzenlemesi, enerji metabolizması ve hücresel su düzenlemesi gibi birçok biyolojik fonksiyonun moleküler düzeyde düzenlemesinde yer aldığı belirtilmiştir (1,7,9). Bu durum, AQP fonksiyonu ve üretimindeki değişimlerin kanser, obezite, beyin hasarı, glokom gibi hastalıklarda terapötik potansiyele sahip olabileceğini düşündürmektedir (9).

AQP'lerin aktivitesinin; kalsiyum, fosforilasyon, pH, ozmolarite ve hormonlar dahil olmak üzere birkaç farklı mekanizma ile düzenlenebildiği belirtilmiştir (7,10). MIP/AQP0 su kanalları, AQP1'in oluşturduğundan daha düşük verimle çalışmasının yanı sıra, Ca^{+2}'ye duyarlıyken, Hg^{+2}'ye duyarsızdır. Ortamın asiditesindeki değişikliklere ise duyarlıdır (Bkz: Tablo I). AQP1 kanalları ise, Hg^{+2} tarafından inhibe edilir. Ca^{+2} ve pH'dan ise bağımsız olduğu belirtilmektedir (10-17). Yayınlarda Ca^{+2} artışının ve asidik eksternal pH'nın AQP5 kanallarının su geçirgenliğini etkilemediği gösterilmiştir (18,19). Histidinlerin ise kanalın giriş kısmındaki su moleküllerinin oryantasyonunu değiştirdiği ve böylece su moleküllerinin geçiş hızını değiştirebildiği öne sürülmektedir (14). pH'ın 5.5'in altında olduğu durumda, AQP6 oositlerinde anyon iletkenliğinin hızlı ve geri dönüşümlü olarak aktive edildiği belirtilmektedir (20). Yapılan başka bir çalışmada da Xenopus oositlerinde hem sığır hem de fare MIP/AQP0 su geçirgenliğinin, eksternal pH 7,5'ten 6,5'e düştükçe arttığı (2-4 kat) bulunmuştur (16,17). Bu etkinin, H^+'nın birinci hücre dışı döngüde (His40) bir histidine bağlanmasının aracılık ettiğini göstermektedir (17). Çinko, Xenopus oositlerinde eksprese edilen sığır MIP/AQP0'ın su geçirgenliğini artırdığı ve asit pH'ının neden olduğu herhangi bir ilave artışı da önlediği bildirilmiştir. His40'tan yoksun olan ne killifish MIP/AQP0 ne de insan AQP1 çinkoya duyarlı değildir (21). Ayrıca, AQP0'da serin-235'in fosforilasyonunun kalmodulin bağlanmasını azalttığı ve sonuç olarak kanalın geçirgenliğini artırdığı da rapor edilen veriler arasındadır (10).

AQP'ler yapısal olarak aktif görünmektedir ve AQP6 dışında, iyon geçirgenliğinin akuaporinlerin genel bir özelliği olmadığı belirtilmiştir (7). Yapılan bir çalışmada, AQP6'nın, Xenopus laevis oositlerinde eksprese edildiğinde, düşük bazal su geçirgenliği sergilediği ancak bilinen su kanalı inhibitörü Hg^{+2} ile muamele edildiğinde su geçirgenliğinin hızla on katına kadar yükseldiği ve buna iyon iletkenliğinin de eşlik ettiği gösterilmiştir (20).

Su geçirgenliği bakımından incelendiğinde AQP0'ın AQP1'den 30 kat ve AQP5'ten yaklaşık 20 kat daha düşük olduğu belirlenmiştir (10,15,22). AQP1 ve AQP5'ten farklı olarak AQP0'ın, su gözeneğinde cıvaya duyarlı sistein kalıntısı olmaması nedeniyle cıva bileşiklerine duyarlı olmadığı bildirilmiştir (10). AQP'lerin her biri standart bir asparajin-prolin-alanin motifi içeren altı transmembran sarmaldan ve iki kısa sarmaldan oluştuğu bilinmektedir (3). Alışılmışın dışında akuaporinlerden AQP11 ve AQP 12, karakteristik akuaporin asparajin-prolin-alanin dizisi motifinden sapmaları ve hücre içi lokalizasyonları bakımından diğer aile üyelerinden farklı olduğu bildirilmiştir (8). Şekil I'de akuaporin 1 kum saati modeli gösterilmiştir. Memeli akuaporinleri, böbrek, beyin ve göz gibi su taşınmasının fonksiyonel olarak önemli olduğu organların epitel ve endotellerinde eksprese edilir. Bununla birlikte, su taşınmasının fizyolojik olarak önemli görünmediği dokularda, AQP7 içeren yağ dokusu, AQP3 içeren deri ve AQP9 içeren lökositler gibi akuaporinler de bulunmaktadır. Bu AQP'lerin fizyolojik rolü kısmen açıklanabilmiştir (7).

Gözdeki Akuaporinler ve İşlevleri

Göz, birden fazla doku tipinden oluşan karmaşık

bir duyu organıdır. Burada yer alan ve ana optik elemanlar olan kornea ve lens ise, şeffaflığı korumak için su hareketinin düzenlenmesinin gerekli olduğu avasküler dokulardandır. Ayrıca retinadaki hücrelerin fonksiyonunun devamı için sıvı dengesinin sağlanması gerektiği bilinmektedir (8). Bu bağlamda gözdeki akuaporinlerin yapılarının küçüklüğüne nazaran büyük görevler üstlendiğini söyleyebiliriz.

İnsanda bulunan 13 akuaporinin tümü oküler dokularda mRNA ve/veya protein seviyesinde tespit edilmiştir (8). Lens fibril hücresinin ana integral membran proteini (MIP26) olan AQP0'ın, plazma membranı boyunca su taşınmasını düzenleyerek lensin korunmasında önemli olduğu düşünülmektedir (7). Her biri farklı fonksiyonel özelliklere sahip olan üç akuaporin; AQP0, AQP1 ve AQP5, oküler lensin farklı bölgelerinde bol miktarda eksprese edilmektedir (10).

AQP'ler, inflamatuar yanıt ve bağışıklık sisteminin kolaylaştırılmasının yanı sıra travma nedeniyle oküler hastalıklar ve oküler yaralanma dahil olmak üzere homeostaz ve stres yanıtlarında yer almaktadır.

Kornea

Kornea dış ortama doğrudan maruz kaldığı için yaralanma ve enfeksiyona karşı oldukça hassas bir yapıdadır. Buradaki yara iyileşme sürecinde çeşitli hücreler, sitokinler, büyüme faktörlerini içeren dinamik, karmaşık bir mekanizma bulunmaktadır. AQP'ler, doku ozmolaritesinin düzenlenmesi ve yara iyileşme mekanizmaları yoluyla homeostazı sağlamaktadır. Buna karşın günümüzde, AQP'lerin disregülasyonunun anormal kornea yara iyileşmesindeki etkisi henüz iyi anlaşılamamıştır (1). AQP'lerin kornea dokusundaki lokalizasyonunu incelediğimizde AQP1 kornea keratositleri ve endotelinde, AQP3 kornea epitelinde, bazal hücrelerde ve stromal hücrelerde ve konjonktivada, AQP4 kornea endotelinde, AQP5 kornea epitelyum ve keratositlerinde, AQP7 anterior korneal epitelyum bazal hücrelerinde, korneal endotelyum ve limbal konjonktival epitelyumda, AQP11 limbal bölgedeki bazal hücre epitelinde bulunduğu gösterilmiştir (23-27).

Lens

Lensin optik özellikleri, hem lens dokusunun mimarisi hem de hücreler tarafından sağlanan şeffaflık ve kırılma gibi özelliklerin bir ürünüdür. Kırılma özelliklerini belirleyen ve optik gücünü yani ışığı bir odak noktasına yakınsama yeteneğini belirleyen iki önemli faktörün kırılma indisi ve merceğin yüzey eğriliği olduğu belirtilmektedir. Lensin hücresel yapısını korumak için, kan desteği olmadığından, besinleri ileten, metabolik atıkları gideren ve daha derin lens hücrelerinin iyonik homeostazını kontrol eden benzersiz bir dahili mikro sirkülasyon sistemine sahip olduğu ifade edilmiştir (10). MIP/AQP0 sadece terminal olarak farklılaşmış lens liflerinde eksprese edilirken, AQP1 lens epitelinde eksprese edilmektedir (13,14). Akuagliseroporinlerden olan AQP7'nin varlığı, insan lensinde immünohistokimyasal olarak gösterilmiştir (10,27).

Akuaporin 5 üretemeyen (AQP5-KO) genetiği değiştirilmiş farelerin lenslerinin morfoloji ve şeffaflık açısından diğer farelerin lenslerine benzediği kaydedilmiştir. Bu nedenle, katarakt oluşumunu test etmek için lensler normal (5,6 mM glikoz) ve hiperglisemik (55,6 mM glikoz) koşullar altında kültür ortamında incelenmiştir. Hiperglisemik kültür ortamında inkübasyondan yirmi dört saat sonra, AQP5-KO lensler, 48 saatte birkaç kat hızlanan hafif opaklaşma gösterirken, normal lenslerin ise 48 saatlik hiperglisemik ortamda kaldıktan sonra bile şeffaf kaldığı gözlemlenmiştir. AQP5-KO lenslerde, su içeriğindeki artış nedeniyle ozmotik şişme gözlemlendiği de elde edilen veriler arasındadır. AQP5'in fibril hücrelerde olmaması, su akışının ve hücre hacminin bozulmasına ayrıca hipoosmoloriteye neden olduğu düşünülmektedir. Bu çalışma, AQP5'in, özellikle stresli koşullar altında koruma sağlayarak şeffaflığı ve homeostazı sürdürmek için lens sıvı sirkülasyonunda kritik bir rol oynayabileceğini ortaya koymaktadır (28).

Su geçirgenliği, hücre zarındaki MIP protein yoğunluğu ile orantılıdır. Ozmotik gradyan rehberliğinde proteinin, yüksek verim elde etmek için Arrhenius aktivasyon enerjisini azaltarak çalıştığı belirtilmiştir. Ayrıca, AQP1 su moleküllerine seçici olarak geçirgen olup bu mekanizma ozmotik gradyanlar tarafından yönlendirilmektedir (12,29). AQP0'ın çok önemli bir işlevi de, diğer lens AQP'lerinde olmayan lens şeffaflığını korumak için önemli olan hücreden hücreye adezyonu özelliğidir. Bu adezyonun olası mekanizmasıyla ilgili yapılan bir çalışmada, AQP0 hücre dışı döngü alanlarındaki pozitif yüklü amino asitlerin, fibril hücrelerin kompakt paketlenmesi için

hücreden hücreye adezyonu gerçekleştirmek üzere plazma zarındaki negatif yüklü lipidlerle etkileşime girdiği açıkça gösterilmiştir (30). MIP proteininin yapışma özelliği, lens lifi hücreleri arasında son derece düzenli sıkı bağlantıları kolaylaştırarak hücre dışı alanı ve hücre sınırlarında ışık saçılmasını en aza indirir; böylece nesneler doğru bir şekilde retinaya odaklanabilir (12,31).

AQP0'ın, CaM ile etkileşimler yoluyla ortaya çıkan Ca^{+2} tarafından su geçirgenliğinin düzenlenmesinde görev yaparak göz merceği homeostazı için gerekli olduğu, ancak altta yatan moleküler mekanizmaların iyi anlaşılamadığı bilinmektedir. Freites ve arkadaşları, CaM bağlanmasının, komşu alt birimler arasında iş birliğini indükleyerek hem hücre dışı hem de hücre içi kapıların kapanmasını teşvik ederek tüm AQP0 tetramerinin kolektif dinamiklerini etkilediğini bulmuşlardır (32). Bunlara ek olarak MIP/AQP0 lens epitelinde eksprese edilen AQP1 ile lens liflerinde eksprese edilir ve su kanalları aracılığıyla lens metabolizmasına ve ozmotik düzenlemeye katılarak lens yapısının, şeffaflığının ve odaklanma yeteneğinin korunmasında önemli bir rol oynamaktadır. Ayrıca, diğer AQP'lerin göz içi basıncı düzenlenmesinde (AQP1 ve AQP4), konjonktival bariyer fonksiyonunda (AQP3), görsel sinyal iletiminde (AQP4) ve lakrimal bezler tarafından gözyaşı oluşumunda (AQP5) yer aldığı belirtilmiştir (12).

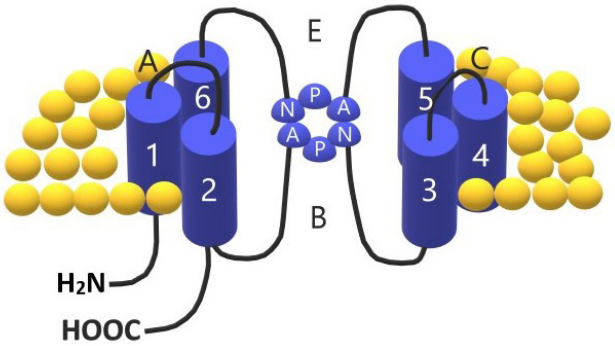
Tablo I: AQP0, AQP1 ve AQP5'in Bazı Özellikleri (10-19).

Özellikleri	AQP0	AQP1	AQP5
pH duyarlılığı	+	-	-
Ca^{+2} duyarlılığı	+	-	-
Hg^{+2} duyarlılığı	-	+	+
Adezyon özelliği	+	-	-

İris, Siliyer Epitelyum ve Lakrimal Bez

AQP1 ve AQP4'ün her ikisinin de iris ve siliyer epitelde bulunduğu, aköz hümör dengesinin düzenlenmesinde ve dolayısıyla göz içi basıncını etkilemede önemli rolü olduğu kaynaklarda ifade edilmiştir (2,7). Yapılan bir çalışmada da AQP1'den ve hem AQP1'den hem de AQP4'ten yoksun farelerde, siliyer epitelyumdan aköz hümör salınımındaki azalmaya bağlı olarak göz içi basıncında önemli düşüşler olduğu gösterilmiştir (33). Ayrıca, AQP3'ün konjonktivada bulunduğu ve bariyer olarak görev yaptığı da belirtilmiştir (6).

Şekil I. Akuaporin 1 Kanalının Yapısı

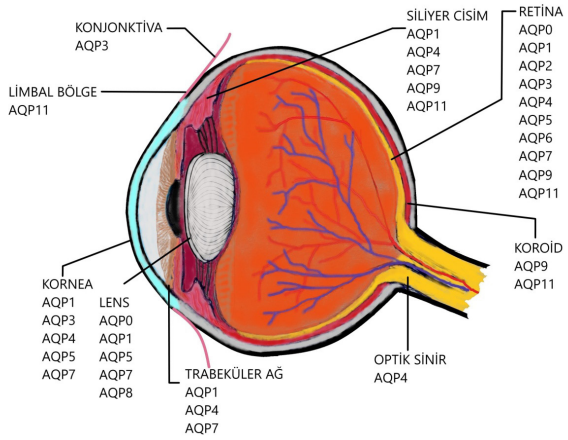


Fare lakrimal bezlerinde, endotel hücrelerinde AQP1 ve AQP5'in varlığı bulunmuş olup, asiner hücrelerde ise AQP3 (bazolateral membran), AQP4 (lateral membran), AQP5 (apikal membran) ve AQP11'in (hücre içi) varlığı gösterilmiştir. Fare lakrimal asiner hücrelerinde AQP4 ve AQP5 sırasıyla bazolateral ve apikal membranlarda lokalize olduğu belirtilmiştir. Bunlara ek olarak, AQP5'in fare lakrimal duktal hücrelerinde de bulunduğu edinilen bilgiler arasındadır (34). İnsan gözünde ise AQP5, lens lifi hücrelerinin epitelinin plazma zarında ve kornea epitelinin plazma zarında bulunmaktadır. Ayrıca lakrimal bezinin asiner hücrelerinin apikal ve bazolateral membranlarında da lokalize olduğu belirtilmiştir (2,6). Duktal hücrelerde eksprese edilen AQP'lerin gözyaşı salgılanmasına katkıda bulunma olasılığının yüksek olduğu düşünülmektedir (34).

Diğer akuaporinlerin gözdeki lokalizasyonlarını incelersek; AQP7, AQP9 ve AQP11'in mRNA kopyaları siliyer cisim, korneo-limbal doku, optik sinir, retina ve sklerada bulunurken; AQP9 ve AQP11 mRNA'larının varlığı da koroidde gösterilmiştir. Bunlara ek olarak; AQP7 kanalları, immüno işaretleme yöntemi ile, kornea epiteli, kornea endoteli, trabeküler ağ endoteli, siliyer epiteli, lens epiteli, retinanın iç ve dış sınırlayıcı membranı, retina pigment epiteli ve gözün tüm kısımlarının kılcal endotelinde tespit edilmiştir. AQP9 kanalları, immün etiketleme yöntemiyle, pigmentsiz siliyer epitel ve retina ganglion hücrelerinde

belirlenirken; AQP11 kanalları ise immüno işaretleme yöntemiyle, korneo-limbal epitelde, pigmentsiz siliyer epitelde ve retinanın iç sınırlayıcı zarında gösterilmiştir (27). Şekil II'de akuaporin kanallarının göz dokularında bulunduğu yerler özetlenmiştir.

Şekil II. Akuaporinlerin Göz Dokularındaki Dağılımları



Akuaporinlerle İlişkili Göz Hastalıkları

AQP kanallarında gelişen düzensizliklerin; katarakt, Sjögren sendromu, glokom, kuru göz hastalığı (AQP4, AQP5), keratokonus (AQP5), nöromiyelitis optika (AQP4), diyabetik maküler ödem (AQP4) gibi gözle ilişkili çeşitli patolojik durumlarda rol aldığı daha önceki çalışmalarda bildirilmiştir (1,7,9,35,36). AQP kanallarının fizyolojik rolleri ve hastalıklarla olan bağlantıları Tablo II'de özetlenmiştir.

Korneal hastalıklar: Korneanın çeşitli hastalıklar nedeniyle şeffaflığını kaybetmesi önemli derecede görme kayıplarına neden olmaktadır. Yapılan bir çalışmada çeşitli kornea örneklerinde dokudaki AQP miktarları ölçülmüştür. Kenney ve diğerleri bu çalışmada AQP üretimindeki anormalliklerin psödofakik/afakik büllöz keratopati kornealarında (azalmış AQP1, artmış AQP3 ve AQP4) ve Fuchs distrofi kornealarında (azalmış AQP1) bulunduğunu göstermişlerdir (24). Bazı potansiyel AQP modülatörleri tanımlanmış olmasına rağmen, daha iyi modülatörlerin geliştirilmesiyle ilgili birtakım zorluklar bulunmaktadır. Bunlar arasında; kısmen AQP'lerin su taşıma fonksiyonunun izlenmesindeki zorluklar ve AQP molekülünün istenilen noktasının hedeflenmesiyle ilgili yaşanan teknik sıkıntıları sayabiliriz (9).

Katarakt: Göz merceğinin şeffaflığını yitirmesi sonucu bulanıklaşması katarakt olarak tanımlanmaktadır (12). Sıklık açısından incelediğimizde dünyadaki görme kaybı sebepleri açısından ilk sıralarda yer almaktadır (37). Katarakt gelişiminin sebepleri her zaman önemli bir araştırma alanı olmuştur. Genlerdeki mutasyonların katarakt gelişimine etkisinin gösterilmesi bu alana olan ilgiyi artırmaktadır. MIP geni, AQP0 olarak da bilinen olgun lenste bol miktarda bulunan bağlantı membran proteinini kodlamaktadır. Lensin normal yapısıyla lens iç sıvı dolaşımının korunmasında kritik bir rol oynadığı bilinmektedir (12). Sıçanlar üzerinde yapılan bir çalışmada lens lifinin MIP/AQP 0, deoksiribonükleaz II beta dahil olmak üzere yaklaşık 100 genin ifadesinin, katarakt olmayan lenslere kıyasla, kataraktlı lenslerin epitel hücrelerinde önemli ölçüde daha az (0.07-0.5 kat) olduğu bulunmuştur (38). Ayrıca AQP0'daki mutasyonların insanlardaki bazı tip konjenital katarakt formlarıyla da ilişkisi olduğu gösterilmiştir (6,7).

Yapılan bir araştırmada, kortikal, nükleer ve posterior subkapsüler katarakt tiplerinin epitel hücrelerinde AQP 0, 1 ve 5 gibi ana akuaporinlerin üretimleri analiz edilmiştir. Beklenildiği gibi hiçbir lens epiteli örneğinde AQP0 varlığı izlenmemiştir. AQP1 ve 5 açısından incelendiğinde, kontrollerle karşılaştırıldığında kataraktlı lens epitel hücrelerinde mRNA düzeyi açısından hiçbir fark bulunmamıştır. Katarakt hastalarından alınan lens epitel hücrelerinin immün blot analizlerinde ise AQP1 protein üretiminde 1,65 kat anlamlı bir artış olduğu gözlenmiştir. En yüksek farklar nükleer kataraktlarda bulunmuştur (2,1 kat artış). AQP1 açısından kortikal kataraktla kontroller karşılaştırıldığında ise anlamlı bir fark bulunamamıştır. AQP5 açısından incelendiğinde ise alt grup analizleri de dahil olmak üzere katarakt ve kontrol arasında anlamlı bir fark bulunamamıştır (39). AQP5 ifadesinin engellendiği lenslerin hiperglisemik ortamda normal lenslere göre daha fazla hacim kazandığı gözlemlenmiştir (28). Ayrıca kataraktlı lens epitel hücrelerinde AQP8 bulunduğu gösterilmiştir (40).

Glokom: AQP'ler, transmembran ozmotik su taşınımını kolaylaştırdığından, glokom patofizyolojisinde yer alan siliyer cismin sıvı iletkenliğinde rol oynayabileceği ifade edilmektedir (41). İlerleyici ve görmeyi tehdit eden bir hastalık olan glokomda gözdeki siliyer cismin, trabeküler ağın, retinanın ve optik sinirin

Tablo II: Akuaporin Kanallarının Fizyolojik Görevleri Ve Hastalıklarla İlişkisi

AQP	Permeabilite	Doku	Fizyolojik fonksiyon	Patolojik fenotip	Referanslar
AQP0	Su,CO_2, askorbik asit, katyonlar	Kornea, lens, ganliyon hücre tabakası	Kornea ve lens şefaflığı	Katarakt, üveit	Frigeri et al, 2007; Varadaraj et al 2018; Sanal 2008, Schey et al 2014
AQP1	Su, CO_2, NH_3, NO, monovolant katyonlar, H_2O_2	Kornea, lens epitelyal hücreleri, trabekular ağ, siliyer cisim, retina pigment epiteli	Kornea ve lens şefaflığı,göz tansiyonu, Retina epitelyal sıvı transportu	Retina dekolmanı, psödofakik bülloz keratopati, glokom	Schey et al 2017; Huang et al, 2021
AQP2	Su	İnternal limitan membran, retinal pigment epiteli	Göz tansiyonu, retina epitelyal sıvı transportu	Diyabetik retinopati, glokom	Huang et al, 2021
AQP3	Su,amonyum, üre, gliserol, H_2O_2	Lakrimal bez, konjonktiva, retina pigment epiteli	Göz yaşı tabakası	Sjögren sendromu	Soyfoo et al, 2018
AQP4	Su,CO_2	Trabekular ağ, siliyer cisim, lakrimal bez, müller hücreler, optik sinir	Göz tansiyonu, göz yaşı tabakası	Sjögren sendromu, retina dekolmanı, Nöromiyelitis optika	Papadopoulos et al, 2012; Soyfoo et al, 2018; Chen et al 2022
AQP5	Su, CO_2, H_2O_2	Kornea epiteli, lens epiteli, fibril hücresi, gangliyon hücre tabakası, iç pleksiform ve iç nükleer tabaka, dış nükleer tabaka, retina pigment epiteli, lakrimal bez	Kornea ve lens şefaflığı, retina epitelyal sıvı transportu	Katarakt, Sjögren sendromu, üveit, retina dekolmanı	Schey et al, 2017
AQP6	Su, CO_2, üre, amonyum, gliserol	Dış pleksiform tabaka	Retina epitelyal sıvı transportu	Hastalıkla ilişkisi henüz raporlanmamış	Shanbagh et al,2018
AQP7	Su, üre, amonyum, gliserol	Lens epitelyal hücreleri, trabeküler ağ endoteli, siliyer cisim, iç limitan membran, dış limitan membran, retina pigment epiteli	Lens şefaflığı	Katarakt, diyabetik retinopati	Schey et al,2014; Chen et al 2022
AQP8	Su, üre, H_2O_2, gliserol, amonyum	Lens epitelyal hücreleri	Lens şefaflığı	Katarakt	Hayashi et al, 2018
AQP9	Su, üre, gliserol	Gangliyon hücre tabakası, iç nükleer tabaka, retina pigment epiteli, siliyer cisim	Retina epitelyal sıvı transportu	Üveit	Tran et al, 2017; Shanbagh et al,2018
AQP11	Su, gliserol	İç limitan membran, limbal bölge, siliyer cisim	Retina epitelyal sıvı transportu	Diyabetik retinopati	Chen et al 2022

etkilendiği belirtilmiştir (42). Yapılan bir çalışmada, hem primer açık-açılı glokom hem de primer kapalı açılı glokomu olan gözlerle glokom olmayan gözler karşılaştırıldığında iriste AQP1 ve AQP2 ekspresyonunda anlamlı artış ve aköz sıvı ozmolalitesinde azalma olduğu gösterilmiştir. Bu bulgular, irisin glokom patofizyolojisinde değişen aköz hümör dinamiklerine dahil olabileceğini düşündürmektedir (41). Diğer taraftan, AQP1 ve AQP4 gen ifadesi engellenmiş farelerin, olağan ön kamara yapılarını koruduğu gözlemlenmiştir (42). Ayrıca AQP1 ve/veya AQP4 yokluğunun göz içi basıncında ve aköz sıvı üretiminde azalmaya sebep olduğu bilinmekle beraber bunun klinik değeri henüz çalışılmamıştır (33,42). AQP9'un retinal ganglion hücresi metabolizması ve hücre apoptoz mekanizmaları ile ilişkilendirildiği belirtilmiştir (42).

Sjogren's Sendromu: Sjögren Sendromu (SS), ekzokrin bezlerin ve daha spesifik olarak tükürük ve lakrimal bezlerin lenfo-plazmositik infiltrasyonu ile karakterize kronik sistemik bir otoimmün hastalıktır. SS'de, göz ve ağız kuruluğu ile hiposalivasyon durumları mevcuttur. Günümüzde bu hastalığın tedavisi olmadığından ancak semptomatik rahatlama sağlanmaktadır (3,43). AQP'lere karşı otoantikorlar nöromiyelitis optika (NMO) ve birincil Sjögren Sendromu (pSS) olmak üzere başlıca iki otoimmün hastalıkta bulunmuştur (35). SS'den kaynaklanan göz kuruluğu gibi bulgular bu hastalıktaki AQP kanallarının rolünü destekleyici kanıtlar sunmaktadır. Bu nedenle, esas olarak SS'de yer alan AQP'lerin modülasyonunun, potansiyel bir terapötik hedef olarak büyük öneme sahip olduğu düşünülmektedir (3). Diğer taraftan, deneysel hayvan modellerinde gen tedavisi üzerinde çalışmalar yapılmaktadır. Yapılan bir çalışmada, AQP1 gen terapisinin SS kemirgen modelinde tükürük ve lakrimal sıvı hareketini eski haline getirdiği ve glandüler inflamasyonu azalttığı

gösterilmiştir (43).

Nöromiyelitis optika: İlk olarak 1984 yılında Eugene Devic tarafından tanımlanan ve bu nedenle genellikle Devic hastalığı olarak adlandırılan nöromiyelitis optika (NMO), merkezi sinir sisteminin otoimmün inflamatuar bir hastalığıdır (35,44). Astrosit su kanalı proteini AQP4'e karşı dolaşımdaki IgG1 antikorlarının keşfi ve AQP4-IgG'nin nöromiyelitis optika gelişimine dahil olduğuna dair kanıtlar, hastalık anlayışımızda devrim yarattığı belirtilmiştir (44). NMO ağırlıklı olarak medulla spinalis ve optik sinirde inflamasyona sebep olmaktadır. Hastaların yaklaşık %70-80'inde anti-AQP4 antikorlarının varlığı gösterilmiştir (35). Tedavi için, aquaporumab (AQP4-IgG bağlanmasının patojenik olmayan antikor blokeri), sivelestat (nötrofil elastaz inhibitörü) ve eculizumab (tamamlayıcı inhibitör) gibi ilaçlar kullanılmaktadır (44). Aquaporumab, kompleman bağımlı sitotoksisite/antikor bağımlı sitotoksisite içermeyen tasarlanmış yüksek afiniteli bir AQP4 antikorudur. Spesifik olarak patojenik AQP4 antikorlarını engelleyebileceği gösterilmiştir (35).

Sonuç

AQP'lerin oküler fizyolojide önemli görevleri olduğundan, bu fonksiyonların anlaşılması oküler sağlığın iyileştirilmesi ve göz hastalıklarının tedavisi için önemlidir. Bazı oküler hastalıklar için gelecekteki tedavilerin, AQP ekspresyonunun ve/veya fonksiyonunun düzenlenmesi yoluyla olması muhtemeldir. AQP'lerin, lens ve kornea şeffaflığının korunmasından aköz hümör üretimine, hücresel homeostazın sürdürülmesine ve retinada sinyal iletiminin düzenlenmesine kadar değişen oküler fonksiyonlarda önemli roller oynadığı tespit edilmiştir. Göz doksusunun fonksiyonunu sürdürmesindeki hayati rolleri ve gelişen hastalıklardaki rolleri düşünüldüğünde, bu durum AQP kanallarının hastalıkların tedavisindeki önemini ve gelecekteki terapötik yaklaşımlar için potansiyel hedefleri temsil etmektedir. AQP'lerin gözle ilgili katarakt, glokom, maküler ödem, korneal ödem, üveit gibi hastalıklarla bağlantısına dayalı araştırmaları içeren gelecekteki çalışmalar, bu hastalıkların etiyolojik faktörlerini ve işlev bozukluklarını azaltabilecek veya tamamen ortadan kaldırabilecek stratejilerin geliştirilmesine yardımcı olabilir.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

A Case of Septic Arthritis and Osteomyelitis Due to Methicillin-Resistant Staphylococcus Aureus in the Shoulder Joint of a Healthy Newborn

Sağlıklı Bir Yenidoğanın Omuz Ekleminde Metisiline Dirençli Stafilokok Aureus'a Bağlı Gelişen Septik Artrit ve Osteomyelit Olgusu

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Vaka Sunumu / Case Report
Doi: https://doi.org/10.52827/hititmedj.1599859
Geliş Tarihi | Received: 11.12.2024
Kabul Tarihi | Accepted: 09.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Kuşkaya M. A Case of Septic Arthritis and Osteomyelitis Due to Methicillin-Resistant Staphylococcus Aureus in the Shoulder Joint of a Healthy Newborn. Hitit Medical Journal 2025;7(2):289-294. https://doi.org/10.52827/hititmedj.1599859

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: MK Tasarım: MK Veri Toplama/Veri İşleme: MK Veri Analizi: MK Makalenin Hazırlanması: MK.
Hasta Onamı: Hastadan yazılı aydınlatılmış onam ve yayın onamı alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MK Design: MK Data Collection/Data Processing: MK Data Analysis: MK Manuscript Preparation: MK.
Informed Consent: Written informed consent and consent for publication were obtained from the patient.
Financial Disclosure: There are no financial funds for this article.

A Case of Septic Arthritis and Osteomyelitis due to Methicillin-Resistant Staphylococcus Aureus in the Shoulder Joint of a Healthy Newborn

ABSTRACT

Acute osteomyelitis with septic arthritis, which is uncommon in neonates, needs to be quickly diagnosed and treated to avoid devastating sequelae. We here in report a case of osteomyelitis with septic arthritis of the shoulder caused by Methicillin-resistant Staphylococcus aureus in a 24-day-old neonate with no preexisting disease is reported. Physical examination revealed swelling and local heat around the right shoulder accompanied by the limitation of spontaneous movements of the right arm and painful crying with careful passive arm motion. A magnetic resonance imaging study revealed the presence of joint fluid in the shoulder joint and swelling of soft tissues. Arthrotomy was done with parenteral antibiotic therapy for six weeks to which the child responded well. We present this case because it is a very rare case of acute septic arthritis and osteomyelitis due to methicillin-resistant Staphylococcus aureus in the shoulder joint, which was previously healthy in the neonatal period.

Keywords: Healthy newborn, osteomyelitis, septic arthritis, shoulder.

ÖZET

Akut septik artrit ve osteomyelit,yenidoğanlarda nadir görülen, sekel oluşmaması için hızlı tanı konulması ve tedavi edilmesi gereken hastalıklardır. 24 günlük, öncesinde sağlıklı olan yenidoğanda metisiline dirençli Staphylococcus aureus'a bağlı omuz ekleminde gelişen akut septik artrit ve osteomyelit olgusunu sunuyoruz. Fizik muayenesinde sağ omuzda lokal ısı artışı ve şişlik, sağ el spontan hareketlerinde kısıtlılık ve pasif el hareketlerinde ağrıya bağlı ağlama görüldü. Manyetik rezonans görüntülemede omuz ekleminde sıvı artımı ve yumuşak dokularda şişlik saptandı. Artrotomi ve sonrasında altı hafta devam eden parenteral antibiyotik tedavisine iyi cevap alındı. Yenidoğan döneminde öncesinde sağlıklı olup, omuz ekleminde metisiline dirençli Staphylococcus aereus'a bağlı gelişen çok nadir bir akut septik artrit ve osteomyelit olgusu olması nedeni ile bu olguyu sunuyoruz.

Anahtar Sözcükler: Omuz, osteomiyelit, sağlıklı, septik artrit, yenidoğan.

Giriş

Osteoartiküler enfeksiyonlar (OAE), yenidoğanlarda sık görülmeyen ancak görüldüğünde ciddi seyreden hastalıklardır. OEA'nin en klasik iki hastalığı osteomyelit ve septik artrittir. Kliniği, semptomları, tanı ve tedavi yöntemleri birbirine çok benzer. Yenidoğanda semptomların silik olması nedeniyle tanı konulması zor ve çoğu kez geçtir (1).

En sık neden olan organizma *staphylococcus aureus*'tur (SA). Hematojen osteomyelit uzun femur ve tibia gibi tübüler kemiklerde gelişme eğilimindedir. OEA %80 oranında bu kemiklerde görülürken, daha az etkilenen bölgeler omuz ve dirsek gibi üst ekstremitelerdir (1,2). Berberian ve arkadaşlarının yaptığı çalışmada 77 osteoartritli yenidoğanın %12,2 si omuzda görülmüştür (2). Sepsis, bakteriyemi, prematürite, travma, umbilikal kateterizasyon, perinatal asfiksi, immun yetmezlikler ve transplasental enfeksiyonlar OEA gelişme riskini arttırır (1,2). Omuz septik artrit ve osteomyeliti yenidoğanlarda çok nadirdir ve literatürde az sayıda olgu bildirilmiştir. Burada önceden sağlıklı olan ve risk faktörü bulunmayan bir yenidoğanda, metisiline dirençli stafilakok aureus (MRSA) enfeksiyonuna bağlı olarak sağ omuzda ve humerusta görülen bir akut osteomiyeliti ve septik artrit olgusu sunulmaktadır.

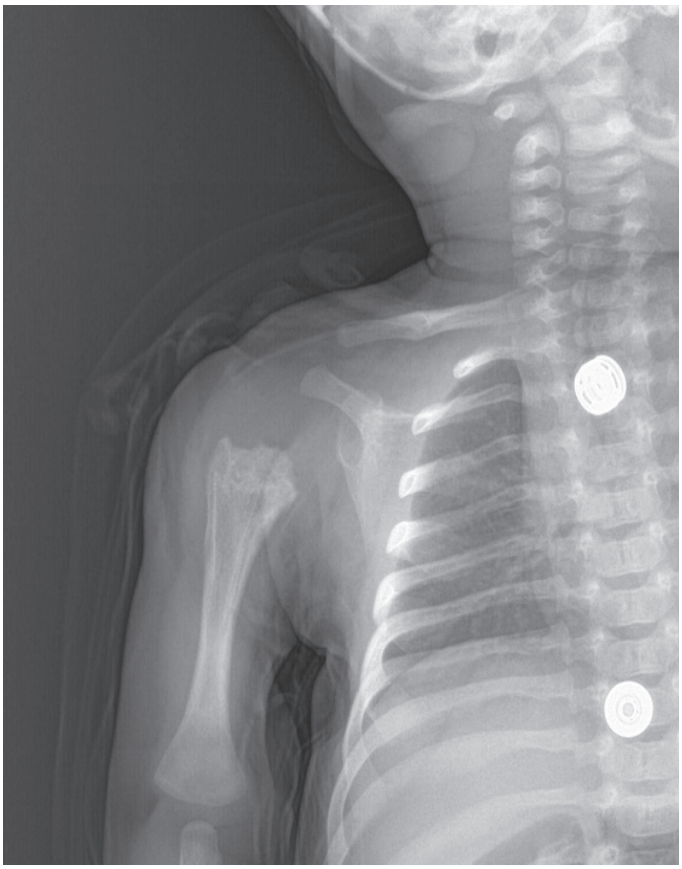
Olgu Sunumu

Bezmialem Vakıf Üniversitesi ortopedi servisine postnatal 24 günlük iken sağ omuzda şişlik ve hareket kısıtlılığı yakınmaları ile başvurdu. Travma veya düşme öyküsü yoktu. Daha önceden hastane yatışı olmamıştı. Bebek akraba olmayan ebeveynlerden, normal bir gebelik sonrası gebeliğinin 38. haftasında 9/10 apgar ile normal spontan vajinal yol ile doğmuştu. Prenatal risk faktörü olmayan ve komplike bir gebelik geçirmeyen 33 yaşındaki annenin 2. çocuğuydu.

Fizik muayene bulgularında ağırlığı 3505 gr (47 p), boy 48 cm (4 p), baş çevresi 36 cm (75 p) idi. Sağ omuzda şişlik, kızarıklık ve ısı artışı mevcut olan, sağ omuz ve kol hareketlerinde kısıtlılık olan hastada radyolojik, klinik ve laboratuvar bulguları değerlendirilerek omuz septik artriti düşünüldü ve omuz eklemi debridmanı yapılmak üzere operasyona alındı. Operasyonda glenohumeral ekleme ulaşılarak, eklem içi pürülan mayiden mikrobiyolojik örnekler alındıktan sonra abse görünümlü enfekte dokular eklem içinde görülerek debride edildi, daha sonra eklem içi 1000 cc serum fizyolojik ile irrige edildikten sonra eklem içine dren konularak anatomisine uygun şekilde kapatıldı ve operasyon sonlandırıldı. Hasta omuz septik artriti ve humerus osteomyeliti tanıları ile aynı hastanenin yenidoğan yoğun bakım ünitesine transfer edildi.

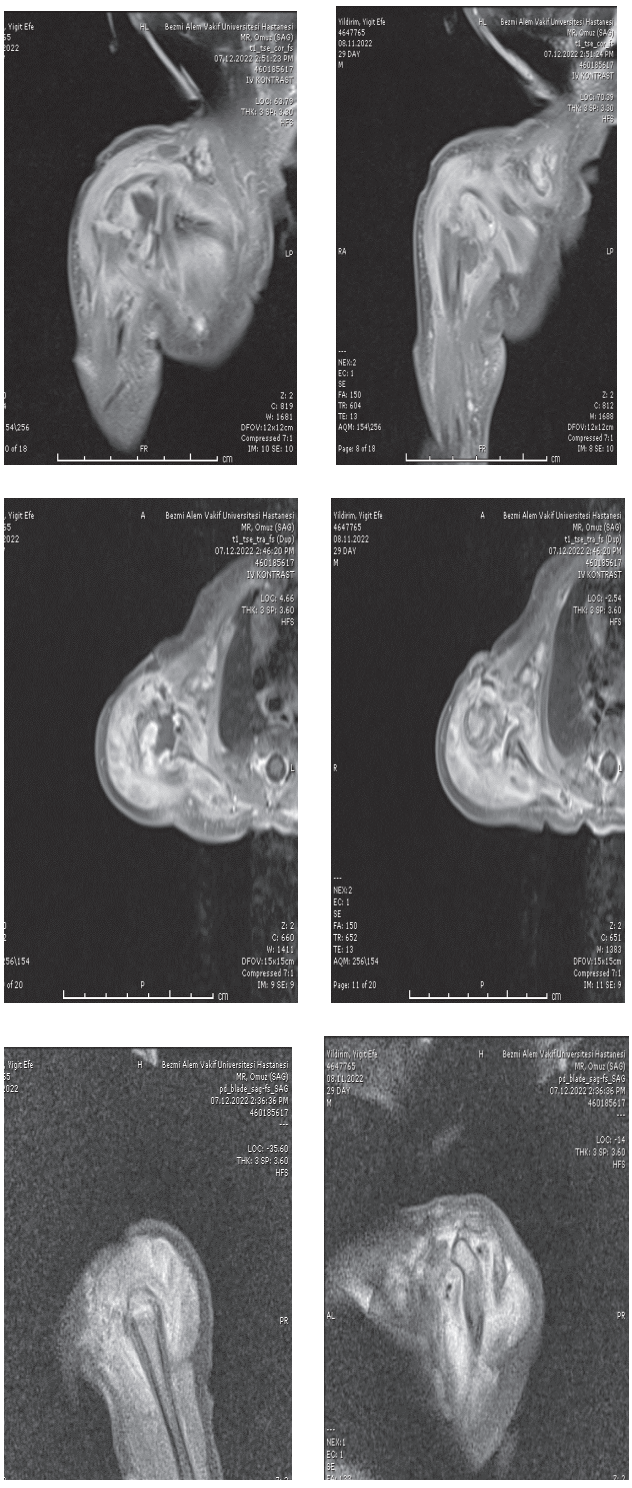
Yenidoğan yoğun bakımda yapılan ilk fizik muayene bulgularında genel durumu orta, renk normal, solunum sistemi ve kardiyolojik muayenesi normal. Batın rahat, organomegali ve lenfadenopati görülmedi. Ateşi 36.6 °C, tansiyon arteryel normal ve satürasyonları %99-100 olarak ölçüldü. Yenidoğan refleksleri emme ve arama aktif, moro solda normal, sağda alınamıyor. Sağ omuz ve kol hareketleri pasif ve aktif hareketle ağrılı. Sağ elde yakalama yok, sol elde yakalama vardı.

Şekil I. Sağ Omuz Grafisinde Lokalize Yumuşak Doku Ödemine ve İntraartiküler Sıvı Birikimine Bağlı Eklem Aralığında Genişleme, Humerus Distalinde Litik Lezyonlar



İlk laboratuvar incelemelerinde WBC: 17140/ mm^3 Hb: 12,8 gr/dl Hct: %36,7 PLT: 658.000/mm^3. C-reaktif protein (CRP): 99,39 mg/dl, diğer biyokimyasal değerler normaldi. Sağ omuz grafisinde lokalize yumuşak doku ödemine ve intraartiküler sıvı birikimine bağlı eklem aralığında genişleme görüldü. (Şekil I)

Şekil II. Sağ Omuz Kontrastlı MR Görüntülemeleri



Glenohumeral eklem aralığında effüzyon aksiller resesi doldurmakta ve aksiller lifleri basılamaktadır. Sağ humeral epifizde fragmantasyon intramedüller sahasından omuz kuşağı posterior ve anterior kesimlerine uzanan intramedüller lokülasyon periostta kalınlık artışı ve omuz kuşağı rotator cuff musküler yapılarında ve deltoid kaslarda myotitik süreç lehine T2 Ag hiperintensitesi ve postkontrast incelemede kontrast tutulumu izlendi. Omuz kuşağı anteriorunda sağ omuz eklemi içerisinden cilde uzanan yaklaşık 2 cm uzunluğunda en geniş yerinde 3 mm ölçülen düzensiz sınırlı periferal kontrastlanan loküle sıvı koleksiyonu izlendi. Glenoid rim kartilaj yapılar oblitere olup, glenoid boyun lokalizasyonuna değin kontrast tutulumları ve periostta kalınlık artışı izlendi. Aksiller lojda multipl lenf nodu izlendi. Akromion kemik trabeküler yapıda inramedüller kontrast tutulumları izlendi. Humerus 1/2 proksimal kesimine değin lameller tip periostta kalınlık artışı gözlenmiştir. Subperiostal effüzyon ve kontrast tutulumları izlendi. Kaput humeride yaygın litik sahalar izlendi.

Kontrastlı sağ omuz magnetik rezonans (MR)'da sağ humeral epifizde intramedüller sahasından omuz kuşağı posterior ve anterior kesimlerine uzanan periostta kalınlık artışı izlendi. Omuz kuşağı anteriorunda sağ omuz eklemi içerisinden cilde uzanan periferal kontrastlanan loküle sıvı koleksiyonu görüldü. Humerus 1/2 proksimal kesimine değin lameller tip periostta kalınlık artışı gözlendi. (Şekil II) Hastada bu bulgularla omuz septik artrit ve humerusda gelişen osteomyelit düşünüldü. Hastaya sağda yakalama refleksinin olmaması nedeniyle sağ brakiyal pleksus MR görüntülemesi de yapıldı ve patolojik bulgu saptanmadı.

Hastanın klinik ve laboratuvar bulgular ve radyoloji görüntüleri ile da omuz septik artriti ve humerusda gelişen osteomyelit düşünüldü. Pediatrik enfeksiyon hastalıkları önerisi ile kan ve yara kültürü alındıktan sonra IV vankomisin ve sefotaksim başlandı. Hastanın izlemlerinde debridman sonrası alınan sinoviyal kültüründe ve kan kültüründe MRSA üredi. Antibiyogramında vankomisine duyarlı olduğu için sefotaksim kesilerek vankomisin ile tedaviye devam edildi. Takipte klinik ve laboratuar olarak düzelen hastanın 2. Günde gelenleri olmayınca dreni çekildi. Vankomisin tedavisi 4 hafta verildikten sonra, tedavi teikoplanin ile 6 haftaya tamamlandı. Kontrol kan kültüründe üreme olmadı. Etiyolojiye yönelik bakılan diğer tetkiklerinde Toksoplazma, rubella, sitomegalovirüs, sifiliz ve herpes grubu (TORCHES) enfeksiyonlar da bakıldı ve normal olarak bulundu. İmmün yetmezlik açısından yapılan tetkikleri (immunglobulinler ve lenfosit alt grupları) normal bulundu. Taburcu edilirken sağda moro refleksi aktif alınıyor ve yakalama refleksi pozitifti. Sağ kol ve omuz hareketleri sırasında kısıtlılık yoktu. Taburculuk sonrası çocuk poliklinik izlemi yanında, ortopedi, pediatrik nöroloji ve fizik tedavi izlemleri de devam etti.

Tartışma

Osteomyelit ve septik artrit görülme sıklığı 1.000 canlı doğumda 0,12, 1.000 yeni doğan yoğun bakım başvurusunda 0,67, ölüm oranı %7,3 olarak bildirilmiştir (3). OEA'nın erken tanısı ve antibiyotik tedavisinin hızlı başlanması kalıcı kemik ve eklem hasarının gelişmesini önler. Yenidoğanlar, immün sistemlerinin olgunlaşmamış olması nedeniyle osteoartiküler

enfeksiyonlara karşı duyarlıdır. Daha büyük çocuklara kıyasla daha az klinik bulgu verir ve bu nedenle septik artrit ve osteomyelit tanısı koymak daha zordur (1,2,4). En sık gözlenen bulgu çoğu kez anne veya hemşire tarafından farkedilen etkilenen ekstremitede haraket kısıtlılığı ve spontan hareketlerin olmamasıdır (psödoparalizi) (1,4). Hastamızda bizi tanıya götüren en belirgin bulgular sağ omuzda şişlik, hassasiyet ve pasif hareketler sırasında ağrı oldu. En çok tutulan kemikler tibia (%50), femur (%30), fibula (%12), humerus ve ulna (%3), radius (%2) dir (1); bizim hastamızda humerus etkilenmişti.

Yenidoğanlarda omuzda gelişen septik artrit ve osteomiyelit birlikteliği nadirdir. 2002 yılında çocuklarda yapılan bir çalışmada omuz ekleminde osteoartrit görülme oranını %3-5 olarak saptamıştır (5). 2010 yılında Berberian ve arkadaşlarının yaptığı çalışmada 77 yenidoğanda septik artrit ve osteomyelit yönünden 99 odak etkilenmiş. Bunların sadece 12'si omuz eklemindeydi. Hepsinde osteoartrit gelişmesi için bir risk faktörü saptanmıştı. OAE'lar için sepsis, bakteriyemi, prematürite, travma, umbilikal kateterizasyon, perinatal asfiksi, immun yetmezlikler ve transplasental enfeksiyonlar risk faktörleri olarak tanımlanmıştır. Hastamızda bu risk faktörleri yoktu. Osteomiyelitli yenidoğanlarda en sık izole edilen organizmanın SA olduğu bildirilmiştir. Septik artrite en sık yol açan organizmalar SA, Grup B streptokok, koagülaz negatif stafilokoklar ve gram-negatif basillerdir (2,3). Bunlar dışında *Streptococcus pyogenes, Streptococcus pneumoniae, Pseudomonas. aeruginosa, Neisseria gonorrhoeae, Haemophilus influenzae* ve *Kingella kingae* nadir görülen diğer etkenlerdir (6,7). Bizim hastamızda literatürle uyumlu olarak kan kültüründe ve sinoviyal kültürde MRSA üredi. Osteomiyelit, metafiz ve epifiz arasındaki vasküler bağlantıların varlığı ile karakterize damarsal anatominin bir sonucu olarak, yenidoğanların yarısından fazlasında sıklıkla septik artrit ile birlikte bulunur. Cerrahi drenaj ve antibiyotik tedavisi birlikte uygulanır. Genel olarak, izole septik artrit en az 2 ila 3 hafta tedavi edilmelidir, ancak SA'a bağlı septik artrit genellikle 4 ila 6 haftalık antibiyotik tedavisi gerektirir. Yeterli antibiyotik tedavisine yanıt vermeyen çocuklarda cerrahi insizyon ve drenaj gerekebilir (6,7). Olgumuzda 4 hafta süre ile intravenöz vankomisin ve daha sonra 2 hafta teikoplanin tedavisi ile toplam 6 hafta parenteral tedavi verildi.

Açık artrotomi, hastalığın kesin tedavisidir. Konservatif tedavi ile eklem semptomlarının ve eklem içi basıncın hafiflemediği durumlarda, en kısa sürede eklem açılmalıdır (8). Bizim hastamızda da ilk gün tanı konur konmaz açık artrotomi ve drenaj uygulanmıştı.

Laboratuvar tetkikleri de septik artrit ve osteomiyelit tanısı koymaya yardımcıdır. CRP, osteoartrit tanısı için duyarlı bir belirteçtir, enfeksiyonun erken dönemde saptanması ve antibiyotik tedavisinin yönlendirilmesinde kullanılabilir. Sunulan olguda CRP 99,85 mg/L'ye yükselmiş ve ardından tedavinin 15. gününde negatif olmuştur. Lökosit sayısı ve prokalsitonin gibi diğer laboratuvar bulguları, hastalığın ilerlemesini ve tedaviyi değerlendirmek için kullanılabilir. Sunulan olguda WBC 17800/ mm^3 'e yükselmiş ve ardından tedavide 10100/mm^3'e düşmüştür. Prokalsitonin başlangıçta bakılamadı, tedavinin 10. gününde negatif idi.

Direkt radyografi, bilgisayarlı tomografi taraması ve MR görüntüleme, tanıyı doğrulamak için kullanılabilecek radyoloji yöntemleridir. Radyografi, osteoartrit şüphesi olan bir yenidoğanda genellikle ilk radyolojik inceleme iken Manyetik rezonans en duyarlı görüntüleme, yöntemidir. Manyetik rezonans görüntüleme ile osteomiyelitte görülen değişiklikler erken dönemde tespit edilebilir ve ayrıca subperiostal apse, yumuşak doku enfeksiyonu ve eklem efüzyonunun belirlenmesi mümkün olur (9). Hastamızın MR görüntülerinde omuz ekleminde eklem sıvısı ve yumuşak dokularda şişlik olduğu görülmüştür (Şekil II). Benzer olgular nadiren bildirilmiştir (10-12). Bunlar erken doğum, umbilikal ven kateterizasyonu veya altta yatan hastalık gibi risk faktörleri ile ilişkilendirilmiştir. Bizim hastamızda bu risk faktörleri yoktu.

Sonuç olarak, sağlıklı yenidoğanlarda omuzda septik artrit ve humerusda osteomiyelit birlikteliği çok nadirdir. Tedavi hem cerrahi drenaj hem de yeterli düzeyde antibiyotik uygulanmasını gerektirir. Neonatologlar, pediyatristler ve pediyatrik ortopedistler sağlıklı yenidoğan bebeklerde osteoartritin görüntülemedeki ve kan kültürlerindeki bulguları da dahil tüm tanısal ipuçlarına daha fazla dikkat etmelidir. Yenidoğanda özellikle bu hastalıktan kuşkulanılması, hastalığın erken tanısı ve ardından başarılı tedavisi için esastır.

Hastamızda hızla uygulanan artrotomi,drenaj ve debridman, sonrasında da 6 haftalık uygun antibiyoterapi sayesinde sekelsiz ve tam iyileşme sağlanmıştır.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B

Nadir Bir Splenomegali Nedeni: Asit Sfingomiyelinaz Eksikliği Tip B

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Vaka Sunumu / Case Report
Doi: https://doi.org/10.52827/hititmedj.1624724
Geliş Tarihi | Received: 22.01.2025
Kabul Tarihi | Accepted: 26.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Demircioğlu H, Demircioğlu S. A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B. Hitit Medical Journal 2025;7(2):295-300. https://doi.org/10.52827/hititmedj.1624724

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HD, SD Tasarım: HD Veri Toplama/Veri İşleme: HD, SD Veri Analizi: HD, SD Makalenin Hazırlanması: HD
Hasta Onamı: Hastadan yazılı aydınlatılmış onam ve yayın onamı alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared no conflicts of interest
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HD, SD Design: HD Data Collection/Data Processing: HD, SD Data Analysis: HD, SD Manuscript Preparation: HD
Informed Consent: Written informed consent and consent for publication was obtained from the patient.
Financial Disclosure: There are no financial funds for this article.

A Rare Cause of Splenomegaly: Acid Sphingomyelinase Deficiency Type B

ABSTRACT

Acid Sphingomyelinase Deficiency is a rare, autosomal recessive inherited metabolic disorder caused by mutations in the SMPD1 gene. It is a pan-ethnic, multisystemic, often progressive, and potentially life-limiting condition, with an age of onset ranging from the first days of life to adulthood. Acid Sphingomyelinase Deficiency results from a deficiency of the enzyme acid sphingomyelinase. In Acid Sphingomyelinase Deficiency type B patients, hepatosplenomegaly and pulmonary pathological changes are frequently observed; however, central nervous system involvement is usually absent. The rarity of the disease and the lack of expertise often lead to misdiagnosis, delayed diagnosis, and limited access to adequate care. In recent years, enzyme replacement therapy with olipudase alfa, which provides an exogenous source of acid sphingomyelinase, has been introduced for children and adults diagnosed with Acid Sphingomyelinase Deficiency without central nervous system involvement, altering the course of the disease. In this case presentation, we aimed to emphasize the consideration of Acid Sphingomyelinase Deficiency in the etiology of splenomegaly.

Keywords: Acid Sphingomyelinase Deficiency, interstitial lung disease, Niemann-Pick disease, splenomegaly, thrombocytopenia.

ÖZET

Asit Sfingomiyelinaz Eksikliği, SMPD1 genindeki mutasyonlardan kaynaklanan nadir bir otozomal resesif geçiş gösteren, başlangıç yaşı yaşamın ilk günlerinden erişkinliğe kadar değişen, pan-etnik, çok nadir, multisistemik, çoğunlukla ilerleyici ve potansiyel olarak yaşamı sınırlayan bir metabolik hastalıktır. Asit Sfingomiyelinaz Eksikliği, asit sfingomiyelinaz enziminin yetersizliğinden kaynaklanır. Asit Sfingomiyelinaz Eksikliği tip-B hastalarda sıklıkla hepatosplenomegali ve akciğerlerde patolojik değişiklikler vardır, ancak genellikle santral sinir sistemi tutulumu yoktur. Hastalığın nadir görülmesi ve uzmanlık eksikliği, yanlış tanıya, teşhisin gecikmesine ve yeterli bakıma erişimin engellenmesine neden olmaktadır. Son yıllarda merkezi sinir sistemi tutulumu olmayan Asit Sfingomiyelinaz Eksikliği tanılı çocuk ve yetişkinlerde, hastalığın seyrini değiştiren, asit sfingomiyelinazın ekzojen bir kaynağını sağlayan bir enzim replasman tedavisi olan olipudaz alfa kullanıma girmiştir. Bu vaka sunumunda splenomegali etyolojisinde Asit Sfingomiyelinaz Eksikliğinin de göz önünde bulundurulmasını vurgulamak istedik.

Anahtar Sözcükler: Asit Sfingomiyelinaz Eksikliği, interstisyel akciğer hastalığı, Niemann-Pick hastalığı, splenomegali, trombositopeni.

Introduction

Acid Sphingomyelinase Deficiency (ASMD) type A and B were previously known as Niemann-Pick disease types A and B, respectively. ASMD-A and ASMD-B are disorders caused by pathogenic variants in the sphingomyelin phosphodiesterase-1 (SMPD1) gene and are characterized primarily by a deficiency in acid sphingomyelinase activity. Niemann-Pick disease type C (NPC) is caused by pathogenic variants in the NPC1 and NPC2 genes, which result in impaired cellular processing and transport of macromolecules, including low-density lipoprotein (LDL) cholesterol and glycosphingolipids (1).

Acid Sphingomyelinase Deficiency Type B typically has a later onset and is less severe than ASMD-A, with a good prognosis in terms of survival into adulthood (1). It is present in all populations worldwide. The overall prevalence of ASMD (types A and B combined) is estimated to be 1 in 250,000 (2). ASMD-B is characterized by the development of hepatosplenomegaly in infancy or childhood. Most affected patients have thrombocytopenia due to hypersplenism. Liver involvement can be severe, with infiltration of foamy histiocytes, ballooning of hepatocytes, and fibrosis observed (3). Other systemic findings include short stature due to delayed skeletal maturation, interstitial lung disease, hyperlipidemia, and ocular abnormalities (macular halos and cherry-red maculas) (4,5). The natural course of the disease is characterized by progressive hypersplenism and a gradual deterioration of lung function (6,7). Most patients with ASMD-B do not have neurological abnormalities. However, a small subset of patients who survive into early childhood may develop varying degrees of central nervous system symptoms, including prolonged nerve conduction velocities, cerebellar signs, cerebrospinal fluid involvement, extrapyramidal involvement, intellectual disability, psychiatric disorders, and peripheral neuropathy (8,9). In this case presentation, we aimed to highlight the importance of considering ASMD in patients with splenomegaly and/or interstitial lung disease.

Case Report

A 54-year-old female patient presented with complaints of shortness of breath, cough, and abdominal distension. It was noted that she had been diagnosed with interstitial lung disease 15 years ago. Ten years ago, splenomegaly was detected following the onset of abdominal swelling and early satiety. The family history revealed that her brother, who also had splenomegaly, passed away in his fifties due to a lung infection. The short-statured patient's physical examination revealed hepatosplenomegaly. When thrombocytopenia was added to these findings, the patient was referred to hematology by her family physician. Her laboratory results showed a leukocyte count of 3300/µL, a neutrophil count of 2340/µL, a lymphocyte count of 700/µL, hemoglobin of 12.6 g/dL, a platelet count of 110,000/µL, total cholesterol of 226.8 mg/dL, triglycerides of 347.8 mg/dL, VLDL cholesterol of 69.56 mg/dL, HDL cholesterol of 12.5 mg/dL, and LDL cholesterol of 144.74 mg/dL. An abdominal ultrasound revealed a liver size of 19.5 cm and a splenic longitudinal axis of 21 cm. High-resolution chest tomography showed increased aeration in the left lower lung, with a 2 cm-diameter thin-walled air cyst observed laterally in the anterobasal segment of the left lower lung. Widespread septal thickening was observed in both lungs. Bronchial wall thickening was noted, along with fibrotic densities extending from the peribronchial area to the pleura. Additionally, consolidation areas were observed in the anterior segment of the left upper lobe and in the basal region of the right lower lobe. Calcification was noted in the anterior segment of the right upper lobe. Sputum cytology revealed lipid-laden macrophages in 10% of all macrophages, with oil red staining, and the lipid load index was 20/400. Prussian blue staining revealed 5% hemosiderin-laden macrophages. Bone marrow biopsy showed PAS (+) benign histiocytic infiltration. These findings suggested a storage disease, prompting enzyme testing. Leukocyte sphingomyelinase enzyme activity was low (0.6 nmol/mg.17s), and plasma chitotriosidase enzyme activity was elevated (352.8 µmol/L.hr). Heterozygous pathogenic variants were identified in the SMPD1 gene. Ocular examination revealed a normal macula. The patient was diagnosed with Acid Sphingomyelinase Deficiency Type B.

Discussion

In the presence of clinical features such as hepatosplenomegaly, thrombocytopenia, interstitial

lung disease, and hyperlipidemia, ASMD-B should be suspected. In ASMD-B patients, central nervous system involvement is typically absent, but hepatosplenomegaly (HSM) and signs of liver failure are commonly observed. Splenomegaly is the most frequent initial finding in ASMD-B, occurring in 78% of patients (10). The enlargement of the spleen is caused by widespread infiltration of lipid-laden macrophages, which gives rise to the "foam cell" appearance, a distinctive pathological feature suggestive of ASMD or other lysosomal storage disorders (11). Other laboratory abnormalities may include liver dysfunction, decreased HDL cholesterol, hypertriglyceridemia, and elevated LDL cholesterol levels (12).

The diagnosis of acid sphingomyelinase deficiency, including ASMD-A or ASMD-B, is confirmed in a clinical context when both alleles of the SMPD1 gene responsible for the disease are identified through molecular genetic testing, or when the residual acid sphingomyelinase activity in peripheral blood leukocytes or cultured skin fibroblasts is less than 10% of the control values (1, 13). ASMD-B is associated with pathogenic variants of the SMPD1 gene. In our patient, an SMPD1 mutation has also been detected. There is some residual activity of the SMPD1 enzyme present in this condition (14). For example, in two studies, acid sphingomyelinase activity in ASMD-B patients was found to be 4% of normal levels, compared to undetectable activity in ASMD-A patients (14, 15). In both ASMD-A and ASMD-B patients, the liver, spleen, lymph nodes, adrenal cortex, airways, and bone marrow are filled with lipid-laden cells. In the bone marrow of ASMD patients, foamy macrophages ("Niemann-Pick" cells) and/or typical "Prussian blue histiocytes" can be observed (16).

In ASMD-B patients, lung involvement can be detected on direct chest radiographs and/or high-resolution computed tomography (HRCT). On HRCT, parenchymal involvement with a reticulonodular pattern, accompanied by interlobular septal thickening, ground-glass opacities, and pulmonary nodules (sometimes calcified) under 1 cm in size, may be observed (17, 18). In our patient's lungs, increased aeration, an air cyst, widespread septal thickening, bronchial wall thickening, fibrotic densities extending from the peribronchial area to the pleura, and calcifications were observed. MRI or CT can be used to calculate liver and spleen volumes. Particularly in splenic imaging, evaluating the accumulated material may benefit from being visible at low resolution on CT or presenting as low echogenicity on ultrasound (USG) (17). In ASMD-B patients, it is important to assess bone age and evaluate for osteopenia/osteoporosis. Dual-energy X-ray absorptiometry (DEXA) is particularly useful in the assessment of osteoporosis (19).

The previously reported case was diagnosed at the age of 41. In this case, the diagnosis was made at the age of 54, which is older compared to the previous case. Similar to the other case, this patient also had splenomegaly, interstitial lung disease, and thrombocytopenia (16).

For patients with ASMD-B, recommended surveillance includes periodic assessments (every 6 to 12 months) of growth and height in children, weight, nutrition, changes in activity levels, bleeding, shortness of breath, abdominal pain, and neurological function in patients of all ages (1). Simultaneously, platelet count, liver enzymes, fasting lipid profile, pulmonary function tests, chest radiography, and skeletal assessment with dual-energy X-ray absorptiometry (DXA) should be monitored (1).

There is currently no curative treatment for patients with ASMD. Experimental therapies, such as bone marrow transplantation, total lung lavage, and amniotic cell transplantation, are being investigated. However, there is insufficient data regarding the short- and long-term outcomes in terms of the risk-benefit ratio (20). Symptomatic pulmonary disease in ASMD-B patients may benefit from supplemental oxygen. Severe bleeding due to thrombocytopenia may require transfusion of blood products. In adults with hyperlipidemia, treatment is recommended to correct elevated total cholesterol levels. In patients with splenomegaly, avoiding contact sports is advised (1).

In acid sphingomyelinase deficiency, enzyme replacement therapy with olipudase alfa, which provides an exogenous source of acid sphingomyelinase, is recommended for both children and adults. Olipudase alfa is a recombinant human acid sphingomyelinase (ASM) being developed to address the symptoms of

ASM deficiency outside the central nervous system. In a placebo-controlled, randomized clinical trial, 36 adult ASMD patients were randomly assigned to receive either olipudase alfa or a placebo in a 1:1 ratio. After one year, olipudase alfa treatment resulted in a greater increase in the predicted mean diffusion capacity of the lungs for carbon monoxide (DLCO) (22% compared to 3% in the placebo group) and a greater reduction in spleen volume (39% decrease compared to a 0.5% increase in the placebo group) and liver volume (28% decrease compared to a 1.5% reduction in the placebo group) (21). In an open-label study involving 20 pediatric ASMD patients, one-year results showed that olipudase alfa treatment was associated with a mean increase of 33% in the expected DLCO (diffusion capacity of the lungs for carbon monoxide) in patients who were able to undergo the test, as well as a reduction in average spleen volume and liver volume, each by more than 40% (22). In August 2022, the U.S. Food and Drug Administration (FDA) approved olipudase alfa for the treatment of symptoms outside the central nervous system in ASMD, the underlying cause of both ASMD-A and ASMD-B.

In conclusion, ASMD-B is one of the rare causes of splenomegaly. Due to its rarity, diagnosis may not be made until later ages, as seen in our patient. Patients with unexplained splenomegaly, interstitial lung disease, short stature, thrombocytopenia, and low HDL levels should be evaluated for ASMD-B. Recent advances in treatment offer hope for reducing disease progression and improving symptoms.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Comment on: "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care"

Yorum: Solunum Yoğun Bakımın Patojen Nadir Alt Solunum Yolu Etkenleri ve Antibiyotik Duyarlılık Durumları

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Mektup / Letter to Editor
Doi: https://doi.org/10.52827/hititmedj.1600114
Geliş Tarihi | Received: 11.12.2024
Kabul Tarihi | Accepted: 25.01.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Comment on: "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care". Hitit Medical Journal 2025;7(2):301-303. https://doi.org/10.52827/hititmedj.1600114

Hakem Değerlendirmesi: Editör tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: AA Tasarım: AA Veri Toplama/Veri İşleme: AA Veri Analizi: AA Makalenin Hazırlanması: AA.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared no conflicts of interest
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: AA Design: AA Data Collection/Data Processing: AA Data Analysis: AA Manuscript Preparation: AA.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Dear Editor,

We are writing to express our views on the recently published article titled "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care" by Özdemir et al (1). We found the manuscript to be a valuable contribution to the field of pulmonology and infectious diseases, particularly in addressing the clinical features and antibiotic resistance of rare lower respiratory tract pathogens.

The study's focus on rarely observed pathogens in respiratory intensive care units (ICUs) fills a critical knowledge gap, especially in understanding their implications for patient outcomes and antimicrobial stewardship. The authors' findings on the correlation between APACHE-II scores and mortality rates are particularly noteworthy, providing important insights for clinical risk assessment.

However, we would like to highlight a few areas where the manuscript could be further enhanced. The study's greatest strength is its focus on rare pathogens. It addresses an understudied area of clinical microbiology by investigating pathogens such as Burkholderia cepacia and Stenotrophomonas maltophilia, which are rarely seen in intensive care units. This focus provides valuable information about the clinical relevance of these organisms and their antibiotic resistance patterns. It also offers comprehensive data on the antibiotic susceptibility profiles of rare pathogens, which is a critical resource for optimizing empirical therapy in intensive care units.

While acknowledging the retrospective nature of the study a more in-depth discussion of how this design may impact the generalizability of the findings would have been valuable. For example the small sample size of 42 patients limited the statistical power of the study which could have been addressed more explicitly.

The study contains a comprehensive dataset, but some tables, particularly Table III on antibiotic susceptibility, could have benefited from additional clarity. For instance, adding a brief legend explaining abbreviations and statistical significance would have made the data more accessible to readers.

While the study provides new data, it could have enriched the discussion if it had been more robustly compared with similar studies. For example, a study by Guitor and Wright highlighted the role of Stenotrophomonas maltophilia as an emerging opportunistic pathogen in ICUs, emphasizing mechanisms of resistance to β-lactam antibiotics (2). Similarly, Dizbay et al. reported on Burkholderia cepacia in Turkish ICUs, and a significant proportion of isolates showed resistance to ceftazidime and carbapenems. Comparing these findings with the susceptibility profiles of the current study could have contextualized the results and provided actionable insights for clinicians (3).

The conclusion could have been further enriched by a discussion of how the study findings could inform policies or protocols for antibiotic use in ICUs. Specific recommendations for empirical therapy tailored to rare pathogens would have been particularly effective.

Overall, the study is a commendable effort that addresses a clinically important issue, albeit with a limited number of patients. We hope these critiques will help further improve the manuscript and increase its impact on the scientific community.

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Response from Author:

Dear Editor,

We sincerely appreciated reading your editorial remarks regarding our manuscript titled "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care". As stated within our article, the limited number of patients is among the primary limitations of the study. Nevertheless, we fully concur with your observation that the resistance profiles of rare pathogens should not be overlooked during empirical treatment planning, particularly in intensive

care settings. We agree that further research is warranted, especially studies focusing on resistance mechanisms and larger patient cohorts. We are grateful for all the constructive and encouraging feedback provided. We will be pleased to take these valuable comments into consideration in our future studies, in which we aim to expand both the number of patients and the scope of data.
Sincerely,

Response from Editor:

The letter to the editor constructively criticizes the article titled "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care" and approaches the authors' findings in a supportive but critical manner. Several suggestions are offered regarding the methodology, findings, and interpretations. The letter to the editor constructively criticizes the article titled "Rare Pathogenic Lower Respiratory Tract Factors and Antibiotic Sensitivity Situations in Respiratory Intensive Care" and approaches the authors' findings in a supportive but critical manner. Several suggestions are offered regarding the method, findings, and interpretations. The letter includes compliments and constructive criticisms of the authors' findings. Both the article and the letter could make a significant contribution if the authors take the feedback given into consideration.
Dr. Selçuk Kayır

HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 2 - Haziran|June 2025

Letter to Editor: Integrating Biochemical Parameters into the Psychological Assessment of Alcohol Dependence

Editöre Mektup: Alkol Bağımlılığının Psikolojik Değerlendirmesine Biyokimyasal Parametrelerin Entegrasyonu

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Mektup / Letter to Editor
Doi: https://doi.org/10.52827/hititmedj.1622405
Geliş Tarihi | Received: 17.01.2025
Kabul Tarihi | Accepted: 17.03.2025
Yayım Tarihi | Published: 23.06.2025

Atıf | Cite As
Demirel G. Integrating Biochemical Parameters into the Psychological Assessment of Alcohol Dependence. Hitit Medical Journal 2025;7(2):304-305. https://doi.org/10.52827/hititmedj.1622405

Hakem Değerlendirmesi: Editör tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: GD Tasarım: GD Veri Toplama/Veri İşleme: GD Veri Analizi: GD Makalenin Hazırlanması: GD.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared no conflicts of interest
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: GD Design: GD Data Collection/Data Processing: GD Data Analysis: GD Manuscript Preparation: GD.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

I read with great interest the study titled "The Relationship Between Childhood Traumatic Experiences and Obsessive Beliefs in Alcohol Use Disorder" by Kiraz and Çelik, which highlights the psychological interplay between obsessive beliefs, childhood trauma, and alcohol use disorder (AUD) (1). This study makes a significant contribution to our understanding of the psychological dimensions of AUD. Although this study provides valuable insights into psychological factors such as anxiety and depressive symptoms, it also highlights the need for further research integrating psychological assessments with biochemical markers. Exploring the interplay between these domains could enrich our understanding of AUD and its underlying mechanisms. Biochemical parameters, such as cortisol, dopamine, serotonin, and inflammatory markers, offer a promising avenue for future research (2). For example:

Stress Hormones: Chronic stress stemming from childhood trauma often affects the hypothalamic-pituitary-adrenal (HPA) axis, leading to altered cortisol levels. Investigating how these hormonal changes correlate with obsessive beliefs and addictive behaviors may reveal potential biomarkers for risk or progression (3).

Neurotransmitters: Abnormal activity in dopaminergic pathways, particularly involving the nucleus accumbens, is closely tied to the reward mechanisms implicated in AUD. Future studies could explore whether this neurochemical dysregulation is also connected to obsessive-compulsive tendencies in AUD patients (4).

Inflammatory Markers: Elevated levels of CRP or IL-6, markers of systemic inflammation, are frequently linked to childhood trauma and mental health disorders. Evaluating their relationship with obsessive beliefs and addiction severity could shed light on the physiological impact of trauma (5).

Oxidative Stress: Markers of oxidative damage, such as malondialdehyde (MDA), or antioxidant enzyme levels like superoxide dismutase (SOD), might help in understanding how physiological stress interacts with psychological vulnerabilities to drive AUD pathology (6).

Integrating these biochemical parameters into future research could provide a more comprehensive perspective on AUD etiology. Such interdisciplinary approaches would enable the development of targeted interventions that address both psychological and physiological dimensions, potentially improving therapeutic outcomes for individuals with AUD. I commend the authors for their groundbreaking work and hope these suggestions inspire future studies that expand on this valuable foundation by integrating biochemical parameters to deepen our understanding of addiction and related psychological factors.

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