# Ağrı Tıp Fakültesi Dergisi

Ekim 2025

Cilt:3 Sayı:3

# Ağrı Medical Journal

Volume:3 Issue:3

October 2025

# Ağrı Tıp Fakültesi Dergisi

# Ağrı Medical Journal


## e-ISSN: 2980-0978

**Dr. Öğr. Üyesi Ezgi KARATAŞ**
*Ağrı İbrahim Çeçen Üniversitesi Tıp Fakültesi Göz Hastalıkları Ana Bilim Dalı*



***İLETİŞİM***
***Ağrı İbrahim Çeçen Üniversitesi Tıp Fakültesi Dekanlığı***
***Erzurum Yolu 4 Km 04100 Ağrı – Türkiye***
***agritipfakultesidergisi@gmail.com***

## Genel Bilgiler

Ağrı Tıp Fakültesi Dergisi (Ağrı Medical Journal; Ağrı Med J) Ağrı İbrahim Çeçen Üniversitesi Tıp Fakültesi'nin resmi yayın organı olan bilimsel bir dergidir. Ağrı Tıp Fakültesi Dergisi yılda 3 defa (Şubat, Haziran ve Ekim), Türkçe veya İngilizce olarak sadece DergiPark üzerinden yapılan çevrimiçi (online) başvuruları kabul etmektedir ve herhangi bir başvuru veya işlem ücreti talep etmemektedir.

## Amaç

Ağrı Tıp Fakültesi Dergisi olarak öncelikli amacımız ülkemizde bilimsel standartlara uygun, bilimsel değeri yüksek, kaliteli ve güncel yayınlar içeren ve kolay erişilebilir bir yayın organı oluşturmaktır. Ülkemiz için öncelikli olarak belirlediğimiz hedeflere ulaşıldıktan sonra, öncelikli amacımızdan taviz vermeden, Ağrı Tıp Fakültesi Dergisi'nin tüm dünyada görünürlüğünü ve kullanılırlığını arttırmayı amaçlamaktayız.

## Kapsam

Ağrı Tıp Fakültesi Dergisi tıp bilimlerindeki (temel tıp bilimleri, dahili tıp bilimleri ve cerrahi tıp bilimleri) tüm etik yönergelere uygun olarak hazırlanmış klinik ve deneysel araştırma makalelerini, olgu sunumlarını, derleme makaleleri, teknik notlar ve editöre mektupları yayınlamaktadır.

## Değerlendirme İlkeleri

Ağrı Tıp Fakültesi Dergisi bağımsız çift kör hakem ilkesine dayanan, açık erişimli ve çevrimiçi bir yayın organıdır. Ağrı Tıp Fakültesi Dergisi daha önce yayınlanmamış veya başka bir yerde yayınlanmak üzere gönderilmemiş orijinal yayınları yayımlayarak tıp literatürüne katkı sağlamayı amaçlamaktadır. Ağrı Tıp Fakültesi Dergisi'ne, kabul edilme sürecindeki değerlendirilmelerde aranan temel özellik 'bilim literatürüne katkı ve özgünlüktür'.

Ağrı Tıp Fakültesi Dergisi 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) uygun olarak yayınlanmaktadır. Ağrı Tıp Fakültesi Dergisi'nin editoryal ve yayın süreçleri, Uluslararası Medikal Dergisi Editörleri Komitesi (International Committee of Medical Journal Editors) (ICMJE), Dünya Tıbbi Editörler Birliği (World Association of Medical Editors) (WAME), Bilim Editörleri Konseyi (Council of Science Editors) (CSE), Yayın Etiği Komitesi (Committee on Publication Ethics) (COPE), Avrupa Bilim Editörleri Derneği (European Association of Science Editors) (EASE) ve Ulusal Bilgi Standartları Örgütü (National Information Standards Organization) (NISO) yönergelerine uygun olarak şekillendirilmiştir.

Ağrı Tıp Fakültesi Dergisi'ne gönderilen yazılarda tüm yazarların bilimsel katkıları bulunmalıdır. Yazar olarak belirlenen isimler çalışmayı planlamalı veya yapmalı veya yazıyı yazmalı veya revize etmelidir. Ayrıca tüm yazarlar makalenin son halini kabul etmelidir.

Makalelerin tıbbi ve etik sorumluluğu yazarlara; telif hakları Ağrı Tıp Fakültesi Dergisi'ne aittir. Makalenin içeriğinde bulunan tüm metin, şekil ve kaynaklardan yazarlar sorumlu olup; kullanılan şekil, tablo veya başka resimlerin telif izinlerinin temini yazarların görevidir. Bahsedilen konular nedeniyle dergiye yapılacak hak taleplerinden yazarlar sorumludur. Çalışmada herhangi bir finansal destek ya da materyal desteği alındıysa, yazarlar tarafından ilişkinin türü de açıkça belirtilerek (danışman, başka anlaşmalar) beyan edilmelidir. Ayrıca herhangi bir ticari ürün, ilaç, ilaç şirketiyle bir ilişki varsa bu durum açıkça belirtilmelidir. Herhangi bir destek veya ilişki mevcut değilse bu durum da başvuru sırasında ve başlık sayfasında açıkça belirtilmelidir.

Yayınlanan makalelerdeki veriler, fikirler ve ifadelerden yazarlar sorumludur ve editörler, editör kurulu, yayıncı ve Ağrı Tıp Fakültesi Dergisi bu konularda herhangi bir sorumluluk kabul etmemektedir.

Tüm makaleler Telif Hakkı Devir Formu eşliğinde gönderilmelidir. Bu form tüm yazarlar tarafından başlık sayfasındaki isim sırasına göre imzalanmalıdır. Bu formu imzalayarak yazarlar, makalenin ve verilerin daha önce başka bir yere gönderilmediği veya başka bir yerde yayınlanmadığını, yazarların makaleye bilimsel katkısının olduğunu ve sorumlulukları kabul ettiklerini beyan etmiş olacaklardır. Telif Hakkı Devir Formu ile yüklenilmeyen yazılar değerlendirmeye alınmayacaktır.

## Contents/ İçindekiler

Editorial/ Editöryal

**Beyond glycemic control: The pleiotropic potential of SGLT-2 inhibitors**

*Glisemik kontrolün ötesinde: SGLT-2 inhibitörlerinin pleiotropik potansiyeli*

Selma Sezen……99

Research Article/ Araştırma Makalesi

**Clinicopathological and prognostic outcomes of endometriosis-associated ovarian cancer**

*Endometriozisle ilişkili over kanserinin klinikopatolojik ve prognostik sonuçları*

Esra Keles, Sahra Sultan Kara, Sadun Sucu……102

Research Article/ Araştırma Makalesi

**University students' sustainable and healthy eating behaviors, along with their environmental literacy: A cross-sectional study**

*Üniversite öğrencilerinin sürdürülebilir ve sağlıklı beslenme davranışları ile çevre okuryazarlığı: Kesitsel bir çalışma*

Arda Borlu, Hasan Durmuş, Neslihan Öner……107

Research Article/ Araştırma Makalesi

**Violence against emergency department healthcare workers: A cross-sectional evaluation of exposure, perceived causes, and outcomes**

*Acil servis sağlık çalışanlarına yönelik şiddet: Maruziyet, algılanan nedenler ve sonuçların kesitsel değerlendirmesi*

Erman Aydoğan, Abuzer Coşkun, Burak Demirci, Burak Akın, Selman Gündoğan……115

Research Article/ Araştırma Makalesi

**Comparison of treatment options based on X-ray and computed tomography findings in patients presenting to the emergency department with foot and ankle trauma**

*Acil servise başvuran ayak ve ayak bileği travmalı hastalarda tedavi seçeneklerinin X-ray ve bilgisayarlı tomografi bulgularına göre karşılaştırılması*

Burcu Özen Karabulut, Mehmet Reşit Öncü……122

Case Report/ Olgu Sunumu

**Intracranial lipoma detected incidentally after trauma: A case report**

*Travma sonrası rastlantısal tespit edilen intrakraniyal lipom: Olgu sunumu*

Yener Çakır, Enes Koç, Mualla Özsöz, Hakan Ak ……130

Case Report/ Olgu Sunumu

**Severe serotonin syndrome due to high-dose venlafaxine: A rare case successfully managed with chlorpromazine**

*Yüksek doz venlafaksine bağlı şiddetli serotonin sendromu: Klorpromazin ile başarıyla yönetilen nadir bir olgu*

Mehmet Batuhan Duman, Hüsnü Serdar Kızıltunç……134

Review Article/ Derleme Makalesi

**The effect of melatonin on breast cancer treatment**

*Meme kanseri tedavisinde melatoninin etkisi*

Derya Şimşekli..……...……..…….139

Review Article/ Derleme Makalesi

**$VEGF_{165}a$ and $VEGF_{165}b$: Molecular effects of opposing isoforms in angiogenesis**

*$VEGF_{165}a$ ve $VEGF_{165}b$: Anjiyogenezde zıt izoformların moleküler etkileri*

Funda Çimen Açıkgül, Seçil Nazife Parlak……..…….147

Letter to Editor/ Editöre Mektup

**An evaluation of child and adolescent mental health services in rural areas of Turkey**

*Türkiye'de kırsal bölgelerde çocuk ve ergen ruh sağlığı hizmetleri üzerine bir değerlendirme*

Ozan Kayar..…….……..……..…….156

Letter to Editor/ Editöre Mektup

**Chronic spontaneous urticaria: Current approaches and the importance of awareness**

*Kronik spontan ürtiker: Güncel yaklaşımlar ve farkındalığın önemi*

Melek Cihanbeylerden….…….……...……...158

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):99-101*
*e-ISSN: 2980-0978*

***Editorial/ Editöryal***
***DOI:10.61845/agrimedical.1811202***

# Beyond glycemic control: The pleiotropic potential of SGLT-2 inhibitors

## Glisemik kontrolün ötesinde: SGLT-2 inhibitörlerinin pleiotropik potansiyeli

Selma Sezen[1]*

[1] *Department of Medical Pharmacology, Faculty of Medicine, Agri Ibrahim Cecen University, Agri, Turkey*

*0000-0001-6575-6149*
*Sorumlu Yazar: Selma Sezen*
*e-mail: selma-sezen@hotmail.com*
*ssezen@agri.edu.tr*

Gönderilme Tarihi: 26/10/2025
Kabul Tarihi: 27/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Sezen S. Beyond glycemic control: The pleiotropic potential of SGLT-2 inhibitors. Ağrı Med J. 2025; 3(3): 99-101.

SGLT inhibitors (SGLTi), used by a large number of patients worldwide, are now regarded by researchers as having pharmacological potential beyond glycemic control due to their pleiotropic effects. In humans, cellular transport of glucose is mediated by glucose transporters (GLUTs). These are divided into two groups: Sodium-glucose co-transporters (SGLT), which actively transport sodium-dependent glucose, and GLUTs, which operate on the principle of facilitated diffusion. GLUTs, which are divided into three subfamilies, are present in all body cells to facilitate the transport of glucose into cells (1, 2). SGLTs, on the other hand, have been identified in many different tissues, including the kidneys, human umbilical cord cells, coronary arteries and vascular smooth muscle cells, brain, thyroid, and uterus. Although many isoforms of SGLTs have been identified, the most commonly known isoforms are SGLT-1 and SGLT-2 (3). Selecting a receptor group present in numerous tissues as a therapeutic target may seem concerning; however, fortunately, the distribution of these receptors varies across tissues.

When the historical development of SGLTi is examined, this time the story begins not with the apple, but with the bark of the apple tree. Although phlorizin, isolated from the bark of apple trees by French chemists, was proposed for the treatment of malaria, fever, and certain infectious diseases, experiments revealed that it caused glucosuria. Strikingly, it was proposed as an experimental animal model of diabetes because symptoms characteristic of diabetic patients, such as glucosuria, polyuria, and weight loss, were observed (4). In the 1900s, phlorizin, which was used to induce diabetes in animals, was later understood through concomitant studies following the characterization of SGLTs to be able to regulate fasting and postprandial glucose levels (5-7). So what happened to phlorizin? After a series of experiments, it was determined to be a potent inhibitor of both SGLT-1 and SGLT-2. Administration of 15–20 g of phlorizin to individuals with diabetes has been reported to cause glucosuria. However, subsequent studies showed that phlorizin's low oral bioavailability, its causing gastrointestinal complaints, and its being an SGLT-1i prevented it from becoming a drug candidate (8). Nevertheless, important data had been recorded, and phlorizin-based analogs began to be synthesized. First, O-glucoside analogs of phlorizin were synthesized, but none were successful. Subsequently, C-glucoside derivatives of phlorizin began to be investigated, and finally, in 2008, dapagliflozin was developed. The first gliflozin to enter clinical use is dapagliflozin. Dapagliflozin received its first approval for clinical use from the EMA in 2012 and from the FDA in 2014. This approval was for achieving glycemic control, in conjunction with diet and exercise, in adult patients diagnosed with Type 2 Diabetes Mellitus (however, this would not be the only approval obtained from the FDA). Shortly thereafter, empagliflozin and canagliflozin also took their place among the gliflozins (8-10).

It was recognized during the testing of phlorizin that SGLT-2i act through the kidney (4). In subsequent studies, their glucose-lowering effects in the kidneys were demonstrated (11). One of the most important clinical risks of developing a drug that aims to reduce blood glucose is hypoglycemia. However, the risk of hypoglycemia associated with SGLT-2i is low. In the kidney of a healthy individual, glucose filtered from the glomerulus enters the tubules and is reabsorbed by SGLT-1 and SGLT-2. SGLT-2 is more densely expressed in the S1 and S2 segments of the renal proximal tubule. It is responsible for a substantial portion of sodium and glucose reabsorption in the renal tubules. By contrast, SGLT-1 is a low-capacity glucose transporter and is present in tissues other than the kidney as well. Thus, even when SGLT-2 is inhibited, it enables a small amount of glucose to be reabsorbed from the renal tubules, thereby reducing the risk of hypoglycemia (12). Several hypotheses have been proposed regarding the renoprotective effects of SGLT-2i. The most notable include activation of tubuloglomerular feedback, reduction of proximal tubular metabolic stress, reduction of hypoxia, reduction of mitochondrial injury, reduction of hyperglycemia-driven inflammation, and reduction of oxidative stress (13). Numerous clinical reports indicate that SGLT-2i reduces the risk of kidney failure and other major renal outcomes by 30–40% not only in patients with diabetes but also in individuals with chronic kidney disease (CKD) without diabetes (14). In a randomized, multicenter clinical trial with 4,289 participants, it was reported that, compared with placebo, those receiving

dapagliflozin had a lower risk of death due to kidney disease or cardiovascular causes. In this study centered on patients with CKD, lower risks of hospitalization related to cardiovascular causes and lower mortality rates were reported in those treated with dapagliflozin (15). The effects of SGLT-2i in combination with other drugs or in individuals with multiple chronic conditions also remain a subject of interest. In a study investigating the effects of 12-week empagliflozin therapy, in addition to angiotensin-converting enzyme inhibitors, on the molecular dynamics of the renin angiotensin system, it was determined that it induced activation of the alternative renin angiotensin system axis in patients with CKD and diabetes (16). In another study involving 507 intensive care patients with acute organ dysfunction, the hypothesis was proposed that dapagliflozin therapy might reduce composite outcomes such as in-hospital mortality, initiation of renal replacement therapy, and length of stay in the intensive care unit. However, the investigators reported that dapagliflozin did not improve clinical outcomes in critically ill patients (17).

Since SGLT-2i has found a place in clinical use, research has focused, in addition to diabetic control, on their protective effects on both the kidney and the cardiovascular system. What actually enabled this to take shape rapidly was the FDA's 2008 guidance, "Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (18). Because SGLT-2i were in the development phase, cardiovascular risks were also evaluated during the studies, and a substantial amount of data was recorded. After they began to be used in the treatment of type 2 diabetes, the diversity of data increased. Zinman and colleagues, in a randomized, double-blind study involving 7,028 patients with type 2 diabetes and lasting approximately three years, reported that once-daily empagliflozin (10 mg or 25 mg) significantly reduced the primary composite cardiovascular endpoint and all-cause mortality compared with placebo (19). In a study including 309,056 patients across six countries, treatment with SGLT-2i in patients with type 2 diabetes and atherosclerotic cardiovascular disease was associated with a lower risk of cardiovascular death and hospitalization for heart failure compared with other glucose-lowering drugs (20). In a study involving 10,142 patients with type 2 diabetes and high cardiovascular risk, canagliflozin therapy was observed to provide a significant reduction in rates of cardiovascular death or hospitalization for heart failure. In this study, regarding the provision of effective outcomes by 100 mg or 300 mg canagliflozin therapy versus placebo, the extent to which treatment duration had an effect is quite striking, debatable, yet inspiring, because the patients were followed for approximately 188 weeks (21).

Owing to its success and mechanism in diabetes treatment, its effects on obesity and metabolic syndrome have also been investigated. In a randomized clinical study involving 24 individuals diagnosed with prediabetes who were not receiving pharmacological therapy, it was determined that after 12 weeks of 10 mg dapagliflozin treatment, patients' body weight, body mass index, waist circumference, fasting blood glucose, and uric acid decreased (22). In overweight and obese women with polycystic ovary syndrome, it was recorded that combination therapy with canagliflozin and metformin, compared with the group receiving metformin monotherapy, resulted in significantly lower total testosterone, area under the curve for glucose, and area under the curve for insulin. On the other hand, they reported that no significant difference was found between the two groups in improving menstrual frequency, weight control, hyperandrogenemia, and alleviating insulin resistance. At the end of this 12-week study, the emphasis in the article is quite valuable: we do not yet fully know the long-term outcomes of SGLT-2 inhibition (23). It has long been known that metabolic alterations affect cellular genomic stability. It has been proposed that the regulation of cellular energy by antidiabetic drugs may, in relation to this, modify the direct and indirect epigenetic effects caused by oncometabolites (24). Indeed, it has been reported that SGLT-2 expression is increased in various cancer types such as prostate, pancreatic, lung, and cervical cancer. In a preclinical study, canagliflozin was shown to significantly suppress the growth of pancreatic cancer cells in vitro and in vivo (25). The results of a meta-analysis suggested that SGLT-2i may reduce the likelihood of anthracycline-induced cardiac problems (26). Meta-analyses report that they are an effective and safe tool for improving the prognosis of patients with cancer and diabetes, and they are in agreement that further research is needed (27,28). The number and diversity of studies on SGLT-2i are increasing by the day. In addition to their beneficial effects in patients, SGLT-2i, which are generally considered safe, are closely monitored for adverse events. We know that SGLT isoforms are present at varying levels across different tissues in the body and that SGLT-2i such as dapagliflozin can cross the blood–brain barrier. In this context, a comprehensive network meta-analysis has proposed that dapagliflozin exerts a novel and specific prophylactic effect against Parkinson's disease (29). In conclusion, this story that began with the bark of the apple tree speaks volumes about the discovery of new drug molecules and the potential to expand the indications of established drugs, and it continues to be rewritten every day.

**Ethical Approval**
Ethics committee approval is not required for this article.

**Conflict of Interest**
The author is the Editor-in-Chief of this journal and was not involved in the peer review or decision-making process for this editorial.

**Financial Disclosure**
No financial support was received for the study.

**Authors' Contributions**
SS: Conceptualization, literature review, Writing-original draft, Writing-review & editing

**Data Sharing Statement**
Not available

## REFERENCES


1. Sano R, Shinozaki Y, Ohta T. Sodium-glucose cotransporters: functional properties and pharmaceutical potential. J Diabetes Investig. 2020;11(4):770–82.
2. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet. 2021;398(10296):262–76.
3. Bendotti G, Montefusco L, Pastore I, Lazzaroni E, Lunati ME, Fiorina P. The anti-inflammatory and immunological properties of SGLT-2 inhibitors. J Endocrinol Invest. 2023;46(12):2445–52.
4. White JR. Apple trees to sodium glucose co-transporter inhibitors: a review of SGLT2 inhibition. Clin Diabetes. 2010;28(1):5–10.
5. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79(5):1510–5.
6. Blondel O, Bailbe D, Portha B. Insulin resistance in rats with non-insulin-dependent diabetes induced by neonatal (5 days) streptozotocin: evidence for reversal following phlorizin treatment. Metabolism. 1990;39(8):787–93.
7. Brichard SM, Henquin JC, Girard J. Phlorizin treatment of diabetic rats partially reverses the abnormal expression of genes involved in hepatic glucose metabolism. Diabetologia. 1993;36:292–8.
8. Helvacı Ö, Helvacı B. A story of serendipities: from phlorizin to gliflozins. Exp Clin Transplant. 2023;21(Suppl 2):105–8.
9. Balakumar P, Sundram K, Dhanaraj SA. Dapagliflozin: glucuretic action and beyond. Pharmacol Res. 2014;82:34–9.
10. Moradi-Marjaneh R, Paseban M, Sahebkar A. Natural products with SGLT2 inhibitory activity: possibilities of application for the treatment of diabetes. Phytother Res. 2019;33(10):2518–30.
11. Chen X, Wang J, Lin Y, Liu Y, Zhou T. Signaling pathways of podocyte injury in diabetic kidney disease and the effect of sodium-glucose cotransporter 2 inhibitors. Cells. 2022;11(23):3913.
12. Dai ZC, Chen JX, Zou R, Liang XB, Tang JX, Yao CW. Role and mechanisms of SGLT-2 inhibitors in the treatment of diabetic kidney disease. Front Immunol. 2023;14:1213473.
13. Wanner C, Nangaku M, Kraus BJ, Zinman B, Mattheus M, Hantel S, et al. How do SGLT2 inhibitors protect the kidney? A mediation analysis of the EMPA-REG OUTCOME trial. Nephrol Dial Transplant. 2024;39(9):1504–13.
14. Upadhyay A. SGLT2 inhibitors and kidney protection: mechanisms beyond tubuloglomerular feedback. Kidney360. 2024;5(5):771–82.
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
16. Antlanger M, Domenig O, Kaltenecker CC, et al. Combined sodium glucose co-transporter-2 inhibitor and angiotensin-converting enzyme inhibition upregulates the renin-angiotensin system in chronic kidney disease with type 2 diabetes: results of a randomized, double-blind, placebo-controlled exploratory trial. Diabetes Obes Metab. 2022;24(5):816–26.
17. Tavares CAM, Azevedo LCP, Rea-Neto Á, et al. Dapagliflozin for critically ill patients with acute organ dysfunction: the DEFENDER randomized clinical trial. JAMA. 2024;332(5):401–11.
18. U.S. Food and Drug Administration. Guidance for industry on diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes; availability. Fed Regist. 2008;73.
19. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
20. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study. Circulation. 2017;136(3):249–59.
21. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation. 2018;138(5):458–68.
22. Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E. Effect of dapagliflozin on insulin secretion and insulin sensitivity in patients with prediabetes. Exp Clin Endocrinol Diabetes. 2020;128(8):506–11.
23. Zhang J, Xing C, Cheng X, He B. Canagliflozin combined with metformin versus metformin monotherapy for endocrine and metabolic profiles in overweight and obese women with polycystic ovary syndrome: a randomized controlled trial. Front Endocrinol (Lausanne). 2022;13:1003238.
24. Benedetti R, Benincasa G, Glass K, et al. Effects of novel SGLT2 inhibitors on cancer incidence in hyperglycemic patients: a meta-analysis of randomized clinical trials. Pharmacol Res. 2022;175:106039.
25. Ren D, Sun Y, Zhang D, et al. SGLT2 promotes pancreatic cancer progression by activating the Hippo signaling pathway via the hnRNPK-YAP1 axis. Cancer Lett. 2021;519:277–88.
26. Mohsin S, Hasan M, Sheikh ZM, et al. Efficacy of SGLT2 inhibitors for anthracycline-induced cardiotoxicity: a meta-analysis in cancer patients. Future Cardiol. 2024;20(7–8):395–407.
27. Fan G, Zuo H, Lin L, Xu C, Yan R. The efficacy and safety of sodium glucose cotransporter 2 inhibitors for patients with anticancer therapy: a meta-analysis of cohort studies. Glob Heart. 2025;20(1):53.
28. Copur S, Yildiz AB, Covic A, Kanbay M. Is there any robust evidence showing that SGLT2 inhibitor predisposes to cancer? Eur J Clin Invest. 2024;54(2):e14131.
29. Tseng PT, Zeng BY, Hsu CW, et al. The pharmacodynamics-based prophylactic benefits of GLP-1 receptor agonists and SGLT2 inhibitors on neurodegenerative diseases: evidence from a network meta-analysis. BMC Med. 2025;23(1):197.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):102-106*
*e-ISSN: 2980-0978*

***Research Article/ Araştırma Makalesi***
***DOI: 10.61845/agrimedical.1674787***

# Clinicopathological and prognostic outcomes of endometriosis-associated ovarian cancer

## Endometriozisle ilişkili over kanserinin klinikopatolojik ve prognostik sonuçları

Esra Keles[1*], Sahra Sultan Kara[2], Sadun Sucu[3]

[1]*Department of Gynecologic Oncology, University of Health Sciences, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye*
[2] *Department of Obstetrics and Gynecology, University of Health Sciences, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye*
[3]*Department of Obstetrics and Gynecology, Division of Perinatology, Ankara Etlik City Hospital, Ankara, Türkiye*

*0000-0001-8099-8883
*0000-0001-5122-829X
*0000-0003-3758-0136

**Sorumlu Yazar:*
*Esra Keles*
*Department of Gynecologic Oncology, University of Health Sciences, Kartal Lütfi Kırdar City Hospital, Istanbul, Türkiye*
*e-mail: dresrakeles@gmail.com*

Gönderilme Tarihi: 12/04/2025
Kabul Tarihi: 12/09/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Keles E, Kara SS, Sucu S. Clinicopathological and prognostic outcomes of endometriosis-associated ovarian cancer. Ağrı Med J. 2025; 3(3):102-106.

**ABSTRACT**

**Aim:** The aim of this study is to investigate the clinicopathological characteristics and prognostic value of endometriosis in patients with ovarian cancer.
**Materials and Methods:** A retrospective analysis was performed on 273 patients with ovarian carcinoma between January 2013 and December 2023. Patients were stratified into endometriosis-associated ovarian carcinoma (EAOC) and non-endometriosis-associated ovarian carcinoma (non-EAOC). Clinicopathological variables, including age, menopausal status, tumor size and volume, FIGO stage, histological subtype, serum tumor markers, and survival outcomes, were evaluated.
**Results:** EAOC patients were significantly younger than non-EAOC patients (respectively 51 ± 11.4 years, 59 ± 11.2 years; p = 0.002). EAOC cases were more frequently diagnosed at FIGO stage I than non-EAOC cases (p = 0.001), whereas FIGO stage (III) disease was more prevalent in the non-EAOC group (p = 0.007). No significant differences were observed in CA-125 levels between groups. CA 19-9 levels were elevated in the EAOC group (p = 0.012). Recurrence rates and survival outcomes did not differ significantly between the groups.
**Conclusion:** EAOC cases were diagnosed at a younger age and presented at an earlier FIGO stage and had elevated CA 19-9 levels. However, survival outcomes did not significantly differ between EAOC and non-EAOC groups.

**Keywords:** *Endometriosis, Ovarian neoplasms, Endometriosis-associated ovarian cancer, Survival outcome*

**ÖZ**

**Amaç**: Bu çalışmanın amacı, over kanseri olan hastalarda endometriozisin klinikopatolojik özelliklerini ve prognostik değerini araştırmaktır.
**Gereçler ve Yöntemler:** Ocak 2013 ile Aralık 2023 tarihleri arasında over karsinomu tanısı alan 273 hasta retrospektif olarak analiz edildi. Hastalar, endometriozisle ilişkili over karsinomu (EAOC) ve endometriozisle ilişkili olmayan over karsinomu (non-EAOC) olmak üzere iki gruba ayrıldı. Yaş, menopoz durumu, tümör boyutu ve hacmi, FIGO evresi, histolojik alt tip, serum tümör belirteçleri ve sağkalım sonuçları gibi klinikopatolojik değişkenler değerlendirildi.
**Bulgular:** EAOC hastaları, non-EAOC hastalarına göre anlamlı düzeyde daha gençti (sırasıyla 51 ± 11,4 yıl, 59 ± 11,2 yıl; p = 0,002). EAOC grubunda FIGO evre I'de tanı alma oranı daha yüksekti (p = 0,001), buna karşılık non-EAOC grubunda evre III hastalık daha yaygındı (p = 0,007). Gruplar arasında CA-125 düzeylerinde anlamlı fark saptanmazken, CA 19-9 düzeyleri EAOC grubunda daha yüksekti (p = 0,012). Nüks oranları ve sağkalım sonuçları gruplar arasında anlamlı fark göstermedi.
**Sonuç:** EAOC hastaları daha genç yaşta ve daha erken FIGO evresinde tanı almakta ve CA 19-9 düzeyleri daha yüksek bulunmaktaydı. Ancak, EAOC ve non-EAOC grupları arasında sağkalım sonuçları açısından anlamlı fark gözlenmedi.

**Anahtar Kelimeler**: *Endometriozis, Over neoplazileri, Endometriozisle ilişkili over kanseri, Sağkalım sonucu*

## INTRODUCTION

Endometriosis, characterized by the presence of endometrial-like tissue in locations outside the uterine cavity, has been associated with the pathogenesis of epithelial ovarian cancer (EOC). This association was first documented by Sampson in 1925, who reported malignant transformation in endometriotic lesions (1). A substantial body of epidemiological evidence consistently demonstrates an elevated ovarian cancer risk in patients with endometriosis, with transformation rates estimated at 1–2.5% and relative risks ranging from 1.3 to 1.9 (2). This association manifests as either malignant progression of endometriosis to invasive carcinoma or the coexistence of both entities, termed endometriosis-associated ovarian cancer (EAOC) (3). Despite refinements to Sampson's criteria, the histopathological classification of EAOC remains contentious (4).

Emerging evidence suggests that EAOC may represent a distinct clinicopathological subset, with patients often presenting at younger ages, earlier FIGO stages, and exhibiting improved survival outcomes compared to non-EAOC (5,6). While some studies have indicated a more favorable prognosis for EAOC compared to non-EAOC, others have not reported a significant survival advantage (7,8). Consequently, this study aimed to investigate the clinicopathological characteristics and prognostic value of endometriosis in patients with ovarian cancer.

## MATERIALS AND METHOD

This retrospective study analyzed 273 patients with histologically confirmed EOC treated at a tertiary gynecologic oncology referral center from January 2013 to December 2023. Ethical approval was obtained from the Research Ethics Committee of the hospital (approval number: 2024/010.99/6/2). As this was a retrospective study, patient consent was not a requirement.

Patients were stratified into EAOC and non-EAOC using Sampson-Scott criteria, which require (i) the coexistence of carcinoma and endometriosis within the same ovary, (ii) the presence of similar histological patterns, (iii) exclusion of metastatic neoplasms, and (iv) histopathological evidence of malignant transition (1,4). Patients with concurrent non-EOC malignancies were excluded.

Overall survival (OS) was defined as the interval from histologic diagnosis to all-cause mortality or censoring at the last follow-up. Progression-free survival (PFS) was calculated from diagnosis to radiologic or pathologic recurrence, disease progression per RECIST 1.1 criteria, or censoring (9). Survival data were extracted from institutional records and national death registries. Loss to follow-up was defined as ≥12 months without clinical contact.

Sociodemographic, clinicopathologic variables were abstracted from electronic health records. Pathologic parameters included maximal tumor diameter, laterality (unilateral/bilateral), FIGO stage (2014 criteria), and histologic subtype (10). Clinical variables comprised age at diagnosis, menopausal status, and preoperative serum CA-125 and CA 19-9 (IU/mL) levels.

### *Statistical Analysis*

Statistical analyses were performed using R version 4.2.1 with RStudio. Age, which demonstrated a normal distribution, was compared between the EAOC and non-EAOC using an independent two-sample Student's t-test. Non-normally distributed variables—including maximum tumor diameter, tumor volume, CA-125, and CA 19-9—were analyzed via the Mann-Whitney U test. Categorical variables, including menopausal status, FIGO stage, endometrial pathology, and chemotherapy/radiotherapy status, were analyzed using Pearson's chi-square test. In instances where expected cell counts were below 5, Fisher's exact test was implemented. Survival outcomes were evaluated using Kaplan-Meier curves followed by log-rank tests. The statistical significance was set at $p < 0.05$.

## RESULTS

Among 273 ovarian cancer cases, 22 (7.9%) met histopathological criteria for EAOC, with the remaining 251 (92.1%) constituting the non-EAOC. Patients in the EAOC group were significantly younger than those in the non-EAOC group (51 ± 11.4 years vs. 59 ± 11.2 years; $p = 0.002$). While the proportion of premenopausal women was higher in the EAOC group, the difference did not reach statistical significance (40.9% vs. 20.7%; $p = 0.057$).

No significant differences were found between the EAOC and non-EAOC groups in terms of median tumor size (10 cm [IQR: 5–14] vs. 7 cm [IQR: 5–11]; $p = 0.136$) or tumor volume (178 $cm^3$ [IQR: 46–685] vs. 68 $cm^3$ [IQR: 16–283]; $p = 0.104$). Preoperative serum CA-125 levels and rates of synchronous endometrial pathology were comparable between groups ($p > 0.05$). CA 19-9 levels were significantly elevated in EAOC (median: 30 U/mL [IQR: 7–204] vs. 9 U/mL [IQR: 4–21]; $p = 0.012$). Unilateral tumor involvement was more frequent in EAOC (68.2% vs. 43.8%; $p = 0.048$), though laterality distribution (left/right/bilateral) did not differ significantly ($p = 0.075$).

EAOC patients were more frequently diagnosed at FIGO stage I (54.5% vs. 20.7%; $p = 0.001$), and whereas FIGO stage III was more prevalent in the non-EAOC group (59.4% vs. 27.3%; $p = 0.007$). Both groups demonstrated similar rates of benign endometrial lesions (EAOC: 90.9% vs. non-EAOC: 92.4%; $p = 0.681$). No significant differences in recurrence ($p = 0.82$) or mortality ($p = 0.76$) were observed (Table 1).

## DISCUSSION

The present study indicated that 7.6% of ovarian carcinoma cases were associated with endometriosis, with approximately 70% of EAOC manifesting as either clear cell or endometrioid carcinoma histology, consistent with the findings of Chul Ju et al (11). This incidence rate is lower than the 10% to 18% reported in earlier studies (12,13). The specific mechanisms that lead to the malignant transformation of endometriotic lesions are not yet fully understood. However, a hypothesis has been postulated that, in women of reproductive age, an altered immune response combined with a hormonal environment marked by estrogen

dominance and progesterone deficiency may contribute to the progression from benign endometriosis to malignant disease (14).

A mounting body of evidence indicates that EAOCs are more frequently diagnosed at earlier stages in comparison to non-EAOCs. Wang et al. documented 88.2% of EAOCs as stage I versus 15.8% of non-EAOCs, while Kumar et al. recorded 49% of EAOCs at FIGO stage I/II (5,12). A similar observation was made by Erzen et al., who reported stage I diagnoses in 67% of EAOCs compared to 27.6% of non-EAOCs (13). The findings of this study are consistent with these observations, with 54.5% of EAOCs in the study group presenting as stage I compared to 20.7% of non-EAOCs, thereby further strengthening the association between endometriosis and earlier stage malignancy.

Consistent with established evidence, EAOCs are predominantly diagnosed in younger patients and at earlier disease stages, with lower histological grades compared to non-EAOCs (16–18). A recent cohort study reinforced this pattern, revealing that EAOC patients were, on average, six years younger and 35% more likely to be premenopausal than non-EAOC patients (19). Mangili et al. similarly reported a mean diagnostic age of 55 years for EAOCs versus 62 years for non-EAOCs (20). Mirroring these trends, our cohort demonstrated a significantly younger mean age in the EAOC group (51 years) relative to non-EAOC cases (59 years), underscoring the distinct clinical profile of endometriosis-associated malignancies.

The diagnosis of EAOC relies on invasive laparoscopy with histopathological confirmation. However, the widespread application of this approach is constrained by its high cost and procedural invasiveness, underscoring the need for non-invasive alternatives. While CA125, a biomarker in ovarian cancer surveillance, exhibits high sensitivity, its low specificity and inconsistent ability to distinguish EAOC from benign endometriosis limit its clinical use (21). Most studies, including ours, found no significant differences in CA125 levels between EAOC and non-EAOC cases (22,23), though Wang et al. reported lower CA125 levels in EAOC versus non-EAOC cases (122.9 U/mL vs. 1377.5 U/mL) (5). These discrepancies highlight the need for more reliable biomarkers. Emerging evidence suggests that biomarkers such as CA19-9 show promise (24). Our study observed elevated CA19-9 levels in EAOC. While CA19-9 is not suggested as a diagnostic marker for endometriosis-associated malignancy, elevated levels warrant thorough clinical evaluation to improve risk stratification and guide management.

The extant research on EAOC has largely centered on its clinicopathological and prognostic distinctions from non-EAOC. However, many of these studies have been constrained by limited sample sizes and have yielded inconsistent findings. While some studies suggest EAOC is diagnosed at an earlier stage and confers a more favorable prognosis (25-27), others report no significant differences in clinical outcomes (28-30). Consistent with these findings, our study observed no significant differences in recurrence rates or survival outcomes between EAOC and non-EAOC, though this may be influenced by sample size and follow-up duration.

**Table 1.** Comparison of clinicopathological characteristics between ovarian cancer patients with and without endometriosis

| Variable | With Endometriosis (n=22) | Without Endometriosis (n=251) | p-value |
|---|---|---|---|
| **Age (mean ± SD) (years)** | 51 ± 11.4 | 59 ± 11.2 | 0.002 |
| **Menopausal Status** | | | |
| *Premenopausal* | 9 (40.9%) | 52 (20.7%) | 0.057 |
| *Postmenopausal* | 13 (59.1%) | 199 (79.3%) | |
| Tumor size (cm) | 10 (5-14) | 7 (5-11) | 0.136 |
| Tumor Volume ($cm^3$) | 178 (46-685) | 68 (16-283) | 0.104 |
| **CA 125 (U/mL)** | 249 (74-1517) | 547 (94-1693) | 0.262 |
| **CA 19-9 (U/mL)** | 30 (7-204) | 9 (4-21) | 0.012 |
| **Laterality of tumor** | | | |
| *Unilateral* | 15 (68.2%) | 110 (43.8%) | 0.048 |
| *Bilateral* | 7 (31.8%) | 141 (56.2%) | |
| **Tumor side** | | | |
| *Left Ovary* | 7 (31.8%) | 52 (20.7%) | 0.075 |
| *Right Ovary* | 8 (36.4%) | 56 (22.3%) | |
| *Both Ovaries* | 7 (31.8%) | 143 (57.0%) | |
| **Tumor Stage** | | | |
| *Stage I* | 12 (54.5%) | 52 (20.7%) | 0.001 |
| *Stage II* | 3 (13.6%) | 32 (12.7%) | N/A |
| *Stage III* | 6 (27.3%) | 149 (59.4%) | 0.007 |
| *Stage IV* | 1 (4.5%) | 18 (7.2%) | N/A |
| **Endometrial Pathology** | | | |
| *Benign* | 20 (90.9%) | 232 (92.4%) | 0.681 |
| *Malignant* | 2 (9.1%) | 19 (7.6%) | |
| **Concurrent Endometrial Pathologies** | | | |
| *Benign* | 20 (90.9%) | 229 (91.2%) | 0.706 |
| *Endometrioid Carcinoma* | 1 (4.5) | 4 (1.6) | |
| *Atypical Hyperplasia* | 1 (4.5) | 4 (1.6) | |
| *Serous Carcinoma* | 0 (0) | 11 (4.4) | |
| *Clear Cell Carcinoma* | 0 (0) | 1 (0.4) | |
| *Carcinosarcoma* | 0 (0) | 2 (0.8) | |
| **Recurrence** | 9 (40.9%) | 112 (44.6%) | 0.911 |
| **Mortality** | 5 (22.7%) | 116 (46.2%) | 0.057 |
| **Chemotherapy** | 21 (95.5%) | 205 (81.7%) | 0.140 |
| **Radiotherapy** | 2 (9.1%) | 9 (3.6%) | 0.219 |

Future research involving larger, multicenter cohorts and extended follow-up durations is essential to deepen our understanding of the pathophysiology of EAOC, improve diagnostic methods, and explore tailored treatment strategies.

This study presents several limitations inherent to its retrospective design, reliance on single-center data, and the small sample size of patients with EAOC, which consequently may affect the generalizability of the findings. The absence of molecular and genetic analyses further constrains our understanding of the mechanistic pathways underlying the malignant transformation associated with endometriosis. Additionally, the incompleteness of clinical data regarding hormonal therapies is a significant shortcoming. Future investigations should aim to incorporate comprehensive molecular profiling to clarify the pathogenesis of EAOC, identify novel biomarkers for early detection, and assess personalized therapeutic modalities, including targeted therapies and immunotherapies, to enhance clinical outcomes.

## CONCLUSION

These findings of the study indicated that patients with EAOC are diagnosed at a younger age and present with an earlier FIGO stage compared to those with non-EAOC. However, survival outcomes did not differ significantly between the groups.

**Ethical Approval**
Ethical approval for this study was provided by the Research Ethics Committee of the Kartal City Hospital (Approval: 2024/010.99/6/2, 26.07.2024). The database management in accordance with privacy legislation and the presented study in accordance with the ethical principle of the Declaration of Helsinki).

**Conflict of Interest**
No potential conflict of interest was reported by the author(s).

**Financial Disclosure**
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors' Contributions**
All authors attest they meet the International Committee for Medical Journal Editors (ICMJE) criteria for authorship. EK: Conceptualization, Data Curation, Writing – Original Draft, Writing –Review & Editing. SSK: Data Curation, Conceptualization, Writing – Original Draft, Writing – Review & Editing. SS: Formal analysis, Writing – Original Draft, Writing –Review & Editing.

All authors participated in the revision of the manuscript and revised the manuscript critically for important intellectual content. All of the authors have read and approved the final version of this manuscript.

**Data Sharing Statement**
The dataset used and analyzed in the study is available from the corresponding author upon reasonable request.

## REFERENCES

1. Sampson J. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. Arch Surg. 1925;10:1–72.
2. Giannella L, Marconi C, Di Giuseppe J, Delli Carpini G, Fichera M, Grelloni C, et al. Malignant Transformation of Postmenopausal Endometriosis: A Systematic Review of the Literature. Cancers. 2021;13(16):4026.
3. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. F1000Research. 2019;8.
4. Scott RB. Malignant changes in endometriosis. Obstet Gynecol. 1953;2:283.
5. Wang S, Qiu L, Lang JH, Shen K, Yang JX, Huang HF, et al. Clinical analysis of ovarian epithelial carcinoma with coexisting pelvic endometriosis. Am J Obstet Gynecol. 2013;208(5):413.e1-5.
6. Kondi-Pafiti A, Papakonstantinou E, Lavazzo C, Grigoriadis C, Salakos N, Gregoriou O. Clinicopathological characteristics of ovarian carcinomas associated with endometriosis. Arch Gynecol Obstet. 2012;285:479–83.
7. Noli S, Cipriani S, Scarfone G, Villa A, Grossi E, Monti E, et al. Long term survival of ovarian endometriosis associated clear cell and endometrioid ovarian cancers. Int J Gynecol Cancer. 2013;23(2):244-8.
8. Orezzoli JP, Russell AH, Oliva E, Del Carmen MG, Eichhorn J, Fuller AF. Prognostic implication of endometriosis in clear cell carcinoma of the ovary. Gynecol Oncol. 2008;110:336–44.
9. Bogani G, Matteucci L, Tamberi S, Ditto A, Sabatucci I, Murgia F, et al. RECIST 1.1 criteria predict recurrence-free survival in advanced ovarian cancer submitted to neoadjuvant chemotherapy. Eur J Obstet Gynecol Reprod Biol. 2019;237:93-9.
10. Prat J; FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26(2):87-9.
11. Ju UC, Kang WD, Kim SM. The effect of concurrent endometriosis on the prognosis of women with ovarian clear cell or endometrioid carcinoma. Int J Gynaecol Obstet. 2019;146(2):177-83.
12. Kumar S, Munkarah A, Arabi H, Bandyopadhyay S, Semaan A, Hayek K, et al. Prognostic analysis of ovarian cancer associated with endometriosis. Am J Obstet Gynecol. 2011;204(1):63.e1-7.
13. Dzatic-Smilijkovic O, Vasiljevic M, Djukic M, Vugdelic R, Vugdelic J. Frequency of ovarian endometriosis in epithelial ovarian cancer patients. Clin Exp Obstet Gynecol. 2011;38:394–8.
14. Chen B, Zhao L, Yang R, Xu T. New insights about endometriosis-associated ovarian cancer: pathogenesis, risk factors, prediction and diagnosis and treatment. Front Oncol. 2024;14:1329133.
15. Erzen M, Rakar S, Klancnik B, Syrjänen K. Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct from other ovarian carcinomas as suggested by

a nested case-control study. Gynecol Oncol. 2001;83(1):100-8.
16. Davis M, Rauh-Hain JA, Andrade C, Boruta DM 2nd, Schorge JO, Horowitz NS, et al. Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. Gynecol Oncol. 2014;132(3):760-6.
17. Komiyama S, Aoki D, Tominaga E, Nobuyuki S, Udagawa Y, Nozawa S. Prognosis of Japanese patients with ovarian clear cell carcinoma associated with pelvic endometriosis: clinicopathologic evaluation. Gynecol Oncol. 1999;72(3):342–6.
18. Lim MC, Chun KC, Shin SJ, Lee IH, Lim KT, Cho CH, et al. Clinical presentation of endometrioid epithelial ovarian cancer with concurrent endometriosis: a multicenter retrospective study. Cancer Epidemiol Biomarkers Prev. 2010;19(2):398-404.
19. Pavone ME, Lyttle BM. Endometriosis and ovarian cancer: links, risks, and challenges faced. Int J Womens Health. 2015;7:663-72.
20. Mangili G, Bergamini A, Taccagni G, Gentile C, Panina P, Viganò P, et al. Unraveling the two entities of endometrioid ovarian cancer: a single center clinical experience. Gynecol Oncol. 2012;126(3):403-7.
21. Lyttle B, Bernardi L, Pavone ME. Ovarian cancer in endometriosis: clinical and molecular aspects. Minerva Ginecol. 2014;66(2):155-64.
22. Taniguchi F, Harada T, Kobayashi H, Hayashi K, Momoeda M, Terakawa N. Clinical characteristics of patients in Japan with ovarian cancer presumably arising from ovarian endometrioma. Gynecol Obstet Invest. 2014;77(2):104–10.
23. Chen B, Zhao L, Yang R, Xu T. New insights about endometriosis-associated ovarian cancer: pathogenesis, risk factors, prediction and diagnosis and treatment. Front Oncol. 2024;14:1329133.
24. Shinmura H, Yoneyama K, Harigane E, Tsunoda Y, Fukami T, Matsushima T, et al. Use of tumor markers to distinguish endometriosis-related ovarian neoplasms from ovarian endometrioma. Int J Gynecol Cancer. 2020;30(6):831–6.
25. Ren T, Wang S, Sun J, Qu JM, Xiang Y, Shen K, et al. Endometriosis is the independent prognostic factor for survival in Chinese patients with epithelial ovarian carcinoma. J Ovarian Res. 2017;10:67.
26. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Significance of ovarian endometriosis on the prognosis of ovarian clear cell carcinoma. Int J Gynecol Cancer. 2018;28(1):11–8.
27. Hermens M, van Altena AM, van der Aa M, Bulten J, van Vliet HAAM, Siebers AG, et al. Ovarian cancer prognosis in women with endometriosis: a retrospective nationwide cohort study of 32,419 women. Am J Obstet Gynecol. 2021;224(3):284.e1–e10.
28. Li Q, Sun Y, Zhang X, Wang L, Wu W, Meng C, et al. Endometriosis-associated ovarian cancer is a single entity with distinct clinicopathological characteristics. Cancer Biol Ther. 2019;20(8):1029–34.
29. Zhao T, Shao Y, Liu Y, Wang X, Guan L, Lu Y. Endometriosis does not confer improved prognosis in ovarian clear cell carcinoma: a retrospective study at a single institute. J Ovarian Res. 2018;11(1):53.
30. Wang H, Chen C, Wang D, Zhu Y, Chen P. Correlation of clinicopathological and prognostic characteristics between endometriosis-associated and primary ovarian cancer. BMC Cancer. 2023;23(1):1210.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):107-114*
*e-ISSN: 2980-0978*

***Research Article/ Araştırma Makalesi***
***DOI: 10.61845/agrimedical.1653683***

# University students' sustainable and healthy eating behaviors, along with their environmental literacy: A cross-sectional study

## Üniversite öğrencilerinin sürdürülebilir ve sağlıklı beslenme davranışları ile çevre okuryazarlığı: Kesitsel bir çalışma

Arda Borlu[1], Hasan Durmuş[1], Neslihan Öner[2*]

[1] *Erciyes University, Faculty of Medicine, Department of Public Health, Kayseri/Türkiye*
[2] *Erciyes University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Kayseri/Türkiye*

*0000-0002-1424-8037
*0000-0001-5719-1475
*0000-0001-6773-4963

**Sorumlu Yazar:*
*Neslihan Öner*
*Erciyes University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Kayseri/Türkiye*
*e-mail:*
*neslihancelik@erciyes.edu.tr*
*nescelik11@hotmail.com*

Gönderilme Tarihi: 08/03/2025
Kabul Tarihi: 04/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Borlu A, Durmuş H, Öner N. University students' sustainable and healthy eating behaviors, along with their environmental literacy: A cross-sectional study. Ağrı Med J. 2025; 3(3):107-114.

**ABSTRACT**

**Aim:** This analytical study aimed to assess the sustainable and healthy eating (SHE) behaviors and the level of environmental literacy among first-year university students.
**Materials and Methods:** The study included 959 students. Data was collected using a socio-demographic questionnaire, the SHE behaviors scale, and the Environmental Literacy for Adults (ELSA) scale. Socio-demographic characteristics were analyzed using Student's t-test, one-way ANOVA, and LSD post-hoc tests. The relationship between SHE behaviors and ELSA scores was evaluated using Pearson correlation. A p-value <0.05 was considered significant.
**Results:** Only 35.8% of students reported being familiar with sustainable nutrition, and just 29.7% could accurately define it. Female students scored higher than male students on both the Sustainable and Healthy Eating (SHE) behaviors scale and the Environmental Literacy for Adults (ELSA) scale. Additionally, students who lived with their families, lived in rural areas, followed a healthy diet, and prepared their own food had higher SHE scores. Students who knew the term "sustainable nutrition" scored significantly higher on SHE behaviors. Believers in and those concerned about climate change also had higher SHE scores. A positive and significant correlation was observed between SHE behaviors and ELSA scores.
**Conclusion:** Promoting education on sustainable and healthy eating among university students supports both personal and environmental health, contributing to achieving United Nations Sustainable Development Goals.

**Keywords:** *Environmental literacy, Students, Sustainability, Sustainable and healthy eating, Universities*

**ÖZ**

**Amaç**: Bu analitik çalışma, üniversite birinci sınıf öğrencilerinin sürdürülebilir ve sağlıklı beslenme (SHE) davranışlarını ve çevre okuryazarlıklarını değerlendirmeyi amaçlandı.
**Gereçler ve Yöntemler:** Çalışmaya 959 öğrenci dahil edildi. Veriler sosyo-demografik bir anket, SHE davranışları ölçeği ve Yetişkinler için Çevre Okuryazarlığı (ELSA) ölçeği kullanılarak toplandı. Sosyo-demografik özellikler Student's t-testi, tek yönlü ANOVA ve LSD post-hoc testleri ile analiz edildi. SHE davranışları ile ELSA puanları arasındaki ilişki Pearson korelasyonu kullanılarak değerlendirildi. P-değerinin <0.05 olması anlamlı kabul edildi.
**Bulgular:** Öğrencilerin sadece %35,8'i sürdürülebilir beslenme hakkında bilgi sahibiydi ve %29,7'si bu kavramı tanımlayabiliyordu. Kız öğrenciler hem SHE davranışlarında hem de ELSA'da erkek öğrencilerden daha yüksek puan aldı. Daha yüksek SHE puanları aile ile yaşama, kırsalda ikamet etme, sağlıklı beslenme ve gıda hazırlama ile ilişkilendirildi. "Sürdürülebilir beslenme" terimini bilen öğrenciler SHE davranışlarında anlamlı derecede daha yüksek puan aldı. İklim değişikliğine inananlar ve iklim değişikliği konusunda endişe duyanlar da daha yüksek SHE puanlarına sahipti. SHE davranışları ile ELSA puanları arasında pozitif ve anlamlı bir korelasyon gözlendi.
**Sonuç:** Üniversite öğrencileri arasında sürdürülebilir ve sağlıklı beslenme konusunda eğitimin teşvik edilmesi hem kişisel hem de çevresel sağlığı destekleyerek sürdürülebilir kalkınma hedeflerine ulaşılmasına katkıda bulunabilir.

**Anahtar Kelimeler**: *Çevre Okuryazarlığı, Öğrenciler, Sürdürülebilirlik, Sürdürülebilir ve sağlıklı beslenme, Üniversiteler*

## INTRODUCTION

Sustainable and healthy eating behaviors, together with environmental literacy, are key determinants that influence individuals' ability to lead a healthy life and contribute to the sustainability of environmental health. While nutritional behaviors play a critical role in the growth and development processes of young generations, environmental literacy includes the skills to understand, evaluate and solve environmental health problems. The interaction between these two important issues can determine not only the individual's contribution to their personal well-being, but also to the sustainability of our planet. Global population growth and the accelerating impact of increased consumption of animal-based foods on climate change have highlighted the importance of promoting sustainable and healthy eating behaviors in society (1-3). Healthy dietary choices among individuals not only ensure an enhancement in their quality of life and life expectancy but also act as a shield against non-communicable chronic diseases. While defining environmental health as a significant factor influencing human well-being (4, 5) the increasing prevalence of unsustainable food production and consumption patterns adversely affects environmental health and, consequently, human health (6). Recent scrutiny highlights that modern eating behaviors and food production systems are not sustainable for humanity's future (5, 7). Social initiatives addressing climate change have gained prominence, emphasizing the pivotal role of environmental education in enhancing knowledge and sensitivity, thereby contributing to a more sustainable and healthier society (8).

To effectively promote environmentally sustainable and healthy eating behaviors, it is crucial to understand the perspectives of university students – the educated and professional candidates of society. This understanding is essential for developing effective teaching and learning arrangements (9-11). Previous studies conducted among university students have reported insufficient knowledge levels regarding "sustainable nutrition" and its practical application in daily life (2, 12). The initial year at university often marks the first-time young adults are tasked with planning their own diets and making independent choices about what to eat. Assessing university students' knowledge levels regarding sustainable and healthy eating behaviors during this formative period is crucial, as these choices and preferences are likely to evolve into habits. This study aims to examine the sustainable and healthy eating behaviors of university students in relation to their environmental literacy.

## MATERIALS AND METHOD

### *Study sample*

This cross-sectional study was conducted with 959 first-year students of Erciyes University in the 2022-2023 academic year. Data was collected between October and December in 2022. The sample size was calculated using G*power 3.1 (13). A two-tailed hypothesis was established for the calculation of the study sample, and the minimum sample size was calculated as 782 students with a small effect size, $\alpha$=0.05, 80% power according to a bivariate correlation analysis. Considering the possibility of missing or incorrect questionnaires, it was decided to include 25% more than the minimum sample size (978 students). Further, to represent the university, the number of students of faculties providing education in different scientific fields was taken into consideration: Medicine and Pharmacy from the health field, Economics and Administrative Sciences and Theology from the social field, Engineering students from the science field were included in the study. The sample of the study was designed to include equal number of students from each scientific field (326 students from each scientific fields). Twelve students from various faculties were excluded from the study due to incomplete questionnaires (7 Medicine, 5 Pharmacy, 1 Theology and 5 Engineering). The study included only those students who volunteered, completed the questionnaire fully, and were present on the day of the survey. Students who did not provide voluntary consent, were absent on the day of data collection, or submitted incomplete or invalid questionnaires were excluded from the study.

### *Ethical procedure*

Ethics committee approval was obtained for this study from Erciyes University Ethics Committee (Date/Approval No: 14.09.2022/618). The procedures followed were according to the ethical standards of the responsible institutional ethics committee and the Helsinki Declaration. The researchers visited the students in their classrooms and explained the purpose of the study. After the verbal consent of the students who wanted to participate in the study was obtained, the questionnaire form was shared with the students who volunteered for the study. The students were given 20 minutes to complete the questionnaire form and the questionnaire form was collected at the end of the time.

### *Data collection instruments*

The data collection instruments consist of three components: the first part, developed by the researchers, includes questions on students' socio-demographic characteristics and opinions about sustainable nutrition, and environmental health; the second part includes the Sustainable and Healthy Eating (SHE) Behaviors Scale; and the third part includes the Environmental Literacy Scale for Adults (ELSA). The SHE behaviors scale, developed by Zakowska-Biemans et al. (14) and with a Turkish validity and reliability study conducted by Köksal et al. (15) was used to assess SHE behaviors. The Turkish version of the SHE behaviors scale consists of 7 subscales and a total of 32 items. These 7 subscales are: "healthy and balanced diet", "quality labels (local and organic)", "reducing meat consumption", "local food, low fat, avoiding food waste", "animal health" and "seasonal food". The items in the scale were rated on a Likert scale and participants were asked to mark each item as "never", "very rarely", "rarely", "sometimes", "often", "very often" or "always" ("never" scores 1 and "always" scores 7) (15). The lowest score that can be obtained from the total scale score and each factor is "1" and the highest score is "7". The factor scores of the subscales are calculated by averaging the scores given to the items in that factor (min 1-max 7). The total scale score is calculated by averaging all factor scores. An increase

in the total score obtained from the scale is associated with healthier and more sustainable eating behaviors (15).

Environmental Literacy Scale for Adults (ELSA) developed by Atabek-Yiğit et al. (16) used to determine the environmental literacy levels. Twenty items in the scale consist of 5-point Likert-type statements defined as "strongly agree" (5), "agree" (4), "undecided" (3), "disagree" (2) and "strongly disagree" (1), with scores corresponding to the values in brackets. Items 3 and 16 were reverse coded. For scoring, 20-46 is considered as "low level", 47-73 as "medium level" and 74-100 as "high level" environmental literacy (16).

***Data analysis***

The normality test was evaluated with the number of data, coefficient of variation, histogram, Q-Q plot, and Skewness–Kurtosis. For ELSA, Skewness = –0.916 (Std. Error = 0.079) and Kurtosis = 0.865 (Std. Error = 0.158); for SHE behavior, Skewness = 0.085 (Std. Error = 0.079) and Kurtosis = 0.353 (Std. Error = 0.158). The results were accepted to be in accordance with the normal distribution. Data was analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL) package program. The normality test was evaluated with the number of data, coefficient of variation, histogram, Q-Q plot and the reliability of the scales used was calculated and Cronbach's alpha results were 0.902 for environmental literacy and 0.919 for sustainable nutrition. Numbers and percentages were presented in the frequency table. The students' SHE behaviors subscale and total scores and socio-demographic characteristics were analyzed using Student t-test in paired groups and one-way ANOVA test in multiple groups. Results were evaluated using post-hoc LSD test in multiple groups. The relationship between SHE behaviors with environmental literacy was evaluated using Pearson correlation test. $p<0.05$ was considered significant.

## RESULTS

The mean SHE behaviors score of the students was 3.78±0.82 (Table 1). The highest mean score between SHE behaviors subscales was "seasonal foods and avoiding food waste" (4.19±0.95) and the lowest one was reducing meat consumption (3.05±1.42) (Table 1).

**Table 1.** The mean scores of the total and the subscales of SHE behaviors

| The subscales of SHE behaviors scale | $\bar{X}$± SD |
|---|---|
| 1. Quality marks | 3.69±1.16 |
| 2. Seasonal foods and avoiding food waste | 4.19±0.95 |
| 3. Animal health | 3.35±1.32 |
| 4. Reducing meat consumption | 3.05±1.42 |
| 5. Healthy and balanced nutrition | 3.97±0.95 |
| 6. Local food | 3.18±1.42 |
| 7. Low fat | 3.90±1.41 |
| Total | **3.78±0.82** |

SHE: Sustainable healthy eating. Descriptive statistics are presented as mean ± SD.

The relationship between students' characteristics and SHE behaviors scores was presented in Table 2. Of the students, 33.4% were enrolled in the Faculty of Engineering and 50.2% were male. Additionally, 45.2% of the students resided in dormitories, and 33.1% reported having good family economic status. The mean SHE behaviors score of the female students (3.88±0.81) was higher than those of the male students (3.68±0.82) ($p<0.001$). The mean SHE behaviors score of the students who lived in rural settlement a decade before starting university ($p<0.001$) and who lived with their families were significantly higher ($p=0.006$).

Among the students, familiarity with the concept of sustainable nutrition was reported by 35.8%, while 29.7% indicated the ability to define sustainable nutrition (Table 3). The mean ELSA score of the students was 74±14.27 (high level). When the distribution of ELSA scores of the students was analyzed, it was found that 4.6% (n=44) were at low level, 32.7% (n=314) were at medium level and 62.7% (n=601) were at high level (Table 3).

Comparison of responses to questions on 'sustainable diets' by gender was presented in Table 3. The rates of female students hearing about the concept of sustainable nutrition, knowing what sustainable nutrition means, thinking that global climate change is happening, thinking that they have an impact on global climate change, and paying attention to behavior to reduce their impact on global climate change were higher than male students (Table 3).

Comparison of the SHE behaviors scores based on students' responses to relevant questions was presented in Table 4. The students stated that they had heard the term of "sustainable nutrition" before and knew what it meant had significantly higher SHE behaviors score ($p=0.001$). The mean score of those who dieted to eat healthily was significantly higher than those who dieted to gain weight and those who did not diet ($p=0.007$). The students who prepared their own food at home had significantly higher SHE behaviors scores. ($p<0.001$).

The students who reported that they had heard the term of "sustainable nutrition" before and knew what it meant had higher SHE behaviors scores ($p=0.001$). The SHE behaviors score of students who followed a diet for healthy eating was higher than those who dieted to gain weight and those who did not diet ($p=0.007$). The students who prepared their own food at home had the highest SHE behaviors score ($p<0.001$). Among the students, the mean SHE behaviors scores were significantly higher among those who believed that global climate change was happening, those who paid attention to their behaviors to reduce climate change, and those who were not concerned about global climate change. ($p<0.001$, for all). Furthermore, positive, and moderately significant relationship was found between SHE behaviors scores and ELSA scores. The relationship between SHE behaviors scores and ELSA scores was shown in Figure 1 (R2: 0.090 (95% Cl: 0.058 - 0.127), $p<0.001$) (Figure 1).

## DISCUSSION

Within the aim of the study, sustainable and healthy eating behaviors, and environmental literacy of 959 university students were evaluated. The average scores of the SHE behavior scale for students were 3.78±0.82 (male: 3.68±0.82, female: 3.88±0.81).

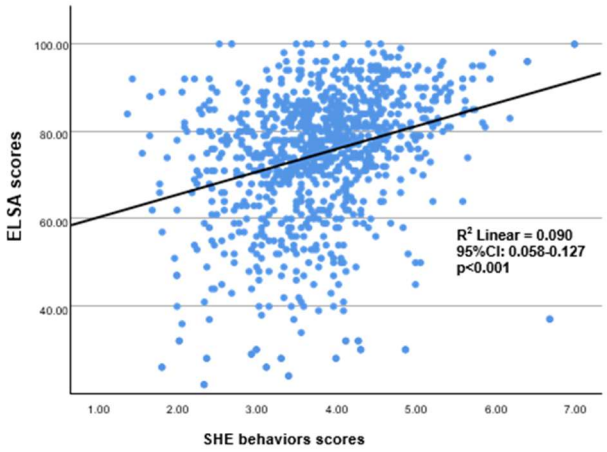



**Figure 1.** The relationship between SHE behaviors scores and ELSA scores

In another study conducted among university students in Turkey using also the SHE behavior scale, male and female students, respectively, in the Nutrition and Dietetics department had scores of 5.06 ± 1.48 and 4.83 ± 0.76, while students in other faculties had scores of 4.23 ± 1.16 and 4.29 ± 0.92 (17).

The lowest scores obtained by students from subscales were related to the sub-dimension concerning reducing red meat consumption. Although the amount of red meat consumed per capita in Turkey is low, red meat is used as the main source of animal protein (18). Meat consumption in the world increased by 54% between 1998 and 2018, and this increase is 85% in developing countries. It has been observed that as the income level increases, the interest in meat consumption increases more (19). Turkey is one of the developing countries and has cultural habits where meat consumption is considered important in individual terms. For this reason, the fact that the least attention is paid to reducing meat consumption in sustainable nutrition is consistent with this.

In this study as well, in line with previous research, the highest scores obtained by students from subscales were related to the one concerning avoiding food waste (14,17). Turkey is a developing country and the income level and women's participation in the labor force are increasing over time. Households spend nearly one-fifth of their expenditures on food (19). This situation brings with it food wastage, the world average of 74 kg per capita food waste is 93 kg for Turkey (19). However, it is below the West Asia average of 110 kg per capita (20). Most of the food waste in Turkey occurs at the production stage and less at the final consumption stage (21). In addition, in 2013, wastage was significantly reduced in campaigns carried out by official institutions to reduce food waste (22). In this study, the fact that seasonal food consumption and avoiding food waste received the highest score in sustainable eating behavior suggests that previous awareness raising activities were effective.

**Table 2.** The relationship between students' characteristics and SHE behaviors scores

| Characteristics | n % | X̄ ± SD | p | F / t |
|---|---|---|---|---|
| **Faculty** | | | | |
| Engineering | 320\33.4 | 3.77±0.84 | 0.090 | 1.978 |
| Economics and Administrative Sciences | 219\22.8 | 3.78±0.80 | | |
| Medicine | 214\22.3 | 3.75±0.84 | | |
| Theology | 106\11.1 | 3.67±0.83 | | |
| Pharmacy | 100\10.4 | 3.97±0.74 | | |
| **Gender** | | | | |
| Male | 481\50.2 | 3.68±0.82 | **<0.001** | 3.834 |
| Female | 478\49.8 | 3.88±0.81 | | |
| **Settlement a decade before starting university** | | | | |
| Urban | 903\94.1 | 3.76±0.82 | **<0.001** | 3.774 |
| Rural | 56\5.9 | 4.13±0.70 | | |
| **Self-reported family' economic status** | | | | |
| Good | 318\33.1 | 3.86±0.80 | 0.080 | 2.599 |
| Moderate | 569\59.3 | 3.74±0.82 | | |
| Bad | 72\7.6 | 3.68±0.90 | | |
| **Accommodation** | | | | |
| Family's house [a] | 337\35.1 | 3.85±0.77 | **0.006** | 4.202 |
| With housemate [b] | 136\14.2 | 3.59±0.85 | | |
| Dormitory [a, c] | 433\45.2 | 3.80±0.82 | | |
| Alone [b, c] | 53\5.5 | 3.60±0.94 | | |
| **Mother's education status** | | | | |
| Below high school | 545\56.8 | 3.77±0.86 | 0.610 | 0.512 |
| High school and above | 414\43.2 | 3.80±0.77 | | |
| **Father's education status** | | | | |
| Below high school | 342\35.7 | 3.77±0.86 | 0.830 | 0.212 |
| High school and above | 617\64.3 | 3.78±0.80 | | |
| **Total** | **959\100.0** | **3.78±0.82** | | |

a, b, c: The difference between groups with different letters was found to be significant.
X̄ ± SD: mean ± standard deviation. Comparisons were conducted using independent samples t-test (for two groups) and One-way ANOVA with LSD post-hoc test (for multiple groups).

**Table 3.** Comparison of responses to questions on 'sustainable diets' by gender

| **Questions about "sustainable nutrition"** | | **Male** | | **Female** | | **Total** | | **p** |
|---|---|---|---|---|---|---|---|---|
| | | **n** | **%** | **n** | **%** | **n** | **%** | |
| Have you heard of "sustainable nutrition" before? | Yes | 150 | 31.2 | 193 | 40.4 | 343 | 35.8 | 0.003 |
| | No | 331 | 68.8 | 285 | 59.6 | 616 | 64.2 | |
| Do you know what "sustainable nutrition" means? | Yes | 129 | 26.8 | 156 | 32.6 | 285 | 29.7 | 0.049 |
| | No | 352 | 73.2 | 322 | 67.4 | 674 | 70.3 | |
| Do you think global climate change is happening? | Yes | 421 | 87.5 | 456 | 95.4 | 877 | 91.4 | <0.001 |
| | No | 60 | 12.5 | 22 | 4.6 | 82 | 8.6 | |
| Do you think you have an impact on global climate change? | Yes | 421 | 87.5 | 456 | 95.4 | 877 | 91.4 | <0.001 |
| | No | 60 | 12.5 | 22 | 4.6 | 82 | 8.6 | |
| Would you pay attention to your behavior to reduce your impact on global climate change? | Yes | 339 | 70.5 | 397 | 83.1 | 736 | 76.7 | <0.001 |
| | No | 142 | 29.5 | 81 | 16.9 | 223 | 23.3 | |
| How concerned are you about global climate change? | I am worried | 170 | 35.3 | 95 | 19.9 | 265 | 27.6 | <0.001 |
| | I am not worried | 311 | 64.7 | 383 | 80.1 | 694 | 72.4 | |
| ELSA score | Low | 27 | 5.6 | 17 | 3.6 | 44 | 4.6 | <0.001 |
| | Moderate | 193 | 40.1 | 121 | 25.3 | 314 | 32.7 | |
| | High | 261 | 54.3 | 340 | 71.1 | 601 | 62.7 | |
| Total | | | | | | **959** | **100.0** | |

**ELSA:** Environmental Literacy for Adults. Chi-square test was applied for categorical variables; Independent samples t-test was used for ELSA scores.

**Table 4.** Comparison of the SHE behaviors scores based on students' responses to relevant questions

| **Questions about "sustainable nutrition"** | **n \ %** | **$\bar{X}$ ± SD** | **p** | **F / t** |
|---|---|---|---|---|
| **Have you ever heard of "sustainable nutrition" before?** | | | | |
| Yes | 343\35.8 | 3.90±0.82 | **0.001** | 3.490 |
| No | 616\64.2 | 3.71±0.82 | | |
| **Do you know what "sustainable nutrition" means?** | | | | |
| Yes | 285\29.7 | 3.91±26.0 | **0.001** | 3.259 |
| No | 674\70.3 | 3.72±26.2 | | |
| **Are you currently on any diet?** | | | | |
| Yes, to lose weight [a] | 214\22.3 | 3.92±0.81 | **0.007** | 4.01 |
| Yes, to put on weight [b] | 90\9.4 | 3.71±0.85 | | |
| Yes, to eat healthy [a, b, c] | 27\2.8 | 4.02±0.93 | | |
| No [b, c] | 628\65.5 | 3.73±0.81 | | |
| **Where do you eat most of your meals?** | | | | |
| In cafeterias [a] | 413\43.1 | 3.77±0.81 | **<0.001** | 13.069 |
| In restaurants and fast-food chains [b] | 158\16.5 | 3.49±0.88 | | |
| At home, I cook for myself [c] | 145\15.1 | 4.07±0.77 | | |
| At home, somebody cook for me [a] | 243\25.3 | 3.80±0.77 | | |
| **Do you think global climate change is happening?** | | | | |
| Yes | 877\91.4 | 3.80±0.83 | **0.020** | 2.388 |
| No | 82\8.6 | 3.57±0.76 | | |
| **Do you think you have an impact on global climate change?** | | | | |
| Yes | 742\77.4 | 3.83±0.83 | **<0.001** | 3.507 |
| No | 217\22.6 | 3.61±0.77 | | |
| **Would you pay attention to your behaviors to reduce your impact on global climate change?** | | | | |
| Yes | 736\76.7 | 3.85±0.81 | **<0.001** | 4.533 |
| No | 223\23.3 | 3.56±0.82 | | |
| **How concerned are you about global climate change?** | | | | |
| I am worried | 265\27.6 | 3.56±0.80 | **<0.001** | 5.102 |
| I am not worried | 694\72.4 | 3.87±0.81 | | |

**[a, b, c]:** The difference between groups with different letters was found to be significant.
**$\bar{X}$ ± SD:** mean ± standard deviation. Independent samples t-test and One-way ANOVA with LSD post-hoc test were applied.

In the study, it was observed that there was no significant difference in the mean scores between the faculties where students were enrolled and the scores, they obtained from the SHE scales. However, in the studies conducted by Yolcuoğlu and Kızıltan (17) with university students in the 3rd and 4th grades, it was found that the average scores of students studying in the Department of Nutrition and Dietetics were higher than the average scores of students in other departments on the SHE scales. The difference between the studies may be attributed to the inclusion of first-year university students in our study. In this context, it is believed that education related to nutrition can contribute to the development of healthy and sustainable dietary behaviors.

It has been observed that individuals who spent most of their pre-university lives in rural areas scored higher on the SHE scales compared to those who spent their lives in urban areas. The urban lifestyle, characterized by competition and a fast-paced environment, coupled with the easy accessibility and enticing presentation of unhealthy foods, has the potential to influence and alter traditional dietary cultures. The traditional dietary culture predominant in rural areas is more sustainable and conducive to a healthy eating style (17). While individuals who spent most of their pre-university years in rural areas seem to maintain their rural dietary habits in the first year of university, these habits may undergo changes over time.

In the study, when comparing the accommodation statuses of the students with the mean of the SHE behavior score, it was observed that students living with their families had higher mean SHE behavior scores than others. Similarly, Yolcuoğlu and Kızıltan's (17) study indicated that the mean for the subscale of choosing seasonal food was higher among students living with their families. In the traditional family structure prevalent in Turkish culture, preparing meals for the family is typically the responsibility of the mother, that is, a woman. Therefore, this result can also be explained by the fact that women are generally more conscious about sustainable and healthy eating (17, 18).

Three quarters of the students thought that they had an impact on climate change and stated that they paid attention to their behavior to reduce their impact on climate change, but the lack of sufficient behavior in sustainable nutrition suggested that students did not have sufficient knowledge about their impact on the environment. In the research conducted by the International Food Council, the impact of sustainability on consumers' preferences was found to be 27% in 2019, 34% in 2020 and 31% in 2021 (23). Although food systems have a serious impact on carbon emissions, the fact that people do not associate their nutritional preferences with this reveals the need for consideration and new studies (24).

35.8% of the students stated that they had heard the term of "sustainable nutrition" before and 29.7% stated that they knew what it meant. In a similar study involving 889 students studying in Istanbul, 58.27% of the students stated that they had heard the term of "sustainable nutrition" before (2). In another study conducted in university students in Turkey, when the rate of hearing the term of "sustainable nutrition" before was examined, it was stated that although the rate was slightly higher in Nutrition and Dietetics students (65.3%), more than half of the students had not heard the term of "sustainable nutrition" before (24.5% of medical students) (25). The reason why hearing the term of "sustainable nutrition" in both studies was higher than in our study may be that three-quarters of the participants in both studies were women. Since women are more protective than men, they are thought to be more protective of the environment and are more careful about sustainable consumption than men (26). In a qualitative study conducted in 10th grade students in Germany, it was shown that not understanding the term of "sustainable nutrition" was common among students (10). Also, the percentage of female students with high environmental literacy was higher than that of males. Other studies in the literature also support the idea that women tend to be more environmentally conscious (17). As a result of this study, it has demonstrated that women are more conscious and exhibit more accurate behaviors in health, environmental, and nutrition matters.

To the best of our knowledge, this study was the first study to reveal the relationship between sustainable and healthy eating behaviors and environmental literacy in university students. It was observed that there was a moderate positive significant relationship between SHE behaviors and environmental literacy (Figure 1).

Having the awareness that sustainable nutrition is an important component of protecting the environment is an important motivation in the development of SHE behaviors. When Health Sciences students were asked about the characteristics that sustainable nutrition should include, it was observed that the students (approximately one fourth) addressed the dimension of "low environmental impact" at the lowest rate (25). In a study conducted in Australian Nutrition and Dietetics major students, it was found that students were most familiar with the environmental aspects of sustainability (27).

Despite its contributions, this study has several limitations. First, its descriptive, analytical design prevents us from drawing causal inferences between sustainable and healthy eating (SHE) behaviors and environmental literacy. Second, the sample was limited to first-year students at a single university, which may reduce the generalizability of findings to students in other years, disciplines, or regions. Third, all data were collected through self-administered questionnaires, introducing the possibility of self-report bias and social desirability effects. Fourth, the uneven distribution of participants across faculties and the relatively small proportion of students from rural backgrounds may have influenced subgroup comparisons. Finally, data were gathered during a single academic semester, so seasonal or time-related fluctuations in dietary practices and environmental awareness could not be captured. Future studies using longitudinal designs, more diverse student populations, and objective behavioral measures are needed to validate and extend these results.

## CONCLUSION

It was determined that although the environmental literacy of university students was high, they were not sufficient to gain sustainable and healthy eating behavior. Being female, living in rural a decade before starting university, having heard the term "sustainable nutrition" before and knowing its meaning were associated with significantly higher SHE behaviors scores. Dieting for healthy nutrition and preparing their own meals at home were also associated with significantly higher SHE behaviors scores. Additionally, believing in global climate change is happening, being aware of their impact on climate change, paying attention to their behaviors to reduce their impact on global climate change, and being worried about global climate change were associated with significantly higher SHE behaviors scores. The students' level of knowledge about sustainable and healthy eating was low. Initiatives to increase their level of knowledge will reinforce students' behavior in this regard. Sustainable and healthy eating behaviors were also associated with environmental awareness.

Organizing education and awareness activities related to sustainable and healthy nutrition for university students will not only contribute to individual health but also to environmental health. This, in turn, will support societies in achieving sustainable development goals.

**Ethical Approval**
Ethics committee approval was obtained for this study from Erciyes University Ethics Committee (Date/Approval No: 14.09.2022/618). The procedures followed were according to the ethical standards of the responsible institutional ethics committee and the Helsinki Declaration.

**Conflict of Interest**
No potential conflict of interest was reported by the authors.

**Financial Disclosure**
No funding.

**Authors' Contributions**
AB: Conceptualization, methodology, data analysis, writing - original draft, writing – reviewing and editing, visualization HD: Conceptualization, methodology, Data analysis, writing – reviewing and editing. NÖ: writing - original draft, writing – reviewing and editing, visualization.

**Data Sharing Statement**
Data are not publicly available because this is an ongoing study. Data can be requested from the corresponding author.

## REFERENCES

1. Harris F, Moss C, Joy EJM, Quinn R, Scheelbeek PFD, Dangour AD, et al. The water footprint of diets: A global systematic review and meta-analysis. Adv Nutr. 2020;11(2):375-86.
2. Yüksel A, Önal Yılmaz H. Evaluation of university students' knowledge of and practices for sustainable nutrition. Int J Agric Environ Food Sci. 2021;5(2):146-56.
3. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;393(10170):447-92.
4. Marlow HJ, Hayes WK, Soret S, Carter RL, Schwab ER, Sabaté J. Diet and the environment: does what you eat matter? Am J Clin Nutr. 2009;89(5):1699-703.
5. Dagevos H, Voordouw J. Sustainability and meat consumption: is reduction realistic? Sustain Sci Pract Policy. 2013;9(2):60-9.
6. Mirón IJ, Linares C, Díaz J. The influence of climate change on food production and food safety. Environ Res. 2023;216:114674.
7. van Dooren C, Marinussen M, Blonk H, Aiking H, Vellinga P. Exploring dietary guidelines based on ecological and nutritional values: A comparison of six dietary patterns. Food Policy. 2014;44:36-46.
8. Shri GU, Tiwari RR. Environmental Literacy among College Students. Indian J Occup Environ Med. 2021;25(3):128-32.
9. Johnston JL, Fanzo JC, Cogill B. Understanding sustainable diets: a descriptive analysis of the determinants and processes that influence diets and their impact on health, food security, and environmental sustainability. Adv Nutr. 2014;5(4):418-29.
10. Dornhoff M, Hörnschemeyer A, Fiebelkorn F. Students' Conceptions of Sustainable Nutrition. Sustainability. 2020;12(13):5242.
11. Foley JA, Ramankutty N, Brauman KA, Cassidy ES, Gerber JS, Johnston M, et al. Solutions for a cultivated planet. Nature. 2011;478(7369):337-42.
12. Innes S, Shephard K, Furnari M, Harraway J, Jowett T, Lovelock B, et al. Greening the Curriculum to Foster Environmental Literacy in Tertiary Students Studying Human Nutrition. J Hunger Environ Nutr. 2018;13(2):192-204.
13. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149-60.
14. Żakowska-Biemans S, Pieniak Z, Kostyra E, Gutkowska K. Searching for a Measure Integrating Sustainable and Healthy Eating Behaviors. Nutrients. 2019;11(1).
15. Köksal E, Bilici S, Çitar Daziroğlu ME, Erdoğan Gövez N. Validity and Reliability of the Turkish Version of the Sustainable and Healthy Eating Behaviors Scale. Br J Nutr. 2022:1-20.
16. Atabek-Yiğit E, Köklükaya N, Yavuz M, Demirhan E. Development and validation of environmental literacy scale for adults (ELSA). J Balt Sci Educ. 2014;13(3):425-35.
17. Yolcuoğlu İZ, Kızıltan G. Effect of nutrition education on diet quality, sustainable nutrition and eating behaviors among university students. J Am Nutr Assoc. 2022;41(7):713-19.
18. Özkaya PT, Dağbağlı S. Usage of Natural Colour Indicators in Packaging Materials for Monitorization of Meat Freshness. Turk J Agric Food Sci Technol. 2021;9(10):1869-75.
19. Whitnall T, Pitts N. Global trends in meat consumption. Agric Commodities. 2019;9(1):96-9.

20. UNEP Food Waste Index Report 2021. Available from: https://www.unep.org/resources/report/unep-food-waste-index-report-2021
21. Salihoglu G, Salihoglu NK, Ucaroglu S, Banar M. Food loss and waste management in Turkey. Bioresour Technol. 2018;248:88-99.
22. Yildirim H, Capone R, Karanlik A, Bottalico F, Debs P, Bilali HE. Food Wastage in Turkey: An Exploratory Survey on Household Food Waste. J Food Nutr Res. 2016;4(8):483-9.
23. Sollid K, Webster AD, Paipongna M, Smith K. Food Perceptions, Beliefs, and Behaviors Amid a Global Pandemic: Results of the International Food Information Council 2021 Food & Health Survey. Nutr Today. 2022;57(1):26-33.
24. Vermeulen SJ, Campbell BM, Ingram JSI. Climate Change and Food Systems. Annu Rev Environ Resour. 2012;37(1):195-222.
25. Akay G LSD. Health Sciences Students Sustainable Nutrition and Environmental Knowledge Levels and Adherence to Mediterranean Diet. Mevlana Med Sci. 2022;2(1):1-6.
26. Bloodhart B, Swim JK. Sustainability and Consumption: What's Gender Got to Do with It? J Soc Issues. 2020;76(1):101-13.
27. Burkhart S, Verdonck M, Ashford T, Maher J. Sustainability: Nutrition and dietetic students' perceptions. Sustainability. 2020;12(3):1072.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):115-121*
*e-ISSN: 2980-0978*

***Research Article/ Araştırma Makalesi***
***DOI:10.61845/agrimedical.1689544***

# Violence against emergency department healthcare workers: A cross-sectional evaluation of exposure, perceived causes, and outcomes

## Acil servis sağlık çalışanlarına yönelik şiddet: Maruziyet, algılanan nedenler ve sonuçların kesitsel değerlendirmesi

Erman Aydoğan [1], Abuzer Coşkun [1], Burak Demirci [1*], Burak Akın[1], Selman Gündoğan [1]

[1] *Department of Emergency Medicine, University of Health Sciences, Istanbul Bağcılar Training and Research Hospital, Istanbul, Türkiye*

*0009-0002-2322-0690
*0000-0003-4824-7021
*0000-0001-6658-7260
*0000-0003-2515-5482
*0000-0001-9795-8087

**Sorumlu Yazar:*
*Burak Demirci*
*Department of Emergency Medicine, University of Health Sciences, Istanbul Bağcılar Training and Research Hospital, Istanbul, Türkiye*
*e-mail: drburakdemirci@hotmail.com*

Gönderilme Tarihi: 02/05/2025
Kabul Tarihi: 28/09/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Aydoğan E, Coskun A, Demirci B, Akın B, Gündoğan S. Violence against emergency department healthcare workers: A cross-sectional evaluation of exposure, perceived causes, and outcomes. Ağrı Med J. 2025; 3(3):115-121.

**ABSTRACT**

**Aim:** The study aimed to evaluate the frequency and forms of violence experienced by healthcare personnel working in the emergency department, accompanied by cause and effect statements of healthcare professionals.
**Materials and Methods:** The study was conducted with 219 emergency service healthcare workers between 01.06.2023-31.08.2023. The data were recorded by asking questions to the employees who volunteered to participate about the situation of being subjected to violence, if so, its nature, and to all participants about the causes and solution suggestions of the violence.
**Results:** Study included 219 people, 122 (55.7%) men and 97 (44.3%) women. Violence affected 108 men (59.0%) and 75 women (41.0%). Doctors were 57 (26%) and nurses were 73 (33%). While 102(55.7%) of individuals subjected to violence were exposed to verbal violence, 120 (65.6%) were most often exposed between 20:00 and 00:00. Sixty-one (33.3%) cases gave a white code due to violence, and 113(61.7%) blamed emergency services' crowding. 77.6% of the participants stated that the concern of being subjected to violence had a negative impact on providing healthy service. Again, 40.4% of violence victims said emergency department reform was needed.
**Conclusion:** The study demonstrated that violence against emergency department healthcare workers is both frequent and multifactorial, often linked to systemic and interpersonal stressors. Findings underscore the need for targeted institutional strategies to reduce violence and its negative consequences on staff performance and care delivery.

**Keywords:** *Emergency department, Violence, Healthcare worker*

**ÖZ**

**Amaç**: Çalışmamızda acil serviste çalışan sağlık personelinin maruz kaldığı şiddetin sıklığını ve biçimlerini, sağlık çalışanlarının neden-sonuç ifadeleri eşliğinde değerlendirmeyi amaçladık.
**Gereçler ve Yöntemler:** Çalışma 01.06.2023-31.08.2023 tarihleri arasında 219 acil servis sağlık çalışanı ile yürütüldü. Çalışmaya gönüllü olan çalışanlara şiddete maruz kalma durumu, maruz kaldıysa niteliği, tüm katılımcılara ise şiddetin nedenleri ve çözüm önerileri hakkında sorular sorularak veriler kaydedildi.
**Bulgular:** Çalışmamıza katılan olgular toplam 219 kişi olup, 122'si (%55,7) erkek ve 97'si (%44,3) kadındı. Şiddete maruz kalanların 108'i (%59,0) erkek, 75'i (%41,0) kadındı. Mesleklerine göre 57 (%26) kişi doktor, 73 (%33) kişi hemşire olarak değerlendirildi. Şiddete maruz kalanların 102 (%55,7)'si sözlü şiddete maruz kalırken, 120 (%65,6) kişi en sık 20:00-00:00 saatleri arasında sözlü şiddete maruz kalmıştır. 61(%33,3) kişi şiddet sonucu beyaz kod verdiğini belirtirken, 113 (%61,7) kişi şiddet nedeni olarak acil servislerdeki kalabalık ortamı göstermiştir. Katılımcıların %77,6'sı şiddete maruz kalma kaygısının sağlıklı hizmet sunumu üzerinde olumsuz etkisi olduğunu belirtmiştir. Yine şiddet mağdurlarının %40,4'ü çözüm için acil servis işleyişinde revizyon gerektiğini belirtti.
**Sonuç:** Çalışma, acil servis sağlık çalışanlarına yönelik şiddetin hem sık hem de çok yönlü olduğunu, genellikle sistem kaynaklı ve kişilerarası stresörlerle bağlantılı olduğunu göstermiştir. Çalışan verimliliği ve hasta bakım hizmetleri üzerindeki olumsuz sonuçları azaltmak için şiddeti önleme amacıyla hedefli kurumsal stratejilere ve çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler**: *Acil servis, Şiddet, Sağlık çalışanı*

## INTRODUCTION

Workplace violence (WPV) directed at healthcare professionals has emerged as a significant global issue and is widely regarded as a major occupational hazard. The World Health Organization (WHO) and International Labour Organization (ILO) define WPV as incidents in which employees are abused, threatened, or assaulted in connection with their work, including during commutes, that pose an explicit or implicit threat to their safety, well-being, or health. Over the last two decades, WPV has been consistently reported across healthcare settings, with a notably high incidence in emergency departments (EDs) (1,2).

Emergency departments constitute a distinct high-risk environment owing to the unpredictability of patient presentations, overcrowding, extended waiting periods, and recurrent interactions with agitated or hostile patients and family members (3,4). Recent systematic evaluations indicate that ED personnel encounter elevated levels of both verbal and physical violence relative to other clinical environments, with verbal aggressiveness frequently identified as the predominant form (5,6).

The COVID-19 pandemic further intensified this problem, heightening public discontent with overwhelmed healthcare systems and increasing occurrences of WPV globally (7,8). Healthcare staff faced the dual challenges of clinical uncertainty and heightened workloads, compounded by antagonism stemming from infection control protocols, visiting limitations, and perceived delays in treatment (9,10). Türkiye has not escaped this trend. National surveys indicate that more than half of Turkish healthcare professionals have experienced some form of WPV, with considerably higher rates among ED personnel (11,12). Contributing factors include overcrowded hospitals, limited resources, communication failures, and a degree of cultural tolerance toward hostility against healthcare workers (13). Despite the implementation of the national "White Code" (Beyaz Kod) system aimed at enhancing reporting and legal safeguards, underreporting persists, and deterrent effects remain limited (14).

In light of these challenges, examining the prevalence, patterns, and consequences of WPV in emergency departments remains a public health priority. The present study therefore aims to assess the prevalence, categories, offenders, and consequences of WPV across all professional groups in a metropolitan tertiary ED, and to explore its implications for workforce sustainability and patient safety.

## MATERIALS AND METHOD

### *Study Design and Population*

This study was conducted as a descriptive and cross-sectional survey among healthcare professionals working in the emergency department at Bagcilar Training and Research Hospital. The study included all occupational groups working in the emergency department, including doctors, nurses, emergency medical technicians (EMTs), paramedics, health officers, cleaning staff, patient transport personnel, security staff, and others such as medical secretaries, administrative officers, and managers. All cases who were emergency room workers and agreed to participate in the study were included. The emergency department employs a total of 316 staff members across all occupational groups, and the study was conducted with 219 volunteers among them between June 1, 2023, and August 31, 2023.

Individuals included in the study were asked to fill out printed case forms with one-on-one questions and answers. All questions were standardized specifically for emergency room healthcare professionals. The occupation, age, gender, education status, whether they were subjected to violence, types of violence, information about the perpetrator, place of violence, time period during which they were subjected to, the situation they think caused them to be subjected to violence, whether they gave a white code, medical support needs, arrest status, punishment status, complaining status, response status, decrease in desire to work, actions to be taken to prevent violence, displaying a different character in order not to be subjected to violence, and the impact of violence anxiety on health service provision, were recorded in the data forms by questioning the relevant answer options. Then, the data were statistically evaluated in a computer environment.

The study included participants that worked in the emergency department, volunteered to participate in the study, and answered all questions completely, while cases that worked outside the emergency department, did not volunteer for the study, and did not answer one or more of the questions were excluded from the study.

The study protocol was approved by the Clinical Research Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (Approval No: 52; Date: April 26, 2023) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

### *Statistical Analysis*

Statistical analysis was performed using IBM SPSS Statistics software (Version 18.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to assess the normality of distribution for continuous variables. Descriptive statistics were reported as frequencies (n) and percentages (%) for categorical variables, and as means ± standard deviations (SD), medians, and minimum–maximum values for continuous variables. For group comparisons of categorical variables, Pearson's Chi-square and Fisher-Freeman-Halton exact tests were used. Since continuous variables did not meet the assumptions for parametric testing, the Mann–Whitney U test was utilized for two-group comparisons. A p-value of $<0.05$ was considered statistically significant.

## RESULTS

Among total of 219 emergency department healthcare workers participated in the study, 183 (83.6%) reported exposure to violence. Those exposed were significantly older than their non-exposed counterparts (mean age: 31.84 vs. 26.55 years, $p < 0.001$). Male participants were more frequently affected than females (59.0% vs. 41.0%, p =

0.029). While exposure appeared more common among doctors, nurses, and security personnel, differences across job groups were not statistically significant. Similarly, educational status showed no meaningful association with violence exposure (Table 1).

**Table 1.** Violence exposure situations of emergency service healthcare workers and age, gender, job group, educational status

| | **Violence (+)** | **Violence (-)** | **All Cases** | **P value** |
|---|---|---|---|---|
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | |
| **Age (year)** | 31.84±7.36 | 26.55±5.42 | 30.97±7.34 | <0.001* |
| **Gender** | **n (%)** | **n (%)** | **n (%)** | |
| Male | 108(59.0) | 14(38.9) | 122(55.7) | 0.029** |
| Female | 75(41.0) | 22(61.1) | 97(44.3) | |
| **Job Group** | | | | |
| Doctor | 53(29.0) | 4(11.1) | 57(26.0) | 0.063*** |
| Nurse | 51(27.9) | 22(61.1) | 73(33.0) | |
| EMT/Paramedic | 1(0.5) | 3(8.3) | 4(1.8) | |
| Health Officer | 14(7.7) | 4(11.1) | 18(8.2) | |
| Cleaning Staff | 8(4.4) | 0(0) | 8(3.7) | |
| Patient Transporter | 16(8.7) | 0(0) | 16(7.3) | |
| Security | 25(13.7) | 0(0) | 25(11.4) | |
| Other | 15(8.2) | 3(8.3) | 18(8.2) | |
| **Educational Status** | | | | |
| Primary School | 3(1.6) | 0(0) | 3(1.4) | 0.512*** |
| Middle/High School | 36(19.7) | 6(16.7) | 42(19.2) | |
| University | 111(60.7) | 27(75.0) | 138(63.0) | |
| Master | 23(12.6) | 3(8.3) | 26(11.9) | |
| Doctorate | 10(5.5) | 0(0) | 10(4.6) | |
| **Total** | 183(100) | 36(100) | 219(100) | |

Mann–Whitney U test (*) was used for continuous variables; Pearson Chi-square (**) and Fisher-Freeman-Halton exact tests (***) were applied for categorical comparisons.

Among those who had experienced violence, verbal aggression was the most frequently reported form (55.7%), followed by physical violence (44.3%). In the majority of cases, both patients and their relatives were involved as perpetrators (62.8%). Nearly all incidents took place in the emergency department setting (96.7%), with a substantial concentration occurring during evening hours (20:00–00:00, 65.6%), indicating a heightened risk during night shifts (Table 2).

Participants most commonly attributed violent incidents to overcrowding and patient load (61.7%), dissatisfaction with treatment outcomes (55.7%), and communication breakdowns (55.2%). Other contributing factors included delays in laboratory results (32.8%), security vulnerabilities within the department (37.7%), and emotional distress following patient deaths (27.9%) (Table 3).

**Table 2.** Type of violence, implementer, violence place and time range data of emergency service workers exposed to violence

| **Violence Details** | | **n** | **%** |
|---|---|---|---|
| **Type of Violence** | Verbal | 102 | 55,7 |
| | Physical | 81 | 44,3 |
| **Implementer** | Patient | 12 | 6,6 |
| | Patient Relative | 56 | 30,6 |
| | Both | 115 | 62,8 |
| **Violence Place** | Emergency Department | 177 | 96,7 |
| | Policlinic | 1 | 0,5 |
| | Inpatient Ward | 2 | 1,1 |
| | Other | 3 | 1,6 |
| **Time Range** | 08:00-12:00 | 6 | 3,3 |
| | 12:00-16:00 | 8 | 4,4 |
| | 16:00-20:00 | 33 | 18,0 |
| | 20:00-00:00 | 120 | 65,6 |
| | 00:00-04:00 | 16 | 8,7 |
| | 04:00-08:00 | 0 | 0 |

Descriptive statistics (frequencies and percentages). No comparative test applied.

**Table 3.** Opinions of those who were subjected to violence about the reason why they were exposed to violence (more than one option is possible)

| **Opinions regarding reason of exposed violence** | **Violence(+)** | |
|---|---|---|
| | **n** | **%** |
| Communication Problem | 101 | 55,2 |
| Large Number of Patients and Crowds | 113 | 61,7 |
| Delay of Consultant Physician | 49 | 26,8 |
| Delay of Lab Result | 60 | 32,8 |
| Death of Case | 51 | 27,9 |
| Dissatisfaction with Treatment | 102 | 55,7 |
| Media Effect | 41 | 22,4 |
| Inability to Find Appointment | 41 | 22,4 |
| Security Vulnerability | 69 | 37,7 |
| Unreasonable | 58 | 31,7 |

Descriptive statistics (frequencies and percentages). No comparative test applied.

Reactions to violence varied widely among staff. Only one-third (33.3%) reported initiating a White Code response. Despite 26.2% requiring medical attention, legal consequences were rare: just 4.9% of perpetrators were arrested, and only 9.8% faced any form of punishment. Nevertheless, the psychological toll was substantial—41.0% considered resigning, and 84.2% reported a decline in motivation to work. The most common immediate reaction was to call security (63.9%), followed by leaving the area (24.0%) or, less frequently, responding with violence (7.7%) (Table 4).

**Table 4.** Data on the health worker and the perpetrator during and after the violence

| Emergency Service Worker Subjected to Violence | | n | % |
|---|---|---|---|
| **White Code Status** | Yes | 61 | 33,3 |
| **Need for Medical Support** | Yes | 48 | 26,2 |
| **Arrest Status** | Yes | 9 | 4,9 |
| **Punishment Status** | Yes | 18 | 9,8 |
| | No | 134 | 73,2 |
| | Not Concluded | 31 | 16,9 |
| **Complaint Status** | Yes | 66 | 36,1 |
| **Thought of Resignation** | Yes | 75 | 41,0 |
| **Decrease in Willingness to Work** | Yes | 154 | 84,2 |
| **Response Status** | I used violence | 14 | 7,7 |
| | I left the area | 44 | 24,0 |
| | I called security | 117 | 63,9 |
| | I left work | 8 | 4,4 |
| **Total** | | 183 | 100 |

Descriptive statistics (frequencies and percentages). No comparative test applied.

Regarding preventive measures, participants most frequently recommended revising emergency department operational procedures (38.8%) and increasing patient education efforts (31.5%). The experience of violence also appeared to affect behavior and professional identity; over half (54.8%) reported changes in their demeanor—often becoming more cautious or withdrawn—while 77.6% noted a negative impact on their professional outlook. These effects were more commonly observed among those who had been directly exposed to violence (Table 5).

## DISCUSSION

Workplace violence transcends individual incidents, embodying wider systemic and cultural issues within the healthcare sector. In addition to the immediate damage inflicted on personnel, violent occurrences erode team cohesion, instill a pervasive atmosphere of dread, and eventually compromise the provision of safe and effective care. Emergency departments offer a distinctive perspective on this issue as they converge patients, relatives, and healthcare providers in contexts frequently marked by haste, uncertainty, and intensified emotions. Analyzing the patterns and repercussions of such violence provides significant insights on the resilience and vulnerabilities of healthcare systems.

Workplace violence in healthcare is now regarded as both an occupational danger and a systemic threat to the quality and safety of patient treatment. Emergency rooms offer a vital framework for analyzing this issue because to their substantial patient volume, unpredictability, and emotionally intense atmosphere (1,3,15,16).

In our study, 83.6% of emergency department personnel indicated exposure to workplace violence. This prevalence exceeds numerous previous national and international estimates. Extensive surveys in Türkiye have generally indicated rates of approximately 50–70% (11,12,17), while systematic reviews and meta-analyses from Europe and North America report prevalence estimates between 50% and 65%, confirming that workplace violence is a widespread challenge across diverse healthcare systems (2,10). In addition, systematic reviews conducted during the COVID-19 period confirmed that nearly half of healthcare workers globally experienced some form of workplace violence (9,10). Subsequent to the COVID-19 pandemic, not only did the frequency of workplace violence become a global concern, but barriers to reporting incidents were also increasingly recognized, particularly among nurses working in tertiary care settings (20). Earlier regional studies, such as those conducted in Jordan, had already highlighted the vulnerability of emergency department nurses and the significant psychological and professional consequences of such violence (21). Together, these findings indicate that the true prevalence of workplace violence may be underestimated, as many incidents remain unreported. The increased incidence may indicate the substantial workload of a tertiary metropolitan emergency department, ongoing post-pandemic demands, and a reporting environment that promoted honest disclosure. The comparatively higher prevalence observed in Türkiye may also reflect structural challenges such as overcrowded emergency departments, longer waiting times, and limited staffing resources, which are consistently reported as aggravating factors in regional studies (12,17).

Verbal aggression was prevalent in our group, aligning with other assessments that identify verbal abuse, threats, and harassment as the majority of events (19,22). Despite a decrease in the frequency of physical assaults, their consequences remain significant. Recent manifestations of violence, such as sexual harassment and discriminatory slurs, have been documented in current ED literature, hence broadening the acknowledged parameters of WPV (23,24).
The bulk of violent occurrences in our analysis transpired between 20:00 and 00:00, corroborating prior research indicating that evening and night shifts are high-risk intervals due to elevated patient loads, restricted administrative supervision, and staff exhaustion (19,25). Particular emergency department sites, especially triage, waiting, and resuscitation areas, have consistently been recognized as ‘hot spots’ for violence, particularly triage areas where initial conflicts often arise, waiting rooms where frustration accumulates, and resuscitation zones where emotions are heightened (19,25). Within our sample, the predominant triggers identified were overcrowding, dissatisfaction with treatment, and communication failures. These characteristics align with findings from other Turkish and Middle Eastern studies, as well as international evidence connecting disappointed expectations and delays to aggressiveness (12,17).

**Table 5.** Solution suggestions of employees, effects of violence on personality behavior and work motivation

| | Violence (-) | | Violence (+) | | All Cases | | P value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **Violence Prevention Ideas** | | | | | | | |
| Patient Education | 13 | 36,1 | 56 | 30,6 | 69 | 31,5 | 0.234* |
| Employee Education | 2 | 5,6 | 1 | 0,5 | 3 | 1,4 | |
| Physical Environment Arrangement | 3 | 8,3 | 26 | 14,2 | 29 | 13,2 | |
| Updating Emergency Service Operations | 11 | 30,6 | 74 | 40,4 | 85 | 38,8 | |
| Increasing the Number of Physicians | 1 | 2,8 | 5 | 2,7 | 6 | 2,7 | |
| Increasing the Number of Auxiliary Health Staff | 2 | 5,6 | 8 | 4,4 | 10 | 4,6 | |
| Increasing the Number of Security | 4 | 11,1 | 13 | 7,1 | 17 | 7,8 | |
| **Different Attitudes Due to Fear of Violence** | | | | | | | |
| Showcasing Different Character (-) | 21 | 58,3 | 78 | 42,6 | 99 | 45,2 | 0.083** |
| Showcasing Different Character (+) | 15 | 41,7 | 105 | 57,4 | 120 | 54,8 | |
| **Negative Impact on Employee Healthcare Provision** | | | | | | | |
| Negative Impact on the Profession (-) | 12 | 33,3 | 37 | 20,2 | 49 | 22,4 | 0.084** |
| Negative Impact on the Profession (+) | 24 | 66,7 | 146 | 79,8 | 170 | 77,6 | |
| **Total** | 36 | 100 | 183 | 100 | 219 | 100 | |

Fisher-Freeman-Halton exact (*) and Pearson Chi-square (**) tests were applied for categorical comparisons.

In our investigation, patients and their relatives were the predominant sources of violence, aligning with other international data (26,27). Physicians (29%) and nurses (27.9%) constituted the most often assaulted groups, indicative of their frontline roles in triage, clinical decision-making, and extended patient interaction. Multiple studies have shown that nurses, especially those who are younger and less experienced, are at the greatest risk of workplace violence (18,28). Security personnel also indicated considerable exposure in our study, underscoring the risks associated with enforcement positions during conflict escalation.

The consequences of WPV in our cohort were significant: 84.2% of staff indicated diminished motivation, 41% contemplated quitting, and 77.6% reported that fear of violence hindered their ability to provide care. These findings correspond with global evidence associating workplace violence (WPV) with burnout, anxiety, depression, post-traumatic stress symptoms, absenteeism, and diminished patient satisfaction (29,30). Furthermore, these adverse outcomes have been shown to compromise patient safety by increasing the risk of errors and reducing the overall quality of care. WPV is widely acknowledged as a patient safety concern: personnel subjected to aggression are more prone to encounter communication challenges, make mistakes, and withdraw from patient-centered care (31).

Notwithstanding the high occurrence, merely one-third of our participants reported incidents via the White Code system, and criminal sanctions were infrequent. This trend of underreporting has been extensively documented and is frequently ascribed to feelings of futility, apprehension of punishment, or the intricacies of reporting mechanisms (14,32). Assessments of the White Code program in Türkiye indicate that although the system offers a standardized documentation method, it fails to exert adequate deterrent effect in the absence of consistent legal enforcement and prompt feedback to personnel (14). Enhancing this system through streamlined procedures, assured legal oversight, and clear communication of results is essential for reinstating staff confidence.

Addressing WPV necessitates comprehensive approaches. Evidence endorses operational improvements aimed at alleviating congestion and minimizing waiting periods, systematic training in communication and de-escalation techniques, environmental adjustments including surveillance and restricted access, and legal frameworks implementing zero-tolerance policies (2,20). Implementing targeted measures during high-risk periods (evenings/nights) and for certain roles (triage nurses, security personnel) can improve efficacy (25,33). Additionally, broad public education initiatives and constructive media involvement are essential to combat the cultural normalization of violence against healthcare personnel, by reshaping societal attitudes, raising awareness about the consequences of such behaviors, and fostering a culture of respect and trust between patients and healthcare providers.

The strengths of our study encompass the inclusion of all professional groups in the emergency department and a comprehensive assessment of time, perpetrators, and perceived triggers. Limitations encompass its single-center design and dependence on self-reported data, which may either underreport or overreport actual prevalence. Future research ought to incorporate multi-center, prospective designs and assess the effects of bundled interventions on staff well-being and patient safety outcomes.

## CONCLUSION

Our research indicates that workplace violence has become a nearly commonplace occurrence for emergency department personnel, with over eighty percent of professionals reporting exposure and numerous individuals facing enduring psychological and professional repercussions. While verbal violence was prevalent, physical attacks, threats, and discriminating behaviors were also pervasive, particularly during high-pressure evening hours when resources were most limited. Nonetheless, reporting was more the exception

than the rule, and legal or institutional repercussions for offenders were infrequent. Workplace violence in healthcare is not an unavoidable occupational risk but a preventable public health emergency. Neglecting this issue compromises the safety and dignity of healthcare providers, as well as the trust, quality, and resilience of emergency care systems. Immediate implementation of targeted operational reforms, legislative safeguards, and a culture transformation that denounces animosity towards healthcare professionals is essential. Addressing this concern decisively is crucial for maintaining the well-being of frontline professionals and the integrity of patient treatment in emergency environments.

**Ethical Approval**

The study was approved by the institutional review board of Kanuni Sultan Suleyman Training and Research Hospital (Date:26/04/2023, Decision No:2024/52). The study was made in following the Declaration of Helsinki for Human Research.

**Conflict of Interest**

The authors declare that they have no conflicts of interest related to this study

**Financial Disclosure**

The authors declared that this study has received no financial support.

**Authors' Contributions**

Conceptualization, E.A., A.C., B.D., B.A.; Data collection and processing, E.A., A.C., B.D.B.A., S.G.; Data analysis and interpretation, E.A., A.C., B.D., S.G.; Literature review, E.A., A.C., B.A., S.G.; Writing, E.A., A.C., B.D., B.A., S.G.; Review and editing, E.A., A.C., B.D.; Supervision, A.C., B.D.

**Data Sharing Statement**

The dataset used and analyzed in the study is available from the corresponding author upon reasonable request.

## REFERENCES

1. Krug EG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. Lancet. 2002;360(9339):1083-88.
2. Aljohani B, Burkholder J, Tran QK, Chen C, Beisenova K, Pourmand A. Workplace violence in the emergency department: a systematic review and meta-analysis. Public Health. 2021;196:186-197.
3. O'Brien CJ, van Zundert AAJ, Barach PR. The growing burden of workplace violence against healthcare workers: trends in prevalence, risk factors, consequences, and prevention - a narrative review. EClinicalMedicine. 2024;72:102641.
4. Di Martino V. Workplace violence in the health sector – Synthesis Report. ILO/WHO/ICN; 2002.
5. Bayram B, Çetin M, Çolak Oray N, Can İÖ. Workplace violence against physicians in Turkey's emergency departments: a cross-sectional survey. BMJ Open. 2017;7(6):e013568.
6. Sari H, Yildiz İ, Çağla Baloğlu S, Özel M, Tekalp R. The frequency of workplace violence against healthcare workers and affecting factors. PLoS One. 2023;18(7):e0289363.
7. Partridge B, Affleck J. Verbal abuse and physical assault in the emergency department: rates of violence, perceptions of safety, and attitudes towards security. Australas Emerg Nurs J. 2017;20(3):139-145.
8. Doehring MC, Chhabra M, Armahizer J, et al. Workplace Violence in a Large Urban Emergency Department. JAMA Netw Open. 2024;7(12):e2444204.
9. Ramzi ZS, Fatah PW, Dalvandi A. Prevalence of Workplace Violence Against Healthcare Workers During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. Front Psychol. 2022;13:896156.
10. Zhang S, Zhao Z, Zhang H, Zhu Y, Xi Z, Xiang K. Workplace violence against healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Environ Sci Pollut Res Int. 2023;30(30):74838-74852.
11. Talas MS, Kocaöz S, Akgüç S. A survey of violence against staff working in the emergency department in ankara, Turkey. Asian Nurs Res (Korean Soc Nurs Sci). 2011;5(4):197-203.
12. Türkmenoğlu B, Sümer HE. Frequency of healthcare workers' exposure to violence in the city center of Sivas. Ankara Med J. 2017;(4):216-225.
13. Atan ŞÜ, Dönmez S. Workplace violence against nurses. Turkish Journal of Forensic Medicine. 2011;25(11):71-80.
14. Aktaş E, Aydemir İ. The Determination of Views of Health Professionals Who Exposed to Violence About the "White Code" Implementation. Turkiye Klinikleri J Health Sci. 2018;3(1):32-47.
15. Rutherford A, Zwi AB, Grove NJ, Butchart A. Violence: a glossary. J Epidemiol Community Health. 2007;61(8):676-80.
16. Menckel E, Viitasara E. Threats and violence in Swedish care and welfare—magnitude of the problem and impact on personnel. Scand J Caring Sci. 2002;16(4):376-85.
17. Karpınar MS, Hakverdi G, Çalışkan SA. Workplace violence against emergency physicians: A cross-sectional study on the role of communication skills. Turk J Emerg Med. 2025;25:123-9.
18. Nowrouzi-Kia B, Chai E, Usuba K, Nowrouzi-Kia B, Casole J. Prevalence of type II and type III workplace violence against physicians: a systematic review and meta-analysis. Int J Occup Environ Med. 2019;10(3):99-110.
19. Pich J, Hazelton M, Sundin D, Kable A. Patient-related violence against emergency department nurses. Nurs Health Sci. 2010;12(2):268-74.
20. Elsharkawy, N., Alruwaili, A., Elsayed Ramadan, O. et al. Barriers to reporting workplace violence: a qualitative study of nurses' perceptions in tertiary care settings. BMC Nurs. 2025;24:395.
21. Darawad MW, Al-Hussami M, Saleh AM, Mustafa WM, Odeh H. Violence against nurses in emergency departments in jordan: nurses' perspective. Workplace Health Saf. 2015;63(1):9-17.
22. Seddik SA, Abdelhai R, Aboushady AT, Nawwar AE, El Essawy RA, Hegazy AA. Violence against healthcare

workers during the COVID-19 pandemic: a cross-sectional survey at Cairo University Hospital. Front Public Health. 2023;11:1277056.
23. La Torre G, Firenze A, Colaprico C, et al. Prevalence and Risk Factors of Bullying and Sexual and Racial Harassment in Healthcare Workers: A Cross-Sectional Study in Italy. Int J Environ Res Public Health. 2022;19(11):6938.
24. Spector PE, Zhou ZE, Che XX. Nurse exposure to physical and nonphysical violence, bullying, and sexual harassment: a quantitative review. Int J Nurs Stud. 2014;51(1):72-84.
25. Crilly J, Chaboyer W, Creedy D. Violence towards emergency department nurses by patients. Accid Emerg Nurs. 2004;12:67-73.
26. Arnetz JE, Arnetz BB. Violence towards health care staff and possible effects on the quality of patient care. Soc Sci Med. 2001;52(3):417-427.
27. Alnaeem MM, Hasan Suleiman K, Alzoubi MM, et al. Prevalence, consequences, and contributing factors beyond verbal and physical workplace violence against nurses in peripheral hospitals. Front Public Health. 2025;12:1418813.
28. Li S, Yan H, Qiao S, Chang X. Prevalence, influencing factors and adverse consequences of workplace violence against nurses in China: A cross-sectional study. J Nurs Manag. 2022;30(6):1801-1810.
29. Kim S, Kitzmiller R, Baernholdt M, Lynn MR, Jones CB. Patient Safety Culture: The Impact on Workplace Violence and Health Worker Burnout. Workplace Health Saf. 2023;71(2):78-88.
30. Benning L, Teepe GW, Kleinekort J, et al. Workplace violence against healthcare workers in the emergency department - a 10-year retrospective single-center cohort study. Scand J Trauma Resusc Emerg Med. 2024;32(1):88.
31. Kafle S, Paudel S, Thapaliya A, Acharya R. Workplace violence against nurses: a narrative review. J Clin Transl Res. 2022;13;8(5):421-424.
32. Arnetz JE, Hamblin L, Ager J, et al. Underreporting of Workplace Violence: Comparison of Self-Report and Actual Documentation of Hospital Incidents. Workplace Health Saf. 2015;63(5):200-210.
33. Menendez CC, Arespacochaga E, Begley R, et al. Prioritizing our Healthcare Workers: The Importance of Addressing the Intersection of Workplace Violence and Mental Health and Wellbeing. NIOSH Science Blog. 2024 May 29. Available from: https://blogs.cdc.gov/niosh-science-blog/2024/05/29/hcw_violence_mh/ (accessed 2025 Sep 15).

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):122-129*
*e-ISSN: 2980-0978*

***Research Article/ Araştırma Makalesi***
***DOI: 10.61845/agrimedical.1787537***

# Comparison of treatment options based on X-ray and computed tomography findings in patients presenting to the emergency department with foot and ankle trauma

## Acil servise başvuran ayak ve ayak bileği travmalı hastalarda tedavi seçeneklerinin X-ray ve bilgisayarlı tomografi bulgularına göre karşılaştırılması

Burcu Özen Karabulut[1*], Mehmet Reşit Öncü[2]

[1]*Ağrı İbrahim Çeçen University, Faculty of Medicine, Department of Emergency Medicine, Ağrı, Türkiye*
[2] *Van Yüzüncü Yıl University, Faculty of Medicine, Department of Emergency Medicine, Van, Türkiye*

*0000-0002-9046-6511
*0000-0001-9296-2554

**Sorumlu Yazar:*
*Burcu Özen Karabulut*
*Ağrı İbrahim Çeçen University, Faculty of Medicine, Department of Emergency Medicine, Ağrı, Türkiye*
*e-mail: bozenkarabulut@agri.edu.tr*

Gönderilme Tarihi: 20/09/2025
Kabul Tarihi: 07/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Karabulut BÖ, Öncü MR. Comparison of treatment options based on X-ray and computed tomography findings in patients presenting to the emergency department with foot and ankle trauma. Ağrı Med J. 2025; 3(3):122-129.

**ABSTRACT**

**Aim:** This study investigated the differences between direct radiography (X-ray) and computed tomography (CT) in detecting pathological findings in patients presenting to the emergency department with foot and/or ankle trauma and evaluated their role in predicting treatment requirements and modifications.
**Materials and Methods:** The study was conducted at the Emergency Department of Van Yüzüncü Yıl University Faculty of Medicine between January 1, 2017, and December 31, 2019. CT and X-ray results, along with clinical data of patients with foot and/or ankle trauma, were retrospectively analyzed.
**Results:** Imaging revealed pathology only on CT in 8.9% of cases, on both CT and X-ray in 24.9%, while the remaining patients had normal imaging results. The mean Glasgow Coma Scale score was significantly lower in patients with pathology detected on both modalities ($p = 0.018$). Patients with CT-only findings were more frequently treated with splinting/casting, whereas surgical intervention rates were significantly higher in those with pathology on both imaging modalities ($p < 0.001$). Furthermore, the need for treatment modification was markedly greater in patients with CT-only pathology compared to other groups ($p < 0.001$).
**Conclusion:** In the management of foot and ankle trauma in the emergency setting, selecting the appropriate imaging modality plays a critical role in enhancing diagnostic accuracy and guiding proper treatment. Particularly, CT is valuable in detecting injuries missed by X-ray, not only informing initial treatment decisions at admission but also providing important predictive value for subsequent treatment modifications.

**Keywords:** *Emergency department, Foot trauma, Ankle trauma, Radiography, Computed tomography*

**ÖZ**

**Amaç**: Bu çalışmada, ayak ve/veya ayak bileği travması ile acil servise başvuran hastalarda direkt radyografi (X-ray) ve bilgisayarlı tomografinin (BT) patolojik bulguları saptamadaki farklılıklarının, tedavi gereksinimi ve değişimini öngörmedeki rolü araştırıldı.
**Gereçler ve Yöntemler:** Çalışma, Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Acil Servisi'nde 1 Ocak 2017–31 Aralık 2019 tarihleri arasında gerçekleştirildi. Ayak ve/veya ayak bileği travması olan hastaların BT ve X-ray sonuçları ile klinik verileri retrospektif olarak değerlendirildi.
**Bulgular:** Görüntüleme sonuçlarına göre hastaların %8,9'unda yalnızca BT'de, %24,9'unda ise hem X-ray hem BT'de patoloji saptanırken geri kalan grupta görüntüleme sonuçları normaldi. Hem X-ray hem BT'de patoloji bulunan olgularda Glasgow Koma Skoru ortalaması daha düşük saptandı ($p=0,018$). Yalnızca BT'de patoloji tespit edilen olgular, daha sık alçı/atel ile tedavi edilirken; her iki görüntülemede patoloji saptananlarda cerrahi girişim oranı anlamlı olarak daha yüksekti ($p<0,001$). Ayrıca sadece BT'de patoloji saptanan olgularda tedavi değişikliği gereksinimi diğer gruplara göre belirgin şekilde fazlaydı ($p<0,001$).
**Sonuç:** Acil serviste ayak ve ayak bileği travmalarının yönetiminde doğru görüntüleme yönteminin seçilmesi, tanısal doğruluğu artırarak uygun tedaviye yön vermede kritik bir rol oynar. Özellikle X-ray ile saptanamayan patolojilerin BT ile ortaya konması, başvuru anında uygulanacak tedavi seçeneğinin belirlenmesinde yol gösterici olmasının yanı sıra tedavi değişikliği gereksinimini öngörmede de önemli katkı sağlayabilir.

**Anahtar Kelimeler**: *Acil servis, Ayak travması, Ayak bileği travması, Radyografi, Bilgisayarlı tomografi*

## INTRODUCTION

Trauma constitutes a significant proportion of emergency department admissions, with extremity injuries accounting for the majority of these cases. Among them, foot and ankle traumas hold particular importance for emergency physicians due to their high incidence and complex anatomical structure (1,2). Recent studies have demonstrated an increase in these injuries across all age groups, emerging as a notable health problem especially in young adults during sports activities and in the elderly population due to falls. Moreover, changes in trauma patterns have been reported in the post-pandemic period, with domestic injuries becoming more prevalent (3,4).

If not treated appropriately, foot and ankle traumas may result in serious functional impairments and long-term complications, most notably post-traumatic osteoarthritis (5–7). Therefore, early and accurate diagnosis is critical for ensuring proper management and guiding the treatment process effectively. However, clinical signs are not always specific; findings such as swelling, pain, and ecchymosis may occur both in minor soft tissue injuries and in severe fractures, complicating the diagnostic process (6,7).

Direct radiography (X-ray) remains the primary imaging modality in diagnosis. Nevertheless, in complex injuries or in cases where radiographs fail to clearly reveal pathologies, computed tomography (CT) provides substantial additional value. CT is superior to radiography in detecting small fractures, stress fractures, and articular surface disruptions (8–10). Recent studies emphasize that CT not only improves diagnostic accuracy but also significantly contributes to surgical planning and treatment strategy modification (11,12). Despite these findings, research assessing the impact of X-ray and CT on treatment approaches, particularly on the need for treatment modification, remains limited. Most of the literature focuses on diagnostic accuracy comparisons, while clinical outcomes directly affecting treatment have not been sufficiently addressed. For this reason, our study not only compares diagnostic modalities but also aims to reveal the contribution of X-ray and CT findings to treatment selection and prediction of possible treatment modifications in the emergency department, thereby offering a unique contribution to the literature.

## MATERIALS AND METHOD

### *Study Setting and Period*

This retrospective study was conducted by reviewing the medical records and imaging data of patients of all age groups who presented with foot and/or ankle trauma to the Emergency Department of Van Yüzüncü Yıl University Faculty of Medicine between January 1, 2017, and December 31, 2019. A total of 370 cases that met the inclusion criteria during the specified period were included. Data were obtained from the hospital information system and patient files.

### *Inclusion and Exclusion Criteria*

Patients admitted to the emergency department with foot and/or ankle trauma, who underwent X-ray and/or CT imaging at admission and had complete clinical and radiological data, were included in the study. Patients with missing clinical or radiological data, those imaged for non-traumatic reasons, and those with duplicate records due to multiple admissions with the same complaint were excluded.

### *Radiological Evaluation*

X-ray was preferred as the initial imaging modality in the patients. Additional CT scans were performed in patients with low Glasgow Coma Scale (GCS) in whom physical examination findings could not be reliably assessed, in cases where no pathology was detected on X-ray but physical examination revealed marked swelling, deformity, tenderness, instability, or inability to bear weight, and in patients scheduled for surgical intervention. CT images were evaluated by radiology specialists, and the information was obtained from official radiology reports. X-ray images were evaluated by both radiology specialists and emergency physicians; the findings were derived from radiology reports as well as assessment notes documented in the emergency physicians' medical records. Based on the findings, patients were classified into three groups:

1. No pathology detected on X-ray or CT,
2. Pathology detected only on CT,
3. Pathology detected on both X-ray and CT.

### *Data Collection and Analyzed Parameters*

Data were retrospectively obtained from the Hospital Information Management System and patient files. For each case, demographic characteristics (age, sex), trauma-related features (mechanism of injury, site of injury, associated injuries), GCS score, radiological findings (X-ray and CT results), and treatment process (treatment modality and treatment modification status) were recorded.

### *Ethical Approval*

Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Van Yüzüncü Yıl University (Date: 12/02/2021, Decision No: 2021/02-10). The study was conducted in accordance with the principles of the Declaration of Helsinki, and patient confidentiality was strictly maintained.

### *Statistical Analysis*

Data were analyzed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as counts and percentages, while continuous variables were expressed as mean ± standard deviation, median, minimum, and maximum values. The distributions of the variables were assessed for normality using the Shapiro–Wilk test and histograms. Comparisons of continuous variables across multiple categories were performed using ANOVA for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. A p-value $< 0.05$ was considered statistically significant.

## RESULTS

A total of 370 patients were included in the study. Of these, 68.9% (n = 255) were male and 31.1% (n = 115) were female. The mean age of the patients was 29.2 ± 16.8 years. Analysis of the trauma mechanism revealed that the most common cause was same-level fall or sprain (79.5%), followed by falls from height (6.8%) and traffic accidents (5.4%).

Regarding the site of injury, 18.4% of cases involved isolated foot injuries, 23.8% involved isolated ankle injuries, and 57.8% involved combined foot and ankle injuries. In addition, 12.2% of patients had associated injuries in other body regions. Among these, extremity injuries were the most common (7.0%), followed by vertebral (0.8%), pelvic (0.5%), head-neck (0.3%), thoracic (0.3%), and abdominal (0.3%) injuries. Furthermore, multiple body region injuries were identified in 3.0% of the cases (Table 1).

**Table 1.** Demographic characteristics, trauma mechanisms and injury sites of the patients (n=370)

| Variable | Subgroup | n | % |
|---|---|---|---|
| Gender | Male | 255 | 68.9 |
| | Female | 115 | 31.1 |
| Age (years, mean ± SD) | 29.2 ± 16.8 | | |
| Mechanism of Trauma | Same-level fall / sprain | 294 | 79.5 |
| | Fall from height | 25 | 6.8 |
| | Traffic accident | 20 | 5.4 |
| | Firearm injury | 4 | 1.1 |
| | Sharp/stabbing object | 4 | 1.1 |
| | Other | 23 | 6.2 |
| Injury Site | Isolated foot | 68 | 18.4 |
| | Isolated ankle | 88 | 23.8 |
| | Foot + ankle | 214 | 57.8 |
| Associated Injuries | Extremity | 26 | 7.0 |
| | Vertebra | 3 | 0.8 |
| | Pelvis | 2 | 0.5 |
| | Head–neck | 1 | 0.3 |
| | Thorax | 1 | 0.3 |
| | Abdomen | 1 | 0.3 |
| | Multiple injuries | 11 | 3.0 |
| | None | 325 | 87.8 |

In 51.9% of patients, no pathology was detected, while fractures were present in 32.2%, and non-fracture injuries such as tendon lacerations, tendon ruptures, and amputations without fractures accounted for 15.9%. When grouped according to imaging methods, no pathology was identified on either X-ray or CT in 66.2% of patients pathology was detected only on CT in 8.9%, and both modalities revealed pathology in 24.9%. Among patients with normal X-ray and CT findings and those with CT-only pathology, 100% had a GCS score of 15, whereas 93.5% of patients with pathology detected on both modalities had a GCS score of 15. The mean GCS values were significantly lower in the group with pathology on both imaging methods ($p = 0.018$).

Analysis of injury mechanisms showed that the most common etiology was same-level fall or sprain (79.5%), and this proportion was particularly higher in the group with normal X-ray and CT findings (87.3%). In contrast, falls from height and traffic accidents were more prominent in patients with detected pathology ($p < 0.001$). Regarding the site of injury, ankle involvement was more common in patients with pathology detected on both X-ray and CT (54.3%), whereas isolated foot injuries were more frequent in patients with CT-only pathology (45.5%) ($p < 0.001$). Evaluation of associated injuries revealed that extremity injuries were the most common (7.0%). Multiple body injuries were observed more frequently in patients with detected pathology (8.7%), and this difference approached statistical significance ($p = 0.051$) (Table 2).

Analysis of treatment approaches revealed that 53% of all patients received medical management, 30.5% were treated with splinting/casting, and 11.4% underwent surgical intervention, while 5.1% either refused treatment or were referred. Significant differences in treatment distribution were observed among the imaging groups ($p < 0.001$). In the group with no pathology on X-ray and CT, medical treatment was the most frequently applied method (80%), whereas splinting/casting was more common in the CT-only pathology group (84.8%), and surgical intervention was more frequently performed in patients with pathology detected on both modalities (42.4%). Treatment modification was defined as the addition of another treatment to the existing one or a complete change in the treatment plan. Overall, treatment modification was identified in 15.1% of all patients. The need for treatment modification was 32.6% in patients with pathology detected on both X-ray and CT, whereas it was significantly higher in the CT-only pathology group at 78.8% ($p < 0.001$) (Table 3).

## DISCUSSION

Foot and ankle traumas are common injuries encountered in emergency departments and pose significant diagnostic challenges. In this study, a retrospective analysis of 370 cases was performed, evaluating both the demographic characteristics and the impact of imaging modalities on treatment processes. Approximately two-thirds of the patients (68.9%) were male, and the mean age was 29.2 years, indicating that such traumas occur predominantly in young and active populations. The most frequent cause of trauma was same-level fall or sprain (79.5%), which is consistent with the predominance of low-energy mechanisms reported in the literature (13).

The ankle joint is a complex structure composed of the articular surfaces of the tibia, fibula, and talus, together with its ligamentous components, and is therefore highly susceptible to trauma (13). In our study, fractures were detected in 32.2% of cases, while non-fracture injuries such as tendon lacerations, tendon ruptures, and amputations without fractures were identified in 15.9%. This finding highlight that in ankle trauma, not only bone fractures but also soft tissue lesions are of critical importance in clinical management.

**Table 2.** Distribution of patients' injury mechanisms, injury sites and associated injuries according to X-ray and CT findings (n = 370)

| Variable | Subgroup | X-ray + CT normal n (%) | Pathology on both X-ray and CT n (%) | Pathology only on CT n (%) | Total n (%) | p |
|---|---|---|---|---|---|---|
| Mechanism of Injury | Traffic accident | 10 (4.1) | 9 (9.8) | 1 (3.0) | 20 (5.4) | <0.001 |
| | Fall from height | 5 (2.0) | 17 (18.5) | 3 (9.1) | 25 (6.8) | |
| | Same-level fall / sprain | 214 (87.3) | 52 (56.5) | 28 (84.8) | 294 (79.5) | |
| | Firearm injury | 0 (0.0) | 4 (4.3) | 0 (0.0) | 4 (1.1) | |
| | Sharp/stabbing object | 2 (0.8) | 2 (2.2) | 0 (0.0) | 4 (1.1) | |
| | Other | 14 (5.7) | 8 (8.7) | 1 (3.0) | 23 (6.2) | |
| Injury Site | Isolated foot | 17 (6.9) | 36 (39.1) | 15 (45.5) | 68 (18.4) | <0.001 |
| | Isolated ankle | 20 (8.2) | 50 (54.3) | 18 (54.5) | 88 (23.8) | |
| | Foot + ankle | 208 (84.9) | 6 (6.5) | 0 (0.0) | 214 (57.8) | |
| Associated Injuries | Head–neck | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0.051 |
| | Thorax | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.3) | |
| | Abdomen | 0 (0.0) | 1 (1.1) | 0 (0.0) | 1 (0.3) | |
| | Pelvis | 2 (0.8) | 0 (0.0) | 0 (0.0) | 2 (0.5) | |
| | Vertebra | 1 (0.4) | 2 (2.2) | 0 (0.0) | 3 (0.8) | |
| | Extremity (other) | 20 (8.2) | 5 (5.4) | 1 (3.0) | 26 (7.0) | |
| | Multiple injuries | 2 (0.8) | 8 (8.7) | 1 (3.0) | 11 (3.0) | |
| | None | 218 (89.0) | 76 (82.6) | 31 (93.9) | 325 (87.8) | |

**Table 3.** General treatment approaches of patients, treatment distributions according to imaging findings and treatment modification rates (n = 370)

| Treatment | Overall (n=370) n (%) | X-ray + CT normal (n=245) n (%) | Pathology on both X-ray and CT (n=92) n (%) | Pathology only on CT (n=33) n (%) | p |
|---|---|---|---|---|---|
| Medical only | 196 (53.0) | 196 (80.0) | 0 (0.0) | 0 (0.0) | <0.001 |
| Splint / Cast | 113 (30.5) | 39 (15.9) | 46 (50.0) | 28 (84.8) | |
| Surgery | 42 (11.4) | 1 (0.4) | 39 (42.4) | 2 (6.1) | |
| Minor surgical procedure | 7 (1.9) | 5 (2.0) | 2 (2.2) | 0 (0.0) | |
| Referral | 2 (0.5) | 0 (0.0) | 2 (2.2) | 0 (0.0) | |
| Refusal of treatment | 10 (2.7) | 4 (1.6) | 3 (3.3) | 3 (9.1) | |
| Treatment modification | 56 (15.1) | - | 30 (32.6) | 26 (78.8) | <0.001 |

Furthermore, the significantly lower GCS values observed in patients with pathology detected on both X-ray and CT (p = 0.018) indicate that traumas in this group tend to present with more severe clinical courses. The literature emphasizes that X-ray often fails to detect posterior and medial malleolar fractures, Tillaux fractures, and complex patterns, whereas CT is superior in demonstrating the degree of comminution, intra-articular fragments, and anatomical relationships (14–17). In our study, the treatment modification rate of 78.8% in patients with CT-only pathology represents a strong finding that supports this body of evidence. In other words, in cases where X-ray is limited, CT emerges not merely as an adjunctive diagnostic tool but as a decisive modality that directly influences treatment strategies.

In our study, the relationship between imaging findings and treatment approaches was found to be statistically significant (p < 0.001). While medical management was the most frequently applied method in the overall patient group (53%), splinting/casting was markedly higher in the CT-only pathology group (84.8%), and the surgical intervention rate was 42.4% in patients with pathology detected on both modalities. This difference demonstrates that factors such as fracture location, degree of

comminution, and extension into the joint space directly influence treatment decisions. The literature similarly reports that fracture classifications play a critical role in prognosis and treatment planning, with surgical requirements being more common in complex fractures involving the articular surface (18,19). Moreover, X-ray has been shown to be insufficient in evaluating the intra-articular extension of fractures, whereas CT is emphasized as necessary in such cases (20). Preoperative CT evaluation of trimalleolar fractures has been reported to alter surgical strategy in approximately one-quarter of cases (21–23). In our findings, the fact that most of the CT-only pathologies were treated with splinting/casting indicates that CT plays a critical role not only in surgical planning but also in guiding conservative treatment approaches.

Treatment modification was required in 15.1% of cases, underscoring the decisive role of imaging findings in clinical management. Notably, the rate of treatment modification was found to be remarkably high at 78.8% in the CT-only pathology group ($p < 0.001$), demonstrating that the diagnostic power of CT directly translates into patient management. Similar findings have been reported in the literature, where CT examinations significantly influenced treatment strategies. Nenopoulos et al. reported that 71.6% of patients evaluated with X-ray alone received conservative treatment, while the surgical rate increased to 65.6% when CT was added (24). Liporace demonstrated that the addition of CT converted conservative treatment plans to surgery in 13% of patients, and Leung et al. showed that in 20% of cases initially planned for surgery after X-ray, surgical approaches were altered following CT evaluation (25,26). In our study, the exceptionally high rate of treatment modification in CT-only pathology cases not only aligns with but also exceeds previously reported results, thereby highlighting the stronger determinant impact of CT on clinical management.

The surgical intervention rate reaching 42.4% in patients with pathology detected on both imaging modalities indicates that the injuries in this group were more complex. In the literature, the critical role of CT in evaluating posterior malleolar fractures has been emphasized. Donohoe et al. reported that plain radiographs identified complex patterns in only 44% of cases, whereas CT increased this rate to 56%, with surgeons altering their surgical approaches in 44% of cases after CT evaluation (27). Meijer et al. reported that the diagnostic accuracy of lateral X-ray measurements was only 22% compared with CT findings (28), while Mangnus and Ferries stated that CT should be preferred in the evaluation of posterior malleolar fractures due to its ability to more accurately reflect joint integrity (29,30). In our study, the significantly higher surgical intervention rates observed in CT-supported cases were consistent with these findings in the literature.

Pediatric cases should also be evaluated with particular clinical attention. Distal tibial physeal fractures are the second most common fractures in children and carry a high risk of secondary complications. In the literature, the sensitivity of X-ray in detecting these fractures has been reported to range between 54% and 90%, with high rates of misclassification particularly in Salter-Harris type III fractures (10,31). Although a separate analysis for pediatric patients was not performed in our study, it is likely that physeal fractures were among the cases with CT-only pathology that required treatment modification. Furthermore, CT has been shown to better demonstrate fracture lines and displacement than X-ray in calcaneal fractures, thereby guiding treatment decisions (32,33). Our findings support this evidence, showing that treatment strategies were altered specifically in cases where pathologies were identified only with CT.

Although talar fractures are rare, they are associated with high-energy trauma, and if not accurately diagnosed, they can lead to serious complications such as avascular necrosis or early osteoarthritis. The sensitivity of X-ray in detecting talar fractures has been reported to be as low as 30%, with diagnostic insufficiency becoming more evident in comminuted and intra-articular fractures (10). Calcaneal fractures are similarly complex; while initially imaged with X-ray, CT is known to delineate fracture lines and displacement much more effectively (33). The literature highlights CT as a powerful tool in evaluating fractures of the ankle joint region, reporting that more than 20% of significant pathologies are missed by X-ray and therefore recommending routine CT scanning (34,35). In our study, the high rate of treatment modification in cases where pathology was detected only by CT ($p < 0.001$) provides supportive evidence consistent with these recommendations.

One of the most frequently overlooked pathologies in ankle trauma is syndesmotic injury. The distal tibiofibular syndesmosis can be easily damaged by fractures or ligamentous injuries, and if not correctly diagnosed, it may result in chronic pain and early osteoarthritis (36). In the literature, X-ray has been reported to have low sensitivity in detecting these injuries, whereas CT demonstrates nearly twice the diagnostic sensitivity; moreover, CT has been shown to be superior in identifying minor injuries, in the postoperative evaluation of reduction, and in accuracy compared with lateral radiographic measurements (37–39). In our study, the treatment modification rate was found to be as high as 78.8% among patients with CT-only pathology ($p < 0.001$), suggesting that syndesmotic injuries may have contributed to this group. Indeed, such injuries have been emphasized in the literature as an important risk factor for early osteoarthritis (35,40). Furthermore, the overall sensitivity of X-ray has been reported as 75%, with particularly low sensitivities for talar (30%) and trimalleolar (17%) fractures, and additional fractures were missed in 22% of cases (10,28,35). Our findings, especially the high rate of treatment modification in the CT-positive group, support these reports and further reinforce the critical role of CT in clinical management.

It is well known that misdiagnosed or missed fractures can lead to long-term complications. The literature reports that Tillaux and Chaput fractures may be easily overlooked on X-ray, with Letts et al. documenting that 5 out of 26 cases in their series were not diagnosed by X-ray (41). Similarly, missed fractures, syndesmotic injuries, or intra-articular loose bodies are among the major risk factors for the development of early osteoarthritis (42,43). Numerous studies have emphasized that untreated syndesmotic injuries, in particular, lead to early arthrosis (44,45). In our study, the

high rate of treatment modification in patients with CT-only pathology ($p < 0.001$) also indicates that CT plays a critical role in preventing such complications.

Our study has certain limitations due to its retrospective design and single-center setting. The exclusion of soft tissue imaging modalities such as MRI and the inability to analyze pediatric cases as a separate subgroup are additional constraints. Moreover, the lack of detailed classification of fracture types limits the generalizability of the results to specific clinical subgroups. Nevertheless, the large patient cohort and the quantitative demonstration of CT's impact on clinical decision-making enhance the originality and significance of the study. In this respect, our research not only contributes to the literature on the role of CT in the diagnosis and management of foot and ankle trauma but also serves as a guide for future prospective and multicenter studies.

## CONCLUSION

Therefore in the management of foot and ankle trauma in the emergency department, selecting the appropriate imaging modality is of critical importance for establishing an accurate diagnosis and determining the proper treatment plan. This study demonstrates that computed tomography, through its superior imaging capacity compared with conventional radiography, can significantly contribute to clinical decision-making, particularly in the evaluation of complex fractures and joint involvement. The findings suggest that CT may serve as a complementary tool both in defining surgical indications and in guiding conservative approaches. However, the limitations of its single-center and retrospective design should be considered, and these results need to be supported by multicenter and prospective studies involving diverse patient groups. In this way, the role of CT in the diagnosis and treatment of foot and ankle trauma will be more clearly established and more strongly defined in clinical practice.

### Ethical Approval

The study was approved by the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (Date: 12/02/2021, Decision No: 2021/02-10).
The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Conflict of Interest

No potential conflict of interest was reported by the authors.

### Financial Disclosure

The authors received no financial support for the research, authorship and publication of this article.

### Authors' Contributions

B.Ö.K. and M.R.Ö. contributed to study design, data collection, analysis, literature review, writing, and editing; M.R.Ö. supervised and provided guidance for the study.

### Data Sharing Statement

The dataset used and analyzed in the study is available from the corresponding author upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, the data is not publicly available.

### *Thesis Note

This article is derived from the specialty thesis titled "Comparison of Treatment Options According to X-ray and Computed Tomography Findings in Patients Presenting to the Emergency Department with Foot and Ankle Trauma" prepared by Dr. Burcu Özen Karabulut.

## REFERENCES

1. Zhao E, Carney D, Chambers M, Ewalefo S, Hogan, M. The role of biologic in foot and ankle trauma-a review of the literature. Curr Rev Musculoskelet Med. 2018;11(3): 495–502.
2. Barile A, Bruno F, Arrigoni F, et al. Emergency and trauma of the ankle. Semin Musculoskelet Radiol. 2017;21(3):282–289.
3. Mo K, Gupta A, Singh P, et al. Emergency department visits for ankle fractures through COVID-19: an analysis of the National Electronic Injury Surveillance System. Foot Ankle Orthop. 2022;7(3):24730114221119188.
4. Mascio A, Greco T, Comisi C, et al. Foot and ankle trauma: Epidemiology before, during, and post covıd-19 pandemic in a level ı trauma center: A 5-year experience and data analysis. J Clin Med. 2024;13(24):7585.
5. Goldstein CL, Schemitsch E, Bhandari M, Mathew G, Petrisor BA. Comparison of different outcome instruments following foot and ankle trauma. Foot Ankle Int. 2010;31(12):1075–1080.
6. Thomas AC, Hubbard-Turner T, Wikstrom EA, Palmieri-Smith RM. Epidemiology of posttraumatic osteoarthritis. J Athl Train. 2017;52(6):491–496.
7. Godoy-Santos AL, de Cesar C, Santini S, Herrera-Pérez M, Valderrabano V, Rammelt S. Pathophysıology of posttraumatıc ankle osteoarthrıtıs: a multıcenter perspectıve. Acta Ortop Bras. 2024;32(3):e282286.
8. De Marchi Neto N, Nesello PFT, Bergamasco JM, Costa MT, Christian RW, Severino NR. Importance of computed tomography in posterior malleolar fractures: Added information to preoperative X-ray studies. World J Orthop. 2023;14(12):868–877.
9. Johnson PT, Fayad LM, Fishman EK. Sixteen-slice CT with volumetric analysis of foot fractures. Emerg Radiol. 2006;12(4):171–176.
10. Avcı M, Kozacı N, Yüksel S, Etli I, Yilmaz Y. Comparison of radiography and computed tomography in emergency department evaluation of ankle trauma. Ann Med Res. 2019;26:867-872.
11. Addala TE, Greffier J, Hamard A, et al. Early results of ultra-low-dose CT-scan for extremity traumas in emergency room. Quant Imaging Med Surg. 2022;12(8):4248–4258.

12. Kalantar SH, Bagheri N, Milan N, et al. Evaluation of treatment planning discrepancies: CT versus plain radiographic findings in patients with foot and ankle trauma. BMC Res Notes. 2024;17(1): 238.
13. Allen SD, Harvey CJ, O'Regan D. Interpretation of ankle and foot radiographs. Br J Hosp Med (Lond). 2006; 67(1): M8–M11.
14. Caracchini G, Pietragalla M, De Renzis A, et al. Talar fractures: radiological and CT evaluation and classification systems. Acta Biomed. 2018;89(1-S):151–165.
15. Sarter M, Krane F, Hockmann J, Leschinger T, Müller LP, Harbrecht A. How Valuable is the CT? Assessment of the Presence of Posterior Malleolar Fractures in Plane Radiographs. Foot Ankle Spec. 2025;14:19386400251351516.
16. Black EM, Antoci V, Lee JT, et al. Role of preoperative computed tomography scans in operative planning for malleolar ankle fractures. Foot Ankle Int. 2013;34(5):697–704.
17. Gibson PD, Bercik MJ, Ippolito JA, et al. The role of computed tomography in surgical planning for trimalleolar fracture. A survey of ota members. J Orthop Trauma. 2017;31(4):e116–e120.
18. Tartaglione JP, Rosenbaum AJ, Abousayed M, DiPreta JA. Classifications in brief: Lauge-hansen classification of ankle fractures. Clin Orthop Relat Res. 2015;473(10):3323–3328.
19. Mulligan M. E. (2000). Ankle and foot trauma. Seminars in musculoskeletal radiology, 4(2), 241–253.
20. Hwang JS, Koury KL, Gorgy G, et al. Evaluation of intra-articular fracture extension after gunshot wounds to the lower extremity: plain radiographs versus computed tomography. J Orthop Trauma. 2017;31(6):334–338.
21. Chen Y, Zhang K, Qiang M, Li H, Dai H. Comparison of plain radiography and CT in postoperative evaluation of ankle fractures. Clin Radiol. 2015;70(8): e74–e82.
22. Angthong C, Atikomchaiwong A, Yoshimura I, et al. Does the addition of computed tomography to computed radiography provide more value to final outcomes and treatment decisions in displaced intra-articular calcaneal fractures? J Med Assoc Thai. 2014;97(9):S1–S9.
23. Kocan J, Joseph E, Mercado P, Haider MN, Pavlesen S, Rohrbacher B. (2024). Computed Tomography Scans and Fixation Rates for Trimalleolar Ankle Fractures Over 10 Years at a Level 1 Trauma Center. Foot Ankle Orthop. 2024;9(1): 24730114231216984.
24. Nenopoulos A, Beslikas T, Gigis I, Sayegh F, Christoforidis I, Hatzokos I. The role of CT in diagnosis and treatment of distal tibial fractures with intra-articular involvement in children. Injury. 2015;46(11): 2177–2180.
25. Liporace FA, Yoon RS, Kubiak EN, et al. Does adding computed tomography change the diagnosis and treatment of Tillaux and triplane pediatric ankle fractures? Orthopedics. 2012;35(2):e208–e212.
26. Leung KH, Fang CX, Lau TW, Leung FK. Preoperative radiography versus computed tomography for surgical planning for ankle fractures. J Orthop Surg (Hong Kong). 2016;24(2), 158–162.
27. Donohoe S, Alluri RK, Hill JR, Fleming M, Tan E, Marecek G. Impact of Computed Tomography on Operative Planning for Ankle Fractures Involving the Posterior Malleolus. Foot Ankle Int. 2017;38(12):1337–1342.
28. Meijer DT, Doornberg JN, Sierevelt IN, et al. Guesstimation of posterior malleolar fractures on lateral plain radiographs. Injury. 2015;46(10):2024–2029.
29. Jubel A, Faymonville C, Andermahr J, Boxberg S, Schiffer G. Einschränkungen der Aussagekraft des konventionellen Röntgenbilds bei Sprunggelenksfrakturen im Alter [Conventional X-Rays of Ankle Joint Fractures in Older Patients are Not Always Predictive]. Z Orthop Unfall. 2017;155(1):45–51.
30. Mangnus L, Meijer DT, Stufkens SA, et al. Posterior malleolar fracture patterns. J Orthop Trauma. 2015;29(9):428–435.
31. Lemburg SP, Lilienthal E, Heyer CM. Growth plate fractures of the distal tibia: is CT imaging necessary?. Arch Orthop Trauma Surg. 2010:130(11):1411–1417.
32. Linsenmaier U, Brunner U, Schöning A, et al. Classification of calcaneal fractures by spiral computed tomography: implications for surgical treatment. European radiology, 2003:13(10):2315–2322.
33. Badillo K, Pacheco JA, Padua SO, Gomez AA, Colon E, Vidal JA. Multidetector CT evaluation of calcaneal fractures. Radiographics. 2011;31(1):81–92.
34. Vosoughi AR, Hoveidaei AH, Roozbehi Z, Heydari Divkolaei SM, Zare S, Borazjani R. Patterns of Ankle Fractures Based on Radiographs and CT Images of 1000 Consecutive Patients. Arch Bone Jt Surg. 2024;12(2): 128–135.
35. Szymański T, Zdanowicz U. Comparison of routine computed tomography and plain X-ray imaging for malleolar fractures-How much do we miss?. Foot Ankle Surg. 2022;28(2):263-268.
36. Yeung TW, Chan CY, Chan WC, Yeung YN, Yuen MK. Can pre-operative axial CT imaging predict syndesmosis instability in patients sustaining ankle fractures? Seven years' experience in a tertiary trauma center. Skeletal Radiol. 2015;44(6):823-829.
37. Sowman B, Radic R, Kuster M, Yates P, Breidiel B, Karamfilef S. Distal tibiofibular radiological overlap: Does it always exist?. Bone Joint Res. 2012;1(2): 20–24.
38. Ebraheim NA, Lu J, Yang H, Mekhail AO, Yeasting RA. Radiographic and CT evaluation of tibiofibular syndesmotic diastasis: a cadaver study. Foot Ankle Int.1997;18(11):693–698.
39. Dikos GD, Heisler J, Choplin RH, Weber, TG. (2012). Normal tibiofibular relationships at the syndesmosis on axial CT imaging. Journal of orthopaedic trauma, 2012;26(7): 433–438.
40. Valkering KP, Vergroesen DA, Nolte PA. Isolated syndesmosis ankle injury. Orthopedics, 2012;35(12):e1705–e1710.
41. Letts R. M. The hidden adolescent ankle fracture. J Pediatr Orthop. 1982;2(2):161–164.
42. Barg A, Pagenstert GI, Hügle T, et al. Ankle osteoarthritis: etiology, diagnostics, and classification. Foot Ankle Clin. 2013;18(3):411–426.

43. Cheng YM, Huang PJ, Hung SH, Chen TB, Lin SY. The surgical treatment for degenerative disease of the ankle. Int Orthop. 2000;24(1): 36–39.
44. Lloyd J, Elsayed S, Hariharan K, Tanaka H. Revisiting the concept of talar shift in ankle fractures. Foot Ankle Int. 2006;27(10):793–796.
45. Switaj PJ, Mendoza M, Kadakia AR. Acute and Chronic Injuries to the Syndesmosis. Clin Sports Med. 2015;34(4):643–677.
46. Elgohary MMI, Abdul Rahim SAA, Ibrahim TAA. Role of MRI in evaluation of traumatic ankle injuries. Egypt J Hosp Med. 2017;69(3):2016-24.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):130-133*
*e-ISSN: 2980-0978*

***Case Report/Olgu Sunumu***
***DOI:10.61845/agrimedical.1604928***

# Intracranial lipoma detected incidentally after trauma: A case report

## Travma sonrası rastlantısal tespit edilen intrakraniyal lipom: Olgu sunumu

Yener Çakır[1*], Enes Koç[1], Mualla Özsöz[1], Hakan Ak[2]

[1] *Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Kırşehir/ Türkiye*
[2]*Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Beyin ve Sinir Cerrahisi Anabilim Dalı, Kırşehir/Türkiye*

*0009-0004-8381-6343*
*0009-0003-2994-5032*
*0009-0003-3549-7555*
*0000-0001-6975-9822*

**Sorumlu Yazar:*
*Yener Çakır*
*Kırşehir Ahi Evran Üniversitesi, Tıp Fakültesi, Kırşehir/ Türkiye*
*e-mail:*
*kevaeryener4835@gmail.com*

Gönderilme Tarihi: 20/12/2024
Kabul Tarihi: 14/08/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:**
Çakır Y, Koç E, Özsöz M, Ak H. Intracranial lipoma detected incidentally after trauma: A case report. Ağrı Med J. 2025; 3(3):130-133.

**ABSTRACT**

Intracranial lipoma is a pathology that is generally asymptomatic and is diagnosed incidentally in the clinic. Although the diagnosis is made incidentally on intracranial imaging of patients who apply to the clinic for different reasons, the appearance of pneumocephalus, especially on computerized tomography (CT) sections, may mislead the physician in the differential diagnosis. The golden standart in the radiological diagnosis of intracranial lipoma is the magnetic resonance imaging (MRI). However, calculating the lesion density in Hounsfield Units in cranial CT examinations can also strengthen the diagnosis. In this case, our approach to the case of intracranial lipoma, which was detected incidentally in a patient admitted to the emergency department due to head trauma, was evaluated in the light of the literature.

**Keywords:** *Intracranial lipoma, Magnetic resonance imaging, Computed tomography, Hounsfield unit*

**ÖZ**

İntrakraniyal lipom genellikle asemptomatik seyreden ve klinikte tesadüfen tanı konulan bir patolojidir. Farklı nedenlerle kliniğe başvuran hastaların intrakraniyal görüntülemelerinde rastlantısal bir şekilde tanı konulmakla birlikte özellikle bilgisayarlı tomografi (BT) kesitlerinde pnömosefali görüntüsü vermesi hekimi ayırıcı tanıda yanıltabilmektedir. İntrakraniyal lipom radyolojik tanısında altın standart manyetik rezonans görüntülemedir. Kraniyal BT tetkiklerinde lezyon yoğunluğunun Hounsfield birimi olarak hesaplanması da tanıyı güçlendirebilmektedir. Bu sunumda kafa travması nedeniyle acil servise başvuran hastada tesadüfen saptanmış olan intrakraniyal lipom vakasına yaklaşımımız literatür eşliğinde değerlendirilmiştir.

**Anahtar Kelimeler**: İntrakraniyal lipom, Manyetik rezonans görüntüleme, Bilgisayarlı tomografi, Hounsfield birimi

## GİRİŞ

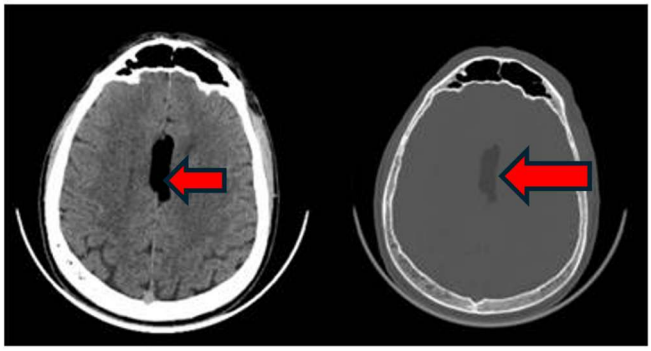
İntrakraniyal lipom (İKL) genellikle asemptomatik seyreden ve klinikte tesadüfen tanı konulan bir patolojidir. İntrakraniyal lezyonların %1'inden daha azını oluşturan bu lezyonlar, hem nadir olması hem de rastlantısal bulunması nedeniyle ayırıcı tanıda atlanabilmektedir (1). Farklı nedenlerle kliniğe başvuran hastaların intrakraniyal görüntülemelerinde rastlantısal bir şekilde tanı konulmaktadır. Özellikle bilgisayarlı tomografi (BT) kesitlerinde pnömosefali görüntüsü vermesi hekimi ayırıcı tanıda yanıltabilmektedir. İKL genellikle asemptomatik seyreden bir lezyon olmakla birlikte nadiren kitle etkisine bağlı olarak semptomatik hale gelebilir. En sık başvuru semptomu baş ağrısıdır. Bunun yanı sıra hastalar nöbet, bilinç bozukluğu, pleji gibi nörolojik semptomlarla başvurabilir (1,2). İKL genellikle orta hat veya orta hatta yakın yerleşim göstermektedirler. En sık yerleşim yerinin korpus kallozum olduğu rapor edilmiştir (3).

İKL'nin radyolojik tanısında BT değerli bilgiler sağlayabilmesine rağmen manyetik rezonans görüntüleme (MRG) tanıda altın standarttır. BT görüntülemelerinde İKL hipodens olarak görülürken, MRG'de hiperintens olarak görülmektedir. İKL'lerin özellikle MRG kesitlerindeki hiperintens görünümü hekime tanı koymada büyük kolaylık sağlayabilmektedir. Kraniyal BT tetkiklerinde lezyon yoğunluğunun Hounsfield birimi olarak hesaplanması da tanıyı güçlendirebilmektedir (4).

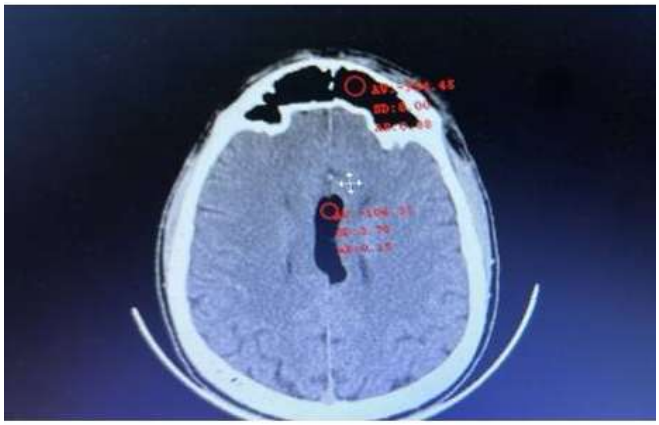
Bu yazıda travma nedeniyle acil servise başvuran hastada rastlantısal olarak tanı konulmuş olan İKL olgusu sunulmaktadır.

## OLGU

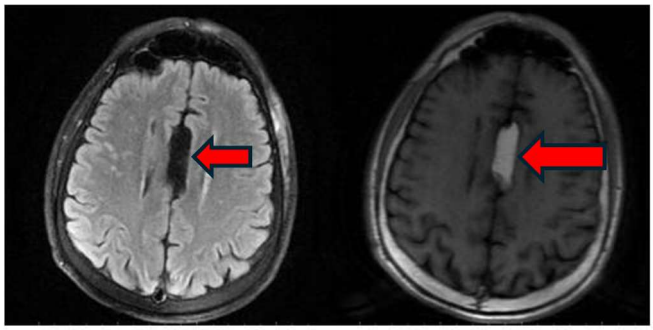
48 yaşında erkek hasta kafasına aldığı darbe sonrası acil servise başvurdu. Burun üzerinde ekimoz ve ödemi mevcuttu. Hastanın özellikle darbenin geldiği yer olan burun bölgesine lokalize olan hafif ağrı dışında şikayeti yoktu. Hastanın bilinci açık olup, kooperasyonu ve oryantasyonu tamdı. Glasgow Koma skoru 15 idi. Nörolojik muayenesinde herhangi bir nörolojik defisite rastlanmadı. Hastanın çekilen beyin BT'sinde supraventriküler bölgede pnömosefali veya lipom ile uyumlu patoloji görülmüştür (Şekil 1). Saptanan lezyon haricinde epidural/subdural kanama gibi kafa içi patoloji ya da kafatası ve/veya maksilofasiyal kırık lehine bir bulguya rastlanmadı. Lezyonun yoğunluğuna baktığımızda -106,33 Hounsfield birimi (HU) olduğu görüldü (Şekil 2). Aynı kesitten ölçülen frontal sinüsteki HU ise 354,45 olarak saptandı. Hastanın ayrıcı tanısını yapmak ve tanımızı güçlendirmek amacıyla kraniyal MRG yapıldı. Yapılan MRG'de supraventriküler bölgede düzgün sınırlı hiperintens lezyon görülmesi üzerine hastaya İKL tanısı konuldu (Şekil 3, Şekil 4). Baş ağrısı dışında herhangi bir semptom ve bulgusu olmayan hastada cerrahi girişim düşünülmemiş olup poliklinik kontrollerine gelmek üzere acil servisten taburcu edildi.



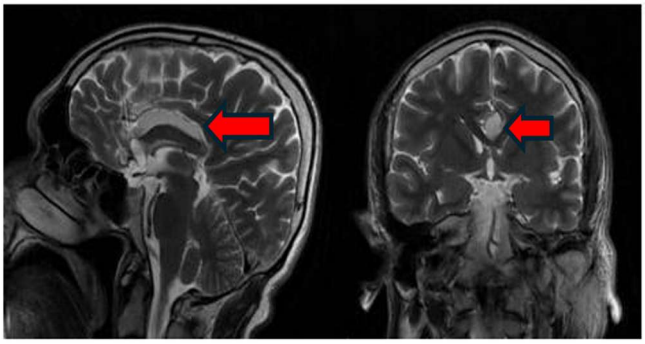
**Şekil 1.** Beyin BT'de parankim ve kemik pencerede supraventriküler bölgede görünen hipodens lezyon



**Şekil 2.** Beyin BT'de görünen lezyona ve frontal sinüse ait yoğunluk ölçümü. Frontal sinüs HU:354,45; Lezyona ait HU:-106,33



**Şekil 3.** Beyin MR' ında T1 ve FLAIR sekansta lezyonun aksiyel kesitte görünümü



**Şekil 4.** Beyin MR'ında T2 sekansta lezyonun sagittal ve koronal kesitte görünümü

## TARTIŞMA

İKL'ler konjenital gelişim gösteren iyi huylu nadir tümörlerdir. Literatürdeki İKL'ler ile ilgili çalışma sayısı sınırlı olup çalışmaların büyük bir kısmı olgu sunumu şeklindedir. Literatürde ilk olarak 1818 yılında Meckel kiazmada İKL tanımlamış, Rokitansky ise 1856 yılında korpus kallozum agenezisini ve perikallozal lipomu bildirmiştir (5). İKL hakkında yapılmış en geniş çalışma 1990 yılında Truwit ve Barokowich tarafından yayınlanmış olan makale olup, 42 olgunun dahil olduğu bu çalışma İKL'lerin yerleşim yerlerinin sıklığı hakkında önemli bilgiler vermektedir. Çalışmada İKL yerleşim yerleri sıklığının, %64 korpus kallozum, %13 infindubular kiazma, %0.06 serebellopontin köşe olduğunu bildirilmiştir (6). Hastamızda da lipom yerleşimi literatür ile uyumlu olarak supraventriküler orta hattaydı.

İntrakraniyal lipomların patogenezini incelediğimizde bu konu ile ilgili birden fazla hipotez olduğu görülmüştür. Bu hipotezler; nöral tüpün gelişimi sırasında kutanöz ektoderm ile mezodermin hatalı ayrışması, ayrışma sürecinde bir bozukluk meydana gelmesi, meninks bağ dokusunun metaplazisi ya da meninkste yağ doku hipertrofisi şeklindedir. Son zamanlarda yapılan bazı çalışmalarda ise İKL'un konjenital bir malformasyon olduğu rapor edilmiştir. İntrauterin dönemde primitif mezenkimal dokunun yanlış şekilde farklılaşması ve ektopik dokuların artıklarından İKL oluştuğu düşünülmektedir (5-7).

İKL'ler çoğu zaman semptom vermediği için tanı da genellikle radyolojik görüntülemeler esnasında rastlantısal olarak konulmaktadır. Bu vaka sunumunda olduğu gibi başka nedenlerle yapılan radyolojik tetkikler esnasında İKL tanısından şüphelenilmektedir. BT'de sınırları kısmen düzgün hipodens görüntü lipom konusunda uyarıcı olmaktadır. Tomografide hipodens görüntünün pnömosefali ile karıştırılması muhtemeldir. Bu nedenle hastanın tomografisi değerlendirilirken pnömosefali yapabilecek kafa tabanı kırığı ve/veya sinüs kırığı varlığına dikkat edilmesi önemlidir. MRG'nin mümkün olmadığı durumlarda hipodens alandan HU ile ölçüm yapılması hastamızda olduğu gibi tanıda yardımcı ek bilgiler sağlayabilir. Bu nedenle özellikle manyetik rezonans görüntülemenin mümkün olmadığı arada kalınan olgularda HU birimi ile ölçüm yapılması hastanın daha hızlı şekilde ileri bir sağlık kuruluşuna sevkini sağlayacaktır. Bu ölçümlerin daha sağlıklı yapılabilmesi ve daha standardize hale getirilmesi durumunda MRG çekilmesine ihtiyaç kalmayacaktır. Bununla birlikte günümüzde MRG, İKL tanısında halen altın standart olmaya devam etmektedir.

İKL'lara yaklaşımda lezyon asemptomatik kaldığı sürece takip önerilmektedir. Semptomatik vakalarda ise mortalite ve nörolojik sekel riski ve lipomun yerleşim yeri göz önünde bulundurularak lipomun eksizyonu veya kraniyal dekompresyon düşünülebilmektedir (8). Cerrahi esnasında lipomların genel olarak çevre dokuya yapışıklık göstermeleri ve nörovasküler yapıları çevrelemeleri mümkündür bu nedenle bu lezyonların cerrahi olarak çıkarılmaya çalışılması yüksek oranda kalıcı sakatlık ve ölüm ile sonuçlanabilmektedir. Bu nedenle cerrahi girişimin kafa içi basınç artışı, ilaçla kontrol altına alınamayan nöbet, ventriküler sistemin tıkanarak hidrosefaliye yol açması ve ilerleyici demans gibi durumlar gelişmediği müddetçe yapılması önerilmemektedir (5). Olgumuzda da lezyonun herhangi bir klinik tabloya yol açmamış olması nedeniyle cerrahi girişim düşünülmemiş olup hasta poliklinik kontrolleri ile takip edilmektedir.

## SONUÇ

Özellikle travma hastaları başta olmak üzere tomografide hipodens lezyon görülen hastalarda ayırıcı tanıda pnömosefali ile lipom arasında kalınan olgularda, hastanın tomografi görüntülerinin pnömosefaliye yol açabilecek kırık varlığı yönünden dikkatlice değerlendirilmesi ve hipodens alanlarda HU ile ölçüm yapılması ve bu ölçüm değerlerinin standardize edilebilmesi önem arz etmektedir. Böylelikle, gereksiz sevklerin ve MRG gibi ileri radyolojik tetkiklere duyulan ihtiyacın azalması sayesinde hem iş yükü hafifleyecek hem de zaman ve maliyet açısından tasarruf sağlanabilecektir.

### Bilgilendirilmiş Onam
Bu olgu sunumu için hastanın bilgilendirilmiş onamı alınmıştır.

### Etik onay
Çalışma etik kurul onayı gerektirmemektedir.

### Çıkar çatışması
Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.

### Finansal destek
Çalışma için herhangi bir mali destek alınmamıştır.

### Yazarların Katkıları
YÇ: Ana fikir/planlama, literatür taraması, yazım. EK: Veri toplama/işleme, veri analizi ve yorumlama, yazım. MÖ: Veri toplama/işleme, literatür taraması, gözden geçirme ve düzeltme. HA: Ana fikir/planlama, veri analizi ve yorumlama, gözden geçirme ve düzeltme

**KAYNAKLAR**

1. Alkhaibary A, Alsubaie N, Alharbi A, et al. Hypothalamic lipoma: Outcome of an ıntracranial developmental lesion. Case RepSurg. 2022;15:7216090.
2. Kalekar T, MS, Reddy LP, Prabhu AS, Lamghare P. Neuroimaging spectrum of ıntracranial lipomas. Cureus. 2023;15(2):e35063.
3. Arshad F, Kulanthaivelu K, Yadav R. Intracranial lipoma: an incidental finding and a rare cause of secondary headache. Int J Neurosci. 2024;4:1-4.
4. Romano N, Castaldi A. Imaging of intracranialfat: from normal findings to pathology. Radiol Med. 2021;126(7):971-8.
5. Ovalıoğlu AÖ, Yılmaz İ, Öğrenci A, Batçık E, Bilge T. İntrakranial lipomlar; iki olgu sunumu. Ş.E.E.A.H. Tıp Bülteni. 2012; 46(4): 217-20.
6. Truwit CL, Barkovich AJ. Pathogenesis of intracranial lipoma: an MR study in 42 patients. AJR. 1990; 155: 855-64.
7. Bellamkonda SK, Vadana B, Kondragunta CR, Balije S. Intracranial lipoma with extracranial subcutaneous componentwith a midline bony defect and persistentfalcinesinus. BJR Case Rep. 2023;9(6):20220011.
8. Elgassim MAM, Wafer A, Ahmed A, Elfaki A, Satti A, Anjum S. Intracranial lipoma extending extracranially in a five-year-old patient. Cureus. 2022;14(2):e21816.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):134-138*
*e-ISSN: 2980-0978*

***Case Report/Olgu Sunumu***
***DOI:10.61845/agrimedical.1716160***

# Severe serotonin syndrome due to high-dose venlafaxine: A rare case successfully managed with chlorpromazine

## Yüksek doz venlafaksine bağlı şiddetli serotonin sendromu: Klorpromazin ile başarıyla yönetilen nadir bir olgu

Mehmet Batuhan Duman[1], Hüsnü Serdar Kızıltunç[2*]

[1] *Department of Internal Medicine, Gebze Fatih State Hospital, Kocaeli, Turkey*
[2]*Department of Internal Medicine, Faculty of Medicine, Amasya University, Amasya, Turkey*

*0000-0003-2654-8640

*0000-0002-2361-5011

**Sorumlu Yazar:*
*Hüsnü Serdar Kızıltunç*
*Department of Internal Medicine, Faculty of Medicine, Amasya University, Amasya, Turkey*
*e-mail: s.kiziltunc@gmail.com*

Gönderilme Tarihi: 14/06/2025
Kabul Tarihi: 13/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:**
Duman MB, Kızıltunç HS. Severe serotonin syndrome due to high-dose venlafaxine: A rare case successfully managed with chlorpromazine. Ağrı Med J. 2025; 3(3): 134-138.

**ABSTRACT**

Serotonin syndrome is a potentially life-threatening clinical condition caused by excessive serotonergic activity within the central nervous system. In this report, we present the case of a 40-year-old woman with a diagnosis of major depressive disorder who developed serotonin syndrome following a suicidal ingestion of 3000 mg extended-release venlafaxine. The patient manifested agitation, clonus, generalized tonic–clonic seizures, and altered mental status. Despite intensive supportive care and administration of oral cyproheptadine, no clinical improvement was achieved. However, following intramuscular administration of 25 mg chlorpromazine, the patient demonstrated rapid neurological and hemodynamic recovery. This case highlights that severe serotonin syndrome may occur after ingestion of a single serotonergic agent at high doses, and that chlorpromazine may provide therapeutic benefit in cases where conventional treatments fail.

**Keywords:** *Serotonin syndrome, Venlafaxine hydrochloride, Chlorpromazine*

**ÖZ**

Serotonin sendromu, merkezi sinir sistemindeki aşırı serotonerjik aktiviteye bağlı olarak gelişen, potansiyel olarak yaşamı tehdit edebilen klinik bir tablodur. Bu yazıda, majör depresif bozukluk tanısıyla takip edilen ve suisidal amaçlı 3000 mg uzatılmış salınımlı venlafaksin alan 40 yaş kadın hastada gelişen serotonin sendromu olgusu sunulmaktadır. Hastada ajitasyon, klonus, jeneralize tonik-klonik nöbet ve bilinç değişikliği gelişmiştir. Yoğun destek tedavisi ve oral siproheptadin uygulanmasına rağmen klinik düzelme sağlanamamıştır. Ancak intramüsküler yoldan 25 mg klorpromazin uygulanmasının ardından hastada hızlı nörolojik ve hemodinamik iyileşme gözlenmiştir. Bu olgu, tek bir serotonerjik ajanın yüksek doz alımı sonrasında ciddi serotonin sendromu gelişebileceğini ve konvansiyonel tedavilerin yetersiz kaldığı durumlarda klorpromazinin terapötik fayda sağlayabileceğini desteklemektedir.

**Anahtar Kelimeler**: *Serotonin sendromu, Venlafaksin hidroklorür, Klorpromazin*

## INTRODUCTION

Serotonin syndrome, also referred to as serotonin toxicity, is a potentially life-threatening condition caused by increased serotonergic activity in the central nervous system. It may arise following therapeutic use, drug interactions, or intentional overdose. Etiologically, the most common agents implicated are selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, triptans, opioids (e.g., tramadol, meperidine), linezolid, and dextromethorphan. Although classically defined by the triad of mental status changes, autonomic instability, and neuromuscular abnormalities, clinical presentation can range from mild symptoms to fatal outcomes (1-4). The severity of findings is generally correlated with the degree of serotonergic excess (5). Mental status changes may include anxiety, agitation, disorientation, or delirium; autonomic findings may involve hyperthermia, tachycardia, hypertension, vomiting, and diarrhea. Neuromuscular manifestations typically include hyperreflexia, clonus (often in the lower extremities), muscle rigidity, and bilateral Babinski sign (3). Life-threatening complications such as seizures and hyperthermia have been reported in severe cases (6). Although serotonin syndrome is usually associated with polypharmacy and drug interactions, it can also result from an overdose of a single serotonergic agent. In this report, we present a rare case of serotonin syndrome following the ingestion of a high dose of extended-release venlafaxine in a suicide attempt. The primary approach to the management of serotonin syndrome is discontinuation of the offending agent and provision of intensive supportive care. In mild to moderate cases, benzodiazepines are commonly employed for sedation. Among the antiserotonergic agents, cyproheptadine is the most frequently used; it is available in oral form and has been shown to be effective, particularly in controlling refractory agitation, hyperthermia, and neuromuscular manifestations. Despite standard treatment, the patient's symptoms remained refractory. Remarkably, they resolved rapidly after intramuscular administration of chlorpromazine, a serotonin antagonist that is not routinely used for serotonin syndrome.

## CASE

A 40-year-old female with a known diagnosis of major depressive disorder was on 75 mg/day of extended-release venlafaxine. She presented to the emergency department one hour after ingesting 40 tablets (3000 mg total) of venlafaxine in a suicide attempt. On arrival, she exhibited with generalized muscle rigidity and agitation. Initial vital signs were blood pressure 116/86 mmHg, heart rate 117 bpm, respiratory rate 14 breaths/min, $SpO_2$ 96% on room air, and body temperature 37.4°C. Gastric lavage and activated charcoal administration were promptly performed. The patient was subsequently transferred to the intensive care unit for close monitoring. Laboratory results on admission were BUN 11 mg/dL, creatinine 0.84 mg/dL, AST 19 U/L, ALT 22 U/L, glucose 104 mg/dL, sodium 139 mEq/L, potassium 3.7 mmol/L, and creatine kinase (CK) 108 U/L. During follow-up, her Glasgow Coma Scale score dropped to E3V4M5, and her pupils were noted to be bilaterally mydriatic. Arterial blood gas showed: pH 7.16; $pCO_2$ 42 mmHg; $HCO_3$ 15.1 mmol/L; $SpO_2$ 80%; and lactate 8.4 mmol/L. She experienced a 15-second generalized tonic-clonic seizure and was treated with intravenous midazolam, followed by endotracheal intubation. Her blood pressure dropped to 84/63 mmHg and heart rate increased to 140 bpm. Intravenous isotonic saline and magnesium sulfate were administered. ECG revealed sinus tachycardia at 136 bpm and a prolonged QTc interval of 545 ms, which improved to 403 ms after treatment. After the ingestion of a high dose of serotonergic agent, the patient manifested spontaneous clonus. A comprehensive review of medical history revealed no concomitant use of additional serotonergic agents or other pharmacological substances. There was no evidence of intravenous drug or stimulant use, nor clinical features suggestive of a withdrawal syndrome related to such agents. Physical examination and laboratory investigations demonstrated no findings consistent with an infectious process. Furthermore, cranial computed tomography did not reveal any additional pathological abnormalities. Taken together, the patient's clinical history, physical examination, laboratory data, and imaging studies supported the diagnosis of serotonin syndrome, established in accordance with the Hunter Serotonin Toxicity Criteria in the context of high-dose serotonergic exposure (Table 1). According to these criteria, in a patient with a history of serotonergic agent use, the presence of any one of the specified clinical findings is sufficient to establish the diagnosis of serotonin syndrome. Despite supportive measures, her vital signs and neurological status did not improve. Oral cyproheptadine 12 mg was administered via a nasogastric tube without clinical improvement over the following two hours. Subsequently, 25 mg intramuscular chlorpromazine was administered. Two hours after chlorpromazine administration, the patient's heart rate normalized to 81 bpm and blood pressure stabilized at 119/65 mmHg. Repeat blood gas analysis showed pH 7.31, $pCO_2$ 28 mmHg, $HCO_3$ 19 mmol/L, and lactate 1.7 mmol/L. She remained hemodynamically stable, and her neurological symptoms progressively improved. She was successfully extubated within 24 hours and transferred to the inpatient ward. All serotonergic agents were discontinued. The patient made a full recovery and was discharged in good condition.

**Table 1.** Hunter serotonin toxicity criteria

| |
|---|
| ➢ Spontaneous clonus |
| ➢ Inducible clonus+ [agitation or diaphoresis] |
| ➢ Ocular clonus + [agitation or diaphoresis] |
| ➢ Tremor + hyperreflexia |
| ➢ Hypertonia + temperature > 38°C + [ocular clonus or inducible clonus] |

**Table 2.** Clinical timeline of the patient

| Time (Hour) | Clinical Status | Interventions | Key Findings |
|---|---|---|---|
| 0 (Arrival) | Agitation, clonus, altered consciousness | Gastric lavage, activated charcoal | GCS E3V4M5, stable vitals |
| +1 h | Generalized seizure | IV midazolam, intubation | Lactate ↑, pH ↓, $SpO_2$ ↓ |
| +2 h | Supportive care + cyproheptadine | Cyproheptadine via NG tube | No improvement |
| +4 h | IM chlorpromazine administration | IM chlorpromazine 25 mg | HR ↓, BP stabilized |
| +6 h | Stabilization of vitals and consciousness | Continued monitoring | Improved neurological status |
| +24 h | Extubation, ICU discharge | Transferred to inpatient ward | Full recovery trajectory |

## DISCUSSION

Serotonin syndrome is a clinical diagnosis and can be easily overlooked, especially in patients with psychiatric disorders who are undergoing pharmacologic treatment. Serotonin syndrome, a diagnosis of exclusion, is established using the Hunter Toxicity Criteria. In patients with a history of serotonergic agent exposure, the presence of any single Hunter criterion is considered sufficient to confirm the diagnosis (Table 1). The absence of specific diagnostic laboratory or imaging findings further complicates recognition. Although most cases follow a benign course and resolve upon discontinuation of the offending agent, high-dose exposure can result in severe neurological and cardiovascular complications with fatal outcomes.

The majority of reported cases in the literature involve drug interactions, especially combinations of antidepressants, antipsychotics, and serotonergic antimicrobials such as linezolid (7). However, serotonin syndrome due to monotherapy overdose with venlafaxine is rarely reported (8,9). Beyond venlafaxine, cases have demonstrated that serotonin toxicity can also develop with isolated bupropion use (10). Our case highlights that even in the absence of polypharmacy, high-dose venlafaxine alone can lead to life-threatening toxicity.

The rapid clinical deterioration observed in our patient was likely due to the cardiotoxic effects of venlafaxine. Although the drug typically causes only mild tachycardia and QT prolongation at therapeutic doses, toxic doses can result in significant arrhythmias and hemodynamic instability (11). Prolongation of the QT interval reflects delayed ventricular repolarization and predisposes affected individuals to potentially life-threatening arrhythmias and torsades de pointes (TdP). The normal range for the rate-corrected QT interval (QTc) is similar in males and females from birth until the start of adolescence, while after puberty and in adults, females have slightly longer QT intervals than males. Before puberty, a QTc <450 ms is considered normal, between 450 and 459 borderline, and ≥460 prolonged. After puberty in males, a QTc between 460 and 469 is borderline and ≥470 is considered prolonged. In post-pubertal females, 460 to 479 is borderline and ≥480 ms is considered prolonged. In our case, the patient developed sinus tachycardia and a markedly prolonged QTc interval (545 ms), which resolved following magnesium sulfate administration. In relation to QT prolongation, the principal role of magnesium sulfate is its use in the treatment of TdP. It stabilizes intracellular ion currents and, by inhibiting L-type calcium channels, reduces the risk of arrhythmia development. For all patients with TdP, IV magnesium sulfate is first-line therapy since it is highly effective for both the treatment and prevention of recurrence of long QT-related ventricular ectopic beats or TdP (12). This underscores the importance of continuous ECG monitoring and prompt correction of QT prolongation in such cases.

Although cranial CT plays no direct role in the diagnosis of serotonin syndrome, it is essential to exclude differential diagnoses such as intracranial hemorrhage or mass lesions. Similarly, while EEG is not a definitive diagnostic tool, it may support the diagnosis or assist in differentiating from other neuropsychiatric conditions. EEG findings in serotonin syndrome may include delta activity, generalized slowing, and triphasic waves (13). Our patient exhibited generalized slowing, which correlated with her clinical presentation. As the diagnosis of serotonin syndrome is primarily one of exclusion, a detailed history, physical examination, and emergency laboratory and imaging studies were conducted. This evaluation effectively ruled out infectious diseases, concomitant drug use, withdrawal syndromes, toxic exposures, and acute central nervous system pathologies such as hemorrhage or ischemia as alternative explanations for the clinical presentation. Following these exclusions, the patient's high-dose venlafaxine exposure and compatibility with the Hunter Toxicity Criteria led to the clinical diagnosis of acute serotonin syndrome.

Laboratory findings in serotonin syndrome are typically nonspecific. In our patient, transient lactic acidosis was observed, likely secondary to hypoxia and impaired perfusion rather than primary serotonergic toxicity. Notably, CK levels remained within normal limits, possibly due to early seizure control and lack of sustained neuromuscular hyperactivity.

The cornerstone of treatment is discontinuation of serotonergic agents and supportive care. With proper treatment, serotonin syndrome usually resolves within 24 h without sequelae (14). Supportive care is the mainstay of therapy and includes the administration of oxygen and intravenous (IV) fluids, continuous cardiac monitoring, and correction of vital signs. Clinicians should provide sufficient oxygen to maintain the oxygen saturation ≥ 94 percent, and give IV crystalloid to treat volume depletion, and to some extent hyperthermia. In overdose cases, early gastric decontamination may help reduce systemic absorption. Vital signs should be closely monitored, and patients should be admitted to intensive care units if needed. Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-HT1A and 5-HT2A antagonistic properties with antiserotonergic properties and is commonly used when supportive care alone is insufficient. It also has weak anticholinergic activity. It is

available in 4 mg tablets or 2 mg/5 mL syrup. When administered as an antidote for serotonin syndrome, an initial dose of 12 mg is recommended, followed by 2 mg every two hours until clinical response is seen. However, it is available only in oral form and may not be effective in all patients (15). Chlorpromazine, although not routinely recommended in treatment guidelines, acts as a serotonin receptor antagonist and has been used in rare cases. In our case, because cyproheptadine failed to produce the anticipated clinical response within an appropriate time interval and the patient's condition was critical, intramuscular chlorpromazine was administered, based on the rationale that it could exert a more rapid therapeutic effect. Subsequently, chlorpromazine led to rapid clinical improvement after failure of cyproheptadine and supportive therapy. Although the available evidence is limited, several authors have suggested that 5-HT2A serotonin antagonists may be justified even in suspected cases of serotonin toxicity as empiric therapy or employed as 'lifesaving' antidotes in cases of severe toxicity (16). A review of the literature revealed only two previously published reports from the 1990s describing the use of chlorpromazine in serotonin syndrome (17,18). One such case documented toxic serotonin syndrome triggered by the concomitant use of a monoamine oxidase inhibitors (MAOI) and a tricyclic antidepressant (TCA), in which a rapid therapeutic response to chlorpromazine was observed.

This case is unique in demonstrating life-threatening serotonin syndrome due to venlafaxine monointoxication, marked QT prolongation in the absence of elevated CK, and successful resolution of symptoms following intramuscular chlorpromazine administration. When serotonergic agents are ingested in high doses, particularly in the context of suicidal attempts, drug-induced metabolic disturbances are often the primary consideration. However, serotonin syndrome must also be carefully considered, as it may develop even with high-dose exposure in the absence of drug interactions. In most patients, serotonin syndrome generally resolves with discontinuation of the offending agents and supportive care. However, it should be remembered that in severe cases, in those unresponsive to cyproheptadine, and in life-threatening situations where a more rapid therapeutic effect is required, chlorpromazine may serve as a potential rescue agent. Further clinical investigation is needed to clarify the role of chlorpromazine in the management of serotonin syndrome.

## CONCLUSION

Serotonin syndrome should always be considered in patients receiving serotonergic agents, particularly in the context of overdose. Although it is typically associated with drug interactions, this case demonstrates that a single-agent overdose of venlafaxine can lead to severe, potentially fatal manifestations. It should be considered that toxic serotonin syndrome may also occur following the administration of other serotonergic agents at high doses. Early recognition, intensive supportive care, and continuous cardiac monitoring are essential to improve outcomes. While cyproheptadine remains the first-line pharmacologic treatment, this case highlights the potential role of chlorpromazine as a therapeutic option in refractory cases. It is important to recognize that chlorpromazine therapy may be considered in patients with critical clinical presentations, given that intramuscular administration has the potential to achieve a more rapid therapeutic response. Further studies are warranted to evaluate the efficacy and safety of chlorpromazine in serotonin syndrome management

**Informed Consent**
An informed consent form was obtained from the patient and/or the patient's legal representative for the collection and publication of the patient's clinical information.

**Conflict of Interest**
The authors have no conflict of interest to declare.

**Financial Disclosure**
The authors declare that no financial support was received for this study.

**Authors' Contributions**
Data collection and processing, M.B.D.; Data analysis and interpretation, M.B.D., H.S.K.; Writing, H.S.K.; Review and editing, M.B.D., H.S.K.

**Data sharing statement**
No new data were created or analyzed in this study. Data sharing is not applicable to this article.

## REFERENCES

1. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112-20.
2. Birmes P, Coppin D, Schmitt L, Lauque D. Serotonin syndrome: a brief review. CMAJ. 2003;168(11):1439-42.
3. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome. Presentation of 2 cases and review of the literature. Medicine (Baltimore). 2000;79(4):201-9.
4. Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. Neurology. 1995;45(2):219-23.
5. Sternbach H. The serotonin syndrome. Am J Psychiatry. 1991;148(6):705-13.
6. Prakash S, Rathore C, Rana K, Prakash A. Fatal serotonin syndrome: a systematic review of 56 cases in the literature. Clin Toxicol (Phila). 2021;59(2):89-100
7. Shouan A, Kumar R, Lal V, Grover S. Linezolid-induced serotonin syndrome. Ind Psychiatry J. 2020;29(2):345-348.
8. Daniels RJ. Serotonin syndrome due to venlafaxine overdose. J Accid Emerg Med. 1998;15(5):333-4.
9. Hanekamp BB, Zijlstra JG, Tulleken JE, Ligtenberg JJ, van der Werf TS, Hofstra LS. Serotonin syndrome and rhabdomyolysis in venlafaxine poisoning: a case report. Neth J Med. 2005;63(8):316-8.
10. Sidlak AM, Koivisto KO, Marino RT, Abesamis MG. Serotonin toxicity from isolated bupropion overdoses. Clin Toxicol (Phila). 2020;58(12):1347-49.
11. Isbister GK. Electrocardiogram changes and arrhythmias in venlafaxine overdose. Br J Clin Pharmacol. 2009;67(5):572-6.

12. Khan IA. Long QT syndrome: diagnosis and management. Am Heart J. 2002;143(1):7-14
13. Krishnamoorthy T, Knighton J, Merton L. The role of electroencephalography in the diagnosis of serotonin syndrome. J Intensive Care Soc. 2016;17(3):258-261.
14. Mikkelsen N, Damkier P, Pedersen SA. Serotonin syndrome-A focused review. Basic Clin Pharmacol Toxicol. 2023;133(2):124-129.
15. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. J Emerg Med. 1998;16(4):615-9.
16. Chiew AL, Isbister GK. Management of serotonin syndrome (toxicity). Br J Clin Pharmacol. 2025;91(3):654-661.
17. Graham PM. Successful treatment of the toxic serotonin syndrome with chlorpromazine. Med J Aust. 1997;166(3):166-7.
18. Gillman PK. Serotonin syndrome treated with chlorpromazine. J Clin Psychopharmacol. 1997;17(2):128-9.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):139-146*
*e-ISSN: 2980-0978*

***Review Article / Derleme Makalesi***
***DOI:10.61845/agrimedical.1688576***

# The effect of melatonin on breast cancer treatment

## Meme kanseri tedavisinde melatoninin etkisi

Derya Şimşekli [1*]

[1] *Ardahan Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Ardahan, Türkiye*

*0000-0002-3904-951X

**Sorumlu Yazar:*
*Derya Şimşekli*
*Ardahan Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Ardahan, Türkiye*
*e-mail:*
*deryasimsekli@ardahan.edu.tr*

Gönderilme Tarihi: 01/05/2025
Kabul Tarihi: 01/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Şimşekli D. The effect of melatonin on breast cancer treatment. Ağrı Med J. 2025; 3(3):139-146.

**ABSTRACT**

This review is designed as a traditional review to determine the effects of melatonin on breast cancer. Breast cancer occurs as a result of abnormal and uncontrolled cell proliferation. It is one of the most common cancers among women in Turkey and globally. When diagnosed early, breast cancer offers a high chance of cure. Treatment options include chemotherapy, surgery, radiotherapy, and hormonotherapy. Melatonin, used in addition to these treatments, has been reported to have positive effects on the disease process and treatment-related complications. Melatonin, with its antioxidant, anti-inflammatory, antiproliferative, antiestrogenic, antiangiogenic, and immunomodulatory effects, can inhibit cell growth in breast cancer treatment. Furthermore, when used in addition to chemotherapy and radiotherapy, it has been found that it can enhance the body's sensitivity to these treatments, enhance the effectiveness of the treatment, improve patients' quality of life, and reduce fatigue. Further high-quality randomized controlled trials are recommended for the use of melatonin during chemotherapy and radiotherapy in patients with breast cancer.

**Keywords:** *Chemotherapy, Breast cancer, Melatonin, Radiotherapy*

**ÖZ**

Bu derleme meme kanseri sürecinde melatoninin etkilerini belirlemek amacıyla geleneksel derleme olarak tasarlanmıştır. Meme kanseri, memedeki hücrelerin anormal ve kontrolsüz şekilde çoğalması sonucunda meydana gelmektedir. Türkiye ve dünyada görülme oranları bakımından kadınlar arasında ön sırada olan kanser türlerinden biridir. Meme kanseri, erken teşhis edildiğinde tedavi şansı yüksek olan bir kanser türüdür. Meme kanseri tedavisinde kemoterapi, cerrahi tedavi, radyoterapi ve hormonoterapi yer almaktadır. Bu tedavilere ek olarak kullanılan melatoninin, hastalık sürecinde ve tedaviye bağlı gelişen sorunlar üzerindeki olumlu etkileri bildirilmiştir. Melatonin, antioksidan, antiinflamatuar, antiproliferatif, antiöstrojenik, antianjiyojenik ve immünmodülatör etkileriyle meme kanseri tedavisinde hücre büyümesini engelleyebilir. Ayrıca kemoterapi ve radyoterapi sürecine ek olarak kullanıldığında bu tedavilere vücudun duyarlılığını arttırarak tedavinin etkisini arttırabileceği, hastaların yaşam kalitesinde artma meydana getirerek yorgunluğu azaltabileceği tespit edilmiştir. Melatoninin, meme kanseri olan hastaların kemoterapi ve radyoterapi sürecinde kullanılarak kanıt değeri yüksek daha fazla randomize kontrollü çalışma yapılması önerilmektedir.

**Anahtar Kelimeler**: *Kemoterapi, Meme kanseri, Melatonin, Radyoterapi*

## GİRİŞ

Meme kanseri, mortalite ve morbidite hızını arttıran, kadınlarda en sık karşılaşılan kronik hastalıklardan biridir. Erken tespit edildiğinde tedavi oranları oldukça yüksek ve ölüm oranı düşüktür. Hastalık özellikle memelerde ele gelen kitlenin hissedilmesi veya rutin taramalar esnasında kitlenin tespit edilmesi ile teşhis edilebilir. Tedavisinde kemoterapi, radyoterapi, cerrahi tedavi ve hormonoterapi yer almaktadır. Hastalığın tedavi sürecinin her aşamasının çeşitli komplikasyonları bulunmaktadır (1). Tedavi sürecinde yaşanan bu komplikasyonların azaltılmasında tamamlayıcı ve alternatif olarak bazı uygulamalar yer alabilmektedir (2). Melatonin, meme kanserinde biyolojik etkileri araştırılan ve tamamlayıcı tedavi potansiyeli bulunan bir moleküldür (3).

Melatonin, epifiz bezinden salgılanan bir nörohormondur. Vücutta sirkadiyen ritmin düzenlenmesinden sorumludur. Yapılan araştırmalarda melatoninin, güçlü bir antioksidan, antiinflamatuar ve antiproliferatif etkisinin olduğu bildirilmiştir. Ayrıca melatoninin meme kanserinde, östrojene bağlı hücre uyarımını bozarak, östrojenle indüklenen hücre proliferasyonunu azalttığı bildirilmiştir (4).

Bu derleme makale, dünya genelinde ve ülkemizde kadınlarda sık görülen meme kanserinin tedavisinde melatonin kullanımının etkilerini incelemek amacıyla hazırlanmıştır.

## GEREÇ VE YÖNTEM

Bu derleme, meme kanseri tedavi sürecinde melatoninin rolünü açıklamak amacıyla literatür incelemesi yöntemiyle hazırlanmıştır. Bir sistematik derleme protokolü içermemektedir. PubMed, Scopus ve Google Scholar veri tabanlarında, "melatonin", "meme kanseri" ve "tedavi" anahtar kelimeleri ve bu terimlerin kombinasyonları ile Türkçe ve İngilizce dillerinde tarama yapılmıştır.

Bu taramada tarih sınırlaması olmaksızın, tam metnine ulaşılabilen çalışmalara erişilmiştir. Meme kanseri tedavisinde melatoninin rolünü ele alan, makaleler dahil edilmiştir. Meme kanseri ile ilişkili olmayan, tedaviye odaklanmayan veya melatonin konusunu içermeyen çalışmalar hariç tutulmuştur.

### Meme Kanseri

Meme kanseri, memedeki hücrelerin anormal ve kontrolsüz bir şekilde çoğalması ile gelişen, kötü huylu (malign) tümör oluşumu ile karakterize bir hastalıktır. Erken müdahale edilmezse, tümör büyüyebilir, çevre dokulara yayılabilir, metastaz yapabilir. Meme kanseri, değiştirilebilir ve değiştirilemeyen birçok risk faktörünün birleşimiyle ortaya çıkabilir. Kadınlar arasında en sık rastlanan kanser türüdür (1).

Dünya Sağlık Örgütü (DSÖ), 2022 yılı verilerine göre meme kanserinin, 2022 yılında dünya genelindeki 670 bin kişinin ölümüne neden olduğu kaydedilmiştir. Yine aynı yıl itibariyle 185 ülkenin 157'sinde kadınlarda en sık görülen kanser olduğu bildirilmiştir (5). Dünya Kanser Araştırma Fonu (World Cancer Research Fund, WCRF) 2022 yılı verilerine bakıldığında ise bu anlamda net bir sayı bildirilmiş ve 2022 yılında 666103 kadının meme kanseri nedeniyle öldüğü bildirilmiştir (6).

Türkiye'de 2017 yılı verilerine göre, kadınlarda en sık görülen kanserin meme kanseri olduğu ve insidansının %5,8 olduğu bildirilmiştir (7). Meme kanseri insidans oranı, özellikle büyük şehirlerde artış göstermekte olup, kırsal alanlarda daha düşük seviyelerde kalmaktadır. Ancak, son yıllarda kentsel ve kırsal ayrımının giderek daha belirsiz hale gelmesi nedeniyle, tüm Türkiye genelinde meme kanserinin artan bir seyir gösterdiği söylenebilir. Meme kanseri sıklığı, yaşla birlikte artan bir eğilim gösterir. Türkiye'de en sık görülen yaş grubu 50-69 yaş arasında olup, bu yaş aralığındaki kadınlarda erken teşhisle birlikte tedavi başarısı daha yüksektir. Ancak, 40 yaş altındaki kadınlarda da meme kanseri vakaları görülmekte, bu vakaların genetik faktörler veya aile öyküsü gibi risk faktörleriyle ilişkili olduğu düşünülmektedir (8).

### Meme Kanserinin Risk Faktörleri

Meme kanseri tanısından önceki ve sonraki süreçte risk faktörlerinin belirlenmesi, değiştirilebilen risk faktörlerine maruziyetin azaltılmasını sağlamak için oldukça önemlidir. Meme kanserine yakalanma riskini etkileyen faktörler kendi içerisinde değiştirebilir ve değiştirilemeyen faktörler olarak ele alınmaktadır. Bu faktörlere Tablo 1'de yer verilmiştir (9).

Meme kanseri vakalarının %5-10'unu kalıtsal meme kanseri oluşturmaktadır. Özellikle birinci derece akrabaları arasında meme kanseri olan bireylerde görülme oranı daha yüksektir. Genetik geçişli meme kanserinde *BRCA1* ve *BRCA2* genlerinde mutasyon görülebilmektedir. Bu genlerin dışında *PTEN*, *TP53*, *CDH1* ve *STK11* genlerindeki mutasyonlarında meme kanserine yol açabildiği bildirilmiştir. Östrojen seviyesindeki anormal artış hücre çoğalmasını ve hücre döngülerini etkileyerek DNA'daki oksidatif hasara neden olabilmektedir. Bu durum da meme kanseri gelişimine neden olabilmektedir. Östrojen maruziyetinin süresini etkileyen menarş ve menopoz yaşı da kadınlarda meme kanseri riski ile ilişkilendirilmiştir (9). D vitamin ile meme kanseri riski arasında ilişki olduğu bildirilmiştir. Yapılan bir çalışmada D vitamin seviyesi normal olan kadınlara göre D vitamin eksikliği olan kadınlarda meme kanseri gelişme riskinin %27 daha fazla olduğu bildirilmiştir (10).

### Meme Kanserinin Tanısı

Meme kanseri tanısı, taramalar ve klinik değerlendirme süreçleri sonucunda yapılan değerlendirmelerle konulmaktadır. Tanıda kullanılan yöntemler üç başlık altında ele alınabilir. Bunlar, tarama yöntemleri, klinik değerlendirme, moleküler ve patolojik incelemelerdir.

Tarama yöntemleri arasında yer alan mamografi, duyarlılık ve özgüllüğünün yüksekliği, mortaliteyi azaltmadaki etkinliği ve uygulanabilirliği nedeniyle meme kanseri taramalarında ve kanser sonrası takip sürecinde ilk sırada tercih edilmektedir (11). Türkiye'de ulusal tarama programları kapsamında, 40–69 yaş arasındaki kadınlara iki yılda bir mamografi çekilmesi önerilmektedir (12). Diğer tarama yöntemleri arasında, meme ultrasonu, manyetik

rezonans görüntüleme (MR), bilgisayarlı tomografi (BT) ve pozitron emisyon tomografisi (PET) yer almaktadır (13).

**Meme Kanserinin Sınıflandırılması ve Semptomları**

Meme kanseri sınıflaması, tümörün histopatolojik ve moleküler özelliklerine göre yapılmaktadır. Sınıflamada tümörün histopatolojik özelliği, östrojen reseptörü (*ER*), progesteron reseptörü (*PR*), insan epidermal büyüme faktörü reseptörü-2 (*HER2*), tümörün hormonal duyarlılık oranları oldukça önemlidir (12).

Histopatolojik sınıflamada, invaziv duktal karsinom, invaziv lobüler karsinom en sık görülen kanser türleridir. Tübüler, müsinöz ve medüller karsinomlar ise daha nadir görülen meme kanseri türleridir.

Moleküler sınıflama ise tedavi planının bireyselleştirilmesi için önemlidir. Moleküler sınıflamada dört farklı alt tip bulunmaktadır. Bunlar, luminal A (*ER* pozitif, *PR* pozitif, *HER2* negatif veya düşük proliferasyona sahip), luminal B (*ER* pozitif, *PR* negatif, *HER2* pozitif veya negatif, yüksek proliferasyona sahip), *HER2* pozitif (*HER2* proteinini aşırı eksprese eden, *ER* negatif, *PR* negatif) ve üçlü negatif tümör (*ER, PR, HER2* negatif) yer almaktadır (12,14). Meme kanseri semptomlarına bakıldığında memelerde veya koltuk altında ele gelen kitle, meme veya koltuk altında ağrı, meme boyutunda değişiklik, meme ucunda içe veya dışa çökme, memelerde asimetrinin olması, meme yüzeyinde şişlik, kızarıklık, meme başında akıntı ve kanamadır. Yapılan bir çalışmada kadınların ilk fark ettiği semptomun %72 oranında memede kitle olduğu bildirilmiştir. Aynı çalışmada kadınların %50'si tespit ettikleri semptomları önemsiz bulduğunu belirtmiştir (15).

**Meme Kanseri Tedavisi**

Meme kanseri tedavisi, tümörün evresine, biyolojik özelliğine ve hastanın genel sağlık durumuna göre belirlenmektedir.

Temelde üç tedavi yöntemi bulunmaktadır. Bunlardan ilki cerrahi tedavidir. Cerrahi tedavide tümörün evresine göre memenin tamamen çıkarıldığı mastektomiden, sadece kitlenin veya koltuk altı lenf bezlerinin alınmasına kadar farklı şekillerde uygulanabilmektedir. Diğer bir tedavi yöntemi radyoterapidir. Bu tedavi yöntemi meme koruyucu cerrahi yapılan hastaların tamamına uygulanmaktadır. Meme kanseri tedavisinde yer alan diğer tedavi türleri ise kemoterapi, hedefe yönelik tedavi, endokrin tedavi, neoadjuvan tedavi, metastatik hastalıkta yapılan tedavi olarak alt gruplara ayrılan sistemik tedavilerdir. Meme kanseri tedavileri esnasında birçok komplikasyon meydana gelebilmektedir. Bunlardan özellikle kemoterapi hastaların yaşam kalitesinin düşmesine neden olabilmektedir (12,13).

**Melatonin ve Meme Kanseri İlişkisi**

Meme kanserinin tedavisinde semptomların, ağrının ve çeşitli nedenle oluşan komplikasyonların yönetiminde tamamlayıcı ve alternatif tedavilere başvurulabilmektedir. Bu tedaviler; alternatif tıbbi sistemler, biyoloji temelli uygulamalar, enerji tedavileri, zihin-vücut temelli yaklaşımlar ve manipülatif ve vücut temelli yaklaşımlar şeklinde beş gruba ayrılabilmektedir. Bunlardan biyolojik temelli uygulamalar içerisinde melatonin, bitkisel ürünler, probiyotikler ve vitaminler yer almaktadır (2,16).

Melatonin, meme kanseri patogenezinde önemli bir yere sahiptir. Araştırmalar, melatoninin özellikle östrojene bağımlı hücre sinyallerini bozarak tümör hücre proliferasyonunu azalttığını ve tümör büyümesini engellediğini ortaya koymuştur.

Melatoninin, prostat kanseri, karaciğer kanseri, pankreas kanseri ve osteosarkomda antitümör etki gösterdiği belirlenmiştir (17–20). Prostat kanserinde, melatonin p53 tümör baskılayıcı proteini aktive ederek LNCaP hücrelerinde apoptotik hücre ölümünü indükleyerek, hücre proliferasyonunun baskılanması ve tümör büyümesini sınırlandırılmasını sağlayarak etki eder (19). Pankreas kanserinde ise p38 MAPK ve JNK sinyal yolaklarını aktive ederek apoptozu arttırmakta, ayrıca ERK1/2 ve NF- κB yolaklarını inhibe ederek hücre proliferasyonunu baskılayarak etki etmektedir (20). Meme kanserinde özellikle östrojene bağımlı hücre sinyalini bozarak östrojenle uyarılan hücrelerin proliferasyonunu azaltır. Yapılan araştırmalarda meme kanserli bireylerdeki melatonin seviyesinin düşük olduğu tespit edilmiştir (21,22). Gece vardiyasında çalışan kadınlarda melatonin sentezindeki bozulmanın da meme kanseri riskini arttırdığı belirtilmiştir (23). Melatonin düzeyindeki azalma, meme kanseri için bilinen bazı risk faktörleriyle ilişkilidir. Örneğin gece vardiyasında çalışma, sirkadiyen ritimt bozuklukları ve uyku düzensizlikleri pineal bez melatonin üretimini azaltır ve östrojen düzeylerinde yükselme meydana gelebilir. Obezite, hormonal dengesizlikler ve menopoz öncesi dönemde yüksek östrojen maruziyeti de melatonin-östrojen dengesini bozarak tümör gelişimini kolaylaştırabilir. Dolayısıyla melatonin, hem biyolojik mekanizmalarla hem de risk faktörleri üzerinde koruyucu bir rol oynayabilir. Bu açıdan meme kanseri sürecinde veya korunmak adına melatonin takviyesinin faydalı olabileceği söylenebilir (21,24).

Melatoninin meme kanseri üzerindeki biyolojik etkileri birçok farklı mekanizma ile önerilmiştir (4,25). Bunlar:

- Melatonin reseptörü 1 (MT1) ve melatonin reseptörü 2 (MT2)'ye bağlanarak hücre içi sinyal yolaklarını aktive edip, kanser hücrelerinin büyümesini engeller ve apoptozu teşvik eder.
- Melatonin, östrojen sentezini azaltarak, östrojen reseptörlerinin aktivitesini baskılayarak ve progesteron reseptörlerini inhibe ederek meme kanseri hücrelerinin büyümesini önleyebilir.
- Melatonin, büyüme faktörlerinin üretimini baskılayarak ve insan epidermal büyüme faktörü 2 (HER2) pozitif meme kanseri hücrelerindeki aktiviteyi düşürerek tümörün büyümesini önleyebilir.
- Tümör hücrelerinin yeni damar oluşturmasını engelleyebilir.
- Doksorubisin gibi bazı kemoterapötik ajanlarla birlikte kullanıldığında bu ilacın etkisini arttırabilir.
- Radyoterapi öncesinde uygulandığında östrojen sentezini baskılayarak, kanser hücresinin radyoterapiye duyarlılığını arttırabilir.

- Yağ metabolizmasını ve hücre içi enerji dengesini düzenleyerek meme kanseri hücresinin büyümesini kısıtlayabilir.

Melatonin, Melatonin Reseptör 1 (MT1) ve Melatonin Reseptör 2'ye (MT2) bağlanarak hücre içi sinyal yolaklarını aktive eder. Bunlar, G-protein bağlı reseptörler olup, siklik adenozin monofosfat (cAMP) ve inositol trifosfat/diasilgliserol (IP3/DAG) yolaklarını düzenleyerek hücre proliferasyonu ve apoptozu etkiler. MT1 reseptör aktivasyonu adenil siklaz aktivitesini inhibe ederek cAMP seviyesinde düşme meydana getirir, bu durumda protein kinaz A sinyali azalır ve hücre döngüsü durur ve apoptoz tetiklenir. MT2 reseptörü ise fosfolipaz yoluyla inositol trifosfat ve diasilgliserol üretimini arttırarak kalsiyum salınımını ve protein kinaz C aktivitesini düzenler. Melatonin ayrıca östrojen sentezini aromataz enzimi inhibisyonu yoluyla azaltır. Aromataz, androjenlerin östrojene dönüşümünü katalizleyen anahtar enzimdir ve melatonin bu enzimin ekspresyonunu baskılayarak östrojen seviyelerini düşürür. Sonuçta östrojen reseptörlerine bağlı proliferatif sinyaller azalır. Ayrıca, melatonin, östrojen reseptörlerinin nükleer transkripsiyon aktivitesini modüle ederek östrojen bağımlı gen ekspresyonunu inhibe eder. Progesteron reseptörleri üzerindeki inhibisyon da benzer şekilde gerçekleşmektedir. Bunların dışında melatonin, melatonin büyüme faktörü ve insan epidermal büyüme reseptörü 2 sinyallerini baskılayarak tümör progresyonunu engeller. Antianjiogenik etkileri ile tümörlerin yeni damar oluşumunu baskılar (26,27). Melatoninin anti-kanser yolakları Şekil 1'de gösterilmiştir.

Yukarıdaki mekanizmaların dışında 2021 yılında yayınlanan bir makalede bağırsak mikrobiyotası, melatonin ve meme kanseri bağlantısı incelenmiş, bağırsak bakteri popülasyonundaki değişimlerin melatonin üretiminde azalmaya neden olarak meme kanseri riskini arttırabileceği tespit bildirilmiştir. Bu durumu ise bağırsak mikrobiyotasındaki değişikliklerin belirli yolaklarla melatonin üretiminin azalmasına yol açarak ortaya koyduğu ifade edilmiştir (28).

**Melatoninin Farmakokinetiği ve Metabolizması**

Melatonin oral yoldan alındığında hızlı ve iyi emilir, emilimi genelde hızlıdır, kan plazma düzeyi oral alım sonrası 20-60 dakika içinde pik düzeye ulaşır. Biyoyararlanımının kişiden kişiye değiştiği bildirilmiştir. Melatonin, karaciğerde CYP1A2 enzimi tarafından metabolize edilir ve sonrasında böbrekler tarafından atılır. Topikal uygulamada ise sistemik dolaşıma ne oranda geçtiği daha az araştırılmıştır. Biyoyararlanım oral alıma göre daha düşük olabilir. Genellikle lokal etki için tercih edilir. Melatoninin intravenöz uygulaması ve oral uygulamasının karşılaştırıldığı 12 erkek gönüllünün dahil edildiği bir çalışmada oral alımda ortalama emilim yarı ömrünün 6,0(3,1) dakika, ortalama tepe zamana ulaşma süresinin 40,8(17,8) dakika, ortanca maksimum plazma konsantrasyonunun 3550,5(2500,5-8057,5) ve biyoyararlanımın medyan değerinin %2,5 olduğu belirlenmiştir. IV uygulamada ise ortalama eliminasyon yarı ömrünün 39,4(3,6) dakika, ortalama dağılım hacminin 1,2(0,6)l/kg olduğu belirlenmiştir. Oral alımdaki biyoyararlanımın oldukça düşük olduğu bildirilmiştir (29). Bir sistematik incelemede melatoninin intranazal yoldan hızlıca emildiği ve biyoyararlanımının da yüksek olduğu ifade edilmiştir. Yine aynı derlemede subkutan melatoninin, oral alıma kıyasla hızlı bir emilim gösterdiği bildirilmiştir (30). Melatonin lipofilik yapıdadır, bu yapı kaynaklı kolayca kan beyin bariyerini geçebilir ve plazma proteinlerine orta düzeyde bağlanabilir. Karaciğerde CYP1A2 enzimi aracılığıyla 6-hidroksimelatonine metabolize edilir, ardından sülfat ve glukoronid konjugatları şeklinde böbreklerden atılır. Farklı uygulama yolları farmakokinetiğinde önemli farklılıklara yol açabilir (31).

Sistematik bir derlemede oral melatoninin biyoyararlanımının %9-33 arasında değiştiği bildirilmiş, melatoninin farmakokinetiğinin ise yaş, kafein, sigara kullanımı, oral kontraseptifler ve beslenmeden etkilendiği tespit edilmiştir (32). Literatür incelemeleri melatoninin birçok farklı yolla uygulanabildiğini, uygulama yollarına göre ise biyoyararlanımının değiştiğini göstermektedir.

**Melatoninin Vücuttaki Etkileri**

Melatonin, epifiz bezinden salgılanan, vücuttaki uyku-uyanıklık döngüsünün düzenlenmesini sağlayan bir hormondur. Biyolojik süreçlerde rol alarak, antikanser, antioksidan, bağışıklık sistemini düzenleyici etkileri söz konusudur. Melatonin gece boyunca salınarak sirkadiyen ritimden sorumludur. Yapay ışıklar ve gece vardiyasında çalışma vücuttaki melatonin seviyesini düşürebilmekte ve vücudun sirkadiyen ritmini bozabilmektedir. Melatonin seviyesindeki düşüş ve sirkadiyen ritim bozuklukları sonucunda, kanser, metabolik hastalıklar ve nörodejeneratif hastalıklar ortaya çıkabilmektedir (33).

Melatoninin anti-kanser etkilerine bakıldığında, östrojen uyarım yollarını baskılayarak östrojene bağımlı kanser hücrelerinin büyümesine engel olduğu söylenebilmektedir. Anti-anjiojenik etkisi kaynaklı tümörün yeni damar oluşturma etkisini ve beslenmesini önler. Melatoninin güçlü bir antioksidan etkisi bulunmaktadır. Bu etkisi kaynaklı serbest radikallerin temizlenmesini DNA hasarı ve oksidatif stresi azaltabilmektedir. Bunun yanı sıra melatoninin doğal katil hücreleri ve T lenfositlerini aktive ederek bağışıklık sistemini güçlendirildiği de bildirilmiştir. Bağışıklık sistemindeki yaşa bağlı gerilemeyi yavaşlatarak, yaşlanmaya bağlı hastalık riskini azaltır (33).

**Meme Kanseri Tedavi Sürecinde Melatonin Kullanımı ve Yapılan Çalışmalar**

Melatonin, meme kanserinin erken evrelerinde destekleyici ajan olarak kullanmaktadır. Melatoninin kemoterapi ve radyoterapinin neden olduğu yan etkilere karşı faydalı olduğu bildirilmiştir (34). Meme kanserli sıçanlarla yapılan preklinik bir çalışmada, melatoninin tek başına tümör hacminde azalma ve tümör çıkış süresinde gecikme sağladığı; tamoksifenin ise kanser insidansını neredeyse tamamen baskıladığı gösterilmiştir. Kombine kullanımda ise melatoninin tamoksifenin antitümör etkisine katkıda bulunduğu bildirilmiştir (35).

Meme kanserinin agresif türlerinden biri olan üçlü negatif meme kanserli hastalarda melatoninin, kanserin ilerlemesini durdurucu etkinliği bildirilmiştir (36). Yapılan bir başka çalışmada melatoninin üçlü negatif meme kanserli farelerin plazma metabolit profilleri üzerindeki etkisi araştırılmıştır. Sonuçta melatoninin meme kanseriyle ilişkili olan metabolit setlerinin seviyelerinde özellikle ışık fazında belirgin bir düşme meydana getirdiği tespit edilmiştir (37).

Melatoninin, meme kanserli hastalarda, hastalığa ve tedavi süreçlerine bağlı olarak meydana gelen yorgunluğa karşı etkili olduğu bildirilmiştir (38,39). Kemoterapi alan meme kanserli hastalara günde 1 mg melatonin alımı sağlanmış ayrıca hem deney hem de plasebo grubuna Akdeniz diyeti uygulanmıştır. Üç ay boyunca sürdürülen bu çalışmanın sonucunda her iki grupta da beden kitle indeksinde azalma meydana gelmiş, fakat sadece melatonin alan grubun kanserle ilişkili yorgunluk seviyesinde azalma olduğu gözlenmiştir (38). Meme kanserinin adjuvan tedavileri öncesinde başlanan ve tedavi sırasında devam ettirilen 18 mg melatoninin hastaların yorgunluk seviyesinde azalma meydana getirdiği bildirilmiştir (39). Bu çalışmaların aksine yapılan bir çalışmada radyoterapi gören meme kanserli hastalarda yorgunluk ve diğer semptomların azaltılmasında melatoninin etkilerini değerlendiren bir çalışmada radyoterapi planlanan erken evre veya duktal karsinoma insitu meme kanserli kadınlarda radyoterapiden bir gün önce başlayarak iki hafta sonrasına kadar oral yoldan günde 20 mg melatonin tedavisi uygulanmıştır. Değerlendirmeler ikinci hafta ve 8. haftalarda yapılmıştır. Araştırma sonucunda erken evre meme kanserli hastalarda melatoninin yorgunluk ve diğer semptomlar üzerinde etkili olmadığı tespit edilmiştir (40). Yorgunluk seviyesinde azalma bildiren Sedighi Pashaki ve arkadaşlarının çalışmasında adjuvan kemoterapi veya radyoterapi alan hastalarda melatonin tedaviye ek olarak kullanılmış (39), Mukhopadhyay ve ark. çalışması ise sadece radyoterapi planlanan erken evre meme kanseri hastalarıyla yürütülmüştür (40). Dolayısıyla hastalarda mevcut olan yorgunluk düzeyinde değişkenliğin olması söz konusudur ve melatoninin etkinliğindeki bu değişimin bu durumdan kaynaklanabileceği düşünülmektedir.

Meme kanserli hastalarda melatoninin uyku bozukluklarını hafifletmede etkili olduğu bildirilmiştir (41). Meme kanseri kaynaklı adjuvan kemoterapi alan hastalarda adjuvan kemoterapinin ilk döngüsü öncesi ve sırasında alınan 20 mg melatoninin, bilişsel bozuklukla ilişkili yan etkileri üzerindeki etkilerini değerlendiren çift kör randomize kontrollü deneysel bir çalışmada melatoninin kemoterapinin oluşturduğu bilişsel işlev, uyku kalitesi ve depresif semptomlar üzerindeki olumsuz etkileri azalttığı tespit edilmiştir (42).

Primer meme kanseri kaynaklı radyoterapi alan hastalarda melatoninin radyasyon dermatitine karşı etkinliğini değerlendiren bir çalışmada cilde günde iki kez 25 mg melatonin krem uygulanmıştır. Sonuçlar haftada bir değerlendirilmiş ve iki haftalık takipte radyasyon dermatitinde azalma olmadığı göstermiştir (43).

Metastatik olmayan meme kanserli 184 hasta ile üç yıllık sürede yürütülen deneysel bir çalışmada deney grubundaki hastalara üç yıl boyunca günde 18 mg melatonin verilmiş ve plasebo grubu ile yaşam kaliteleri karşılaştırılmıştır. Araştırma sonucunda sağlıkla ilgili yaşam kalitesinde melatonin uygulanan grupta hem zamansal süreçte hem de gruplar arası karşılaştırmada anlamlı düzeyde bir artış olduğu saptanmıştır (44).

Bir sistematik derlemede, meme kanseri hastalarında kemoterapinin istenmeyen etkilerine karşı melatoninin tedavi edici potansiyeli derlenmiştir. Bu derleme sonucunda kemoterapiye ek alınan melatoninin yaşam kalitesini arttırabileceği, günlük 20 mg melatoninin bir yıllık sağ kalım oranını arttırdığı ve güvenli bir takviye olduğu bildirilmiştir (45). Melatoninin meme kanserli hastalarda sağ kalım üzerinde etkileriyle ilgili çelişkili bilgiler söz konusudur. Başka bir çalışmada melatoninin sağ kalıma etkisini belirlemek üzere 2005-2015 yılları arasında İsveç'teki meme kanseri tanısı alan hasta kayıtları retrospektif şekilde incelenmiş, sonuçta bunların %2.5'inin melatonin kullandığı görülmüştür. Yapılan tek değişkenli analizde melatoninin meme kanserine bağlı sağ kalım üzerinde koruyucu etkisinin olduğu görülürken, çok değişkenli analizde bu etkisinin olmadığı bildirilmiştir (46).

Yapılan bir derlemede görme engeli olan kadınlarda meme kanseri insidansının %57'lere kadar azaldığı, fakat melatoninle incelenmemesi kaynaklı bu durumun doğrudan melatonine atfedilmesi uygun değildir. Bununla birlikte, görme engellilerde gece ışığa maruziyetin olmaması nedeniyle melatonin salınımının daha düzenli olabileceği ve bu durumun meme kanseri riskini azaltmada rol oynayabileceği düşünülmektedir. Melatoninin antiöstojenik, antioksidan, onkostatik ve immünmodülatör özellikleri kaynaklı meme kanseri sürecinde kullanılabileceği bildirilmiştir (47).

Melatoninin güvenli kullanımı ve potansiyel yan etkilerine ilişkin yapılan klinik çalışmalardan elde edilen bulgular genellikle olumlu yöndedir. Fakat uzun süreli kullanımla ilgili verilerin sınırlı olduğu ve bu anlamda daha fazla çalışmanın yapılması gerektiği düşünülmektedir.
Melatonin kısa ve orta vadeli kullanımda genellikle iyi tolere edilmekte, ciddi yan etkilerin nadiren meydana geldiği bildirilmektedir. En sık bildirilen yan etkilerin ise baş ağrısı, baş dönmesi, uyuklama ve mide bulantısı olduğu tespit edilmiştir. Bu yan etkilerin ise tedaviye gerek duyulmadan kendiliğinden geçebildiği saptanmıştır (48).

Melatoninin uzun süreli kullanımıyla ilgili ise sınırlı çalışma bulunmaktadır. Literatürde yer alan bir derleme çalışmasında düşük ve orta dozlarda melatonin (5-6 mg/gün veya daha az) kullanımının güvenli olduğu bildirilmiş, uzun süreli melatonin kullanımına ilişkin araştırmaların ise yetersiz olduğu ek araştırmalara ihtiyaç duyulduğu bildirilmiştir (49). Zwart ve ark. (2018) yaptıkları bir çalışmada kronik uyku başlangıcı insomniyası nedeniyle melatonin tedavisi alan 6-12 yaş arasında 69 çocuğa ortalama 7.1 yıl (1-12 yıl) süre ile melatonin tedavisi uygulanmış ve ciddi bir yan etkiye rastlanmadığı bildirilmiştir. En sık ortaya çıkan yan etkilerin hafif düzeyde baş ağrısı ve bulantı olduğu saptanmıştır. Bununla birlikte katılımcıların yaklaşık üçte biri ergenlik başlangıçlarının yaşıtlarına göre daha geç olduğunu fark etmiş, bu durumda dışardan verilen melatoninin ergenlik döneminde fizyolojik olarak azalan endojen melatonin düzeylerini maskeleyerek pubertal gelişimi geciktirebileceği endişesini gündeme getirmiştir. Ancak bu bulgu sınırlı sayıda

vaka üzerinde elde edildiğinden, melatoninin pubertal gelişim üzerindeki uzun süreli etkisinin netleştirilmesi açısından daha kapsamlı çalışmalara ihtiyaç duyulmaktadır (50).

Literatürdeki çalışmalar incelendiğinde melatonin dozlarının 1-25 mg arasında geniş bir yelpazede kullanıldığı görülmektedir. Kemoterapi alan meme kanserli hastalarda günde 1 mg melatonin kullanımının yorgunluk seviyesinde azalma meydana getirdiği çalışmalar olduğu gibi, 20-25 mg gibi yüksek dozlarla melatonin kullanıldığı çalışmalarda mevcuttur. Bu heterojen doz farklılıkları, optimal dozun belirlenmesini güçleştirmekte ve sonuçların karşılaştırılmasını zorlaştırmaktadır. Dolayısıyla, melatonin meme kanseri tedavisindeki yorgunluk ve diğer semptomlar üzerindeki etkilerinin netleştirilebilmesi için doz, uygulama süresi ve hasta özelliklerini de dikkate alan randomize kontrollü çalışmaların yapılması gerekmektedir.

## SONUÇ VE ÖNERİLER

Bu derlemede melatoninin meme kanseri tedavi sürecindeki etkinliği incelenmiş olup, mevcut çalışmalar derlenmiştir. Melatoninin, antioksidan, antiinflamatuar, antiproliferatif, antiöstrojenik, antianjiojenik, immünmodülatör etkileri sayesinde meme kanseri tedavi sürecinde hücre büyümesini engelleyebileceği ve olumlu etkileri olabileceği görülmektedir. Ayrıca, kemoterapi ve radyoterapi sürecine ek olarak kullanıldığında bu tedavilere vücudun duyarlılığını arttırarak tedavinin etkisini arttırabileceği, hastaların yaşam kalitesinde artma meydana getirerek yorgunluğu azaltabileceği tespit edilmiştir. Fakat sağ kalım üzerindeki etkileri konusunda çelişkili çalışmalar olduğu, tek değişkenli analizlerde sağ kalım üzerinde etkili bulunurken, çok değişkenli analizlerde etkisinin anlamlı olmadığı saptanmıştır. Yanı sıra radyoterapiye bağlı yorgunluk ve dermatitte de etkisinin sınırlı olduğu belirlenmiştir. Bu sonuçlardan hareketle aşağıdaki spesifik araştırma konuları önerilmiştir;

- Hormon reseptör pozitif, *HER2* pozitif ve üçlü negatif meme kanseri alt tipleri için ayrı ayrı randomize kontrollü çalışmalarda melatoninin etkinliğinin değerlendirilmesi,
- Farklı meme kanseri türleri ve tedavileri esnasında kullanımı ve etkinliğini karşılaştıran çalışmaların planlanması,
- Melatoninin uzun süreli etkilerinin belirlenmesi amacıyla 3-5 yıllık izlem süreli prospektif çalışmaların yapılması,
- Melatoninin sağ kalım üzerine etkilerinin belirlenmesi,
- Menopoz durumu, tedaviye başlama zamanı ve eşlik eden tedaviler açısından alt grup değerlendirmelerinin yapılması önerilmektedir.

**Etik Kurul Onayı**
Derleme olduğundan etik kurul iznine gerek yoktur.

**Çıkar Çatışması**
Bu yazı için herhangi bir çıkar çatışması yoktur.

**Finansal Açıklama**
Bu makale için herhangi bir finansal destek alınmamıştır.

**Yazar Katkıları**
DŞ; araştırma tasarımı, literatür tarama, makale yazımı, eleştirel inceleme

**Veri paylaşım beyanı**
Bu çalışma bir geleneksel derleme olduğundan, analiz edilen veya üretilen birincil veri bulunmamaktadır.

## KAYNAKLAR

1. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Prim. 2019; 5(1):66.
2. Subramani R, Lakshmanaswamy R. Complementary and alternative medicine and breast cancer. Prog Mol Biol Transl Sci. 2017; 151:231–74.
3. Sanchez-Barcelo EJ, Mediavilla M, Alonso-Gonzalez C, Rueda N. Breast cancer therapy based on melatonin. Recent Pat Endocr Metab Immune Drug Discov. 2012; 6(2):108–16.
4. Kubatka P, Zubor P, Busselberg D, et al. Melatonin and breast cancer: Evidences from preclinical and human studies. Crit Rev Oncol Hematol. 2018; 122:133–43.
5. World Health Organization. Breast cancer. Accessed Jan 28, 2025. https://www.who.int/news-room/fact-sheets/detail/breast-cancer#:~:text=Overview,producing lobules of the breast
6. World Cancer Research Fund. Breast cancer statistics. Accessed Jan 28, 2025. https://www.wcrf.org/preventing-cancer/cancer-statistics/breast-cancer-statistics
7. International Agency for Research on Cancer. Cancer Over Time. Accessed Jan 28, 2025. https://gco.iarc.fr/overtime/en/dataviz/bars?sexes=1_2&mode=cancer&populations=792&years=2017&key=cum_risk&types=0_1
8. T.C. Sağlık Bakanlığı. 2018 yılı verileri. Türkiye Kanser İstatistikleri. Accessed Jan 28, 2025. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/Dokumanlar/Istatistikler/Kanser_Rapor_2018.pdf
9. Xu H, Xu B. Breast cancer: Epidemiology, risk factors and screening. Chinese J Cancer Res. 2023; 35(6):565–83.
10. Park S, Lee DH, Jeon JY, et al. Serum 25-hydroxyvitamin D deficiency and increased risk of breast cancer among Korean women: a case–control study. Breast Cancer Res Treat. 2015; 152(1):147–54.
11. Reeves R, Kaufman T. Mammography. In: StatPearls. StatPearls Publishing, Treasure Island (FL); Accessed Sep 28, 2025. https://www.ncbi.nlm.nih.gov/books/NBK559310/
12. T.C. Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü. Meme kanseri korunma, tarama, tanı, tedavi ve izlem klinik rehberi. Accessed Jan 28, 2025. https://dosyamerkez.saglik.gov.tr/Eklenti/38131,memekanskr20200720pdf.pdf?0
13. Wang L. Early diagnosis of breast cancer. Sensors (Switzerland). 2017; 17(7):1572.
14. Viale G. The current state of breast cancer classification. Ann Oncol. 2012; 23:x207–10.

15. Moodley J, Cairncross L, Naiker T, Constant D. From symptom discovery to treatment - women's pathways to breast cancer care: A cross-sectional study. BMC Cancer. 2018; 18(1):312.
16. National Center for Complementary and Integrative Health (NCCIH). Strategic Plan FY 2021-2025. Accessed Sep 28, 2025. https://www.nccih.nih.gov/about/nccih-strategic-plan-2021-2025
17. Fathizadeh H, Mirzaei H, Asemi Z. Melatonin: An anti-tumor agent for osteosarcoma. Cancer Cell Int. 2019; 19(1):319.
18. Fernández-Palanca P, Méndez-Blanco C, Fondevila F, Tuñón MJ, et al. Melatonin as an antitumor agent against liver cancer: An updated systematic review. Antioxidants. 2021; 10(1):103.
19. Kim CH, Yoo YM. Melatonin induces apoptotic cell death via p53 in LNCaP cells. Korean J Physiol Pharmacol. 2010; 14(6):365–9.
20. Sheibani M, Hosseinzadeh A, Fatemi I, Naeini AJ, Mehrzadi S. Practical application of melatonin for pancreas disorders: protective roles against inflammation, malignancy, and dysfunctions. Pharmacol Reports. 2025; 77(2):315–32.
21. Innominato PF, Lim AS, Palesh O, et al. The effect of melatonin on sleep and quality of life in patients with advanced breast cancer. Support Care Cancer. 2016; 24(3):1097–1105.
22. Yang WS, Deng Q, Fan WY, Wang WY, Wang X. Light exposure at night, sleep duration, melatonin, and breast cancer: A dose-response analysis of observational studies. Eur J Cancer Prev. 2014; 23(4):269–76.
23. Pham TT, Lee ES, Kong SY, et al. Night-shift work, circadian and melatonin pathway related genes and their interaction on breast cancer risk: evidence from a case-control study in Korean women. Sci Rep. 2019; 9(1): 10982.
24. Sedighi Pashaki A, Sheida F, Moaddab Shoar L, et al. A randomized, controlled, parallel-group, trial on the long-term effects of melatonin on fatigue associated with breast cancer and its adjuvant treatments. Integr Cancer Ther. 2023; 22: 15347354231168624.
25. Pardi PC, Turri JAO, Bayer LHCM, et al. Biological action of melatonin on target receptors in breast cancer. Rev Assoc Med Bras. 2024; 70(3): e20231260.
26. Nikolaev G, Robeva R, Konakchieva R. Membrane melatonin receptors activated cell signaling in physiology and disease. Int J Mol Sci. 2022; 23(1):471.
27. Tse LH, Cheung ST, Lee S, Wong YH. Real-time determination of intracellular cAMP reveals functional coupling of gs protein to the melatonin MT1 receptor. Int J Mol Sci. 2024; 25(5):2919.
28. Laborda-Illanes A, Sánchez-Alcoholado L, Boutriq S, et al. A new paradigm in the relationship between melatonin and breast cancer: Gut microbiota identified as a potential regulatory agent. Cancers (Basel). 2021; 13(13):3141.
29. Andersen LPH, Werner MU, Rosenkilde MM, et al. Pharmacokinetics of oral and intravenous melatonin in healthy volunteers. BMC Pharmacol Toxicol. 2016; 17(1):8.
30. Zetner D, Andersen LPH, Rosenberg J. Pharmacokinetics of alternative administration routes of melatonin: A systematic review. Drug Res (Stuttg). 2016; 66(04):169–73.
31. Hardeland R. Melatonin metabolism in the central nervous system. Curr Neuropharmacol. 2010; 8(3):168–81.
32. Harpsøe NG, Andersen LPH, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: A systematic review. Eur J Clin Pharmacol. 2015; 71(8):901–9.
33. Claustrat B, Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015; 61(2–3):77–84.
34. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: A meta-analysis of randomized controlled trials. Cancer Chemother Pharmacol. 2012; 69(5):1213–20.
35. Kubatka P, Bojková B, Mníchová-Chamilová M, Adámeková E, Ahlers I, Ahlersová E, et al. Effects of tamoxifen and melatonin on mammary gland cancer induced by N-methyl-N-nitrosourea and by 7, 12-dimethylbenz (a) anthracene, respectively, in female Sprague-Dawley rats. Folia Biol (Praha). 2001; 47(1):5–10.
36. Yang A, Peng F, Zhu L, et al. Melatonin inhibits triple-negative breast cancer progression through the Lnc049808-FUNDC1 pathway. Cell Death Dis. 2021; 12(8):712.
37. Junior RP, Chuffa LG de A, Simão VA, et al. Melatonin regulates the daily levels of plasma amino acids, acylcarnitines, biogenic amines, sphingomyelins, and hexoses in a xenograft model of triple negative breast cancer. Int J Mol Sci. 2022; 23(16):9105.
38. Nimee F, Gioxari A, Papandreou P, et al. The effect of melatonin supplementation on cancer-related fatigue during chemotherapy treatment of breast cancer patients: A double-blind, randomized controlled study. Cancers (Basel). 2024; 16(4):802.
39. Sedighi Pashaki A, Mohammadian K, Afshar S, et al. A randomized, controlled, parallel-group, trial on the effects of melatonin on fatigue associated with breast cancer and its adjuvant treatments. Integr Cancer Ther. 2021; 20: 1534735420988343.
40. Mukhopadhyay ND, Khorasanchi A, Pandey S, et al. Melatonin supplementation for cancer-related fatigue in patients with early stage breast cancer receiving radiotherapy: A double-blind placebo-controlled trial. Oncologist. 2024; 29(2):e206–12.
41. Seo K, Kim JH, Han D. Effects of Melatonin supplementation on sleep quality in breast cancer patients: a systematic review and meta-analysis. Healthc. 2023; 11(5):675.
42. Palmer ACS, Zortea M, Souza A, et al. Clinical impact of melatonin on breast cancer patients undergoing chemotherapy; effects on cognition, sleep and depressive symptoms: A randomized, double-blind, placebo-controlled trial. PLoS One. 2020; 15(4):e0231379.
43. Zetner D, Kamby C, Christophersen C, et al. Effect of melatonin cream on acute radiation dermatitis in patients with primary breast cancer: A double-blind, randomized, placebo-controlled trial. J Pineal Res. 2023; 75(1):e12873.
44. Keshtpour Amlashi Z, Sheida F, Anbiaee R, et al. The effect of melatonin on increasing the health related quality of life in non-metastatic breast cancer patients: Three-

year follow up a clinical trial. Integr Cancer Ther. 2024; 23: 15347354241237520.
45. Ramos E, Egea J, López-Muñoz F, Gil-Martín E, Romero A. Therapeutic potential of melatonin counteracting chemotherapy-induced toxicity in breast cancer patients: A systematic review. Pharmaceutics. 2023; 15(6):1616.
46. Pistiolis L, Khaki D, Kovács A, Olofsson Bagge R. The effect of melatonin intake on survival of patients with breast cancer—A population-based registry study. Cancers (Basel). 2022; 14(23):5884.
47. Minella C, Coliat P, Amé S, et al. Protective role of melatonin in breast cancer: what we can learn from women with blindness. Cancer Causes Control. 2022; 33(1):1–13.
48. Andersen LPH, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. Clin Drug Investig. 2016; 36(3):169–75.
49. Givler D, Givler A, Luther PM, et al. Chronic administration of melatonin: Physiological and clinical considerations. Neurol Int. 2023; 15(1):518–33.
50. Zwart TC, Smits MG, Egberts TC, Rademaker CM, Van Geijlswijk IM. Long-term melatonin therapy for adolescents and young adults with chronic sleep onset insomnia and late melatonin onset: evaluation of sleep quality, chronotype, and lifestyle factors compared to age-related randomly selected population cohorts. Healthcare. 2018; 6(1):23.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):147-155*
*e-ISSN: 2980-0978*

***Review Article/ Derleme Makalesi***
***DOI:10.61845/agrimedical.1684066***

# VEGF$_{165}$a and VEGF$_{165}$b: Molecular effects of opposing isoforms in angiogenesis

## VEGF$_{165}$a ve VEGF$_{165}$b: Anjiyogenezde zıt izoformların moleküler etkileri

Funda Çimen Açıkgül [1*], Seçil Nazife Parlak[2]

[1] *Department of Microbiology, Faculty of Medicine, Ağrı İbrahim Çeçen University, Türkiye*
[2] *Department of Histology and Embryology, Faculty of Medicine, Ağrı İbrahim Çeçen University, Türkiye*

**ABSTRACT**

This review aims to comparatively examine the structural differences, receptor interactions, downstream signaling effects, and pathophysiological roles of the two main isoforms of the *VEGF*A gene, VEGF$_{165}$a and VEGF$_{165}$b, which arise from alternative splicing of exon 8. Recent experimental and clinical studies conducted between 2020 and 2025 in both human and animal models were systematically reviewed to evaluate the biological functions, receptor-binding properties, and pro- and anti-angiogenic effects of VEGF$_{165}$b. VEGF$_{165}$a promotes endothelial cell proliferation, migration, and vascular permeability by activating VEGFR-2 through PI3K/Akt and MAPK/ERK pathways. In contrast, VEGF$_{165}$b binds to the same receptors but induces weak signaling and competitively inhibits the effects of VEGF$_{165}$a. While VEGF$_{165}$b is predominantly expressed in healthy tissues, a shift in favor of VEGF$_{165}$a is observed in pathological conditions such as cancer, proliferative diabetic retinopathy, and age-related macular degeneration. Conversely, excessive VEGF$_{165}$b expression is associated with impaired angiogenesis in diseases such as peripheral artery disease, systemic sclerosis, and preeclampsia. Disruption in the VEGF$_{165}$ isoform balance underlies many diseases characterized by either excessive or insufficient angiogenesis. In this context, isoform-specific therapeutic strategies—such as the modulation of alternative exon usage via splice-switching oligonucleotides—may allow the development of more precise and targeted vascular therapies in the future. The VEGF$_{165}$a/VEGF$_{165}$b ratio also holds promise as a biomarker for guiding personalized angiogenesis-modulating treatments.

**Keywords:** *Angiogenesis, Alternative splicing, Isoforms, Vascular endothelial growth factor A, VEGFR-2, Signal transduction*

*0000-0002-8904-1444*
*0000-0001-9577-986X*

**Sorumlu Yazar:*
*Funda Çimen Açıkgül*
*Department of Microbiology, Faculty of Medicine, Ağrı İbrahim Çeçen University, Türkiye*
*e-mail: fundacimenacikgul@gmail.com*

Gönderilme Tarihi: 25/04/2025
Kabul Tarihi: 03/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Çimen Açıkgül F, Parlak SN. VEGF165a and VEGF165b: Molecular effects of opposing ısoforms in angiogenesis. Ağrı Med J. 2025; 3(3):*147-155*.

**ÖZ**

Bu derleme, *VEGFA* geninin alternatif ekzon 8 bölgesinden türeyen iki ana izoformu olan VEGF$_{165}$a ve VEGF$_{165}$b'nin yapısal farklılıklarını, reseptör etkileşimlerini, sinyal yolakları üzerindeki etkilerini ve bu izoformların hastalıklardaki patofizyolojik rollerini karşılaştırmalı olarak incelemeyi amaçlamaktadır. İnsan ve hayvan modellerinde yapılan deneysel ve klinik çalışmalara ait 2020–2025 yılları arasındaki güncel literatür taranmış, VEGF$_{165}$b'nin biyolojik işlevleri, reseptör bağlanma özellikleri, pro- ve anti-anjiyogenik etkileri ile ilgili bulgular sistematik olarak derlenmiştir. VEGF$_{165}$a, VEGFR-2 üzerinden PI3K/Akt ve MAPK/ERK yolaklarını aktive ederek endotel hücre proliferasyonu, göçü ve damar geçirgenliğini artırırken; VEGF$_{165}$b bu reseptörlere bağlanmasına rağmen sinyallemeyi zayıf biçimde tetiklemekte ve VEGF$_{165}$a'nın etkilerini kompetitif olarak baskılamaktadır. VEGF$_{165}$b ekspresyonu sağlıklı dokularda baskın iken, kanser, proliferatif diyabetik retinopati ve yaşa bağlı makula dejenerasyonu gibi hastalıklarda VEGF$_{165}$a lehine bir dengesizlik gözlenmektedir. Öte yandan, periferik arter hastalığı, sistemik skleroz ve preeklampsi gibi durumlarda VEGF$_{165}$b'nin aşırı ekspresyonu yetersiz anjiyogenez ile ilişkilidir. VEGF$_{165}$ izoform dengesindeki bozulmalar, anjiyogenez fazlalığı ya da yetersizliği ile seyreden birçok hastalığın temelinde yer almaktadır. Bu bağlamda, izoformlara özgü tedavi yaklaşımları (örneğin splice-switching oligonükleotidlerle alternatif ekson kullanımının yönlendirilmesi) gelecekte daha hassas ve hedefe yönelik damar tedavileri geliştirilmesine olanak sağlayabilir. VEGF$_{165}$a/VEGF$_{165}$b oranının biyobelirteç olarak kullanımı, kişiye özel anjiyogenez modülasyonuna yönelik önemli bir potansiyel taşımaktadır.

**Anahtar Kelimeler**: *Anjiyogenez, Alternatif dizi birleştirme, İzoformlar, Vasküler endotelyal büyüme faktörü A, VEGFR-2, Sinyal iletimi*

## INTRODUCTION

Vascular endothelial growth factor A (*VEGFA*) is one of the most important molecules that regulate blood vessel formation and maintain vascular integrity (1). Through alternative mRNA splicing, *VEGFA* produces several isoforms, among which $VEGF_{165}$ is the most common and biologically active. $VEGF_{165}$ is a heparin-binding glycoprotein that can exist in both soluble and extracellular matrix-bound forms. This allows it to deliver spatially controlled signals to surrounding cells (2). By binding to its main endothelial receptors— Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1; Flt-1) and Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2; KDR/Flk-1)—$VEGF_{165}$ activates intracellular signaling pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (3). These pathways support endothelial cell survival, proliferation, migration, and the formation of new blood vessels (4).

$VEGF_{165}$ plays a key role in several physiological processes including embryonic vascular development, postnatal angiogenesis, wound healing, and neurovascular protection. However, when $VEGF_{165}$ is overexpressed in an uncontrolled manner, it can lead to pathological angiogenesis *in diseases such as cancer, diabetic retinopathy (DR), and* age-related macular degeneration (AMD). Tumors rely on $VEGF_{165}$-induced angiogenesis to grow and spread, while in the eye, excessive $VEGF_{165}$ increases vascular permeability, causing edema and vision loss (5, 6).

Importantly, $VEGF_{165}$ is not a single molecule—it includes two splice variants with different effects: the pro-angiogenic $VEGF_{165}$a and the anti-angiogenic $VEGF_{165}$b. These variants differ due to an alternative splicing event in exon 8 of the *VEGFA* gene, which changes the last six amino acids of the protein (7). This small change significantly alters how each isoform interacts with receptors and affects signaling. $VEGF_{165}$b was first described in 2002 and was initially classified as a natural inhibitor of angiogenesis. However, recent studies have shown that $VEGF_{165}$b may act as a weak agonist in some situations. Therefore, its effects can vary depending on the biological context (8).

This review compares the structural differences, receptor interactions, and cellular effects of $VEGF_{165}$a and $VEGF_{165}$b. It also discusses how the balance between these isoforms influences diseases with excessive or insufficient angiogenesis, such as cancer, retinal disorders, ischemia, fibrosis, and preeclampsia. The literature was reviewed to evaluate the varying roles of $VEGF_{165}$b, and recent therapeutic approaches targeting isoform-specific expression or function are discussed. Understanding the regulatory balance between $VEGF_{165}$a and $VEGF_{165}$b could help develop more targeted and safer angiogenesis-based therapies.

### $VEGF_{165}$ isoforms

The human *VEGFA* gene contains eight exons. Alternative splicing at exon 8 produces two functionally distinct $VEGF_{165}$ isoforms. When the proximal splice site of exon 8 (exon 8a) is used, it generates the pro-angiogenic isoform $VEGF_{165}$a. In contrast, use of the distal splice site (exon 8b) results in $VEGF_{165}$b, which has anti-angiogenic properties. Exons 1 through 5 are common to all isoforms and encode the core domains of *VEGFA*, while exon 8a or 8b determines the unique C-terminal sequence. $VEGF_{165}$a and $VEGF_{165}$b are identical except for their final six amino acids: $VEGF_{165}$a ends in CDKPRR, a strongly basic sequence, while $VEGF_{165}$b ends in SLTRKD, which is less positively charged. Although this difference is small, it has a major impact on receptor binding and signaling (8, 9).

Both $VEGF_{165}$a and $VEGF_{165}$b bind to VEGF receptors 1 and 2 with similar affinity. However, only $VEGF_{165}$a efficiently activates these receptors. It induces VEGFR-2 dimerization and phosphorylation, triggering downstream signaling pathways such as PI3K/Akt and MAPK/ERK, which promote endothelial cell proliferation and migration. $VEGF_{165}$b, on the other hand, binds to VEGFR-2 but does not activate it fully. Instead, it holds the receptor in an inactive state and prevents $VEGF_{165}$a from binding, acting as a competitive inhibitor. In cell studies, $VEGF_{165}$b leads to little or no activation of Akt or ERK, in sharp contrast to the strong signals induced by $VEGF_{165}$a (10). One key reason for this difference is co-receptor interaction. $VEGF_{165}$a contains a heparin-binding domain at its C-terminus that allows it to bind to neuropilin-1 (NRP1) and heparan sulfate proteoglycans. NRP1 enhances VEGFR-2 signaling. The unique CDKPRR tail of $VEGF_{165}$a is essential for this binding. Since $VEGF_{165}$b lacks this sequence, it cannot recruit NRP1 effectively. As a result, $VEGF_{165}$b–VEGFR-2 complexes are formed without sufficient co-receptor support, leading to weak or incomplete signaling. Additionally, the more acidic tail of $VEGF_{165}$b may reduce its ability to bind to the extracellular matrix, limiting receptor clustering and signaling efficiency (11).

$VEGF_{165}$b may also affect VEGFR-1 differently than $VEGF_{165}$a. VEGFR-1 has a higher affinity for VEGF but a lower signaling capacity and is often considered a decoy receptor. Studies suggest that in ischemic tissues, $VEGF_{165}$b can bind to VEGFR-1 and block its pro-angiogenic signaling. For example, in a diabetic mouse model of peripheral artery disease (PAD), ischemia led to increased $VEGF_{165}$b expression, which in turn inhibited VEGFR-1–signal transducer and activator of transcription 3 (STAT3) signaling. Neutralizing $VEGF_{165}$b restored VEGFR-1 phosphorylation and improved angiogenesis, without significantly affecting VEGFR-2. These findings suggest $VEGF_{165}$b may act as a fine-tuner of VEGFR-1 activity in specific physiological conditions (12).

$VEGF_{165}$a is strongly pro-angiogenic. It stimulates all key steps of angiogenesis: endothelial proliferation and migration, matrix remodeling, nitric oxide (NO) production leading to vasodilation, and increased vascular permeability. By loosening endothelial junctions, it also enhances microvascular permeability (13).

In contrast, $VEGF_{165}$b does not promote new blood vessel formation. Instead, it antagonizes $VEGF_{165}$a's effects and can suppress angiogenesis. In several animal models, externally applied $VEGF_{165}$b has reduced pathological angiogenesis. However, $VEGF_{165}$b is not completely inactive. It may deliver low-level survival signals to endothelial cells

without promoting their proliferation or migration. For example, another anti-angiogenic isoform, VEGF121b, was shown to protect endothelial cells from apoptosis under stress despite inhibiting their movement. This suggests that $VEGF_{165}b$ and related isoforms may support vessel stability without triggering angiogenic growth (8).

The balance between $VEGF_{165}a$ and $VEGF_{165}b$ varies depending on tissue state. In healthy adult tissues, $VEGF_{165}b$ and other anti-angiogenic isoforms (collectively called VEGFxxxb) are more highly expressed than pro-angiogenic isoforms. This helps maintain vascular stability. During active angiogenesis—for instance, in the placenta during pregnancy or in wounded tissue—the balance shifts toward $VEGF_{165}a$. Hypoxia increases total *VEGFA* expression through hypoxia-inducible factor-1 alpha (HIF-1α) and favors production of $VEGF_{165}a$. Growth factors and hormones also push splicing toward the pro-angiogenic form. When angiogenesis is no longer needed, $VEGF_{165}b$ levels rise again to restore balance. For example, after wound healing or at the end of the menstrual cycle, $VEGF_{165}b$ may help return the tissue to a quiescent state. This dynamic regulation allows *VEGFA* activity to be finely tuned after transcription (14) (Table 1).

$VEGF_{165}a$ exerts its pro-angiogenic effects by binding to endothelial receptors and activating key intracellular kinase pathways. VEGFR-2 is the principal mediator of these signals. Upon $VEGF_{165}a$-induced dimerization of VEGFR-2 on the cell surface, specific intracellular tyrosine residues undergo autophosphorylation. This initiates several downstream cascades: the Ras–MAPK/ERK pathway (which drives endothelial proliferation), the PI3K–Akt pathway (promoting cell survival and NO production), and focal adhesion kinase pathways (facilitating cell migration and vascular permeability). A key outcome of this signaling is the upregulation of endothelial nitric oxide synthase (eNOS), resulting in local vasodilation and increased microvascular permeability—hallmarks of VEGF activity. Additionally, $VEGF_{165}a$ promotes extracellular matrix remodeling via protease induction and recruits bone marrow-derived endothelial progenitor cells to sites of neovascularization (15).

Although VEGFR-1 also binds $VEGF_{165}a$ with high affinity, its signaling capacity is weaker. In various contexts, VEGFR-1 can function as a decoy receptor, sequestering $VEGF_{165}a$, or as an active signaling receptor—particularly in monocytes, macrophages, and pathological angiogenesis—through pathways such as STAT3. Furthermore, $VEGF_{165}a$'s C-terminal heparin-binding domain facilitates interaction with NRP1, a co-receptor that enhances VEGFR-2 signaling. This interaction promotes high-density VEGF presentation at the endothelial surface, amplifying signal transduction (15, 16).

In contrast, $VEGF_{165}b$ lacks the C-terminal motif required for NRP1 binding and fails to induce significant phosphorylation of VEGFR-2. It acts as a partial agonist or a competitive antagonist by binding VEGFR-2 and inducing receptor dimerization without triggering a full conformational activation. Consequently, $VEGF_{165}b$ produces minimal downstream activation of MAPK or Akt signaling. Notably, recent studies suggest $VEGF_{165}b$ may preferentially bind to VEGFR-1 and suppress its activity. In a mouse model of PAD, $VEGF_{165}b$ acted as an endogenous VEGFR-1 inhibitor. Neutralizing $VEGF_{165}b$ restored VEGFR-1–STAT3 signaling and improved angiogenesis without affecting VEGFR-2 activity. This finding challenges the prior assumption that $VEGF_{165}b$ solely antagonizes VEGFR-2, highlighting its role in fine-tuning the balance between VEGFR-1 and VEGFR-2 signaling (12).

**Table 1.** Comparison of $VEGF_{165}a$ and $VEGF_{165}b$ Isoforms

| **Feature** | $VEGF_{165}a$ (Pro-angiogenic) | $VEGF_{165}b$ (Anti-angiogenic) |
|---|---|---|
| **Exon 8 Splice Site** | Proximal (exon 8a) | Distal (exon 8b) |
| **C-terminal Sequence** | CDKPRR (basic, + charge) | SLTRKD (less basic, more acidic) |
| **Amino Acid Difference** | Final 6 amino acids: CDKPRR | Final 6 amino acids: SLTRKD |
| **Receptor Binding** | Binds VEGFR-1 and VEGFR-2 | Binds VEGFR-1 and VEGFR-2 |
| **Receptor Activation** | Efficiently activates VEGFR-2 | Weak or no activation of VEGFR-2 |
| **Downstream Signaling** | Strong PI3K/Akt, MAPK/ERK activation | Little/no PI3K/Akt, MAPK/ERK signal |
| **Co-receptor Interaction** | Binds neuropilin-1 (NRP1) and HSPGs | Poor NRP1 binding |
| **Matrix Binding** | Strong (via basic tail) | Weaker (more acidic tail) |
| **Effect on VEGFR-1** | May activate or act as decoy | Can block VEGFR-1 signaling |
| **Angiogenic Activity** | Potent stimulator of angiogenesis | Inhibits angiogenesis |
| **Cellular Effects** | Promotes proliferation, migration, NO production, permeability | May provide survival signals, does not promote proliferation or migration |
| **Expression in Tissues** | Upregulated in active angiogenesis (e.g., placenta, wounds, tumors) | Dominant in healthy adult tissues, upregulated post-healing |
| **Physiological Role** | Drives vessel growth and remodeling | Maintains vascular quiescence, opposes excess angiogenesis |
| **Response to Hypoxia/GFs** | Upregulated by HIF-1α, growth factors, hormones | Not upregulated by hypoxia; increased as angiogenesis resolves |

VEGFR: Vascular Endothelial Growth Factor Receptor,
NRP1: Neuropilin-1,
HSPGs: Heparan Sulfate Proteoglycans,
PI3K: Phosphoinositide 3-Kinase,
Akt: Protein Kinase B,
MAPK: Mitogen-Activated Protein Kinase,
ERK: Extracellular Signal-Regulated Kinase,
HIF-1α: Hypoxia-Inducible Factor 1-alpha,
GF: Growth Factor

Moreover, external factors such as metabolic stress can influence *VEGFA* isoform expression via splicing regulators. For instance, in an atherosclerosis model induced

by a high-fat diet, upregulation of the splicing kinase SR protein kinase 1 (SRPK1) favored $VEGF_{165}a$ production over $VEGF_{165}b$, enhancing pathological angiogenesis (17).

**Pathophysiological roles of $VEGF_{165}a$ and $VEGF_{165}b$ in disease**

The ratio between $VEGF_{165}a$ and $VEGF_{165}b$ plays a pivotal role in regulating angiogenic activity across various pathological conditions. An imbalance—either through excessive $VEGF_{165}a$ or insufficient $VEGF_{165}b$—can drive disease progression. Below, the contributions of these isoforms are examined in the context of cancer biology (18).

**Cancer and tumor angiogenesis**

Many tumors exploit the VEGF pathway to promote angiogenesis and support their growth. *VEGFA*, particularly the $VEGF_{165}a$ isoform, is commonly overexpressed in malignancies and correlates with poor clinical outcomes. High levels of $VEGF_{165}a$ in the tumor microenvironment stimulate the development of structurally abnormal and hyperpermeable blood vessels, thereby facilitating tumor expansion and metastasis. In breast cancer, for example, elevated $VEGF_{165}$ expression is associated with more aggressive phenotypes. Additionally, $VEGF_{165}a$ may function in an autocrine manner, supporting tumor cell survival independent of angiogenesis (19).

In contrast, $VEGF_{165}b$ is frequently downregulated in tumors. A shift in *VEGFA* mRNA splicing towards exon 8a leads to suppression of VEGFxxxb isoforms, including $VEGF_{165}b$. Clinical studies have shown significantly reduced $VEGF_{165}b$ expression in melanoma and colon carcinoma tissues compared to adjacent non-cancerous counterparts. This loss removes a key inhibitory control on angiogenesis, enabling unregulated vessel sprouting—an essential component of the "angiogenic switch" during tumor development (20).

However, the presence and regulation of $VEGF_{165}b$ in tumors appear context-dependent. Some reports indicate that $VEGF_{165}b$ may still be expressed in certain cancers and may even be upregulated in response to anti-angiogenic or hormonal therapies. For instance, in subsets of breast cancer, $VEGF_{165}b$ expression increased following treatment, suggesting it might function as a feedback regulator under specific conditions. Yet, the mere presence of $VEGF_{165}b$ does not guarantee effective angiogenesis inhibition; its function depends on the relative abundance of $VEGF_{165}a$ and other angiogenic factors (21).

A study by Catena et al. (2010) clarified this complexity by demonstrating that the efficacy of $VEGF_{165}b$ in suppressing tumor growth depends on baseline $VEGF_{165}a$ levels. In tumors with high $VEGF_{165}a$ expression, $VEGF_{165}b$ competes for VEGFR binding, reducing signaling and inhibiting angiogenesis. In contrast, in tumors with low VEGF expression, $VEGF_{165}b$'s weak signaling may paradoxically provide a minimal angiogenic stimulus. Thus, $VEGF_{165}b$ can either inhibit or, in rare contexts, modestly support angiogenesis, depending on the tumor microenvironment (22).

Therapeutically, increasing $VEGF_{165}b$ levels in tumors has shown promise in preclinical models. Overexpression or delivery of $VEGF_{165}b$ in xenograft models such as prostate cancer, renal cell carcinoma, and Ewing's sarcoma led to reduced angiogenesis and slowed tumor growth. These findings support the concept that shifting the $VEGF_{165}a/VEGF_{165}b$ ratio toward the anti-angiogenic isoform may impair tumor vascularization. However, such interventions are likely to be most effective in tumors with strong $VEGF_{165}a$-driven angiogenesis. In cancers where angiogenesis is VEGF-independent, $VEGF_{165}b$-based therapies may have limited efficacy or even counterproductive effects (14).

**Diabetic retinopathy and ocular neovascular disease**

Pathological angiogenesis in the eye – as seen in proliferative diabetic retinopathy (PDR) and neovascular AMD – is largely driven by excess *VEGFA*. In the retinal milieu of diabetic patients with retinopathy, there is a pronounced skew toward the pro-angiogenic isoform. Clinical samples show that the ratio of $VEGF_{165}b$ to total *VEGFA* is significantly lower in the ocular fluids of diabetics with retinopathy compared to diabetics without retinopathy. In other words, PDR patients have relatively deficient $VEGF_{165}b$ (or an excess of $VEGF_{165}a$), removing an inhibitory constraint and permitting aberrant blood vessel proliferation in the retina (23).

This insight has spurred interest in supplementing $VEGF_{165}b$ for therapeutic effect in eye diseases. Experimental studies have delivered recombinant $VEGF_{165}b$ into animal models of retinal neovascularization. Remarkably, a single intravitreal injection of $VEGF_{165}b$ significantly reduced pathological preretinal neovascular growth in an ischemic retinopathy model, without adversely affecting the normal retinal vessels. This contrasts with standard anti-VEGF drugs (like bevacizumab or ranibizumab), which indiscriminately neutralize all *VEGFA* isoforms and therefore can somewhat affect the healthy vasculature. $VEGF_{165}b$ appears to specifically counteract the pathological angiogenic drive ($VEGF_{165}a$-mediated) while sparing baseline vasculature – likely because $VEGF_{165}b$ won't fully shut down the minimal VEGF signals needed for maintenance. Additionally, $VEGF_{165}b$ can mitigate vascular leakage. In diabetic rats, intravitreal $VEGF_{165}b$ administration reduced retinal vascular permeability and edema. This is an important finding since macular edema (due to leaky vessels) is a major cause of vision loss in DR. By stabilizing endothelial junctions (perhaps by blocking $VEGF_{165}a$-induced junction disassembly), $VEGF_{165}b$ could help control edema (23).

Current anti-VEGFA therapies for DR and wet AMD consist of antibodies or decoy receptors that sequester all *VEGFA* isoforms – effectively neutralizing both $VEGFA_{165}a$ and $VEGFA_{165}b$. These treatments (e.g., ranibizumab, aflibercept, and off-label bevacizumab) have markedly improved clinical outcomes by inhibiting pathological neovascularization and preserving visual function in a substantial proportion of patients (24, 25).

However, they pose a theoretical concern: by neutralizing $VEGFA_{165}b$ alongside $VEGFA_{165}a$, they may inadvertently eliminate an endogenous protective factor (8).

Indeed, chronic anti-VEGF therapy has been associated with choroidal vessel atrophy and progressive degeneration of the outer retina in AMD, possibly reflecting excessive suppression of physiological VEGF signaling (26). The retina relies on a finely regulated *VEGFA* level for homeostasis – excessive amounts promote macular edema and pathological neovascularization, whereas insufficient levels may compromise the viability of the retinal pigment epithelium and the integrity of the choroidal vasculature (26).

This raises a compelling question: could ocular neovascular diseases be treated by selectively inhibiting $VEGFA_{165}a$ while preserving or enhancing $VEGFA_{165}b$? Theoretically, yes. An isoform-specific inhibitor that selectively neutralizes $VEGFA_{165}a$ but spares $VEGFA_{165}b$ could suppress pathological angiogenesis with fewer adverse effects on physiological retinal function (8). Alternatively, exogenous administration of $VEGFA_{165}b$, or upregulation of its expression via splicing modulation, may provide an intrinsic anti-angiogenic effect. Although such approaches have not yet reached clinical implementation, they represent a next-generation strategy in precision ocular therapy: modulating isoform balance rather than employing indiscriminate *VEGFA* blockade. Notably, $VEGFA_{165}b$ has been tested in non-human primate models without significant toxicity, indicating its potential for therapeutic application or biomimetic use—though challenges such as its short half-life and possible immunogenicity must be considered (27).

**Peripheral ischemia (peripheral artery disease)**

Ischemic diseases like PAD trigger a compensatory angiogenic response – hypoxic tissues upregulate *VEGFA* to try to grow collateral vessels. However, in chronic ischemia (especially with comorbidities like diabetes), this response often fails. A surprising discovery is that $VEGF_{165}b$ may play a role in this failure (26). In diabetic models of limb ischemia, $VEGF_{165}b$ expression was found to increase in ischemic muscle, even as total *VEGFA* levels rose. The induced $VEGF_{165}b$ acted as a brake on angiogenesis, contributing to the poor recovery of blood flow. When researchers neutralized $VEGF_{165}b$ with an antibody, the ischemic limbs showed significantly improved angiogenesis: blood flow and capillary density increased, essentially "unleashing" vessel growth that had been restrained. This provided direct evidence that $VEGF_{165}b$ was a maladaptive factor in the context of PAD (28).

Mechanistically, as noted earlier, $VEGF_{165}b$ in diabetic ischemia appears to hinder VEGFR-1–mediated angiogenic pathways, which become important when VEGFR-2 signaling is impaired by diabetes. Diabetes is known to cause endothelial dysfunction (e.g., reduced NO production), so VEGFR-2's usual pro-angiogenic signals are blunted. In that setting, alternate routes (like VEGFR-1–STAT3 signaling through inflammatory cells) might help – but $VEGF_{165}b$ prevents VEGFR-1 from contributing. By removing $VEGF_{165}b$, those alternate pathways can engage and partially compensate for the VEGFR-2 impairment, thus restoring angiogenesis.

These findings have spurred interest in isoform-specific pro-angiogenic therapies for ischemia. For instance, one could envision an antibody or small molecule that selectively inhibits $VEGF_{165}b$ without blocking $VEGF_{165}a$. Such a therapy might boost the patient's own angiogenesis in conditions like critical limb ischemia or even ischemic heart disease, especially in individuals where standard pro-angiogenic treatments have failed. In essence, instead of adding more growth factors, this approach would involve removing an endogenous inhibitor ($VEGF_{165}b$) to tilt the balance toward angiogenesis. This strategy contrasts with oncology and ophthalmology, aiming to enhance angiogenesis by inhibiting an anti-angiogenic isoform.

Early experimental support for this concept comes from a recent study in choroidal neovascularization (CNV) model (an eye model of pathological angiogenesis). There, use of an SRPK1 inhibitor – a drug that shifts splicing towards the VEGFxxxb isoforms – was able to abort new vessel growth (29). By increasing $VEGF_{165}b$ relative to $VEGF_{165}a$, the SRPK1 inhibitor suppressed angiogenesis in the CNV model. Translating that to ischemic disease, one might do the opposite (inhibit splicing towards $VEGF_{165}b$ or activate splicing toward $VEGF_{165}a$) to encourage angiogenesis. For example, an activator of SRPK1 or of the splicing factor serine/arginine-rich splicing factor 1 (SRSF1) could theoretically reduce $VEGF_{165}b$ production and favor $VEGF_{165}a$, boosting angiogenic capacity in ischemic tissues. Although these strategies remain theoretical and require further validation, modulating the $VEGF_{165}a/b$ ratio represents a promising approach for future therapeutic development in vascular diseases.

**Fibrosis and systemic sclerosis**

Systemic sclerosis (SSc) – a fibrotic autoimmune disease – provides another striking example of $VEGF_{165}b$'s impact. SSc patients suffer from severe peripheral ischemia (e.g., in the skin and digits) despite having high circulating VEGF levels. The microvasculature shows rarefaction (loss of vessels) and poor angiogenic repair. A key finding is that $VEGF_{165}b$ is markedly overexpressed in SSc. Skin biopsies from SSc patients have significantly higher $VEGF_{165}b$ mRNA and protein compared to healthy controls (30). In fact, plasma $VEGF_{165}b$ is elevated in SSc and correlates with the degree of capillary loss (30, 31).

This overabundance of the anti-angiogenic isoform offers an explanation for the long-standing puzzle in SSc: why is angiogenesis impaired even though *VEGFA* (normally pro-angiogenic) is elevated? The "angiogenic paradox" in SSc is that total VEGF is high (the body is desperately trying to grow vessels in response to chronic ischemia), but because so much of that VEGF is the $VEGF_{165}b$ isoform, the net effect is anti-angiogenic. Essentially, the pro-angiogenic signal is canceled out by the concurrent presence of $VEGF_{165}b$, leading to futile angiogenesis attempts and persistent tissue ischemia.

This insight positions $VEGF_{165}b$ as both a biomarker and a potential therapeutic target in SSc. High $VEGF_{165}b$ levels could indicate a more severe microvasculopathy (e.g., worse nailfold capillary loss and digital ulcers) (30). Therapeutically, strategies to reduce $VEGF_{165}b$ or block its function might restore angiogenic competence in SSc patients. For example, one could imagine using a neutralizing

antibody against $VEGF_{165}b$ in SSc skin—similar to how it was done in the PAD model—to promote new vessel growth and wound healing. Alternatively, downregulating the splicing factors that favor exon 8b in SSc endothelial cells could shift the balance back to $VEGF_{165}a$. Indeed, studies have noted dysregulation of splicing regulators in SSc (e.g., elevated SRPK1), which might contribute to the high $VEGF_{165}b$ production (32).

It is worth noting that the VEGF pathway in SSc is complex. Other factors (like soluble VEGFR-1 and endostatin) are also elevated and inhibit angiogenesis. Nonetheless, $VEGF_{165}b$ appears to be a significant piece of the puzzle. Manetti et al. (2011) demonstrated that overexpression of $VEGF_{165}b$ in an SSc context led to insufficient angiogenesis, and that patients with SSc had high $VEGF_{165}b$ linked to their capillary loss (30). This underscores that tackling $VEGF_{165}b$ in SSc could be beneficial. Any intervention, however, would need to be careful not to tip the balance too far and cause aberrant angiogenesis or edema.

**Pre-eclampsia**

Pre-eclampsia is a pregnancy-related hypertensive disorder marked by poor placental vascular development and endothelial dysfunction. While much attention has focused on VEGF inhibitors like sFlt-1 (soluble VEGFR-1) in pre-eclampsia, evidence suggests that *VEGFA* splicing may also be altered (33). The placenta is one of the few normal tissues that predominantly expresses pro-angiogenic VEGFxxxa isoforms, as robust angiogenesis is essential during pregnancy. In healthy pregnancy, $VEGF_{165}b$ levels in maternal plasma gradually rise but remain relatively low in the placenta to allow adequate blood vessel formation. However, in pre-eclampsia, studies have indicated aberrant $VEGF_{165}b$ expression in placental tissue. Some preliminary reports found higher $VEGF_{165}b$ levels in pre-eclamptic placentas or plasma compared to normal pregnancies. For instance, one study noted that women who developed pre-eclampsia failed to upregulate $VEGF_{165}b$ in the first trimester to the same extent as normotensive pregnancies, but later in pregnancy their $VEGF_{165}b$ became inappropriately elevated. The net effect could be insufficient angiogenesis in early placentation, leading to poor placental perfusion and the subsequent cascade of pre-eclampsia symptoms.

The data on $VEGF_{165}b$ in pre-eclampsia are still emerging and, at times, conflicting. Some studies show lower early $VEGF_{165}b$ levels, while others report higher levels later in pregnancy. Nonetheless, the central concept is that a shift toward the anti-angiogenic isoform within the uteroplacental unit could contribute to the shallow trophoblast invasion and limited spiral artery remodeling that characterize pre-eclampsia (34).

If validated, $VEGF_{165}b$ could serve both as a biomarker—such as first-trimester plasma $VEGF_{165}b$ levels predicting pre-eclampsia risk—and as a therapeutic target. For example, strategies aimed at reducing $VEGF_{165}b$ or enhancing $VEGF_{165}a$ expression in the placenta might improve angiogenesis and pregnancy outcomes. Further research is required to determine the safety, feasibility, and potential efficacy of targeting $VEGFA_{165}b$ in the context of pregnancy without compromising fetal development (32).

**Summary of isoform imbalance in disease**

Across diverse pathological contexts—including cancer, ocular disease, PAD, SSc, and pre-eclampsia—a common theme emerges: the $VEGF_{165}a/VEGF_{165}b$ ratio is critical (8). Pathological angiogenesis (as observed in tumors and PDR) is typically associated with a skew toward $VEGF_{165}a$, reflecting excessive pro-angiogenic signaling with insufficient inhibitory control (26). In contrast, conditions characterized by impaired angiogenesis—such as chronic ischemia and SSc—are often marked by elevated $VEGF_{165}b$ levels, indicating excessive suppression of vascular growth stimuli (8, 30).

This dichotomy suggests that therapeutic restoration of isoform balance could serve as a unifying strategy: inhibiting $VEGF_{165}a$ in diseases of excessive angiogenesis, or conversely, inhibiting $VEGF_{165}b$ (or enhancing $VEGF_{165}a$) in diseases of insufficient angiogenesis. Indeed, ongoing studies and clinical trials are investigating both directions. Conventional agents like bevacizumab exemplify the former approach, although they non-selectively target all *VEGFA* isoforms. In contrast, newer strategies—such as splicing modulators or isoform-specific antibodies—represent more precise and promising alternatives.

**Discussion and Therapeutic Perspectives**

The dual-isoform nature of $VEGF_{165}$ has prompted a reevaluation of traditional views on VEGF in angiogenesis. Several controversies and areas of active research have emerged in recent years:

***1. Conflicting data on $VEGF_{165}b$ in tumors***

Early studies highlighted $VEGF_{165}b$ as a tumor-suppressive, anti-angiogenic factor—demonstrating, for example, that adding $VEGF_{165}b$ could slow the growth of certain tumor xenografts (8). However, later findings complicated this picture. Some studies reported that $VEGF_{165}b$ did not inhibit tumor growth, and in some models, it even appeared to promote it (35). This paradox was addressed by Catena et al., who proposed that the effect of $VEGF_{165}b$ depends on the prevailing levels of pro-angiogenic $VEGF_{165}a$ (22).

In VEGF-rich tumors, $VEGF_{165}b$ competes with $VEGF_{165}a$ and reduces net angiogenic signaling, thereby limiting tumor growth. In contrast, in VEGF-poor tumors, $VEGF_{165}b$ may deliver baseline VEGFR stimulation that would otherwise be absent, potentially enhancing angiogenesis and growth. This nuanced view reconciles conflicting data and underscores the therapeutic principle that $VEGF_{165}b$-based treatments may only be beneficial in high-*VEGFA* contexts. Stratifying patients according to tumor VEGF expression profiles may support more tailored therapeutic approaches in line with emerging principles of personalized oncology.

***2. Debate over the existence and levels of VEGF$_{165}$b***

Following its initial identification, VEGFA$_{165}$b encountered skepticism concerning its biological significance. Detection of VEGFAxxxb isoforms presented notable technical challenges, as various research groups employing ELISA or PCR methodologies reported inconsistent findings. For example, while one study suggested that VEGFAxxxb mRNA constituted over 50% of total VEGFA transcripts in healthy tissues, other investigations failed to detect it at comparable levels in similar samples (7, 8).

Such discrepancies were subsequently attributed to differences in assay sensitivity and specificity. The advent of isoform-specific antibodies and optimized PCR primer designs has since enabled more accurate detection, establishing that VEGFA$_{165}$b is indeed broadly expressed and biologically active (3). Nonetheless, its expression levels vary depending on tissue type and pathological context. For instance, data obtained using validated detection systems confirm that VEGFA$_{165}$b is detectable in normal renal tissue but markedly reduced or absent in many renal carcinoma specimens (7). These early inconsistencies underscore the critical importance of employing highly specific and sensitive tools when investigating isoform biology.

***3. Therapeutic Implications – Toward Isoform-Specific VEGF Targeting***

The clinical success of anti-VEGF agents—such as bevacizumab in oncology or aflibercept in the management of ocular neovascular diseases—has firmly established *VEGFA* as a therapeutically valid molecular target. However, these agents act in a non-selective manner, neutralizing all *VEGFA* isoforms and consequently inhibiting both pathological and physiological angiogenesis. This broad suppression can result in significant adverse effects, including hypertension, proteinuria, delayed wound healing, and, particularly in ophthalmic applications, choriocapillaris atrophy (36, 37).

In light of these limitations, current research has increasingly focused on the development of more refined and selective strategies. Isoform-specific modulation represents a promising approach, wherein selective inhibition of VEGFA$_{165}$a may be beneficial in disorders characterized by excessive angiogenesis (such as cancer and AMD), while selective inhibition of VEGFA$_{165}$b—or conversely, promotion of VEGFA$_{165}$a—may prove advantageous in conditions marked by insufficient angiogenesis, including PAD and SSc (3).

In ophthalmology, therapeutic strategies aimed at promoting exon 8b splicing or exogenous administration of VEGFA$_{165}$b have been proposed to attenuate pathological neovascularization while preserving physiological vascular integrity (4). Conversely, in ischemic disorders such as PAD or myocardial infarction, upregulation of VEGFA$_{165}$a expression through activation of SRPK1 or modulation of splicing factors such as SRSF1 may enhance therapeutic revascularization (5).

Another innovative strategy involves the use of splice-switching oligonucleotides (SSOs), which are synthetic RNA molecules designed to modulate pre-mRNA splicing patterns. SSOs could potentially be tailored to inhibit exon 8b inclusion—thus favoring VEGFA$_{165}$a expression—or, alternatively, to promote exon 8b usage when VEGFA$_{165}$b is desired. Although SSOs are currently under investigation in the context of other diseases, such as Duchenne muscular dystrophy, their application in angiogenesis modulation presents a compelling therapeutic opportunity. Nonetheless, the efficient and tissue-specific delivery of these molecules—particularly to complex sites such as the placenta or ischemic myocardium—remains a major technical hurdle (6).

***4. Biomarker potential***

VEGF$_{165}$b is being actively investigated as a biomarker for angiogenic status. For example, one study found that low first-trimester plasma VEGF$_{165}$b predicted the later onset of pre-eclampsia. In oncology, a high VEGF$_{165}$b-to-total *VEGFA* ratio may indicate a restrained angiogenic phenotype and better prognosis, whereas a low ratio may suggest an aggressive, angiogenesis-driven tumor. Measuring VEGF isoform ratios could inform treatment selection—e.g., patients with low VEGF$_{165}$b tumors may benefit from anti-VEGF therapy, while those with high VEGF$_{165}$b may not.

## CONCLUSION

VEGF$_{165}$ exemplifies how alternative splicing of a single gene can generate functionally distinct protein isoforms that precisely regulate essential biological processes such as angiogenesis. Although VEGF$_{165}$a and VEGF$_{165}$b are derived from the same gene and possess nearly identical amino acid sequences, they exert diametrically opposing effects on vascular biology. VEGF$_{165}$a is a potent stimulator of neovascularization, whereas VEGF$_{165}$b acts as a critical physiological inhibitor. The dynamic balance between these two isoforms is essential for the maintenance of vascular homeostasis and is frequently perturbed in pathological conditions (5, 29).

Recent studies conducted between 2020 and 2025 have significantly advanced our understanding of the mechanisms by which VEGF$_{165}$b mediates its anti-angiogenic effects. These include competitive binding to VEGF receptors, particularly VEGFR-2, and selective modulation of VEGFR-1 signaling pathways (29). Furthermore, accumulating evidence supports its functional relevance in diseases characterized by aberrant angiogenesis, such as diabetic ischemia, systemic fibrotic disorders, and ocular neovascular pathologies.

From a clinical perspective, profiling the VEGF$_{165}$a/VEGF$_{165}$b expression ratio in individual patients holds promise for improving the precision of anti-angiogenic therapies. In disorders marked by excessive angiogenesis—such as cancer and PDR—therapeutic strategies aimed at enhancing or mimicking VEGF$_{165}$b activity may help suppress abnormal vessel proliferation without entirely abrogating physiological VEGF signaling (7, 38). Conversely, in conditions characterized by impaired neovascularization, including chronic non-healing wounds, PAD and SSc, targeted inhibition of VEGF$_{165}$b or upregulation of VEGF$_{165}$a may facilitate reparative angiogenesis (38).

Future therapeutic avenues may include isoform-specific monoclonal antibodies, small-molecule splicing modulators, or gene therapy vectors designed to modulate *VEGFA* pre-mRNA splicing with high specificity. Preclinical success with SSOs, which redirect *VEGFA* splicing toward a desired isoform, underscores the translational potential of this approach (38, 39).

In conclusion, investigation of $VEGF_{165}$ isoforms has not only enriched our understanding of the fine-tuned regulation of angiogenesis but also opened new therapeutic horizons. While $VEGF_{165}$a continues to serve as a primary therapeutic target in oncology and ophthalmology, $VEGF_{165}$b is increasingly recognized as both a diagnostic biomarker and a potential therapeutic agent. By focusing on the relative balance of VEGF isoforms rather than total *VEGFA* levels, future treatments may achieve a more nuanced modulation of angiogenesis—suppressing it where it is detrimental and promoting it where it is required.

Ongoing clinical trials assessing $VEGF_{165}$b expression levels and splicing-directed interventions will be (39) crucial in translating these molecular insights into tangible clinical benefit. Ultimately, the $VEGF_{165}$a/$VEGF_{165}$b axis illustrates a broader biological principle: that subtle changes in splice isoform expression can have profound effects on disease progression, and targeting this regulatory layer may define the next era in vascular and regenerative medicine.

**Ethical Approval**

This article is a literature-based review and does not involve human participants or animal experiments; therefore, ethical approval was not required.

**Conflict of Interest**

The authors declare that they have no conflict of interest regarding the publication of this article.

**Financial Disclosure**

No specific grant was received from any funding agency in the public, commercial, or not-for-profit sectors for this work.

**Authors' Contributions**

FÇA: Conceptualization, literature review, and drafting of the manuscript.

SNP: Literature review, critical revision, and final approval of the manuscript.

All authors read and approved the final version of the manuscript.

**Data Sharing Statement**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## REFERENCES

1. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Rom J Morphol Embryol. 2018;59(2):455-67.
2. Teran M. Modulation of vascular endothelial growth factor receptor affinity by neuropilin-1 and heparan sulfate proteoglycans 2016.
3. Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. Clinical science. 2005;109(3):227-41.
4. Guo Y-J, Pan W-W, Liu S-B, Shen Z-F, Xu Y, Hu L-L. ERK/MAPK signalling pathway and tumorigenesis. Experimental and therapeutic medicine. 2020;19(3):1997-2007.
5. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. Cell. 2019;176(6):1248-64.
6. Alsaab HO, Al-Hibs AS, Alzhrani R, Alrabighi KK, Alqathama A, Alwithenani A, et al. Nanomaterials for antiangiogenic therapies for cancer: a promising tool for personalized medicine. International journal of molecular sciences. 2021;22(4):1631.
7. Bates DO, Cui T-G, Doughty JM, Winkler M, Sugiono M, Shields JD, et al. $VEGF_{165}$b, an inhibitory splice variant of vascular endothelial growth factor, is down-regulated in renal cell carcinoma. Cancer research. 2002;62(14):4123-31.
8. Woolard J, Wang W-Y, Bevan HS, Qiu Y, Morbidelli L, Pritchard-Jones RO, et al. $VEGF_{165}$b, an inhibitory vascular endothelial growth factor splice variant: mechanism of action, in vivo effect on angiogenesis and endogenous protein expression. Cancer research. 2004;64(21):7822-35.
9. Raja A, Ganta V. Synthetic Antiangiogenic Vascular Endothelial Growth Factor—A Splice Variant Revascularizes Ischemic Muscle in Peripheral Artery Disease. Journal of the American Heart Association. 2024;13(20):e034304.
10. Melo CFOR, Navarro LC, De Oliveira DN, Guerreiro TM, Lima EdO, Delafiori J, et al. A machine learning application based in random forest for integrating mass spectrometry-based metabolomic data: a simple screening method for patients with Zika virus. Frontiers in bioengineering and biotechnology. 2018;6:31.
11. Parker MW, Xu P, Li X, Vander Kooi CW. Structural basis for selective vascular endothelial growth factor-A (VEGFA) binding to neuropilin-1. Journal of Biological Chemistry. 2012;287(14):11082-9.
12. Ganta VC, Choi M, Kutateladze A, Annex BH. $VEGF_{165}$b modulates endothelial VEGFR1–STAT3 signaling pathway and angiogenesis in human and experimental peripheral arterial disease. Circulation research. 2017;120(2):282-95.
13. Ferrara N, Gerber H-P, LeCouter J. The biology of VEGF and its receptors. Nature medicine. 2003;9(6):669-76.
14. Peiris-Pagès M. The role of $VEGF_{165}$b in pathophysiology. Cell adhesion & migration. 2012;6(6):561-8.
15. Wang X, Bove AM, Simone G, Ma B. Molecular bases of VEGFR-2-mediated physiological function and pathological role. Frontiers in Cell and Developmental Biology. 2020;8:599281.
16. Peach CJ, Mignone VW, Arruda MA, Alcobia DC, Hill SJ, Kilpatrick LE, et al. Molecular pharmacology of

VEGFA isoforms: binding and signalling at VEGFR2. International journal of molecular sciences. 2018;19(4):1264.
17. Batlle R, Andrés E, Gonzalez L, Llonch E, Igea A, Gutierrez-Prat N, et al. Regulation of tumor angiogenesis and mesenchymal–endothelial transition by p38α through TGF-β and JNK signaling. Nature communications. 2019;10(1):3071.
18. Bates DO, Catalano PJ, Symonds KE, Varey AH, Ramani P, O'Dwyer PJ, et al. Association between VEGF splice isoforms and progression-free survival in metastatic colorectal cancer patients treated with bevacizumab. Clinical Cancer Research. 2012;18(22):6384-91.
19. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nature Reviews Cancer. 2002;2(10):795-803.
20. Varey A, Rennel E, Qiu Y, Bevan H, Perrin R, Raffy S, et al. $VEGF_{165}b$, an antiangiogenic VEGFA isoform, binds and inhibits bevacizumab treatment in experimental colorectal carcinoma: balance of pro-and antiangiogenic VEGFA isoforms has implications for therapy. British journal of cancer. 2008;98(8):1366-79.
21. Karsten MM, Beck MH, Rademacher A, Knabl J, Blohmer J-U, Jückstock J, et al. $VEGFA_{165}b$ levels are reduced in breast cancer patients at primary diagnosis but increase after completion of cancer treatment. Scientific reports. 2020;10(1):3635.
22. Catena R, Larzabal L, Larrayoz M, Molina E, Hermida J, Agorreta J, et al. VEGF 121 b and VEGF $_{165}$ b are weakly angiogenic isoforms of VEGFA. Molecular cancer. 2010;9:1-14.
23. Jiang F, Chong L, Du S, Duan Y, Wang Y, Wang J, et al. Decreased ratio of $VEGF_{165}b$/VEGF in aqueous humor predicts progression of diabetic retinopathy. Ophthalmic Research. 2020;63(6):517-23.
24. Zhao Y, Singh RP. The role of anti-vascular endothelial growth factor (anti-VEGF) in the management of proliferative diabetic retinopathy. Drugs in context. 2018;7:212532.
25. Amadio M, Govoni S, Pascale A. Targeting VEGF in eye neovascularization: What's new?: A comprehensive review on current therapies and oligonucleotide-based interventions under development. Pharmacological research. 2016;103:253-69.
26. Campochiaro PA. Ocular neovascularization. Journal of molecular medicine. 2013;91:311-21.
27. Kilic Ü, Kilic E, Järve A, Guo Z, Spudich A, Bieber K, et al. Human vascular endothelial growth factor protects axotomized retinal ganglion cells in vivo by activating ERK-1/2 and Akt pathways. Journal of Neuroscience. 2006;26(48):12439-46.
28. Manetti M, Guiducci S, Romano E, Ceccarelli C, Bellando-Randone S, Conforti ML, et al. Overexpression of $VEGF_{165}b$, an inhibitory splice variant of vascular endothelial growth factor, leads to insufficient angiogenesis in patients with systemic sclerosis. Circulation research. 2011;109(3):e14-e26.
29. Nowak DG, Woolard J, Amin EM, Konopatskaya O, Saleem MA, Churchill AJ, et al. Expression of pro-and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors. Journal of cell science. 2008;121(20):3487-95.
30. Manetti M, Guiducci S, Ibba-Manneschi L, Matucci-Cerinic M. Impaired angiogenesis in systemic sclerosis: the emerging role of the antiangiogenic $VEGF_{165}b$ splice variant. Trends in cardiovascular medicine. 2011;21(7):204-10.
31. Guiducci S, Distler O, Distler J, Matucci-Cerinic M. Mechanisms of vascular damage in SSc—implications for vascular treatment strategies. Rheumatology. 2008;47(suppl_5):v18-v20.
32. Nowak DG, Amin EM, Rennel ES, Hoareau-Aveilla C, Gammons M, Damodoran G, et al. Regulation of vascular endothelial growth factor (VEGF) splicing from pro-angiogenic to anti-angiogenic isoforms: a novel therapeutic strategy for angiogenesis. Journal of Biological Chemistry. 2010;285(8):5532-40.
33. Levine RJ, Maynard SE, Qian C, Lim K-H, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. New England journal of medicine. 2004;350(7):672-83.
34. Bills VL, Hamdollah-Zadeh M, Soothill PW, Harper SJ, Bates DO. The role of VEGFA $_{165}$ b in trophoblast survival. BMC Pregnancy and Childbirth. 2014;14:1-8.
35. Rennel ES, Harper SJ, Bates DO. Therapeutic potential of manipulating VEGF splice isoforms in oncology. Future Oncology. 2009;5(5):703-12.
36. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nature reviews Drug discovery. 2016;15(6):385-403.
37. Saint-Geniez M, Kurihara T, Sekiyama E, Maldonado AE, D'Amore PA. An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris. Proceedings of the National Academy of Sciences. 2009;106(44):18751-6.
38. Harper SJ, Bates DO. VEGFA splicing: the key to anti-angiogenic therapeutics? Nature Reviews Cancer. 2008;8(11):880-7.
39. Havens MA, Hastings ML. Splice-switching antisense oligonucleotides as therapeutic drugs. Nucleic acids research. 2016;44(14):6549-63.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):156-157*
*e-ISSN: 2980-0978*

***Letter to Editor/ Editöre Mektup***
***DOI:10.61845/agrimedical.1780046***

# An evaluation of child and adolescent mental health services in rural areas of Turkey

## Türkiye'de kırsal bölgelerde çocuk ve ergen ruh sağlığı hizmetleri üzerine bir değerlendirme

Ozan Kayar[1]*

[1] *Çankırı Karatekin Üniversitesi, İnsan ve Toplum Bilimleri Fakültesi, Psikoloji Bölümü, Çankırı/Türkiye*

*0000-0002-1269-3719*
*Sorumlu Yazar: Ozan Kayar*
*e-mail: pskozan@gmail.com*

Gönderilme Tarihi: 08/09/2025
Kabul Tarihi: 03/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Kayar O. An evaluation of child and adolescent mental health services in rural areas of Turkey. Ağrı Med J. 2025; 3(3):156-157.

Okuyucu ve Kavakcı'nın 2025 yılında Ağrı Tıp Fakültesi Dergisi'nin ikinci sayısında yayımlanan "Doğu Anadolu'da Bir İlçe Devlet Hastanesindeki Çocuk ve Ergen Psikiyatri Hastalarının Demografik ve Klinik Özellikleri" başlıklı makalesini büyük bir ilgiyle okudum (1). Türkiye'de çocuk ve ergen psikiyatrisi alanındaki araştırmalar çoğunlukla üniversite hastaneleri veya büyük şehirlerdeki uygulama-araştırma merkezlerinde yürütülmektedir (2). Bu nedenle, ilçe düzeyindeki bir devlet hastanesinde gerçekleştirilen bu kapsamlı çalışma, literatüre katkı sağlamasının yanı sıra kırsal bölgelerdeki sağlık politikalarının şekillendirilmesine ışık tutması açısından da oldukça değerlidir.

Çalışmadan elde edilen bulgular, erkek çocuklarda dikkat eksikliği hiperaktivite bozukluğu (DEHB), otizm spektrum bozukluğu ve gelişimsel dil bozukluklarının; kızlarda ise depresyon, anksiyete bozuklukları ve obsesif kompulsif bozukluğun (OKB) daha sık görüldüğünü ortaya koymaktadır. Tanı dağılımı yaşa göre de farklılaşmakta; erken çocuklukta gelişimsel bozukluklar, orta çocuklukta DEHB ve özgül öğrenme bozuklukları, ergenlik döneminde ise anksiyete bozuklukları ve depresyon öne çıkmaktadır. Bu tablo, çocuk ve ergen ruh sağlığında yaş ve cinsiyete bağlı farklılıkların klinik tedavi planlamalarına yansıtılması ve gelecek araştırmalarda dikkate alınması gerektiğini göstermektedir. Bununla birlikte, bulguların ışığında tartışılabilecek bazı sınırlılıklar ve tamamlayıcı noktalar da bulunmaktadır.

Çalışmanın metodolojik katkıları değerli olmakla birlikte, uygulanan tedavi yöntemleri açısından yalnızca farmakoterapiye odaklanıldığı görülmektedir. Bu yaklaşım, çocuk ve ergen ruh sağlığı alanında ilaç tedavisinin tek başına yeterli olduğu izlenimi yaratabilir. Öte yandan güncel uluslararası kılavuzlar, farmakoterapinin çoğu durumda psikososyal müdahalelerle birlikte ya da onların ardından uygulanmasını önermektedir. Özellikle "Amerikan Çocuk ve Ergen Psikiyatri Akademisi (AACAP)" ve "İngiltere Sağlık ve Bakım Mükemmellik Enstitüsü (NICE)" kılavuzlarında, DEHB, depresyon, anksiyete bozuklukları ve OKB'de bilişsel-davranışçı terapi (BDT), ebeveyn eğitimi, aile terapisi ve okul temelli programların farmakoterapiye eşlik eden veya kimi durumlarda öncelikli seçenekler olduğu vurgulanmaktadır (3,4). DEHB tedavisinde ilaçlar dikkati artırıp dürtüselliği ve aşırı hareketliliği azaltabilir; ancak davranışsal müdahaleler, aile desteği ve okul iş birliği olmadan bu etkinin kalıcı kazanımlara dönüşmesi zordur (5). Benzer şekilde, çocukluk çağı depresyonu ve anksiyete bozukluklarında kanıta dayalı psikoterapiler, ilaç tedavisi kadar etkili bulunmakta; hatta hafif ve orta şiddetteki olgularda ilk basamak tedavi olarak önerilmektedir (4,6). Bununla birlikte, Türkiye'de özellikle devlet hastanelerinde görev yapan hekimlerin yoğun hasta yükü ve sınırlı muayene süreleri, psikososyal müdahalelerin düzenli ve sistematik biçimde uygulanmasını güçleştirmektedir. Bu kurumsal kısıtlılıklar, klinik pratikte farmakoterapinin ön planda görünmesine yol açabilmektedir. Gelecek çalışmalarda psikososyal ve psikoterapötik müdahalelerin de ayrıntılı biçimde kayda geçirilmesi hem tedavi tercihlerini hem de bu tercihleri şekillendiren sağlık sistemi koşullarını bütüncül olarak değerlendirmeye katkı sağlayacaktır.

Çalışmada ayrıca, ayakta tedavi kliniğinde nitelikli psikolog bulunmadığı için zihinsel engellilik tanısında standart psikometrik testlerin uygulanamadığı belirtilmiştir. Bu durum metodolojik bir sınırlılığın ötesinde, Türkiye'de kırsal bölgelerde çocuk ve ergen ruh sağlığı hizmetleriyle ilgili yapısal bir sorunu da öne çıkmaktadır. İlçe devlet hastanelerinde özellikle klinik psikologların yetersiz istihdamı, tanı ve tedavi sürecinin büyük ölçüde çocuk ve ergen psikiyatristleri tarafından yürütülmesine yol açmaktadır (7). Buna karşın büyük hastanelerde klinik psikologlar; ayrıntılı değerlendirmeler, ailelere yönelik psikoeğitim ve psikoterapi uygulamalarıyla sürece aktif biçimde katkıda bulunmakta; bu yönleriyle çocuk ve ergen psikiyatristlerinin en yakın işbirlikçileri arasında yer almaktadır. Bunun yanı sıra sosyal hizmet uzmanları, çocuk gelişimciler ve psikiyatri hemşireleri gibi diğer ruh sağlığı profesyonellerinin de yerel ölçekte sınırlı sayıda olması, çok disiplinli hizmetlerin yaygınlaştırılmasını zorlaştırmaktadır. Bu bağlamda kırsal bölgelerde klinik psikolog kadrolarının artırılması ve farklı disiplinlerden uzmanların da sürece etkin katılımının sağlanması, çocuk ve ergen ruh sağlığı hizmetlerinin bütüncül ve sürdürülebilir biçimde yürütülmesi açısından büyük önem taşımaktadır (2,8).

Çalışmanın bir diğer önemli çıktısı, sağlık politikalarıyla ilişkilidir. Başvuruların en yoğun 7–12 yaş grubunda gerçekleşmesi, okul ortamında düzenlenecek ruh sağlığı taramaları ve öğretmenlere yönelik eğitim

programlarının gerekliliğine işaret etmektedir. Klinik psikologlar, rehber öğretmenler ve çocuk psikiyatristlerinin iş birliğiyle kırsal bölgelerde yürütülecek tarama ve psikoeğitim uygulamaları, sorunların erken dönemde fark edilmesine ve tedaviye erişimin kolaylaşmasına katkı sağlayabilir (9). Ayrıca psikotrop ilaç kullanım oranının yaklaşık %35 gibi görece düşük bir düzeyde kalması, bazı ailelerin farmakoterapiye yönelik çekinceleri olabileceğini düşündürmektedir. Bu noktada, ilaç ve psikoterapi entegrasyonunun yararlarını ailelere aktaran psikoeğitim programları, damgalama algısını azaltma ve tedaviye uyumu güçlendirme açısından etkili olabilir (3).

Sonuç olarak Okuyucu ve Kavakcı'nın çalışması, değerli epidemiyolojik verilerin yanı sıra özellikle kırsal bölgelerde çocuk ve ergen ruh sağlığı hizmetlerinin nasıl geliştirilebileceğine dair önemli ipuçları da sunmaktadır. Dolayısıyla aktarılan görüşler, mevcut bulgulara eleştiri değil, tamamlayıcı bir katkı olarak değerlendirilmelidir. Bu çalışmanın hem ulusal sağlık politikalarına hem de akademik literatüre yön verici bir etki yaratacağına inanıyor, yazarlara değerli emekleri için içtenlikle teşekkür ediyorum.

**Etik Kurul Onayı**
Bu çalışma için etik kurul onayı gerekmemektedir.

**Çıkar Çatışması**
Yazar, makaleye ilişkin herhangi bir çıkar çatışması olmadığını beyan eder.

**Finansal Açıklama**
Çalışma için herhangi bir mali destek alınmamıştır.

**Yazar Katkıları**
OK: Ana fikir/planlama, veri toplama/işleme ve yorumlama, literatür taraması, yazım, eleştirel inceleme

**Veri paylaşım beyanı**
Bu makale özgün araştırma verisi içermemektedir. Çalışma, mevcut literatür ve yazarın akademik değerlendirmelerine dayanmaktadır. Bu nedenle veri paylaşımı uygulanabilir değildir.

**KAYNAKLAR**

1. Okuyucu M, Kavakcı M. Doğu Anadolu'da bir ilçe devlet hastanesindeki çocuk ve ergen psikiyatri hastalarının demografik ve klinik özellikleri. Ağrı Med J. 2025;3(2):83-92.
2. Bilkay Hİ, Sarı T, Gürhan N. Türkiye'de çocuk-ergen ruh sağlığına yönelik kısa bir inceleme. ÇG-D. 2023;6(12):78-92.
3. Luxton R, Kyriakopoulos M. Depression in children and young people: identification and management NICE guidelines. Arch Dis Child Educ Pract Ed. 2022;107(1):36-38.
4. Pringsheim T, Gaudet LA, Pillay J, et al. Evidence-based guidelines for anxiety, depression, obsessive-compulsive disorder and Tourette syndrome in children and youth: a rapid review. J Can Acad Child Adolesc Psychiatry. 2024;33(3):171-205.
5. Peterson BS, Trampush J, Maglione M, et al. Treatments for ADHD in children and adolescents: a systematic review. Pediatrics. 2024;153(4):e2024065787.
6. Walter HJ, Abright AR, Bukstein OG, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. J Am Acad Child Adolesc Psychiatry. 2023;62(5):479-502.
7. Tonyalı A, Karaçetin G. Koruyucu ve Toplum Temelli Ruh Sağlığı Açısından Çocuk ve Ergen Psikiyatrisi Uygulamaları. Özgen Hergül G, ed. Psikiyatri uygulamalarının koruyucu ve toplum temelli boyutları. Türkiye Klinikleri; 2022:13-20.
8. Aksoy ŞG. Koruyucu ve Toplum Temelli Psikiyatri Uygulamalarında Psikoloğun Rolü. Özgen Hergül G, ed. Psikiyatri uygulamalarının koruyucu ve toplum temelli boyutları. Türkiye Klinikleri; 2022:66-71.
9. Bıdık G, Sisman FN. Çocuk ve adölesanlarda psikososyal iyilik halini geliştirmeye yönelik okul temelli ruh sağlığı programları: sistematik inceleme. J Psychiatric Nurs. 2021;12(4):350-361.

*Ağrı Tıp Fakültesi Dergisi 2025 3(3):158-159*
*e-ISSN: 2980-0978*

***Letter to Editor/ Editöre Mektup***
***DOI:10.61845/agrimedical.1782782***

# Chronic spontaneous urticaria: Current approaches and the importance of awareness

## Kronik spontan ürtiker: Güncel yaklaşımlar ve farkındalığın önemi

Melek Cihanbeylerden[1]*

[1] *Ağrı Eğitim ve Araştırma Hastanesi, Alerji ve Klinik İmmünoloji Kliniği, Ağrı, Türkiye*

*0000-0002-0810-087X*
*Sorumlu Yazar: Melek Cihanbeylerden*
*e-mail: ytse_jammm@hotmail.com*

Gönderilme Tarihi: 12/09/2025
Kabul Tarihi: 24/10/2025
Yayınlanma Tarihi: 29/10/2025

**Cite this article:** Cihanbeylerden M. Chronic spontaneous urticaria: Current approaches and the importance of awareness. Ağrı Med J. 2025; 3(3): 158-159.

Toplum sağlığını etkileyen ve yaşam kalitesini önemli ölçüde düşüren hastalıklar arasında yer alan Kronik Spontan Ürtiker (KSÜ), görülme sıklığı ve tedavi zorluklarıyla dikkat çekmektedir. Nüfusun yaklaşık %1'ini etkileyen bu hastalık, yalnızca ciltte görülen lezyonlarla sınırlı kalmayıp yaşam kalitesini önemli ölçüde bozar ve sıklıkla uzun süreli tedavi gerektirir (1, 2). KSÜ, genellikle altı haftadan uzun süren ve kendiliğinden gelişen kaşıntılı kabarıklıklar (ürtiker plakları) ve/veya anjiyoödem ataklarıyla seyreden, karmaşık bir hastalık tablosudur. Hastalığın çoğu vakasında belirgin bir tetikleyici saptanamaması, tanı ve tedavi süreçlerini daha da zorlaştırmaktadır (1).

KSÜ'de mast hücrelerinin uygunsuz aktivasyonundan sorumlu tutulan iki temel otoimmün mekanizma öne sürülmüştür. Bunlardan ilki, Tip 1 (otoalerjik KSÜ) olarak tanımlanır. Bu mekanizmada, bağışıklık sistemi vücudun kendi dokularına karşı IgE tipi otoantikorlar üretir. Bu otoantikorlar, alerjenlere karşı gelişen IgE antikorlarına benzer şekilde kendi antijenlerine bağlanarak mast hücrelerinin aktive olmasına neden olur. İkinci mekanizma ise Tip 2b (otoimmün KSÜ) olarak adlandırılır. Bu durumda, IgG tipi otoantikorlar, mast hücreleri üzerindeki yüksek afiniteli IgE reseptörlerine (FCεRI) ve/veya doğrudan IgE'ye bağlanarak mast hücrelerinin uyarılmasına yol açar (1, 3). Her iki otoimmün süreçte de sonuç, tipik olarak kaşıntılı döküntüler ve/veya anjiyoödem ataklarıyla kendini gösteren KSÜ semptomlarıdır. Bu mekanizmalar hastalığın otoimmün yönünü güçlü biçimde desteklese de, KSÜ yalnızca otoimmün nedenlerle açıklanamayacak kadar çok bileşenli ve heterojen bir hastalıktır (2). Bu nedenle, hastalığın değerlendirilmesinde bütüncül ve bireyselleştirilmiş bir yaklaşım büyük önem taşır.

Dünya Ürtiker Günü vesilesiyle bu yazıda KSÜ'nün hastalar üzerindeki etkisi, güncel tedavi yaklaşımları, tanı ve izlemde kullanılan araçlar ve farkındalık çalışmalarının öneminin vurgulanması amaçlanmıştır.

Ürtiker atakları genellikle gün içinde ani şekilde başlar ve 24 saat içinde kaybolur. Ancak KSÜ hastalarında bu ataklar tekrar edici, dirençli ve öngörülemez özellik gösterir. Her ne kadar ciltle sınırlı gibi görünse de, yapılan çalışmalarda hastaların %60'ından fazlasının uyku bozukluğu, konsantrasyon kaybı, sosyal izolasyon ve anksiyete gibi sorunlar yaşadığı belirlenmiştir (2). Bu açıdan KSÜ sadece dermatolojik değil, aynı zamanda psikolojik ve sosyal yönleri olan sistemik bir hastalık olarak ele alınmalıdır. Örneğin, bir hastanın gece boyunca kaşıntı sebebiyle uyuyamaması, ertesi gün iş performansını düşürmekte, sosyal ilişkilerini zedelemekte ve hatta depresyon riskini artırmaktadır. Bu durumu daha iyi anlamak için hastaların deneyimlerine kulak vermek gerekir. Hastalar, hastalığın dışarıdan fark edilmese de yaşam kalitelerini önemli ölçüde etkilediğini ifade etmektedir.

KSÜ tanısı genellikle klinik olarak konulmakla birlikte, spesifik biyobelirteçler olmaması, nedeniyle tanı, dışlama yöntemine dayandırılmaktadır (4). Bazı olgularda tiroid otoantikorları, otoimmün hastalıklar veya enfeksiyonlara ilişkin ipuçları bulunabilir. Ancak çoğu hastada tetikleyici neden saptanamaz ve bu durum hastayı olduğu kadar hekimin de tedavi motivasyonunu zorlayabilir. Tanının ardından, hastalığın ciddiyetini ve kontrol düzeyini değerlendirmek amacıyla Ürtiker Aktivite Skoru (ÜAS7) ve Ürtiker Kontrol Testi (ÜKT) gibi ölçekler yaygın olarak kullanılmaktadır (5). ÜAS7, 7 gün boyunca kaşıntı ve lezyon sayısını puanlayarak hastalığın şiddetini nicel olarak ortaya koyar. ÜKT ise hastanın yaşam kalitesi üzerindeki etkiyi ve tedaviye yanıtı değerlendirerek, bireysel yaklaşımları kolaylaştırır.

KSÜ tedavisinde hedef, tam semptom kontrolü ve yaşam kalitesinin en üst düzeye çıkarılmasıdır. Güncel kılavuzlara göre tedavinin ilk aşaması, ikinci nesil H1 antihistaminiklerle başlar (4). Bu ilaçlar sedatif etki göstermeden semptomları baskılayabilmektedir. Ancak yaklaşık olarak hastaların yarısında standart dozlar yeterli gelmez ve dozun dört katına kadar artırılması gerekebilir. Bu doz artışının güvenli olduğu birçok çalışma ile gösterilmiştir (6). Eğer yüksek doz antihistaminiklere rağmen semptomlar devam ederse, omalizumab adlı biyolojik ajan tedaviye eklenir. Anti-IgE monoklonal antikoru olan bu ilaç, mast hücreleri üzerindeki IgE reseptörlerini bloke ederek etkisini gösterir. Klinik çalışmalarda, omalizumab kullanan hastaların %60–80'inde ilk dört hafta içinde anlamlı düzelme sağlandığı gösterilmiştir (7, 8). Bazı hastalarda omalizumab tedavisi kesildikten sonra da hastalık kontrol altında kalmaya devam etmektedir. Bu, ilacın immün yanıt modülasyonunda kalıcı etkiler yaratabileceğine işaret etmektedir. Öte yandan,

tedavinin ani kesilmesi bazı olgularda relapsa yol açabildiğinden, kademeli azaltılarak bırakılması önerilmektedir (9). Omalizumab'ın etkisiz kaldığı ya da kontrendike olduğu KSÜ' de, özellikle otoimmun özellik gösterenlerde, siklosporin A etkili bir alternatiftir. Düşük dozlarda dahi etkili olabilen bu ajan, immünsüpresif etkileri nedeniyle dikkatli hasta seçimi ve yakın izlem gerektirir (10).

KSÜ yönetiminde sadece ilaç tedavisine odaklanmak yeterli değildir. Hastalığı tetikleyebilecek çevresel ve fizyolojik faktörlerin belirlenmesi ve yönetimi kritik önem taşır. Nonsteroid antienflamatuar ilaçlar (NSAİİ), alkol, enfeksiyonlar, stres, uykusuzluk, aşırı sıcaklık değişimleri gibi faktörler atakları tetikleyebilir (1, 3). Ancak önemli bir husus da şudur: Her tetikleyici, her hastada aynı etkiyi yaratmaz. Bu nedenle hastaya diyetler veya gereksiz ilaç yasakları uygulamak, yaşam kalitesini daha da düşürebilir. Bunun yerine, kişiselleştirilmiş bir yaklaşım benimsenmeli, her öneri hasta gözlemiyle desteklenmelidir. KSÜ'nin uzun süreli ve belirsizliklerle dolu doğası hem hastada hem hekimde çaresizlik hissi yaratabilir. Bu noktada hastaya, hastalığın kronik doğası ve tedavi sürecinin aşamaları açık şekilde anlatılmalı, beklentiler gerçekçi olarak yönetilmelidir. Ayrıca, hastaların sosyal destek ihtiyacı da göz ardı edilmemelidir. Özellikle ağır KSÜ yaşayan bireylerde psikolojik destek, yaşam kalitesini artırabilir. Dermatolog, alerji uzmanı, psikiyatrist ve hatta diyetisyen iş birliğini içeren multidisipliner bir yaklaşım, hasta yönetiminde başarıyı artırabilir. KSÜ, yalnızca kaşıntılı kabarıklıklarla tanımlanamayacak kadar karmaşık ve çok boyutlu bir hastalıktır. Her hastanın kliniği, tetikleyicileri, tedavi yanıtı ve psikososyal durumu farklılık gösterebilir. Bu nedenle, bireyselleştirilmiş, basamaklı ve multidisipliner bir yaklaşım esastır.

Dünya Ürtiker Günü, bu hastalığın toplumda daha iyi anlaşılması ve farkındalık oluşturulması için önemli bir fırsattır. Sağlık çalışanlarının güncel tedavi algoritmalarına hakim olmaları, hastalara empatik yaklaşmaları ve bilimsel gelişmeleri takip etmeleri hem bireysel hem toplumsal hastalık yükünü azaltacaktır. Toplumda KSÜ'ye yönelik önyargıların kırılması, hastaların yalnız olmadıklarının hissettirilmesi ve tedaviye erişimin kolaylaştırılması ise hepimizin sorumluluğudur.

**Etik Kurul Onayı**
Bu çalışma için etik kurul onayı gerekmemektedir.

**Çıkar Çatışması**
Yazar, makaleye ilişkin herhangi bir çıkar çatışması olmadığını beyan eder.

**Finansal Açıklama**
Çalışma için herhangi bir mali destek alınmamıştır.

**Yazar Katkıları**
MC: Ana fikir/planlama, veri toplama/işleme ve yorumlama, literatür taraması, yazım, eleştirel inceleme

**Veri paylaşım beyanı**
Bu makale özgün araştırma verisi içermemektedir. Çalışma, mevcut literatür ve yazarın akademik değerlendirmelerine dayanmaktadır. Bu nedenle veri paylaşımı uygulanabilir değildir.

## KAYNAKLAR

1. Kocatürk E, Chu DK, Türk M, et al. Management of chronic spontaneous urticaria made practical: what every clinician should know. J Allergy Clin Immunol Pract. 2025;13(9):2252-2269.
2 Zuberbier T, Ensina LF, Giménez-Arnau A, et al. Chronic urticaria: unmet needs, emerging drugs, and new perspectives on personalised treatment. Lancet. 2024;404(10450):393-404.
3. Kolkhir P, Muñoz M, Asero R, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol. 2022;149(6):1819-31.
4 Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766.
5. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014;133(5):1365-72.e6.
6. Xiao X, Xue P, Shi Y, et al. The efficacy and safety of high-dose non-sedating antihistamines in chronic spontaneous urticaria: a systematic review and meta-analysis of randomized clinical trials. BMC Pharmacol Toxicol. 2023;24(1):23.
7. Maurer M, Rosén K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-35.
8. Soegiharto R, Aghdam MA, Sørensen JA, et al. Multinational drug survival study of omalizumab in patients with chronic urticaria and potential predictors for discontinuation. JAMA Dermatol. 2024;160(9):927-35.
9. Türk M, Kocatürk E, Ertaş R, et al. A global perspective on stepping down chronic spontaneous urticaria treatment: results of the Urticaria Centers of Reference and Excellence SDown-CSU study. Clin Transl Allergy. 2024;14(2):e12343.
10. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. J Allergy Clin Immunol Pract. 2018;6(2):586-99.