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E-posta: actamednicomedia@kou.edu.tr

nicomediamedj@gmail.com

Tel: +90 (262) 303 70 04

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Research Article | Araştırma Makalesi

THE EFFECT OF PREVIOUS ADENOTONSILLECTOMY ON THE RISK OF CONTRACTING COVID-19 AND THE SEVERITY OF THE DISEASE IN PEDIATRIC POPULATION

PEDİATRİK POPÜLASYONDA GEÇİRİLMİŞ ADENOTONSİLLEKTOMİNİN COVID-19'A YAKALANMA RİSKİ VE HASTALIĞIN ŞİDDETİ ÜZERİNDEKİ ETKİSİ

Ahmet Kara[1], Halil Elden[1], Engin Okur[1*]

[1]Sakarya University, Faculty of Medicine, Department of Otorhinolaryngology, Sakarya, Türkiye.

ABSTRACT

Objective: The effect of the Waldeyer's lymphatic ring at the entry point of respiratory pathogens has essential functions in forming the immune response in childhood, and its effect on the frequency and severity of Coronavirus disease 2019 (Covid-19) is not clearly known. The objective of this study is to analyze the occurrence and severity of Covid-19 in pediatric patients undergoing adenotonsillectomy surgery.

Methods: Patients aged 3-15 with a history of adenotonsillectomy were compared to a control group in terms of the incidence and severity of Covid-19.

Results: In patients undergoing adenotonsillectomy, a Covid test positivity rate of 1.5% was observed, compared to 2.7% in the control group, indicating a statistically significant difference. However, there was no disparity between the two groups regarding disease severity.

Conclusion: Adenotonsillectomy does not elevate the risk of Covid 19 infection in children. In fact, individuals who have undergone this surgery exhibit a decreased incidence of Covid-19 infection.

Keywords: COVID-19, coronavirus, adenotonsillectomy, immunity

ÖZ

Amaç: Solunum yolu patojenlerinin giriş noktasındaki Waldeyer lenfatik halkasının etkisi, çocukluk çağında immün yanıtın oluşmasında önemli işlevlere sahip olup, Covid-19 hastalığının sıklığı ve şiddeti üzerine etkisi net olarak bilinmemektedir. Bu çalışmanın amacı adenotonsillektomi ameliyatı geçiren çocuk hastalarda Covid-19 hastalığının ortaya çıkışını ve ciddiyetini analiz etmektir.

Yöntem: Adenotonsillektomi öyküsü olan 3-15 yaş arası hastalar, Covid-19 hastalığının görülme sıklığı ve şiddeti açısından kontrol grubuyla karşılaştırıldı.

Bulgular: Adenotonsillektomi yapılan hastalarda Covid testi pozitiflik oranı %1,5, kontrol grubunda ise %2,7 olarak görüldü ve bu da istatistiksel olarak anlamlı bir farka işaret ediyor. Ancak hastalığın şiddeti açısından iki grup arasında fark yoktu.

Sonuç: Adenotonsillektomi çocuklarda Covid 19 enfeksiyonu riskini artırmamaktadır. Aslında bu ameliyatı geçiren kişilerde Covid-19 enfeksiyonu görülme sıklığında azalma görülüyor.

Anahtar Kelimeler: COVİD-19, coronavirüs, adenotonsillektomi, bağışıklık

***Corresponding author/İletişim kurulacak yazar:** Engin Okur; Sakarya University Faculty of Medicine, 54000, Korucuk, Sakarya, Türkiye.
Phone/Telefon: +90 (543) 905 61 68, **e-mail/e-posta:** enginokur95@gmail.com
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Introduction

Coronavirus disease 2019 (Covid-19), caused by the 2019 novel coronavirus (SARS–CoV–2), may cause severe systemic organ failures. According to data from the World Health Organization (WHO), since the beginning of the pandemic, around 250 million cases of Covid-19 have been diagnosed, resulting in approximately 5 million deaths.[1] It is known that children under the age of 5 account for approximately 1.8% of the total cases, and children between the ages of 5-15 make up 6.3% of the total cases. It has been determined that the rate of the population aged 15 and under in total deaths is 0.2%.[1] According to the American Academy of Pediatrics' data, the mortality rate in individuals who had Covid-19 in childhood in the United States is 0.03%.[2]

Although some of the factors, such as; age, gender, chronic diseases, smoking exposure, and immune system response, are emphasized for the severity differences of the disease, the exact reasons are unknown. However, it is a fact that it is milder in the pediatric group.[3,4] Various hypotheses have been proposed to explain the reasons for this difference. For example, in the pediatric age group, other viruses may compete with SARS-CoV-2 in the mucosa of the lung and respiratory tract and limit spreading of the virus or low expressions of the angiotensin - converting enzyme-2 (ACE-2) receptors may reduce the viral load in this group.[5,6]

The effect of the Waldeyer's lymphatic ring at the entry point of respiratory pathogens has essential functions in forming the immune response in childhood, and its effect on the frequency and severity of Covid 19 disease is not clearly known. The pharyngeal tonsil, which is a part of Waldeyer's ring, is very important in forming an effective immune response with predominantly T lymphocytes (especially CD8 T lymphocytes) and the effective antiviral cytokines especially interferon-alpha (IFN-a). It also contributes to mucosal immunity with secretory IgA, IgM, and IgG released from leukocytes on its mucosal surface. Palatine tonsils, another part of Waldeyer's ring, are also Mucosa Associated Lymphoid Tissue (MALT) related secondary lymphoid organs showing B and T cell activity.[7] While the function of adenoid and tonsil tissue is more prominent between the ages of 4-7, they start to regress from the adolescence period.[8]

Adenotonsillectomy (AT) is the most performed otorhinolaryngologic surgery in childhood because of obstructive hypertrophy and/or recurrent infections of the upper respiratory tract. Nevertheless, studies examining the effect of adenotonsillectomy on Covid-19 are very limited. This study investigated the incidence and severity of Covid-19 in the pediatric population undergoing adenotonsillectomy by conducting a comparative analysis with a control group, marking the inaugural comparison of its kind in the literature.

Methods

This retrospective study protocol was approved by the Ethics Committee of Sakarya University Faculty of Medicine (No: 74624) and was conducted in full accordance with the Declaration of Helsinki and Turkish laws and regulations. The files of patients aged 3-15 years who underwent AT between 2010 and 2020 in Sakarya University Faculty of Medicine, Ear Nose and Throat Clinic were scanned retrospectively. The AT group was formed by excluding the patients who did not have at least one year after the adenotonsillectomy operation, patients with missing or incorrect contact information, and patients with any autoimmune or hematological comorbidity. Subsequently, individuals with similar age and gender characteristics to the AT group, who presented to our clinic during the same period with diagnoses such as general examinations, nasal fractures, ear and hearing examinations, lymphadenitis, etc., and who had no history of AT, no diagnosis of immunodeficiency or hematological diseases, and complete contact information, were selected as the control (C) group. After the study and control groups were formed, the Covid-19 reverse transcription-polymerase chain reaction (rRT-PCR) test results of all participants included in the study were evaluated via the Public Health Management System (HSYS) for comparison.

All individuals testing positive on the rRT-PCR test were assessed based on their findings and symptoms, categorized into mild, moderate, severe, and critical disease as outlined in the World Health Organization's clinical management guide for Covid-19 (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1), last updated on January, 2021. Subsequently, patients who underwent thoracic computed tomography (CT) imaging were radiologically evaluated for disease severity using the classification system established by Kunwei and colleagues.[9]

IBM SPSS version 26.0 for Windows statistical software (IBM Corporation, Armonk, New York, USA) was utilized for statistical analysis. Mean ± standard deviation represented continuous variables, while categorical variables were presented as percentages. Normality of distribution was assessed using Kolmogorov-Smirnov analysis, and non-parametric tests were favored based on the results. Mann-Whitney U test was employed for group-wise comparisons, and the Chi-square test was utilized for comparing categorical variables. Significance was established for p values less than 0.05.

Results

The files of 2089 patients who underwent AT in our clinic between January 2010 and January 2020 were reviewed retrospectively. As a consequence of this procedure, 286 patients were disqualified from the study due to not meeting the inclusion criteria. Out of the remaining 1803 patients, 804 (44.6%) were female; 999 (55.4%) were

males. The mean age in the AT group was 10.52 ± 2.89 (range 3-15 years). After the file scans of 1954 individuals, who could be considered the control group, 124 were found to be unsuitable and excluded from the study. Thus, a control group consisting of 1830 people was formed. The mean age in the control group was 10.95 ± 2.95 (range 3-15 years). 783 (42.8%) of the control group were women; 1047 (57.2%) of them were men. When comparing the groups based on age and gender data, no significant difference was observed between the two groups (p=0.505; p=0.17) (Table 1).

When the rRT-PCR test results for Covid-19 were analyzed for both groups, it was seen that 27 (1.5%) participants in the AT group were positive. In the control group, this rate was determined as 2.7% (50 participants). There was a statistically significant difference between the groups (p=0.001) (Table 1).

When the patients with positive test results were divided into groups according to the severity of disease, no patients were found to have a severe or critical disease, while 2 (7.4%) of the patients in the AT group and one (2%) of the patients in the C group had moderate complaints. The remaining patients of both groups experienced mild symptoms of Covid 19. The patients in both groups had no covid-19-associated multisystem inflammatory disease (MIS-C) illness with prolonged fever, abdominal pain, rash, hypotensive shock, and myocardial dysfunction.[10] No statistically significant difference was found between the groups in terms of disease severity (p=0.242) (Table 1).

Table 1. Demographics characteristics and RT-PCR positivity rates of the groups

		Adenotonsillectomy (n=1803)	Control (n=1830)	p
Gender	*Female*	804 (44.6%)	783 (42.8%)	0.17
	Male	999 (55.4%)	1047 (57.2%)	
Age		11[5]	11[5]	0.505
SARS-CoV-2 rRT – PCR test positivity rate		27 (1.5%)	50 (2.7%)	0.001*
WHO Classification	*Mild*	25 (92.6%)	49 (98.0%)	0.242
	Moderate	2 (7.4%)	1 (2.0%)	
	Severe	0%	0%	
	Critical	0%	0%	

Three patients in the AT group had positive rR-PCR test results and two in the C group had thorax CT imaging. When the semiquantitative visual total severity scores were evaluated, severity score was found as 1 in one patient in the control group, while it was found as 0 in the remaining four thoracic CT images. Since the number of thorax CTs images examined was few, the groups could not be compared statistically.

Discussion

The Waldeyer ring is a vital component of the immune system and plays a key role in countering bacterial and viral infections entering through the upper respiratory tract, with a particularly significant role in the pediatric population. Numerous studies report no long-term adverse effects of adenotonsillectomy on the immune system. However, conflicting evidence exists regarding its impact on respiratory tract infections.[8,11] Some studies suggest increased infections after adenotonsillectomy, while others indicate decreased.[12-14] Similarly, conflicting results have emerged regarding the relationship between adenotonsillectomy and COVID-19 outcomes.

Murugesan et al. reported a higher frequency of COVID-19 among individuals who had undergone adenotonsillectomy.[15] In contrast, a study conducted by our team in adult patients revealed a lower COVID-19 test positivity rate in the adenotonsillectomy group compared to controls (4% vs. 6.8%).[16] A large cohort study further supported these findings, suggesting that adenoidectomy and adenotonsillectomy may reduce the incidence of COVID-19.[17] The data presented in the present study similarly demonstrate a lower frequency of COVID-19 in pediatric cases that underwent surgery compared to those in a control group. This potential protective effect may be related to the dual role of lymphatic tissues of Waldeyer ring tissue. While they are integral to eliciting humoral and cellular immune responses, they can also serve as a reservoir for pathogens, potentially facilitating viral colonization and increasing infection risk.[7,18-20]

Pharyngeal and palatine tonsils are crucial for B cell activation and differentiation, triggering various immune responses, such as antibody production and complement activation.[21,22] During this process, it has been demonstrated that they secrete various pro-inflammatory and anti-inflammatory cytokines. The severe clinical symptoms of COVID-19, often linked to excessive cytokine production (cytokine storm), raise questions about whether Waldeyer's ring contributes to disease severity. By this pathophysiological process, the study of Chiang et al. indicated that mortality rates were lower in the tonsillectomy group.[23] However, other studies conducted by Kara et al. and Yang et al. concluded that tonsillectomy has no significant positive or negative effect on COVID-19 prognosis.[16,17] Our findings in this study are also consistent with those of these two studies. Nonetheless, further research is required to elucidate the precise mechanisms underlying these observations.

The presented study has some limitations. This single-center study design may limit the generalizability of findings. The study did not evaluate the procedure's effects in a fully healthy population without prior hospital admissions. Moreover, comparisons with larger, community-based cohorts were not conducted. However, a key strength of this study is its large pediatric sample size, which partially offsets these limitations.

In conclusion, our study contributes to the existing literature by demonstrating that adenotonsillectomy does not pose an additional risk for COVID-19 infection in the pediatric population. On the contrary, the incidence of COVID-19 was lower in individuals who underwent this procedure. Future studies involving larger, multicenter cohorts could investigate the potential effects of

adenotonsillectomy on multisystem inflammatory syndrome in children (MIS-C) and explore cytokine profiles during COVID-19 infection in this population.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research protocol was submitted to and approved by the Sakarya University Ethics Committee. (25/20/2021 - 74624).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

The authors have contributed equally.

Financial Disclosure

None.

References

1. World Health Organization. Children and adolescents: COVID-19. WHO; 2021. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1.
2. American Academy of Pediatrics. Children and COVID-19: State-level data report. American Academy of Pediatrics; 2021. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/.
3. Mantovani A, Rinaldi E, Zusi C, Beatrice G, Saccomani MD, Dalbeni A. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res*. 2021;89(4):733-737. doi:10.1038/s41390-020-1015-2
4. Kari JA, Shalaby MA, Albanna AS, et al. Coronavirus disease in children: A multicentre study from the Kingdom of Saudi Arabia. *J Infect Public Health.* 2021;14(4):543-549. doi:10.1016/j.jiph.2021.01.011
5. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. *Turk J Med Sci.* 2020;50(SI-1):592-603. doi:10.3906/sag-2004-174
6. Brodin P. Why is COVID-19 so mild in children?. *Acta Paediatr.* 2020;109(6):1082-1083. doi:10.1111/apa.15271
7. Onal M, Onal O, Turan A. Can secondary lymphoid organs exert a favorable effect on the mild course of COVID-19 in children?. *Acta Otolaryngol.* 2021;141(1):83-84. doi:10.1080/00016489.2020.1814965
8. Bitar MA, Dowli A, Mourad M. The effect of tonsillectomy on the immune system: A systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol.* 2015;79(8):1184-1191. doi:10.1016/j.ijporl.2015.05.016
9. Li K, Fang Y, Li W, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol.* 2020;30(8):4407-4416. doi:10.1007/s00330-020-06817-6
10. Palabiyik F, Akcay N, Sevketoglu E, Hatipoglu N, Sari EE, Inci E. Imaging of Multisystem Inflammatory Disease in Children (MIS-C) Associated With COVID-19. *Acad Radiol.* 2021;28(9):1200-1208. doi:10.1016/j.acra.2021.05.030
11. Yan Y, Song Y, Liu Y, et al. Short- and long-term impacts of adenoidectomy with/without tonsillectomy on immune function of young children <3 years of age: A cohort study. *Medicine (Baltimore).* 2019;98(19):e15530. doi:10.1097/MD.0000000000015530
12. Byars SG, Stearns SC, Boomsma JJ. Association of Long-Term Risk of Respiratory, Allergic, and Infectious Diseases With Removal of Adenoids and Tonsils in Childhood. *JAMA Otolaryngol Head Neck Surg.* 2018;144(7):594-603. doi:10.1001/jamaoto.2018.0614
13. Choi HG, Park B, Sim S, Ahn SH. Tonsillectomy Does Not Reduce Upper Respiratory Infections: A National Cohort Study. *PLoS One.* 2016;11(12):e0169264. Published 2016 Dec 30. doi:10.1371/journal.pone.0169264
14. Chung SD, Hung SH, Lin HC, Chen KC. Decreased clinic visits for acute respiratory infections following an adult tonsillectomy: A population-based study. *Am J Otolaryngol.* 2017;38(4):488-491. doi:10.1016/j.amjoto.2017.05.004
15. Murugesan R, Sagar P, Kumar R, et al. Long Term Impact of Adeno-tonsillectomy on Immunity Against Respiratory Viral Infections; Evidence Deduced During COVID-19 Pandemic. *Indian J Pediatr.* Published online May 7, 2024. doi:10.1007/s12098-024-05125-x
16. Kara A, Elden H, Okur E, et al. Impact of tonsillectomy on COVID-19 pandemic: an observational study of the incidence and prognosis. *Acta Otolaryngol.* 2021;141(9):857-859. doi:10.1080/00016489.2021.1970803
17. Yang Y, Hu K, Modig K, et al. Surgical removal of tonsils and risk of COVID-19: a nested case-control study using data from UK Biobank and AMORIS Cohort. *BMC Med.* 2024;22(1):460. doi:10.1186/s12916-024-03587-6
18. Kaygusuz I, Alpay HC, Gödekmerdan A, et al. Evaluation of long-term impacts of tonsillectomy on immune functions of children: a follow-up study. *Int J Pediatr Otorhinolaryngol.* 2009;73(3):445-449. doi:10.1016/j.ijporl.2008.11.014
19. Mücke W, Huber HC, Ritter U. Mitteilung über die Keimbesiedelung der Gaumenmandeln bei gesunden Kindern im Einschulalter [The microbe colonization of the palatine tonsils of healthy school age children]. *Zentralbl Hyg Umweltmed.* 1994;196(1):70-74.
20. Endo LH, Ferreira D, Montenegro MC, et al. Detection of Epstein-Barr virus in tonsillar tissue of children and the relationship with recurrent tonsillitis. *Int J Pediatr Otorhinolaryngol.* 2001;58(1):9-15. doi:10.1016/s0165-5876(00)00446-8
21. Agren K, Andersson U, Litton M, Funa K, Nordlander B, Andersson J. The production of immunoregulatory cytokines is localized to the extrafollicular area of human tonsils [published correction appears in Acta Otolaryngol (Stockh) 1996;116(6):918]. *Acta Otolaryngol.* 1996;116(3):477-485. doi:10.3109/00016489609137876
22. Johnson BS, Laloraya M. A cytokine super cyclone in COVID-19 patients with risk factors: the therapeutic potential of BCG immunization. *Cytokine Growth Factor Rev.* 2020;54:32-42. doi:10.1016/j.cytogfr.2020.06.014
23. Chiang PH, Liu HK, Chen YL, Wang YH, Wei JC. Association between tonsillectomy and COVID-19 in chronic tonsillitis patients. *Br J Surg.* 2023;110(11):1553-1554. doi:10.1093/bjs/znad291

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Research Article | Araştırma Makalesi

FACTORS ASSOCIATED WITH PLACEMENT FAILURE OF SECOND-GENERATION LARYNGEAL MASK AIRWAY: A RETROSPECTIVE CLINICAL STUDY

İKİNCİ JENERASYON LARİNGEAL MASKE HAVAYOLUNDA YERLEŞTİRME BAŞARISIZLIĞI İLE İLİŞKİLİ FAKTÖRLER: RETROSPEKTİF KLİNİK BİR ÇALIŞMA

Zehra Ipek Arslan Aydin[1*], Ipek Izgin Avci[1*], Ibrahim Erkut Avci[2]

[1]Kocaeli University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Kocaeli, Türkiye. [2]Kocaeli University, Faculty of Medicine, Department of Urology, Kocaeli, Türkiye.

ABSTRACT

Objective: The laryngeal mask airway (LMA) is important for airway management during anesthesia practice. Rarely, when it cannot be placed, it requires alternative interventions. In this study, we aimed to identify factors associated with second-generation LMA placement failure.

Methods: Between 2021 and 2023, medical records of consecutive patients who underwent ureteroscopy for urolithiasis under general anesthesia were retrospectively reviewed. Exclusion criteria were: age <18 years and endotracheal intubation as the first preference for airway management. Patients were divided into two groups: (1) those who were successful in LMA placement; and (2) those in whom LMA placement failed. LMA placement failure and associated factors, including body mass index (BMI), gender, mallampati score, thyromental distance, cervical spine mobility, structural status of teeth, American Society of Anesthesiology score (ASA), and history of difficult airway, were evaluated.

Results: 188 patients analysed: Male gender (67%), ASA-2 was the majority (56%), and the patients had a mean age of 52.9±14.44 and a BMI of 28.9±5.62 kg/m^2. Placement of LMA was successful on initial attempt in 173 (92%); LMA number 4 was most commonly used (57%). Fifteen patients required intubation when the LMA did not settle after three attempts. Comparison of the successful and failed placement groups showed: 14/15 (93.3%) were male (p=0.024). A significant prolongation of anesthesia occurred in patients in whom LMA was not placed (p=0.017).

Conclusion: LMA placement failure occurred in 8% of this cohort and most of these patients were male. After LMA placement failure, anesthesia time is significantly prolonged.

Keywords: Laryngeal Mask Airway, difficult, urogenital surgery, adult

ÖZ

Amaç: Laringeal maske hava yolu (LMA), anestezi uygulaması sırasında hava yolu yönetimi açısından önemlidir. Nadiren yerleştirilemediğinde alternatif müdahaleler gerektirir. Bu çalışmada ikinci nesil LMA yerleştirme başarısızlığıyla ilişkili faktörleri belirlemeyi amaçladık.

Yöntem: 2021-2023 yılları arasında genel anestezi altında ürolitiazis nedeniyle üreteroskopi yapılan ardışık hastaların tıbbi kayıtları retrospektif olarak incelendi. Hariç tutma kriterleri şunlardı: yaş <18 ve hava yolu yönetiminde ilk tercihin endotrakeal entübasyon olması. Hastalar iki gruba ayrıldı: (1) LMA yerleştirmede başarılı olanlar ve (2) LMA yerleştirmenin başarısız olduğu kişiler. LMA yerleştirme başarısızlığı ve vücut kitle indeksi (BMI), cinsiyet, mallampati skoru, tiromental mesafe, servikal omurga hareketliliği, dişlerin yapısal durumu, Amerikan Anesteziyoloji Derneği skoru (ASA) ve zor hava yolu öyküsü gibi ilişkili faktörler değerlendirildi.

Bulgular: Analiz edilen 188 hasta: Erkek cinsiyet (%67), ASA-2 çoğunluktaydı (%56), hastaların ortalama yaşı 52,9±14,44 ve BMI 28,9±5,62 kg/m2 idi. LMA'nın yerleştirilmesi 173 hastada (%92) ilk denemede başarılı oldu; En sık kullanılan LMA 4 numaraydı (%57). Üç denemeden sonra LMA yerleşmeyince 15 hastada entübasyon gerekti. Başarılı ve başarısız yerleştirme gruplarının karşılaştırılması şunu gösterdi: 14/15 (%93,3) erkekti (p=0,024). LMA takılmayan hastalarda anestezi süresinde anlamlı uzama meydana geldi (p=0,017).

Sonuç: LMA yerleştirme başarısızlığı bu grubun %8'inde meydana geldi ve bu hastaların çoğu erkekti. LMA yerleştirme başarısızlığından sonra anestezi süresi önemli ölçüde uzar.

Anahtar Kelimeler: Laringeal Maske, zor, ürogenital cerrahi, erişkin

***Corresponding author/İletişim kurulacak yazar:** Ipek Izgin Avci; Kocaeli University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Kocaeli, Türkiye
Phone/Telefon: +90 (538) 501 79 27, **e-mail/e-posta:** izginipek@gmail.com
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Introduction

Since the invention of supraglottic airway devices in 1981 and their subsequent introduction into clinical practice in 1988, their use during general anesthesia has gained popularity for airway maintenance.[1-3] The guidelines advise using the second-generation laryngeal mask airway (LMA) as the initial option for routine airway management and managing of the difficult airway.[3,4] It is recommended to avoid repeated attempts at inserting a supraglottic airway device, as this increases the risk of airway trauma. Instead, an alternative technique should be used to maintain oxygenation and ventilation.[3,4]

The advantages of the LMA over endotracheal intubation include minor hemodynamic changes and reduced risk of cough, laryngospasm, soft tissue trauma, and sore throat.[1,5,6] Although LMAs are considered safe supraglottic airway devices, they can sometimes be challenging to place.[7] A simple, objective, predictive score to identify patients at risk for difficult LMA placement is not currently available. However, a risk identification analysis based on a comprehensive airway assessment must first be performed to obtain such a score. Although there are many studies on LMAs, research on difficult LMA placement is limited.[2,5]

In this study, we aimed to determine risk factors in patients with second-generation LMA placement failure by retrospectively examining the records of patients who underwent ureteroscopy (URS) for urolithiasis. The second objective was to increase the available published evidence concerning factors affecting LMA placement failure.

Methods

In this retrospective study, we reviewed two hundred and fifty-eight patients who underwent elective URS for kidney or ureteral stones at Kocaeli University Hospital between 2021 and 2023. The exclusion criteria encompassed individuals who were below the age of eighteen years and those for whom endotracheal intubation was the primary approach for airway management. The study was approved by the local ethics committee (Approval number: KOÜ GOKAEK-2023/04.08).

The preoperative and intraoperative anesthesia medical records were reviewed. Variables associated with difficult airway for each patient included mallampati classification, thyromental distance (TMD), degree of neck movement, and being edentulous, having removable dentures or natural teeth. Among the demographic data, age, weight, height, body mass index (BMI), gender, American Society of Anesthesiology (ASA) physical status classification, and history of difficult airway were included. It was also recorded if the person performing the preoperative examination was an instructor or a research assistant and whether the person performing the airway management was an anesthesia technician, a research assistant, or an instructor. The ventilation technique was determined by examining the anesthesia monitoring forms of the patients. The patients were classified into three groups: those who underwent endotracheal tube (ETT) insertion without attempting LMA insertion, those who underwent successful LMA insertion, and those who underwent ETT insertion following the failure of LMA insertion. The anesthesia monitoring charts were consulted to obtain the sizes of the ETT and the second-generation LMA inserted during the procedure.

In our center, the LMA ProSeal™ is inserted in patients scheduled to undergo URS without requiring neuromuscular blocking agents if their comorbidity status is favorable. However, an ETT may be the airway intervention of preference in cases with multiple comorbidities. When two attempts to insert the LMA ProSeal™ fail, the LMA Protector™ is used as the next step; if that also fails, an ETT is used to intubate the patient. Direct laryngoscopy is the first attempt at this stage, and if this is unsuccessful, intubation is performed with video-laryngoscopy.

Statistical Analysis

Data analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to analyze quantitative data. The normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Numeric data that follow a normal distribution are presented as mean ± standard deviation (SD), and numeric data that do not follow a normal distribution are presented as median and interquartile ranges (IQR). Categorical data are expressed as numbers and percentages. The means were compared using an Independent Sample t-test, while the Mann-Whitney U test was used to compare medians. To compare two sets of categorical data, the Chi-Square test was used. A *p*-value of less than 0.05 was considered statistically significant.

Results

Between 2021 and 2023, elective URS was performed under general anesthesia on 258 patients in the operating theater of our hospital. Of these 258 patients, 15 were under 18 years of age. Of the remaining 243 patients, 55 were intubated directly with ETT due to multiple comorbidities. Thus, 188 patients who met the study criteria were included in the study. The demographic characteristics of the patients are presented in Table 1. Some patients' demographic data were not recorded or whose airway parameters were not evaluated due to COVID-19. There are missing data was presented for mallampati classification, TMD, neck movement, tooth structure in Table 2. There was one patient with a history of difficult airway. When fully recorded airway parameters were analyzed, 62% of the first airway examinations in 188 patients were performed by the anesthesia research assistant. The airway management of 173 patients (92%) was successfully

achieved at the first attempt with the LMA ProSeal™, with the number 4 size of LMA ProSeal™ being used the most (57%).

Table 1. Demographic characteristics of the patients.

Number of patients	188
Gender	
Female, n, (%)	62 (33.0)
Male, n, (%)	126 (67.0)
ASA physical status classification, median, [range]	2 [1-4]
ASA 1, n, (%)	50 (26.6)
ASA 2, n, (%)	105 (55.9)
ASA 3, n, (%)	32 (17.0)
ASA 4, n, (%)	1 (0.5)
Age (years), mean ± SD	52.85 ±14.439
Height (cm), mean ± SD	168.40 ±9.091
Weight (kg), mean ± SD	81.49 ±14.841
BMI (kg/m²), mean ± SD	28.85 ±5.624

ASA, American Society of Anesthesiology; SD, Standard deviation; BMI, Body mass index

The outcomes of preoperative airway evaluation and intraoperative airway management are detailed in Table 2. An anesthesia technician performed airway management in 60% of the patients. The mean anesthesia time was 86.8±29.3 minutes. An 8.0 ETT was used in 73% of the 15 patients (8%) in whom the second-generation LMAs (ProSeal™ and Protector™) did not settle after three attempts. Records show that direct laryngoscopy failed in three patients, and they were intubated with an angled spoon video-laryngoscope. The records did not detail how the other 12 patients were intubated.

Comparative outcomes regarding LMA placements that were either successful or failed are presented in Table 3. Male gender was significantly more prevalent in the unsuccessful group compared to the group in which LMA was successful (p=0.024). The anesthesia time of patients in whom LMA was not inserted was also significantly prolonged (104.00±39.06 vs 85.32±27.90 min;p=0.017). In terms or the other parameters compared between groups (age, BMI, ASA score, the person performing the preoperative anesthesia examination, and airway management) there was no difference between the successful and unsuccessful groups (p>0.05 for all). Additionally, there were no statistically significant differences between females and males for age, body mass index, and ASA scores in a gender-based assessment (Table 4).

Discussion

The most notable findings in our study were that LMA failure was significantly more common in male patients and mean anesthesia time was longer in the group with LMA failure. In a study that retrospectively examined the data of patients who underwent elective, non-obstetric surgery between 2008 and 2010, LMA Unique™ was used by anesthesia assistants as the first airway intervention in sixty-nine patients, and it was reported that female gender and neck circumference >44 cm were independent predictive factors for LMA Unique™ failure.[8] In a study involving 15,795 patients using LMA Unique™ between 2006 and 2009, LMA could not be placed in 1.1% of the patients, and these patients were subsequently intubated.[9] Moreover, male gender and having obstructive sleep apnea (OSA) were reported to be significant predictive factors for unsuccessful LMA placement. In addition, BMI >29 kg/m^2, TMD <6 cm, limited neck movement, thick neck, bad teeth, active smoking, and moving the surgical table have also been reported to cause LMA failure. In this study, anesthesia assistants performed airway interventions, as in the present study.[9]

Table 2. Preoperative airway assessment and intraoperative airway management results.

The person who performed preoperative examination	
Anesthesia instructor, n, (%)	71 (37.8)
Research assistant, n, (%)	117 (62.2)
Mallampati Classification	
1, n, (%)	23 (12.2)
2, n, (%)	42 (22.3)
3, n, (%)	6 (3.2)
Missing data, n, (%)	117 (62.2)
Thyromental distance	
<6 cm, n, (%)	5 (2.7)
≥6 cm, n, (%)	82 (43.6)
Missing data, n, (%)	101 (53.7)
Neck movement	
Normal, n, (%)	80 (42.6)
Limited, n, (%)	1 (0.5)
Missing data, n, (%)	107 (56.9)
Tooth structure	
Normal, n, (%)	58 (30.9)
Prosthesis, n, (%)	14 (7.4)
Missing data, n, (%)	116 (61.7)
Airway management	
LMA, n, (%)	173 (92.0)
ETT after LMA, n, (%)	15 (8.0)
The person who performed airway intervention	
Anesthesia technician, n, (%)	112 (59.6)
Anesthesia instructor or research assistant, n, (%)	76 (40.4)
LMA size (number)	
3, n, (%)	15 (8.5)
4, n, (%)	99 (57.2)
5, n, (%)	59 (34.1)
Endotracheal Tube size (number)	
7, n, (%)	1 (6.7)
7.5, n, (%)	1 (6.7)
8, n, (%)	11 (73.3)
8.5, n, (%)	2 (13.3)
Anesthesia time (min), mean ± SD	86.81 ±29.259

LMA, Laryngeal mask airway; ETT, Endotracheal tube; SD, standard deviation

Table 3. The comparative analysis of the outcomes of successful and unsuccessful LMA placement cohorts.

	LMA Placement Successful (*n*=173)	**LMA Placement Failure** (*n*=15)	***p value***
Age (years), mean ± SD	52.64 ±14.515	54.87 ±13.410	0.567
Weight (kg), mean ± SD	81.16 ±15.144	85.40 ±10.329	0.289
Height (cm), mean ± SD	168.05±9.128	172.47±7.809	0.071
BMI (kg/m²), mean ± SD	28.84±5.643	28.98±5.589	0.925
Anesthesia time (min), mean ± SD	85.32 ±27.902	104.00 ±39.060	**0.017**
ASA physical status classification, median, (IQR)	2 (1-2)	2 (2-3)	0.351
Gender			
Female	61 (98.4)	1 (1.6)	**0.024**
Male	112 (88.9)	14 (11.1)	
The person who performed preoperative examination			
Anesthesia instructor, n, (%)	66 (91.5)	5 (8.5)	0.712
Research assistant, n, (%)	107 (93.0)	10 (7.0)	
The person who performed airway intervention			
Anesthesia technician, n, (%)	101 (90.2)	11 (9.8)	0.258
Anesthesia instructor or research assistant, n, (%)	72 (94.7)	4 (5.3)	
Variables with missing data			
Thyromental distance, n, (%)	80 (92.0)	7 (8.0)	
<6 cm, n, (%)	5 (100.0)	0 (00.0)	0.496
≥6 cm, n, (%)	75 (91.5)	7 (8.5)	
Neck movement n, (%)	74 (91.4)	7 (8.6)	
Normal, n, (%)	74 (92.5)	6 (7.5)	0.086
Limited, n, (%)	0 (00.0)	1 (100.0)	
Tooth structure, n, (%)	67 (93.1)	5 (6.9)	
Normal, n, (%)	53 (91.4)	5 (8.6)	0.575
Prosthesis, n, (%)	14 (100.0)	0 (00.0)	
Mallampati Classification, n, (%)	65 (91.5)	6 (8.5)	0.812
Median (IQR)	2 (1-2)	2 (1-2)	

ASA, American Society of Anesthesiology; SD, Standard deviation; BMI, Body mass index; IQR, Interquartile range; kg, kilogram; cm, centimeter. The bold p values indicate a significant comparison with p<0.05.

Table 4. Gender-based assessment of age, body mass index, and ASA scores.

	Female (*n*=62)	**Male** (*n*=126)	***p value***
Age (years), mean ± SD	53.08 ±14.400	52.68 ±14.469	0.859
BMI (kg/m²), mean ± SD	30.20±7.302	28.18±4.466	0.062
ASA physical status classification, median, (IQR)	2 (1-2)	2 (2-2)	0.269

ASA, American Society of Anesthesiology; SD, Standard deviation; BMI, Body mass index; IQR, Interquartile range.

In a report about using the second-generation supraglottic airway device, the LMA Supreme™, difficult LMA placement was noted in 18.3%, and the LMA failure rate was 2.1%. For difficult LMA placement, female gender and mallampati score of 3-4 were the strongest indicators, as well as mouth opening <3 cm, limited neck movement, difficulty with mask ventilation, large tonsils, using a pillow thicker than 3 cm when placing the LMA, and not using muscle relaxants were significant determinants of settlement.[10] The LMA failure rate was around 8% in our study. This higher failure rate may be due to the higher male gender, more than two thirds of the cohort, and the fact that muscle relaxants were not used.

Risk factors reported for difficult LMA placement in the 2021 Canadian difficult airway guideline are absence of teeth or poor oral care, limited mouth opening, mallampati score of 3-4, limited head and neck movement, not using muscle relaxants, neck circumference >44 cm, patient not lying supine, using desflurane, choosing a smaller size LMA than recommended by the manufacturer, and making many placement attempts.[11] In addition, it has been shown that limitation in mouth opening, mallampati score of 3-4, neck flexion and extension movement limitation are predicting LMA failure and that as many predictive criteria as possible should be evaluated in the preoperative period.[4,12] Compared to intubation with ETT, LMA is easier to place, causes less sore throat and less pain when swallowing, and user errors are less common.[13] In terms of who performed airway management, our research found no significant difference between success or failure of LMA placement and who performed the airways management.

It has been shown that second-generation LMAs provide greater protection against aspiration because they have

a bite block, gastric drainage channels, and allow high oropharyngeal leak pressures.[4,14] We routinely use second-generation LMA ProSeal™ with our patients. We chose the LMA Protector™ for the third trial because it has a second gastric drainage channel, the highest initial placement rate of 93%, and the highest oropharyngeal leak pressure of 32 cm H2O.[15]

A study showed that instead of weight-based selection in suitable candidates for LMA selection, TMD-based selection allowed easier LMA placement with less manipulation required.[16] It has been shown in a prospective study that LMA number 4 had the best first-attempt success rate and was placed in a shorter time compared to LMA number 5 in >70 kg obese Chinese male patients.[17]. A retrospective study of 19,693 cases showed that LMAs 4 and 5 had a higher failure rate than LMAs 2 and 3.[18] A further study reported that a choice based on pinna size was more appropriate when choosing the LMA ProSeal™ size to be used, compared to a choice based on weight.[19] A recently reported study found that deciding LMA size by grouping based on neck circumference was more accurate.[20]

LMA placement may be more challenging in males due to the higher prevalence of OSA syndrome and increased airway resistance and obstruction. In a retrospective study covering a three year period, male gender, age >45 years, TMD < 6cm, and neck movement limitation were determined as risk factors for difficult LMA placement.[21] The same authors later proposed a scoring system to predict difficult supraglottic airway ventilation, with male gender = 1 point, age >45 = 1 point, TMD <6 cm = 3 points, presence of neck movement limitation = 2 points (total 7 points) and they reported the score threshold for difficult LMA placement was 4.[22]

The current study has some limitations. There are deficiencies in the data as preoperative oropharyngeal examinations of patients could not be performed routinely during the COVID-19 pandemic. Most airway parameters are also subjective and not based on measurement. Since it is a study conducted in adults, findings are not generalizable to pediatric patients.

Conclusions

Male gender increases the risk of LMA failure and LMA failure prolongs the anesthesia time. The results of this study may be generalized to all surgeries and patients in whom LMA will be placed.

Description

This article was presented as an oral presentation at TARK 2-5 November 2023, Antalya, Türkiye.

Compliance with Ethical Standards

The study was approved by the local ethics committee (Approval number: KOÜ GOKAEK-2023/04.08).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

İAİ, AZİ: Study idea, hypothesis, study design; İAİ, AİE: Material preparation, data collection and analysis; İAİ, AZİ: Writing the first draft of the article; İAİ, AİE, AZİ: Critical review of the article finalization and publication process.

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None.

References

1. Brimacombe J. The advantages of the LMA over the tracheal tube or facemask: a meta-analysis. *Can J Anaesth*. 1995;42(11):1017-23. doi:10.1007/BF03011075.
2. Brain AIJ. The laryngeal mask—a new concept in airway management. *Br J Anaesth.* 1983;55(8):801-6. doi:10.1093/bja/55.8.801.
3. Caplan R, Benumof J, Berry F. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway. An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology.* 2003;98(5):1269-77. doi:10.1097/00000542-200305000-00032.
4. Frerk C, Mitchell VS, McNarry AF. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *Br J Anaesth.* 2015;115(6):827-48. doi:10.1093/bja/aev371.
5. Tartari S, Fratantonio R, Bomben R. Laryngeal mask vs tracheal tube in pediatric anesthesia in the presence of upper respiratory tract infection. *Minerva Anestesiol.* 2000;66(6):439-43.
6. Jamil SN, Alam M, Usmani H. A study of the use of laryngeal mask airway (LMA) in children and its comparison with endotracheal intubation. *Indian J Anaesth*. 2009;53(2):174.
7. Buckham M, Brooker M, Brimacombe J. A comparison of the reinforced and standard laryngeal mask airway: ease of insertion and the influence of head and neck position on oropharyngeal leak pressure and intracuff pressure. *Anaesth Intensive Care*. 1999;27(6):628-31. doi:10.1177/0310057X9902700612.
8. Katsiampoura AD, Killoran PV, Corso RM. Laryngeal mask placement in a teaching institution: analysis of difficult placements. *F1000Res*. 2015;4. doi:10.12688/f1000research.6415.1.
9. Ramachandran SK, Mathis MR, Tremper KK. Predictors and clinical outcomes from failed Laryngeal Mask Airway Unique™: a study of 15,795 patients. *Anesthesiology.* 2012;116(6):1217-26. doi:10.1097/ALN.0b013e318255e6ab.
10. Di Filippo A, Adembri C, Paparella L. Risk factors for difficult Laryngeal Mask Airway LMA-Supreme™(LMAS) placement in adults: a multicentric prospective observational study in an Italian population. *Minerva Anestesiol*. 2021;87:533-40. doi:10.23736/S0375-9393.20.15001-6.
11. Law JA, Duggan LV, Asselin M. Canadian Airway Focus Group updated consensus-based recommendations for management of the difficult airway: part 2. Planning and implementing safe management of the patient with an anticipated difficult airway. *Can J Anaesth.* 2021;68(9):1405-36. doi:10.1007/s12630-021-02008-z.

12. Orozco-Díaz É, Álvarez-Ríos JJ, Arceo-Díaz JL. Predictive factors of difficult airway with known assessment scales. *Cir Cir*. 2010;78(5):393-9.
13. Almeida G, Costa A, Machado H. Supraglottic airway devices: a review in a new era of airway management. *J Anesth Clin Res*. 2016;7(1):2155-61.
14. Endlich Y, Hore PJ, Baker PA. Updated guideline on equipment to manage difficult airways: Australian and New Zealand College of Anaesthetists. *Anaesth Intensive Care*. 2022;50(6):430-46. doi:10.1177/0310057X221082664.
15. Shariffuddin II, Chaw SH, Ng LW. Clinical performance of the LMA Protector™ airway in moderately obese patients. *BMC Anesthesiol.* 2020;20:1-8. doi:10.1186/s12871-020-01100-z.
16. Weng M, Ding M, Xu Y. An evaluation of thyromental distance-based method or weight-based method in determining the size of the laryngeal mask airway supreme: A randomized controlled study. *Medicine*. 2016;95(9). doi:10.1097/MD.0000000000002902.
17. Chen J, Chen C, Xu W. Size selection of the Ambu AuraOnce laryngeal mask in Chinese men weighing> 70 kg: a pilot study. *J Int Med Res*. 2021;49(5):03000605211016689. doi:10.1177/03000605211016689.
18. Vannucci A, Rossi IT, Prifti K. Modifiable and nonmodifiable factors associated with perioperative failure of extraglottic airway devices. *Anesth Analg.* 2018;126(6):1959-67. doi:10.1213/ANE.0000000000002659.
19. Ravi R, Mohan V, Badhe AS. Comparison of weight-based and pinna size–based selection of ProSeal laryngeal mask airway in paediatric population–A prospective exploratory trial. *Indian J Anaesth*. 2019;63(1):36. doi:10.4103/ija.IJA_423_18.
20. Aghadavoudi O, Shetabi H, Saryazdi H. Assessment of neck characteristics for laryngeal mask airway size selection in patients who underwent an elective ocular surgery; A cross-sectional study. *Bull Emerg Trauma*. 2022;10(2):77. doi:10.30476/BEAT.2022.94356.1338.
21. Saito T, Liu W, Chew S. Incidence of and risk factors for difficult ventilation via a supraglottic airway device in a population of 14 480 patients from South-East Asia. *Anaesthesia.* 2015;70(9):1079-83. doi:10.1111/anae.13153.
22. Saito T, Chew S, Liu W. A proposal for a new scoring system to predict difficult ventilation through a supraglottic airway. *Br J Anaesth..* 2016;117(suppl 1):i83-i6. doi:10.1093/bja/aew191.

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Research Article | Araştırma Makalesi

RISK FACTORS ACCELERATING CONVERSION FROM VATS TO THORACOTOMY

AKCİĞER KANSERİ İÇİN VİDEO YARDIMLI TORAKOSKOPİK CERRAHİ SIRASINDA TORAKOTOMİYE DÖNÜŞÜMÜ TAHMİN ETMEK İÇİN BİR RİSK PUANLAMA MODELİ GELİŞTİRME

Onur Derdiyok[1*]

[1]Şişli Hamidiye Etfal Training and Research Hospital, Department of Thoracic Surgery, İstanbul, Türkiye.

ABSTRACT

Objective: This study aimed to create a risk scoring model to foresee unexpected conversions to thoracotomy during video-assisted thoracoscopic surgery (VATS) for lung cancer. By identifying the factors contributing to these conversions, surgical planning and patient outcomes can be enhanced.

Methods: A retrospective analysis was performed on 240 patients who underwent VATS for lung cancer from January 2019 to December 2024. Among these, 26 patients required conversion to thoracotomy. Various clinical and perioperative factors were examined to identify predictors of conversion through univariate and multivariate logistic regression analyses. A risk scoring model was subsequently developed based on these factors, and its predictive performance was assessed.

Results: Of the 240 patients, 26 (10.8%) needed conversion to thoracotomy. Key predictors of conversion identified through multivariate analysis included larger tumor size (OR 2.5, 95% CI 1.2-5.3), central tumor location (OR 3.1, 95% CI 1.5-6.4), and reduced forced expiratory volume (FEV1) (OR 2.8, 95% CI 1.3-6.0). The risk scoring model exhibited strong predictive accuracy with an area under the receiver operating characteristic (ROC) curve of 0.82.

Conclusion: The developed risk scoring model effectively predicts the likelihood of conversion to thoracotomy during VATS for lung cancer. This model serves as a valuable tool for preoperative planning and patient counseling, thereby potentially improving surgical outcomes and resource allocation.

Keywords: Risk Scoring model, conversion to thoracotomy, vats

ÖZ

Amaç: Bu çalışmanın amacı, akciğer kanseri için video yardımlı torakoskopik cerrahi (VATS) sırasında torakotomiye beklenmedik dönüşümleri öngörmek için bir risk puanlama modeli oluşturmaktır. Bu dönüşümlere katkıda bulunan faktörleri belirleyerek cerrahi planlama ve hasta sonuçları iyileştirilebilir.

Yöntem: Ocak 2019'dan Aralık 2024'e kadar akciğer kanseri için VATS geçiren 240 hasta üzerinde retrospektif bir analiz yapıldı. Bunlardan 26'sında torakotomiye dönüşüm gerekti. Tek değişkenli ve çok değişkenli lojistik regresyon analizleri yoluyla dönüşümün öngörücülerini belirlemek için çeşitli klinik ve perioperatif faktörler incelendi. Daha sonra bu faktörlere dayalı bir risk puanlama modeli geliştirildi ve öngörücü performansı değerlendirildi.

Bulgular: 240 hastadan 26'sında (%10,8) torakotomiye dönüşüm gerekti. Çok değişkenli analizle belirlenen dönüşümün temel öngörücüleri arasında daha büyük tümör boyutu (OR 2,5, %95 CI 1,2-5,3), merkezi tümör konumu (OR 3,1, %95 CI 1,5-6,4) ve azaltılmış zorunlu ekspiratuvar hacim (FEV1) (OR 2,8, %95 CI 1,3-6,0) yer almaktadır. Risk puanlama modeli, 0,82'lik alıcı işletim karakteristiği (ROC) eğrisi altındaki alanla güçlü bir öngörü doğruluğu sergilemiştir.

Sonuç: Geliştirilen risk puanlama modeli, akciğer kanseri için VATS sırasında torakotomiye dönüşüm olasılığını etkili bir şekilde öngörür. Bu model, ameliyat öncesi planlama ve hasta danışmanlığı için değerli bir araç görevi görerek potansiyel olarak cerrahi sonuçları ve kaynak tahsisini iyileştirir.

Anahtar Kelimeler: Risk puanlama modeli, torakotomiye dönüşüm, vats

***Corresponding author/İletişim kurulacak yazar:** Onur Derdiyok; Şişli Hamidiye Etfal Training and Research Hospital, Department of Thoracic Surgery, İstanbul, Türkiye
Phone/Telefon: +90 (541) 769 06 77, **e-mail/e-posta:** onur_derdiyok@hotmail.com
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Introduction

Video-assisted thoracoscopic surgery (VATS) has revolutionized the approach to lung cancer resection, offering significant advantages over traditional thoracotomy, including reduced postoperative pain, shorter hospital stays, and faster recovery times. However, conversion to thoracotomy is still required in certain cases due to various factors. Reported conversion rates in the literature range from 5% to 23%. Particularly, factors such as larger tumor size, central tumor location, and compromised pulmonary function are known to increase the likelihood of conversion. This study aims to predict these factors to enhance surgical planning and patient management.

Video-assisted thoracoscopic surgery has revolutionized the approach to lung cancer resection, offering significant advantages over traditional open thoracotomy, including reduced postoperative pain, shorter hospital stays, and faster recovery times[1]. Despite these benefits, the risk of unexpected conversion to thoracotomy remains a notable concern, with reported conversion rates varying from 5% to 23%. Conversion to thoracotomy is often necessitated by factors such as extensive adhesions, uncontrolled bleeding, or inability to achieve adequate resection margins[2].

Understanding the risk factors that lead to conversion is critical for improving surgical planning and patient outcomes. Identifying patients at higher risk of conversion can help in preoperative counseling, optimizing resource allocation, and potentially reducing the incidence of conversions[3]. This study aims to develop a risk scoring model based on preoperative and intraoperative factors to predict the likelihood of conversion to thoracotomy during VATS for lung cancer.

Methods

Patients were excluded from the study based on the following criteria: incomplete clinical data, emergency surgery, and those who required alternative surgical techniques due to early postoperative complications. Additionally, patients with benign lung diseases or those undergoing immunosuppressive therapy were also excluded from the study.

Patient Selection

In this retrospective study, we reviewed the medical records of 240 patients who underwent VATS for lung cancer resection at our institution between January 2019 and December 2024. Patients with incomplete data or those who underwent emergency surgery were excluded from the analysis. The study protocol received approval from the institutional review board, and informed consent was obtained from all participants.

Data Collection

We gathered demographic and clinical data, including age, gender, smoking history, comorbidities, tumor characteristics (size, location, histology), and results from preoperative pulmonary function tests (PFTs). Additionally, perioperative variables such as surgery duration, intraoperative blood loss, and reasons for conversion were documented.

Statistical Analysis

Data were analyzed using SPSS software (version 25.0). Continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate logistic regression analysis was conducted to identify potential predictors of conversion to thoracotomy. Variables with a p-value<0.05 in the univariate analysis were included in the multivariate logistic regression model. A risk scoring model was developed based on the significant predictors identified in the multivariate analysis. The predictive accuracy of the model was evaluated using the area under the receiver operating characteristic (ROC) curve.

Results

Patient Demographics and Clinical Characteristics

Of the 240 patients included in the study, 140 (58.3%) were male, and the median age was 65 years (range, 45-80 years). Twenty-six patients (10.8%) required conversion to thoracotomy. Table 1 summarizes the demographic and clinical characteristics of the patients.

Table 1. Demographic and clinical characteristics of the patients

Characteristic	Overall (n=240)	Conversion (n=26)	No Conversion (n=214)	P-value
Age (years)	65 (45-80)	68 (50-78)	64 (45-80)	0.153
Male, n (%)	140 (58.3)	18 (69.2)	122 (57.0)	0.229
Smoking history, n (%)	160 (66.7)	20 (76.9)	140 (65.4)	0.228
Tumor size (cm)	3.5 ± 1.2	4.3 ± 1.5	3.4 ± 1.1	0.001*
Central location, n (%)	75 (31.3)	15 (57.7)	60 (28.0)	0.003*
FEV1 (% predicted)	80.2 ± 15.4	70.1 ± 13.8	81.5 ± 15.1	0.004*

*: Significant at p<0.05; n: Number

Predictors of Conversion

Univariate analysis identified several factors significantly associated with conversion to thoracotomy, including larger tumor size, central tumor location, and reduced FEV1. These variables were included in the multivariate logistic regression analysis, which confirmed that larger tumor size (OR 2.5, 95% CI 1.2-5.3, p=0.015), central tumor location (OR 3.1, 95% CI 1.5-6.4, p=0.002), and reduced FEV1 (OR 2.8, 95% CI 1.3-6.0, p=0.008) were independent predictors of conversion (Table 2).

Table 2. Predictors of conversion

Variable	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Tumor size (cm)	2.1 (1.3-3.5)	0.002*	2.5 (1.2-5.3)	0.015*
Central location	3.4 (1.6-7.1)	0.001*	3.1 (1.5-6.4)	0.002*
FEV1 (% predicted)	2.6 (1.4-5.0)	0.003*	2.8 (1.3-6.0)	0.008*

*Significant at p<0.05

Risk Scoring Model

A risk scoring model was developed based on the significant predictors identified in the multivariate analysis. Each predictor was assigned a score proportional to its odds ratio. The total risk score was calculated for each patient, and the model's predictive accuracy was evaluated using the ROC curve (Table 3), which showed an area under the curve (AUC) of 0.82, indicating good predictive performance.

Table 3. ROC Curve for the Risk Scoring Model

Risk Factor	Score
Tumor size > 4 cm	2
Central location	3
FEV1 < 70% predicted	2

Discussion

The unexpected conversion to thoracotomy during video-assisted thoracoscopic surgery for lung cancer remains a significant clinical challenge, affecting patient outcomes and healthcare resource utilization. Despite advancements in minimally invasive surgical techniques, conversion rates have remained considerable, ranging from 5% to 23% in various studies. This study aimed to develop a risk scoring model to predict such conversions, thereby improving surgical planning and patient management[4].

Our analysis identified three significant independent predictors of conversion to thoracotomy: larger tumor size, central tumor location, and reduced forced expiratory volume (FEV1). These findings align with prior research, which highlights the increased complexity associated with larger and centrally located tumors. Larger tumors pose greater technical challenges due to their size and potential involvement with adjacent structures, complicating adequate resection through VATS. Central tumors, situated near major blood vessels and bronchial structures, elevate the risk of intraoperative complications such as bleeding and the need for more extensive dissection, which can necessitate conversion to thoracotomy.

Reduced FEV1, indicative of compromised pulmonary function, also emerged as a significant predictor, consistent with previous studies that emphasize the importance of preoperative pulmonary function tests in surgical risk assessment. Patients with lower FEV1 are at a higher risk for postoperative complications and may present technical challenges during VATS, making conversion to thoracotomy a safer and more controlled option[5].

The risk scoring model developed in this study incorporates these key predictors, offering a practical tool for preoperative risk assessment. With an area under the ROC curve of 0.82, the model demonstrates good predictive accuracy, making it a valuable addition to the preoperative evaluation process. This model enables the stratification of patients into different risk categories, facilitating tailored surgical planning and patient counseling[6].

By identifying high-risk patients preoperatively, surgeons can better prepare for potential intraoperative challenges, allocate resources more efficiently, and enhance patient counseling regarding the likelihood of conversion and associated risks. High-risk patients might benefit from more extensive preoperative planning, including detailed discussions about the possibility of conversion and its implications, as well as ensuring the availability of necessary resources and expertise during surgery[7].

Several risk models and scoring systems have been proposed to predict conversion during VATS. For instance, Tamura et al. developed a model based on tumor size, location, and patient comorbidities, showing comparable predictive performance to our model. However, our model differs by including specific pulmonary function parameters, providing a more comprehensive assessment of the patient's operative risk.

Furthermore, the inclusion of detailed statistical analyses, such as multivariate logistic regression, enhances the robustness of our model. Our study's retrospective design and the larger sample size of 240 patients strengthen the validity and generalizability of the findings compared to some previous studies with smaller cohorts or less detailed analyses.

Despite its strengths, this study has several limitations. First, as a retrospective analysis, it is subject to inherent biases and limitations associated with data collection from medical records. Retrospective studies often face challenges such as incomplete data and variability in clinical practices over time. To mitigate these limitations, we carefully selected our patient cohort and ensured rigorous data verification processes. However, prospective studies are needed to validate the risk scoring model in diverse patient populations and clinical settings to confirm its applicability and accuracy.

Second, the study was conducted at a single institution, which may limit the generalizability of the findings to other settings with different patient demographics and surgical practices. Multicenter studies involving a broader range of institutions would help validate the model across different clinical environments and enhance its utility. Future research should focus on prospective validation of the model, ideally in multicenter studies, to encompass a broader range of patient populations and surgical techniques. Additionally, incorporating advanced imaging techniques

and machine learning algorithms could enhance the predictive accuracy of the model, allowing for more personalized risk assessment and surgical planning[8].

Moreover, while the identified predictors are robust, there may be other unmeasured factors influencing the risk of conversion, such as surgeon experience, intraoperative decision-making, and specific anatomical variations. Future studies should aim to include these variables to further refine the predictive model. Integrating intraoperative data and real-time decision support systems could provide a more dynamic and accurate assessment of conversion risk[9].

The development of a reliable risk scoring model has significant implications for clinical practice. It enables better preoperative stratification of patients, facilitating informed discussions about surgical risks and expectations. For high-risk patients, alternative surgical strategies or enhanced intraoperative monitoring could be considered to mitigate the risk of conversion. Additionally, the model can aid in resource allocation, ensuring that high-risk cases are scheduled with adequate staffing and support[10].

In conclusion, the risk scoring model developed in this study provides a valuable tool for predicting the likelihood of conversion to thoracotomy during VATS for lung cancer. By incorporating significant predictors such as tumor size, location, and pulmonary function, the model enables better preoperative risk stratification and surgical planning. Implementing this model in clinical practice can improve patient outcomes by enhancing preoperative counseling, optimizing resource allocation, and preparing for potential intraoperative challenges. Further prospective studies are needed to validate and refine the model, ensuring its applicability in diverse clinical settings.

Compliance with Ethical Standards

This single-center, retrospective study was conducted between January 2019 and December 2024 at a research and training hospital, and done in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the local ethical committee (date: 10/10/2023, No: 4029).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

OD: Study idea, hypothesis, study design, material preparation, data collection and analysis, writing the first draft of the article, critical review of the article finalization and publication process.

Financial Disclosure

None.

References

1. McKenna RJ Jr, Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. *Ann Thorac Surg*. 2006;81:421-425. doi:10.1016/j.athoracsur.2005.07.078.
2. Swanson SJ, Herndon JE. 2nd, D'Amico TA, et al. Video-assisted thoracic surgery lobectomy: report of CALGB 39802—a prospective, multi-institution feasibility study. *J Clin Oncol*. 2007;25:4993-4997. doi:10.1200/JCO.2007.12.6649.
3. McKenna RJ, Fischel RJ, Wolf R, et al. Complications of video-assisted thoracic surgery resection for lung cancer. *Chest*. 1994;106:1793-1796.
4. Deslauriers J, Ginsberg RJ, Piantadosi S, et al. Prospective randomized trial of thoracoscopic lobectomy versus conventional lobectomy for early-stage lung cancer: initial results of an American College of Surgeons Oncology Group Trial. *J Clin Oncol*. 2002;20:428-433.
5. Ferguson MK, Vigneswaran WT. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. *Ann Thorac Surg*. 2008;85(4):1158-64. doi:10.1016/j.athoracsur.2007.12.071.
6. Brunelli A, Xiumé F, Refai M, et al. Risk-adjusted morbidity, mortality, and failure to rescue after pulmonary resection in a thoracic surgical unit. *J Thorac Cardiovasc Surg*. 2007;134:846-849.
7. Tamura M, Matsumoto I, Saito D, et al. Video-assisted thoracic surgery lobectomy: prospective feasibility study using a risk-scoring system. *Surg Today*. 2014;44:230-235.
8. Roviaro G, Varoli F, Rebuffat C, et al. Major pulmonary resections: pneumonectomies and lobectomies. *Ann Thorac Surg*. 1993;56(3):779-783. doi:10.1016/0003-4975(93)90979-r.
9. Solaini L, Prusciano F, Bagioni P, et al. Video-assisted thoracic surgery (VATS) lobectomy: patients' outcome and advantages. *J Thorac Dis*. 2004;18:261-264.
10. Yang HX, Woo KM, Sima CS, et al. Long-term survival based on the surgical approach to lobectomy for clinical stage I non-small cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. *Ann Surg*. 2017;265(2):431-437. doi:10.1097/SLA.0000000000001708.

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Research Article | Araştırma Makalesi

INVESTIGATION OF CONDITIONED MEDIA-MEDIATED COMMUNICATION BETWEEN PANCREATIC CANCER CELLS AND NEURONS

PANKREAS KANSERİ HÜCRELERİ VE NÖRONLAR ARASINDA KOŞULLU BESİYERİ ARACILI ETKİLEŞİMİN ARAŞTIRILMASI

Didem Karakas[1*]

[1]Acibadem Mehmet Ali Aydinlar University, Graduate School of Health, Medical Biotechnology, Istanbul, Turkiye.

ABSTRACT

Objective: Pancreatic cancer (PCa) is one of the deadliest cancers characterized by prominent pathological changes in nerves. PCa cells invade nerves, termed neural invasion, driven by bidirectional interactions between cancer cells and nerves, leading to severe pain and shorter survival. However, understanding of this communication remains limited, particularly in cell culture experiments. Therefore, we investigated the effect of soluble factors derived from neurons and PCa cells on the behavior of each cell type.

Methods: SH-SY5Y cells were differentiated into neurons and the differentiation efficacy was confirmed by immunofluorescence staining and Western blot. PANC-1 and BxPC-3 PCa cells were exposed to conditioned media (CM) from neurons, and changes in migration and invasion were evaluated by wound healing and transwell invasion assays, respectively. Similarly, neurons were treated with CM derived from PANC-1 or BxPC- 3 cells, and changes in migration and neuronal markers were assessed..

Results: Neuron-derived CM showed no significant impact on PCa cell migration and invasion. Similarly, exposure of neurons to CM from PCa cells did not significantly affect their migration, but slightly increased neurite formation.

Conclusion: This study provides preliminary information on the potential effect of CM on the interaction between PCa cells and neurons. However, the absence of other cell types (such as fibroblasts and Schwann cells) in the study design may explain the lack of expected changes. Therefore, different culture models and further research are needed to investigate the role of cells and factors that may contribute to cancer-neuron interactions.

Keywords: Pancreatic cancer, neurons, conditoned media, cell migration, invasion

ÖZ

Amaç: Pankreas kanseri (PKa), sinirlerde belirgin patolojik değişikliklerle karakterize, en ölümcül kanserlerden biridir. Kanser hücreleri ve sinirler arasındaki çift yönlü etkileşimler sonucu PKa hücrelerinin sinirleri istila ettiği bilinmektedir. Nöral invazyon olarak adlandırılan bu durum, hastalarda şiddetli ağrı ve kısa sağkalım süreleriyle ilişkilidir. Sinirler ve kanser hücreleri arasındaki ilişkinin anlaşılmasına yönelik bazı çalışmalar bulunmakla birlikte, özellikle bu kapsamdaki hücre kültürü çalışmaları oldukça sınırlıdır. Bu nedenle, bu çalışmada, nöronlardan ve PKa hücrelerinden salınan faktörlerin her bir hücre tipinin davranışları üzerindeki etkisini araştırılmıştır.

Yöntem: SH-SY5Y hücreleri nöronlara farklılaştırıldı ve farklılaşma etkinliği immünofloresan boyama ve Western blot ile doğrulandı. PANC-1 ve BxPC-3 kanser hücreleri nöronlardan elde edilen koşullu besiyerine (CM) maruz bırakıldıktan sonra migrasyon ve invazyon yeteneklerindeki değişiklikler sırasıyla yara iyileşmesi ve matrijel invazyon deneyi ile değerlendirildi. Benzer şekilde, nöronlar PANC-1 veya BxPC-3 hücrelerinden elde edilen besiyerine maruz bırakıldı ve nöronların migrasyon ve nöronal belirteçlerdeki değişiklikler değerlendirildi.

Bulgular: Nöronlardan toplanan besiyerinin, PKa hücrelerinin migrasyon ve invazyonu üzerinde anlamlı bir etki göstermediği görüldü. Benzer şekilde, PKa hücrelerine ait besiyerinin nöronlara uygulanmasının, nöronların migrasyonunu anlamlı şekilde etkilemediği, ancak nörit oluşumunu arttırdığı bulundu.

Sonuç: Nöronlardan toplanan besiyerinin, PKa hücrelerinin migrasyon ve invazyonu üzerinde anlamlı bir etki göstermediği görüldü. Benzer şekilde, PKa hücrelerine ait besiyerinin nöronlara uygulanmasının, nöronların migrasyonunu anlamlı şekilde etkilemediği, ancak nörit oluşumunu arttırdığı bulundu.

Anahtar Kelimeler: Pankreas kanseri, nöron, koşullu besiyeri, hücre migrasyonu, invazyon

***Corresponding author/İletişim kurulacak yazar:** Didem Karakas; Acibadem Mehmet Ali Aydinlar University, Graduate School of Health, Medical Biotechnology, Kayisdagi Cad. No:32, 34752, Istanbul, Türkiye
Phone/Telefon: +90 (216) 500 43 07, **e-mail/e-posta:** didem.zeybek@acibadem.edu.tr
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Introduction

Pancreatic cancer (PCa) is one of the most lethal and aggressive cancer types among all major cancers.[1] The close relationship between cancer cells and nerves is recognized as one of the main factors responsible for its aggressive nature. This vicious communication results in neuropathic alterations, including increased nerve density (neural sprouting), nerve size (neural hypertrophy), infiltration of immune cells (neuritis), and invasion of cancer cells (neural invasion).[2]

The invasion of cancer cells into nerves has been demonstrated in many cancer types, such as pancreatic,[3,4] prostate,[5] gastric,[6,7] head and neck cancers.[8,9] Cancer cells use the nerves as an alternative route for metastasis since the nerves provide a less chaotic and stressful environment compared to blood circulation. Thus, the invasion of nerves by cancer cells is closely associated with aggressive tumor growth and metastasis.[10,11] Besides, the interaction of cancer cells with nerves leads to increased pain. The nerve-rich anatomical features of the pancreas facilitate nerve-cancer interaction, making neural invasion a primary cause of PCa-related pain. Furthermore, the number and size of the nerves around tumor tissues are associated with poor overall survival in PCa patients.[12]

Despite the increasing number of studies highlighting the importance of the reciprocal interaction between nerves and cancer cells, most studies focus on only one direction of this interaction, and the mechanisms regulating this interaction remain still unclear. Using neurons in a culture environment is challenging because adult neurons are post-mitotically arrested cells. Using dorsal root ganglion (DRG)-derived mouse neurons is one way to obtain neurons; however, ethical considerations and differences between species (i.e, mouse neurons-human cancer cells) reduce their potential for use in cell culture studies. An alternative approach, the differentiation of neuroblastoma cells into neurons, is commonly preferred due to the high reproducibility of cell lines and the absence of ethical concerns.

Here, we investigated the effect of soluble factors derived from neurons and PCa cells on the migration and invasion abilities of these cells. Briefly, neurons were differentiated from neuroblastoma cells, and the efficacy of differentiation was confirmed by immunofluorescence staining and Western blot. Then, conditioned media (CM) were collected from PCa cells and neurons, and applied to the culture media of each cell type. Following 24 or 48 hours of incubation, changes in cell behaviors, such as invasion and migration, were evaluated. In summary, no significant changes were detected in either cell type after CM exposure. One possible reason for this outcome is that the factors in the CM may be too diluted to induce observable changes. Another possibility is that other cell types, such as pancreatic stellate cells (PSCs) and Schwann cells, may need to be present in the tumor microenvironment (TME) and interact with cancer cells to induce the expected changes. In conclusion, further investigation is needed to elucidate CM-mediated bidirectional interactions between neurons and cancer cells.

Methods

Cell lines and culture conditions

SH-SY5Y human neuroblastoma cell line was purchased from the American Type Culture Collection (ATCC) (Manassas, VA, USA). Human PCa cell lines, PANC-1 and BxPC-3, were kindly gifted by Dr. Mumin Alper Erdogan (Izmir Katip Celebi University, Turkey) and Dr. Konstantinos Dimas (University of Thessaly, Greece), respectively. Cells were cultured in Dulbecco's modified Eagle's medium (DMEM): Ham's F12 supplemented with 10% fetal bovine serum (FBS) and 100-U/ml penicillin-streptomycin solution. All cultured cells were maintained at 37°C with 5% CO2 and 95% air and screened for mycoplasma by PCR.

Neuronal differentiation and characterization

SH-SY5Y cells were treated with all-trans-retinoic acid (ATRA) to induce neuronal differentiation. For this purpose, the cells were cultured in T75 cell culture flasks until they reached 70-80% confluency. The medium was then replaced with differentiation medium* and the cells were cultured for 6 days by refreshing the media every 3 days.

The differentiation efficiency of the cells was assessed by evaluating the cells for the presence of neurite structures via phase-contast microscopy and immunofluorescence staining for β-III tubulin. Additionally, changes in the expression of neuronal markers such as neuron-specific enolase (NSE), neuronal nuclear protein (NeuN), and Nestin were assessed via Western blot.

**Differentiation medium composition; DMEM:F12 medium-containing 10 µM ATRA, supplemented with 1% FBS, 1X B27 supplement, and 1% P/S.*

Conditioned media (CM) collection

To evaluate the effect of soluble factors released from both PCa cells and neurons on cell behaviors, CM were collected from cancer cells and neurons. PANC-1 or BxPC-3 cells were cultured in T75 flasks until they reached 80% confluency. Then, the media were replaced with FBS-free medium, and the cells were incubated for an additional 24 hours. Following the incubation period, the media were collected and centrifuged at 2000 rpm for 30 minutes at

+4°C to remove cellular debris. The supernatant was carefully transferred to fresh tubes without disturbing the pellet, and the tubes were kept at +4°C until use.

For collection of neuron-conditioned media, SH-SY5Y cells were first differentiated into neurons as explained above. The media were then replaced with FBS-free media (without ATRA). After 24 hours of incubation with FBS-free media, conditioned media were collected via centrifugation. All conditioned media were freshly prepared and immediately used for the experiments avoiding freeze-thaw cycles.

Wound healing assay

To measure changes in cell motility and migration, an in vitro wound healing assay was performed. Briefly, PANC-1 and BxPC-3 cells were seeded into 24-well plates and cultured until they reached ~80% confluency. Similarly, SH-SY5Y cells were seeded into 24-well plates and differentiated into neurons as mentioned above. Wounds were then carefully made on the cell layer using 200 µl sterile pipette tips. Immediately after scratching, the wells were carefully washed with PBS, and the cell culture media were replaced with conditioned media. Wounds were photographed using a phase-contrast microscope (Nikon Instruments Inc., USA) to determine the wound width at 0 hours. Cells were exposed to CM for 48 hours, and wound areas were photographed at 24 and 48 hours. Wound closure was calculated by comparing the wound distances at 0 hours with those taken at 24 and 48 hours using ImageJ software (National Institutes of Health, Bethesda, MD). All experiments were performed at least twice in duplicate.

Transwell invasion assay

PCa cells or neurons were seeded on the top of transwell inserts (8-µm-pore size) coated with Matrigel. The lower chambers of the inserts were filled with 500 µl of 50% CM containing 10% FBS as chemoattractant. After 24 hours, the invading cells were fixed and stained with 0.5% crystal violet prepared in methanol. Cells remaining on the upper side of the membrane were removed by gently wiping with a cotton swab, and the membranes were photographed. The number of invaded cells was quantified by counting at least six fields per membrane using ImageJ software. Results were expressed as the mean number of invaded cells from duplicate measurements.

Immunofluorescence staining

The efficacy of neuronal differentiation was evaluated by immunofluorescence staining. SH-SY5Y cells were seeded onto round coverslips pre-coated with Poly-L-lysine and differentiated into neurons as described above. For the staining procedure, the cells were fixed with 4% paraformaldehyde and permeabilized with 0.1% Triton X-100. Subsequently, the cells were blocked with 10% normal goat serum. Following 24 hours incubation with β-III tubulin antibody (1:200 dilution), a secondary antibody conjugated with FITC was added, and the cells were visualized under a fluorescence microscope. Undifferentiated SH-SY5Y cells were used as a control group for comparison with differentiated cells.

Western blotting

To confirm neuronal differentiation and evaluate the effects of PCa cell-derived CM on the expression of neuronal proteins, Western blot analysis was performed. First, cells were lysed in radioimmunoprecipitation assay (RIPA) buffer containing protease and phosphatase inhibitors. Total protein concentrations were determined using the Pierce BCA protein assay kit (Thermo Scientific, USA). Equal amounts of protein (30 µg) were loaded onto 4-15% gradient SDS-PAGE gels and separated by electrophoresis. Subsequently, the proteins were transferred to polyvinylidene fluoride (PVDF) membranes (Bio-Rad, USA). The membranes were probed with specific primary antibodies against β-III tubulin, NSE, NeuN, and Nestin, followed by horseradish peroxidase (HRP)-conjugated secondary antibodies (Cell Signaling Technology, USA). β-actin was used as the loading control.

Statistical analyses

The data are expressed as the mean ± standard error from at least two independent experiments. Statistical analysis was performed using one way ANOVA to determine statistical significance. P values indicate the probability of the means compared, being equal with *P<0.05, **P<0.01, ***P <0.001, and ****P <0.0001. ANOVA calculations were conducted using GraphPad software (version 10).

Results

Neurons were differentiated from neuroblastoma cells

The increased number and size of nerves in tumor are known to be associated with poor overall survival. As shown in Figure 1A, PDAC patients with high TUB3 expression, a neural marker, have shorter overall survival compared to patients with low TUB3 expression. We therefore aimed to investigate bidirectional interaction between PCa cells and neurons to understand the effect of each cell type on the other.

Briefly, SH-SY5Y neuroblastoma cells were differentiated into neurons via ATRA treatment, as illustrated in Fig. 1B. The efficacy of differentiation was confirmed by morphological evaluation under phase-contrast microscope. While SH-SY5Y neuroblastoma cells typically grow as cluster-like structures without cell extensions, differentiated neurons have small extensions, called axons, indicating they acquired neuronal morphology (Fig. 1C). The presence of β-III tubulin-positive axons was further confirmed by immunofluorescent staining (Fig. 1C). Besides, cells were observed to lose their proliferation ability when they differentiated into neurons. Additionally, the expression of neuron-related proteins, NSE and NeuN, was evaluated by Western blot (Fig. 1D). As shown in the figure, differentiated neurons have higher expression of NSE and NeuN than neuroblastoma cells. Consistently, the expression of the neuroblastoma- specific protein, Nestin, was evaluated. While neuroblastoma cells displayed high expression of Nestin, differentiated neurons did not exhibit Nestin expression (Fig. 1D).

Neuron-derived CM slightly increased cell migration in PANC1 cells but not in BxPC-3 cells

To investigate the effect of neuron-derived factors on the migration and invasion of PCa cells, CM was collected from neurons. PANC-1 and BxPC-3 cells were then

exposed to neuron- derived CM, and changes in their migration ability were assessed by wound healing assay.

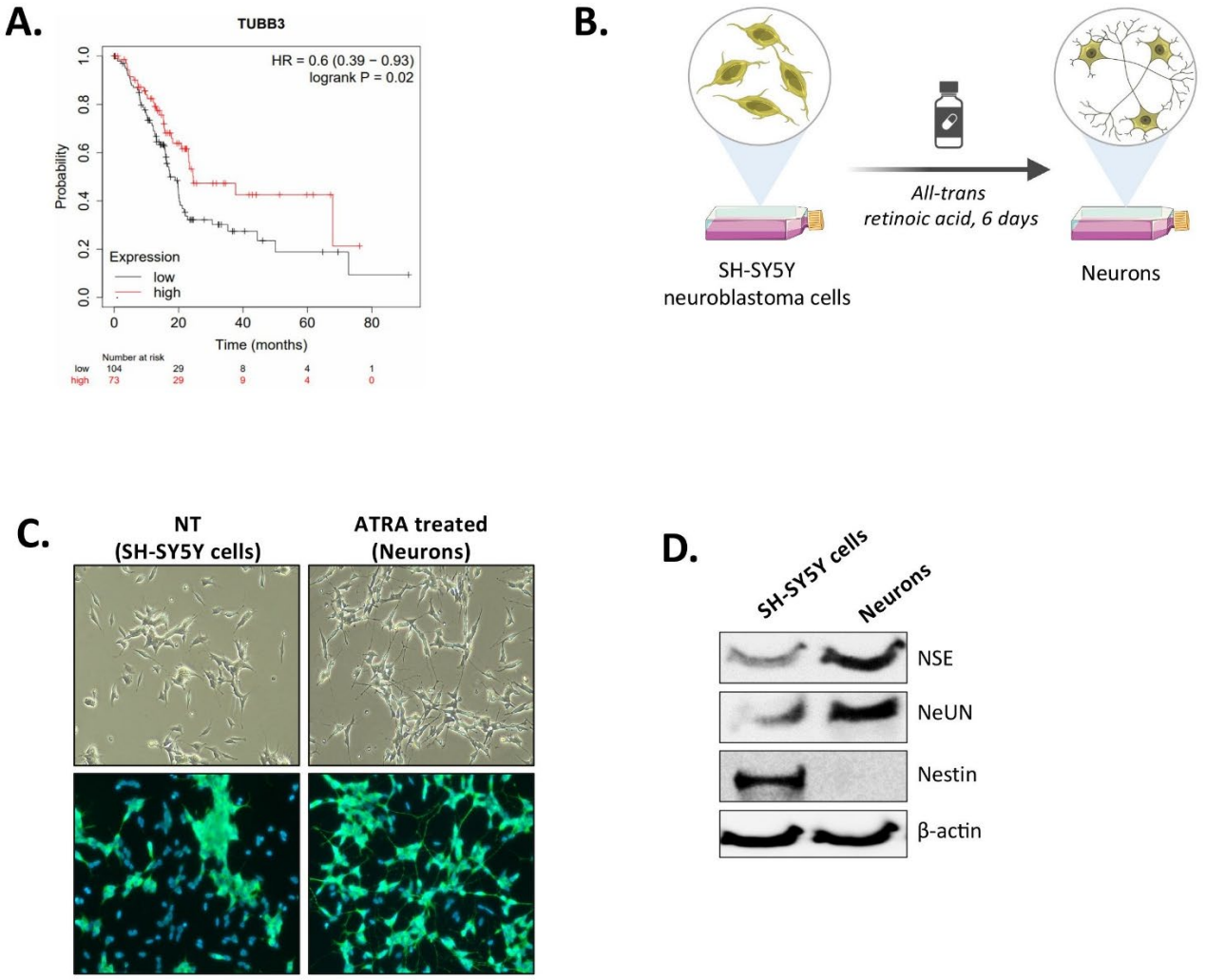

Figure 1. Neuronal differentiation and characterization. (A) The high levels of neuronal marker, TUB1, is associated with shorter overall survival in PCa patients. Kaplan-Meier survival analysis of the TCGA PCa database showed the overall survival rates of PCa patients with high and low expression of TUB1. (B) Schematic illustration for differentiation of SH- SY5Y neuroblastoma cells into neurons. (C) Phase-contrast images and β-III tubulin staining for confirmation of neuronal differentiation. The phase image shows presence of neuronal extensions, neurites, in neurons. Similarly, β-III tubulin positive neurites were observed in neurons. (D) Western blot analysis for neuron-specific proteins. ⍰-actin was used as loading control. ATRA; All-trans retinoic acid, NSE; neuron specific enolase, NeuN; neuronal nuclear protein.

The results showed that neuron-derived CM slightly increased the migration of PANC-1 cells but did not significantly affect the migration of BxPC-3 cells (Fig. 2A). Besides, 24 hours of incubation of PCa cells with neuron-derived CM did not alter the invasion capability of either cell type (Fig. 2B, C).

PCa cell-derived CM did not alter migration and invasion of neurons but slightly increased neurite formation

In the next step, to evaluate the effect of PCa cell-released factors on neurons, we collected CM from both PANC-1 and BxPC-3 cells. We then applied CM from each cell type to neurons, and assessed changes in migration and neurite formation. As shown in Fig. 3A, neither PANC-1 CM nor BxPC-3 CM resulted a change in the migration ability of neurons. Surprisingly, both PANC- 1 and BxPC-3 CM caused a slight induction in the formation of new neuronal extensions from neurons, known as neurites (Fig. 3B, C).

Discussion

PCa is one the most lethal cancers among among major solid tumors, with a 5-year survival rate barely above 10%.[1] Survival after diagnosis is around 4-6 months for the majority of patients.[13] Patients are generally diagnosed in the middle to late stage of disease during clinical consultation, as PCa tumors often lack specific symptoms.[14] Thus, the majority of patients are diagnosed at an advanced stage with metastatic tumors, leading to a survival rate of approximately 3%.[15] The unique TME of PCa is responsible for the aggressive and lethal nature of this cancer. In addition to cancer cells, the TME consist of various components such as fibroblasts, immune cells,

adipocytes, blood and lymphatic vessels and the extracellular matrix. There is a dynamic and reciprocal relationship between cancer cells and the TME, which contributes to all hallmarks of cancer.[16]

In addition to blood and lymph vessels, the presence of nerves within tumors has been observed in many cancer types, particularly in PCa.[12,17] The pancreas is a well-innervated organ by autonomic nervous system, and during tumorigenesis this nerve-rich nature facilitates nerve-cancer interactions. The close interaction between nerves and cancer cells is associated with poorer overall survival in PCa patients, making the presence of nerves in PCa tumors an independent prognostic factor.[4] In a study conducted in 2021, PCa patients were categorized into nerve-positive (+) and nerve-negative (-) groups based on the presence or absence of nerves in their tumors. The results revealed that the survival rate of nerve (+) patients was significantly lower compared to nerve (-) patients. Additionally, nerve size was compared between normal pancreas and cancer tissues, showing a significant increase in nerve size in cancer tissues. Furthermore, patients with tumors containing larger nerves had shorter survival rates than those with relatively smaller nerves.[12]

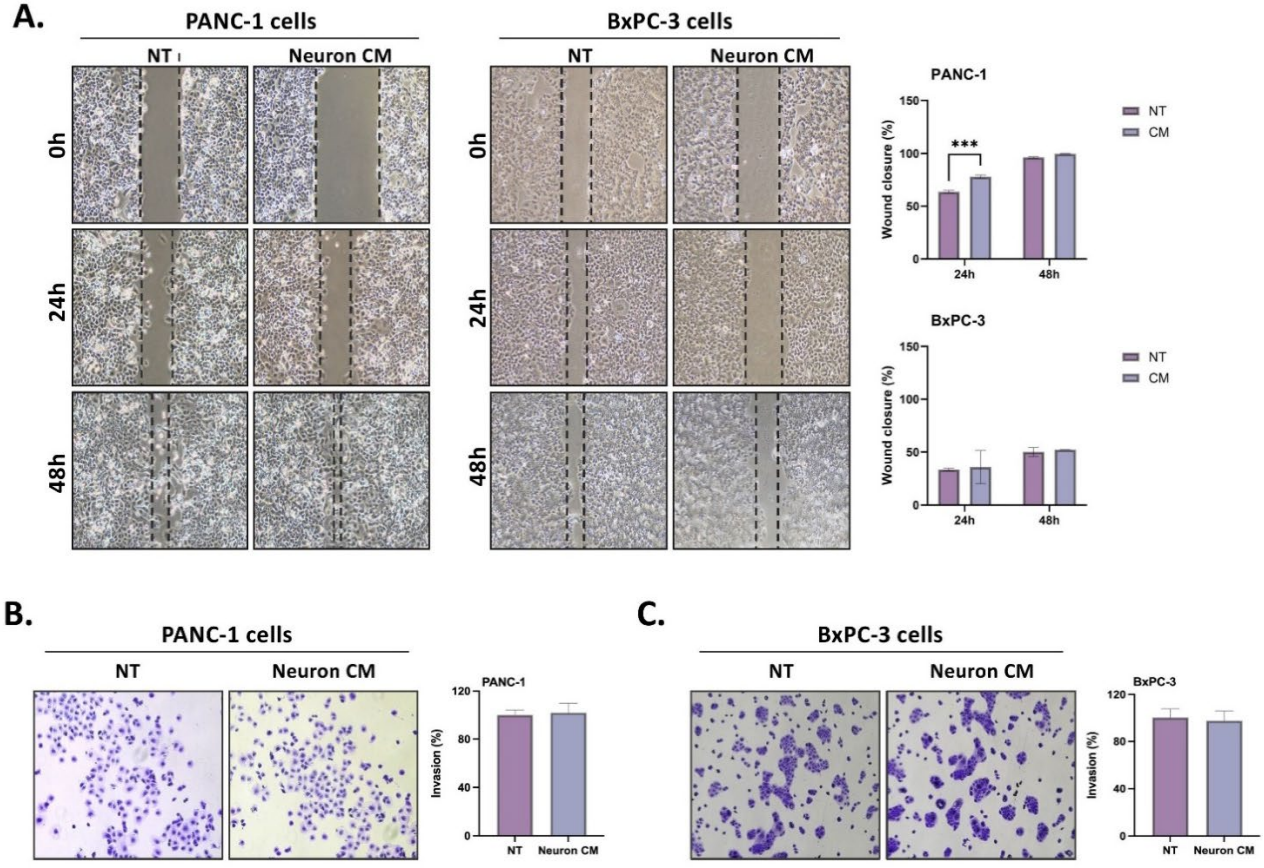

Figure 2. Neuron-derived conditioned media (CM) did not significantly affect migration and invasion of PCa cells. (A) Two different PCa cells, PANC-1 and BxPC-3, were exposed to CM-derived from neurons and the migration of cells were assessed by wound healing assay. Representative images of migrated cells and the quantified data after 24 and 48 hours of CM exposure. (B, C) Changes in the invasion ability of PANC-1 and BxPC-3 cells after 48 hours CM exposure.

In addition to the presence of nerves within the tumor, cancer cells are known to invade nerves, a phenomenon referred as neural invasion, which is observed in 80-100% of PCa cases. Neural invasion is considered an alternative route for metastatis and is correlated with increased pain and poor prognosis.[2,3] So far, several factors involved in the vicious interactions between nerves and cancer cells have been identified. Nerve-derived molecules, such as neurotransmitters and chemokines, have been reported to promote aggressive characteristics of PCa, including proliferation, migration, and invasion. A study performed in mouse models of PCa showed

that neuron-derived chemokines, CXCL10 and CCL21, increased the migration of tumor cells toward neurons.[18] Moreover, various neurotransmitters, including norepinephrine, serotonin, GABA, substance P, and glutamate, released by tumor-infiltrating nerves, have been shown to induce the proliferation, migration, and invasion of PCa cells.[19-24] PCa cells, on the other hand, secrete neuromodulatory molecules, such as neural growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF), to protomote neural remodeling and facilitate cancer-nerve interactions.[2]

Despite recent studies focusing on understanding the molecular mechanisms underlying PCa cell-nerve interactions, there are still missing points that need to be addressed. Therefore, the use of cell culture models to mimic cancer-nerve interaction is a need for conducting functional and molecular analyses. Here, we therefore focused on the bidirectional interaction between PCa

cells and neurons, and evaluated the effects of this interaction on the behavior of both cell types. For this purpose, neurons were differentiated from SH-SY5Y neuroblastoma cells, and the success of differentiation was confirmed by immunofluorescent staining and Western blot.

In the literature, mature neurons are known to have β-III tubulin positive axons.[25] Consistently, we observed the formation of new extensions from cell bodies, termed neurite formation (or axonogenesis), using β-III tubulin staining. Additionally, the expression of neuron-specific markers, neuron specific enolase (NSE) and neuronal nuclear protein (NeuN),[26,27] was confirmed by Western blot analysis. Furthermore, Nestin expression is known to downregulated during neuronal differentiation.[28] Consistent with this information, we observed a dramatic decrease in Nestin expression in the differentiated cells.

Then, we collected CM from both PCa cells and neurons and applied CM to the culture media of each respective cell type. After 24 or 48 hours of incubation, we evaluated changes in cell behavior, such as invasion and migration. Although some studies have examined the effect of CM on PCa cells, most research focuses on only one direction of this bidirectional interaction, typically focusing on changes in PCa cells.[29-31] In contrast, our study aimed to obtain preliminary data on the effects of factors released from one cell type on the other.

As a result of our CM experiments, no significant changes were observed in either cell type after CM exposure. There might be some reasons for this outcome. Firstly, the factors in CM may be too diluted to induce observable changes. To address this, we plan to reproduce our data using more concentrated CM, obtained through specific filters and ultracentrifugation. Secondly, the presence of other cell types in the TME, such as PSCs and Schwann cells, might be required to stimulate changes through interaction with the cells. PSCs are one of the most common cell types in the PCa TME and play critical roles in the aggressive nature of PCa.[32] Although the effect of PSCs on PCa cells are quite well-documented, their impact -either directly or indirectly- on nerve-cancer interactions remains unknown. Therefore, incorporating these cells into cell culture experiments may more accurately mimic the TME.

Similar to PSCs, Schwann cells are key components of peripheral nerves. They play critical roles in the development, maintenance, function, and regeneration of peripheral nerves. In addition to their physiological functions, Schwann cells are known to have critical roles in neuron-cancer interactions. Recent studies indicate that Schwann cells serve as the first contact point in the neural invasion process. These cells have been shown to recruit and guide cancer cells toward nerves.[33] Considering their role in neural invasion, incorporating Schwann cells into culture experiments, alongside neurons, may provide additional insights.

In summary, our results provide preliminary data for the effect of CM derived from PCa cells and neurons on the migration of both cell types. As we discussed above, further modifications and optimizations may be required to obtain more significant results. Therefore, additional investigation is needed to fully elucidate the bidirectional interaction between neurons and cancer cells.

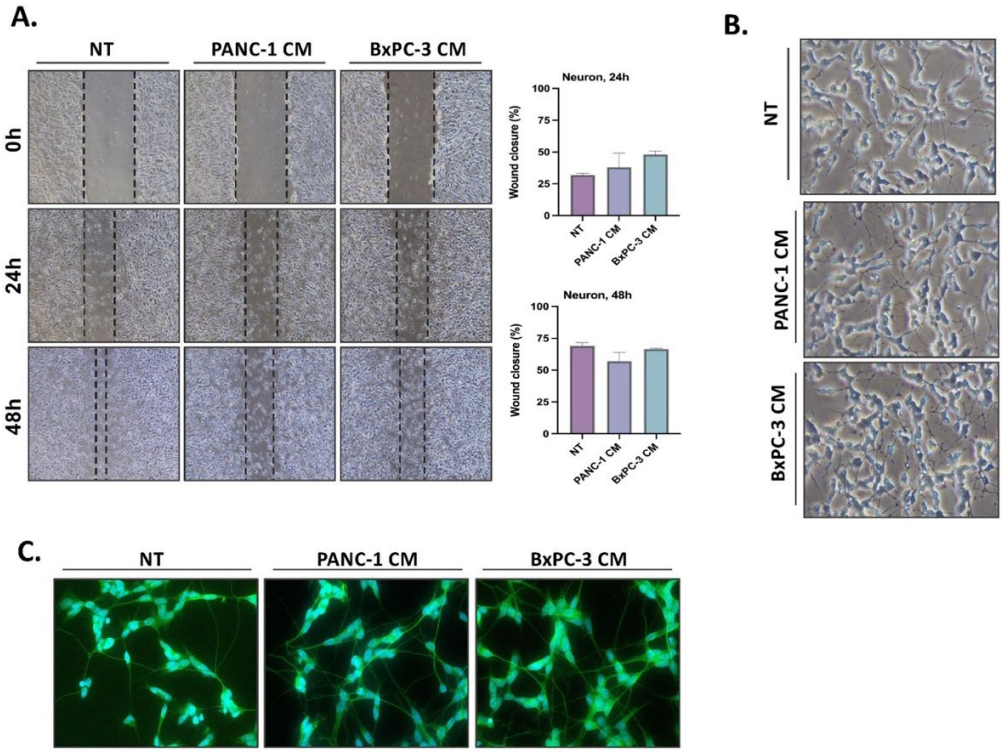

Figure 3. CM derived from PCa cells did not change migration, but induced neurite formation in neurons. (A) Neurons were treated with CM-derived from either PANC-1 and BxPC-3 cells and changes in their migration ability were evaluated. (B) The changes in the cellular extensions, neurites, axons, were evaluated by phase-contrast microscope. (C) The effect of PCa CM on neurite formation were also evaluated by immunofluorescent staining with β-III tubulin antibody.

Ethical Approval

The study does not require ethics committee approval, since no animal or human material were used in the study.

Conflict of Interest

The author declares no conflicts interests.

Author Contributions

DK: Concept-Design; Data Collection and/or Processing; Analysis and/or Interpretation; Literature Review; Writer; Critical Review

Financial Support

None

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17-48. doi:10.3322/caac.21763.
2. Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. *Nat Rev Gastroenterol Hepatol*. 2015;2(11):649-659. doi:10.1038/nrgastro.2015.166.
3. Bapat AA, Hostetter G, Von Hoff DD, Han H. Perineural invasion and associated pain in pancreatic cancer. *Nat Rev Cancer.* 2011;11:695–707. doi:10.1038/nrc3131
4. Schorn S, Demir IE, Haller B, et al. The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma-A systematic review and meta-analysis. *Surg Oncol.* 2017;26:105-115. doi:10.1016/j.suronc.2017.01.007
5. Lubig S, Thiesler T, Müller S, Vorreuther R, Leipner N, Kristiansen G. Quantitative perineural invasion is a prognostic marker in prostate cancer. *Pathology.* 2018;50:298-304. doi:10.1016/j.pathol.2017.09.013
6. Aurello P, Berardi G, Tierno SM, et al. Influence of perineural invasion in predicting overall survival and disease-free survival in patients with locally advanced gastric cancer. *Am J Surg.* 2017;213:748-753. doi:10.1016/j.amjsurg.2016.05.022
7. España-Ferrufino A, Lino-Silva LS, Salcedo-Hernández RA. Extramural perineural invasion in pT3 and pT4 gastric carcinomas. *J Pathol Transl Med.* 2018;52:79-84. doi:10.4132/jptm.2017.11.01
8. Cracchiolo JR, Xu B, Migliacci JC, et al. Patterns of recurrence in oral tongue cancer with perineural invasion. *Head Neck.* 2018;40:1287-1295. doi: 10.1002/hed.25110
9. Schmitd LB, Scanlon CS, D'Silva NJ. Perineural invasion in head and neck cancer. *J Dent Res.* 2018;97:742-750. doi: 10.1177/0022034518756297
10. Jobling P, Pundavela J, Oliveira SM, et al. Nerve-Cancer Cell Cross-talk: A Novel Promoter of Tumor Progression. *Cancer Res.* 2015;75(9):1777-1781. doi:10.1158/0008-5472.CAN-14-3180
11. Dwivedi S, Krishnan A. Neural invasion: a scenic trail for the nervous tumor and hidden therapeutic opportunity. *Am J Cancer Res.* 2020;10(8):2258-2270.
12. Ferdoushi A, Griffin N, Marsland M, et al. Tumor innervation and clinical outcome in pancreatic cancer. *Sci Rep.* 2021;11(1):7390. doi:10.1038/s41598-021-86831-w
13. Chari ST, Kelly K, Hollingsworth MA, et al. Early detection of sporadic pancreatic cancer: summative review. *Pancreas.* 2015;44(5):693-712. doi:10.1097/MPA.0000000000000368
14. Liu Z, Gou A, Wu X. Liver metastasis of pancreatic cancer: the new choice at the crossroads. *Hepatobiliary Surg Nutr.* 2023;12(1):88-91. doi:10.21037/hbsn-22-489
15. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi:10.3322/caac.21442
16. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell.* 2012;21(3):309-322. doi:10.1016/j.ccr.2012.02.022
17. Schmitd LB, Perez-Pacheco C, D'Silva NJ. Nerve density in cancer: Less is better. *FASEB Bioadv.* 2021;3(10):773-786. doi:10.1096/fba.2021-00046
18. Hirth M, Gandla J, Höper C, et al. CXCL10 and CCL21 Promote Migration of Pancreatic Cancer Cells Toward Sensory Neurons and Neural Remodeling in Tumors in Mice, Associated With Pain in Patients. *Gastroenterology.* 2020;159(2):665-681. doi:10.1053/j.gastro.2020.04.037
19. Huang XY, Wang HC, Yuan Z, Huang J, Zheng Q. Norepinephrine stimulates pancreatic cancer cell proliferation, migration and invasion via beta-adrenergic receptor-dependent activation of P38/MAPK pathway. *Hepatogastroenterology.* 2012;59:889-893. doi:10.5754/hge11476
20. Qian W, Lv S, Li J, et al. Norepinephrine enhances cell viability and invasion, and inhibits apoptosis of pancreatic cancer cells in a Notch1 dependent manner. *Oncol Rep.* 2018;40:3015-3023. doi:10.3892/or.2018.6696
21. Jiang SH, Li J, Dong FY, et al. Increased serotonin signaling contributes to the warburg effect in pancreatic tumor cells under metabolic stress and promotes growth of pancreatic tumors in mice. *Gastroenterology.* 2017;153:277-291. doi:10.1053/j.gastro.2017.03.008
22. Takehara A, Hosokawa M, Eguchi H, et al. Gamma-aminobutyric acid (GABA) stimulates pancreatic cancer growth through overexpressing GABAA receptor pi subunit. *Cancer Res.* 2007;67:9704-9712. doi:10.1158/0008-5472.CAN-07-2099
23. Munoz M, Covenas R. Involvement of substance P and the NK-1 receptor in pancreatic cancer. *World J Gastroenterol.* 2014;20:2321-2334. doi:10.3748/wjg.v20.i9.2321
24. Herner A, Sauliunaite D, Michalski CW, et al. Glutamate increases pancreatic cancer cell invasion and migration via AMPA receptor activation and Kras-MAPK signaling. *Int J Cancer.* 2011;129 2349- 2359. doi:10.1002/ijc.25898
25. Moskowitz PF, Smith R, Pickett J, Frankfurter A, Oblinger MM. Expression of the class III beta- tubulin gene during axonal regeneration of rat dorsal root ganglion neurons. *J Neurosci Res.* 1993;34(1):129-134.
26. Isgrò MA, Bottoni P, Scatena R. Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. *Adv Exp Med Biol.* 2015;867:125-143. doi:10.1007/978-94-017-7215-0_9
27. Gusel'nikova VV, Korzhevskiy DE. NeuN As a Neuronal Nuclear Antigen and Neuron Differentiation Marker. *Acta Naturae.* 2015;7(2):42-47.
28. Dahlstrand J, Lardelli M, Lendahl U. Nestin mRNA expression correlates with the central nervous system progenitor cell state in many, but not all, regions of developing central nervous system. *Brain Res Dev Brain Res.* 1995;84:109–29.
29. Banh RS, Biancur DE, Yamamoto K, et al. Neurons Release Serine to Support mRNA Translation in Pancreatic Cancer. *Cell.* 2020;183(5):1202-1218. doi:10.1016/j.cell.2020.10.016

30. Hung YH, Wang HC, Hsu SH, et al. Neuron-derived neurotensin promotes pancreatic cancer invasiveness and gemcitabine resistance via the NTSR1/Akt pathway. *Am J Cancer Res.* 2024;14(2):448-466. doi:10.62347/UAKN9541
31. Göhrig A, Hilfenhaus G, Rosseck F, et al. Placental growth factor promotes neural invasion and predicts disease prognosis in resectable pancreatic cancer. *J Exp Clin Cancer Res.* 2024;43(1):153. doi:10.1186/s13046-024-03066-z
32. Wang Z, He R, Dong S, Zhou W. Pancreatic stellate cells in pancreatic cancer: as potential targets for future therapy. *Front Oncol.* 2023;13:1185093. doi:10.3389/fonc.2023.1185093
33. Azam SH, Pecot CV. Cancer's got nerve: Schwann cells drive perineural invasion. *J Clin Invest.* 2016;126(4):1242-1244. doi:10.1172/JCI86801

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Research Article | Araştırma Makalesi

GLOBAL RESEARCH TRENDS ON TNF-ALPHA POLYMORPHISMS IN PSORIASIS DISEASE'S BETWEEN 1975 AND 2024

1975 ILE 2024 ARASINDA PSORIASIS HASTALIĞINDA TNF-ALFA POLIMORFIZMLERI ÜZERINE GLOBAL ARAŞTIRMA TRENDLERI

Yasemin ADALI[1,2], Veli Kaan AYDIN[1], Yasemin BERBEROĞLU[1,*], Aylin KÖSELER[1]

[1]Pamukkale University Faculty of Medicine, Department of Biophysics, Denizli, Turkiye. [2]Queen's University Belfast, Centre for Public Health, Faculty of Medicine, Dentistry and Biomedical Sciences, Belfast, United Kingdom (Visiting Researcher)

ABSTRACT

Objective: The immune system is the source of the inflammatory, persistent skin condition known as psoriasis. Despite recent major advancements in the pathology of psoriasis, no bibliometric investigation associating TNF-Alpha polymorphisms to psoriasis has been conducted. The objective of this study was to better understand the development trend and boundaries of the area by using bibliometrics to assess the focal point and research overview of TNF-Alpha Polymorphisms and Psoriasis.

Methods: The Web of Science database was searched on March 26, 2024, with the terms "resilienc*" in the title and "tumo$r necrosis factor* or TNF or tumo$r necrosis factor*" and "polymorphism* or variant* or variation* or SNP*" and "psoriasis OR psoriatic*" in the topic. There were 400 documents in *Web of Science Core Collection* and all documents extracted without time frame restrictions. Visualizations created by web-r.org were made using web-based R analytics developed with bibliometric analysis.

Results: Since 2012, research on the relationship between psoriasis and TNF-Alpha polymorphisms has increased significantly. The research that received the most attention was published in Dermatology and the British Journal, with Nair RP receiving the most citations. China, the United States, and Italy were the most productive nations. "Association," "Rheumatoid Arthritis," and "Susceptibility" appeared most frequently in the KeyWordPlus analysis.

Conclusion: Future researchers may find the results of this study useful in their work, and it may present new avenues for investigating TNF-alpha polymorphisms and psoriasis.

Keywords: TNF-alpha polymorphism, psoriasis, bibliometric analysis, biblioshiny, R study

ÖZ

Amaç: Bağışıklık sistemi, sedef hastalığı olarak bilinen iltihaplı, kalıcı cilt rahatsızlığının kaynağıdır. Sedef hastalığının patolojisinde son zamanlardaki önemli gelişmelere rağmen, TNF-Alfa polimorfizmlerini sedef hastalığıyla ilişkilendiren hiçbir bibliyometrik araştırma yürütülmemiştir. Bu çalışmanın amacı, TNF-Alfa Polimorfizmleri ve Psoriasis'in odak noktasını ve araştırma genel bakışını değerlendirmek için bibliyometrik kullanarak alanın gelişim eğilimini ve sınırlarını daha iyi anlamaktır.

Yöntem: Web of Science veritabanı 26 Mart 2024'te, başlıkta "resilienc*" terimleri ve konu başlığında "tumor necrosis factor* or TNF or tumo$r necrosis factor*" ve "polymorphism* or variant* or vary* or SNP*" ve "psoriasis OR psoriatic*" terimleriyle arandı. Web of Science Core Collection'da 400 belge vardı ve tüm belgeler zaman çerçevesi kısıtlaması olmadan çıkarıldı. Web-r.org tarafından oluşturulan görselleştirmeler bibliyometrik analiziyle geliştirilen web tabanlı R analizi ile yapıldı.

Bulgular: 2012'den bu yana, sedef hastalığı ve TNF-Alfa polimorfizmleri arasındaki ilişki üzerine yapılan araştırmalar önemli ölçüde arttı. En fazla ilgi gören araştırma Dermatology ve British Journal'da yayınlandı ve Nair RP en fazla atıfı aldı. En üretken ülkeler Çin, Amerika Birleşik Devletleri ve İtalya oldu. "Association", "Romatoid Arthritis" ve "Susceptibility" KeyWordPlus analizinde en sık görülen ifadelerdir.

Sonuç: Gelecekteki araştırmacılar bu çalışmanın sonuçlarını çalışmalarında faydalı bulabilir ve TNF-alfa polimorfizmleri ve sedef hastalığını araştırmak için yeni yollar sunabilir.

Anahtar Kelimeler: : TNF-alfa polimorfizmi, sedef hastalığı, bibliyometrik analiz, biblioshiny, R study

***Corresponding author/İletişim kurulacak yazar:** Yasemin BERBEROĞLU; Pamukkale University Faculty of Medicine, Department of Biophysics, Denizli, Turkiye.
Phone/Telefon: +90 (505) 013 37 73 **e-mail/e-posta:** yasemins@pau.edu.tr
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Introduction

Psoriasis is a chronic, recurrent inflammatory skin condition. It is characterized by the development of red, scaly skin lesions as a result of hyper-proliferation of epidermal keratinocytes, which has a significant negative impact on the quality of life of patients.[1] Tumor necrosis factor-Alpha (TNF-α) is a key proinflammatory cytokine that promotes inflammatory pathways that exacerbate hallmark symptoms of psoriasis, such as redness and lesions. TNF-α triggers proinflammatory response and apoptosis by binding to TNF receptor 1 (TNFR1) and anti-inflammatory and cell survival pathways by binding to TNF receptor 2 (TNFR2). Overproduction of TNF-α plays a key role in the pathogenesis of autoimmune diseases such as psoriasis.[2] Also, TNF-α inhibitors are first-generation biologics that have been used for many years and are used to evaluate drug efficacy in psoriasis clinical trials.[3] Previous preclinical studies have demonstrated a considerable elevation of serum TNF-α levels in psoriasis patients.[4] Thus, functional TNF-α polymorphisms may impact an individual's susceptibility to psoriasis in addition to potentially influencing TNF-α's normal biological function.[4] The impact of polymorphisms in genes related to the disease's pathogenic environment, metabolism, or mechanism of action on the effectiveness of these medications has been evaluated via precision medicine research.[5]

British intelligence scientist Alan Pritchard initially suggested bibliometrics in 1969.[6] A common research method that makes use of quantitative tools to evaluate the impact of research and analyze vast amounts of scientific data is bibliometric analysis. It can be useful in attempting to comprehend scholarly and intellectual trends and provide insight into newly emerging fields.[7]

As a result of increased publication volume and the accessibility of computer analysis software, bibliometrics research efficiency and accuracy have recently increased. Because software visualization makes the results easier to understand, bibliometrics is a popular research method that has been widely used in the medical field.

The relationship between TNF-α Polymorphisms and Psoriasis has not been well studied bibliometrically. The aim of the study was to identify significant contributions and current research status, as well as to anticipate future development prospects and research trends on TNF-α Polymorphisms and Psoriasis.

Methods

Ethics statement

This study does not involve human participants, and hence, ethical approval was not required.

Study design

Bibliometric analysis is being used in this descriptive study.

Search strategy

The data collected from the Web of Science Core Collection (WoSCC) and advance search was conducted using keywords: “tumor necrosis factor* or TNF or tumor necrosis factor*” and “polymorphism* or variant* or variation* or SNP*” and “psoriasis OR psoriatic*”, Later, the results were refined in the WOS database according to index for Science Citation Index Expanded and Emerging Sources Citation Index publication type which are original articles only. The search was set to include articles published between 1975 to 2024. As a result of these inclusion criteria, 400 documents were presented in total without any timeframe restriction, language or WoSCC category limitation. All bibliographic data were exported from the WoS database and interpreted using analytical bibliometric methods.

Data analysis

A summary of the data analysis results was provided, along with visualizations. The open-source R package Bibliometrix was used to perform bibliometric analyses. Data matrices for publication trends, journal rankings, authorship analysis, the most productive countries, author collaboration patterns, Trend Topics, KeyWords Plus analysis, and the most cited articles were created using bibliometrix (biblioshiny).[6] Additionally, the publication was subjected to a quantitative analysis using Microsoft Office Excel 2019.

Results

An overview of the bibliographic data

Table 1 summarizes the statistics from the bibliography. Across 400 documents, it is observed that there are 30.36 citations on average per document, and 2.65 citations annually. This suggests the impact and well-citation of the literature on this subject are noteworthy. Additionally, international co-authorship appears in 18.75% of the studies.

Table 1. Summary of bibliographic statistics related with psoriasis and TNF-α polymorphisms (n=400)

Description	Results
Main information about data	
Timespan	1993-2024
Sources (Journals. Books. etc.)	195
Number of documents	400
Annual growth rate (%)	4.57
Document average age	9.35
Average citations per doc	30.36
Average citation per year	2.65
References	11251
Document contents	
Keywords plus term	1109
Author's keywords	858
Authors	
Number of authors	2525
Number of authors of single-authored docs	2
Authors collaboration	
Number of single-authored docs	2
Co-Authors per Doc	7.64
International co-authorships (%)	18.75
Document types	
Article	397
Article; early access	2
Article; proceedings paper	1

Annual scientific production

The annual scientific output of psoriasis and TNF-α polymorphisms published papers included in the WoSCC database from 1993 to 2024 is shown in Table 2. Since 1993, the number of scientific studies on resilience produced annually has been in the single digits until 2006. Between 2012 and 2023, over 20 relevant papers were published, indicating a step increase in the annual production of scientific research since 2012. In 2021 (n = 29) and 2023 (n = 29), the greatest number published in a single year happened.

While the total number of citations has generally increased over time, a significant peak occurred in 2009 and then a decline was observed. This suggests that while research activity in the field has increased, the average impact of individual studies may have decreased. (Table 2 and Figure 1)

Table 2. Annual scientific output associated with psoriasis and TNF-α polymorphisms and average number of article citations per year (n=400)

Year	Number of articles	Total citations	Mean total citations per article	Mean total citations per year	Citable years	Citable years
1993	2	101	50.5	1.58	32	32
1997	2	222	111	3.96	28	28
1998	1	36	36	1.33	27	27
1999	3	159	53	2.04	26	26
2000	4	253	63.25	2.53	25	25
2001	6	372	62	2.58	24	24
2002	7	360.99	51.57	2.24	23	23
2003	9	383.04	42.56	1.93	22	22
2004	1	17	17	0.81	21	21
2005	2	166	83	4.15	20	20
2006	10	324	32.4	1.71	19	19
2007	12	602.04	50.17	2.79	18	18
2008	8	1088.96	136.12	8.01	17	17
2009	12	1614	134.5	8.41	16	16
2010	15	583.95	38.93	2.6	15	15
2011	10	347	34.7	2.48	14	14
2012	26	1464.06	56.31	4.33	13	13
2013	25	920	36.8	3.07	12	12
2014	19	365.94	19.26	1.75	11	11
2015	24	649.92	27.08	2.71	10	10
2016	27	467.1	17.3	1.92	9	9
2017	24	378.96	15.79	1.97	8	8
2018	23	359.95	15.65	2.24	7	7
2019	23	255.07	11.09	1.85	6	6
2020	15	163.05	10.87	2.17	5	5
2021	29	267.09	9.21	2.3	4	4
2022	24	184.08	7.67	2.56	3	3
2023	29	38.86	1.34	0.67	2	2
2024	8	2	0.25	0.25	1	1

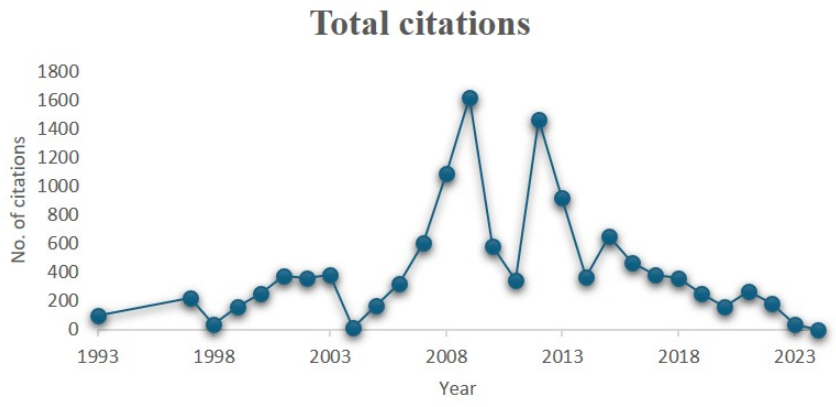

Figure 1. Yearly, average article citations associated with psoriasis and TNF-α polymorphisms.

Active journals

This study's 400 documents came from 195 different sources. Figure 2 displays the top 20 journals. In order, the most relevant journals were Journal of Rheumatology, Journal of The European Academy of Dermatology and Venereology, Journal of Investigative Dermatology, Plos One and British Journal of Dermatology.

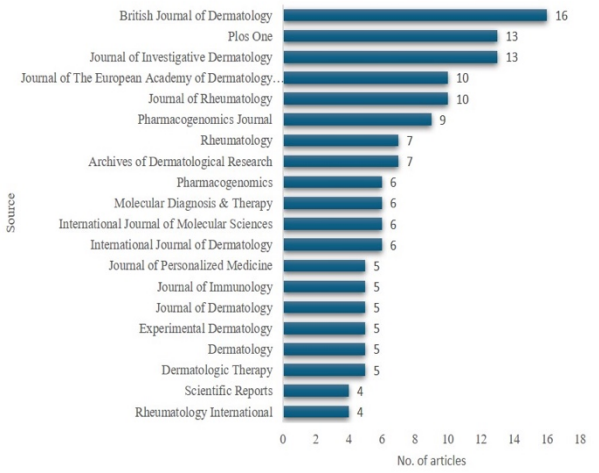

Figure 2. Most relevant sources associated with psoriasis and TNF-α polymorphisms.

In 1997, the Journal of Investigative Dermatology published the first research on patient and nursing resilience, and it continued to publish the most until 2012. Following the publication of a few relevant studies in the British Journal of Dermatology in 2001, it appears this journal has currently published a greater number of articles compared to Plos One (Figure 3).

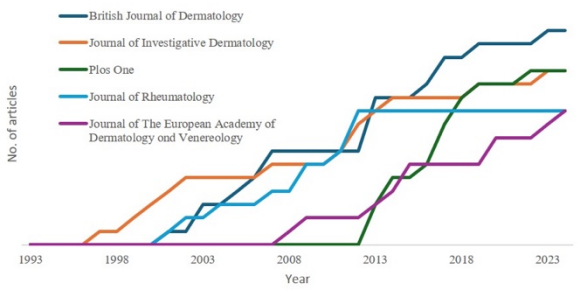

Figure 3. Article source growth plot of documents related with psoriasis and TNF-α polymorphisms.

Authorship analysis

Two authors of single-authored studies were among the 2957 authors who contributed in total to the retrieved documents. Each author contributed a total of 9.5 documents to the co-authored publication. Figure 4 lists the ten most productive writers. Out of all 2957 authors, four or more documents were produced by each of the top 10 authors.

The most productive author was Dauden E. from Instituto de Investigación Sanitaria La Princesa, with fourteen articles (3.5%) out of 400. Dauden E. conducted the most research in 2022 and started publishing relevant studies in 2012. Reich K., Rahman P., and Abad-Santos F. were the following most productive researchers. Of all these prominent writers, they started their research the earliest in 2012 and kept up a steady pace until 2022. Each of the remaining top 10 list authors authored four articles.

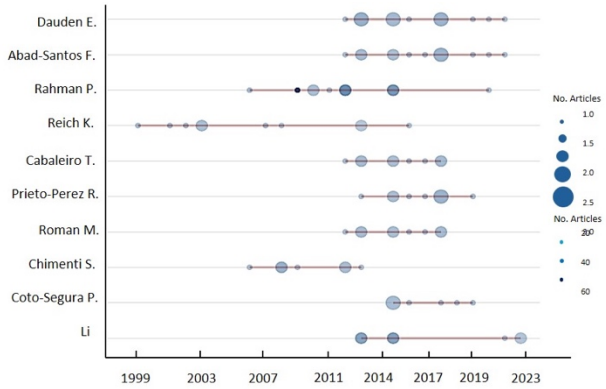

Figure 4. Top 10 authors and their production annually.

Italy, China, the USA, Spain, and Germany were the top five countries that generated the highest number of publications on TNF-α polymorphism and psoriasis, with 56, 55, 41, 36, and 29 articles respectively (Figure 5). Within the total of 400 documents, the United States represented 14% (56 out of 400). Collectively, the first five countries accounted for 54.25% of all published articles out of 400 countries, which is equivalent to 217 out of 400.

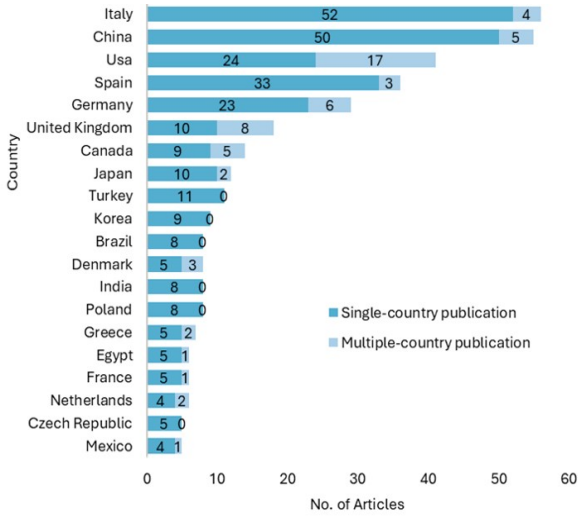

Figure 5. Most productive countries worldwide

KeyWords Plus analysis

1108 KeyWords Plus terms were used in the KeyWords Plus analysis. In Figure 6, the top 20 most frequently occurring KeyWords Plus terms are displayed as an overlay visualization map. The terms "polymorphisms" (n=53), "association" (n=95), "disease" (n=60), "susceptibility" (n=75), and "rheumatoid arthritis" (n=84) were the most encountered.

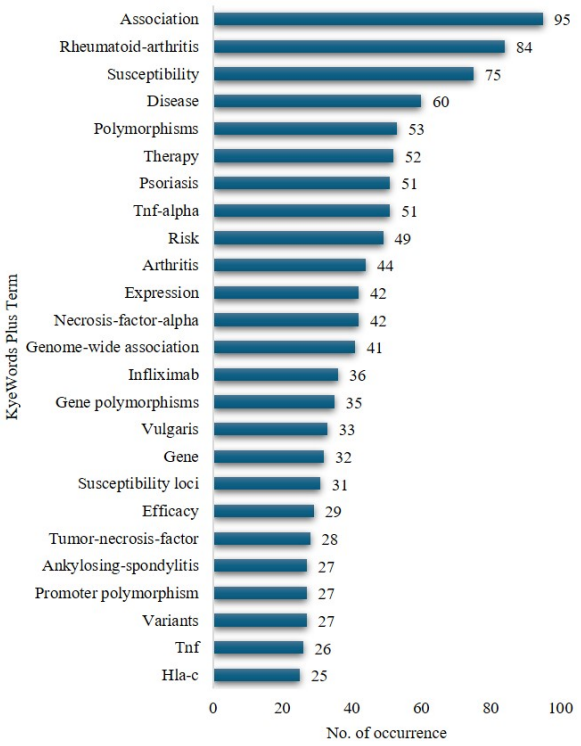

Figure 6. KeyWords Plus analysis of psoriasis and TNF-α polymorphisms

Trend in topics

The terms "predictor," "recommendation," "mice," and "differentiation" were trending in 2023, whereas the terms "predict response," "gene polymorphisms," "psoriatic arthritis," "pathogenesis," and "risk" were popular in 2019. The trend topics for 2016 included "association," "therapy," and "infliximab." The year with the highest term frequency over the whole period was 2016. Finding the relationships between different terms requires more than just using keyword frequencies. Figure 7 displays topic trends by year.

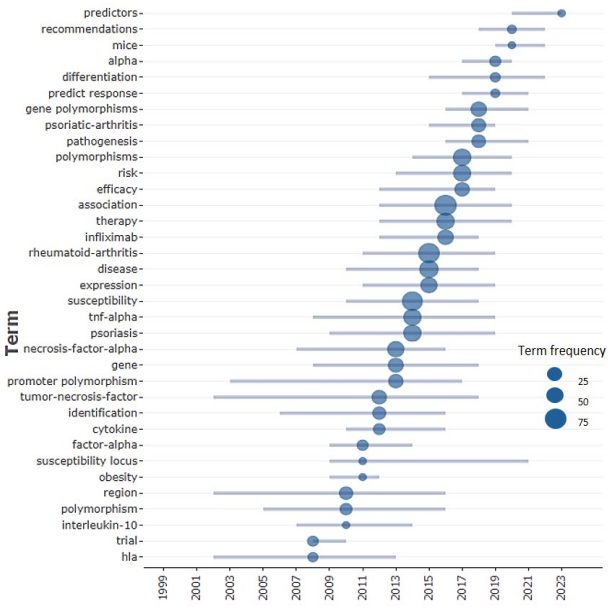

Figure 7. Trends in topic of psoriasis and TNF-α polymorphisms

In the KeyWords Plus Co-occurrence network, each Keywords Plus term is shown as a node, and each instance of a word pair is included as a link. The weight allocated to a pair of terms in a link between these two KeyWords Plus terms is based on their co-occurrence frequency in numerical articles. Through this process, a weighted network is generated. Each weight is denoted by the number of links, and the weights are proportionally indicated by the thickness of the links.

Figure 8 illustrates the KeyWords Plus terms associated with each of the three clusters. Regarding TNF-α polymorphisms and psoriasis, the terms "association," "psoriasis," "polymorphisms," and "genome-wide association" seemed to be most frequently used. The second-largest concept in the cluster with "rheumatoid arthritis" as its central term was "therapy".

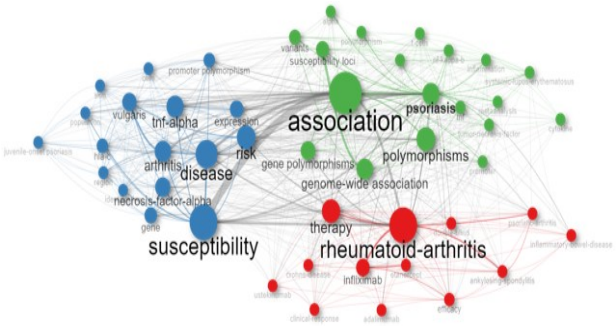

Figure 8. KeyWords Plus co-occurrence network analysis of psoriasis and TNF-α polymorphisms

Most globally cited documents

Table 3 displays the top ten documents that have been cited worldwide. The most frequently cited article was written by Nair et al. and published in Nature Genetics in 2009 under the title "Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways.".[8] This article was cited 1080 times. "Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture" is the title of Stuart et al.'s most recent publication from 2015.[9] From its online publication in December 2020 until the search date of this manuscript, it received 207 citations, establishing it as the study with the greatest citation count within a short timeframe.

Discussion

This paper presents the initial bibliometric analysis that specifically examines TNF-α polymorphisms and psoriasis. It offers a comprehensive analysis of the intellectual framework and scientific direction within this field. R-based Biblioshiny web-programme has enabled the visualization of knowledge graphs and the identification of significant authors, organizations, and research clusters.

The present study investigated the scientific advancements and developing trends in the distribution of articles on TNF-α polymorphisms and psoriasis.

Table 3. Most globally cited articles

Rank	Bibliographic information	No. of total citation
1	Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, Gudjonsson JE, Li Y, Tejasvi T, Feng BJ, Ruether A. Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways. Nature genetics. 2009;41(2):199-204. https://doi.org/10.1038/ng.311	1080
2	Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, Wise C, Miner A, Malloy MJ, Pullinger CR, Kane JP. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS genetics. 2008;4(4):e1000041. https://doi.org/10.1371/journal.pgen.1000041	535
3	Gregory AP, Dendrou CA, Attfield KE, Haghikia A, Xifara DK, Butter F, Poschmann G, Kaur G, Lambert L, Leach OA, Prömel S. TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis. Nature. 2012;488(7412):508-11. https://doi.org/10.1038/nature11307	276
4	Jordan CT, Cao L, Roberson ED, Duan S, Helms CA, Nair RP, Duffin KC, Stuart PE, Goldgar D, Hayashi G, Olfson EH. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. The American Journal of Human Genetics. 2012;90(5):796-808. https://doi.org/10.1016/j.ajhg.2012.03.013	271
5	Boisson B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M, Belkadi A, Picard C, Abel L, Fieschi C, Puel A. An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity. 2013;39(4):676-86. https://doi.org/10.1016/j.immuni.2013.09.002	211
6	Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, Ellinghaus E, Chandran V, Callis-Duffin K, Ike R, Li Y. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. The American Journal of Human Genetics. 2015;97(6):816-36. https://doi.org/10.1016/j.ajhg.2015.10.019	207
7	Kaluza W, Reuss E, Grossmann S, Hug R, Schopf RE, Galle PR, Maerker-Hermann E, Hoehler T. Different transcriptional activity and in vitro TNF-α production in psoriasis patients carrying the TNF-α 238A promoter polymorphism. Journal of Investigative Dermatology. 2000;114(6):1180-3. https://doi.org/10.1046/j.1523-1747.2000.00001.x	188
8	Naldi L, Addis A, Chimenti S, Giannetti A, Picardo M, Tomino C, Maccarone M, Chatenoud L, Bertuccio P, Caggese E, Cuscito R. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis: evidence from the Psocare project. Dermatology. 2008;217(4):365-73. https://doi.org/10.1159/000156599	171
9	Tonel G, Conrad C, Laggner U, Di Meglio P, Grys K, McClanahan TK, Blumenschein WM, Qin JZ, Xin H, Oldham E, Kastelein R. Cutting edge: a critical functional role for IL-23 in psoriasis. The Journal of Immunology. 2010;185(10):5688-91. https://doi.org/10.4049/jimmunol.1001538	170
10	Höhler T, Kruger A, Schneider PM, Schopf RE, Knop J, Rittner C, zum Büschenfelde KH, Märker-Hermann E. A TNF-α promoter polymorphism is associated with juvenile onset psoriasis and psoriatic arthritis. Journal of Investigative Dermatology. 1997;109(4):562-5. https://doi.org/10.1111/1523-1747.ep12337469	165

Recent years have seen a substantial increase in research investigating the association between psoriasis and TNF-α polymorphisms.

The bibliometric analysis of publications on psoriasis and TNF-α polymorphisms reveals a growing research community and an increase in scientific output since 2012. However, the decline in average citations suggests that while the field is active, the impact of individual studies may be decreasing. Further analysis is needed to understand the underlying reasons for this trend and to identify potential areas for future research.

In the analysis of current study showed that the most productive countries were Italy, Chine, and USA. However, another Bibliometric analyses of publications on biologics in psoriasis between 2004 and 2023 show active research, especially in China and the United States.[10] Also, Steven R. Feldman and organizations such as the University of Manchester are among the most prolific contributors in tfhis field. İn the current bibliometric analysis, the most related research was published in the British Journal ond Dermatlogy and Nair RP was the highest number of citation author.[10] The growth rate of published articles in the bibliometric analysis results, the continuous growth of dermatological research, particularly in the area of psoriasis and TNF-α polymorphisms, demonstrates the importance of this research area and its potential to contribute to improved patient outcomes.

The terms most often come across in the KeyWord Plus analysis were “association”, “rheumatoid arthritis” and “susceptibility”. Recent research trends have emphasized the role of TNF-α polymorphisms in the pathogenesis of psoriasis, highlighting their potential as genetic susceptibility factors in this autoimmune and inflammatory disease.

While bibliometric analysis is a useful scientific method for estimating the research status in a certain scientific subject, it is important to note that the publications reviewed in this analysis may not completely reflect the entire literature on resilience due to biases associated with databases and language. Notwithstanding, these results provide a comprehensive summary of current investigation trends on resilience in association to TNF-α polymorphisms and psoriasis.

In conclusion, over the past decade, there has been a substantial demand for research on TNF-α Polymorphisms and Psoriasis. This study is important for analyzing the overall research and publication patterns of studies pertaining to psoriasis. The potential relationship between TNF-α polymorphisms and psoriasis is highlighted by this bibliometric study, which will direct future research efforts in the search for more potent treatments.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

YA and AK: The main idea and hypothesis of the study, YA: theory development, YA and VKA: contributed to materials and methods, YA: data analysis, YA and YB:

manuscript writing, YA: preparation of the publication format.

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References

1. Wang L, Zhou H. A Meta-Analysis of the Relationship between Tumor Necrosis Factor-α Polymorphisms and Psoriasis. *Dermatology.* 2021;237(1):39-45. doi:10.1159/000502255
2. Chokshi A, Demory Beckler M, Laloo A, Kesselman MM. Paradoxical Tumor Necrosis Factor-Alpha (TNF-α) Inhibitor-Induced Psoriasis: A Systematic Review of Pathogenesis, Clinical Presentation, and Treatment. *Cureus.* 2023;15(8):e42791. doi:10.7759/cureus.42791.
3. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. International journal of molecular sciences, 2019;20(6):1475.
4. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. *Cytokine.* 2015;73(2):342-350. doi:10.1016/j.cyto.2014.12.014
5. Jiménez CM, Ramírez CP, Martín AS, et al. Influence of genetic polymorphisms on response to biologics in moderate-to-severe psoriasis. *J Pers Med.* 2021;11(4). doi:10.3390/jpm11040293
6. Aria M, Cuccurullo C. bibliometrix: An R-tool for comprehensive science mapping analysis. *J Informetr.* 2017;11(4):959-975. doi:10.1016/j.joi.2017.08.007
7. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: An overview and guidelines. *J Bus Res.* 2021;133:285-296. doi:10.1016/j.jbusres.2021.04.070
8. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways. *Nature Genetics.* 2009;41(2):199-204. doi:10.1038/ng.311
9. Stuart PE, Nair RP, Tsoi LC, et al. Genome-wide Association Analysis of Psoriatic Arthritis and Cutaneous Psoriasis Reveals Differences in Their Genetic Architecture. *Am J Hum Genet.* 2015;97(6):816-836. doi:10.1016/j.ajhg.2015.10.019
10. Wang Y, Li J, Guo C, Yang G, Lin H, Zhang Y. Bibliometric analysis and description of research trends in the treatment of psoriasis with biologic agents in the past two decades (2004–2023). *J Dermatol Treat.* 2024;35(1). doi:10.1080/09546634.2024.2346282

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Research Article | Araştırma Makalesi

EVALUATION OF YOUTUBE VIDEOS ON CALCANEUS FRACTURES IN TERMS OF RELIABILITY AND QUALITY

KALKANEUS KIRIKLARINA İLİŞKİN YOUTUBE VİDEOLARININ GÜVENİLİRLİK VE KALİTE AÇISINDAN DEĞERLENDİRİLMESİ

Umit Gok[1*], Sibel Balci[2]

[1]Kocaeli Derince Training and Research Hospital, Orthopaedic and Traumatology Department, Kocaeli, Türkiye. [2]Kocaeli University, Faculty of Medicine, Department of Bioistatistics and Medical İnformation, Kocaeli, Türkiye.

ABSTRACT

Objective: The aim of the study is evaluating the realibity and quality and the reliability of Youtube video contents concerning calcaneal factures.

Methods: We searched the terms of calcaneus fracture on Youtube and total of 57 videos evaluated. The following variables were collected for each video: number of views, duration in minutes and seconds, video source/uploader type, content type, days since upload, view ratio (views/day), and number of likes. The general features of the videos were evaluated in eight categories, video uploaders were evaluated in five categories, and video contents were evaluated in three categories. The Global Quality Scale (GQS), The Journal of the American Medical Association (JAMA) score, DISCERN scores were used to assess each video.

Results: The median view ratio was 19.68 (interquartile range 9.39-37.3), median number of views were 28788 views. The median JAMA score was 2 (interquartile range (IQR) 2-3), GQS score was 3 (interquartile range 2-3) and DISCERN score was 39 (interquartile range 29,5-46). The most common video uploader were physicians (43.9%), disease specific information was the most viewed video content (52.6%). Academic sources were the best on median DISCERN (46), JAMA score (3) and GQS scores (3). Also disease specific disorders videos had the greatest median DISCERN (46), JAMA (3) and GQS scores (3).

Conclusion: The Reliability, transparency and content of YouTube videos on calcaneus fractures measured by GQS and DISCERN scores are intermediate but JAMA scores were poor. Increasing video quality will provide better guidance to patients in such diseases like calcaneus fractures that are difficult to follow and treat.

Keywords: Patient education, calcaneus fracture, Youtube, quality analysis

ÖZ

Amaç: Çalışmanın amacı kalkaneus kırıklarına ilişkin Youtube video içeriklerinin gerçekliğini, kalitesini ve güvenilirliğini değerlendirmektir.

Yöntem: Youtube'da 'kalkaneus kırığı' terimi aranarak ve toplam 57 video değerlendirildi. Her video için görüntüleme sayısı, dakika ve saniye cinsinden süre, video kaynağı/yükleyici türü, içerik türü, yüklemeden bu yana geçen gün sayısı, görüntüleme oranı (görüntüleme/gün) ve beğeni sayısı değişkenleri değerlendirildi. Videoların genel özellikleri sekiz kategoride, video yükleyicileri beş kategoride ve video içerikleri üç kategoride değerlendirildi. Her videoyu değerlendirmek için Küresel Kalite Ölçeği (GQS), The Journal of the American Medical Association (JAMA) puanı, DISCERN puanları kullanıldı..

Bulgular: Median görüntüleme oranı 19.68 (aralık 9.39-37.3), median görüntüleme sayısı 28788 görüntülemeydi. median JAMA skoru 2 (aralık (IQR) 2-3), GQS skoru 3 (aralık 2-3) ve DISCERN skoru 39'du (aralık 29,5-46). En sık video yükleyenler hekimlerdi (%43,9), hastalığa özgü bilgiler grubu, en çok görüntülenen video içeriğiydi (%52,6). Akademik kaynaklar median DISCERN (46), JAMA skoru (3) ve GQS skorları (3) konusunda en iyisiydi. Ayrıca hastalığa özgü tanımlar kategorisindeki videolar en yüksek median DISCERN (46), JAMA (3) ve GQS skorlarına (3) sahipti.

Sonuç: GQS ve DISCERN puanları ile ölçülen kalkaneus kırıkları hakkındaki YouTube videolarının güvenilirliği, şeffaflığı ve içerik kalitesi orta düzeydedir ancak JAMA puanları zayıftır. Video kalitelerinin artırılması, takip ve tedavisi zor olan kalkaneus kırıkları gibi hastalıklarda hastalara daha iyi rehberlik sağlayacaktır.

Anahtar Kelimeler: Hasta eğitimi, kalkaneus kırıkları, Youtube, kalite analizi

***Corresponding author/İletişim kurulacak yazar:** Umit Gok; Kocaeli Derince Training and Research Hospital, Orthopaedic and Traumatology Department, 41100, Kocaeli, Türkiye
Phone/Telefon: +90 (505) 944 87 55, **e-mail/e-posta:** drumitgok@hotmail.com
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Introduction

Internet use has become one of the primary options for health information sources. Studies have shown that approximately 40% of patients do a web search regarding their complaints before applying to a health institution and these numbers will increase over time.[1] YouTube is a popular site for videos containing health-related information with more than 2.7 billion users each month and one billion hours of video watched each day.[2,3] YouTube videos enable visual and audio education of healthcare personnel and patients in terms of diagnosis, treatment and follow-up of diseases.[4] It has also been shown that 75% of patients' decisions regarding the treatment of their disease are influenced by information obtained through online health searches, therefore, it is important that these videos provide accurate and reliable information.[5] However, the content quality of youtube health videos is sometimes needs to be questioned. Because YouTube does not have a process to ensure the content accuracy of videos, many patients may encounter unreliable information and misinformation about their condition. This situation has been reported in previous Youtube videos studies such as hallux valgus, plantar fasiitis, shoulder instability …vs and quality, transparency and reliability was found low.[1]

Even though calcaneal factures have difficult surgical technique, long treatment process and high morbidity and complication rates, Youtube videos on calcaneal fractures have not been evaluated yet.[6] The aim of the study is evaluating the quality and reliability of Youtube videos about calcaneal fractures.

Methods

The term "calcaneus fracture" was searched on Youtube and most suitable 57 videos were extracted to Microsoft Excel program (Redmond, WA) in January 2024. Videos with less than 10000 views were not included in the study. English language, acceptable audio and visual quality and primary content on calcaneus fractures were the inclusion criterias for the videos. The videos that have only audio or visual content were excluded from the examination.

The variables which were collected from each video are; duration of minutes, video source/uploader, number of views, days since upload, view ratio (view/days), number of likes and content type.

Physician, nonphysician, academic, medical source and patient were category of the video source/uploader.

Disease spesific information, patient experience, surgical technique or approaches and nonsurgical management were the content types. Since the number of videos in nonsurgical management was statistically insufficient, they were added to dissease specific disorders group because they were similar in content.

We used the JAMA score for evaluating the video transparency and reliability. The GQS used for measuring the educational quality of videos and the DISCERN score was used for assessing the quality of online information.[4,7-9] The JAMA score basically consists of four parts (bibliography, up to dateness, authorship and cophyright) and evaluated between 0 and 4 points by giving 1 point for each criteria. The GQS was categorized between 1 (lowest quality)- 5 (highest quality). The DISCERN consist 15 questions (each question is scored between 1-5), first 8 questions for evaluating the reliability of the video, the next 6 questions for detailing the treatment options and the fifteenth question for evaluating the overall quality of the video. The overall quality of the video. Between totally 63-75 considered excellent points, 51-62 good, 39-50 medium, 27-38 insufficient, and 16-26 are considered very insufficient.

The 'Human Ethics and Consent to Participate' statement and 'consents of participants' are not applicable, because this article does not contain any studies with human participants or animals performed by any of the authors.

Stastistical Analysis

IBM SPSS 29.0 (IBM Corp., Armonk, NY, USA) used for all statistical analysis. Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the normality assumption. Continuous variables were presented with median and interquartile range (IQR) since the normality assumption did not hold. Categorical variables were summarized as counts and percentages. Kruskal-Wallis test was used for carrying out the comparisions between groups and Dunn's test was used for the multiple comparisons. A p-value<0.05 was considered statistically significant.

Results

Total duration of 57 videos were 522 minutes (min) 24 seconds (sec) and the overall median video length were 320 sec (range 22 sec-726 sec). The total number of views were 2844441 (range 10000-386287), and the median were 28788 views. The total number of likes were 21564 (range 0-3500), and the median number of likes were 189 (IQR 109,5-322) likes. The total days since upload were 129420 (range 95-5110), and the median number of total days since upload were 2555 (IQR 885-3650) days. The median view ratio was 19.68 (IQR 9.39-37.3) views/day (range 2.93-433.11). The most common video source/uploader were the physicians (25 videos, 43.9%), the others were academic sources (11 videos, 19.3%), patients (9 videos, 15.8%), nonphysicians (6 videos, 10.5%) and the medical sources (6 videos, 10.5%). The disease specific information was the most common content type (30 videos, 52.6%) and the others were surgical techniques (18 videos, 31.6%), patients experiences (9 videos, 15.8%) (Table 1). The median overall JAMA benchmark score was 2 (interquartile range (IQR) 2-3), GQS score was 3 (interquartile range 2-3) and DISCERN score was 39 (interquartile range 29,5-46). Academic sources had the greatest median DISCERN (46), JAMA (3) and GQS scores (3) (p<0.001). No significant difference found in number of views, view ratio and

number of likes (Table 2). Also similarly on video content type analysis, disease specific disorders videos had the greatest median DISCERN (46), JAMA (3) and GQS scores (3) (Table 3) and no significant difference in number of views, view ratio and number of likes.

Discussion

Orthopedic studies about quality analysis of Youtube videos are usually focused on orthopaedic diseases like scoliosis, carpal tunnel syndrome, hip arthritis, knee ligament injuries, shoulder diseases and arthroplasty. Foot and ankle studies are usually about hallux valgus. According to our literature searches this is the first study which has focused on calcaneal fractures.

Low like and video ratio rates shows that YouTube videos about calcaneal fractures are not as popular as other orthopaedic topics. This low number of views can be explain by the incidance of calcaneal fractures in adeolescent and young adult population who use YouTube more actively. Also we thaught that the aesthetic and sport topics are more interesting for this group patients.[7-15]

Table 1. Descriptive statistics for YouTube videos (n=57)

	Median (IQR)
DISCERN	39 (29.5-46)
JAMA	2 (2-3)
GQS	3 (2-3)
View ratio	19.68 (9.39-37.3)
Number of views	28788 (14889.5-68000)
Days since upload	2555 (885-3650)
Duration in sec.	320 (148-726)
Number of likes	189 (109.5-322)
	n (%)
Video source/uploader	
Physician	25 (43.9)
Medical source	6 (10.5)
Patient	9 (15.8)
Nonphysician	6 (10.5)
Academic	11 (19.3)
Content type	
Surgical technique	18 (31.6)
Patient experience	9 (15.8)
Disease specific information/ Nonsurgical management	30 (52.6)

IQR: Interquartile range, n: Number

Table 2. Comparisons of video sources/uploaders

	Physician (n=25) Median (IQR)	**Medical Source (n=6) Median (IQR)**	**Patient (n=9) Median (IQR)**	**Nonphysician (n=6) Median (IQR)**	**Academic (n=11) Median (IQR)**	**p***
DISCERN	44 (30-48)[a]	35.5 (31.5-40.75)[ab]	25 (23.5-25.5)[b]	43 (41.75-43.75)[a]	46 (32-50)[a]	**<0.001**
JAMA	3 (1.5-3)[a]	2 (2-2.25)[ab]	1 (1-2)[b]	2.5 (2-3)[ab]	3 (2-3)[a]	**0.004**
GQS	3 (3-3)[ac]	2.5 (2-4)[bc]	2 (1-2)[b]	3 (3-3)[a]	3 (3-4)[abc]	**<0.001**
View ratio	23.28 (14.13-37.98)[ac]	18.45 (3.71-29.11)[ab]	9.58 (6.08-16.57)[b]	41.785 (29.39-70.89)[c]	18.26 (6.65-30.09)[abc]	**0.048**
Number of views	39201 (14889.5-73539.5)	26627 (10931-50889.5)	14000 (12593-56000)	30508.5 (24500-79960.25)	26000 (18489-71482)	0.481
Days since upload	1825 (730-3270)	3650 (2412.5-3741.25)	3650 (1277.5-4197.5)	730 (730-2007.5)	2555 (1095-2920)	0.069
Duration in sec.	278 (125.5-627.5)[a]	167 (114.25-491.75)[ab]	272 (131-458)[ab]	311.5 (219.25-947.25)[ab]	1156 (393-1723)[b]	**0.020**
Number of likes	180 (116.5-299.5)[ab]	32 (0-106.25)[a]	183 (120.5-253.5)[ab]	502 (260.75-1100)[b]	208 (177-598)[ab]	**0.014**

IQR: Interquartile range
Boldface p values indicate statistically significant differences.
The values with different superscript letters in a row are significantly different.
*Kruskal-Wallis test

Table 3. Comparisons of content types

	Surgical Technique (n=18) Median (IQR)	**Patient Experience (n=9) Median (IQR)**	**Disease Specific Information/ Nonsurgical Management (n=30) Median (IQR)**	**p***
DISCERN	30.5 (28.75-32)[a]	25 (23.5-25.5)[a]	46 (43-48.25)[b]	**<0.001**
JAMA	2 (1-2.25)[a]	1 (1-2)[a]	3 (2.75-3)[b]	**<0.001**
GQS	3 (2-4)[a]	2 (1-2)[b]	3 (3-3)[a]	**<0.001**
View ratio	21.89 (9.68-31.97)	9.58 (6.09-16.57)	23.88 (10.99-39.04)	0.108
Number of views	27741.5 (15334.25-86555.25)	14000 (12593-56000)	30508.5 (17000-68099.75)	0.383
Days since upload	2555 (1003.75-3285)	3650 (1277.5-4197.5)	2022.5 (730-3102.5)	0.415
Duration in sec.	561.5 (190.25-726)	272 (131-458)	270 (129-842.5)	0.298
Number of likes	179.5 (49.75-358.5)	183 (120.5-253.5)	242 (140.5-483.5)	0.425

IQR: Interquartile range
Boldface p values indicate statistically significant differences.
The values with different superscript letters in a row are significantly different.
*Kruskal-Wallis test

YouTube videos about calcaneus fractures were found to be of intermediate quality in terms of DISCERN and GQS scores, respectively. In addition, JAMA scores were poor. We think that the reason why they are at intermediate level is that the majority of the videos belong to academics and surgeons. However, the videos of academics and physicians were also found to be weak in terms of references and source citations. These results are better than the previously reported findings from YouTube studies of other orthopaedic topics, including hallux valgus, total shoulder arthroplasty and patellofemoral instability.[16-18]

In our study, the GQS, DISCERN and JAMA scores of videos uploaded by patients were statistically worse than those uploaded by other sources. This indicates that the doctors' videos are of a higher quality in terms of content. This may indicate that the videos uploaded by doctors are more scientific. Also we think that the patient videos are made to produce content that will artract the attention of the audience, rather than to provide medical information. However, similar to some of the previous studies, we didn't found any significant correlation between number of likes, video view ratio, number of views and the scores.[14,18,19] This shows that the likes do not correlate with the content quality of the video, and there are other studies showing that videos of low content quality have more likes.[20,21]

When the videos are evaluated in terms of video content, DISCERN, JAMA and GQS scores of the DSI group were found to be significantly higher than other content groups. Again similar to previous studies and our video uploader analysis, we didn't find any significant difference in view ratio, number of views and likes of content groups.[17] We think that if video content is scientifically and technically intense, it is more difficult to reach non-medical audience. Medical videos have the lowest like rates because they provide more tecnical information.

This study has some limitations. First of all, the search was made using a single term. In addition to calcaneus fractures, terms such as heel fractures could also be added to the search. Also, the situation we want to investigate while doing the study; The aim was to examine the data that patients who would use the internet regarding their diseases would obtain as a result of their searches. Aiming to evaluate all the data on the internet in a single study does not seem possible with today's techniques. Although the entire YouTube database is scanned, another limitation is that this search is only in English.

Conclusions

Although the overall reliability, transparency and content quality of Youtube videos on calcaneal fractures as measured by DISCERN and GQS scores were moderate, the overall educational and video quality as measured by JAMA was poor. As a result of our study, it was concluded that the videos about calcaneus fractures on YouTube do not have sufficient reliability or quality for patient education, especially about complications. Therefore, it may be an option that recommending the high-quality information websites or videos about calcaneal fractures to relevant healthcare professionals and patient.

Compliance with Ethical Standards

Because of this article does not contain any studies with human participants or animals performed by any of the authors; 'Human Ethics and Consent to participate' declaration and 'consents of participants' are not applicable.

Conflict of Interest

All authors have declared that there was no conflict of interest.

Author Contributions

ÜG: Data collection, processing; SB: Statistical analysis; ÜG: Literature search and writing.

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References

1. Abed V, Sullivan MB, Skinner M, et al. Youtube is a poor-quality source for patient information regarding patellar dislocations. *Arthroscopy. Sports Medicine, and Rehabilitation.* 2023;5(2):459-464. doi:10.1016/j.asmr.2023.01.014
2. Baker JD, Baig Y, Siyaji ZK, et al. Assessing the quality and credibility of publicly available videos on cervical fusion: Is YouTube a reliable educational tool? *Int J Spine Surg.* 2021;15:669-675. doi:10.14444/8088
3. YouTube Official Blog: Statistics for YouTube [Internet]. San Bruno, CA: YouTube. (2022) Accessed: May 2022: https://blog.youtube/press/.
4. Erdem MN, Karaca S. Evaluating the accuracy and quality of the information in kyphosis videos shared on YouTube. *Spine* (Phila Pa 1976). 2018;43:E1334-9. doi:10.1097/BRS.0000000000002691
5. Kyle N. Kunze, Kevin H. Alter, Matthew R. Cohn, Amar S. Vadhera, Nikhil N. Verma, Adam B. Yanke, Jorge Chahla. YouTube videos provide low-quality educational content about rotator cuff disease. *Clin Shoulder Elbow.* 2022;25(3):217-223. doi:10.5397/cise.2022.00927
6. Davis D, Seaman TJ, Newton EJ. Calcaneus Fractures. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024, https://www.ncbi.nlm.nih.gov/books/NBK430861/
7. Charnock D, Shepperd S, Needham G, Gann R. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. *J Epidemiol Community Health.* 1999;53(2):105-111. doi:10.1136/jech.53.2.105
8. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet. *JAMA.* 1997;277(15):1244-1245.
9. Kunze KN, Krivicich LM, Verma NN, Chahla J. Quality of Online Video Resources Concerning Patient Education for

the Meniscus: A Youtube-Based Quality-Control Study. 2020;36(1):233-238. doi:10.1015/j.arthro.2019.07.033
10. Cassidy JT, Fitzgerald E, Cassidy ES, et al. YouTube provides poor information regarding anterior cruciate ligament injury and reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2018;26(3):840-845. doi:10.1007/s00167-017-4514x
11. Tekin SB, Bozgeyik B: Quality and Content Analysis of Hallux Valgus Videos on YouTube. *J Foot Ankle Surg.* 2023;62(1):85-90. doi:10.1053/j.jfas.2022.05.003
12. Staunton PF, Baker JF, Green J, Devitt A. Online curves: a quality analysis of scoliosis videos on YouTube. Spine (Phila Pa 1976). 2015; 40(23):1857-1861. doi:10.1016/j.arthro.2014.06.009
13. MacLeod MG, Hoppe DJ, Simunovic N, Bhandari M, Philippon MJ, Ayeni OR. YouTube as an information source for femoroacetabular impingement: a systematic review of video content. *Arthroscopy.* 2015;31(1):136-142. doi:10.1016/j.arthro.2014.06.009
14. Mert A, Bozgeyik B. Quality and Content Analysis of Carpal Tunnel Videos on YouTube. *Indian Journal of Orthopaedics.* 2022;56:73-78. doi:10.1007/s43465-021-00430-5
15. Uzun M, Cingoz T, Duran ME, Varol A, Celik H. The videos on YouTube related to hallux valgus surgery have insufficient information. *Foot Ankle Surg.* 2022;28(4):414-417. doi:10.1016/j.fas.2021.05.009
16. Uzun M, Cingoz T, Duran ME, Varol A, Celik H. The videos on YouTube related to hallux valgus surgery have insufficient information*. Foot Ankle Surg.* 2022;28(4):414-417. doi:10.1016/j.fas.2021.05.009
17. Yüce A, İğde N, Ergün T, Mısır A. YouTube provides insufficient information on patellofemoral instability. *Acta Orthop Traumatol Turc.* 2022;56(5): 306-310. doi:10.5152/j.aott.2022.22005
18. Martinez VH, Ojo D, Gutierrez-Naranjo JM, Proffitt M, Hartzler RU. The Most Popular YouTube Videos About Shoulder Replacement Are of Poor Quality for Patient Education. *Arthroscopy, Sports Medicine, and Rehabilitation.* 2023;5(3):623-628. doi:10.1016/j.asmr.2023.03.001. ecollection 2023 Jun.
19. Özbek EA, Armangil M, Karaca MO, Merter A, Dursun M, Kocaoğlu H. Evaluation of the Reliability and Quality of Information in Carpal Tunnel Syndrome Shared on YouTube. *J Wrist Surg.* 2022;11:295-301. doi:10.1055/s-0041-1735231
20. Kumar N, Pandey A, Venkatraman A, Garg N. Are video sharing web sites a useful source of information on hypertension? *J Am Soc Hypertens.* 2014;8(7):481-490. doi:10.1016/j.jash.2014.05.001
21. Lee JS, Seo HS, Hong TH. YouTube as a source of patient information on gallstone disease. *World J Gastroenterol.* 2014;20(14):4066-4070. doi:10.3748/wjg.v20.i14.4066

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NON-EROZİF REFLÜ HASTALIĞININ TANISINDA İMPEDANS-PH METRENİN ROLÜ: KLİNİK BULGULAR VE REFLÜ KARAKTERİZASYONU

THE ROLE OF IMPEDANCE-PH MONITORING IN THE DIAGNOSIS OF NON-EROSIVE REFLUX DISEASE: CLINICAL FINDINGS AND REFLUX CHARACTERIZATION

Yasemin Bakkal Temi[1*], Altay Çelebi[2], Ömer Şentürk[3], Deniz Öğütmen Koç[4], Göktuğ Şirin[2], Uğur Korkmaz[5], Ali Erkan Duman[2], Gökhan Dindar[6], Neslihan Bozkurt[7], Sadettin Hülagü[2]

[1]Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Tıbbi Onkoloji Bilim Dalı, Kocaeli, Türkiye. [2]Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Gastroenteroloji Bilim Dalı, Kocaeli, Türkiye. [3]Medikal Park Göztepe Hastanesi, İstanbul, Türkiye. [4]Gaziosmanpaşa Taksim İlkyardım Eğitim Araştırma Hastanesi, İstanbul, Türkiye. [5]Lokman Hekim İstanbul Hastanesi, İstanbul, Türkiye. [6]Kocaeli Şehir Hastanesi, Kocaeli, Türkiye. [7]Beykoz Devlet Hastanesi, İstanbul, Türkiye.

ÖZ

Amaç: Gastroözofageal reflü hastalığı (GÖRH), mide içeriğinin özofagusa geri dönmesiyle gelişen semptomlar ve komplikasyonlardan oluşur. Non-erozif reflü hastalığı (NERH) olan hastalarda, pH metre sıklıkla normal bulunsa da semptomların devam ettiği saptanmıştır. Bu çalışma, NERH hastalarında impedans-pH metrenin tanıdaki rolünü ve reflü karakterizasyonunun klinik bulgularla ilişkisini incelemeyi amaçlamaktadır.

Yöntem: Eylül 2009 ile Şubat 2011 tarihleri arasında, Kocaeli Üniversitesi Gastroenteroloji Polikliniği'ne tipik reflü semptomlarıyla başvuran ve endoskopik incelemede özofajit tespit edilmeyen 40 hastanın verileri retrospektif olarak incelendi. Hastaların 24 saatlik ambulatuar özofageal impedans-pH monitörizasyonu verileri manuel olarak analiz edildi. Klinik semptomlar ile impedans-pH verileri arasındaki ilişki analiz edildi.

Bulgular: Hastaların yaş ortalaması 42 (22-65) yıl olup, 23'ü (%58) kadın, 17'si (%42) erkektir. Pirozis sıklığı haftada birden fazla olan hastaların %95,8'inde hafif asit reflü tespit edilmiştir (p=0,029). Asit reflü grubunda pirozis şiddeti anlamlı şekilde daha yüksek bulunurken (p=0,04), gaz reflüsü olan hastalarda hafif asit reflü sayısı daha yüksek tespit edilmiştir (p=0,005).

Sonuç: Çalışmamız, non-erozif reflü hastalarında yalnızca asit reflüsünün değil, hafif asit reflüsünün de semptom gelişiminde önemli bir rol oynayabileceğini göstermektedir. Özofajit gelişmese bile gaz ve karma reflü tiplerinin semptomlarla ilişkili olduğu tespit edilmiştir. İmpedans-pH monitörizasyonu, asit dışı reflülerin tanısında pH metreden daha kapsamlı bilgi sağlamaktadır ve NERH hastalarının yönetiminde öncelikli bir tanı yöntemi olmalıdır.

Anahtar Kelimeler: İmpedans-pH monitörizasyonu, Non-erozif reflü hastalığı, asit dışı reflü

ABSTRACT

Objective: Gastroesophageal reflux disease (GERD) is characterized by symptoms and complications resulting from the backflow of gastric contents into the esophagus. Although pH monitoring often appears normal, symptoms persist in patients with nonerosive reflux disease (NERD). The objective of this research was to examine the effectiveness of impedance pH monitoring in identifying NERD and explore its relationship with reflux characteristics and clinical observations.

Method: The data of 40 patients who presented with classic reflux symptoms and were found to have no esophagitis upon endoscopic examination at the Kocaeli University Gastroenterology Clinic between September 2009 and February 2011 were retrospectively analyzed. The 24-hour ambulatory esophageal impedance-pH monitoring data were manually analyzed. The relationship between the clinical symptoms and impedance pH data was also assessed.

Results: The patients' average age 42 (range, 22-65) years, with 23 (58%) females and 17 (42%) males. Acid reflux was detected in 95.8% of the patients who experienced heartburn more than once per week (p=0.029). The severity of heartburn was significantly higher in the acid reflux group (p=0.04), whereas the number of patients with mild acid reflux was significantly higher among those with gas reflux (p=0.005).

Conclusion: The findings of our research indicate that both severe and mild forms of acid reflux may contribute significantly to symptom manifestation in individuals diagnosed with non-erosive reflux disease. It has been found that gas and mixed reflux types are associated with symptoms, even in the absence of esophagitis. Compared to pH monitoring alone, impedance-pH monitoring offers a more comprehensive assessment for identifying non-acid reflux. As such, it should be considered the preferred diagnostic approach when managing patients with NERD.

Keywords: Impedance-pH monitoring, Non-erosive reflux disease, non-acid reflux

*** İletişim kurulacak yazar/Corresponding author:** Yasemin Bakkal Temi; Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Tıbbi Onkoloji Bilim Dalı, 41001, Umuttepe, İzmit, Kocaeli, Türkiye.
Telefon/Phone: +90 (262) 303 75 75, **e-mail/e-posta:** yasemintemi1@hotmail.com
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Giriş

Gastroözofageal reflü hastalığı (GÖRH), mide içeriğinin özofagusa geri kaçması sonucu gelişen semptomlar ve komplikasyonlarla karakterize, klinik açıdan önemli bir sağlık sorunudur. GÖRH, dünya genelinde yaklaşık %10-25 oranında bir prevalansa sahiptir.[1,2] GÖRH, endoskopik ve histopatolojik bulgulara dayalı olarak üç farklı fenotipte sınıflandırılmaktadır: Eroziv olmayan reflü hastalığı (NERH), eroziv özofajit, ve Barrett özofagusu. NERH, endoskopik incelemede özofagus mukozasının normal olarak görüldüğü, ancak reflü semptomlarının varlığı ile tanımlanır.[3] NERH reflü hastalığının en sık karşılaşılan tipi olup, yaklaşık %60-70 oranında görülmektedir.[4] GÖRH genellikle pirozis ve regürjitasyon gibi semptomlarla kendini göstermekle birlikte, atipik olarak, göğüs ağrısı, diş erozyonu, kronik öksürük, larenjit veya astım gibi ekstraözofageal semptomlarla da ortaya çıkabilir.[5,6]

Geleneksel olarak, GÖRH tanısında kullanılan 24 saatlik pH-metre yöntemi, yalnızca asit reflüsünü tespit etme kapasitesine sahiptir. Bu sınırlılık, hastaların önemli bir bölümünde tanısal yetersizliklere yol açabilmekte ve asit dışı ya da zayıf asit reflülerin varlığını ortaya koyamamaktadır. Bu durumda, yanlış bir şekilde "fonksiyonel heartburn" tanısı konulması riski artmakta ve hastaların uygun tedaviye yönlendirilmesi zorlaşmaktadır. İmpedans-pH monitörizasyonu ise reflü materyalinin pH değerine ek olarak fiziksel özelliklerini (gaz, sıvı, karma) de değerlendirerek daha kapsamlı bir tanısal yaklaşım sunmaktadır. Bu yöntem, reflü türlerinin daha doğru bir şekilde sınıflandırılmasına ve özellikle asit dışı reflülerin tanınmasına imkan sağlar.[7]

Bu çalışmada amaç, NERH olan hastalarda, özofageal impedans-pH monitörizasyonu kullanarak reflü türlerini (asit reflü, zayıf asit reflü, asit dışı reflü ve reflü olmayan) saptamak ve bu türlerin klinik semptomlarla ilişkisini değerlendirmektir.

Yöntem

Bu çalışmada, Eylül 2009 ile Şubat 2011 tarihleri arasında Kocaeli Üniversitesi Gastroenteroloji Polikliniği'ne pirozis ve/veya regürjitasyon gibi tipik reflü semptomları ile başvuran ve konvansiyonel endoskopi ile özofajit tespit edilmeyen hastaların verileri retrospektif olarak değerlendirildi. Çalışmaya, reflü semptom anketini eksiksiz doldurmuş ve 24 saatlik intralüminal özofageal impedans-pH monitorizasyonu tamamlanan, Son 4 hafta içerisinde proton pompa inhibitörü (PPI) veya H2 reseptör blokeri kullanmayan hastalar dahil edildi. Endoskopik özofajit tespit edilenler veya eksik veri bulunan hastalar çalışma dışında bırakıldı. Çalışmaya başlamadan önce Kocaeli Üniversitesi Etik Kurulu'ndan çalışma için onay alındı (KOÜ.İAEK 2010/49).

İntralüminal özofageal impedans-pH monitorizasyonu işlemi öncesinde, hastaların alt özofagus sfinkter yerini tayin etmek için manometrik inceleme yapıldı. Hastalar, ambulatuar impedans-pHmetre ile 24 saat boyunca günlük aktivitelerine devam etti. Bu süreçte elde edilen kayıtlar manuel olarak analiz edildi. Reflü epizotları, impedans ve pH değişikliklerine göre asit, zayıf asit ve asit dışı reflü olarak sınıflandırıldı. Sıvı, gaz ve karma reflüler, toplam zaman ve pH<4 geçen süreler, reflü epizot sayıları ve diğer ilgili parametreler ayrı ayrı değerlendirildi. Değerlendirme yapılırken, Zerbib ve ark. 2005 yılında sağlıklı bireyler üzerinde gerçekleştirdikleri araştırmadaki normal değerler referans alındı.[8]

Reflü semptomlarının değerlendirilmesinde, Ege Üniversitesi tarafından doğrulanan ve Türk popülasyonu için uyarlanmış bir reflü anketi kullanıldı.[9] Bu ankette yer alan regürjitasyon ve pirozis süresi, sıklığı ve şiddeti, göğüs ağrısı, yutma güçlüğü, hazımsızlık, şişkinlik, gibi parametreler incelendi.

İstatistiksel Analiz

Veriler SPSS 17.0 yazılımı kullanılarak analiz edilmiştir. Kategorik değişkenler arasındaki karşılaştırmalarda "ki-kare testi" uygulanmış, ancak alt gruplardaki hasta sayısının yetersiz olduğu durumlarda "Fischer's exact testi" tercih edilmiştir. Sonuçlar %95 güven aralığı ile incelenmiştir. Sürekli değişkenler normal dağılım göstermediği için, bu değişkenlerin analizi nonparametrik yöntemlerden "Mann-Whitney U testi" ile yapılmıştır. İstatistiksel anlamlılık seviyesi $p<0,05$ olarak kabul edilmiştir.

Bulgular

Bu çalışmaya, klasik reflü semptomları olan ve endoskopisinde özofajiti bulunmayan 40 hasta dahil edilmiştir. Hastaların yaş ortalaması 42±13 yıl (22-65) olarak hesaplanmıştır. Kadın hasta sayısı 23 (%57,5), erkek hasta sayısı 17 (%42,5) olarak belirlenmiştir. Ortalama vücut kitle indeksi (VKİ) 26,5±4,7 kg/m² (19,5-35,8) olarak saptanmıştır.

Semptomların Sıklığı, Şiddeti ve Süresi

Hastalarda pirozis sıklığı; 13 hastada (%32,5) haftada 1 kez, 13 hastada (%32,5) haftada 2-6 kez, 11 hastada (%27,5) her gün, 3 hastada (%7,5) ise hiç görülmemiştir. Pirozis şiddeti %52,5 hastada orta, %22,5'inde şiddetli, %17,5'inde ise hafif olarak değerlendirilmiştir. Regürjitasyon sıklığı ise hastaların %55'inde haftada 2-6 gün, %17,5'inde her gün ve %27,5'inde haftada 1 kez olarak tespit edilmiştir. Göğüs ağrısı (%55), yutma güçlüğü (%40), hazımsızlık (%80) ve şişkinlik (%82,5) gibi semptomlar da sıklıkla bildirilmiştir. Pirozis ve regürjitasyon süreleri sırasıyla 4,12±3,17 yıl ve 3,80±2,85 yıl olarak hesaplanmıştır.

Semptomlar ve İmpedans Bulguları Arasındaki İlişki

Pirozis semptomu haftada 1'den fazla olan 24 hastanın 23'ünde hafif asit reflü saptanırken, pirozisi haftada 1 ve daha az olan 16 hastanın yalnızca 5'inde hafif asit reflü görülmüştür ($p=0,029$). Diğer semptomlar ile hafif asit reflü arasında anlamlı bir ilişki saptanmamıştır. Asit reflü, asit dışı reflü ve reflüsü olmayan hasta gruplarında

yapılan analizlerde semptomlar açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (Tablo 1).

DeMeester pH skoru 14,72'nin üzerinde olan ve toplam asit reflü yüzdesi ≥%4 olan hastalar "asit reflü grubu", diğer hastalar ise "asit dışı reflü grubu" olarak sınıflandırılmıştır. Asit reflü grubu ile reflüsü olmayan grup karşılaştırıldığında, pirozis şiddeti asit reflü grubunda anlamlı şekilde daha yüksek bulunmuştur (p=0,04). Asit reflü hastalarında pirozis sıklığı, regürjitasyon sıklığı ve şiddeti daha yüksek olmasına rağmen, reflüsü olmayan gruptaki düşük hasta sayısı nedeniyle istatistiksel anlamlılık elde edilememiştir.

Asit dışı reflü grubu ile reflüsü olmayan grup karşılaştırıldığında, asit dışı reflü grubunda pirozis sıklığı daha yüksek bulunmuştur (p=0,05). Ancak diğer parametrelerde anlamlı bir fark tespit edilmemiştir.

Tablo 1. Semptomlar ve İmpedans Bulguları Arasındaki İlişki

Klinik bulgu	Hafif Asit Reflü (n=34)			Asit Dışı Reflü (n=3)			Asit Reflü (n=16)			Reflüsü Olmayan (n=5)		
	p	OR	GA	p	OR	GA	p	OR	GA	p	OR	GA
Pirozis sıklığı	0,03	10,4	1,1- 100,6	1,0	1,4	0,1-16,4	0,4	2,3	0,5-10,3	0,1	0,1	0,0-1,3
Pirozis şiddeti	0,2	3,9	0,6-23,4	0,6	0,7	0,6-0,9	0,7	1,7	0,3-8,7	0,1	0,2	0,0-1,2
Regürjitasyon Şiddeti	0,3	3,3	0,6-19,4	0,5	0,7	0,6-0,9	0,7	1,4	0,3-7,1	0,1	0,2	0,0-1,4
Göğüs Ağrısı	0,6	1,2	1,0-1,4	0,4	3,2	0,2-42,2	0,3	1,2	1,0-1,5	1,0	0,8	0,7-0,9
Yutma Güçlüğü	1,0	1,4	0,2-8,7	0,6	3,3	0,3-39,7	0,3	2,9	0,1-16,2	0,6	0,3	0,0-3,3
Hazımsızlık	0,3	1,3	1,1-1,6	0,5	0,5	0,3-39,7	0,7	0,4	0,0-4,0	0,6	0,8	0,6-0,9
Şişkinlik	1,0	0,9	0,1-9,5	1,0	0,8	0,7-0,9	0,6	1,5	0,6-1,4	1,0	0,8	0,1-8,7

OR: Olasılık oranı GA: Güven aralığı

Reflü Türlerinin Klinik ve İmpedans Bulguları ile Karşılaştırılması

Gaz, sıvı ve karma reflü türleri değerlendirildiğinde, gaz reflü ortalaması 85,60±87 (1-403), karma reflü 97,15±89,8 (6-462) ve sıvı reflü 30,8±28,9 (0-134) olarak bulunmuştur. Klinik semptomlar açısından, pirozis sıklığı ve şiddeti ile sıvı, gaz ve karma reflü arasında anlamlı bir fark tespit edilmemiştir (sırasıyla p=0,5, p=1,00, p=0,20).

Reflü Türleri ile İmpedans Bulgularının Karşılaştırılması

Sıvı reflüsü olanlarda hafif asit reflü sayısı ortalama 145,69 iken, olmayanlarda 77,26 olarak bulunmuştur (p=0,005). Gaz reflüsü olan hastalarda, hafif asit reflü sayısı ortalama 114,97 iken, gaz reflüsü olmayan hastalarda bu değer 26,57 olarak tespit edilmiştir (p=0,005). Gaz reflüsü olan hastalarda asit reflü sayısı belirgin şekilde düşük bulunmuştur (p=0,006). Karma reflüsü olan hastalarda 24 saat bolusa maruz kalma yüzdesi anlamlı şekilde daha yüksektir (p=0,016).

Tartışma

Pirozis ve regürjitasyon, GÖRH'ün en sık görülen semptomları arasında kabul edilmektedir.[10] Bununla birlikte, semptomların varlığı tek başına ayırıcı tanıya ulaşmak için yeterli değildir.[10,11] Bu semptomlara sahip hastalar, GÖRH spektrumunun yanı sıra, akalazya, özofageal dismotilite veya fonksiyonel mide yanması gibi 'reflü dışı' durumlarla da karşı karşıya olabilirler. Tipik olarak bu semptomlarla başvuran hastalara PPI tedavisi önerilir ve çoğu zamanda semptom iyileşmesine katkı sağlayabilir.[12] Çalışmamızda asit reflü grubu ile reflüsü olmayan grup karşılaştırıldığında, pirozis şiddeti asit reflü grubunda anlamlı şekilde daha yüksek bulunmuştur (p=0,04). Bu semptomatik hastaların PPI tedavisine verdikleri dramatik iyileşmeyi destekler.

Gastroözofageal reflü hastalığında tipik semptomlardan pirozis ve regürjitasyon, genellikle asit reflü ile ilişkilendirilmektedir. Bununla birlikte çalışmamızda, hafif asit reflüsü ile pirozis sıklığı arasında istatistiksel olarak anlamlı bir ilişki olduğu belirlenmiştir (p=0,029). Bu bulgu, NERH'de yalnızca asit reflüsünün değil, hafif asit reflüsünün de semptom oluşumunda rol oynayabileceğini göstermektedir. Savorino ve ark. yapmış olduğu çalışma, asit dışı reflünün de semptomları tetikleyebileceğini göstermiştir.[13] Bu sonuçlar, asit reflü materyali dışındaki reflülerinde semptoma neden olabileceğini destekler.

Bu çalışmada pirozis dışında kalan klinik parametrelerin, impedans-pH monitörizasyon verileri ile örtüşmediğini ve bu semptomların tek başına reflü tanısı koymada yeterli olmadığını tespit ettik. Özellikle regürjitasyon, göğüs ağrısı, yutma güçlüğü, hazımsızlık ve şişkinlik gibi semptomlar, impedans-pH metre ile ölçülen reflü tipleri arasında anlamlı farklar göstermemiştir. Bu bulgular, kesin tanı için objektif testler ile değerlendirme yapılmasının önemli olduğunu ortaya koymaktadır. Uluslararası diğer çalışmalar da benzer şekilde, klinik semptomların reflü tanısında tek başına yeterli olmadığını ve fonksiyonel testlerin gerekliliğini vurgulamaktadır.[14]

İmpedans-pH monitorizasyonu, yalnızca reflü materyalinin asidik, hafif asidik veya asit dışı özelliklerini ölçmekle kalmayıp, aynı zamanda reflü bolusunun fiziksel özelliklerini de değerlendiren önemli bir yöntemdir. Bu teknik sayesinde sıvı, gaz ve karma reflü tipleri objektif olarak ölçülebilmektedir. Yapılan analizlerde, gaz ve karma reflü ortalamaları daha yüksekken, sıvı reflü ortalaması daha düşük seviyelerde bulunmuştur. Karma reflünün NERH'da daha sık semptoma neden olabileceği görülmüştür.[15,16] Bulgularımız, gaz ile karma reflü tiplerinin, özofajit gelişmeksizin semptomlara neden olabileceğini düşündürmektedir.

Çalışmamızın en önemli sınırlılığı, retrospektif bir çalışma olması nedeniyle dahil etme kriterlerini karşılayan yalnızca 40 hastanın yer almasıdır. Bu durum, elde edilen bulguların genellenebilirliğini ve istatistiksel gücünü sınırlamaktadır. NERH ve asit dışı reflü arasındaki ilişkinin daha kapsamlı ve güvenilir bir şekilde değerlendirilmesi için prospektif daha geniş hasta gruplarını içeren prospektif çalışmalara ihtiyaç vardır.

Sonuç olarak, asit dışı reflü özofagus mukozasına daha az zarar vermekle birlikte, non-erozif reflü hastalarında reflü semptomlarının gelişiminde önemli bir rol oynamaktadır. Çalışmamız, NERH hastalarının hafif asit reflüsüne karşı daha duyarlı olduğunu göstermektedir. Özellikle PPI tedavilerine yanıt vermeyen hastaların yönetiminde asit dışı reflünün dikkate alınması gerekmektedir. Asit dışı reflü hastalarının önemli bir orana sahip olduğu ve pH-metrenin tek başına yetersiz kaldığı NERH tanısında impedans-pH metre ilk tercihlerden biri olmalıdır.

Açıklama

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YBT, AÇ, ÖŞ, SH: Çalışmanın fikrinin geliştirilmesi, hipotezin oluşturulması ve çalışma tasarımının hazırlanması; YBT, DÖK, GŞ, UK, AED, GD, NB: Materyal hazırlama, veri toplama ve analizinin gerçekleştirilmesi, istatistiksel değerlendirme; YBT: Makalenin ilk taslağının yazılması; AÇ, ÖŞ, SH: Makalenin nihai halinin düzenlenmesi ve yayın sürecinin eleştirel değerlendirilmesi.

Kaynaklar

1. Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112(5):1448-1456. doi:10.1016/s0016-5085(97)70025-8
2. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2014;63(6):871-880. doi:10.1136/gutjnl-2012-304269
3. Fass R, Ofman JJ. Gastroesophageal reflux disease--should we adopt a new conceptual framework? *Am J Gastroenterol*. 2002;97(8):1901-1909. doi:10.1111/j.1572-0241.2002.05912.x
4. Fass R. Erosive Esophagitis and Nonerosive Reflux Disease (NERD): Comparison of Epidemiologic, Physiologic, and Therapeutic Characteristics. *Journal of Clinical Gastroenterology*. 2007;41(2):131. doi:10.1097/01.mcg.0000225631.07039.6d
5. Hom C, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2013;42(1):71-91. doi:10.1016/j.gtc.2012.11.004
6. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920; quiz 1943. doi:10.1111/j.1572-0241.2006.00630.x
7. Frazzoni M, de Bortoli N, Frazzoni L, Tolone S, Savarino V, Savarino E. Impedance-pH Monitoring for Diagnosis of Reflux Disease: New Perspectives. *Dig Dis Sci*. 2017;62(8):1881-1889. doi:10.1007/s10620-017-4625-8
8. Zerbib F, des Varannes SB, Roman S, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol Ther*. 2005;22(10):1011-1021. doi:10.1111/j.1365-2036.2005.02677.x
9. Kitapcioglu G, Mandiracioglu A, Bor S. Psychometric and methodological characteristics of a culturally adjusted gastroesophageal reflux disease questionnaire. *Dis Esophagus*. 2004;17(3):228-234. doi:10.1111/j.1442-2050.2004.00413.x
10. Kahrilas PJ. Diagnosis of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol*. 2003;98(3 Suppl):S15-23. doi:10.1016/s0002-9270(03)00011-x
11. Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet*. 1990;335(8683):205-208. doi:10.1016/0140-6736(90)90287-f
12. Giannini EG, Zentilin P, Dulbecco P, Vigneri S, Scarlata P, Savarino V. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. *Am J Gastroenterol*. 2008;103(2):267-275. doi:10.1111/j.1572-0241.2007.01659.x
13. Savarino E, Tutuian R, Zentilin P, et al. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol*. 2010;105(5):1053-1061. doi:10.1038/ajg.2009.670
14. Soto Pérez JC, Icaza ME, Vargas F, Valdovinos Díaz MA. [Non-erosive gastroesophageal reflux disease. Incidence of clinical forms, characteristics of esophageal exposure to acid and symptomatic correlations]. *Rev Gastroenterol Mex*. 2003;68(2):113-119.
15. Emerenziani S, Sifrim D, Habib FI, et al. Presence of gas in the refluxate enhances reflux perception in non-erosive patients with physiological acid exposure of the oesophagus. *Gut*. 2008;57(4):443-447. doi:10.1136/gut.2007.130104
16. Bredenoord AJ, Weusten BLAM, Timmer R, Smout AJPM. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. *Am J Gastroenterol*. 2006;101(11):2470-2475. doi:10.1111/j.1572-0241.2006.00945.x

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Research Article | Araştırma Makalesi

COMPARISON OF MUSCULOSKELETAL SYSTEM PROBLEMS OF UNIVERSITY STUDENTS WHO PLAY AND DO NOT PLAY GUITAR

GİTAR ÇALAN VE ÇALMAYAN ÜNİVERSİTE ÖĞRENCİLERİNİN KAS-İSKELET SİSTEMİ PROBLEMLERİNİN KARŞILAŞTIRILMASI

Oguzhan Bahadır Demir[1,2*], Taha Erim[1], Irem Nur Bagci[1], Ghazal Mohorramzadeh[1] Canan Baydemir[3]

[1]Sakarya University of Applied Sciences, Faculty of Health, Physiotherapy and Rehabilitation Department, Sakarya, Türkiye. [2]Sakarya University of Applied Sciences, Physiotherapy and Rehabilitation Application and Research Center, Sakarya, Türkiye. [3]Kocaeli University, Faculty of Medicine, Basic Medical Sciences, Biostatistics and Medical Informatics, Kocaeli, Türkiye.

ABSTRACT

Objective: Musculoskeletal disorders can be observed in many professions, including professional musicians. The aim of this study is to compare musculoskeletal system problems between university students who play guitar as a leisure activity and those who do not.

Methods: The study included 64 university students aged 18-30, comprising 32 guitar players (guitar players group) and 32 non-guitar players (non-guitar players group). Pain levels of participants were assessed using the Short-Form McGill Pain Questionnaire (SF-MPQ), while the physical condition and functionality of their elbows and upper extremities were evaluated using the Quick Disability of Arm, Shoulder and Hand (Q-DASH) and the Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) for musculoskeletal disorders.

Results: At the end of the study, differences were found between the two groups in CMDQ data for the back, right knee, and left knee ($p<0.05$). It was determined that guitar-playing students had more discomfort in the upper back region compared to non-guitar players ($p=0.048$), while non-guitar-playing students reported more discomfort in the right ($p=0.012$) and left knee ($p=0.006$) regions compared to guitar players.

Conclusion: In our study, there was a statistically significant difference in upper back pain in students who played guitar compared to those who did not play guitar. There was a statistically significant difference in knee pain in non-guitar players compared to those who played guitar. It is recommended that students who play guitar should be given physical ergonomics training and strengthening-stretching exercises for possible musculoskeletal problems.

Keywords: Musculoskeletal pain, music, postural disorders, risk facotors

ÖZ

Amaç: Çalışma ile ilgili Kas İskelet Sistemi Rahatsızlıkları, profesyonel müzisyenler de dahil olmak üzere birçok meslekte görülebilmektedir Bu çalışmanın amacı serbest zaman aktivitesi olarak gitar çalan üniversite öğrencileri ile enstrüman çalmayan üniversite öğrencileri arasındaki kas-iskelet sistemi problemlerini karşılaştırmaktır.

Yöntem: Çalışmaya 32 gitar çalan (gitar çalanlar grubu) ve 32 gitar çalmayan (gitar çalmayanlar grubu) olmak üzere 18-30 yaş arasında 64 üniversite öğrencisi dahil edildi. Katılımcıların ağrı seviyelerinin değerlendirilmesi Kısa-Form McGill-Melzack Ağrı Anketi (SF-MPQ), dirsek ve üst ekstremitelerinin fiziksel durumu ve fonksiyonelliği değerlendirilmesi Quick-Disability of Arm, Shoulder and Hand (Q-DASH) ve kas-iskelet sistemi rahatsızlıkları Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) ile değerlendirildi.

Bulgular: Çalışmanın sonunda iki grubun CMDQ sırt, sağ ve sol diz verilerinde farklılık tespit edildi ($p<0,05$). Gitar çalan öğrencilerin sırt bölgesinde rahatsızlıklarının gitar çalmayanlara göre daha fazla olduğu, gitar çalmayan öğrencilerin sağ ve sol diz bölgesi rahatsızlıklarının gitar çalan öğrencilere göre daha fazla olduğu tespit edildi..

Sonuç: Çalışmamızda, gitar çalan öğrencilerde, gitar çalmayanlara kıyasla sırt ağrısı istatistiksel olarak anlamlı bir farklılık göstermiştir. Gitar çalmayanlarda, gitar çalanlara göre diz ağrısı istatistiksel olarak anlamlı bir farklılık göstermiştir. Gitar çalan öğrencilere, oluşabilecek kas-iskelet sistemi problemlerine yönelik fiziksel ergonomi eğitimi ve kuvvetlendirme-germe egzersizleri verilmesi önerilir.

Anahtar Kelimeler: Kas-iskelet sistemi ağrısı, müzik, öğrenciler, duruş bozuklukları, risk faktörleri

***Corresponding author/İletişim kurulacak yazar:** Oğuzhan Bahadır Demir; Physiotherapy and Rehabilitation Department, Faculty of Health, Sakarya University of Applied Sciences, Sakarya, Türkiye
Phone/Telefon: +90 (532) 670 84 59, **e-mail/e-posta:** oguzhandemir@subu.edu.tr
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Introduction

Playing an instrument is a complex performance that requires the development and adaptation of the neuromuscular and somatosensory systems. Musicians spend a significant amount of their time practicing over the years to develop these complex movements.[1] Musicians may experience musculoskeletal disorders (MSDs) due to the long-term static activity of the proximal muscles of the torso and upper extremities, as well as the repetitive movements of the small finger and wrist muscles.[2]

Playing-related musculoskeletal disorders (PRMDs) associated with playing an instrument are defined as conditions that include symptoms such as pain, loss of control, numbness, and tingling that hinder the ability to play the instrument at a comfortable level.[3] Risk factors for instrument-related MSDs include instrument size, shape, weight, and type, playing technique, playing position and posture of the musician, duration and intensity of playing, repertoire, and performance stress.[3,4] Amateur musicians typically spend less time playing instruments compared to professional musicians, and their playing styles and techniques may vary. Sudden increases in playing time can be a risk factor for PRMDs associated with playing instruments in amateur musicians.[3,4]

Due to the lack of longitudinal studies on the etiology of PRMDs observed in musicians, no causal relationships have been established.[5] Various etiological factors, including occupational, personal, environmental, and psychosocial factors, may also contribute to these disorders.[6] Similar to musicians, university students can also experience MSDs.[7] The prevalence of musculoskeletal pain among university students, particularly medical students, has been found to be high, while it has been noted that there is no relationship between long study hours and computer use and MSDs outside of medical students.[8] Among university students enrolled in health programs, the highest prevalence of musculoskeletal pain in the last seven days has been reported in the spine, particularly in the cervical and lumbar regions, followed by the upper extremity, especially the shoulder region.[9]

In the literature, there is no study comparing the MSDs of university students who play guitar as a leisure activity with those who do not play any musical instrument. This study aims to compare pain and MSDs between university students who play guitar and those who do not play any musical instrument.

Methods

Participants were selected from students studying at the Faculty of Health Sciences of a university located in western Turkey. No sampling method was used in the study; instead, students who agreed to participate after information was provided in student WhatsApp groups constituted the sample after a pilot study conducted. Students who agreed to participate were informed about the purpose, duration, the nature of the procedures to be carried out, and the assessment methods, through written, verbal, and visual communication. Among the students who accepted to participate, those meeting the inclusion criteria were divided into two groups: guitar players and non-guitar players. University students who did not play any instrument were referred to as the "Non-Guitar Players Group," while those who played guitar were referred to as the "Guitar Players Group."

Inclusion criteria for the study were determined as being between 18-30 years of age, being a university student, and being willing to participate in the study. The non-guitar players group included students who had never played any instrument and had no musical background, while the guitar players group included students who had been playing guitar for at least one year and had received guitar training at a music institution or had previously received music training and were still playing guitar. Students with injuries that would affect performance, symptoms of nerve compression, those regularly taking medication for chronic pain treatment, those diagnosed with disc lesions, those with inflammatory joint disorders/orthopedic problems, and non-university students were excluded from the study.

Ethical approval was obtained from the ethics committee of a state university (2023, 37/13), institutional permission was granted from the university where the study was conducted, and written and verbal consent was obtained from the participating students. The rules stated in the Declaration of Helsinki were followed throughout the research.

In the assessment, after obtaining individuals socio-demographic information, pain levels were evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ), the physical condition and functionality of their elbows and upper extremities were evaluated using the Quick Disability of Arm, Shoulder, and Hand (Q-DASH), and musculoskeletal disorders were assessed using the Cornell Musculoskeletal Discomfort Questionnaire (CMDQ). The data collection was conducted face-to-face. The Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) was developed at Cornell University, and its Turkish reliability study was conducted by Erdinç O. *et al*. (2009). The CMDQ examines the frequency, intensity, and impact on work ability of musculoskeletal discomfort in 20 body parts over a period of 7 days. Responses on the frequency, severity, and work interference scales can be used for calculations in percentages or weights. The frequency scale assesses the frequency of experiencing musculoskeletal discomfort: "Did not feel at all: 0, felt 1-2 times during the week: 1.5, felt 3-4 times during the week: 3.5, felt once every day: 5, felt several times every day: 10." The severity scale evaluates the intensity of musculoskeletal discomfort: "Mildly severe: 1, moderately severe: 2, very severe: 3." The work interference scale assesses the impact of musculoskeletal discomfort on work ability: "Did not interfere *at all*: 1, interfered a little: 2, interfered a lot: 3".[10]

The Quick Disability of the Arm, Shoulder, and Hand (Q-DASH) is a self-reported questionnaire that measures the physical functions and symptoms of patients with upper extremity problems. The Q-DASH (Quick-DASH) questionnaire is a shortened version of the full thirty-item DASH questionnaire, created to develop a short, reliable, and valid measure of physical function and symptoms related to upper extremity musculoskeletal disorders. It contains eleven items and is similar to the DASH questionnaire in scoring and properties. Each item has five response options, and the total score for the scale is calculated from the individual item scores (0 = no disability and 100 = most severe disability). The first eight items of the Q-DASH measure the patient's daily living functions and social activity limitations. The ninth question assesses pain intensity, and the tenth question evaluates the sensation of "tingling" in the upper extremity. The last question is designed to assess sleep problems related to pain. The Q-DASH has been shown to be a more effective version than the DASH, preserving measurement properties. Its Turkish reliability study was conducted by Doğan S. K. *et al*. (2010).[11]

The Short-Form McGill Pain Questionnaire (SF-MPQ) was developed by Dr. Melzack at McGill University in Canada in 1971. It is a self-administered pain questionnaire for patients with various diagnoses experiencing severe pain. It assesses both the quality and intensity of pain. The McGill-Melzack Pain Questionnaire (MPQ) is a multidimensional tool for pain assessment, consisting of three main sections. The first section describes how the pain feels, the second relates to the time course of the pain, and the third assesses the strength of the pain. In the first section, words that describe current pains are provided, and the respondent is asked to circle only the words that best describe their pain. The second section asks the respondent to use words that describe the pain and then inquires what alleviates the pain and what exacerbates it. The third section uses words representing increasing pain intensity to answer questions in the survey by writing the corresponding number of the pain descriptor in the space next to each question, totaling six questions. Points for responses are indicated numerically next to each answer in the questionnaire. The scores are summed, resulting in a total score between 0 and 112. In addition to the three main sections, there is a section featuring a human model to describe where the pains are located in the body. The practitioner marks the area of pain and describes it as "deep," "superficial," or "both deep and superficial." The Short-Form McGill Pain Questionnaire (SF-MPQ) consists of 15 defined words rated on the "intensity" scale (11 sensory, 4 perceptual). The total of the intensity levels of the selected words results in three pain scores. There is one question for current pain intensity and a Visual Analog Scale (VAS) for average pain. The Turkish reliability study was conducted by Yakut Y. *et al*. (2006).[12]

In the analysis of data obtained from the study, mean and standard deviation values were used for normally distributed data obtained by measurement, median (25th – 75th Percentile) values for non-normally distributed data, and frequency and proportion values for categorical data. The normality of the measurement data was assessed using the Shapiro-Wilk test. The t-test was used for comparisons of normally distributed measurement data and the Mann-Whitney U test for comparisons of non-normally distributed measurement data. The Chi-square test was used for the analysis of categorical data. Data were analyzed using the SPSS 29 (IBM Corp., Armonk, NY, USA) software package.

Results

A total of 64 students participated in the study, comprising guitar players (n=32) and non-guitar players (n=32). Among the guitar players group, 15 were female (%46.9) and 17 were male (%53.1), while in the non-guitar players group, 13 were male (%40.6) and 19 were female (%59.4). The average duration of guitar playing for students in the guitar players group was 5.79 ± 6.20 hours per week, or 58.59 ± 54.82 minutes per day. There was no statistically significant difference in gender between the groups (p=0.453). The average age of the participants was 21.65 ± 1.72 years, and there was no statistically significant difference in demographic characteristics between the groups (Table 1).

Table 1. Demographic Characteristics of Participants

	Guitar Players Mean ± SD	Non-guitar Players Mean ± SD	*p*
Age (Year)	21.84 ± 2.23	21.46 ± 0.98	0.389
Body Mass Index (BMI)	22.89 ± 3.44	22.43 ± 3.15	0.578
Gender	15f- 17m	19f- 13m	0.453

f: female, m: male. Significance level p<0.05. Mann-Whitney U test and Chi-square test.

There was no statistically significant difference between the Q-DASH and SF-MPQ data of both groups (p>0.05) (Table 2).

Table 2. Participants' Q-DASH and SF-MPQ Data

	Guitar Players Median (25th - 75th Percentile)	Non-guitar Players Median (25th - 75th Percentile)	*p*
Q-DASH	16.00(13.00-21.00)	15.00(12.25-17.00)	0.162
Sensory Pain Score	4.00(3.00-6.00)	2.00(0.00-6.50)	0.094
Perceptual Pain Score	1.00(0.00-2.00)	0.00(0.00-2.00)	0.230
Total Pain Intensity	5.00(3.00-9.00)	2.50(0.25-8.50)	0.092
VAS (Visual Analog Scale)	3.00(1.00-4.00)	1.00(1.00-4.00)	0.101

*Significance level p<0.05. Mann-Whitney U test.

No statistically significant difference was found among the participants Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) data for the neck, right shoulder, left shoulder, right upper arm, left upper arm, lower back, right forearm, left forearm, right wrist, left wrist, hip, right thigh, left thigh, right calf, left calf, right foot, and left foot parameters (p>0.05).

Table 3. Participants' CMDQ Data

	Guitar Players Median (25th - 75th Percentile)	Non-guitar Players Median (25th - 75th Percentile)	*p*
Neck	3.00(0.37-6.75)	1.50(0.00-6.00)	0.217
Right shoulder	1.50(0.00-3.50)	0.00(0.00-3.00)	0.343
Left shoulder	1.50(0.00-3.50)	0.00(0.00-3.00)	0.146
Upper Back	3.00(0.00-14.00)	1.50(0.00-3.37)	**0.048***
Right Upper Arm	0.00(0.00-0.00)	0.00(0.00-0.00)	0.731
Left Upper Arm	0.00(0.00-0.00)	0.00(0.00-0.00)	0.353
Lower Back	1.50(0.00-6.00)	1.50(0.00-5.75)	0.813
Right Forearm	0.00(0.00-0.00)	0.00(0.00-0.00)	0.226
Left Forearm	0.00(0.00-0.00)	0.00(0.00-0.00)	0.981
Right Wrist	0.75(0.00-1.50)	0.00(0.00-1.12)	0.073
Left Wrist	0.00(0.00-1.50)	0.00(0.00-1.12)	0.105
Hip	0.00(0.00-0.00)	0.00(0.00-1.50)	0.265
Right Thigh	0.00(0.00-1.50)	0.00(0.00-0.00)	0.059
Left Thigh	0.00(0.00-1.50)	0.00(0.00-0.00)	0.082
Right Knee	0.00(0.00-0.00)	0.00(0.00-2.62)	**0.012***
Left Knee	0.00(0.00-0.00)	0.00(0.00-3.00)	**0.006***
Right Calf	0.00(0.00-0.00)	0.00(0.00-0.00)	0.456
Left Calf	0.00(0.00-0.00)	0.00(0.00-0.00)	0.610
Right Foot	0.00(0.00-0.00)	0.00(0.00-0.00)	0.953
Left Foot	0.00(0.00-0.00)	0.00(0.00-1.12)	0.835

*Significance level p<0.05. : Statistically significant (p<0.05). Mann-Whitney U test.

However, a statistically significant difference was found between the CMDQ data for the upper back (p=(0.048), right knee (p=0.012),and left knee (p=0.006) of both groups (p<0.05). The CMDQ data of the participants are presented in Table 3.

Discussion

In our study comparing musculoskeletal disorders (MSDs) among university students who play guitar and those who do not, we found that guitar-playing students reported a higher prevalence of upper back-related complaints than their non-guitar-playing counterparts. Furthermore, non-guitar-playing students reported more issues in their right and left knee regions compared to those who played guitar.

Musicians undergo rigorous training and conditioning to develop the skills necessary for accurate and effective instrument performance. As a result, they typically practice for an average of 5- 6 hours per day.[13] Remaining in a static position for long hours while playing an instrument, can lead to excessive strain on the body, resulting in pain and injuries accompanied by muscle imbalances and postural changes.[14] The prevalence of PRMDs among music students varies between 43% and 63%, whereas this rate exceeds 80% among professional musicians.[15] The average guitar playing duration of the students participating in our study was below the ideal time, and the PRMDs of guitar players were similar to those of non-players. A study conducted by Kaczorowska *et al*. reported a positive relationship between the hours spent playing an instrument weekly, the total years of playing, pain severity, and the frequency of discomfort. They concluded that as the weekly instrument playing time and the total playing years increased, the severity of pain also increased.[16] In another study by Robitaille *et al*., involving 488 musicians, it was found that increasing playing time by 7 hours per week resulted in approximately a 15% increase in pain frequency. The study concluded that there is a relationship between playing time and both pain frequency and intensity, but no relationship was found with other risk factors.[17]

When we review the literature, in a study conducted by Martins *et al*., that supports our findings, 140 musicians aged 18-55 were examined. It was reported that 15.7% of musicians experiencing PRMDs did not practice at all, 72.9% practiced only once a week, and 11.4% practiced daily. Participants reported their most common discomforts over the past 12 months in the following order: wrist/hand, shoulder, back, and lower back, foot/ankle, hip, and elbow regions. They concluded that there was no relationship between sociodemographic structure, lifestyle, general health, and instrument practice with musculoskeletal injuries.[18]

In another study involving 792 students from health-related departments of universities conducted by Morais *et al*., the most common musculoskeletal problems were found in the spine region (74.9%). The cervical spine (51.0%) and lumbar spine (54.5%) had the highest prevalence of musculoskeletal problems. The upper extremity (54.1%) (Shoulder region 40.4%), and lower extremity (43.6%) (Knees 26.4%) were also identified as regions with high prevalence.[19] It was found that students without leisure activities experienced more musculoskeletal problems. In our study, the higher incidence of right and left knee problems among non-guitar-playing health department students compared to guitar players may be attributed to the lack of leisure activities among non-players.

According to a study conducted by Zalpour *et al*., it was found that the complaints related to the spine region were the highest among musicians (57.7%), while

complaints related to the lower extremities were much lower (7.9%). The most common complaints in the upper extremity were found among string instrument players (25.7%), while the lowest complaints were observed in musical groups (5.7%).[20] Similar to the result obtained in our study, where students who do not play the guitar have more right and left knee discomfort, a study conducted by Poot E. F. M. *et al*. to evaluate health department students reported that the most common complaints were neck, left shoulder, right shoulder, back, left upper arm, right upper arm, right and left knee.[21] Similarly, in our study, non-guitar-playing students reported more knee discomfort. In another study examining PRMDs in 60 musicians, the most common problems were lumbar spine (46% in men & 94% in women), cervical spine (27% in men & 50% in women), and upper extremities (27% in men & 50% in women). The region with the least complaints was found to be the lower extremities (7.5% in men & 3% in women).[16] A study by Portnoy *et al*. found that guitar players who sit while playing had a forward and rightward inclination of the spine.[22] In our study, 32 total guitar players, 31 of them were playing guitar while seated, and the high incidence of back discomfort may be related to sitting while playing the guitar.

The limitations of our study include its single-center design and the lack of assessment of participants' physical activity levels, cell phone use and joint laxity. We believe that further studies evaluating the physical activity levels and joint laxity of participants are necessary in this area.

In our study, there was a statistically significant difference in upper back pain between guitar-playing students and those who did not play guitar. Conversely, non-guitar-playing students exhibited statistically significant differences in knee pain compared to guitar players. It is recommended that guitar-playing students receive physical ergonomics training and strength/stretching exercises to address potential musculoskeletal issues.

Ethical Approval

The study protocol was approved by Ethics Committee of Sakarya University of Applied Sciences (numbered (2023, 37/13)).

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

OBD, TE: Consept; OBD, TE, INB: Design; TE, INB, GM: Data Collection and Processing; OBD, CB: Analysis and Interpretation; TE, INB, GM: Literature Search; OBD, TE, CB: Writing, Reviewing and Editing. All the authors read and approved the final manuscript.

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References

1. Chan C, Ackermann B. Evidence-informed physical therapy management of performance-related musculoskeletal disorders in musicians. *Front Psychol.* 2014;5:706. doi:10.3389/fpsyg.2014.00706.
2. Wilke C, Priebus J, Biallas B, Froböse I. Motor activity as a way of preventing musculoskeletal problems in string musicians. *Med Probl Perform Art.* 2011;26(1):24-29.
3. Wilson IM, Doherty L, McKeown L. Perceptions of Playing-Related Musculoskeletal Disorders (PRMDs) in Irish traditional musicians: a focus group study. Work. 2014;49(4):679-88. doi:10.3233/WOR-131737.
4. Cruder C, Barbero M, Koufaki P, Soldini E, Gleeson N. Prevalence and associated factors of playing-related musculoskeletal disorders among music students in Europe. Baseline findings from the Risk of Music Students (RISMUS) longitudinal multicentre study [published correction appears in *PLoS One.* 2021;16(10):e0258608. doi:10.1371/journal.pone.0258608.
5. Baadjou VAE, Roussel NA, Verbunt JAMCF, Smeets RJEM, de Bie RA. Systematic review: risk factors for musculoskeletal disorders in musicians. *Occup Med* (Lond). 2016;66(8):614-622. doi:10.1093/occmed/kqw052
6. Shahanawaz SD, Acar T, Krishna V. Disability and severity of playing related soft tissue injuries among professional guitar players: *A cross-sectional survey. EJMCM.* 2020;*7*(02):4767-4771.
7. Alsaadi SM. Musculoskeletal Pain in Undergraduate Students Is Significantly Associated with Psychological Distress and Poor Sleep Quality*. Int J Environ Res Public Health.* 2022;19(21):13929. doi:10.3390/ijerph192113929
8. Hasan M, Yaqoob U, Ali S, Siddiqui A. Frequency of Musculoskeletal Pain and Associated Factors among Undergraduate Students. *Case Reports in Clinical Medicine.* 2018;7:131-145. doi:10.4236/crcm.2018.72011.
9. Morais BX, Dalmolin GL, Andolhe R, Dullius AIDS, Rocha LP. Musculoskeletal pain in undergraduate health students: prevalence and associated factors. *Rev Esc Enferm USP*. 2019;53:e03444.doi:10.1590/S1980-220X20180144034 44.
10. Erdinc O, Hot K, Ozkaya M. Turkish version of the Cornell Musculoskeletal Discomfort Questionnaire: cross-cultural adaptation and validation. *Work*. 2011;39(3):251-260. doi:10.3233/WOR-2011-1173.
11. Koldas Dogan S, Ay S, Evcik D, Baser O. Adaptation of Turkish version of the questionnaire Quick Disability of the Arm, Shoulder, and Hand (Quick DASH) in patients with carpal tunnel syndrome. *Clin Rheumatol*. 2011;30(2):185-191. doi:10.1007/s10067-010-1470-y.
12. Yakut Y, Yakut E, Bayar K, Uygur F. Reliability and validity of the Turkish version short-form McGill pain questionnaire in patients with rheumatoid arthritis. *Clin Rheumatol*. 2007;26(7):1083-1087. doi:10.1007/s10067-006-0452-6.
13. Chesters L, Sharp K. Edition, illustrated. *Pearson Education Australia*; 2003. ISBN 0757843883, 9780757843884.
14. Uluocak DS. Türkiye'de Cumhuriyet'in ilk elli yılında klasik gitar eğitimi: Paleologos ve öğrencileri. *Sahne ve Müzik.* Temmuz 2015;(1):60-80.
15. Kok LM, Groenewegen KA, Huisstede BMA, Nelissen RGHH, Rietveld ABM, Haitjema S. The high prevalence of playing-related musculoskeletal disorders (PRMDs) and its associated factors in amateur musicians playing in student orchestras: A cross-sectional study. *PLoS One*.

2018;13(2):e0191772. doi:10.1371/journal.pone.0191772.

16. Kaczorowska A, Mroczek A, Lepsy E *et al*. Musculoskeletal pain in professional symphony orchestra musicians. *Med Sci Pulse.* (2021);15(3):38-43. doi:10.5604/01.3001.0015.0633.
17. Robitaille J, Tousignant-Laflamme Y, Guay M. Impact of Changes in Playing Time on Playing-Related Musculoskeletal Pain in String Music Students. *Med Probl Perform Art.* 2018;33(1):6-13. doi:10.21091/mppa.2018.1003.
18. Martins R, Andrade A, Martins C, Albuquerque C, Sales T. Musculoskeletal injuries in musical arts professional: prevalence and determinants. *AJS*. 2018:71-76.
19. Morais BX, Dalmolin GL, Andolhe R, Dullius AIDS, Rocha LP. Musculoskeletal pain in undergraduate health students: prevalence and associated factors. *Rev Esc Enferm USP*. 2019;53:e03444. doi:10.1590/S1980-220X2018014403 444.
20. Zalpour C, Ballenberger N, Avermann F. A Physiotherapeutic Approach to Musicians' Health - Data From 614 Patients From a Physiotherapy Clinic for Musicians (INAP/O). *Front Psychol*. 2021;12:568684. doi:10.3389/fpsyg.2021.568684.
21. Mohd Poot EF, Nordin NA. Musculoskeletal disorders (MSD), stress, and elements of home environment among health sciences students in Malaysia. Healthscope: *The Official Research Book of Faculty of Health Sciences*, UiTM, 2022;5(2):24-31. Retrieved from https://healthscopefsk.com/index.php/research/article/view/285
22. Portnoy S, Cohen S, Ratzon NZ. Correlations between body postures and musculoskeletal pain in guitar players. *PLoS One.* 2022;17(1):e0262207. doi:10.1371/journal.pone. 0262207.

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Research Article | Araştırma Makalesi

A RETROSPECTIVE COMPARATIVE ANALYSIS OF THE TEMPORAL DYNAMICS OF ACUTE CORONARY SYNDROMES DURING THE PERI-PANDEMIC (COVID-19) PERIOD

PERİ-PANDEMİ (COVID-19) DÖNEMİNDE AKUT KORONER SENDROMLARIN ZAMANSAL DİNAMİKLERİNİN RETROSPEKTİF KARŞILAŞTIRMALI ANALİZİ

Abdulkadir Cakmak[1*], Omer Kertmen[1]

[1]Amasya University, Faculty of Medicine, Department of Cardiology, Amasya, Türkiye.

ABSTRACT

Objective: The COVID-19 pandemic, caused by SARS-CoV-2, disrupted global healthcare systems and significantly influenced cardiovascular health. This study examines the temporal trends of acute coronary syndromes (ACS), including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (USAP), across pre-pandemic, pandemic, and post-pandemic periods.

Methods: This retrospective observational study was conducted at a single tertiary cardiovascular center involving patients diagnosed with ACS from January 2018 to June 2024. Patients were stratified into three cohorts: pre-pandemic (January 2018-February 2020), pandemic (March 2020-April 2022), and post-pandemic (May 2022-June 2024).

Results: The incidence of STEMI and NSTEMI significantly increased in the post-pandemic period compared to those in the other periods ($p<0.001$). The number of USAP cases was significantly lower during the pandemic and post-pandemic periods ($p<0.01$). Temporal analyses revealed a positive correlation between time and STEMI/NSTEMI cases ($p<0.0001$). However, USAP incidence showed no significant correlation with time. These trends suggest that delayed healthcare access and pandemic-related inflammatory and thrombotic mechanisms are key drivers of increased myocardial infarction cases.

Conclusion: The findings underscore the enduring impact of the pandemic on ACS presentations, highlighting the need for adaptive healthcare systems. Strategies incorporating anti-inflammatory approaches and resilient healthcare frameworks are essential for mitigating the long-term cardiovascular consequences of future crises. Further multicenter studies are recommended to validate these findings and to enhance our understanding of the mechanisms involved.

Keywords: Acute coronary syndromes, COVID-19, NSTEMI, STEMI, USAP

ÖZ

Amaç: SARS-CoV-2'nin neden olduğu COVID-19 pandemisi, küresel sağlık sistemlerini ciddi şekilde etkileyerek kardiyovasküler sağlığı derinden etkilemiştir. Bu çalışma, pandemi öncesi, pandemi ve pandemi sonrası dönemlerde ST-yükselmeli miyokard enfarktüsü (STEMI), ST-yükselmesiz miyokard enfarktüsü (NSTEMI) ve stabil olmayan angina pektoris (USAP) gibi akut koroner sendromların (AKS) zamansal eğilimlerini değerlendirmektedir.

Yöntem: Bu retrospektif gözlemsel çalışma, Ocak 2018 ile Haziran 2024 tarihleri arasında bir üçüncü basamak kardiyovasküler merkezde AKS tanısı alan hastaları içermektedir. Hastalar üç kohorta ayrılmıştır: pandemi öncesi (Ocak 2018-Şubat 2020), pandemi (Mart 2020-Nisan 2022) ve pandemi sonrası (Mayıs 2022-Haziran 2024).

Bulgular: STEMI ve NSTEMI insidansı, diğer dönemlere kıyasla pandemi sonrası dönemde anlamlı şekilde artmıştır ($p<0,001$). USAP vakalarının sayısı ise pandemi ve pandemi sonrası dönemlerde anlamlı olarak daha düşüktür ($p<0,01$). Zamansal analiz, STEMI/NSTEMI vakaları ile zaman arasında pozitif bir korelasyon olduğunu göstermiştir ($p<0,0001$). Ancak USAP insidansı ile zaman arasında anlamlı bir korelasyon saptanmamıştır. Bu eğilimler, pandemiye bağlı gecikmiş sağlık hizmetlerine erişim ile inflamatuvar ve trombotik mekanizmaların miyokard enfarktüsü vakalarındaki artışın ana nedenleri olduğunu ortaya koymaktadır.

Sonuç: Bulgular, pandeminin AKS sunumları üzerindeki kalıcı etkisini vurgulamakta ve adaptif sağlık sistemlerine duyulan ihtiyacı işaret etmektedir. Gelecekteki krizlerin uzun vadeli kardiyovasküler sonuçlarını azaltmak için anti-inflamatuvar yaklaşımlar içeren stratejiler ve dirençli sağlık sistemleri gereklidir. Bu bulguların doğrulanması ve ilgili mekanizmaların daha iyi anlaşılması için çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akut koroner sendromlar, COVID-19, NSTEMI, STEMI, USAP

***Corresponding author/İletişim kurulacak yazar:** Abdulkadir Cakmak; Amasya University, Faculty of Medicine, Department of Cardiology, Amasya, Türkiye.
Phone/Telefon: +90 (358) 218 40 00, **e-mail/e-posta:** cakmaka6@gmail.com
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Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has profoundly affected global healthcare systems, extending far beyond its well-characterized respiratory pathology to impose significant burdens on cardiovascular health.[1] COVID-19 is progressively recognized as a multi-systemic disease with significant complications for the cardiovascular system, including heightened risks of myocardial infarction (MI), thrombotic events, and other major adverse cardiac events (MACE).[2] The pathophysiology of myocardial injury in the context of COVID-19 is multifaceted, encompassing both direct and indirect mechanisms. These include viral infiltration of cardiomyocytes, exacerbated systemic inflammatory responses, endothelial dysfunction, and the induction of a hypercoagulable state.[3] Collectively, these interrelated mechanisms have exacerbated the global burden of cardiovascular disease during the pandemic. Both the acute and chronic sequelae of COVID-19 on cardiovascular health are marked by an increased incidence of acute coronary syndromes (ACS), including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (USAP).[4-6]

Acute MI, defined as sustained myocardial ischemia culminating in irreversible myocardial necrosis, persists as a principal contributor to global morbidity and mortality.[7] The COVID-19 pandemic has further illuminated the complex interrelationship between systemic inflammatory cascades and underlying cardiovascular comorbidities, underscoring an augmented incidence and severity of MI presentations.[1,8] Direct viral infiltration into endothelial cells precipitates widespread endothelitis, which, in turn, contributes to atherosclerotic plaque instability and thrombotic complications.[9] In addition, the systemic hyperinflammatory response, characterized by the so-called cytokine storm, coupled with a hypercoagulable state, predisposes patients to ACS.[10,11] Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), play critical roles in endothelial dysfunction, fostering plaque rupture and subsequent myocardial injury.[12-14]

In addition to the direct pathophysiological consequences of SARS-CoV-2 infection, the indirect effects of the pandemic have profoundly impacted cardiovascular outcomes.[15,16] Delays in seeking emergency medical care, driven by the fear of contacting SARS-CoV-2, along with extensive disruptions in healthcare delivery, has resulted in delays in seeking emergency medical care for acute cardiovascular events. Such delays have contributed to increased rates of out-of-hospital cardiac arrest and worsened clinical presentations upon hospital admission.[17] Additionally, decreased access to healthcare services, compounded by an overwhelming burden on healthcare infrastructure, has led to suboptimal management of ACS during the pandemic, resulting in increased in-hospital mortality and adverse clinical outcomes.[18]

The incidence of ACS, including STEMI, NSTEMI, and USAP, has demonstrated significant temporal variability throughout the various phases of the pandemic. Retrospective analyses have documented a notable decline in hospital admissions for ACS during the initial stages of the pandemic, followed by a subsequent increase in the incidence of delayed presentations and associated complications.[19-21] Nevertheless, a comprehensive evaluation of ACS incidence spanning the pre-pandemic, pandemic, and post-pandemic periods remains limited. This gap constrains our ability to fully understand of how healthcare disruptions and viral pathogenicity collectively influence cardiovascular health. The present study aims to undertake a rigorous retrospective evaluation of the incidence of acute coronary syndromes during the COVID-19 pandemic, with comparative analyses involving the pre-pandemic and post-pandemic periods.

Methods

This retrospective observational study was conducted at a single tertiary cardiovascular center, involving patients diagnosed with ACS from January 2018 to June 2024. All adult patients who were diagnosed with ACS based on clinical symptoms and signs, electrocardiography (ECG) changes, cardiac biomarker evaluation and who underwent coronary angiography were included in the study.

In the present study, STEMI was defined as the detection of ST-segment elevation (or ST-segment elevation equivalent) on the ECG of a patient with ischemic symptoms. NSTEMI was defined as the detection of elevated cardiac injury markers without ST-segment elevation on the ECG of a patient with ischemic symptoms. USAP was defined as myocardial ischemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. Angina lasting more than 20 minutes at rest, new-onset severe angina, and angina with increasing frequency and duration were also considered USAP. Patients with incomplete clinical records, those who did not undergo coronary angiography, and those who experienced in-hospital mortality unrelated to cardiovascular causes were excluded.

The first COVID-19 case was reported on March 11, 2020 by the Ministry of Health of the Republic of Türkiye. When the two-week incubation period of the virus is also taken into account, according to official statements, the period before March 2020 in Türkiye was considered as the pre-pandemic period; the period when protective measures, including masks, were increased and a full lockdown was experienced was considered as the pandemic period; and the period after April 2022, when strict measures were relaxed and many obligations due to the pandemic were officially lifted, was considered as the post-pandemic period. Accordingly, the patients

were categorized into three temporal cohorts based on their admission period: pre-pandemic (January 2018 to February 2020), pandemic (March 2020 to April 2022), and post-pandemic (May 2022 to June 2024). The study was approved by the Amasya University Non-Interventional Clinical Research Ethics Committee (Date: 26 November 2024, No: 2024/123).

Data Collection and Measured Outcomes

Patient data were retrospectively collected from the electronic health records (EHRs) of the hospital. Temporal cohort assignment was based on the date of hospital admission. The outcome was the incidence of ACS during the pre-pandemic, pandemic, and post-pandemic periods. All included subjects had valid and complete information for all study variables. Our hospital is the only hospital in the city, and the cardiology department accepts patients and performs coronary angiography procedures on a 7/24 basis. Before, during and after the pandemic, a limited number of patient referrals were made to other centers with higher bed capacity nearby, but the number of referrals did not differ in the relevant periods.

Statistical Analysis

The statistical analyses were conducted using SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation. The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. One-way analysis of variance (ANOVA) was performed for intergroup comparisons of variables with a normal distribution, followed by Tukey's post-hoc test for multiple comparisons. Data that did not follow a normal distribution were analyzed using the Kruskal-Wallis test, followed by Dunn's multiple comparison test. Correlation analyses were performed using Pearson's correlation test for parametric data, and Spearman's correlation test for nonparametric data. A p value of <0.05 was considered indicative of statistical significance.

Results

The total number of ACS cases during the pre-pandemic, pandemic and post-pandemic periods were 1860, 1488 and 2216, respectively. A total of 431, 456 and 617 patients were diagnosed with STEMI, 954, 872 and 1303 were diagnosed with NSTEMI, and 475, 160 and 296 patients were diagnosed with USAP during the pre-pandemic, pandemic and post-pandemic periods, respectively.

The average number of cases diagnosed with STEMI and NSTEMI per month was significantly higher in the post-pandemic period than in the pre-pandemic and pandemic periods (p<0.001; Figure 1A and B). On the other hand, the average number of cases diagnosed with USAP per month was significantly lower during the pandemic and post-pandemic periods compared to pre-pandemic period (p<0.01; Figure 1C). However, the total number of ACS cases per month was significantly higher during the post-pandemic period than that during the pre-pandemic period (p<0.05, Figure 1D).

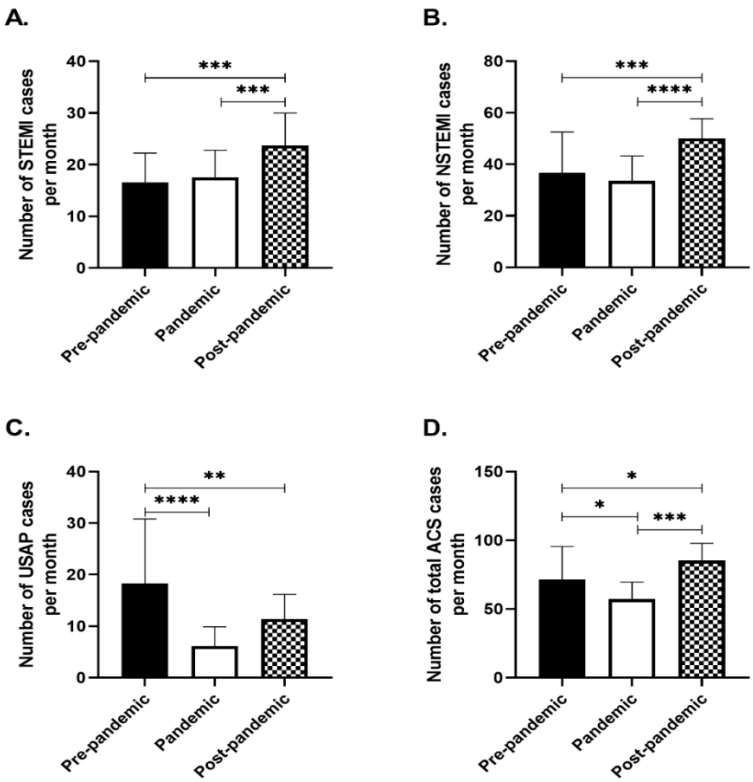

Figure 1. Number of **(A)** STEMI, **(B)** NSTEMI, **(C)** USAP and **(D)** total ACS cases per month during pre-pandemic, pandemic and post-pandemic periods (*p<0.05, **p<0,01, ***p<0,001 and ****p<0,0001; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; USAP, unstable angina pectoris; ACS, acute coronary syndromes).

The number of STEMI and NSTEMI cases showed a moderately positive correlation with time (Pearson r= 0.4823 and Pearson r= 0.4594, respectively; p<0.0001; Figure 2A and B), reflecting an increasing trend across the pre-pandemic, pandemic, and post-pandemic periods. However, there was no significant correlation between the number of USAP cases and time (Spearman r=−0.08669, p=0.4505, Figure 2C), indicating that the diagnosis of USAP did not vary across the pre-pandemic, pandemic, and post-pandemic periods. In contrast, a weak to moderate positive correlation was observed between the total number of ACS cases and time (Pearson r=0.3226, p=0.0040, Figure 2D). This trend suggests a gradual increase in ACS cases across the pre-pandemic, pandemic, and post-pandemic periods.

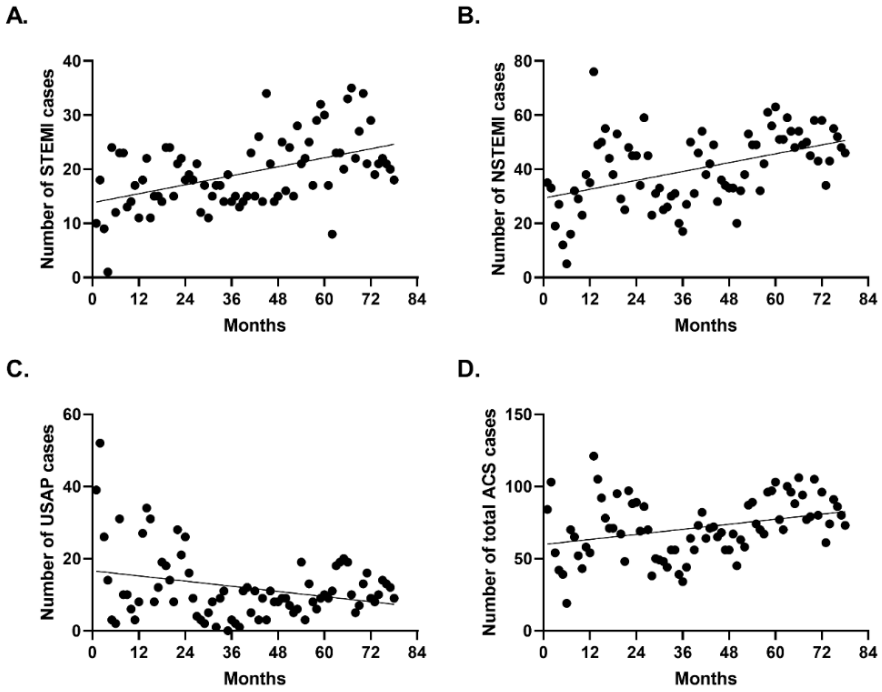

Figure 2. Number of **(A)** STEMI, **(B)** NSTEMI, **(C)** USAP and **(D)** total ACS cases throughout the study period. (STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; USAP, unstable angina pectoris; ACS, acute coronary syndromes)

Discussion

The present study represents a detailed retrospective evaluation of the temporal patterns of ACS across the pre-pandemic, pandemic, and post-pandemic phases of the COVID-19 era. The findings elucidate significant oscillations in ACS incidence, reflecting the intricate interrelation between the direct pathophysiological impacts of SARS-CoV-2 infection and the indirect consequences stemming from disruptions in healthcare delivery, public health infrastructure, and patient healthcare-seeking behaviors. These findings are critical for understanding the broader implications of global crises on cardiovascular health and identifying strategic targets for intervention.

The documented escalation in ACS cases, particularly STEMI and NSTEMI, during the post-pandemic phase lends robust support to the hypothesis that pandemic-induced delays in healthcare access exacerbated underlying cardiovascular risk profiles[22]. Fear of SARS-CoV-2 exposure and widespread healthcare system disruptions appeared to contribute significantly to this phenomenon, promoting disease progression and culminating in a rise in more severe ACS presentations during the post-pandemic period[23,24]. In a randomized study conducted by Soylu et al., it was found that the time STEMI patients continued to stay at home after the onset of chest pain during the pandemic period and the time to first admission to the hospital were considerably longer than in the pre-pandemic period. Door-to-balloon time and high procedural success were found to be similar in both periods[25]. Additionally, several societal and healthcare-related factors may help explain the observed rise in STEMI/NSTEMI incidence during the post-pandemic period. Following the initial phases of the COVID-19 pandemic, many healthcare centers resumed standard operations with enhanced safety measures, which likely alleviated concerns about seeking in-person treatment[26]. Concurrently, individuals who had postponed care during lockdowns or pandemic surges may have subsequently presented for catch-up diagnoses, contributing to an increase in recorded acute coronary events[27]. Additionally, successful vaccination campaigns and ongoing public health efforts may have improved patient confidence in hospital environments, further encouraging prompt medical attention for suspected cardiac symptoms[28,29]. Taken together, these developments likely converged to bolster healthcare engagement and reporting, thereby contributing to the increase in STEMI/NSTEMI incidence seen in the aftermath of the pandemic. Furthermore, the inflammatory milieu engaged by COVID-19, compounded

by endothelial dysfunction and a prothrombotic state, likely accelerated atherosclerotic processes, thereby amplifying the frequency and severity of MI[30-32]. These pathophysiological dynamics underscore the necessity of incorporating anti-inflammatory and endothelial-protective strategies into cardiovascular care frameworks, particularly during the post-pandemic recovery phase.In contrast to the significant fluctuations observed in STEMI and NSTEMI cases, the incidence of USAP remained relatively stable across the pre-pandemic, pandemic, and post-pandemic phases. This lack of significant variation may reflect the unique pathophysiology of USAP, which is frequently characterized by transient ischemic periods without the sustained myocardial necrosis observed in MI. It is plausible that patients experiencing USAP symptoms maintained similar healthcare-seeking behaviors across all phases, as the symptoms may not have been perceived as severe enough to evoke the same levels of pandemic-related care avoidance as seen in MI. Furthermore, the pathophysiological mechanisms driving USAP may be less influenced by the inflammatory and thrombotic effects of COVID-19, which appears to play a more substantial role in pathogenesis of STEMI and NSTEMI[33]. The relatively stable incidence of USAP highlights the need for further investigation into whether this subset of ACS represents a less sensitive to pandemic-induced disruption and how its management can be optimized during healthcare crises.

The temporal trends observed in this investigation provide critical insight into the persistent cardiovascular sequelae of the pandemic. The progressive rise in MI cases across the pre-pandemic, pandemic and post-pandemic phases likely reflects a multifactorial interplay of residual inflammatory and thrombotic effects associated with SARS-CoV-2 infection, disruptions in routine healthcare delivery, and delayed identification of preexisting cardiovascular pathologies[34,35]. These observations align with the extant literature underscoring the sustained adverse effects of pandemics on chronic disease trajectories, particularly in the cardiovascular domain. Moreover, the pandemic's-associated psychological and physiological stressors, including prolonged social isolation, economic uncertainties, and diminished physical activity, may have further exacerbated cardiovascular risk factors, potentiating the observed trends[36,37].

While the strengths including the reliance on a large dataset, several limitations must be acknowledged. The retrospective design inherently limits causal inference and introduces potential selection bias. Furthermore, the single-center focus restricts the generalizability of the findings, particularly across regions with differing healthcare infrastructures and pandemic responses. Future research should prioritize multicenter prospective studies to validate these findings and elucidate the underlying mechanisms with greater granularity. Additionally, there is imperative to identify and address the needs of populations disproportionately affected by pandemic-induced healthcare disruptions, through targeted interventions and resource allocation. Moreover, while our single-center design enabled us to collect comprehensive patient-level data under uniform protocols, we recognize that differences in local healthcare systems, pandemic response measures (e.g., timing and severity of lockdowns), and resource allocation could lead to variations in the incidence and management of acute coronary events in other regions. Moreover, demographic factors, public health policies, and levels of healthcare trust may differ markedly between geographic areas, potentially influencing patient behavior, such as willingness to seek care, and thus shaping observed outcomes. By acknowledging these region-specific factors, we underscore that our findings, although relevant, should be interpreted with caution when extrapolating to broader national or international contexts.

In conclusion, the findings of the present study highlight the profound and enduring impact of the COVID-19 pandemic on ACS presentation, extending well beyond its acute phase. These findings underscore the importance of embedding cardiovascular care into pandemic alertness strategies to avert comparable disruptions in future crises. Strengthening public health infrastructure, streamlining healthcare delivery, and enhancing chronic disease management are crucial for the mitigation of long-term cardiovascular sequelae of global health emergencies. Finally, the results suggest for the establishment of resilient, adaptive healthcare systems capable of ensuring continuity of care for both acute and chronic conditions amidst unprecedented challenges. Realizing these goals necessitates a multidisciplinary approach involving policymakers, clinicians, researchers, and community stakeholders, fostering the development of sustainable, equitable healthcare models that prioritize cardiovascular health within the broader context of global health security.

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and approved by Amasya University Non-Interventional Clinical Research Ethics Committee (Date: 26 November 2024, No: 2024/123).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

AC, OK: Study idea, hypothesis, study design, material preparation, data collection and analysis writing the first draft of the article, Critical review of the article finalization and publication process.

Financial Disclosure

None.

References

1. Vosko I, Zirlik A, Bugger H. Impact of COVID-19 on Cardiovascular Disease. *Viruses*. 2023;15(2). doi:10.3390/v15020508
2. Hilser JR, Spencer NJ, Afshari K, et al. COVID-19 Is a Coronary Artery Disease Risk Equivalent and Exhibits a Genetic Interaction With ABO Blood Type. *Arterioscler Thromb Vasc Biol*. 2024;44(11):2321-2333. doi:10.1161/atvbaha.124.321001
3. Del Prete A, Conway F, Della Rocca DG, et al. COVID-19, Acute Myocardial Injury, and Infarction. *Card Electrophysiol Clin*. 2022;14(1):29-39. doi:10.1016/j.ccep.2021.10.004
4. Kite TA, Pallikadavath S, Gale CP, Curzen N, Ladwiniec A. The Direct and Indirect Effects of COVID-19 on Acute Coronary Syndromes. *Heart Fail Clin*. 2023;19(2):185-196. doi:10.1016/j.hfc.2022.08.002
5. Calvão J, Amador AF, Costa CMD, et al. The impact of the COVID-19 pandemic on acute coronary syndrome admissions to a tertiary care hospital in Portugal. *Rev Port Cardiol*. 2022;41(2):147-152. doi:10.1016/j.repc.2021.01.007
6. Sucato V, Sausa G, Gambino G, et al. The impact of coronavirus disease 2019 on acute coronary syndrome: Differences between epidemic waves. *Am Heart J Plus*. 2024;44:100422. doi:10.1016/j.ahjo.2024.100422
7. Neri M, Riezzo I, Pascale N, Pomara C, Turillazzi E. Ischemia/Reperfusion Injury following Acute Myocardial Infarction: A Critical Issue for Clinicians and Forensic Pathologists. *Mediators Inflamm*. 2017;2017:7018393. doi:10.1155/2017/7018393
8. Vidal-Perez R, Brandão M, Pazdernik M, et al. Cardiovascular disease and COVID-19, a deadly combination: A review about direct and indirect impact of a pandemic. *World J Clin Cases*. 2022;10(27):9556-9572. doi:10.12998/wjcc.v10.i27.9556
9. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418. doi:10.1016/s0140-6736(20)30937-5
10. Silva MJA, Ribeiro LR, Gouveia MIM, et al. Hyperinflammatory Response in COVID-19: A Systematic Review. *Viruses*. 2023;15(2). doi:10.3390/v15020553
11. Wolf A, Khimani F, Yoon B, et al. The mechanistic basis linking cytokine storm to thrombosis in COVID-19. *Thromb Update*. 2022;8:100110. doi:10.1016/j.tru.2022.100110
12. Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L. Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutical Approaches. *Int J Mol Sci*. 2021;22(8). doi:10.3390/ijms22083850
13. Zhang H, Dhalla NS. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. *Int J Mol Sci*. 2024;25(2). doi:10.3390/ijms25021082
14. Dri E, Lampas E, Lazaros G, et al. Inflammatory Mediators of Endothelial Dysfunction. *Life (Basel)*. 2023;13(6). doi:10.3390/life13061420
15. Yugar-Toledo JC, Yugar LBT, Sedenho-Prado LG, Schreiber R, Moreno H. Pathophysiological effects of SARS-CoV-2 infection on the cardiovascular system and its clinical manifestations-a mini review. *Front Cardiovasc Med*. 2023;10:1162837. doi:10.3389/fcvm.2023.1162837
16. Krishna BA, Metaxaki M, Sithole N, Landín P, Martín P, Salinas-Botrán A. Cardiovascular disease and covid-19: A systematic review. *IJC Heart & Vasculature*. 2024;54:101482. doi:10.1016/j.ijcha.2024.101482
17. Czeisler M, Marynak K, Clarke KEN, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(36):1250-1257. doi:10.15585/mmwr.mm6936a4
18. Banerjee A, Chen S, Pasea L, et al. Excess deaths in people with cardiovascular diseases during the COVID-19 pandemic. *Eur J Prev Cardiol*. 2021;28(14):1599-1609. doi:10.1093/eurjpc/zwaa155
19. Braiteh N, Rehman WU, Alom M, et al. Decrease in acute coronary syndrome presentations during the COVID-19 pandemic in upstate New York. *Am Heart J*. 2020;226:147-151. doi:10.1016/j.ahj.2020.05.009
20. Quintero-Martinez JA, Espinoza J, Celli D, et al. Acute Coronary Syndrome During the Era of COVID-19: Perspective and Implications Using Google Trends. *CJC Open*. 2024;6(7):908-914. doi:10.1016/j.cjco.2024.03.002
21. Showkathali R, Yalamanchi R, Sankeerthana MP, et al. Acute Coronary Syndrome admissions and outcome during COVID-19 Pandemic-Report from large tertiary centre in India. *Indian Heart J*. 2020;72(6):599-602. doi:10.1016/j.ihj.2020.09.005
22. Ghasemzadeh N, Kim N, Amlani S, et al. A Review of ST-Elevation Myocardial Infarction in Patients with COVID-19. *Heart Fail Clin*. 2023;19(2):197-204. doi:10.1016/j.hfc.2022.08.007
23. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. *J Pers Med*. 2022;12(8). doi:10.3390/jpm12081295
24. Haileamlak A. The impact of COVID-19 on health and health systems. *Ethiop J Health Sci*. 2021;31(6):1073-1074. doi:10.4314/ejhs.v31i6.1
25. Soylu K, Coksevim M, Yanık A, Bugra Cerik I, Aksan G. Effect of Covid-19 pandemic process on STEMI patients timeline. *Int J Clin Pract*. 2021;75(5):e14005. doi:10.1111/ijcp.14005
26. Mafham MM, Spata E, Goldacre R, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet*. 2020;396(10248):381-389. doi:10.1016/s0140-6736(20)31356-8
27. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J*. 2020;41(22):2083-2088. doi:10.1093/eurheartj/ehaa409
28. Borrelli E, Grosso D, Vella G, et al. Impact of COVID-19 on outpatient visits and intravitreal treatments in a referral retina unit: let's be ready for a plausible "rebound effect". *Graefes Arch Clin Exp Ophthalmol*. 2020;258(12):2655-2660. doi:10.1007/s00417-020-04858-7
29. Chhabra ST, Kaur G, Aggarwal R, et al. Outpatient attendance in COVID pandemic lockdown: An observational study. *Indian Journal of Cardiovascular Disease in Women*. 2023;8(1):18-24.
30. Ambrosino P, Calcaterra IL, Mosella M, et al. Endothelial Dysfunction in COVID-19: A Unifying Mechanism and a Potential Therapeutic Target. *Biomedicines*. 2022;10(4). doi:10.3390/biomedicines10040812
31. Oikonomou E, Souvaliotis N, Lampsas S, et al. Endothelial dysfunction in acute and long standing COVID-19: A prospective cohort study. *Vascul Pharmacol*. 2022;144:106975. doi:10.1016/j.vph.2022.106975

32. Sagris M, Theofilis P, Antonopoulos AS, et al. Inflammatory Mechanisms in COVID-19 and Atherosclerosis: Current Pharmaceutical Perspectives. *Int J Mol Sci*. 2021;22(12). doi:10.3390/ijms22126607
33. Diar Bakerly N, Smith N, Darbyshire JL, et al. Pathophysiological Mechanisms in Long COVID: A Mixed Method Systematic Review. *Int J Environ Res Public Health*. 2024;21(4). doi:10.3390/ijerph21040473
34. Liuzzo G, Volpe M. SARS-CoV-2 infection markedly increases long-term cardiovascular risk. *Eur Heart J*. 2022;43(20):1899-1900. doi:10.1093/eurheartj/ehac168
35. Romero Starke K, Kaboth P, Rath N, et al. Cardiovascular disease risk after a SARS-CoV-2 infection: A systematic review and meta-analysis. *J Infect*. 2024;89(3):106215. doi:10.1016/j.jinf.2024.106215
36. Pietrabissa G, Simpson SG. Psychological Consequences of Social Isolation During COVID-19 Outbreak. *Front Psychol*. 2020;11:2201. doi:10.3389/fpsyg.2020.02201
37. Andrade A, D'Oliveira A, Dos Santos KM, et al. Impact of social isolation caused by the COVID-19 pandemic on the mood profile of active and sedentary older adults: physical activity as a protective factor. *Front Public Health*. 2023;11:1221142. doi:10.3389/fpubh.2023.1221142

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Research Article | Araştırma Makalesi

TRENDS AND FORECASTS OF OVERWEIGHT PREVALENCE IN TÜRKİYE: A TIME SERIES ANALYSIS USING ARIMA MODELS

TÜRKİYE'DE AŞIRI KİLOLU PREVALANSININ EĞİLİMLERİ VE TAHMİNLERİ: ARIMA MODELLERİNİ KULLANAN BİR ZAMAN SERİSİ ANALİZİ

Hülya Özen[1*], Doğukan Özen[2]

[1]University of Health Sciences, Gülhane Faculty of Medicine, Department of Medical Informatics, Ankara, Türkiye. [2]Ankara University, Faculty of Veterinary Medicine, Department of Biostatistics, Ankara, Türkiye.

ABSTRACT

Objective: This study aimed to fit Autoregressive Integrated Moving Average (ARIMA) models to the prevalence of overweight in Türkiye's overall, female, and male populations and to forecast future trends using the best-performing ARIMA models.

Methods: The dataset comprised annual overweight prevalence values for Türkiye's overall, female, and male populations from 1974 to 2022, obtained from the World Health Organization and World Bank Group databases. The dataset was divided into training and test sets in a chronological sequence with the ratio 80:20, respectively. Training sets were used to fit ARIMA models, while test sets were used to evaluate the predictive performance of the models. Best ARIMA models were chosen based on various evaluation metrics.

Results: The best models were identified as ARIMA (1,3,1) for the overall population, ARIMA (1,3,1) for females, and ARIMA (3,3,1) for males, yielding the lowest error metrics. These models effectively captured the increasing trend in overweight prevalence. Short-term forecasts indicated that the upward trend is likely to continue in the near future.

Conclusion: This study contributes to a foundational understanding of the trajectory of overweight prevalence in Türkiye, providing a basis for evidence-based interventions and long-term health planning.

Keywords: Overweight prevalence, ARIMA models, time series, public health

ÖZ

Amaç: Bu çalışmanın amacı, Türkiye'nin genel, kadın ve erkek nüfusundaki aşırı kilolu prevalansı verilerine Otoregresif Entegre Hareketli Ortalama (ARIMA) modellerini uygulamak ve en iyi performans gösteren ARIMA modellerini kullanarak gelecekteki eğilimleri tahmin etmektir.

Yöntem: Çalışmadaki veri seti, Dünya Sağlık Örgütü ve Dünya Bankası Grubu veri tabanlarından elde edilen 1974-2022 yılları arasında Türkiye'nin genel, kadın ve erkek nüfuslarına ait yıllık aşırı kilolu prevalans değerlerinden oluşmaktadır. Veri seti, kronolojik bir sıra ile 80:20 oranında, sırasıyla eğitim ve test setlerine bölünmüştür. Eğitim setleri ARIMA modellerinin oluşturulması için kullanılırken, test setleri modellerin tahmin performansını değerlendirmek için kullanılmıştır. Çeşitli değerlendirme ölçütlerine göre en iyi ARIMA modelleri seçilmiştir.

Bulgular: En iyi modeller genel nüfus için ARIMA (1,3,1), kadınlar için ARIMA (1,3,1) ve erkekler için ARIMA (3,3,1) olarak belirlenmiş ve en düşük hata metriklerini vermiştir. Bu modeller aşırı kilolu prevalansındaki artış eğilimini etkili bir şekilde yakalamıştır. Kısa vadeli tahminler, artış eğiliminin yakın gelecekte de devam edeceğini göstermektedir.

Sonuç: Bu çalışma, Türkiye'de aşırı kilolu prevalansının gidişatının temelden anlaşılmasına katkıda bulunarak kanıta dayalı müdahaleler ve uzun dönemde sağlık planlaması için bir temel oluşturmaktadır.

Anahtar Kelimeler: Aşırı kilolu prevalansı, ARIMA modelleri, zaman serisi, halk sağlığı

***Corresponding author/İletişim kurulacak yazar:** Hülya Özen; University of Health Sciences, Gülhane Faculty of Medicine, Department of Medical Informatics, Ankara, Türkiye.
Phone/Telefon: +90 (312) 567 15 00 (4037), **e-mail/e-posta:** hulya_ozen@yahoo.com
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Introduction

Overweight has become a significant public health challenge globally, affecting populations across all age groups and socioeconomic levels. The World Health Organization (WHO) defines being overweight as a condition characterized by excessive fat deposits, with a body mass index value of 25 or greater. According to WHO reports, 2.5 billion adults over the age of 18 were overweight in 2022. This indicates that 43% of adults over the age of 18 were overweight (43% of men and 44% of women), which is higher than the 25% of people over the age of 18 who were overweight in 1990.[1] This trend has considerable outcomes for public health, as being overweight is associated with various chronic diseases, including cardiovascular disease, type 2 diabetes, certain types of cancer, stroke, dyslipidemia, osteoarthritis, and musculoskeletal disorders.[2-4] Türkiye, like many other countries, is affected by an increase in the number of people categorized as overweight. According to the latest Turkish Health Bulletin published by the Turkish Statistical Institute (TUIK), 47.6% of the population aged 15 and over were overweight in 2008, but this rate increased to 55.8% in 2022.[5] This increase brings serious costs to the healthcare system and reduces the quality of life of individuals.

In the field of epidemiology, utilization of time-series forecasting models, which is constructed upon historical data, are commonly met. These models serve as a valuable tool for making consistent forward-looking predictions, thereby facilitating the identification of disease trends and enabling health authorities to anticipate potential future risks. Unlike the limitations of simple linear models, time series models can control seasonality, trends, and other complexities found in the data.[6,7]

Despite the rising prevalence of overweight in Türkiye, existing studies have primarily focused on cross-sectional analyses, regional variations, and associations with other health factors.[8-10] However, these approaches do not provide insights into future trends, which are essential for proactive public health planning. To our knowledge, no previous studies have specifically applied time-series forecasting models to predict the prevalence of overweight in Türkiye. By addressing this gap, our study provides a data-driven approach to forecasting overweight prevalence. It is crucial to accurately estimate the prevalence of overweight individuals using historical data to develop effective health policies.

This study aims to analyze the trends and forecast the prevalence of overweight in Türkiye using Autoregressive Integrated Moving Average (ARIMA) models. By leveraging historical data on the prevalence of overweight from WHO and The World Health Group health databases, we aim to (i) evaluate the performance of different ARIMA models and identify reliable forecasting models for prevalence of overweight in the overall, female, and male populations of Türkiye, (ii) to make future forecasts on the prevalence values. The results of this study may provide useful information to health professionals in planning and prioritizing interventions to reduce the increasing rates of overweight in Türkiye.

Methods

Dataset

Data used in this study were collected from the open-access databases of WHO and the World Bank.[11,12] The dataset comprises annual data on the prevalence of overweight in the Turkish population aged 18 and over, spanning the period from 1975 to 2022. In addition to the overall prevalence values, the dataset also includes the prevalence values of the female and male populations aged 18 and over.

Autoregressive Integrated Moving Average (ARIMA) Models

Autoregressive Integrated Moving Average (ARIMA) models are statistical models used to predict future values of univariate time-series data proposed by Box and Jenkins.[13] ARIMA is an extension of the Autoregressive Moving Average (ARMA) model that combines the two components: past observations and past error terms of observations. ARMA models are useful for stationary time-series data where the values fluctuate around a constant mean and variance, showing no long-term trends or seasonality. However, real-world data sets frequently exhibit non-stationary structures. ARIMA models can handle such time-series data with trend or seasonality by applying differencing transformations until the time series become stationary.[14] The process of first-order differencing a non-stationary series is expressed in (1)

$$y'_t = y_t - y_{t-1} \quad (1),$$

where y'_t is the first-ordered difference value, y_t and y_{t-1} are the values taken at time t and t-1, respectively. For higher-order differencing (d-th order), it is recursively applied:

$$y_t^{(d)} = \Delta^d y_t = \Delta(\Delta^{d-1} y_t) \quad (2),$$

where $\Delta y_t = y_t - y_{t-1}$.

The ARIMA model consists of three parameters, which are p, d and q. Parameter p is the number of lagged observations, d is the number of times the original series is differenced to make it stationary, and q is the number of lagged errors used in the model. A general formula of ARIMA (p,d,q) is given in (3):

$$y_t = c + \phi_1 y_{t-1} + \phi_2 y_{t-2} + \cdots + \phi_p y_{t-p} - \theta_1 e_{t-1} \theta_2 e_{t-2} - \cdots - \theta_q e_{t-q} + e_t \quad (3),$$

where y_t is the predicted time series value, c is the constant, ϕ_i autoregressive terms, θ_j moving average terms and e_t is the error term.[15]

This study employed a data partitioning strategy, with an 80:20 ratio, to ensure robust performance evaluation and to avoid the issue of overfitting. The raw data sets were divided into two distinct subsets: the training set, comprising 80% of the data, and the test set, comprising the remaining 20%. This separation was achieved by partitioning the data set into two distinct periods, the

earlier as the training set and the latter as the test set, to maintain the chronological sequence.[16,17] The training set comprised the values from 1975 to 2012, while the test set included the values from 2013 to 2022.

The training set was employed for model fitting, while the test set was utilized for the evaluation of the predictive performance of the ARIMA models. In the model fitting process, the Augmented Dickey-Fuller (ADF) test was initially applied to evaluate the stationarity of the series.[18] After the series were made stationary by differencing, p and q values, the other parameters of ARIMA models, were determined by using partial autocorrelation (PACF) and autocorrelation (ACF) graphs, respectively. It is recommended that during the process of fitting potential ARIMA models, parsimony models be constructed by selecting small p and q values to avoid the phenomenon of overfitting.[15] In all models, parameter estimations were performed using the maximum likelihood method. In the final stage of the model fitting process, the Box-Ljung test was employed to check whether the residuals (errors) of ARIMA models are uncorrelated, which is a key assumption for the model to be valid.[19]

The predictive performance of the potential ARIMA models was evaluated with Mean Error (ME), Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), Mean Absolute Percentage Error (MAPE), and Mean Absolute Scaled Error (MASE) using test set values. ME is calculated as the mean of the differences between the observed and predicted values, indicating overall bias in the predictions. MAE is the average of the absolute differences between observed and predicted values, measuring prediction accuracy regardless of direction. RMSE is calculated as the square root of the average of the squared differences between the observed and predicted values. This weighting gives greater importance to larger errors. MAPE is the mean of absolute percentage errors between observed and predicted values, expressed as a percentage to standardize across different scales. Finally, MASE is the mean absolute error scaled relative to the mean absolute error of a naive benchmark model, enabling model comparisons across datasets. MASE value is expected to be less than 1 for a good prediction performance. The smaller the evaluation metrics obtained from the test set, the better the predictive performance.[17] In the final stage, prevalence values of overweight for the years between 2023 and 2032 were forecasted for each population using the best predictive ARIMA models.

All calculations for this study were conducted using R version 4.2.2 and R Studio (version: 2023.09.1+494).[20,21] Model fitting and the evaluation of predictive performance were utilized with the package 'lubridate',[22] package 'forecast',[23] and package 'tseries'.[24] Forecasting graphs were drawn with the package 'ggplot2'.[25]

Results

The stationarity of the time series was examined during the fitting of ARIMA forecast models for the overall, female and male populations using the prevalence of overweight values between 1974 and 2012. The ADF test results for the original time series of the populations indicated that no stationarity was present in the overall (p=0.8501), female (p=0.9363), and male (0.8887) populations. Consequently, differencing procedures were employed to address this issue. Following the application of third-order differencing, stationarity was observed in the prevalence series of the overall (p=0.01), female (p=0.028), and male (p=0.01) populations.

The potential p and q values for the stationary series were determined using PACF and ACF plots, as illustrated in Figure 1. Upon analysis of the plots, it was determined that the values crossing the 5% significance line in the PACF plot for the overall series were at lag 1 and 2, thus chosen for the p parameter. Similarly, the q parameter was chosen as 1 and 2, where the values crossed the significance threshold in the ACF plot. A similar approach was employed to determine the potential p values for the female series, which were found to be 1 and 2, and 1 for q. For the male series, the potential p values were 1, 2, 3, and 4, while the q value was 1. In all series, delays greater than 5 were not evaluated to provide parsimony models. Following the fitting of potential ARIMA models for all series, the Box-Ljung test was used to assess whether the errors of the models exhibit autocorrelation. The models fitted for the overall series, namely ARIMA (1,3,1) (p=0.860), ARIMA (2,3,1) (p=0.866), ARIMA (1,3,2) (p=0.867) and ARIMA (2,3,2) (p=0.870), were found to exhibit no autocorrelation. Similarly, no autocorrelation was identified in the models fitted for the female series, ARIMA (1,3,1) (p=0.950) and ARIMA (2,3,1) (p=0.996), and in the models fitted for the male series, which are ARIMA (1,3,1) (p=0.403), ARIMA (2,3,1) (p=0.809), ARIMA (3,3,1) (p=0.965) and ARIMA (4,3,1) (p=0.997).

Predictive performance metrics of the fitted potential ARIMA models are given in Table 1. Upon the assessment of four different ARIMA models fitted for the overall population, it was observed that the MASE values were consistently below one across all models. Although the lowest MASE value was observed in the ARIMA (1,3,2) model, the remaining metrics, which are ME, MAE, RMSE, and MAPE, provided the lowest values and indicated that the ARIMA (1,3,1) model should be employed. In the context of a comparative analysis of two different ARIMA models for the female population, it was observed that all evaluation metrics belonging to ARIMA (1,3,1) presented the lowest values, thus indicating that ARIMA (1,3,1) was the optimal model. Finally, an examination of the ARIMA models fitted for the male population revealed that the ARIMA (4,3,1) model was not a suitable fit, as evidenced by its high ME, MAE, RMSE, MAPE and MASE values. It was determined that ARIMA (3,3,1), which exhibited the lowest evaluation metrics among the other models, was the most appropriate fit (Table 1).

Once the best ARIMA models had been identified for each population, prevalence forecasts were calculated using these models for the years 2023 to 2032. The resulting forecasts are presented as points with associated 95% confidence intervals for each year in Table 2.

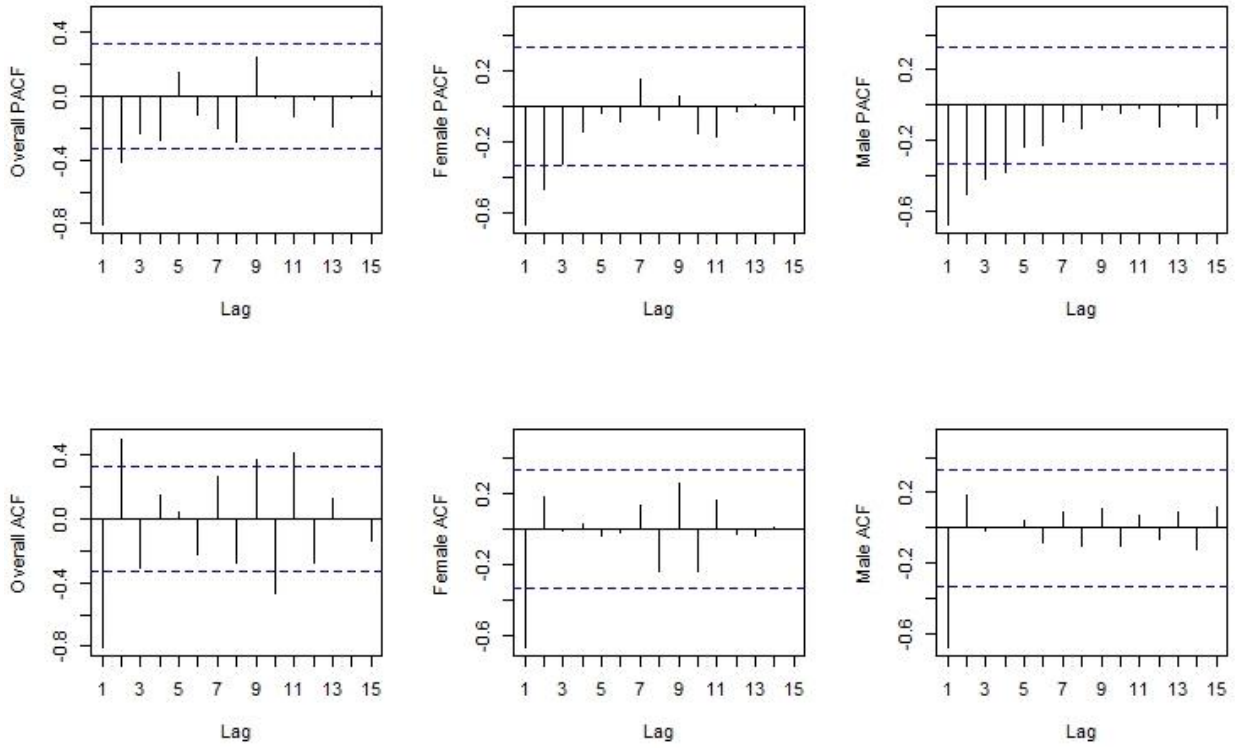

Figure 1. Partial autocorrelation (PACF) and autocorrelation (ACF) plots of third-order difference series of overweight prevalence in the overall, female, and male populations

Tablo 1. The test set-based prediction performance metrics of the potential ARIMA models

Population	Models	ME	MAE	RMSE	MAPE	MASE
Overall	ARIMA (1,3,1)*	0.4483	0.4723	0.6478	0.6965	0.5964
	ARIMA (2,3,1)	0.4543	0.4772	0.6546	0.7038	0.6026
	ARIMA (1,3,2)	0.4551	0.4779	0.6555	0.7047	0.3034
	ARIMA (2,3,2)	0.4586	0.4807	0.6595	0.7090	0.6071
Female	ARIMA (1,3,1)*	0.5002	0.5150	0.7254	0.7294	0.6781
	ARIMA (2,3,1)	0.5431	0.5525	0.7718	0.7827	0.7274
Male	ARIMA (1,3,1)	-0.1942	0.1942	0.2237	0.3005	0.2326
	ARIMA (2,3,1)	-0.1828	0.1828	0.2124	0.2827	0.2189
	ARIMA (3,3,1)*	-0.1419	0.1419	0.1609	0.2198	0.1699
	ARIMA (4,3,1)	-1.0874	1.0874	1.1627	1.6882	1.3020

*ARIMA: Autoregressive Integrated Moving Average, ME: Mean Error, MAE: Mean Absolute Error, RMSE: Root Mean Squared Error, MAPE: Mean Absolute Percentage Error, MASE: Mean Absolute Scaled Error, *;best predictive model in each population*

Tablo 2. Point and 95% confidence level forecasts for the prevalence of overweight in overall, female, and male populations using the best fit ARIMA models (%)

Year	Overall[1]			Female[2]			Male[3]		
	Point	LCL	UCL	Point	LCL	UCL	Point	LCL	UCL
2023	67.769	62.863	72.675	70.600	65.738	75.463	66.684	59.933	73.436
2024	68.000	62.188	73.812	70.933	65.391	76.476	67.131	59.458	74.804
2025	68.209	61.401	75.017	71.255	64.998	77.513	67.571	58.926	76.216
2026	68.396	60.499	76.294	71.566	64.558	78.574	68.004	58.337	77.671
2027	68.562	59.480	77.643	71.865	64.071	79.659	68.430	57.691	79.169
2028	68.706	58.342	79.069	72.153	63.538	80.767	68.849	56.989	80.709
2029	68.828	57.082	80.574	72.429	62.960	81.899	69.261	56.229	82.292
2030	68.928	55.697	82.159	72.695	62.336	83.053	69.666	55.414	83.918
2031	69.007	54.186	83.828	72.949	61.667	84.231	70.064	54.541	85.586
2032	69.064	52.545	85.582	73.191	60.952	85.430	70.454	53.612	87.296

LCL: Lower confidence limit, UCL: Upper confidence limit, [1]: ARIMA (1,3,1) model for overall population prevalence, [2]: ARIMA (1,3,1) model for female population prevalence, [3]: ARIMA (3,3,1) model for male population prevalence

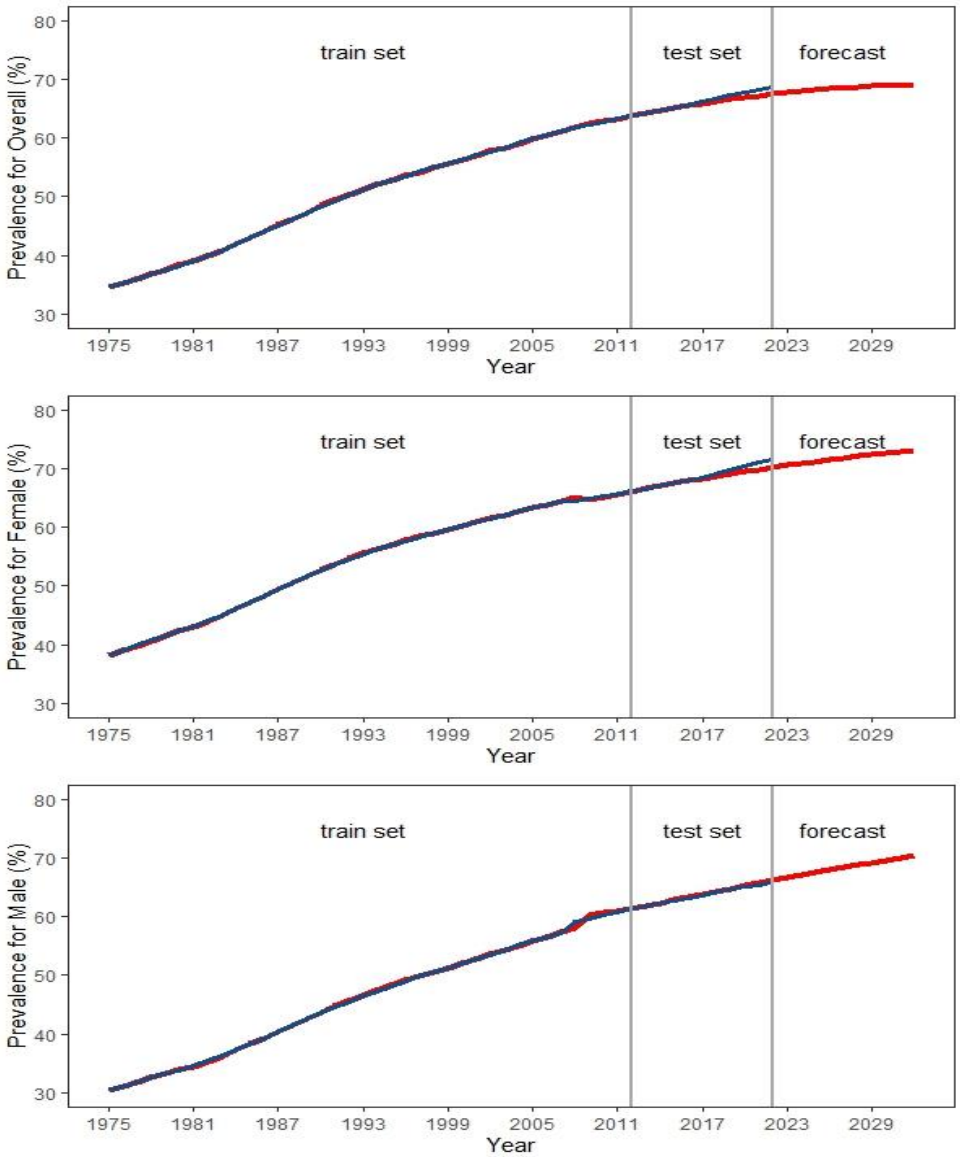

Figure 2. Best ARIMA models' forecast plots for the overweight prevalence of overall, female, and male populations

Figure 2 presents the original series and forecasted prevalence values based on the best-fitted ARIMA models of each population. In the plots where the periods of model fitting (train set), evaluation (test set), and future forecasts (forecast) are shown in detail, blue lines indicate the original series, while red lines show the point forecasted prevalence values. It was observed that the model fitted for the male population was superior in terms of compliance with the test set in comparison to other models. Upon examination of the forecasted data, it was evident that the increasing trend in prevalence values will persist in the following years.

Discussion

This study was conducted with the objective of fitting ARIMA models for the future prevalence of overweight in overall, female, and male populations of Türkiye, and making forecasts for a short-term future using the best-fitted ARIMA models. The models were fitted using annual prevalence data from 1974 to 2022, sourced from the WHO and World Health Group databases. The data sets were divided chronologically for use as the training and test sets, respectively, in the model fitting and model evaluation stages. In contrast to many time series studies that employ ARIMA, a more rigorous approach was taken in selecting the best ARIMA model, whereby model performance was evaluated with observations not included in the model fitting process.[16,17]

The prevalence of overweight in the Turkish population, both in children and adults, has been the subject of several studies. The studies are predominantly cross-sectional in design and aim to ascertain the prevalence of overweight and the risk factors associated with it.[26-29] It is consistently highlighted in the literature that the prevalence of overweight and obesity is on the rise across Türkiye, with a higher prevalence observed in the female population compared to the male population. It has been established that the rise in childhood obesity is associated with maternal overweight and the level of parental education.[26] Additionally, it has been irrefutably demonstrated that there is a relationship between hypertension and overweight in adults.[27] To the best of our knowledge, no studies have specifically focused on forecasting the prevalence of overweight in Türkiye using time series models.

This study highlights the utility of time series models in forecasting the prevalence of overweight, offering a data-driven approach for anticipating trends in Türkiye. As Table 1 and Figure 2 are examined, it becomes evident that the models exhibiting the lowest prediction error are those pertaining to the male population. It can be thought that the slightly higher error rate in the overall and female populations is due to the low amount of overfitting that occurs during the model-fitting process. Nevertheless, the fact that the MASE values for the best ARIMA models of the populations are below one indicates that these models are effective in forecasting the prevalence of overweight.

Our results indicate that ARIMA models capture the underlying trends in the data effectively, offering credible forecasts for the future burden of overweight. These forecasts reveal a potential continued increase in the prevalence of overweight, aligning with global trends observed in similar demographic and socioeconomic settings.[30] From a public health perspective, forecasts indicating an upward trend, as highlighted in previous studies, suggest an increasing burden on healthcare resources and underscore the need for comprehensive prevention and management strategies.[31] These results underscore the importance of preemptive action to address the prevalence of overweight in Türkiye.

The selected ARIMA models demonstrated good fits, as indicated by evaluation metrics, suggesting its reliability in short-term forecasting. However, one limitation of the model lies in its reliance on historical data, which may not fully account for future changes in lifestyle, policy interventions, or health promotion efforts that could influence overweight trends. Incorporating exogenous variables, such as income level, urbanization rate, or healthcare access, could potentially enhance the model's predictive accuracy, especially for long-term forecasts. Another limitation of this study is the lack of data from the years preceding 1974. The incorporation of additional data into the training set has the potential to enhance the model and substantiate a more robust trend. It is recommended that future research concentrate on enhancing the model's applicability by integrating socioeconomic and behavioral variables, as well as expanding the dataset to capture longer historical trends. Moreover, further studies could focus on translating these forecasts into actionable public health strategies to mitigate the rising burden of overweight. Finally, this study did not compare ARIMA models with alternative forecasting methods, such as machine learning-based approaches or other time series models (e.g., exponential smoothing or state-space models). Exploration of these methods in future research could provide insights into whether alternative models offer enhanced predictive capabilities in estimating overweight prevalence trends.

This study employed the ARIMA models to model the prevalence of overweight in the overall, female, and male populations of Türkiye, as well as to forecast short-term future prevalence. The increasing trend in the prevalence of overweight in Türkiye was emphasized. The results of this study can inform policymakers in the development of realistic, evidence-based interventions for reducing overweight prevalence and guiding resource allocation to high-risk demographics.

Compliance with Ethical Standards

Ethical approval was not required

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contribution

HÖ, DÖ: Concept; HÖ: Data collection and/or processing; HÖ, DÖ: Analysis and/or interpretation; HÖ: Literature review; HÖ, DÖ: Writing article.

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References

1. World Health Organization. Obesity and Overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Published: March 2024. Accessed: Sep 1, 2024.
2. Burton BT, Foster WR. Health implications of obesity: an NIH Consensus Development Conference. *J Am Diet Assoc*. 1985;85(9):1117-1121. doi:10.1016/S0002-8223(21)03768-8
3. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC public health*. 2009;9:1-20. doi:10.1186/1471-2458-9-88
4. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *Jama*. 1999;282(16):1523-1529. doi:10.1001/jama.282.16.1523
5. Türkiye İstatistik Kurumu. Türkiye Sağlık Araştırması Bülteni. https://data.tuik.gov.tr/Bulten/Index?p=Turkiye-Saglik-Arastirmasi-2022-49747. Published: June 2023. Accessed: Sep 10, 2024.
6. Gandon S, Day T, Metcalf CJE, Grenfell BT. Forecasting epidemiological and evolutionary dynamics of infectious diseases. *Trends Ecol Evol*. 2016;31(10):776-788. doi:10.1016/j.tree.2016.07.010
7. Nobre FF, Monteiro ABS, Telles PR, Williamson GD. Dynamic linear model and SARIMA: a comparison of their forecasting performance in epidemiology. *Stat Med*. 2001;20(20):3051-3069. doi: 10.1002/sim.963
8. Bozkurt M, Güngör Y. Kentsel Alanda Yaşayan Okul Çağındaki Çocuklarda Kilololuluk ve Obezite Görülme Sıklığının Belirlenmesi. *J Child*. 2021;21(2):128-135. doi:10.26650/jchild.2021.874569
9. Işık Ü, Bağcı B, Aktepe E, Kılıç F, Pirgon Ö. Obezite Tanılı Ergenlerde Eşlik Eden Psikiyatrik Bozuklukların Araştırılması. *Turk J Child Adolesc Ment Health*. 2020;27(2):85-90. doi:10.4274/tjcamh.galenos.2020.76486
10. Kılınç E, Kartal A. Lise öğrencilerinde sedanter yaşam, beslenme davranışları ve fazla kilololuluk-obezite arasındaki ilişkinin değerlendirilmesi: Bir Vaka Kontrol Çalışması. *Dokuz Eylul Univ Hem Fak Elektron Derg*. 2022;15(1):30-39. doi:10.46483/deuhfed.898847
11. World Bank Group. Health Nutrition and Population Statistics. https://databank.worldbank.org/source/health-nutrition-and-population-statistics#. Accessed: Sep 1,2024.
12. World Health Organization. The Global Health Observatory. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-overweight-among-adults-bmi--25-(age-standardized-estimate)-(-). Accessed: Sep 1,2024.
13. Box GE, Jenkins GM. Time Series Analysis: Forecasting and Control. San Francisco: Holden Bay; 1976.
14. Cerqueira V, Torgo L, Soares C. Machine learning vs statistical methods for time series forecasting: Size matters. *arXiv preprint arXiv:190913316*. 2019. doi:10.48550/arXiv.1909.13316
15. Nielsen A. Practical time series analysis: Prediction with statistics and machine learning. 1st Edition.California: O'Reilly Media; 2019.
16. Hyndman R. Athanasopoulos G. Forecasting: principles and practice. 2nd Edition. OTexts; 2018.
17. Shmueli G, Lichtendahl Jr KC. Practical Time Series Forecasting With R. 2nd Edition. Axelrod Schnall Publishers; 2016.
18. Dickey DA, Fuller WA. Likelihood ratio statistics for autoregressive time series with a unit root. *Econometrica*. 1981:1057-1072. doi:10.2307/1912517
19. Ljung GM, Box GE. On a measure of lack of fit in time series models. *Biometrika*. 1978;65(2):297-303. doi:10.1093/biomet/65.2.297
20. R Core Team. R: A language and environment for statistical computing [computer software]. Version 4.2.2. Vienna, Austria: R Foundation for Statistical Computing; 2021. Available from: https://www.R-project.org/.
21. RStudio Team. RStudio: Integrated Development Environment for R [computer software]. Version 2023.09.1+494. Boston, MA: RStudio, PBC; 2023. Available from: http://www.rstudio.com/.
22. Grolemund G, Wickham H. Dates and Times Made Easy with lubridate. J Stat Softw. 2011;40(3):1-25. Available from: https://www.jstatsoft.org/v40/i03/.
23. Hyndman R, Athanasopoulos G, Bergmeir C, et al. forecast: Forecasting functions for time series and linear models [computer software]. Version 8.23.0. Melbourne, Australia: Monash University; 2024. Available from: https://pkg.robjhyndman.com/forecast/.
24. Trapletti A, Hornik K. tseries: Time Series Analysis and Computational Finance [computer software]. Version 0.10-58. Vienna, Austria: R Foundation for Statistical Computing; 2024. Available from: https://CRAN.R-project.org/package=tseries.
25. Wickham H. ggplot2: Elegant Graphics for Data Analysis. 2nd ed. New York, NY: Springer-Verlag; 2016.
26. Karaketir ŞG, Lüleci NE, Eryurt MA, Emecen AN, Haklıdır M, Hıdıroğlu S. Overweight and obesity in preschool children in Turkey: A multilevel analysis. *J Biosoc Sci*. 2023;55(2):344-366. doi:10.1017/S0021932022000025
27. Hatemi H, Yumuk VD, Turan N, Arik N. Prevalence of overweight and obesity in Turkey. *Metab Syndr Relat Disord*. 2003;1(4):285-290. doi:10.1089/1540419031361363
28. Gültekin T, Özer BK, Akın G, Bektaş Y, Sağir M, Güleç E. Prevalence of overweight and obesity in Turkish adults. *Anthropol Anz*. 2009:205-212. doi:10.1127/0003-5548/2009/0297
29. Çelmeli G, Çürek Y, Gülten ZA, et al. Remarkable increase in the prevalence of overweight and obesity among school age children in Antalya, Turkey, between 2003 and 2015. *J Clin Res Pediatr Endocrinol*. 2019;11(1):76. doi:10.4274/jcrpe.galenos.2018.2018.0108
30. Ampofo AG, Boateng EB. Beyond 2020: Modelling obesity and diabetes prevalence. *Diabetes Res Clin Pract*. 2020;167:108362. doi:10.1016/j.diabres.2020.108362
31. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health*. 2022;7(9):e009773. doi:10.1136/bmjgh-2022-009773

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Araştırma Makalesi | Research Article

GÖZ KAPAĞI KİTLELERİNİN KLİNİK VE HİSTOPATOLOJİK ÖZELLİKLERİ: TEK MERKEZLİ RETROSPEKTİF DEĞERLENDİRME

CLINICAL AND HISTOPATHOLOGICAL FEATURES OF EYELID MASSES: SINGLE CENTER RETROSPECTIVE EVALUATION

Büşra Yılmaz Tuğan[1*], Diba Bulluti[1]

[1]Kocaeli Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Kocaeli, Türkiye.

ÖZ

Amaç: Bu çalışmada göz kapağı kitlesi ile kliniğimize başvuran hastalarının temel özelliklerini, lokalizasyonunu, yaşa ve cinsiyete özel prevalansını, klinik ve histolojik tanılar arasındaki uyumu araştırmayı amaçladık.

Yöntem: 2019-2024 yılları arasında göz kapağında kitle yakınmasıyla Oküloplasti Birimi'nde tetkik edilen 127 olgunun (127 kapak kitlesi) tıbbi kayıtları retrospektif olarak değerlendirildi. Değerlendirilen parametreler arasında cinsiyet, başvurudaki yakınma, yakınmanın başladığı yaş, hekime başvuru yaşı, yakınmanın başlangıcından başvuruya kadar geçen süre, yakınma olan taraf (sağ/sol), lokalizasyon ve histopatolojik tanı yer aldı.

Bulgular: 127 olgunun 57'si (%44,9) erkek, 70'i (%55,1) kadındı. Olguların yaş ortalaması 53.7±19.5 idi. Tüm göz kapağı kitlelerinin 9'u (%7,1) enflamatuar, 118'i (%92,9) non-enflamatuar olduğu görüldü. Tüm göz kapağı kitlelerinin %87,4'ü iyi huylu, %12,60'sı kötü huylu lezyonlardı. Tüm lezyonların 71'i (%55,9) sağ, 56'sı (%44,1) sol kapakta idi. Lezyonların en çok üst kapakta yerleştiği gözlemlendi. Büyüyen kitle ve kahverengi lezyon şikâyeti hekime başvurunun en yaygın sebepleri arasında yer alırken, hastaların uzun süredir devam eden ve büyüyen yara olarak tarifledikleri ülser benzeri düzensiz lezyonların, kötü huylu tümörler için önemli bir bulgu olduğu belirlendi. En sık görülen iyi huylu göz kapağı kitlesi skuamöz papilloma 14 (%1,6) idi. Grubumuzda en sık rastlanan kötü huylu göz kapağı tümörü, 13 (%81,3) olgu ile bazal hücreli karsinomdu.

Sonuç: Göz kapağındaki şüpheli her türlü lezyonun erken dönemde cerrahi olarak çıkarılması veya eksizyonel biyopsi ile histopatolojik değerlendirme yapılması hem görme fonksiyonunun hem de hastanın yüz estetiğinin korunarak anatomik bütünlüğünün sağlanması açısından büyük önem taşımaktadır.

Anahtar Kelimeler: Göz kapağı, skuamöz papillom, bazal hücreli karsinom

ABSTRACT

Objective: In this study, we aimed to investigate the basic characteristics, localization, age- and gender-specific prevalence, and the agreement between clinical and histological diagnoses of patients who applied to our clinic with eyelid tumors.

Method: Medical records of 127 patients (127 eyelid tumors) who were examined in Medical Faculty Eye Clinic Oculoplasty Unit between 2019-2024 with eyelid tumor complaints were retrospectively evaluated. Gender, complaint at presentation, age at which complaint started, age at presentation to the physician, time from the beginning of complaint to presentation, side with complaint (right/left), localization, and histopathological diagnosis were the evaluated parameters.

Results: 57 (44.9%) of 127 cases were male and 70 (55.1%) were female. The mean age of the cases was 53.7±19.5. Among all eyelid tumors, 9 (7.1%) were inflammatory, while 118 (92.9%) were non-inflammatory. Of all eyelid tumors, 87.4% were benign and 12.60% were malignant. Of all lesions, 71 (55.9%) were on the right and 56 (44.1%) were on the left eyelid. The lesions were mostly located on the upper eyelid (58; 45.7%). While the complaint of a growing tumor or brown lesion was the most common reason for consulting a physician, it was observed that ulcer-like irregular lesions that patients described as long-standing and growing wounds were an important finding for malignant tumors. The most common benign eyelid tumor was squamous papilloma 14 (12.6%). Basal cell carcinoma was the most common malignant eyelid tumor in our group with 13 cases (81.3%).

Conclusion: Early excision or histopathological examination with excisional biopsy of any suspicious lesion on the eyelids is important for ensuring anatomical integrity without altering both the visual system and the patient's facial appearance.

Keywords: Eyelid, squamous papilloma, basal cell carcinoma

***İletişim kurulacak yazar/Corresponding author:** Büşra Yılmaz Tuğan; Kocaeli Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Kocaeli, Türkiye.
Telefon/Phone: +90 (262) 303 75 75 **e-posta/e-mail:** busrayilmaz87@hotmail.com
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Giriş

Göz kapaklarının görevi gözü dış etkenlerden korumak, kornea ve konjonktivayı nemli tutmaktır. Pratik olarak göz kapakları ön ve arka olmak üzere iki ayrı lamelden oluşurlar. Kapak cildi ve orbikülaris okuli ön lameli, tars ve konjonktiva ise arka lameli meydana getirir. Üst kapak cildi incedir ve her bir göz kırpma sırasında kapağın hareketine izin verir. Üst kapaktaki yapısal duruma ters olarak alt kapak cildinde dikey fazlalık bulunmaz. Üst ve alt göz kapağı derisinin hemen altında orbicularis okuli kası bulunur. Bu, istemsiz göz kapağı kapanmasından (göz kırpma) sorumludur.[1] Üst göz kapağı kanlanmasının çoğunu internal karotid arterden alır. Alt göz kapağı kanının çoğunu dış karotid arterden alır. Üst ve alt göz kapaklarının medial kısımları submandibular lenf düğümlerine drene olan lenf dolaşımına sahiptir. Üst ve alt göz kapaklarının lateral kısımları pre-auriküler lenf düğümlerine drene olur. Üst göz kapağının duyusu V. kranial sinirin oftalmik dalı tarafından sağlanır. Alt göz kapağının duyusu ise V. kranial sinirin maksiller dalı tarafından sağlanır.[2]

Göz kapağı tümörleri klinik oftalmoloji pratiğinde en sık görülen neoplazilerdir. Cilt kanserlerinin %10'u göz kapaklarında yerleşir.[3] Lokalizasyona ilişkin olarak, farklı yazarlar benzer yüzdeler göstermektedir, vakaların %50'si alt göz kapağında, yaklaşık %25'i medial kantusta, %15'i üst göz kapağında ve yaklaşık %5-8'i lateral kantusta yer almaktadır.[4,5,6,7] Göz kapağı tümörleri klinik davranışlarına göre iyi huylu veya kötü huylu olarak ve köken aldıkları doku veya hücreye göre sınıflandırılabilir.

Yanoff ve Duker[8] göz kapakları kitlelerini kaynak aldıkları dokulara göre şöyle sınıflamışlardır:

Göz Kapağı Kitlelerinin Sınıflandırılması

A- İyi Huylu Kitleler

1. Epitelyal kitleler
2. Adneksiyal kitleler
3. Vasküler kitleler
4. Nöral kitleler
5. Ksantomatöz kitleler
6. Melanositik kitleler
7. Enflamatuar kitleler

B- Kötü Huylu Kitleler

1. Epitelyal kitleler
2. Adneksiyal kitleler
3. Vasküler kitleler
4. Melanositik kitleler
5. Diğer İyi Huylu Kitleler

İyi huylu göz kapağı lezyonları genellikle yapılan rutin bir muayene sırasında bulunur. En yaygın iyi huylu inflamatuar lezyonlar arasında şalazyon ve piyojenik granülom bulunur. Enfeksiyöz lezyonlar arasında verruca vulgaris, molluscum contagiosum ve hordeolum bulunur. İyi huylu neoplastik lezyonlar arasında skuamöz hücreli papillom, epidermal inklüzyon kisti, dermoid/epidermoid kist, edinilmiş melanositik nevüs, seboreik keratoz, hidrokistoma, Zeiss kisti ve ksantelazma bulunur. Predispozan faktörler, lezyonun süresi ve büyüme hızı, hassasiyet, akıntı veya kanama semptomları ile ilgili soruları içeren dikkatli bir öykü, dikkatli klinik gözlemle birleştirildiğinde, lezyonu gözlemlemek mi yoksa biyopsi ve histopatolojik analiz için mi sevk etmek gerektiği belirlenecektir.[9]

Göz kapağının en yaygın kötü huylu tümörleri arasında bazal hücreli karsinom, skuamöz hücreli karsinom, sebase hücreli karsinom, melanom ve Merkel hücreli karsinom bulunur. Kötü huylu tümör şüphesi olduğunda biyopsi ve histopatolojik analiz için sevk yapılmalıdır. Endikasyon olduğunda tedavi cerrahi eksizyon, radyoterapi, kemoterapi, immünoterapi, kriyocerrahi veya lazer tedavilerinden oluşur.[10]

Bu çalışmada göz kapağı kitlesi ile kliniğimize başvuran hastalarının temel özelliklerini, lokalizasyonunu, yaşa ve cinsiyete özel prevalansını, klinik ve histolojik tanılar arasındaki uyumu araştırmayı amaçladık.

Yöntem

Bu çalışmada, 2019-2024 yılları arasında göz kapağında kitle şikayetiyle Oküloplasti Birimi'nde tetkik edilen, cerrahi tedavi uygulanan ve düzenli olarak kontrole gelen 127 olgunun (127 kapak kitlesi) tıbbi kayıtları, aşağıdaki parametreler doğrultusunda retrospektif olarak incelenmiştir: cinsiyet, başvuru şikâyeti, şikayetin başladığı yaş, hekime başvuru yaşı, şikayetin başlangıcından başvuruya kadar geçen süre, şikayetin olduğu taraf (sağ/sol), lokalizasyon ve histopatolojik tanı. Düzenli kontrole gelmeyen, muayene kayıtları eksik olan ya da histopatolojik tanıları netleşmeyen olgular çalışmaya dahil edilmemiştir. Olguların başvuru şikayetleri, kitlenin lokalizasyonu ve varlık süreleri gibi veriler bir tabloya aktarılmıştır. Ayrıca, yaş ve cinsiyet bazında histopatolojik tanılar karşılaştırılmış ve izlem sonuçları gözden geçirilmiştir. Patolojik sonuçlara göre hastalar tekrar muayeneye çağrılmış, kontrol sırasında gerekli görülen olguların fotoğrafları çekilerek arşivlenmiştir.

İstatistiksel değerlendirme, 10240642 seri numaralı "IBM SPSS İstatistik 19, Armonk, NY, ABD" istatistik programı kullanılarak gerçekleştirilmiştir. Ölçülebilir verilerin normal dağılıma uygunluğu, tek örnek Kolmogorov-Smirnov testiyle incelenmiş, normal dağılım göstermeyen gruplar arasında kıyaslama yapmak için ise Mann-Whitney U testi uygulanmıştır. Değişkenler arasındaki ilişkiler, Spearman korelasyon analiziyle değerlendirilmiş; niteliksel verilerde ise Pearson χ^2 ve Yates düzeltmeli χ^2 testleri kullanılmıştır. Tanımlayıcı istatistikler için medyan (min-max) değerleri ve aritmetik ortalama ± standart sapma kullanılmıştır. İstatistiksel anlamlılık sınırı $p<0,05$ olarak belirlenmiştir.

Bulgular

Çalışmamızda 127 olgunun 57'si (%44,9) erkek, 70'i (%55,1) kadındı. Olguların yaş ortalaması 53.7±19.5 idi. Tüm göz kapağı kitlelerinin 9'u (%7,1) enflamatuar, 118'i (%92,9) non-enflamatuar olduğu görüldü. Tüm göz kapağı kitlelerinin %87,4'ü iyi huylu, %12,60'sı kötü huylu lezyonlardı. Kötü huylu göz kapağı lezyonlarının tümü

non-enflamatuar karakterde iken, iyi huylu göz kapağı lezyonların tümü enflamatuar karakterde idi. Göz kapağı lezyonlarının yerleşim yerlerine göre dağılımı incelendiğinde, tüm lezyonların %55,9'u sağ göz kapağında, %44,1'i ise sol göz kapağında yer almaktadır. Lezyonların en fazla üst kapakta (%45,7) görüldüğü, bunu sırasıyla alt kapak (%27,6), medial kantus (%17,3) ve lateral kantus (%9,4) takip etmektedir (Tablo 1).

Başvuru sırasındaki şikayetler, iyi ve kötü huylu tümörlü hastalar arasında benzerlik göstermektedir. En sık görülen başvuru sebepleri arasında büyüyen kitle ve kahverengi lezyonlar yer alırken, kötü huylu tümörlerde, hastaların uzun süre boyunca büyüyen ve ülser benzeri düzensiz lezyonlar olarak tanımladıkları şikayetlerin önemli bir belirti olduğu gözlemlenmiştir. Ayrıca, olguların %63,8'i kitle şikayetiyle hekime 12 aydan önce başvururken, %36,2'si ise 12 aydan sonra başvurmuştur (Tablo 1).

Tablo 1. Göz kapağı kitlelerinin klinik özellikleri

Kitle Özellikleri	n (%)
Kitlenin natürü	
Enflamatuar	9 (7,1)
Non-enflamatuar	118 (92,9)
İyi huylu/kötü huylu	
İyi huylu	110 (87,4)
Kötü huylu	17 (12,6)
Tarafı	
Sağ	71 (55,9)
Sol	56 (44,1)
Lokalizasyon	
Üst kapak	58 (45,7)
Alt kapak	35 (27,6)
Medial kantus	22 (17,3)
Lateral kantus	12 (9,4)
Başvuru süresi	
<12 ay	81 (63,8)
>12 ay	46 (36,2)

İyi huylu göz kapağı tümörlerini kaynak aldıkları dokuya göre incelediğimizde, ilk sırayı %40,5 oranıyla epitelyal tümörler aldı. Bunu sırasıyla %20,7 oranıyla ksantomatöz tümörler, %18,0 ile melanositik tümörler, %13,5 ile adneksiyel tümörler ve %7,2 ile vasküler tümörler takip etti (Tablo 2). En sık görülen iyi huylu göz kapağı kitlesi skuamöz papillom 14 (%12,6) idi. Skuamöz papillomayı sıklık sırasına göre intradermal nevüs 13 (%11,7), ksantelazma 13 (%11,7), şalazyon 10 (%9), hidrokistoma 10 (%9), seboreik keratoz 9 (%8,1), epidermal kist 5 (%4,5), hemanjiom 3 (%2,7), verruka vulgaris 3 (%2,7), bileşik nevüs 2 (%1,8), dermoid kist 2 (%1,8), hidroadenoma 2 (%1,8), siringoma 2 (%1,8) izliyordu. Hiperkeratoz, basit duktus kisti,molluskum kontagiozum, keratinöz kist, fibroepitelyal polip, liken sklerozus, vs. birer kitle ile nadir görülen tümörlerdi. İyi huylu göz kapağı kitlelerinin histopatolojik dağılımı Tablo 3'te gösterilmiştir.

Bazal hücreli karsinom [13 (%81,3)] olgu grubumuzda en sık görülen kötü huylu göz kapağı tümörüydü. Onu skuamöz hücreli karsinom [2 (%12,5)] ve keratoakantom [1 (%6,3)] takip etti. Kötü huylu tümörlerin histopatolojik dağılımı Tablo 3'te görülmektedir. İyi huylu tümörler cinsiyet dağılımı yani cinsiyetin tümör oluşumunda rolü açısından incelendiğinde kadınlarda daha fazla görüldüğü saptandı (Şekil 1). Kitlelerin yaşla ilişkisi incelendiğinde; iyi huylularda 10'unun (%9) 0-19 yaş grubunda, 20'sinin (%18) 20-39 yaş grubunda, 38'inin (%34,2) 40-59 yaş grubunda, 37'sinin (%33,3) 60-79 yaş grubunda, 6'sının (%5,4) 80 yaş ve üzerinde olduğu görüldü (Şekil 2).

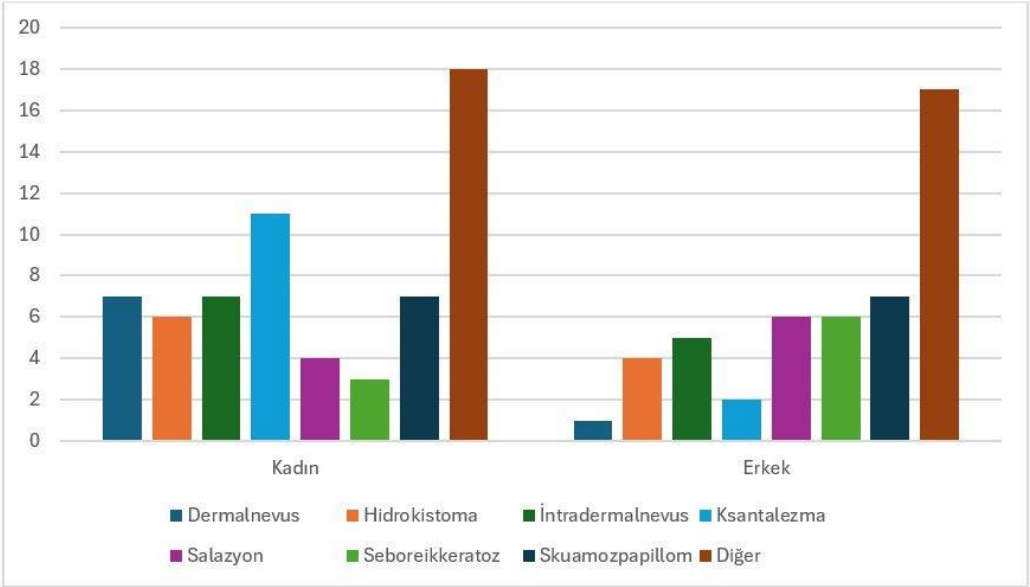
127 kapak kitlesine uygulanan cerrahi tedavi sonrası nüks oranı %3,9'du (5 tümör). Komplikasyon gelişme oranı ise %0,8 (1 tümörde) görüldü.

Tablo 2. İyi huylu göz kapağı tümörlerini kaynak aldıkları dokuya göre sınıflanması

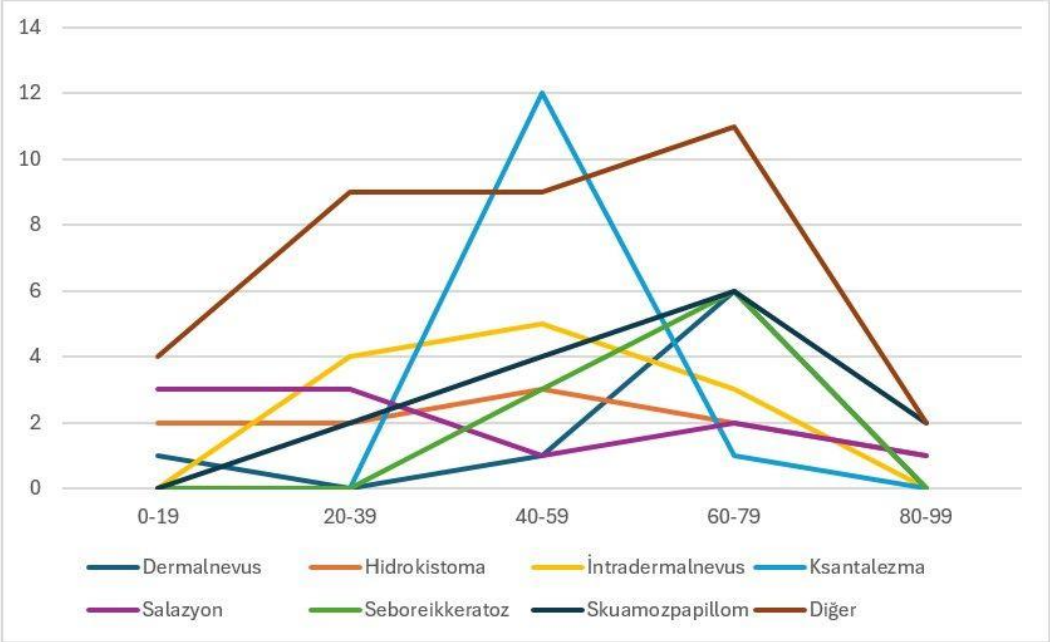
Kaynak Aldıkları Doku	n (%)
Ksantomatöz tümörler	23 (20,7)
Melanositik tümörler	20 (18,0)
Adneksiyel tümörler	15 (13,5)
Vasküler tümörler	8 (7,2)

Tablo 3. Göz kapağı kitlelerinin histopatolojik dağılımı

Histopatolojik Tanı	n (%)
İyi huylu	
Skuamözpapillom	14 (12,6)
İntradermal nevus	13 (11,7)
Ksantalezma	13 (11,7)
Şalazyon	10 (9)
Hidrokistoma	10 (9)
Seboreik Keratoz	9 (8,1)
Epidermal Kist	5 (4,5)
Hemanjioma	3 (2,7)
Verruka vulgaris	3 (2,7)
Bileşik nevus	2 (1,8)
Dermoid kist	2 (1,8)
Hidroadenoma	2 (1,8)
Siringoma	2 (1,8)
Kötü huylu	
Bazal hücreli karsinom	13 (81,3)
Skuamöz hücreli karsinom	2 (12,5)
Keratoakantom	1 (6,3)



Şekil 1. Histopatolojik sınıflamaya göre cinsiyet dağılımı



Şekil 2. Histopatolojik sınıflamaya göre yaş dağılımı

Tartışma

Göz kapağındaki kitlelerle başvuran hastaların klinik bulguları, yaş, cinsiyet, tümör türleri ve lokalizasyonları ile histopatolojik tanılar arasındaki uyumun değerlendirildiği bu çalışmada, 127 hastanın 57'si (%44,9) erkek, 70'i (%55,1) kadın olup, yaş ortalaması 53.7±19,5 olarak tespit edilmiştir. Çömez ve ark.[11] 2006 yılında 281 hastanın 130'unun (%46,26) erkek, 151'inin (%53,74) kadın olduğunu, başvuru yaş ortalamasının ise 48.2 olduğunu belirtmiş; Özkılıç ve ark.[12] ise 737 hastanın 406'sının (%55) kadın, 331'inin (%45) erkek olduğunu ve başvuru yaş ortalamasının 41,3 olduğunu bildirmiştir. Bu veriler, bizim çalışmamızla benzerlik göstermektedir.

Aurora ve Blodi[13] araştırmalarında, enflamatuar lezyonların göz kapağı kitlelerinin %12'sini oluşturduğunu, Çömez ve ark.[11] ise bu oranı %33,12 olarak bulmuşlardır. Bizim çalışmamızda ise göz kapağındaki tüm kitlelerin 9'u (%7,1) enflamatuar, 118'i (%92,9) ise non-enflamatuar tümörlerden oluşmaktaydı. Lezyonların lokalizasyonu incelendiğinde, tüm göz kapağı kitlelerinin %55,9'u sağ göz kapağında, %44,1'i sol göz kapağında yer almaktadır. İyi huylu tümörlerin lokalizasyonları konusunda literatürdeki çalışmalar farklı sonuçlar sunmakla birlikte, bu konuda belirgin bir genel özellik tespit edilememiştir.[18,19] Çalışmamızda, göz kapağı tümörlerinin %87,4'ü iyi huylu, %12,6'sı ise kötü huylu tümörlerdir. Aurora ve Blodi[13] 1970 yılında, bu oranları iyi huylu tümörler için %76, kötü huylu tümörler için ise %24

olarak belirlemişlerdir. Abdi ve ark.[15] ise iyi huylu tümörlerin oranını %59,9, kötü huylu tümörlerin oranını %41,1 olarak bildirmişlerdir. Diğer çalışmalar da benzer şekilde iyi huylu tümörlerin daha yüksek oranda olduğunu göstermektedir.

Olguların başvuru şikayetlerinde, büyüyen kitle ve kahverengi lezyonlar en yaygın yakınmalar arasındaydı. Çömez ve ark.[11] çalışmalarında da benzer şekilde %83 oranında kitle ve şişlik şikayetlerinin en sık başvuru sebebi olduğunu saptamışlardır.

İyi huylu tümörler doku tiplerine göre sınıflandığında, en sık görülen tümör tipi %40,5 ile epitelyal tümörlerdir. Bunu sırasıyla ksantomatöz tümörler (%20,7), melanositik tümörler (%18,0), adneksiyel tümörler (%13,5) ve vasküler tümörler (%7,2) takip etmektedir. Çömez ve ark.[11] çalışmalarında, 179 iyi huylu non-enflamatuar tümörde epitelyal tümörlerin %57,54 oranında en yaygın tür olduğunu belirtmişlerdir. Aurora ve Blodi[13] ile Uzun ve ark.[14] da benzer şekilde epitelyal tümörlerin ilk sırada yer aldığını bildirmişlerdir.

İyi huylu göz kapağı tümörleri arasında en sık görülen lezyon %12,6 oranıyla skuamöz papillomdu. Bunu sırasıyla intradermal nevüs (%11,7), ksantelazma (%11,7), şalazyon (%9), hidrokistoma (%9), seboreik keratoz (%8,1) gibi lezyonlar takip etmiştir. Çömez ve ark.[11] (çalışmalarında ise en sık görülen iyi huylu göz kapağı tümörleri sırasıyla şalazyon (%32,76), skuamöz papillom (%16,02) ve nevüs (%7,67) olarak bildirilmiştir. Yalaz ve ark.[16] çalışmalarında dermoid kistlerin %32 oranıyla en sık görülen iyi huylu tümör olduğunu saptamıştır.

Kötü huylu tümörler arasında bazal hücreli karsinomun görülme sıklığı, Türkiye'deki çalışmalarda %64 ile %94 arasında değişmektedir.[12,20,21] Bizim çalışmamızda da bazal hücreli karsinom, kötü huylu tümörler arasında %81,3 ile en yüksek orana sahipti.

İyi huylu tümörlerin cinsiyet dağılımına bakıldığında, kadınlarda daha fazla görüldüğü saptanmıştır. Abdi ve ark.[15] bu oranı erkekler lehine 1,37 olarak bulmuşlardır. Deshpande ve ark.[22] 2003 yılında yayımladıkları çalışmada kadın/erkek oranını 0,89/1 olarak saptamışlardır. Thakur ve ark.[23] ise bu oranı 1,05/1 olarak belirlemişlerdir.

Cerrahi tedavi sonrası nüks oranı, çalışmamızda %3,9 (5 tümör) olarak tespit edilmiştir. Çömez ve ark.[11] nüks oranını %15,79, Soysal ve ark.[20] ise %10,56 olarak bildirmişlerdir.

Sonuç olarak, göz kapağında şüphe uyandıran her türlü lezyonun erken dönemde eksize edilerek veya eksizyonel biyopsi ile histopatolojik olarak incelenmesi hem görme sistemi hem de hastanın yüz görünümünün korunması açısından büyük önem taşımaktadır.

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Kaynaklar

1. Uysal Y. Göz kapağının benign-malign tümörleri. Türk Oftalmoloji Derneği Yayın no:6. Temel Oküler Onkoloji; 2008. S.17-56.
2. Cochran ML, Lopez MJ, Czyz CN. Anatomy, Head and Neck: Eyelid. 2023 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29493929.
3. Myers M, Gurwood AS. Periocular malignancies and primary eye care. *Optometry*. 2001;72(11):705-712.
4. Saleh GM, Desai P, Collin JR, Ives A, Jones T, Hussain B. Incidence of eyelid basal cell carcinoma in England: 2000-2010. *Br J Ophthalmol*. 2017;101(2):209-212. doi:10.1136/bjophthalmol-2015-308261
5. Wong CS, Strange RC, Lear JT. Basal cell carcinoma. *BMJ*. 2003;327(7418):794-798. doi:10.1136/bmj.327.7418.794
6. Cook BE Jr, Bartley GB. Epidemiologic characteristics and clinical course of patients with malignant eyelid tumors in an incidence cohort in Olmsted County, Minnesota. *Ophthalmology*. 1999;106(4):746-750. doi:10.1016/S0161-6420(99)90161-6
7. Bagheri A, Tavakoli M, Kanaani A, et al. Eyelid masses: a 10-year survey from a tertiary eye hospital in Tehran. *Middle East Afr J Ophthalmol*. 2013;20(3):187-192. doi:10.4103/0974-9233.114788
8. Yanoff M, Duker S. Oftalmoloji. İstanbul: Hayat Tıp Kitapevi. 2007:698-720.
9. Ziętek M, Nowacki M, Wierzbicki J, et al. The report and analysis concerning the usefulness of basic telemedicine tools in the skin cancer diagnostic screening process during COVID-19 pandemics. *Postepy Dermatol Alergol*. 2022;39(1):189-194. doi:10.5114/ada.2022.113605
10. Rana H, Stokkermans TJ, Purt B, Chou E. Malignant Eyelid Lesions. 2023 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 35881732.
11. Çömez AT, Akçay L, Karadağ O. Göz Kapağı kitlelerinin histopatolojik ve epidemiyolojik değerlendirilmesi. *Turk J Ophthalmol.* 2007;37(2):84-92.
12. Özkılıç E, Peksayar G. Kapak tümörlerinin epidemiyolojik açıdan değerlendirilmesi. *Turk J Ophthalmol.* 2003 Jul;33(4):631-640.
13. Aurora A, Blodi F. Lesions of the eyelids. A clinicopathologic study. *Surv Ophthalmol.* 1970;15:94-104.
14. Uzun A, Gündüz K, Erden E, Heper AO. İyi huylu gözkapağı tümörlerinde klinik ve histopatolojik tanı. *Turk J Ophthalmol.* 2012;42(1):43-46. doi:10.4274/tjo.42.63825
15. Abdi U, Tyagi N, Maheshwari V, Gogi R, Tyagi SP. Tumours of eyelid: a clinicopathologic study. *J Indian Med Assoc*. 1996;94(11):405-418.
16. Yalaz M, Varınlı S, Varınlı İ. Oftalmik tümör ve tümör benzeri lezyonların klinikopatolojik değerlendirilmesi. *Türk Oftalmol Gaz.* 1990;20:462-466.
17. Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. A retrospective study of 5504 cases and

review of literature. *Am J Dermatopathol*. 2009;31(3):256-262. doi:10.1097/DAD.0b013e3181961861

18. Chang CH, Chang SM, Lai YH, et al. Eyelid tumors in southern Taiwan: a 5-year survey from a medical university. *Kaohsiung J Med Sci*. 2003;19(11):549-554. doi:10.1016/S1607-551X(09)70505-4
19. Ten-Seldam RE J, Helwig EB. Histological typing of skin tumours. Geneva: World Health Organization. 1974;48-9.
20. Soysal HG, Albayrak A. Göz kapaklarının primer malign tümörleri. *Türk Oftalmol Gaz*. 2001;31:370-377.
21. Margo CE, Mulla ZD. Malignant tumors of the eyelid: a population-based study of non-basal cell and non-squamous cell malignant neoplasms. *Arch Ophthalmol*. 1998;116(2):195-198. doi:10.1001/archopht.116.2.195
22. Deshpande AH, Munshi MM. Fine needle capillary sampling of eyelid masses. A study of 70 cases. *Acta Cytol*. 2003;47(3):349-358. doi:10.1159/000326532
23. Thakur SK, Sah SP, Lakhey M, Badhu BP. Primary malignant tumours of eye and adnexa in Eastern Nepal. *Clin Exp Ophthalmol*. 2003;31(5):415-417. doi:10.1046/j.1442-9071.2003.00688.x

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Araştırma Makalesi | Research Article

YAPAY TEMPORAL KEMİK İLE DİSEKSİYON VE SANAL GERÇEKLİK CERRAHİ ANATOMİ EĞİTİMİ UYGULAMALARININ YARARLILIĞININ DEĞERLENDİRİLMESİ

UTILITY ANALYSES OF ARTIFICIAL TEMPORAL BONE DISSECTION AND VIRTUAL REALITY SURGICAL ANATOMY TRAINING APPLICATIONS

Murat Öztürk[1*], Bülent Topuz[2], Serkan Aytaç Kılıç[3]

[1]Kocaeli Üniversitesi, Tıp Fakültesi, KBB Ana Bilim Dalı, Kocaeli, Türkiye. [2]Pamukkale Üniversitesi, Tıp Fakültesi, KBB Ana Bilim Dalı, Denizli, Türkiye. [3]İskenderun Devlet Hastanesi, KBB, Hatay, Türkiye.

ÖZ

Amaç: Bu çalışmanın amacı yapay temporal kemik modelinde diseksiyon ile sanal gerçeklik cerrahi anatomi eğitimin yararlılığının araştırılmasıdır.

Yöntem: Yapay temporal kemik ile diseksiyon gerçekleştiren ve sanal gerçeklik ile cerrahi anatomi eğitimine katılan uzmanlık öğrencilerinden anket ile geribildirim alındı ve uygulamaların yararlılığı değerlendirildi.

Bulgular: Yapay kemik ile diseksiyon %90,7 faydalı ve çok faydalı, %87,5 gerçek anatomiye uygun, %78,1 gerçek kemiğe benziyor ve çok benziyor bulundu. Faydası az ya da faydasız değerlendiren olmadı. Sanal gerçeklik eğitimi ise %87,5 faydalı ve çok faydalı olarak bulundu.

Sonuç: Her iki yöntemde yüksek oranda faydalı olarak değerlendirilmiştir. Olası ekonomik, lojistik, etik avantajları, tekrarlanabilir ve kolay ulaşabilir olmaları nedenleri ile klasik eğitim ile kombine olarak kullanılmaları faydalı görünmektedir.

Anahtar Kelimeler: Temporal kemik, yapay kemik, mastoidektomi, sanal gerçeklik

ABSTRACT

Objective: The purpose of this study is to analyze the utility of artificial temporal bone dissection and virtual reality surgical anatomy training applications.

Method: The utility of the applications was analyzed by the feedback survey of the residents who participate the artificial temporal bone dissection and virtual reality surgical anatomy training courses.

Results: The artificial bone dissection was considered 90.7% beneficial or very beneficial, 87.5% similar to real anatomy, 78.1% similar or very similar to real bone. No one considered it little beneficial or useless. The virtual reality training was considered 87.5% beneficial or very beneficial.

Conclusion: Both methods were considered highly useful. When combined with standard training, they seem to be beneficial due to their repetitive and easily available nature, as well as potential economic, logistical, and ethical advantages.

Keywords: Temporal bone, artificial bone, mastoidectomy, virtual reality

*** İletişim kurulacak yazar/Corresponding author:** Murat Öztürk; Kocaeli Üniversitesi Tıp Fakültesi, KBB Ana Bilim Dalı, 41001, Umuttepe, İzmit, Kocaeli, Türkiye.
Telefon/Phone: +90 (262) 303 75 00, **e-mail/e-posta:** muratozturk@kocaeli.edu.tr
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Giriş

Temporal kemiğin birçok hastalığının cerrahi tedavisinde mastoidektomi ilk ve önemli aşamayı oluşturmaktadır. Kulak cerrahilerinin bu temel basamağı iyi bir anatomik bilgi ve el becerisini gerektirmektedir. Bu cerrahiye yeni başlayanların gerek mikroskop gerekse tur kullanma yeteneklerini geliştirebilmek için öncelikle kadavra üzerinde mastoidektomi gerçekleştirmeleri gerekmektedir. Fakat kadavraya ulaşmakta yaşanan teknik, ekonomik ve lojistik problemler, etik kaygılar ve olası enfeksiyöz ajanların bulaşı gibi çekinceler, yeterli sayılarda kadavra diseksiyonu yapılmasını güçleştirmektedir. Cerrahi anatomi ve tekniklerin iyi bilinmesi de çok önemlidir, fakat bölgenin anatomisinin görece karışık ve küçük olması, önemli yapıları içermesi, modellerle göstermekteki güçlükler, bu eğitimi zorlaştırabilmektedir. Genel olarak Kulak Burun Boğaz Hastalıkları eğitiminde, kendine has zorluklar içeren kulak cerrahilerinin öğrenilmesinin yeni ve farklı eğitim yöntemleri ile desteklenmesi yararlı olacaktır.

Gelişen ve yaygınlaşan teknolojilerle birlikte 3D yazıcılarla uygun materyaller kullanılarak yapılan yapay temporal kemik modelleri ile diseksiyon ekonomik ve pratik bir şekilde kadavra temini sorununun aşılmasına yardımcı olmaktadır.[1] Böylelikle gerek temporal kemik anatomisine üç boyutlu olarak hâkim olma becerisi gerekse mikroskop ve tur kullanma becerileri geliştirilebilmektedir.

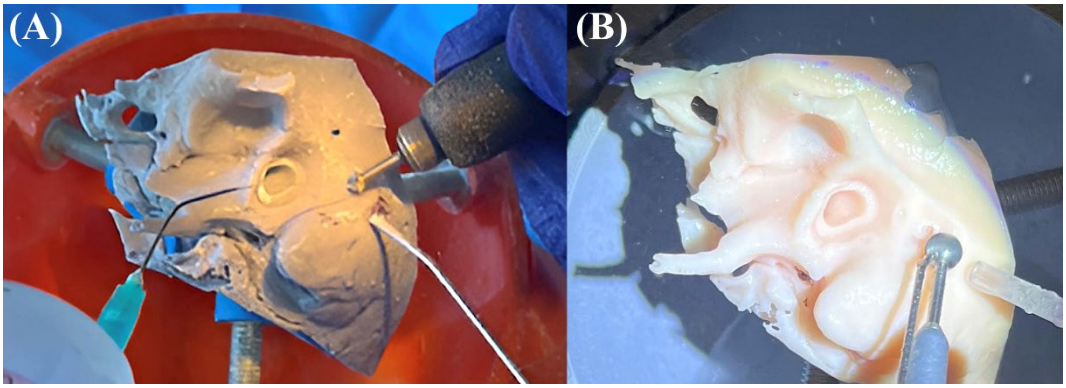
Bu çalışma ile, yerli olarak üretilen ve Türkiye'de yaşayan insanların tomografileri referans alınarak geliştirilen yapay temporal kemik modelinde Kulak Burun Boğaz Hastalıkları uzmanlık öğrencileri tarafından uygulanan cerrahi diseksiyonun ve sanal gerçeklik ile cerrahi anatomi eğitiminin verimliliğinin ve yararlılığının araştırılması hedeflenmiştir.

Yöntem

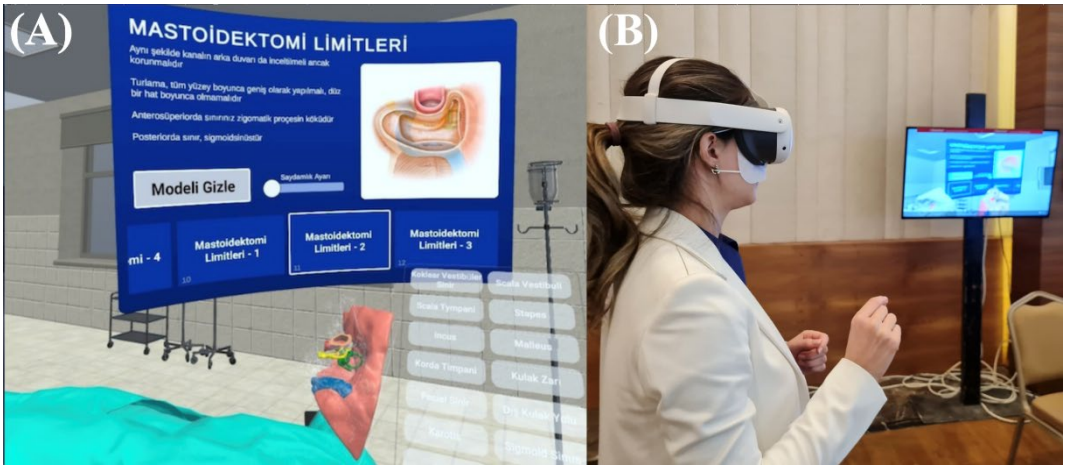
Bu pilot çalışma için 45. Türk Ulusal Kulak Burun Boğaz ve Baş Boyun Cerrahisi Kongresi (2024, Girne, Kıbrıs) esnasında Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği tarafından ücretsiz olarak düzenlenen yapay temporal kemik ile diseksiyon ve sanal gerçeklik ile cerrahi anatomi eğitimi kursları değerlendirmeye alındı. Farklı asistanlık kıdem yılında olan ve daha önce mastoidektomi yapmış ya da yapmamış asistanlardan oluşan ve Türkiye'nin farklı şehirlerindeki eğitim kurumlarında çalışan 50 kişilik kursiyerlere kurs sonrasında online anket düzenlendi. Tüm katılımcıların gönüllülük esası ile 10 soruluk ankete katılması rica edildi, katılmak istemeyen veya anketi doldurmayanlar çalışma dışı bırakıldı. Bu geribildirim anketi ile katılımcıların detaylı olarak 5 yıllık uzmanlık eğitiminin hangi kıdem yılında yer aldıkları, daha önce temporal kemik diseksiyon kursuna katılıp katılmadıkları, daha önce mastoidektomi gerçekleştirip gerçekleştirmedikleri ortaya konuldu, yapay temporal kemik modelini anatomiye uygunluk ve gerçek kemik hissi verme oranı, genel olarak diseksiyon ve sanal gerçeklik deneyim ve yararlılıklarını değerlendirmeleri istendi. Değerlendirme soruları genel olarak 5 seçenekli giderek artan ya da azalan sayısal olarak ilişkilendirilmiş cevaplar ile değerlendirildi. Ankete katılanların cevaplarının ortalamaları alınarak farklı kategorilerde yapay modelin yararlılığı ve verimliliği araştırıldı. Benzeri kursların etkinliğinin artırılması için varsa katılımcıların önerileri ayrıca ortaya konuldu.

Bu kurs için Piri Teknoloji® (Çanakkale, Türkiye) tarafından üretilen S001 modeli yapay temporal kemik (Resim 1) ve Sanal Gerçeklik sistemi (Resim 2) kullanıldı. Modeller Blender (The Blender Foundation, Hollanda), Sanal Gerçeklik ise Unity (Unity Software, Danimarka) yazılımı kullanılarak yaratılmıştır. Teknik çizimler için Fusion 360 (Autodesk, San Francisco, Amerika Birleşik Devletleri) yazılımı, anatomik nesnelerin üzerine detaylı dokular eklemek için Substance Painter (Adobe, San Jose, Amerika Birleşik Devletleri) kullanılmıştır. Tüm katılımcılara operasyon mikroskopu, cerrahi tur ve aspirasyon sistemi kurularak temporal kemik diseksiyonu yapma imkânı sağlandı. Kurs esnasında katılımcılara tecrübeli eğitimciler eşlik etti.

Sanal Gerçeklik kursu için ise kursiyerlere öncesinde kısa bir adaptasyon eğitimi verildi, sanal maketlerin tutulması, yönünün değiştirilmesi ve menüler arasında dolaşabilmeleri sağlandı. Deneyim esnasında sürekli olarak teknik destek verildi, kursiyerin gördükleri ve hareketleri monitöre yansıtılarak eğitmen ve teknik ekip tarafından görülebilmesi de sağlandı.



Resim 1. Yapay temporal kemik diseksiyon modeli: A ve B



Resim 2. Sanal gerçeklik ile cerrahi anatomi eğitimi: A. Sanal gerçeklik model ve eğitim menüsü görünümü, B. Uygulamanın dışarıdan görünümü.

Çalışma için Yerel Etik Kurul'dan KOU-GOKAEK-2024/498 numarası ile etik kurul onayı alındı. Dataların toplanması ve değerlendirilmesi için Google Forms (CA, ABD), Microsoft Excel (Washington, ABD) ve Sosyal Bilimler için İstatistik Paketi (SPSS) (Chicago, ABD) kullanıldı.

Bulgular

Kursa katılım gösteren 50 kişi içerisinden 44 katılımcının, uygun şekildeki anket ile geribildirimleri ve değerlendirmeleri çalışmamıza dahil edildi. Çalışmaya katılanların uzmanlık eğitimindeki kıdem yılları değerlendirildiğinde; katılımcıların 9'u (%20,5) 5.yıl, 7'si (%15,9) 4.yıl, 20'si (%45,5) 3.yıl, 8'i (%18,2) 2.yıl kıdeminde idi. On iki (%27,3) kişi daha önce temporal kemik diseksiyon kursuna katılmışken, 32 (%72,7) kişi daha önce herhangi bir diseksiyon kursuna katılmamıştı. Yirmi bir (%47,7) kişi daha önce mastoidektomi gerçekleştirmiş iken, 23 (%52,3) kişi daha önce hiç mastoidektomi gerçekleştirmemiş idi.

Yapay temporal kemik ile diseksiyon (Grafik 1) ve Sanal gerçeklik ile cerrahi anatomi eğitimi (Grafik 2) etkinlik ve yararlığı değerlendirildiğinde ise;

Yapay temporal kemik ile yaşanılan deneyim %68,8 çok faydalı, %21,9 faydalı, %9,4 orta olarak değerlendirdi, faydası az ya da faydasız olarak değerlendiren olmadı.

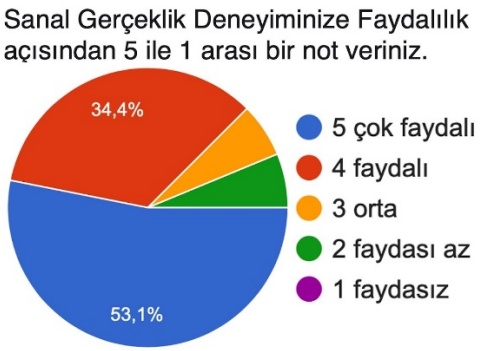
Yapay kemiğin gerçek anatomiye uygunluğu %87,5 uygun, %12,5 kısmen uygun olarak değerlendirildi, uygun değildi olarak değerlendiren olmadı.

Ne kadar gerçek kemik hissi verdiği değerlendirildiğinde %40,6 çok benziyor, %37,5 benziyor, %21,9 orta olarak değerlendirdikleri gözlendi, az benziyor ya da hiç benzemiyor olarak değerlendiren olmadı. Daha önce mastoidektomi yapan 22 (%50,0) katılımcının yanıtları ayrıca değerlendirildiğinde; %31,8 çok benziyor, %63,6 benziyor, %4,6 orta olarak değerlendirdikleri gözlendi, az benziyor ya da hiç benzemiyor olarak değerlendiren olmadı.

Katılımcıların tamamı (%100) "yapay temporal kemik ile diseksiyonu çalışma arkadaşlarınıza önerir misiniz" sorusuna evet yanıtını verdi.

Sanal gerçeklik ile eğitim %53,1 çok faydalı, %34,4 faydalı, %6,2 orta, %6,2 faydası az olarak değerlendirildi, faydasız olarak değerlendiren olmadı (Grafik 2).

Grafik 1. Yapay temporal kemik ile diseksiyonun değerlendirilmesi ve elde edilen sonuçlar: A. Deneyim ve faydalılık, B. Gerçek kemik hissi, C. Anatomiye uygunluk.



Grafik 2. Sanal gerçeklik ile deneyim faydalılık sonuçları.

Benzeri kursların daha faydalı olması için katılımcıların önerileri ise; diseksiyon için ayrılan sürenin uzatılması, eğitimci sayısının artırılması ve böylece diğer kursiyer ile ilgilenirken beklemek zorunda kalınmaması, çalışma ortamının geliştirilmesi, mikroskop ve tur kalitesi daha da iyi olabilir, farklı boyutta modellerin geliştirilmesi, anatomik yapıların renklendirilmesi, föy veya videolarla desteklenmesi, benzer kursların tekrarı ve artırılması ile tüm asistanların ulaşabilmesi, şeklinde oldu.

Tartışma

Temporal kemiğin cerrahi anatomisinin iyi bilinmesi ve mastoidektominin ideal bir şekilde yapılması kulak hastalıklarının cerrahi tedavilerinin temel basamaklarını oluşturmaktadır. Dolayısı ile özellikle uzmanlık eğitimi sırasında bu eğitimin iyi bir şekilde verilebilmesi şarttır. Bu amaçla en sık kullanılan eğitim metodu temporal kemik kadavra diseksiyonlarıdır. Kadavra diseksiyonu öncesi teorik içerikli ön hazırlık yapılması ve diseksiyonun tecrübeli eğiticiler ile gerçekleştirilmesi önemlidir. Kadavra diseksiyonlarının maaliyeti görece yüksek olmaktadır. Lojistik gereklilikler nedeniyle kadavraların transportunda zorluklar yaşanabilir. Potansiyel olarak kadavralar enfeksiyöz ajanları bulaştırabilir. Anatomik varyasyonlar, geçirilmiş travma ya da cerrahiler standardize diseksiyon yapılmasına engel olabilir. Kadavraya ulaşılsa dahi tekrar miktarı az sayılarda kalabilmektedir.

Kulak cerrahisinin ve özellikle tur kullanımının hassas bir şekilde yapılması gerekir. Önemli anatomik yapılar tanınmalı, hasara uğrayabilecek yapılara temastan kaçınılmalıdır. Kemik zincirin, semisirküler kanalların, fasiyal sinirin tanınması ve korunması gerekir. Isı ve mekanik hasar riski nedeniyle istemsiz tur teması yapılmamalıdır. Turun önemli anatomik yapılara hafif fakat kontrolsüz teması bile işitme kaybı ya da fasiyal paralizi gibi ciddi komplikasyonlara neden olabilir. Yapay temporal kemik modeli ile yapılan uygulama anatominin anlaşılması, tur ve operasyon mikroskobu kullanılması, göz el koordinasyonu ve cerrahi becerinin gelişmesi açısından faydalı görünmektedir.

Bu pilot çalışma, Türkiye'de üretilmiş yapay temporal kemik modeli ile diseksiyonun faydalılığını ve yararlılığını değerlendiren ülkemizdeki ilk çalışmadır. Farklı asistanlık kıdemlerinde ve daha önce mastoidektomi yapmış ya da yapmamış uzmanlık öğrencileri ile yapay temporal kemik diseksiyonunun etkinliği ve yararlılığı değerlendirilmiş, genel olarak yararlı, faydalı ve gerçek temporal kemiğe benzer bulunmuştur. Katılımcıların tamamı yapay temporal kemik ile diseksiyonu eğitim alacak diğer asistan arkadaşlarına önermiştir.

Ülkemiz dışındaki çalışmalar değerlendirildiğinde, yapay temporal kemik modelleri ile diseksiyonların yararlılığının ve validasyonunun araştırıldığı, genel olarak bu çalışmalarda yapay kemik ile diseksiyon eğitiminin faydalı ve yararlı olduğu ve olabileceği görülmüştür.[1,2,3]

Üç boyutlu yazıcılar da kullanılan materyalin içeriği önem arz etmektedir ve uygun karışımlar hazırlandığında oldukça yüksek oranda gerçek kemik hissi elde edilebilmektedir. Çalışmamızda toplamda %78,1 oranda çok benziyor ve benziyor oranı görülmüş, az benzediğini ya da hiç benzemediğini düşünen olmamıştır. Gerçek kemiğe benzemesi yapılan diseksiyondan elde edilecek ve gerçek hayatta faydalı olabilecek diseksiyon el becerisinin gelişmesi ve tur ile kemik etkileşiminin anlaşılması açısından önemlidir.

Kadavraya kıyasla yapay temporal kemiklerin hepsinin aynı anatomik özelliklere sahip olması ve standardize olması, ilk kez bu cerrahi gerçekleştirecek adaylar açısından avantaj sağlayabilir. Yine her modelin aynı anatomik yapı ve ölçülere sahip olması eğitimcilerin oryantasyonunu ve farklı kişilere diseksiyon yaptırmalarını kolaylaştırabilir görünmektedir. Ayrıca, farklı anatomik varyasyon ya da hastalık modelleri geliştirilerek, gerçek hayatta karşılaşılabilecek özel durumlar ve hastalıklar açısından tecrübe kazanımı da sağlanabilir ve bu kadavraya kıyasla önemli bir avantaj olabilir. Kadavra ile diseksiyonda bebek ya da erken yaşlarda kadavra bulmak zordur, özellikle koklear implant gibi cerrahiler daha küçük kemiklerde uygulanmaktadır. Yapay kemik ile istenilen boyutlarda modellerin yapılması mümkün ve kolaydır.

Ülkemizde ve benzer ekonomik koşullara sahip birçok ülkede kadavrada temporal kemik diseksiyonu görece maliyetli olması ve uygun şartların sağlanmasındaki güçlükler nedeniyle genellikle asistanlığın ileriki yıllarına bırakılmaktadır. Daha önce hiç tur kullanmamış bir adayın öncelikle yapay temporal kemik modelinde tur tutmayı ve kullanmayı öğrenmesi sağlanabilir görünmektedir. Böylece daha ekonomik ve pratik bir şekilde temporal kemik diseksiyon eğitimi verilebilir görünmektedir. Bu durum, kadavra ile eğitime kıyasla, daha erken yapabilme ve daha fazla sayıda tekrarlama şansı sağlayabilir.

Yapay kemikler gerçek kemiğin yerini almalı şeklinde düşünülmesinden değil, eğitimi kolaylaştırabilir, ulaşılabilirliği arttırabilir ve daha fazla tekrar sağlayabilir şeklinde düşünülmesi gerektiği kanaatindeyiz. Gelecekteki daha iyi anatomik modellemeler ve kemik hissi veren yapay kemikler yapılabilir. 3d yazıcı teknolojisindeki gelişmelerinde ek olumlu katkıları olacaktır. Modellerin yerli üretim olması maliyeti azaltabilir, lojistiği kolaylaştırabilir ve maliyeti azaltabilir. Daha yakın ve kolay ulaşılabilir iletişimle ülkemize ve hastalarımıza daha çok benzeyen modellerin yapılabilir.

Yapay kemik için kullanılan materyalin insan sağlığına zarar vermemesi (gerek temas gerek inhalasyonla) gerekmektedir. Bu nedenle zararsız maddelerin seçilmesi ve uygulama esnasında kadavra diseksiyonunda olduğu gibi, cerrahi önlük, eldiven, gözlük ve maske kullanılması gerekir. Turlama ile ortaya çıkan materyal parça ve tozu aspiratörlerin yardımı ile ortamdan uzaklaştırılmalıdır. İnsan sağlığına zarar vermeyecek materyaller kullanılarak üretilen yapay kemiklerle enfeksiyon riski ve etik sorunlarla karşılaşılmayacaktır.

Sanal gerçeklik uygulaması eğitim alacakların ameliyathane ortamını taklit eder şekilde, kendilerini içinde hissettikleri bir kurulum ile, cerrahi anatomi ve maketleri 3 boyutlu olarak inceleme, yapıları ayrı ayrı ve birbiri içindeki ilişkilerini görme imkânı vermektedir.[4] Normal bir maket modele kıyasla daha detaylı, büyük, farklı renklerle yapıların belirlenebildiği, birbiri ile ilişkilerin ve özellikle daha içte derinde kalan yapıların daha iyi ortaya konulabildiği bir uygulama ve öğrenme imkânı verebilmektedir. Yazılımda yapılacak güncellemelerle daha hızlı ve kolay bir şekilde maket ve modellerin güncellenmesi mümkün olabilmektedir. Karışık anatomisi nedeniyle temporal kemik eğitiminde her türlü imkân ve teknolojinin kullanılarak farklı öğrenme araçlarının eğitime dahil edilmesi mantıklı olacaktır. Klasik modellere kıyasla belirgin avantajı olmadığını gösteren çalışmalar olmakla birlikte, klasiğin dışında yeni ve farklı bir metot olması katılımcıların ilgisini çekebilmektedir ve farklı bir açı ile anatomi ve cerrahi yöntemlere bakma imkânı sunmaktadır.[4] Yazılımların gelişmesi ve iyileştirmeler ile modellemelerin başarısı ve etkinliği de zamanla artabilir görünmektedir.

Çalışmanın limitasyonları değerlendirildiğinde ise; sadece 44 kişinin yanıtları değerlendirmeye alınmıştır, dolayısı ile örneklem büyüklüğü görece az olarak değerlendirilebilir. Daha fazla kişinin katıldığı kurslar ile veya birden fazla kursların toplam sonuçları ile daha güçlü sonuçlar elde edilebilir. Kursun bir kongre esnasında kısıtlı zaman ve ortamda değil, ameliyathane ya da diseksiyon merkezi gibi daha ideal bir ortamda yapılması da verimliliği artıracaktır.

Bu çalışma yapay temporal kemik modellerinin ve sanal gerçeklik ile temporal kemik cerrahi anatomi eğitiminin yararlılığını değerlendirildiği ülkemizdeki ilk çalışmadır. Yapay kemik ile temporal kemik diseksiyonu gerçek mastoidektomiyi taklit edebilmektedir ve katılımcılar büyük oranda yararlı ve faydalı bulmuştur. Daha ekonomik ve ulaşılabilir olması, etik problemler içermemesi, enfeksiyon bulaş riski olmaması, daha fazla tekrarlanabilmesi gibi nedenlerle tercih edilebilir ve temporal kemiğin cerrahi anatomisinin anlaşılması ve el becerilerinin gelişmesini sağlayabilir görünmektedir. Görece karışık bir anatomisi olan temporal kemik için hem yapay modeller hem de sanal gerçeklik gibi alternatif eğitim yöntemleri cerrahi tecrübenin oluşmasına ve gelişmesine katkı sağlayacaktır. Klasik kadavra ve eğitim yöntemleri ile kombinasyonlar ile daha da iyi sonuçlar alınabilir.

Teşekkür

Gerçekleştirilen kurslara desteklerinden ötürü Türk KBB ve BBC Derneğine, Eğitimci desteklerinden ötürü Otoloji Nörootoloji Derneğine, Sayın Gülhan Konak (Duymer) ve Sayın Yahya Doğan'a (Piri Teknoloji) teşekkür ederiz.

Etik Standartlara Uygunluk

Çalışma için Yerel Etik Kurul'dan KOU-GOKAEK-2024/498 numarası ile etik kurul onayı alınmıştır.

Çıkar Çatışması

Yazarların çıkar çatışması yoktur.

Finansal Destek

Araştırma için herhangi bir destek alınmamıştır

Yazar Katkısı

MÖ: Yazının tasarım, dizayn, veri toplanması, yazım, kritik gözden geçirme ve son onay aşamalarında rol almıştır; BT: Yazının tasarım, dizayn, kritik gözden geçirme ve son onay aşamalarında rol almıştır; SAK: Yazının dizayn, veri toplanması, son gözden geçirme aşamalarında rol almıştır. Tüm yazarlar yazının son halini onaylamaktadır.

Kaynaklar

1. Frithioff A, Frendø M, Pedersen DB, Sørensen MS, Wuyts Andersen SA. 3D-Printed Models for Temporal Bone Surgical Training: A Systematic Review. *Otolaryngol Head Neck Surg*. 2021;165(5):617-625. doi:10.1177/0194599821993384
2. Boillat M, Bonnet AS, Groubatch F, Falanga A, Gillet R, Parietti-Winkler C. Analysis of the milling response of an artificial temporal bone developed for otologic surgery in comparison with human cadaveric samples. *Med Eng Phys*. 2024;131:104220. doi:10.1016/j.medengphy.2024.104220
3. Kurichiyil SH, Whittaker JD, Dalton CL. Face and Content Validation of Artificial Temporal Bone Dissection for Otolaryngology Training. *J Laryngol Otol*. Published online October 25, 2024. doi:10.1017/S0022215124001774
4. Everad F, Albrecht T, Kromeier J, et al. A Virtual Reality Anatomy Model of the Temporal Bone in ORL Residency Training-Gain or Gadget?. *J Med Educ Curric Dev*. 2024;11:23821205241281506. Published 2024 Oct 9. doi:10.1177/23821205241281506

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Araştırma Makalesi | Research Article

DEPRESYON DÜZEYİNİN GEBELİKTEKİ BULANTI KUSMA ŞİDDETİNE ETKİSİ

EFFECT OF DEPRESSION LEVEL ON SEVERITY OF NAUSEA AND VOMITING IN PREGNANCY

Hayal Uzelli Şimşek[1*], Firdaus Mamleeva[1], Ercan Koçkaya[1], Özge Senem Yücel Çiçek[1]

[1]Kocaeli Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları Ana Bilim Dalı, Kocaeli, Türkiye.

ÖZ

Amaç: Bu çalışmanın amacı, gebeliğin ilk trimesterinde meydana gelen bulantı-kusma şiddeti ile depresyon düzeyleri arasındaki ilişkiyi araştırmaktır.

Yöntem: Çalışma, 84 gebe üzerinde gerçekleştirilmiştir. Katılımcılar, depresyon düzeyleri değerlendirilerek depresif ve depresif olmayan gebelerin oluşturduğu iki gruba ayrılmıştır. Ardından bulantı-kusma şiddeti, Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-24) ölçeği ile, depresyon düzeyleri ise Hasta Sağlık Anketi (PHQ-9) ile ölçülmüştür.

Bulgular: Çalışma sonucunda, depresif ve non-depresif gruplar arasında bulantı-kusma şiddeti sayısal yeterlilik olmadığı için karşılaştırılamadı. Her iki grup da genellikle hafif ve orta şiddette bulantı-kusma semptomları bildirmiştir. Şiddetli bulantı-kusma oranları ise her iki grupta da düşük bulunmuştur. Ayrıca, depresyonun bulantı-kusmanın şiddeti üzerinde doğrudan bir etkisi gözlemlenmemiştir.

Sonuç: Gebelikte depresyonun, bulantı-kusma şiddetini doğrudan etkileyen bir faktör olmadığı görülmüştür. Bu bulgular, depresyon ve bulantı-kusma arasındaki ilişkiyi daha iyi anlayabilmek için biyolojik ve psikolojik diğer etmenlerin de göz önünde bulundurulması gerektiğini işaret etmektedir.

Anahtar Kelimeler: Hiperemezis gravidarum, gebelikte bulantı-kusma, depresyon, PHQ-9 anketi, PUQE-24 ölçeği

ABSTRACT

Objective: This study aims to investigate the relationship between the severity of nausea and vomiting during the first trimester of pregnancy and depression levels.

Method: The study was conducted with 84 pregnant women, who were divided into two groups based on their depression status: depressed and non-depressed. Depression levels were assessed using the Patient Health Questionnaire (PHQ-9), while the severity of nausea and vomiting was measured using the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-24) scale.

Results: The severity of nausea and vomiting could not be compared between the depressive and non-depressive groups due to the lack of numerical adequacy. Both groups generally reported mild to moderate symptoms, with severe nausea and vomiting being rare in both groups. Furthermore, no direct relationship was observed between depression and the severity of nausea and vomiting.

Conclusion: Depression during pregnancy does not appear to directly affect the severity of nausea and vomiting. These findings suggest that other biological and psychological factors should be considered in understanding the relationship between depression and nausea/vomiting during pregnancy.

Keywords: Hyperemesis gravidarum, nausea and vomiting in pregnancy, depression, PHQ-9 questionnaire, PUQE-24 scale

*** İletişim kurulacak yazar/Corresponding author:** Hayal Uzelli Şimşek; Kocaeli Üniversitesi, Tıp Fakültesi, Kadın Hastalıkları Ana Bilim Dalı, Kocaeli, Türkiye
Telefon/Phone: +90 (262) 303 84 33, **e-mail/e-posta:** jinekolog.dr@hotmail.com
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Giriş

Gebeliğin bulantı-kusması, 16. gebelik haftasından önce başlayan ve başka nedenlerin dışlandığı bulantı ve/veya kusma şikayeti olarak tanımlanmaktadır.[1] Sıklığı %90'a kadar çıkmakta olup bunların sadece %10'unda 3-4 gün süren hospitalizasyon gerektirecek kadar şiddetli bulantı-kusma, dehidratasyon, elektrolit imbalansı ve kilo kaybı izlenebilmektedir.[1,2] Hiperemezis gravidarum (HG) olarak adlandırılan bu durum gebelerin %0,3-3,6'sında izlenen, yaşam kalitesini ve normal şekilde yeme-içme yeteneğini etkileyen, fiziksel ve sosyal aktivitelerini engelleyen ve psikolojik sorunlara yol açan ciddi bir NVP türüdür.[1-3] NVP ve HG'un ana mekanizmasının beyin sapı üzerinde etkili bir hormon olan büyüme farklılaşma faktörü-15'e (GDF15) karşı aşırı duyarlılıkla ilişkili olduğu açıklanmıştır. HG hastalarında β-hCG düzeylerinin daha yüksek saptandığı raporlanmış[4-6] olsa da hastalarda β-hCG değil, dolaşımda normalden daha yüksek GDF15 seviyeleri tespit edilmiştir. Bu nedenle β-hCG'nin nedensel olma olasılığı düşük olarak nitelendirilmiştir.[1] HG etiyolojisi net bilinmemekle birlikte birkaç etkenin etiyolojide yeri belirlenmiştir. Literatürdeki bilgilere göre daha önceki gebeliklerinde veya annesinde HG öyküsünün olması, GDF15 ekspresyonuyla ilişkili genetik varyantların tespiti, gebenin 20 yaşından genç olması, çoğul gebelik, molar gebelik öyküsü, tiroid hastalığı (hipertiroidizm), gebelikte estrojen kullanımı, bazı psikiyatrik hastalıklar, diabetes mellitus, astım ve gastrointestinal hastalıklar HG için risk faktörleri arasında saptanmıştır.[1-3,7] Biz ise bu çalışmada, öncelikle Hasta Sağlığı Anketi (PHQ-9) ile gebelerin depresyon düzeylerini, ardından da Gebeliğe Özgü Bulantı Kusma Şiddetinin Belirlenmesi (PUQE-24) Ölçeği ile bulantı-kusma şiddetini değerlendirdik.

Gebelikte bulantı-kusma şiddetini sınıflandıran PUQE ölçeği 2002'de ilk Koren ve ark. tarafından tasarlanmıştır.[8] Sonrasında Ebrahimi ve ark. tarafından son 24 saati değerlendiren PUQE-24 validasyonu yapılmıştır.[9] PUQE-24 Türkçe geçerlilik ve güvenilirliği ise Yılmaz ve ark. tarafından yapılmış olup Türkçe versiyonunun Cronbach's Alpha kat sayısı 0,75 olarak belirlenmiştir.[10] Birçok çalışmada gebelerde geçerli, güvenilir ve validasyonu yüksek bir ölçüm aracı olduğu kabul edilmektedir.[1-3,11]

PHQ-9 anketi, birinci basamakta depresyon ve diğer psikiyatrik bozuklukların kriterlere dayalı teşhisini koyabilmek için tasarlanmıştır. Depresyon şiddetinin bir ölçüsü olarak yapı geçerliliğini de kanıtlamıştır. Aynı zamanda depresyon tedavi sonuçlarının izlenmesinde de kullanılmaktadır.[12] Bu ölçeğin Türkçe geçerlilik ve güvenilirlik çalışması Sarı ve ark. tarafından yapılmıştır. [13] Çalışmamızda bu anketleri kullanarak depresyonun gebelikteki bulantı-kusma etyolojisindeki rolünü değerlendirmek istedik.

Yöntem

Kocaeli Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından onaylanmış (GOKAEK-2024/08.19) olan çalışmada tüm katılımcılara gönüllü olur formu imzalatılmıştır. Kocaeli Üniversitesi Hastanesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda 1 Nisan–30 Haziran 2024 tarihleri arasında gebe polikliniğine rutin kontrol amaçlı başvuran 18 yaş üstü, 8+0 ile 12+6 haftalık tekil gebeler çalışmaya dahil edildi. Dışlama kriterleri arasında; 1- öncesinde bulantı-kusma belirtileri ile seyreden herhangi bir enfeksiyon, psikiyatrik bozukluk, metabolik, gastrointestinal veya endokrin hastalık varlığı; 2- kronik hastalık varlığı; 3- öncesinde geçirilmiş depresyon veya psikiyatrik hastalık öyküsü varlığı; 4- yardımla üreme teknikleri ile gebe kalmış olmak vardı. Tiroid hastalıkları HG ile ve çeşitli duygusal bozukluklarla ilişkili[14] olduğu için özellikle dışlandı.

Yapılan bir çalışmadan[3] elde edilen sonuçlar kullanılarak $\alpha = 0,05$, Power $(1-\beta) = 0,90$ için PASS 11 programı ile güç analizi yapıldığında örneklem büyüklüğü her bir grup için 38 olmak üzere toplam 76 hasta olarak hesaplandı. Bu kriterlere uygun ancak çalışmadan ayrılma olasılığına karşı toplam 92 gebeye PHQ-9 anketi ve PUQE-24 ölçeği uygulandı. Sekiz gebe dışlama kriterlerine göre ayrıldı, 84 gebenin verileri çalışıldı (Şekil 1).

Öncelikle PHQ-9 anket sonuçlarına göre hastalar iki gruba ayrıldı. PHQ-9, DSM-IV kriterlerine göre depresyonun 9 belirtisini sorgulamaktadır ve diğer depresyon tarama ölçümleriyle karşılaştırılabilir makul bir duyarlılık ve özgüllüğe sahiptir. PHQ-9'a göre depresyonu olmayan (1-4 puan) veya hafif depresyon (5-9 puan) tanısı alan yani 1-9 arasında puan alan hastalar kontrol grubu olarak düşünülen "non-depresif" grubu oluşturdu. Puanı 10-27 arasında yani orta dereceli (10-14 puan), orta şiddette (15-19 puan) ve ağır (20-27 puan) depresyon tanılarını alan gebeler çalışma grubu olarak "depresif" grubu oluşturdu.

Ardından PHQ-9'a göre oluşturulmuş bu 2 gruba bulantı-kusma şiddetini değerlendirebilen PUQE-24 ölçeği uygulandı. PUQE-24 skorlaması, gebelikte validasyonu yüksek olan güvenilir bir ölçektir. Ölçeğin Türkçe validasyon çalışması da yapılmış olup güvenirliği kanıtlanmıştır. Bu anket ile 24 saatlik süre içerisinde var ise bulantı süresi, kusma atak sayısı ve istem dışı öğürme sayısı şeklinde 3 soru sorulmaktadır. Her soru için şiddetine bağlı olarak 1'den 5'e kadar puan verildiği için toplam puan 3-15 arasında değerlendirilmektedir. Semptom yokluğunda 3 olan puan en şiddetli durumda 15 olmaktadır. Toplam puan 7'den az ise "hafif", 7-12 arasında ise "orta" ve 12'nin üstü ise "şiddetli bulantı-kusma" olarak sınıflandırılmaktadır. Her 2 grupta bu sonuçlar istatistiksel olarak değerlendirildi ve depresyon düzeyi ile gebelikteki bulantı-kusma şiddeti arasında ilişki olup olmadığı incelendi.

Bu anket sorularına ek olarak yaş, boy, ağırlık, gravida, parite, abort öyküsü, eğitim durumu, sosyoekonomik düzeyi ile aile yapısı gibi tanımlayıcı verilerin yanında, eşlik etme olasılığı yüksek mide yanması, kabızlık, reflü gibi şikayetler de sorgulandı.

İstatistik

İstatistiksel değerlendirme IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) ile yapıldı. Normal dağılıma uygunluk

Kolmogorov-Smirnov testi ile değerlendirildi. Normal dağılım gösteren değişkenler ortalama ±standart sapma, normal dağılım göstermeyen değişkenler medyan (25.-75. yüzdelik) olarak verildi. Kategorik değişkenler frekans (yüzde) olarak verildi. Gruplar arasındaki farklılık normal dağılıma sahip olan değişkenler için bağımsız örneklem t testi ile, normal dağılıma sahip olmayan değişkenler için Mann-Whitney U testi ile belirlendi. Kategorik değişkenler arasındaki ilişkiler Ki-kare analizi belirlendi. Hipotez testlerinde p<0,05 istatistiksel önemlilik için yeterli kabul edildi.

Bulgular

Rutin kontrol amacıyla polikliniğimize başvuran 8+0 ile 12+6 haftalık, toplam 84 gebe çalışmaya dahil edildi. Çoğu çalışmada olduğu gibi[15,16] cut-off değeri 10 olarak alındı ve PHQ-9 anketine göre 1-9 puan alan 43 hasta "non-depresif" grubu, 10-27 puan alan 41 hasta ise "depresif" grubu oluşturdu (Şekil 1).

Tüm hastaların tanımlayıcı verileri elde edilmiştir (Tablo 1). Gebeler içinde en yüksek yaş 42 idi. Hastaların 37 (%44)'sinin ilk gebeliği iken 40 (%47,6)'ı nullipardı. 84 gebenin PHQ-9 skoru ortalama 9 (5,25-13) iken PUQE-24 skoru ortalama 7 (5-9) idi. Hastaların 39 (%46,4)'unda hafif, 43 (%51,2)'ünde orta, 2 (%2,4)'ünde şiddetli bulantı-kusma vardı.

Her 2 grup arasında demografik ve klinik veriler karşılaştırıldı (Tablo 2). Her 2 grup arasında yaş, gravida, parite, abort sayısı, gebelik haftası, VKİ, eğitim durumu, sosyoekonomik düzey, aile yapısı, ketonüri ve hematokrit açısından istatistiksel olarak anlamlı fark tespit edilmedi.

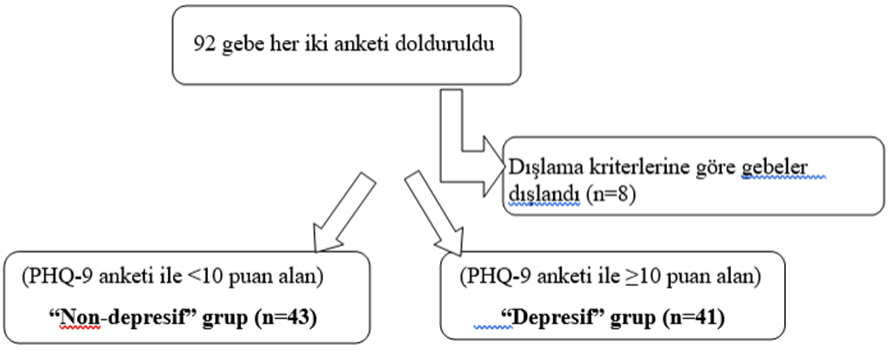
Gruplar arasında PUQE-24 skorlarının karşılaştırıldığı görülmektedir (Tablo 3). Bulantı süresini değerlendiren ilk soru için medyan skor, çalışma grubunda 3 (2-5), kontrol grubunda ise 3 (1-4) idi. Gruplar arasında anlamlı bir fark yoktu (p=0,299). İkinci ve üçüncü soruların medyan skorları da her 2 hasta grubu arasında benzerdi (sırasıyla p=0. 0,812 ve p=0,249). Her iki gruptaki gebelerin çoğu hiç kusmadıklarını ancak günde 1-3 kez bulantı meydana geldiğini ifade ettiler.

Total PUQE-24 skorlamasına göre, depresif olan gebelerin %46,3'ü hafif bulantı-kusma yaşarken, %51,2'si orta ve %2,4'ü şiddetli bulantı-kusma deneyimledi. Non-depresif gebelerin %46,5'i hafif, %51,2'si orta ve sadece %2,3'ü şiddetli bulantı-kusma şikayetine maruz kaldı. Total PUQE-24 skoru çalışma grubunda 7 (5-9) ve kontrol grubunda 7 (3-8) idi. Her 2 grup arasında bulantı-kusma şiddeti açısından sayısal yeterlilik olmadığı için karşılaştırılamadı.

Tablo 1. Çalışmaya katılan hastaların tanımlayıcı verileri sunulmuştur.

	Tüm hastalar (n=84)
Yaş, mean ±SD	29.11±5.087
Gebelik haftası, median (IQR)	10 (9-11)
VKİ, (kg/m^2), median (IQR)	25.975 (23.215-28.468)
Gravida, median (IQR)	2 (1-3)
Parite, median (IQR)	1 (0-1)
Abort, median (IQR)	0 (0-1)
İlk trimesterda ağırlık (kg)[a] artışı*, median (IQR)	2 (2-4)
İlk trimesterda ağırlık (kg)[a] azalışı*, median (IQR)	2 (1.5-3)
Eğitim durumu, n(%)	
İlkokul	14 (16.7)
Ortaokul	15 (17.9)
Lise	21 (25)
Üniversite/ Yüksek lisans	34 (40.5)
Sosyoekonomik düzey, n(%)	
Asgari altı	7 (8.3)
Orta	73 (86.9)
Asgari Üstü	4 (4.8)
Aile yapısı, n(%)	
Çekirdek	74 (88.1)
Geniş	10 (11.9)
Ketonüri, n(%)	
negatif	77 (91.7)
+	1 (1.2)
++	3 (3.6)
+++	3 (3.6)
Hematokrit[b], median (IQR)	34.60 (32.93-36.60)
PUQE-24 skoru, median (IQR)	7 (5-9)
PHQ9 skoru, median (IQR)	9 (5.25-13)
Bulantı-kusma şiddeti, n(%)	
Hafif (<7)	39 (46.4)
Orta (8-12)	43 (51.2)
Şiddetli (13-15)	2 (2.4)
Mide Yanması n(%)	29 (34.5)
Reflü, n(%)	14 (16.7)
Kabızlık, n(%)	29 (34.5)

IQR: Interquartile Range; *gebelik boyunca ağırlıklarının artma ve azalma miktarı; a: kg: kilogram;
b: hematokrit (%) eritrosit hacmi/toplam kan hacmi.



Şekil 1. Çalışmanın akış diagramı

Tablo 2. Her 2 grup arasında demografik ve klinik verilerin karşılaştırılması izlenmektedir.

	Non-depresif grup (n=43)	Depresif grup (n=41)	*p*
Yaş, mean ±SD	28.79 ±4.907	29.44 ±5.311	0.562
Gravida, n(%)			
1	22 (51.2)	15 (36.6)	
2	11 (25.6)	9 (22)	NA
3-üstü	10 (23.3)	17 (41.4)	
Parite, n(%)			
Nullipar	24 (55.8)	16 (39)	0.186
Multipar	19 (44.2)	25 (61)	
Abort, n(%)			
0	33 (76.7)	29 (70.7)	NA
1-üstü	10 (23.3)	12 (29.2)	
Gebelik haftası	10 (9-11)	10 (9-11)	0.361
VKİ	25.59 (23-28)	26.4 (23.7-31.6)	0.210
Eğitim Durumu, n(%)			
İlkokul	7 (16.3)	7 (17.1)	0.675
Ortaokul	6 (14)	9 (22)	
Lise	10 (23.3)	11 (26.8)	
Üniversite/ Yüksek lisans	20 (46.4)	14 (34.1)	
Sosyoekonomik düzey, n(%)			
Asgari altı	5 (11.6)	2 (4.9)	NA
Orta	34 (79.1)	39 (95.1)	
Asgari Üstü	4 (9.3)	0 (0)	
Aile yapısı, n(%)			
Çekirdek	40 (93)	34 (82.9)	0.190
Geniş	3 (7)	7 (17.1)	
Ketonüri, n(%)			
Negatif	35 (85.4)	39 (97.5)	0.109
Pozitif	6 (14.6)	1 (2.5)	
Hematokrit*, (%)	34.40 (33.00-36.90)	34.70 (32.66-36.35)	0.704

IQR: Interquartile range; NA: Not applicable; *eritrosit hacmi/toplam kan hacmi.

Tablo 3. Her iki grup arasında PUQE-24 skorlama sonuçları ve eşlik eden ilişkili bazı durumlar kıyaslanmıştır.

	Non-depresif grup (n=43)	Depresif grup (n=41)	*p*
PUQE-24 skoru toplam*	7 (3-8)	7 (5-9)	0.279
PUQE 1 (bulantı süresi/24saat)*	3 (1-4)	3 (2-5)	0.299
PUQE 2 (kusma sayısı/24saat)*	1 (1-2)	1 (1-2)	0.812
PUQE 3 (öğürme sayısı/24saat)*	2 (1-3)	2 (1-3)	0.249
PUQE skor şiddeti, n(%)			
Hafif bulantı-kusma (skor <7)	20 (46.5)	19 (46.3)	
Orta bulantı-kusma (skor 8-12)	22 (51.2)	21 (51.2)	NA
Şiddetli bulantı-kusma (skor 13-15)	1 (2.3)	1 (2.4)	
Mide Yanması, n(%) kalsın	13 (30.2)	16 (39.0)	0.537
Reflü, n(%)	5 (11.6)	9 (22.0)	0.329
Kabızlık, n(%)	16 (37.2)	13 (31.7)	0.764
İlk trimesterda ağırlık artışı*	2 (1-3)	3 (2-5)	0.069
İlk trimesterda ağırlık azalışı*	2 (1.88-3)	2 (1-6.5)	0.780

*Veriler median (%25-75 percentil) olarak verilmiştir. a: Pregestasyonel ağırlığa göre; IQR: Interquartile range; NA: Not applicable; PUQE: Pregnancy-unique quantification of emesis (Gebeliğe özgü bulantı ölçümü).

Mide yanması şikayeti çalışma grubunda %39,0, kontrol grubunda %30,2 gebede izlendi. İstatistiksel olarak anlamlı sonuç izlenmedi (p=0,537). Reflü ve kabızlık şikayeti de her 2 grup arasında istatistiksel olarak anlamlı değildi (sırasıyla p=0,329; p=0,764). İlk trimesterde çalışma grubunda ağırlık artışı 3 (2-5), kontrol grubunda 2 (1-3) olup istatistiksel olarak anlamlı değildi (p=0,069). Ağırlık azalışı ise çalışma grubunda 2 (1-6,5), kontrol grubunda 2 (1,88-3) idi. Ancak istatistiksel olarak anlam elde edilemedi (p=0,780).

Tartışma

Kilo kaybı, dehidratasyon ve elektrolit dengesizliği gibi subjektif semptomların[17] yanında objektif bazı skorlama yöntemleri de gebelikteki bulantı-kusma şiddetini değerlendirmede kullanılabilmektedir. [2] Bunlardan PUQE-24 ölçeğinin bulantı-kusma şiddeti değerlendirilmesinde geçerli ve güvenilir bir araç olduğu çoğu çalışmada ifade edilmiştir. [1,2,18] Biz de cut-off değerimize göre depresyon olmayan ve depresif gebelerde bulantı-kusma şiddetini PUQE-24 ölçeğini kullanarak değerlendirmek istedik. Ancak çalışmamız depresyon düzeyinin gebelikte bulantı ve kusma şiddeti üzerinde anlamlı bir etkisi olmadığını göstermiştir. Depresyon düzeyi için de gebelere yönelik validasyonu da yapılmış[19] olan PHQ-9 anketi kullandık.

Gebelikte bulantı-kusma şiddetinin depresyon düzeyi ile ilişkisi, literatürde tartışmalı sonuçları olan ve çok çalışılmış bir konudur. Çalışmamızda yer alan verilerle uyumlu olarak bazı çalışmalar gebeliğin şiddetli bulantı-kusması ile depresyon arasında ilişki olmadığını savunmuştur.[20-22] Genelde HG tanısı olan ve olmayan gruplar arasında depresyon açısından çalışmalar yapılmış olup depresyon ile bulantı-kusma şiddeti açısından eş zamanlı tarayan çalışma ise azdı. [14,22] HG tanısı olan ve olmayan gebeler üzerinde yapılan karşılaştırmalı çalışmalarda HG ile ilişkili depresyonun HG'un bir nedeni olmaktan ziyade doğrudan bir sonucu olduğu gösterilirken[5.14], aynı şekilde yapılan başka çalışmalarda HG'lu hastaların çoğunda depresif semptomlar izlenmiş ve depresyonun HG'un bir nedeni olduğu iddia edilmiştir.[23,24] Senturk ve ark., HG'un gebelerin mental sağlığını kötü etkilediğini ve bu depresif semptomların postpartum dönemde de devam edebildiğini ifade etmişlerdir.[25] Uzun süreli gebeliğin bulantı-kusmasında da postpartum depresyon gelişme riskinin yüksek olduğu raporlanmıştır.[26] Biz ise depresif olan ve olmayan hastalarda bulantı-kusma şiddetini değerlendirdik ancak 2. ve 3. trimester ile postpartum dönem mental sağlıkları ile ilgili ek bir çalışma yapmadık.

Tanımlayıcı ve korelasyonel bir çalışmaya göre bulantı-kusması şiddetli olan gebelerin daha fazla depresif semptom gösterdiği, depresif olanların da daha şiddetli bulantı-kusma yaşadığı tespit edilmiştir.[3] Ek olarak, HG'lu gebelerin ilk trimesterda fiziksel ve psikolojik sağlıkları ile birlikte sosyal ve kişisel yaşamlarının da olumsuz yönde etkilendiği bildirilmiştir.[3,14,18,23] Oluşturulmuş bir sistematik kılavuzda gebeliğin bulantı-kusmasının

yarattığı baskı sonucunda anlayış ve destek eksikliği, sağlıklı beslenememe, olumlu bir hamilelik deneyiminin kaybından duyulan üzüntü, işten uzak kalma ve mali baskılar, izolasyon, aileye bakamama, başkalarının bunun psikosomatik olduğuna inanması, doktorların tedavi sağlama konusunda isteksiz olduğu algısının meydana geldiği ve dolayısıyla da depresif semptomların gebeliğin bulantı-kusma şiddeti ile ilişkili olduğu ifade edilmiştir.[1] Halihazırda bulantı-kusmadan bağımsız olarak gebelikte depresif bozukluğun yaygınlığı, gebe olmayan kadınlardaki oranlara benzer olsa da kötü maternal ve fetal sonuçlarla ilişkilidir.[15,27] Gebedeki depresyon ve anxiete için prevalans oranı %9-19 arasında değişmektedir.[15] Gebelerde depresif semptomların taraması rutin olarak önerilmese de risk olan hastalarda uygulanması gerektiği vurgulanmıştır.[27] Bu nedenle bulantı-kusma yaşayan gebelerin rutin kontrollerinde hem fiziksel hem de ruhsal sağlık durumlarının değerlendirilmesi ve gerekirse psikolojik destek için yönlendirilmesi gerektiği eklenmiştir.[1]

Ketonüri dehidratasyon için gebelikte bir gösterge değildir ve bulantı-kusma şiddeti için kullanılmamalıdır.[1] Bizim çalışmamızda da iki grup arasında anlamlı bir fark tespit edilememiştir. Gerçekten de depresif olmayan gebe grubunda daha fazla ketonüri izlendiği ve şiddetli bulantı-kusması olan gebelerin hiçbirinde 3+ ketonüri olmadığı tespit edildi. 2024 yılında yapılan bir çalışmaya göre HG tanısı olan ve olmayan hastalar arasında hematokrit değerinde anlamlı bir fark tespit edilemedi.[7] Çalışmamızda da 2 grup arasında bulantı-kusma şiddeti açısından fark olmadığı gibi hematokrit değerleri arasında da anlamlı bir fark yoktu. Şiddetli bulantı-kusma gebelikte önemli miktarda kilo kaybına yol açabilmektedir.[28] Ancak çalışmamızda her 2 grupdaki gebelerde hem ağırlık azalması hem de ağırlık artışında anlamlı fark yoktu.

Çalışmamızda depresyonun mide yanması, kabızlık ve reflü gibi semptomların şiddetini etkilemediği izlenmiştir. Reflü hastalarında yapılan bir anket çalışmasında depresyonun reflü başlangıcı ve prognozunda etkili olduğu ifade edilmiştir.[29] Kesitsel olan ve 12,352 hastada yapılan çalışmada kabızlığın depresyonla önemli ölçüde ilişkili olduğu gösterilmiştir. Kabızlığı olan kişilerde, olmayanlara göre önemli ölçüde daha yüksek oranda eşlik eden majör depresyon tespit edildi. Yaş, cinsiyet, diyet, risk davranışları ve yaygın komplikasyonlara göre yapılan alt grup analizleri istatistiksel olarak anlamlı etkileşimler göstermedi ve kabızlık ile depresyon arasındaki ilişkinin tüm alt gruplarda sabit olduğu da eklendi.[30] Majör depresif bozukluğu olan hastalar arasında gastrointestinal semptomları olan hastalarda depresyon şiddetinin daha yoğun olduğu tespit edildi.[31] Ancak bizim çalışmamızda depresif olan gebelerde gastrointestinal semptomları açısından anlamlı bir fark yoktu. Gelir düzeyinde meydana gelen bir miktar artışın ruh sağlığı üzerinde olumlu etkisi olduğu tespit edilmiştir. Ancak aynı durum eğitim düzeyi ile de ilgilidir, eğitim düzeyi arttıkça depresyon olasılığı da artmaktadır.[32] Çalışmamızda ise gelir ve eğitim düzeylerine göre depresyon düzeylerinin farklı olmadığı izlendi.

Sonuç olarak, gebelerde depresyonun bulantı-kusma şiddeti üzerinde doğrudan anlamlı bir etkisi olmadığı tespit edildi. Ancak, depresyonun gebelik sürecindeki diğer psikolojik ve fiziksel semptomlarla olan etkileşimi dikkate alındığında, riskli gebelerde depresyon taramasının ve gereği halinde uygun tedavisinin önemini vurgulamak gerektiği açıktır. Gebelikte bulantı-kusma şiddeti, hormonal ve biyolojik faktörlerle daha fazla ilişkilidir ve depresyon, semptomların şiddetini doğrudan etkilemeyebilir. Ancak bu şikayet her gebede aynı şiddette olmayıp destek ve tedavilerinde de farklılık olacağı unutulmamalıdır.[1] Bu alanda daha geniş çaplı, çok merkezli ve prospektif kontrollü çalışmaların yapılması, depresyonun gebelikteki bulantı-kusma üzerinde etkilerini daha ayrıntılı bir şekilde anlamamıza yardımcı olacaktır.

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HUŞ, ÖZYÇ: Protokol/proje geliştirme; HUŞ, FM: Veri toplama; HUŞ: Veri yönetimi; HUŞ, FM, EK, ÖSYÇ: Makale yazımı/düzenlemesi.

Kaynaklar

1. Nelson-Piercy C, Dean C, Shehmar M, et al. Royal College of Obstetricians and Gynaecologists. The Management of nausea and vomiting in pregnancy and hyperemesis gravidarum (Green-top Guideline No. 69). *BJOG.* 2024;131(7):e1-e30. doi:10.1111/1471-0528.17739
2. Yucel Cicek OS, Demir M. Evaluation of nausea and vomiting severity in pregnancies conceived through assisted reproduction. *Gynecol Obstet Reprod Med*. 2022;28(1):56-61. doi:10.21613/GORM.2022.1278
3. Nacar G, Derman G, Güzel İnal C. Hiperemezis gravidarumlu gebelerde depresif semptomlar ve kişilik özelliklerinin bulantı kusma şiddeti ile ilişkisi. *Samsun Sağlık Bilimleri Dergisi*. 2023;8(2):323-338. doi:10.47115/jshs.1179397
4. Haberal A, Turgut F, Koç S, Tüfekçi F. Hiperemezis gravidarum olgularında serum beta-hcg düzeyleri ve tiroid fonksiyonlarının incelenmesi. *Medical Network Klinik Bilimler Kadın Doğum*. 1995;1(4):44-46.
5. Aksoy H, Aksoy Ü, Karadağ Öİ, ve ark. Depression levels in patients with hyperemesis gravidarum: a prospective case–control study. *Springerplus*, 2015;4:34. doi:10.1186/s40064-015-0820-2
6. Yeniçeri H, Işıkalan MM, AcarA. Hiperemezis gravidarumun maternal anksiyete ve depresyon düzeyleri ile ilişkisi. *Sakarya Tıp Dergisi*. 2021;11(2):253-258. doi:10.31832/smj.823762

7. Onder D, Birsen MB, Erturk D, ve ark. An evaluation of serum blood parameters and amyloid-A levels in women with hyperemesis gravidarum; A prospective observational study. *Medicine (Baltimore)*. 2024;103(38):e39695. doi:10.1097/MD.0000000000039695
8. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *Am J Obstet Gynecol*. 2002;186(5 Suppl Understanding):S228-231. doi:10.1067/mob.2002.123054
9. Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. *J Obstet Gynaecol Can*. 2009;31(9):803-807. doi: 10.1016/ S1701-2163(16)34298-0.
10. Yilmaz T, Dinç Kaya H, Günaydin S, Güdücü N, Dişsiz M. Psychometric properties of the Pregnancy-Unique Quantification of Emesis (PUQE-24) Scale. *J Obstet Gynaecol*. 2022;42(6):1739-1745. doi:10.1080/01443615.2022.2036961
11. Evrenol Öçal S, Şimşek Çetinkaya Ş. Türkiye'de gebelikte fizyolojik semptomlara özgü ölçeklerin kullanımı. *Kastamonu Üniversitesi Sağlık Bilimleri Fakültesi Dergisi*. 2023;2(2):42-51. doi:10.59778/sbfdergisi.1326792
12. Rathore JS, Jehi LE, Fan Y, et al. Validation of the Patient Health Questionnaire-9 (PHQ-9) for depression screening in adults with epilepsy. *Epilepsy Behav*. 2014;37:215-220. doi:10.1016/j.yebeh.2014.06.030
13. Sarı YE, Kökoğlu B, Balcıoğlu H, Bilge U, Çolak E, Unluoğlu İ. Turkish reliability of the patient health questionnaire-9. *Biomedical Research – India*. 2016;Special İssue:S460-S462.
14. Kjeldgaard HK, Eberhard-Gran M, Benth JŠ, Vikanes ÅV. Hyperemesis gravidarum and the risk of emotional distress during and after pregnancy. *Arch Womens Ment Health*. 2017;20(6):747-756. doi:10.1007/s00737-017-0770-5
15. Rondung E, Massoudi P, Nieminen K, et al. Identification of depression and anxiety during pregnancy: A systematic review and meta-analysis of test accuracy. *Acta Obstet Gynecol Scand*. 2024;103(3):423-436. doi:10.1111/aogs.14734
16. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ*. 2012;184(3):E191-196. doi:10.1503/cmaj.110829
17. Lee NM, Saha S. Nausea and vomiting of pregnancy. *Gastroenterol Clin North Am*. 2011;40(2):309-334, vii. doi:10.1016/j.gtc.2011.03.009
18. Hada A, Minatani M, Wakamatsu M, Koren G, Kitamura T. The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-24): Configural, measurement, and structural ınvariance between nulliparas and multiparas and across two measurement time points. *Healthcare (Basel)*. 2021;9(11):1553. doi:10.3390/healthcare9111553
19. Sidebottom AC, Harrison PA, Godecker A, Kim H. Validation of the Patient Health Questionnaire (PHQ)-9 for prenatal depression screening. *Arch Womens Ment Health*. 2012;15(5):367-374. doi:10.1007/s00737-012-0295-x
20. Azlan WAW, Ramalingam M, Razali R, Abdullah MF, Rahman FNA. Anxiety, depression and marital satisfaction in women with hyperemesis gravidarum: A comparative cross-sectional study in Hospital Tengku Ampuan Rahimah, Klang, Malaysia. *Asia Pac Psychiatry*. 2022;14(1):e12416. doi:10.1111/appy.12416
21. Koot MH, Grooten IJ, van der Post JAM, et al. Determinants of disease course and severity in hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol*. 2020;245:162-167. doi:10.1016/j.ejogrb.2019.12.021
22. Bozzo P, Koren G, Nava-Ocampo AA, Einarson A. The incidence of nausea and vomiting of pregnancy (NVP): a comparison between depressed women treated with antidepressants and non-depressed women. *Clin Invest Med*. 2006;29(6):347-350.
23. Simşek Y, Celik O, Yılmaz E, Karaer A, Yıldırım E, Yoloğlu S. Assessment of anxiety and depression levels of pregnant women with hyperemesis gravidarum in a case-control study. *J Turk Ger Gynecol Assoc*. 2012;13(1):32-36. doi:10.5152/jtgga.2012.01
24. Kasap E. Hiperemezis gravidarumlu hastalarda anksiyete ve depresyon test skorları. Selçuk Tıp Dergisi. 2018;34(4):155-159.
25. Senturk MB, Yıldız G, Yıldız P, Yorguner N, Çakmak Y. The relationship between hyperemesis gravidarum and maternal psychiatric well-being during and after pregnancy: controlled study. *J Matern Fetal Neonatal Med*. 2017;30(11):1314-1319. doi:10.1080/14767058.2016.1212331
26. Iliadis SI, Skalkidou A, Ranstrand H, Georgakis MK, Axfors C, Papadopoulos FC. Self-harm thoughts postpartum as a marker for long-term morbidity. *Front Public Health*. 2018;6:34. doi:10.3389/fpubh.2018.00034
27. Thombs BD, Arthurs E, Coronado-Montoya S, et al. Depression screening and patient outcomes in pregnancy or postpartum: a systematic review. *J Psychosom Res*. 2014;76(6):433-446. doi:10.1016/j.jpsychores.2014.01.006
28. Fejzo MS, Trovik J, Grooten IJ, et al. Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nat Rev Dis Primers*. 2019;5(1):62. doi:10.1038/s41572-019-0110-3
29. Wang R, Wang J, Hu S. Study on the relationship of depression, anxiety, lifestyle and eating habits with the severity of reflux esophagitis. *BMC Gastroenterol*. 2021;21(1):127. doi:10.1186/s12876-021-01717-5
30. Wang P, Shen X, Wang Y, Jia X. Association between constipation and major depression in adult Americans: evidence from NHANES 2005-2010. *Front Psychiatry*. 2023;14:1152435. doi:10.3389/fpsyt.2023.1152435
31. Yan M, Chen J, Liu F, Li H, Zhao J, Guo W. Abnormal default mode network homogeneity in major depressive disorder with gastrointestinal symptoms at rest. *Front Aging Neurosci*. 2022;14:804621. doi:10.3389/fnagi.2022.804621
32. Yılmaz B, Kara O. Eğitim ve gelir düzeyinin depresyon üzerindeki etkisi: Türkiye sağlık araştırmasından kanıtlar. *Uluslararası Sosyal ve Ekonomik Çalışmalar Dergisi*. 2024;5(1):1-22. doi:10.62001/gsijses.1403327

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Research Article | Araştırma Makalesi

BIOCHEMICAL AND HISTOLOGICAL ANALYSIS OF COLLAGEN CONTENT IN LUNG, LIVER AND KIDNEY TISSUES OF RATS TREATED WITH *BETA VULGARIS* L. VAR. CICLA

BETA VULGARIS L. VAR. CICLA VERİLEN SIÇANLARIN AKCİĞER, KARACİĞER VE BÖBREK DOKULARINDAKİ KOLLAJEN MİKTARININ BİYOKİMYASAL VE HİSTOLOJİK ANALİZİ

Burcin Alev-Tuzuner[1*], Aleyna Muhan[2], Sehkar Oktay[3], Esin Ak[4], Sevim Tunali[5], Refiye Yanardag[5], Aysen Yarat[3]

[1]Istanbul Gelisim University, Faculty of Dentistry, Department of Basic Medical Sciences, Biochemistry & Life Sciences and Biomedical Engineering Application and Research Centre, Istanbul, Türkiye. [2]Marmara University, Institute of Health Science, Department of Histology and Embryology, Istanbul, Türkiye. [3]Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Biochemistry, Istanbul, Türkiye. [4]Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Histology and Embryology, Istanbul, Türkiye. [5]Istanbul University-Cerrahpaşa, Faculty of Engineering, Department of Chemistry, Istanbul, Türkiye.

ABSTRACT

Objective: Collagen is a fundamental component of the extracellular matrix (ECM) and plays a critical role in organ structure, cellular functions, and wound healing. *Beta vulgaris* L. var. cicla (chard) is known for its diverse bioactive compounds, including vitamins, flavonoids, and nitrates. Chard has been associated with numerous health benefits, such as antioxidant, anti-inflammatory, and antidiabetic effects. This study investigates the impact of chard on collagen content in vital organs, specifically the lung, liver, and kidney.

Methods: The rats divided into two groups: the control and the chard given group. The chard extract was administered to rats at a dose of 100 mg/kg per day for 7 days. On the 8th day, the rats were sacrificed, and tissues from the lung, kidney, and liver were collected. The collagen content was measured using both biochemical and histological analyses.

Results: Chard administration exhibited tissue-specific effects on collagen content: it increased collagen in the lung, decreased it in the liver significantly, and had no effect on kidney collagen. These biochemical changes were supported by histological results in the lung and kidney; however, no significant histological changes were observed in the liver. These varied effects might be related to differences in collagen metabolism and regulatory mechanisms across tissues.

Conclusion: The findings suggest that chard, due to its distinct effects on collagen synthesis and ECM remodeling, holds promise as a potential therapeutic agent for applications such as wound healing, tissue strengthening, and antifibrotic therapy. Further studies on the mechanisms underlying these effects are necessary to fully understand the potential of chard in clinical applications.

Keywords: Chard, collagen content, lung, kidney, liver

ÖZ

Amaç: Kollajen, ekstraselüler matriksin (ECM) temel bir bileşenidir ve organ yapısı, hücresel işlevler ve yara iyileşmesinde kritik bir rol oynar. *Beta vulgaris* L. var. cicla (pazı), vitaminler, flavonoidler ve nitratlar dahil olmak üzere çeşitli biyoaktif bileşenleriyle bilinir. Pazı, antioksidan, anti-inflamatuar ve antidiyabetik etkiler gibi çok sayıda sağlık yararıyla ilişkilendirilmiştir. Bu çalışma, pazının akciğer, karaciğer ve böbrek gibi hayati organlardaki kollajen miktarı üzerindeki etkisini araştırmaktadır.

Yöntem: Sıçanlar iki gruba ayrıldı: kontrol ve pazı verilen grup. Pazı ekstresi sıçanlara 7 gün boyunca günde 100 mg/kg dozda verildi. 8. günde sıçanlar sakrifiye edildi ve akciğer, böbrek ve karaciğer dokuları toplandı. Kollajen miktarı hem biyokimyasal hem de histolojik analizler kullanılarak ölçüldü.

Bulgular: Pazı uygulaması, kollajen içeriği üzerinde dokuya özgü etkiler gösterdi: akciğerdeki kollajeni artırdı, karaciğerdeki kollajeni önemli ölçüde azalttı ve böbrek kollajeni üzerinde hiçbir etkisi olmadı. Bu biyokimyasal değişiklikler, akciğerdeki ve böbrekteki histolojik sonuçlarla desteklendi; ancak karaciğerde önemli bir histolojik değişiklik gözlenmedi. Bu çeşitli etkiler, dokular arasında kollajen metabolizmasındaki ve düzenleyici mekanizmalardaki farklılıklarla ilişkili olabilir.

Sonuç: Bulgular pazının kollajen sentezi ve ECM'nin yeniden şekillenmesi üzerindeki belirgin etkileri nedeniyle yara iyileşmesi, doku güçlendirme ve antifibrotik tedavi gibi uygulamalar için potansiyel bir terapötik ajan olarak umut vadettiğini göstermektedir. Pazının klinik uygulamalardaki potansiyelini tam olarak anlamak için bu etkilerin altında yatan mekanizmalar üzerine daha fazla çalışma gereklidir.

Anahtar Kelimeler: Pazı, kollajen miktarı, akciğer, böbrek, karaciğer

***Corresponding author/İletişim kurulacak yazar:** Burcin Alev Tuzuner; Istanbul Gelisim University, Faculty of Dentistry, Department of Basic Medical Sciences, Biochemistry, Istanbul, 34315, Türkiye.
Phone/Telefon: +90 (212) 422 70 00 **e-mail/e-posta:** btuzuner@gelisim.edu.tr
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Introduction

Collagen is an essential component of the extracellular matrix (ECM) in the development of connective tissues such as cartilage, tendons, and ligaments, as well as various organs, including skin, heart, liver, kidneys, lungs, blood vessels and bones.[1] In addition to its structural role, it has important cellular functions including adhesion, migration, autophagy, apoptosis and proliferation.[2] Collagen belongs to a family of fibrous proteins characterized by a triple-helical structure. More than 30 different types of collagen have now been identified and documented.[1] The primary collagen types found in the ECM are collagen types I and III, although types IV, V, VI, and VIII are also present. Fibroblasts are capable of producing collagen in the tissues. Matrix metalloproteinases (MMPs) such as collagenases and gelatinases play a critical role in collagen turnover by breaking down intact and damaged fibrillar collagen, respectively. They occur in development, wound healing, and major inflammatory diseases.[1,3] Under the normal physiological conditions, there is a balance between collagen production and breakdown. While collagen degradation is linked to inflammation, angiogenesis, and re-epithelialization, collagen biosynthesis is linked to the healing of wounds. Since the injury and healing of a tissue requires a tightly regulated process, defects in the collagen turnover lead to pathological diseases, including fibrosis.[1] Wound healing and fibrotic diseases have some common features. Collagen deposition is an essential and usually reversible aspect of wound healing. However, in cases of severe or repeated tissue injuries or disruptions in the healing process, it becomes a key factor in the transition from normal tissue repair to an irreversible fibrotic state.[4] Changes in the original tissue architecture of an organ caused by elevated collagen levels can lead to stiffness and a loss of functional cells, ultimately impairing the organ's function.[5]

Beta vulgaris L. var. cicla, commonly known as chard, is a green leafy, low-cost vegetable whose bioactive compounds have been the subject of research for their health benefits. It is a member of the Chenopodiaceae family and is distributed all over the world, being widely used in many traditional dishes. The leaves can be eaten raw in a salad, cooked separately, or combined with the stems. Chard has many chemical compounds such as fatty acids, phospholipids, glycolipids, polysaccharides, pectins, saponins, flavonoids, phenolic acid, betalain, vitamins A, B, C E, K, calcium, iron, phosphorus, zinc, magnesium, potassium, copper and manganese. These certain bioactive compounds' effects have been shown to be hepatoprotective,[6] anti-cancer and anti-inflammatory,[7] anti-diabetic,[8] anti-acetylcholinesterase and antioxidant[9-12.] The medicinal value of chard is also well documented.[13-15]

As collagen is crucial for healthy organs, the present study examined whether chard has an effect on the amount of collagen in vital organs, such as the lungs, liver and kidneys, through biochemical and histological analyses. The characteristics of bioactive compounds can create challenges for their use as potential therapeutic agents. There is a lack of comparison of the effects on normal groups based on tissue distribution in the body after consumption. The results of the study may help clarify the relationship between chard consumption and health outcomes in terms of collagen content.

Methods

Chemicals

All chemicals used in the experiments were of analytical purity and were purchased from Merck (Darmstadt, Germany), Sigma-Aldrich (St. Louis, MO, USA), and Fluka (Buchs, Switzerland).

Plant Extract

Chard leaves were sourced from markets in Istanbul, Türkiye, and authenticated by Prof. Dr. Kerim Alpınar from Istanbul University Faculty of Pharmacy (Voucher specimen number: 67901). The leaves were rinsed with distilled water and air-dried at 25°C. A total of 100 g of dried chard leaves were boiled in 1 L of distilled water for 8 hours, reaching the boiling point. After filtration, the water was removed using a rotary evaporator, and the resulting chard extract was weighed. It was dissolved in distilled water to be administered to the animals.

Animal Groups

The study was carried out with the permission of the Marmara University Animal Experiments Local Ethics Committee (Approval No: 19.2024.mar). The twenty female Sprague-Dawley rats of 3 months old, weighing 250-350 g, were chosen to be used. The experiment consisted of control group (C, n=6) and chard given group (chard, n=6). In the C group, rats received saline (0.9 %NaCl) orally. In the chard group, rats were administered chard extract by gavage at a dose of 100 mg/kg per day for 7 days. On the eighth day, the rats were sacrificed, and lungs, kidneys and liver tissues were collected. Tissues were fixed in 10% formaldehyde for detection of collagen density by histological and biochemical analyses.

Biochemical Analysis of Tissue Collagen

Tissue collagen was measured by the colorimetric method.[16] Five-micrometer-thick lungs, kidney and liver sections were cut from each paraffin block and placed on glass slides. Six slides were collected from each animal, with each slide having 2 tissue sections. An avarage of slides was calculated and used for analysis. The tissue sections were deparaffinized with xylene, rehydrated in a graded series of alcohol solutions, and stained with a saturated solution of picric acid in distilled water containing 0.1% fast green (Sigma-Aldrich F7252) and 0.1% of sirius red (Fluka 43665). Sections were incubated in the dark, at room temperature for 30 minutes. Then, sections were rinsed and transferred to a test tube containing 1 mL of absolute methanol and 0.1 N NaOH (1:1, v/v). The tubes were gently mixed until the color

was eluted completely. Absorbance of the eluted color was read at 540 nm and 605 nm by spectrophotometer. Collagen content of tissues were calculated using the formula below. The results were expressed as a collagen ratio (%).

Non-collagenous protein (mg) = Absorbance at 605 nm / 2.08

Collagen (mg) = [Absorbance at 540 nm - (0.291 x Absorbance at 605 nm)] / 38.4

Collagen ratio (%) = (mg Collagen x 100) / (mg Collagen + mg Non-collagenous protein)

Histological Analysis of Tissue Collagen

After fixation with 10% formaldehyde, tissues were processed routinely for paraffin embedding. Five-micrometer-thick paraffin sections were stained with Masson's trichrome for collagen fiber detection. Stained sections were photographed with a camera (Olympus DP72, Tokyo, Japan) attached to a photomicroscope (Olympus BX51, Tokyo, Japan). To calculate the percentage of the mean area of collagen fiber deposition, five images from five non-overlapping areas in each tissue samples were analyzed, with quantification carried out using ImageJ software (ImageJ, v.2.1, NIH, USA).

Statistical Analyses

Statistical analyses were performed using GraphPad Prism 9.0.1 (GraphPad Software, San Diego, CA, USA). For every group, the data were presented as mean ± standard error (SE). The results were analysed statistically with the Student's t-test, according to normal distribution. p-values below 0.05 are regarded as significant.

Results

Biochemical Analysis

The collagen content in tissues was shown in Figure 1. No change was observed in kidney tissue. A decrease was found in the liver ($p<0.001$), an increase was found in the lung tissues ($p<0.0001$) in the chard group compared to the control group.

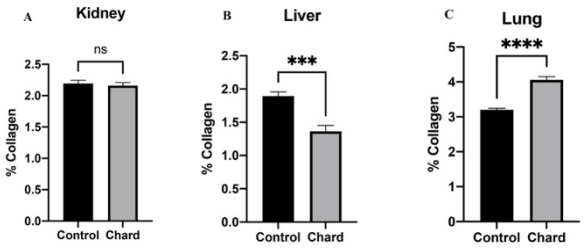

Figure 1. Collagen content in the kidney, liver and lung tissues of the control and chard given group.
Values are given as mean ± standard error. Each group consists of six rats. ***p<0.001, ****p<0.001 means significantly different from control group, ns means not significant.

Histological Analysis

The mean area percentage of collagen fibers in Masson's trichrome stained sections was shown in Figure 2. With the administration of chard, an increase was observed in lung tissue ($p<0.05$), while no statistically significant changes were observed in the liver and kidney tissues.

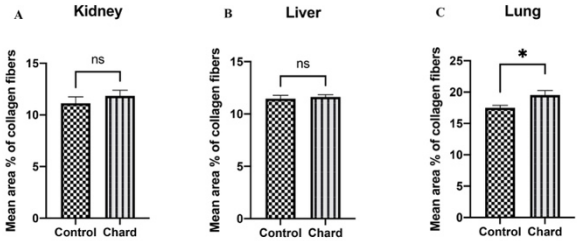

Figure 2. The percentage of the mean area of collagen fiber deposition in the kidney, liver, and lung tissues.
Values are given as mean ± standard error. Each group consists of six rats. *p<0.05 means significantly different from control group, ns means not significant.

In Figure 3, the collagen distribution in the kidney, liver, and lung samples were shown for the control and chard groups. In the kidney tissue sections of the control and chard groups, collagen fibers were detected in the renal corpuscle and tubulointerstitial area. No statistically significant difference in collagen density was found between the control and chard groups. In the liver tissue sections of the control and chard groups, collagen fibers were detected in the parenchyma and portal areas. Similarly, no statistically significant difference was found in collagen density between the control and chard groups. In the lung sections of the control and chard groups, collagen fibers were detected in the inter-alveolar septa, around the bronchioles, and the vessels. The amount of collagen fibers in the chard group was significantly higher than in the control group ($p<0.05$).

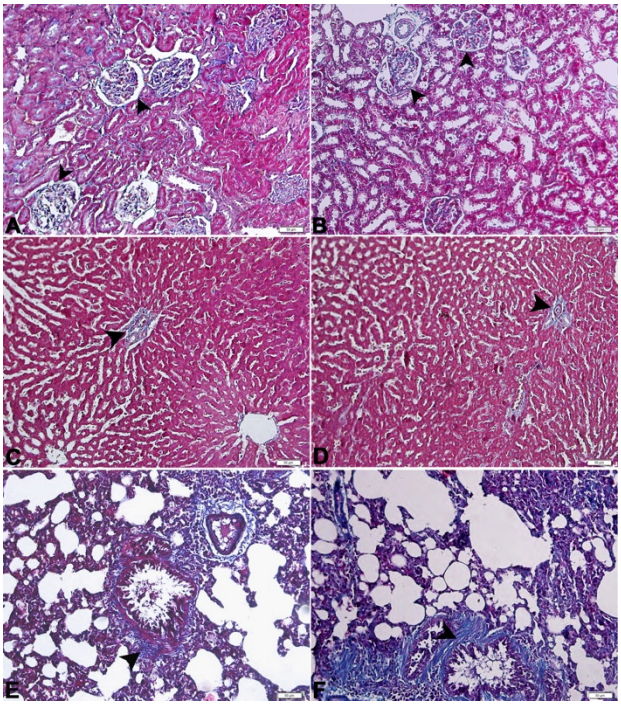

Figure 3. Representative light micrographs of control (A, C, and E) and chard (B, D and F) groups. Collagen fibers (arrowheads) in the renal corpuscle of kidney samples (A and B). Collagen

fibers (arrowheads) in the portal areas of liver samples (C and D). Collagen fibers (arrowheads) around bronchioles in lung samples (E and F). Masson trichrome (with aniline blue) staining. Scale bars: 50μm

Discussion

Collagen is produced and modified by fibroblasts and many other cell types. In general, each tissue has its own distinct ECM with a complex three-dimensional structure.[1] Additionally, fibroblasts can degrade collagen using specialized enzymes known as collagenases. They have critical role in degradation and remodeling of ECM.[17] Collagen molecules are made up of various amino acids, including glycine, proline, hydroxyproline, and alanine. Three polypeptide chains are joined together to form alpha triple helices. Disulfide bonds are established both within individual polypeptide chains and between neighboring chains. Vitamin C and iron are essential for the formation of these bonds. These bonds provide structure and stability to the triple-helix collagen macromolecule. This structure, along with the involvement of modified amino acids, makes collagen biosynthesis a complex process requiring multiple factors both inside and outside the cell.[18] The synthesis of collagen, an essential structural protein in the body, can be supported by a diet rich in amino acids, which constitute the protein's primary structure, along with cofactors such as vitamin C and iron.[19] Chard contains carbohydrates, fats, proteins, fibers, carotenoids, flavonoids, minerals, pigments, non-flavonoid phenolics, and vitamins. In particular, the leaves are rich in fiber, magnesium, iron, flavonoids, and vitamin C, making chard one of the best sources of these nutrients.[13,14]

In addition to collagen's role in supporting tissue structure, excessive collagen accumulation is a hallmark of organ fibrosis. The overexpression of collagen in fibrotic kidneys, liver and lungs is a key factor in tissue dysfunction. As fibrosis advances, the amount and distribution of collagen undergo significant changes.[17,20,21] Inhibiting key enzymes in collagen synthesis or promoting collagen degradation via overexpression of MMPs could help accelerate fibrosis resolution, presenting a potential therapy.[18] Therefore, understanding the impact of chard on collagen levels in various tissues is essential for advancing health insights. The effect that is decreased of cardiac collagen and MMP-1 levels with Swiss chard juices in barium chloride intoxicated rats has been reported.[22] However, there is no study to clarify the effect of chard extract on collagen content in healty animals.

Experimental Design and Duration

The dose and duration of chard were determined based on the study by Ustundag et al.[23] The administered chard dose and treatment period in this study, 100 mg/kg/day for 7 days, align with procedures applied in other animal studies investigating its antioxidant properties[24,25] and are considered an effective dose and appropriate duration to induce metabolic changes. Based on the results of the present study, a 7-day treatment period was sufficient to observe changes in collagen levels, but longer treatment durations may offer further insights into the effects of chard on collagen content.

Kidney

Collagen is a key component of the kidney and is extensively distributed across all kidney tissues. In the context of healthy kidney, type I and III collagen, are the most common collagen in the interstitial matrix of the kidney, type IV collagen is a key component of the glomerular basement membrane, and type VI is found in the interstitium, the intima and adventitia layers of the kidney vasculature.[21] Normal collagen molecules interact with extracellular matrix proteins to create an appropriate microenvironment for renal cells, influencing their physiological functions. Abnormalities in collagen can interfere with the connection between renal cells and matrix molecules, leading to various kidney diseases.[17] Thus, the collagen turnover pathway is a primary target for drugs aimed at addressing the progression of certain types of kidney disease. Our findings showed that kidney collagen content remained unchanged after chard administration. This conclusion is further corroborated by our histological findings. Yanardag et al. showed that chard extracts partially reduced degenerative changes in the kidneys of STZ-induced diabetic rats; however, serum urea and creatinine levels did not differ from those of the control group.[9] The lack of effect of chard on kidney collagen levels, despite its impact on the lungs and liver, likely results from the precise regulation of collagen production in specific tissues and cell types, primarily controlled at the transcriptional level.[26] Another reason could be that collagen turnover (synthesis and breakdown) rates might vary across organs[1] and may make kidney less responsive to the modulatory effects of chard's bioactive compounds. However, studies in the literature indicate that flavonoids impact kidney collagen. A study by Zhou et al. found that curcumin, which was a kind of flavonoid, decreased the accumulation of collagen in the kidney of animals with unilateral ureteral obstruction.[27] Furthermore, Ren et al. showed that quercetin, which was another kind of flavonoid, suppressed collagen deposition in the obstructive kidneys.[28]

Liver

Our current study showed that the effect of chard application on collagen levels varied between different tissues. We found that chard treatment reduced liver collagen levels; however, this reduction could not be demonstrated histologically. This suggested that the liver's collagen turnover might have been altered by chard administration, but the structural changes in the liver may not have become apparent during the experiment. In a healthy liver, interstitial fibrillar collagens like types I, III, and V are mainly found in the space of Disse, the portal tract, and central vein walls. Basement-type collagen, primarily type IV, is located in

the sinusoidal walls, forming a network, as well as around bile ducts. Both types are present in low amounts, just enough for normal function.[18] The collagen content of tissues is influenced by changes in both the synthesis and degradation rates of collagen.[29] Chard, which is rich in vitamin E, may have reduced collagen synthesis. It is known that vitamin E inhibits proliferation and collagen synthesis of hepatic stellate cells.[30] The inhibition or reversal of hepatic stellate cell activity is a potential therapeutic strategy for liver fibrosis.[31] Polyphenolic compounds and polyphenol-rich extracts have been shown to improve collagen homeostasis in the liver.[32] The water extract of chard leaves is rich in phenolic compounds, including vanillic acid, caffeine, ellagic acid and pyrogallol, as well as flavonoids, such as hesperidin, rosmarinic acid, luteolin, and derived from apigenin namely vitexin.[33,34] Treatment with apigenin has been shown to alleviated hepatic fibrosis models through the TGF-β1/Smad3 and p38/PPARα signaling pathways. Protein expressions of collagen 1 and matrix metalloproteinase inhibitor 1 were decreased, while expression of matrix metalloproteinase 2 was found to be increased with apigenin treatment.[35] It has been reported that, in cholestasis-related liver injury, rosmarinic acid suppresses matrix-producing cells and fibrogenic changes by reducing hepatic collagen and hydroxyproline content and inhibiting matrix metalloproteinases and tissue inhibitor of metalloproteinases mRNA expression.[36] Since liver fibrosis can occur in numerous diseases, the discovery of effective anti-fibrotic treatments would represent a major advancement by addressing a critical medical need. Thanks to its high antioxidant properties[37,38] chard may have the potential to ameliorate the initial tissue damage that triggers liver fibrosis, suggesting that its ability to reduce liver collagen could have a positive effect on fibrosis treatment during administration.

Lung

The lung functions as a biomechanically dynamic organ. Collagen in the healthy lungs creates a dense fibrous network throughout the major airways, bronchi, and bronchioles, offering the strength and stability necessary for their proper function. The lung parenchyma, the area responsible for gas exchange, contains as an interstitial matrix primarily composed of collagens I and III. The basement membrane includes collagens IV, VI, and XVII. Collagens in the lung's basement membrane and interstitial space serve as essential molecular frameworks for key physiological processes, including fibroblast proliferation, migration, and adhesion.[20] The load-bearing capacity of lung tissue is attributed to its collagen content, along with elastin fibers and glycosaminoglycans. Lung diseases are partially associated with changes in the composition, quantity, and organization of the extracellular matrix in different compartments of the lung.[39] Collagen provides tensile strength, while elastin enables extensibility and elastic recoil in the airways. Together, they likely influence both bronchoconstriction and the reopening of airways. An increase in collagen and elastic fiber content in the airway walls may contribute to persistent obstruction in asthmatic airways. Nevertheless, it has also been suggested that increased collagen may have a protective role by stiffening the airways, thereby resisting the forces generated by airway smooth muscle contraction.[40] We found an increase in lung collagen after chard was administered and we demonstrated the increase in collagen in the lung histologically. Sacan and Yanardag have explained that chard has high proline content.[10] Findings in the study by Shaw et al. suggest that the presence of proline and vitamin C can enhance collagen production and improve tissue mechanics in engineered ligaments.[41] Vitamin C, which is abundant in chard, is involved in collagen synthesis, helping to preserve the integrity of blood vessels and lung tissue. Vitamin C is thought to support the integrity of the endothelial barrier, which is crucial in preventing fluid leakage into the lungs. This could aid in the repair and regeneration of damaged lung tissue in acute respiratory distress syndrome.[42] It enhances collagen mRNA production in fibroblasts.[43] In the present study, the high proline and vitamin C content in chard may contribute to increased collagen levels in the lungs. Because the lungs are directly exposed to high levels of oxygen, they are more susceptible to oxidative injury; therefore, protecting the lungs is important. Additionally, we suggest that chard's antioxidant and anti-inflammatory properties may help protect collagen from degradation and contribute to maintaining lung integrity. Chard is also high in nitrate. In the oral cavity, bacteria and xanthine oxidase reduce nitrate to nitrite, which is then converted to NO by xanthine oxidoreductase, deoxyhemoglobin, myoglobin, respiratory chain enzymes, vitamin C, polyphenols, and protons.[44] For many years, it has been recognized that nitrates promote bronchial relaxation. Increased intake of nitrate-rich green leafy vegetables, along with dietary nitrate supplementation, has been shown to improve endothelial and cardiovascular function, offering a potential approach to modulate vascular disease development in conditions such as hypertension, diabetes, and atherosclerosis.[45] Hu et al. also reported that dietary nitrate enhanced skin microvascular density in the wound area, encouraging cell expression and collagen fiber deposition.[46] In the present study, the increase in collagen in the lung may also be related to the nitrate content of chard. Collagen accumulation relies on various factors, including the rates of gene transcription and mRNA translation, post-translational modifications, secretion processes, and the degradation of newly synthesized collagen.[47] Collagen metabolism and accumulation are precisely regulated by collagenases and their inhibitors. This study also suggests that increased collagen accumulation in the lung may occur through the collagenolytic pathway, a mechanism that chard may potentially modulate. To clarify this area of study, the effects of chard on MMPs and TIMPs should be thoroughly investigated. Apart from all this, increased collagen in lung tissue should also be considered in relation to pulmonary fibrosis development. Therefore,

individuals at risk of lung fibrosis may need to limit their consumption of chard.

The main limitation of the present study is that tissue biochemical parameters were not estimated. We were also unable to fully explain the most likely mechanisms underlying chard's effects on the differences in collagen metabolism across tissues. However, the aim of the this study was not the investigation of these mechanisms, but, first of all, showing whether the chard, which we consume as a food, affects collagen levels in liver, kidney and lung in healthy individuals. The possible mechanisms of the impacts of chard will be evaluated in further studies.

In conclusion, the use of complementary and alternative medicine, including dietary supplements with plant-derived phytochemicals, is increasingly popular for health promotion and treatment. Vegetables like chard are affordable, widely accessible, and generally more acceptable to patients than conventional drugs, suggesting that their consumption could serve as a potential therapeutic option. Chard, in particular, may have the potential to influence collagen production across various tissues. It increased collagen in the lungs, reduced it in the liver, and had no effect on kidney collagen levels. Given its diverse effects, chard showed promise for development as a therapeutic agent across a range of applications, including wound healing, tissue strengthening, and antifibrotic therapy. Nevertheless, individuals with fibrosis may consider limiting their intake of chard.

Ethical Approval

The study was carried out with the permission of the Marmara University Animal Experiments Local Ethics Committee (Approval No: 19.2024.mar).

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Concept & Design: AY, RY; Data Collection or Processing: BAT, AM, SO, EA, ST; Analysis or Interpretation: BAT, AM, SO, EA; Resources: AY, RY, EA; Writing – original draft preparation: AY, RY, BAT, EA; Writing – review and editing: BAT, AM, SO, EA, ST, RY, AY; Supervision: AY, RY.

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References

1. Singh D, Rai V, Agrawal DK. Regulation of collagen I and collagen III in tissue injury and regeneration. *Cardiol Cardiovasc Med.* 2023;7(1):5–16. doi:10.26502/fccm.92920302
2. Williams L, Layton T, Yang N, Feldmann M, Nanchahal J. Collagen VI as a driver and disease biomarker in human fibrosis. *FEBS J.* 2022; 289(13):3603–3629. doi:10.1111/febs.16039
3. Van Doren SR. Matrix metalloproteinase interactions with collagen and elastin. *Matrix Biol.* 2015; 44–46:224–231. doi:10.1016/j.matbio.2015.01.005
4. Distler JHW, Györfi AH, Ramanujam M, Whitfield ML, Königshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. *Nat Rev Rheumatol*. 2019;15(12):705–730. doi:10.1038/s41584-019-0322-7
5. Westra I. *Precision-cut liver slices: an ex vivo model for the early onset and end-stage of liver fibrosis*. Dissertation. University of Groningen; 2014.
6. Hashem AN, Soliman MS, Hamed MA, Swilam NF, Lindequist U, Nawwar MA. Beta vulgaris subspecies cicla var. flavescens (Swiss chard): Flavonoids, hepatoprotective and hypolipidemic activities. *Pharmazie*. 2016;71(4):227–232. doi:10.1691/ph.2016.5821
7. Ninfali P, Antonini E, Frati A, Scarpa ES. C-Glycosyl flavonoids from Beta vulgaris cicla and betalains from Beta vulgaris rubra: antioxidant, anticancer and antiinflammatory activities-A review. *Phytother Res*. 2017;31(6):871-884. doi:10.1002/ptr.5819.
8. Yanardag R, Colak H. Effect of chard (Beta vulgaris l. var. cicla) on blood glucose levels in normal and alloxan-induced diabetic rabbits. *Pharm Pharmacol Commun*. 1998;4(6):309–311. doi:10.1111/j.2042-7158.1998.tb00702.x
9. Yanardağ R, Bolkent Ş, Ozsoy-Saçan Ö, Karabulut-Bulan Ö. The effects of chard (Beta vulgaris L. var. cicla) extract on the kidney tissue, serum urea and creatinine levels of diabetic rats. *Phytother Res.* 2002;16(8):758-761. doi:10.1002/ptr.1041.
10. Sacan O, Yanardag R. Antioxidant and antiacetylcholinesterase activities of chard (Beta vulgaris L. var. cicla). *Food Chem Toxicol*. 2010;48(5):1275–1280. doi:10.1016/j.fct.2010.02.022
11. Sacan O, Ertik O, Ipci Y, Kabasakal L, Sener G, Yanardag R. Protective effect of chard extract on glycoprotein compounds and enzyme activities in streptozotocin-induced hyperglycemic rat lungs. *Bulg Chem Commun.* 2018;50(1):119-123. doi:10.26650/experimed.2021.879204
12. Ertik O, Sacan O, Kabasakal L, Şener G, Yanardağ R. Protective effect of chard extract on glycoprotein compounds and advanced oxidation protein product levels in diabetic rat livers. *Experimed.* 2021;11(1):27-32. doi:10.26650/experimed.2021.879204
13. Gamba M, Raguindin PF, Asllanaj E, et al. Bioactive compounds and nutritional composition of Swiss chard (*Beta vulgaris* L. var. cicla and flavescens): A systematic review. *Crit Rev Food Sci Nutr*. 2021;61(20):3465–3480. doi:10.1080/10408398.2020.1799326
14. Mzoughi Z, Chahdoura H, Chakroun Y, et al. Wild edible Swiss chard leaves (Beta vulgaris L. var. Cicla): Nutritional, phytochemical composition and

biological activities. *Food Res Int.* 2019 119:612-621. doi:10.1016/j.foodres.2018.10.039.

15. Trifunovic S, Topalovic A, Knezevic M, Vajs V. Free radicals and antioxidants: antioxidative and other properties of Swiss chard (Beta vulgaris L. subsp. cicla). *Agric For.* 2015;61(2):73-92. doi:10.17707/AgricultForest.61.2.06
16. López-De León A, Rojkind M. A simple micromethod for collagen and total protein determination in formalin-fixed paraffin-embedded sections. *J Histochem Cytochem.* 1985;33(8):737–743. doi:10.1177/33.8.2410480
17. Huang A, Guo G, Yu Y, Yao L. The roles of collagen in chronic kidney disease and vascular calcification. *J Mol Med.* 2021;99(1):75–92. doi:10.1007/s00109-020-02014-6
18. Luangmonkong T, Parichatikanond W, Olinga P. Targeting collagen homeostasis for the treatment of liver fibrosis: Opportunities and challenges. *Biochem Pharmacol*. 2023;215:115740. doi:10.1016/j.bcp.2023.115740
19. Añazco C, Ojeda PG, Guerrero-Wyss M. Common beans as a source of amino acids and cofactors for collagen biosynthesis. *Nutrients.* 2023;15(21):4561. doi:10.3390/nu15214561
20. Mereness JA, Mariani TJ. The critical role of collagen VI in lung development and chronic lung disease. *Matrix Biol Plus.* 2021;10:100058. doi:10.1016/j.mbplus.2021.100058
21. Rasmussen DGK, Boesby L, Nielsen SH, et al. Collagen turnover profiles in chronic kidney disease. *Sci Rep.* 2019;9(1):16062. doi:10.1038/s41598-019-51905-3
22. Gabal AMS, Morsy MG. Impact of beetroot (Beta vulgaris rubra) and/or Swiss chard (Beta vulgaris cicla) juices oral administration against barium chloride-induced hypokalemia, atpase disturbance, and heart and lung toxicity in rats. *Asian J Pharm Clin Res.* 2020;13(8):218–224. doi:10.22159/ajpcr.2020.v13i8.38232
23. Ustundag UV, Tunali S, Alev B, et al. Effects of chard (*Beta Vulgaris* L. var. cicla) on cardiac damage in valproic acid–induced toxicity. *J Food Biochem.* 2016;40(2):132-139. doi:10.1111/jfbc.12202
24. Sulakhiya K, Patel VK, Saxena R, Dashore J, Srivastava AK, Rathore M. Effect of Beta vulgaris Linn. leaves extract on anxiety-and depressive-like behavior and oxidative stress in mice after acute restraint stress. *Pharmacogn Res.* 2016;8(1):1-7. doi:10.4103/0974-8490.171100.
25. Tunali S, Cimen ES, Yanardag R. The effects of chard on brain damage in valproic acid-induced toxicity. *J Food Biochem.* 2020;44(10):e13382. doi:10.1111/jfbc.13382.
26. Alexakis C, Maxwell P, Bou-Gharios G. Organ-specific collagen expression: Implications for renal disease. *Nephron Exp Nephrol*. 2006;102(3-4):e71–e75. doi:10.1159/000089684
27. Zhou X, Zhang J, Xu C, Wang W. Curcumin ameliorates renal fibrosis by inhibiting local fibroblast proliferation and extracellular matrix deposition. *J Pharmacol Sci.* 2014;126(4):344–350. doi:10.1254/jphs.14173FP
28. Ren J, Li J, Liu X, et al. Quercetin inhibits fibroblast activation and kidney fibrosis involving the suppression of mammalian target of rapamycin and β-catenin signaling. *Sci Rep.* 2016;6(1):23968. doi:10.1038/srep23968
29. Zhou S, Salisbury J, Preedy VR, Emery PW. Increased collagen synthesis rate during wound healing in muscle. *PLoS One.* 2013;8(3):e58324. doi:10.1371/journal.pone.0058324
30. Zhan Y, Wang Y, Wei L, Chen H. Effects of vitamin E on the proliferation and collagen synthesis of rat hepatic stellate cells treated with IL-2 or TNF-alpha. *Chin Med J (Engl).* 2003;116(3):472-474.
31. Zhang F, Zhuge YZ, Li YJ, Gu JX. S-adenosylmethionine inhibits the activated phenotype of human hepatic stellate cells via Rac1 and Matrix metalloproteinases. *Int Immunopharmacol.* 2014;19(2):193–200. doi:10.1016/j.intimp.2014.01.021
32. Kozłowska M, Brzóska MM, Rogalska J, Galicka A. The impact of a polyphenol-rich extract from the berries of Aronia melanocarpa L. on collagen metabolism in the liver: A Study in an in vivo model of human environmental exposure to cadmium. *Nutrients.* 2020;12(9):2766. doi:10.3390/nu12092766.
33. Ninfali P, Angelino D. Nutritional and functional potential of Beta vulgaris cicla and rubra. *Fitoterapia.* 2013;89:188–199. doi:10.1016/j.fitote.2013.06.004
34. Zein H, Hashish AEMS, Ismaiel GHH. The antioxidant and anticancer activities of Swiss chard and red beetroot leaves. *Curr Sci Int.* 2015;4(4):491-498.
35. Ji J, Yu Q, Dai W, et al. Apigenin alleviates liver bibrosis by Inhibiting hepatic stellate cell activation and autophagy via TGF-β1/Smad3 and p38/PPARα pathways. *PPAR Res.* 2021;2021:6651839. doi:10.1155/2021/6651839.
36. Lin SY, Wang YY, Chen WY, et al. Hepatoprotective activities of rosmarinic acid against extrahepatic cholestasis in rats. *Food Chem Toxicol.* 2017;108(Pt A):214-223. doi:10.1016/j.fct.2017.08.005.
37. Gezginci-Oktayoglu S, Sacan O, Bolkent S, et al. Chard (Beta vulgaris L. var. cicla) extract ameliorates hyperglycemia by increasing GLUT2 through Akt2 and antioxidant defense in the liver of rats. *Acta Histochem.* 2014;116(1):32-39. doi:10.1016/j.acthis.2013.04.016.
38. Ozsoy-Sacan O, Karabulut-Bulan O, Bolkent S, Yanardag R, Ozgey Y. Effects of chard (Beta vulgaris L. var cicla) on the liver of the diabetic rats: a morphological and biochemical study. *Biosci Biotechnol Biochem.* 2004;68(8):1640-1648. doi:10.1271/bbb.68.1640.
39. Burgess JK, Gosens R. Mechanotransduction and the extracellular matrix: Key drivers of lung pathologies and drug responsiveness. *Biochem Pharmacol.* 2024;228:116255. doi:10.1016/j.bcp.2024.116255
40. Setlakwe EL, Lemos KR, Lavoie-Lamoureux A, Duguay JD, Lavoie JP. Airway collagen and elastic fiber

content correlates with lung function in equine heaves. *Am J Physiol Lung Cell Mol Physiol.* 2014;307(3):L252-60. doi:10.1152/ajplung.00019.2014.

41. Shaw G, Lee-Barthel A, Ross ML, Wang B, Baar K. Vitamin C-enriched gelatin supplementation before intermittent activity augments collagen synthesis. *Am J Clin Nutr.* 2017;105(1):136-143. doi:10.3945/ajcn.116.138594.
42. Boretti A. Intravenous vitamin C against acute respiratory distress syndrome: A narrative review. *PharmaNutrition.* 2024;27:100365. doi:10.1016/j.phanu.2023.100365
43. Baião DDS, Silva DVTD, Paschoalin VMF. Beetroot, a remarkable vegetable: Its nitrate and phytochemical contents can be adjusted in novel formulations to benefit health and support cardiovascular disease therapies. *Antioxidants (Basel).* 2020;9(10):960. doi:10.3390/antiox9100960
44. Ogoshi T, Yatera K, Mukae H, Tsutsui M. Role of nitric oxide synthases in respiratory health and disease: Insights from triple nitric oxide synthases knockout mice. *Int J Mol Sci.* 2024;25:9317. doi:10.3390/ijms25179317
45. Liu Y, Croft KD, Mori TA, Gaspari TA, Kemp-Harper BK, Ward NC. Long-term dietary nitrate supplementation slows the progression of established atherosclerosis in ApoE-/- mice fed a high fat diet. *Eur J Nutr.* 2023;62(4):1845-1857. doi:10.1007/s00394-023-03127-7
46. Hu X, Wang L, Deng J, et al. Dietary nitrate accelerates the healing of infected skin wounds in mice by increasing microvascular density. *Biochem Biophys Res Commun.* 2023;686:149176. doi:10.1016/j.bbrc.2023.149176.
47. Van Hoozen BE, Grimmer KL, Marelich GP, Armstrong LC, Last JA. Early phase collagen synthesis in lungs of rats exposed to bleomycin. *Toxicology.* 2000;147(1):1-13.doi:10.1016/s0300483x(00)00142-6.

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YOĞUN BAKIM ÜNİTESİNDE ÇALIŞAN DOKTORLARIN YAPAY ZEKA İLE İLGİLİ BAKIŞ AÇILARI

PERSPECTIVES OF INTENSIVE CARE UNIT DOCTORS ON ARTIFICIAL INTELLIGENCE

Kamuran Uluç[1]

[1]Muş Devlet Hastanesi, Muş, Türkiye.

ÖZ

Amaç: Bu çalışma yoğun bakım ünitelerinde görev yapan doktorların yapay zeka (YZ) teknolojilerine ilişkin bilgi düzeylerini, bu teknolojilere yönelik tutum ve algılarını değerlendirmeyi amaçlamaktadır. Ayrıca, doktorların YZ'nin yoğun bakım süreçlerindeki mevcut ve potansiyel uygulama alanlarına dair doktorların görüşlerini ve bu teknolojilere yönelik endişelerini ortaya koymak amaçlanmıştır.

Yöntem: Kesitsel bir araştırma olarak tasarlanan bu çalışmada, yoğun bakım ünitelerinde çalışan doktorlara yönelik bir anket kullanılmıştır. Anket, Google Formlar aracılığıyla çevrimiçi olarak uygulanmış ve bir ay boyunca erişime açık bırakılmıştır. Ankette demografik veriler, YZ konusundaki bilgi düzeyleri, tutumlar ve endişelerle ilgili toplam 15 soru yer almıştır. Veriler, Statistical Package for the Social Sciences (SPSS) 22.0 programı kullanılarak analiz edilmiştir.

Bulgular: Çalışmaya 411 kişi katılmış ancak eksiksiz yanıt veren 406 kişinin verileri değerlendirmeye alınmıştır. Katılımcıların %90,05'i YZ'nin tıpta kullanımını duyduğunu, %91,54'ü ise YZ sistemlerinin yararlı olabileceğini düşünmektedir. Bununla birlikte, yoğun bakımda YZ'nin kendi mesleki kararlarının yerini alabileceğini düşünenlerin oranı %13,93 ile sınırlı kalırken, %68,41'i bu görüşe katılmamıştır. Katılımcıların %1,49'u klinik karar süreçlerinde yalnızca YZ'nin görüşüne güveneceğini belirtirken, %37,31'i YZ yerine kendi görüşlerine güvenmeyi tercih ettiğini ifade etmiştir. Öte yandan, %61,19'u ise karar vermeden önce ikinci bir uzman görüşüne ihtiyaç duyacağını belirtmiştir. Yasal ve etik sorumluluklar açısından katılımcıların %65,92'si işlemin sorumluluğunun her durumda hekime ait olması gerektiğini vurgulamıştır. Yapay zekanın en yaygın desteklenen kullanım alanları; %79,85 ile görüntüleme sonrası tanı, %73,13 ile epikriz yazımı ve %69,4 ile kültür sonuçlarına göre antibiyoterapi kararı olmuştur. Katılımcıların %96,27'si YZ sistemlerinde teknik sorunlar yaşanabileceğini, %89,55'i ise veri güvenliği konusundaki risklerden endişe duyduğunu ifade etmiştir.

Sonuç: Bu çalışma yoğun bakım doktorlarının YZ teknolojilerine karşı genel olarak olumlu bir tutum sergilediklerini ancak bu teknolojilerin etkin entegrasyonunda yasal etik ve teknik zorlukların önemli bir rol oynadığını göstermektedir. YZ'nin yoğun bakım süreçlerinde verimliliği artırma ve hasta sonuçlarını iyileştirme potansiyeli büyüktür. Doktorların bilgi düzeylerini artıracak eğitim programları ve endişelerini ele alacak düzenlemeler, bu teknolojilerin klinik uygulamalarda benimsenmesini kolaylaştıracaktır.

Anahtar Kelimeler: Yapay zeka, yoğun bakım ünitesi, klinik karar desteği, doktor tutumları

ABSTRACT

Objective: This study aims to assess the knowledge levels, attitudes, and perceptions of intensive care unit (ICU) physicians regarding artificial intelligence (AI) technologies. Additionally, it seeks to explore physicians' perspectives on the current and potential applications of AI in intensive care processes, as well as their concerns about these technologies.

Method: Designed as a cross-sectional study, this research utilized a survey targeting physicians working in ICUs. The survey was administered online via Google Forms and remained accessible for one month. It comprised 15 questions covering demographic data, AI-related knowledge levels, attitudes, and concerns. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0.

Results: A total of 411 participants responded to the survey; however, data from 406 participants who completed the questionnaire in full were included in the analysis. Among the respondents, 90.05% were aware of AI applications in medicine, and 91.54% believed that AI systems could be beneficial. However, only 13.93% of participants thought that AI could replace their professional decision-making in the ICU, whereas 68.41% disagreed with this notion. While 1.49% stated that they would rely solely on AI for clinical decision-making, 37.31% preferred to rely on their own judgment. Additionally, 61.19% indicated that they would seek a second expert opinion before making a decision. Regarding legal and ethical responsibilities, 65.92% of participants emphasized that the physician should always be held accountable for medical procedures. The most commonly supported AI applications were post-imaging diagnosis (79.85%), discharge summary documentation (73.13%), and antibiotic therapy decision-making based on culture results (69.4%). Furthermore, 96.27% of respondents acknowledged the potential for technical issues in AI systems, and 89.55% expressed concerns regarding data security risks.

Conclusion: This study demonstrates that ICU physicians generally have a positive attitude toward AI technologies; however, legal, ethical, and technical challenges play a significant role in their effective integration. AI holds substantial potential to enhance efficiency and improve patient outcomes in intensive care settings. Educational programs to increase physicians' knowledge and regulatory measures addressing their concerns may facilitate the adoption of these technologies in clinical practice.

Keywords: Artificial intelligence, intensive care unit, clinical decision support, physician attitudes

***İletişim kurulacak yazar/Corresponding author:** Kamuran Uluç; Yoğun Bakım Ünitesi, Muş Devlet Hastanesi, Muş, Türkiye.
Telefon/Phone: +90 (436) 212 06 70 **e-posta/e-mail:** kamuranuluc@hotmail.com
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Giriş

Yapay zeka (YZ), çeşitli görevlerin yerine getirilmesinde insan zekasını taklit eden, topladığı bilgilere dayanarak kendisini geliştiren ve insan benzeri işlevleri gerçekleştirebilen bir sistemdir. Makine öğrenmesi (MÖ), YZ'nin bir alt dalı olarak matematiksel modellerle müdahale olmadan kararlar oluştururken, gelişmiş hesaplama gücü sayesinde bu modeller hızla gelişmektedir. Yapay zeka ve MÖ tıpta giderek yaygınlaşarak hastalık kalıplarının erken tanınmasıyla kompleks sorunlara etkili çözümler sunmaktadır. Bu teknolojiler, rutin iş yükünü azaltarak hekimin karmaşık klinik kararlara daha fazla zaman ayırmasını sağlama potansiyeline sahiptir.[1,2]

Yapay zeka, hasta yönetimi, klinik karar desteği, hasta izleme ve sağlık müdahaleleri gibi alanlarda sağlık hizmetlerini iyileştirmek amacıyla kullanılmaktadır. Sağlık sistemine dengeli bir YZ entegrasyonu, hizmetlerin daha verimli ve etkili hale gelmesini sağlayabilir[3]. Yoğun bakımda kullanılan YZ ve MÖ tutumları; hasta teşhisi, tedavi planlaması ve hasta sonuçları üzerinde belirgin etkilere sahiptir. Zaman içinde yoğun bakım tıbbının uygulanış biçimini de kaçınılmaz olarak dönüştürecektir. Bu nedenle klinikte doğrulanmış, yüksek kaliteli, doğru ve eşitlikçi modellerin hayata geçirilmesi büyük önem taşımaktadır.[1]

Yoğun bakım üniteleri, hastane içinde büyük veriye geçiş ve YZ'nin hem araştırmalarda hem de yakın gelecekte klinik uygulamalarda kullanımı açısından en elverişli ortamdır. Bu ünitede hastalar, olası kötüleşmeleri gösteren fizyolojik değişiklikleri erkenden saptamak amacıyla yakın takibe alınır. Hemşireler; hastaların nörolojik durumunu, ilaç uygulamaları dahil tüm girdi-çıktılarını detaylı şekilde kaydeder. Yatak başı monitörleri ise bu süreci kolaylaştırarak kesintisiz ve yoğun veri akışı sağlar.[4]

Yoğun bakımda YZ'nin kullanımı temelde şu alanları kapsar: hastalık teşhisi, hastalık ilerleyişinin (klinik kötüleşmenin) öngörülmesi ve sepsis, septik şok ve akut solunum sıkıntısı sendromu (ARDS) gibi spesifik hastalık fenotipleri veya endotiplerinin tanımlanması.[5]

Bu çalışmanın amacı, yoğun bakım ünitesinde çalışan doktorların YZ teknolojileri konusundaki bilgi düzeylerini ve bu teknolojilere yönelik tutumlarını değerlendirmektir. Ayrıca, YZ'nin yoğun bakım süreçlerindeki potansiyel uygulama alanlarına ve doktorların bu teknolojilere ilişkin endişelerine ışık tutmaktır.

Yöntem

Çalışmamız, anket niteliğinde kesitsel bir çalışma olarak düzenlenmiştir. Bu çalışma için Sağlık Bilimleri Üniversitesi Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan onay alınmıştır (Tarih: 13.07.2023 ve Karar No: 2023-364). Çalışma, Helsinki Deklarasyonu'na uygun olarak gerçekleştirilmiştir. Anket, yoğun bakım ünitesinde çalışan doktorlara yönelik olarak hazırlanmıştır. Farklı ülkelerde yapılan anketlerden yararlanılarak oluşturulan bu form, Google Formlar üzerinden hazırlanmış ve 1 ay süreyle erişime açık bırakılmıştır. Anket bağlantısı, katılımcılara WhatsApp (WhatsApp Inc, Menlo Park, CA, USA) grupları aracılığıyla iletilmiştir. Ankete katılım zorunlu olmayıp, belirlenen süre içinde anketi doldurmayan kişiler katılmayı reddetmiş olarak kabul edilmiştir. Çalışmaya dahil edilme kriterleri; yoğun bakım ünitesinde görev yapan, ankete katılmayı kabul eden ve anket sorularını eksiksiz yanıtlayan gönüllü doktorları kapsamaktadır. Dışlama kriterleri ise; ankete katılmayı reddeden ve anket sorularını eksik yanıtlayan doktorlardır.

Katılımcılara, anketin başlangıcında çalışmanın amacı ve niteliği hakkında bilgilendirme yapılarak onamları alınmıştır. Anketin herhangi bir bölümünde katılımcılardan isim, soy isim veya çalıştıkları kurum gibi kişisel bilgilerin paylaşılması istenmemiştir. Anket soruları, tarafsızlık ilkesine uygun olarak hazırlanmış ve katılımcı yanıtlarının yönlendirilmemesi esas alınmıştır. Anketin tamamlanması için herhangi bir zaman kısıtlaması getirilmemiştir.

Anket 15 sorudan oluşmaktadır. İlk altı soru demografik verileri değerlendirmek amacıyla cinsiyet, yaş, görev yapılan sağlık kurumunun niteliği, akademik ünvan, hekimlik mesleğindeki süre, yoğun bakım ünitesindeki çalışma süresi ile ilgili soruları içermektedir. Diğer dokuz soru katılımcıların YZ konusundaki bilgi, tutum ve davranışlarını değerlendirmeyi amaçlamaktadır. Katılımcıların yanıtlarını 3'lü Likert ölçeği ile (*katılmıyorum, kararsızım, katılıyorum*) değerlendirmeleri istenmiştir.

Anketin, uygulanabilirlik ve içerik açısından değerlendirilmesi amacıyla, ilk test aşamasında yoğun bakım ünitesinde çalışan 7 hekim tarafından test edilip gerekli kontroller yapıldıktan sonra son şekli verilmiştir.

Ankete 411 kişi katıldı ancak tüm soruları yanıtlamayan 5 katılımcı çalışma kapsamı dışında bırakıldı. Analizler anketi eksiksiz dolduran 406 katılımcının verileri üzerinden gerçekleştirildi. Çalışmaya dahil edilen 406 kişiden 4'ü anketteki "*Yapay zekayı hiç duydunuz mu?*" sorusuna "*Hayır*" cevabı verdikleri için diğer soruları cevaplamadı. Yapay zeka ile ilgili diğer sorulara cevap veren 402 kişinin cevapları üzerinden değerlendirme yapıldı.

İstatistiksel Analiz

Kategorik veriler, sayı (n) ve yüzde (%) ile, normal dağılıma uyan numerik veriler ise ortalama (Ort.) ve standart sapma (SS) olarak tanımlandı. Anket sorularına verilen yanıtlar sonucunda elde edilen veriler, Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 22.0 programına girilerek analiz edildi.

Bulgular

Demografik Veriler

Katılımcıların %61,08'ini (n=248) kadınlar, %38,92'sini (n=158) ise erkeklerden oluşmaktadır. Katılımcıların yaş ortalaması 39,44 ± 9,07 yıl olup, yaş aralığı 25 ile 63 arasında değişmektedir. Çalışılan kurumlar arasında en

yüksek oran %32,02 olup, bu oran Devlet üniversitesi hastaneleri ve Eğitim ve Araştırma hastanelerinde eşit olarak gözlenmiştir. Mesleki ünvan dağılımında en büyük grubu %28,57 ile uzman hekimler oluştururken, hekimlik süresi ağırlıklı olarak 0-10 yıl (%41,87) arasında değişmektedir. Yoğun bakım ünitesinde çalışma süresi en çok 0-5 yıl (%40,64) olarak belirlenmiştir (Tablo 1).

Tablo 1. Demografik veriler

	n (%)
Cinsiyet	
Kadın	248 (61,08)
Erkek	158 (38,92)
Yaş (yıl)	
ort ± SS	39,44 ± 9,07
21-30	68 (16,75)
31-40	183 (45,07)
41-50	101 (24,88)
51-60	48 (11,82)
61 ve üzeri	6 (1,48)
Çalışılan kurum	
Devlet üniversite hastanesi	130 (32,02)
Eğitim ve araştırma hastanesi	130 (32,02)
Şehir hastanesi	69 (17,00)
Devlet hastanesi	46 (11,33)
Özel hastane	26 (6,40)
Vakıf üniversite hastanesi	5 (1,23)
Ünvan	
Profesör	34 (8,37)
Doçent	32 (7,88)
Doktor öğretim üyesi	20 (4,93)
Yan dal uzmanı	96 (23,65)
Uzman	116 (28,57)
Asistan	108 (26,60)
Hekim olarak çalışılan süre (yıl)	
0-10	170 (41,87)
11-20	144 (35,47)
21-30	49 (12,07)
31 ve üzeri	43 (10,59)
Yoğun bakım ünitesinde olarak çalışılan süre (yıl)	
0-5	165 (40,64)
6-10	122 (30,05)
11-20	94 (23,15)
21 ve üzeri	25 (6,16)

* n: Sayı, %: Yüzde, ort: Ortalama, SS: Standart Sapma

Yapay Zeka Uygulamaları Hakkında Bilgi ve Görüşler

Katılımcıların %90,05'i YZ'nin tıp alanındaki uygulamalarını duyduğunu, %91,54'ü ise bu sistemlerin faydalı olabileceğini ifade etmiştir. Ancak, yoğun bakımda YZ'nin işlerinin yerine geçebileceğini düşünenlerin oranı %13,93 ile sınırlı kalırken, %68,41'i bu görüşe katılmamaktadır. Yoğun bakımda alınan kararlar arasında katılımcıların %37,31'i, YZ'nin kararlarına kıyasla kendi görüşlerine güveneceğini belirtirken %61,19'u, ikinci bir uzman görüşüne başvurmayı tercih etmiştir. Yasal ve etik sorumluluk açısından, %65,92 oranında işlemi gerçekleştiren doktorun sorumlu tutulması gerektiği düşünülmektedir (Tablo 2).

Yapay Zeka ile Desteklenen Karar Alanları

Yapay zeka destekli karar sistemlerinden tanı süreçlerinde yararlanabileceğini düşünenlerin oranı %80,6, tedavi süreçlerinde %68,91 ve hasta takibinde %84,08 olarak belirlenmiştir. Bununla birlikte, tedavi alanında kararsızlık oranı %19,65 ile diğer alanlara kıyasla daha yüksektir (Tablo 3).

Yapay Zeka ile Uygulama Alanları

Yapay zeka destek sistemlerinin yoğun bakımda en fazla desteklendiği alanlar epikriz yazımı (%73,13), kültür sonuçlarına göre antibiyoterapi kararı (%69,4), görüntüleme sonrası tanının konması (%79,85) ve hasta yakınlarına bilgi verilmesi (%69,9) olmuştur. Bununla birlikte, beslenme kararları (%46,02) ve sedasyon/analjezi düzeylerinin ayarlanması (%49,25) gibi alanlarda destek oranı daha düşüktür. Mekanik ventilatör ayarları (%57,71) ve ECMO kararları (%54,73) gibi kritik müdahaleler orta düzeyde desteklenmiştir. Deliryumun erken fark edilmesi (%62,44) ve elektrolit replasman kararları (%67,66) gibi klinik süreçlerde YZ'nin etkili olabileceği düşünülmektedir (Tablo 4).

Yapay Zeka ile İlgili Endişeler

Katılımcıların %96,27'si YZ sistemlerinde teknik sorunlar yaşanabileceğini, %89,55'i veri güvenliği konularında endişe duyduğunu ifade etmiştir. Ayrıca, hatalı tıbbi uygulama durumunda yasal sorumluluğun tartışmalı bir alan olduğu belirtilmiş ve %92,29 oranında bu konuda sorun yaşanabileceği vurgulanmıştır. Katılımcıların %81,34'ü YZ'nin bireysel klinik değerlendirmeye duyulan güveni azaltabileceğini düşünürken, %69,9'u bu sistemlerin komplikasyonları azaltabileceğine inanmaktadır (Tablo 5).

Tartışma

Yapay zekanın sağlık alanında kullanım potansiyeli üzerine artan ilgi, özellikle yoğun bakım ünitelerinde klinik karar süreçlerine destek sağlama konusundaki çalışmaları öne çıkarmaktadır. Oliver ve ark. çalışmasında hekimlerin büyük bir kısmı tıpta YZ'ye karşı olumlu (%42,9, 130/303) veya çok olumlu (%27,1, 82/303) bir tutum sergilemiş, bu da katılımcıların üçte ikisinden fazlasını oluşturmaktadır. Katılımcıların %18,2'si (55/303) bu konuda nötr bir duruş sergilerken, yalnızca %5,6'sı (17/303) olumsuz veya çok olumsuz bir görüş bildirmiştir.[6] Çalışmamızda benzer şekilde hekimlerin büyük bir kısmı YZ'nin faydalı olabileceğine inandıklarını ifade etmişlerdir. Bu durum, teknolojinin sağlık alanına entegrasyonunun genel olarak olumlu algılandığını, ancak bireysel çekincelerin tamamen ortadan kalkmadığını göstermektedir.

Tablo 2. Yapay zeka uygulamaları hakkında bilgi ve görüşler

	Toplam n=402 (%)	Asistan n=108 (%)	Uzman n=112 (%)	Yan dal uzmanı n=96 (%)	Doktor öğretim üyesi n=20 (%)	Doçent n=32 (%)	Profesör n=34 (%)
Yapay zekanın tıp alanında uygulamalarını duydunuz mu?							
Evet	362 (90,05)	88 (81,48)	98 (87,5)	92 (95,83)	20 (100,0)	32 (100,0)	32 (94,12)
Hayır	40 (9,95)	20 (18,52)	14 (12,5)	4 (4,17)	0 (0,0)	0 (0,0)	2 (5,88)
Yapay zekanın tıbbi uygulamalarda faydalı olabileceğini düşünüyor musunuz?							
Evet	368 (91,54)	95 (87,96)	104 (92,86)	89 (92,71)	20 (100,0)	28 (87,5)	32 (94,12)
Hayır	5 (1,24)	5 (4,63)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Kararsızım	29 (7,21)	8 (7,41)	8 (7,14)	7 (7,29)	0 (0,0)	4 (12,5)	2 (5,88)
Yapay zekanın yoğun bakımda yaptığınız işin yerine geçebileceğini düşünüyor musunuz?							
Evet	56 (13,93)	20 (18,52)	10 (8,93)	10 (10,42)	4 (20,0)	6 (18,75)	6 (17,65)
Hayır	275 (68,41)	64 (59,26)	82 (73,21)	70 (72,92)	14 (70,0)	24 (75,0)	21 (61,76)
Kararsızım	71 (17,66)	24 (22,22)	20 (17,86)	16 (16,67)	2 (10,0)	2 (6,25)	7 (20,59)
Yoğun bakımda hastanızın tedavisi sürecinde yapay zeka ile sizin kararınız farklı ise hangisini kabul edersiniz?							
Kendi Görüşüm	150 (37,31)	32 (29,63)	34 (30,36)	51 (53,12)	6 (30,0)	18 (56,25)	9 (26,47)
Yapay Zekanın görüşü	6 (1,49)	2 (1,85)	2 (1,79)	0 (0,0)	2 (10,0)	0 (0,0)	0 (0,0)
İkinci bir uzman görüşü	246 (61,19)	74 (68,52)	76 (67,86)	45 (46,88)	12 (60,0)	14 (43,75)	25 (73,53)
Yapay zeka karar destek sistemlerinin neden olabileceği hukuksal/etik sorumluluk kime ait olmalıdır?							
Yapay zeka kullanımına onay veren hasta/hasta yakını	57 (14,18)	23 (21,3)	15 (13,39)	9 (9,38)	4 (20,0)	0 (0,0)	6 (17,65)
Yapay zeka yazılımını geliştiren firma	80 (19,9)	16 (14,81)	27 (24,11)	19 (19,79)	6 (30,0)	2 (6,25)	10 (29,41)
İşlemi gerçekleştiren doktor	265 (65,92)	69 (63,89)	70 (62,5)	68 (70,83)	10 (50,0)	30 (93,75)	18 (52,94)

* n: Sayı, %: Yüzde

Tablo 3. Yoğun bakım ünitesinde takip edilen hastalar için kararlar alırken yapay zeka karar destek sistemlerinden hangi noktalarda faydalanabileceğini düşünürsünüz

	Toplam n=402 (%)	Asistan n=108 (%)	Uzman n=112 (%)	Yan dal uzmanı n=96 (%)	Doktor öğretim üyesi n=20 (%)	Doçent n=32 (%)	Profesör n=34 (%)
Tanı							
Kararsızım	58 (14,43)	25 (23,15)	17 (15,18)	6 (6,25)	2 (10,0)	8 (25,0)	0 (0,0)
Katılmıyorum	20 (4,98)	11 (10,19)	3 (2,68)	4 (4,17)	0 (0,0)	0 (0,0)	2 (5,88)
Katılıyorum	324 (80,6)	72 (66,67)	92 (82,14)	86 (89,58)	18 (90,0)	24 (75,0)	32 (94,12)
Tedavi							
Kararsızım	79 (19,65)	21 (19,44)	25 (22,32)	10 (10,42)	2 (10,0)	16 (50,0)	5 (14,71)
Katılmıyorum	46 (11,44)	9 (8,33)	20 (17,86)	10 (10,42)	3 (15,0)	0 (0,0)	4 (11,76)
Katılıyorum	277 (68,91)	78 (72,22)	67 (59,82)	76 (79,17)	15 (75,0)	16 (50,0)	25 (73,53)
Takip							
Kararsızım	37 (9,2)	14 (12,96)	4 (3,57)	10 (10,42)	0 (0,0)	9 (28,12)	0 (0,0)
Katılmıyorum	27 (6,72)	5 (4,63)	18 (16,07)	2 (2,08)	0 (0,0)	2 (6,25)	0 (0,0)
Katılıyorum	338 (84,08)	89 (82,41)	90 (80,36)	84 (87,5)	20 (100,0)	21 (65,62)	34 (100,0)

* n: Sayı, %: Yüzde

Tablo 4. Yoğun bakımda yapay zeka karar destek sistemleri tarafından

		Toplam n=402 (%)	Asistan n=108 (%)	Uzman n=112 (%)	Yan dal uzmanı n=96 (%)	Doktor öğretim üyesi n=20 (%)	Doçent n=32 (%)	Profesör n=34 (%)
Hastanın epikrizinin yazılması	*Katılıyorum*	294 (73,13)	82 (75,93)	85 (75,89)	62 (64,58)	16 (80,0)	24 (75,0)	25 (73,53)
	Katılmıyorum	77 (19,15)	20 (18,52)	20 (17,86)	21 (21,88)	4 (20,0)	6 (18,75)	6 (17,65)
	Kararsızım	31 (7,71)	6 (5,56)	7 (6,25)	13 (13,54)	0 (0,0)	2 (6,25)	3 (8,82)
Hasta yakınlarına bilgi verilmesi	*Katılıyorum*	281 (69,9)	23 (21,3)	20 (17,86)	27 (28,12)	7 (35,0)	13 (40,62)	10 (29,41)
	Katılmıyorum	100 (24,88)	79 (73,15)	87 (77,68)	62 (64,58)	13 (65,0)	19 (59,38)	21 (61,76)
	Kararsızım	21 (5,22)	6 (5,56)	5 (4,46)	7 (7,29)	0 (0,0)	0 (0,0)	3 (8,82)
Hastanın beslenme kararının verilmesi	*Katılıyorum*	185 (46,02)	49 (45,37)	49 (43,75)	38 (39,58)	11 (55,0)	19 (59,38)	19 (55,88)
	Katılmıyorum	171 (42,54)	53 (49,07)	50 (44,64)	39 (40,62)	7 (35,0)	11 (34,38)	11 (32,35)
	Kararsızım	46 (11,44)	6 (5,56)	13 (11,61)	19 (19,79)	2 (10,0)	2 (6,25)	4 (11,76)
Hastanın kültür sonuçlarına göre antibiyoterapi kararı	*Katılıyorum*	279 (69,4)	78 (72,22)	83 (74,11)	60 (62,5)	11 (55,0)	18 (56,25)	29 (85,29)
	Katılmıyorum	97 (24,13)	26 (24,07)	25 (22,32)	25 (26,04)	7 (35,0)	12 (37,5)	2 (5,88)
	Kararsızım	26 (6,47)	4 (3,7)	4 (3,57)	11 (11,46)	2 (10,0)	2 (6,25)	3 (8,82)
Hastanın mekanik ventilatöre bağlanma/ weaning kararı	*Katılıyorum*	215 (53,48)	37 (34,26)	31 (27,68)	23 (23,96)	9 (45,0)	8 (25,0)	16 (47,06)
	Katılmıyorum	124 (30,85)	57 (52,78)	65 (58,04)	55 (57,29)	9 (45,0)	20 (62,5)	9 (26,47)
	Kararsızım	63 (15,67)	14 (12,96)	16 (14,29)	18 (18,75)	2 (10,0)	4 (12,5)	9 (26,47)
Hastanın ECMO'ya bağlanma/ ayrılma kararı	*Katılıyorum*	220 (54,73)	36 (33,33)	31 (27,68)	31 (32,29)	9 (45,0)	8 (25,0)	19 (55,88)
	Katılmıyorum	134 (33,33)	62 (57,41)	69 (61,61)	45 (46,88)	11 (55,0)	20 (62,5)	13 (38,24)
	Kararsızım	48 (11,94)	10 (9,26)	12 (10,71)	20 (20,83)	0 (0,0)	4 (12,5)	2 (5,88)
Hastaya SRRT başlanma kararı	*Katılıyorum*	193 (48,01)	38 (35,19)	36 (32,14)	50 (52,08)	11 (55,0)	12 (37,5)	23 (67,65)
	Katılmıyorum	170 (42,29)	56 (51,85)	67 (59,82)	36 (37,5)	9 (45,0)	16 (50,0)	9 (26,47)
	Kararsızım	39 (9,7)	14 (12,96)	9 (8,04)	10 (10,42)	0 (0,0)	4 (12,5)	2 (5,88)
Beyin ölümü tanısının konması	*Katılıyorum*	225 (55,97)	57 (52,78)	38 (33,93)	17 (17,71)	9 (45,0)	9 (28,12)	18 (52,94)
	Katılmıyorum	148 (36,82)	47 (43,52)	70 (62,5)	65 (67,71)	11 (55,0)	19 (59,38)	13 (38,24)
	Kararsızım	29 (7,21)	4 (3,7)	4 (3,57)	14 (14,58)	0 (0,0)	4 (12,5)	3 (8,82)
Yoğun bakım yatış kararının verilmesi	*Katılıyorum*	200 (49,75)	41 (37,96)	38 (33,93)	29 (30,21)	13 (65,0)	17 (53,12)	19 (55,88)
	Katılmıyorum	157 (39,05)	55 (50,93)	61 (54,46)	51 (53,12)	7 (35,0)	11 (34,38)	15 (44,12)
	Kararsızım	45 (11,19)	12 (11,11)	13 (11,61)	16 (16,67)	0 (0,0)	4 (12,5)	0 (0,0)
Yoğun bakım taburculuk kararının verilmesi	*Katılıyorum*	245 (60,95)	29 (26,85)	22 (19,64)	19 (19,79)	11 (55,0)	6 (18,75)	18 (52,94)
	Katılmıyorum	105 (26,12)	69 (63,89)	77 (68,75)	57 (59,38)	9 (45,0)	22 (68,75)	11 (32,35)
	Kararsızım	52 (12,94)	10 (9,26)	13 (11,61)	20 (20,83)	0 (0,0)	4 (12,5)	5 (14,71)
Yapılan görüntülemeler sonrası olası tanının konması	*Katılıyorum*	321 (79,85)	84 (77,78)	86 (76,79)	81 (84,38)	16 (80,0)	24 (75,0)	30 (88,24)
	Katılmıyorum	48 (11,94)	18 (16,67)	16 (14,29)	6 (6,25)	2 (10,0)	4 (12,5)	2 (5,88)
	Kararsızım	33 (8,21)	6 (5,56)	10 (8,93)	9 (9,38)	2 (10,0)	4 (12,5)	2 (5,88)
Hastaya sepsis tanısının konması ve tedaviye başlanması	*Katılıyorum*	222 (55,22)	54 (50,0)	67 (59,82)	50 (52,08)	11 (55,0)	12 (37,5)	28 (82,35)
	Katılmıyorum	139 (34,58)	42 (38,89)	37 (33,04)	33 (34,38)	7 (35,0)	16 (50,0)	4 (11,76)
	Kararsızım	41 (10,2)	12 (11,11)	8 (7,14)	13 (13,54)	2 (10,0)	4 (12,5)	2 (5,88)
Mekanik ventilatör ayarlarının yapılması	*Katılıyorum*	232 (57,71)	68 (62,96)	64 (57,14)	50 (52,08)	15 (75,0)	12 (37,5)	23 (67,65)
	Katılmıyorum	135 (33,58)	30 (27,78)	39 (34,82)	34 (35,42)	5 (25,0)	18 (56,25)	9 (26,47)
	Kararsızım	35 (8,71)	10 (9,26)	9 (8,04)	12 (12,5)	0 (0,0)	2 (6,25)	2 (5,88)
Hastaların günlük elektrolit replasman kararları	*Katılıyorum*	272 (67,66)	72 (66,67)	71 (63,39)	62 (64,58)	16 (80,0)	23 (71,88)	28 (82,35)
	Katılmıyorum	96 (23,88)	28 (25,93)	30 (26,79)	23 (23,96)	4 (20,0)	7 (21,88)	4 (11,76)
	Kararsızım	34 (8,46)	8 (7,41)	11 (9,82)	11 (11,46)	0 (0,0)	2 (6,25)	2 (5,88)
Sedasyon/analjezi düzeylerinin ayarlanması	*Katılıyorum*	198 (49,25)	58 (53,7)	47 (41,96)	33 (34,38)	11 (55,0)	17 (53,12)	32 (94,12)
	Katılmıyorum	160 (39,8)	38 (35,19)	51 (45,54)	49 (51,04)	9 (45,0)	11 (34,38)	2 (5,88)
	Kararsızım	44 (10,95)	12 (11,11)	14 (12,5)	14 (14,58)	0 (0,0)	4 (12,5)	0 (0,0)
Hastada deliryum gelişmesini önceden fark etmesi	*Katılıyorum*	251 (62,44)	63 (58,33)	72 (64,29)	54 (56,25)	14 (70,0)	20 (62,5)	28 (82,35)
	Katılmıyorum	97 (24,13)	28 (25,93)	28 (25,0)	25 (26,04)	4 (20,0)	8 (25,0)	4 (11,76)
	Kararsızım	54 (13,43)	17 (15,74)	12 (10,71)	17 (17,71)	2 (10,0)	4 (12,5)	2 (5,88)

* n: Sayı, %: Yüzde, ECMO: Ekstrakorporal membran oksijenizasyonu, SRRT: Sürekli renal replasman tedavisi

Tablo 5. Yoğun bakımda yapay zeka karar destek sitemleri ile ilgili aşağıdaki ifadeler konusunda düşünceniz

		Toplam n=402 (%)	Asistan n=108 (%)	Uzman n=112 (%)	Yan dal uzmanı n=96 (%)	Doktor öğretim üyesi n=20 (%)	Doçent n=32 (%)	Profesör n=34 (%)
Yapay zeka tabanlı sistemlerle başa çıkmada zorluklar oluşabilir	*Katılıyorum*	291 (72,39)	81 (75,0)	79 (70,54)	74 (77,08)	15 (75,0)	24 (75,0)	18 (52,94)
	Katılmıyorum	75 (18,66)	16 (14,81)	24 (21,43)	14 (14,58)	2 (10,0)	6 (18,75)	13 (38,24)
	Kararsızım	36 (8,96)	11 (10,19)	9 (8,04)	8 (8,33)	3 (15,0)	2 (6,25)	3 (8,82)
Sistemlerin kullanımında teknik sorunlar yaşanabilir	*Katılıyorum*	387 (96,27)	104 (96,3)	107 (95,54)	92 (95,83)	18 (90,0)	32 (100,0)	34 (100,0)
	Katılmıyorum	6 (1,49)	2 (1,85)	2 (1,79)	0 (0,0)	2 (10,0)	0 (0,0)	0 (0,0)
	Kararsızım	9 (2,24)	2 (1,85)	3 (2,68)	4 (4,17)	0 (0,0)	0 (0,0)	0 (0,0)
Veri güvenliği konusunda sorunlar oluşabilir	*Katılıyorum*	360 (89,55)	94 (87,04)	101 (90,18)	83 (86,46)	18 (90,0)	32 (100,0)	32 (94,12)
	Katılmıyorum	35 (8,71)	12 (11,11)	8 (7,14)	11 (11,46)	2 (10,0)	0 (0,0)	2 (5,88)
	Kararsızım	7 (1,74)	2 (1,85)	3 (2,68)	2 (2,08)	0 (0,0)	0 (0,0)	0 (0,0)
Hatalı tıbbi uygulama durumunda yasal sorumluluk sorunu oluşabilir	*Katılıyorum*	371 (92,29)	98 (90,74)	101 (90,18)	96 (100,0)	16 (80,0)	30 (93,75)	30 (88,24)
	Katılmıyorum	23 (5,72)	4 (3,7)	9 (8,04)	0 (0,0)	4 (20,0)	2 (6,25)	4 (11,76)
	Kararsızım	8 (1,99)	6 (5,56)	2 (1,79)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
Bireysel klinik değerlendirmeye duyulan güven kaybına neden olabilir	*Katılıyorum*	327 (81,34)	96 (88,89)	81 (72,32)	75 (78,12)	16 (80,0)	28 (87,5)	31 (91,18)
	Katılmıyorum	54 (13,43)	8 (7,41)	20 (17,86)	15 (15,62)	4 (20,0)	4 (12,5)	3 (8,82)
	Kararsızım	21 (5,22)	4 (3,7)	11 (9,82)	6 (6,25)	0 (0,0)	0 (0,0)	0 (0,0)
Yapay zekanın kullanılması ile komplikasyonların oranı azalabilir	*Katılıyorum*	281 (69,9)	72 (66,67)	86 (76,79)	65 (67,71)	13 (65,0)	22 (68,75)	23 (67,65)
	Katılmıyorum	66 (16,42)	16 (14,81)	15 (13,39)	11 (11,46)	7 (35,0)	8 (25,0)	9 (26,47)
	Kararsızım	55 (13,68)	20 (18,52)	11 (9,82)	20 (20,83)	0 (0,0)	2 (6,25)	2 (5,88)

* n: Sayı, %: Yüzde

Bir başka çalışmada katılımcıların büyük bir kısmı YZ kavramına aşinaydı (%97, 62/64 kişi) ve çoğunluğu YZ'nin hekimlik görevlerinde kendilerine destek olabileceğine inanıyordu (%86, 55/64 kişi). Katılımcıların çoğu YZ'nin gelecekte işlerini devralacağına inanmadığını belirtti (%72, 46/64 kişi). Bununla birlikte, YZ'yi işlerini destekleyecek kadar anlayıp anlamadıkları konusunda kararsız kaldılar (%41, 26/64 kişi katıldı veya tamamen katıldı; %19, 12/64 kişi katılmadı veya tamamen katılmadı). Yine de katılımcıların %86'sı (55/64 kişi), YZ tabanlı karar destek sistemlerinin (YZ-KDS) yoğun bakım ünitelerinde yarar sağlayacağına inandığını ifade etti.[7] Çalışmamızda da hekimlerin YZ'nin tamamlayıcı bir rol oynayabileceğini düşündüğü tespit edilmiştir. Özellikle YZ'nin karar destek araçları olarak etkili olduğu, ancak klinik ve yasal sorumluluğun hekimlerde kalması gerektiği görüşü hakimdi.

Yapılan bir çalışma YZ tabanlı karar destek sistemlerinin uygulanma öncesi sürecini üç ana başlık altında değerlendirmiştir: hekimlerin yoğun bakım ünitesinden taburculuk kararlarına ilişkin mevcut karar verme davranışları, YZ'ye dair görüşleri ve klinik uygulamada YZ-KDS araçlarının kullanımı ile uygulanmasına yönelik tercihleri. Bulgular, neredeyse tüm yoğun bakım hekimlerinin YZ'ye aşina olduğunu ve bu konuda olumlu beklentiler taşıdığını göstermiştir; 64 hekimden 55'i (%86), YZ'nin hekimlik görevlerinde kendilerine destek olabileceğine inandığını ifade etmiştir. Taburculuk kararlarının her zaman karmaşık görülmemesine rağmen, 64 hekimden 59'u (%92) taburculuk kararı destek aracının değerli olabileceğini düşünmüştür. YZ-KDS aracının geliştirildiği merkezdeki hekimler, YZ konusunda daha fazla bilgi sahibi olduklarını ve genel olarak YZ'nin destekleyici rolüne daha fazla güvendiklerini belirtmişlerdir. Ayrıca, bu hekimler, taburculuk kararları için geliştirilen bir YZ-KDS aracının faydalı olacağına dair daha güçlü bir inanç sergilemişlerdir. Buna karşılık geliştirme merkezi dışındaki hekimler, aracın tahminlerinde etkili olan faktörleri anlamaya daha fazla önem vermiştir.[7] Diğer çalışmalarda da hekimler arasında YZ-KDS aracının kullanımına yönelik olumlu bir tutum olduğu bulunmuştur.[8–11] Çalışmamızdaki bulgular da YZ'nin özellikle karar verme süreçlerinde destekleyici bir araç olarak algılandığını göstermektedir. Bu hem klinik etkinliği artırabilecek hem de karar süreçlerinde hız kazandırabilecek bir potansiyel taşımaktadır.

Elektronik sağlık kaydı verileri, farklı hasta lokasyonları ve başlangıç serum kreatinin düzeylerini esas alarak, serum kreatininindeki değişimlerden önce yaklaşan akut böbrek hasarını yüksek doğrulukla tahmin edebilmektedir. Bu modelin gerçek zamanlı kullanımıyla, akut böbrek hasarı riski yüksek olan hastalara erken müdahale imkanı sağlanabilir.[12] Bu bulgu çalışmamızdaki klinik karar destek sistemlerinin potansiyel faydalarıyla örtüşmektedir. Katılımcılar özellikle böbrek yetmezliği gibi kritik durumlarda (SRRT başlanma kararı) YZ'nin erken uyarı mekanizmalarını destekleyeceğini belirtmişlerdir.

Awad ve ark. YBÜ mortalitesini öngörebilmek amacıyla MIMIC-II veri tabanındaki 11.722 ilk yatıştan oluşan veri kümesinde karar ağaçları, random forest ve naïve Bayes gibi çeşitli MÖ yöntemlerini kullanmıştır. Bu çalışmada demografik, fizyolojik ve laboratuvar bulgularından elde edilen özellikler temel alınmıştır. Ortaya konan modeller, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi–II

(APACHE-II), ardışık organ yetmezliği değerlendirmesi (SOFA) ve Basitleştirilmiş Akut Fizyoloji Skoru (SAPS) gibi mevcut skorlama sistemlerinden daha yüksek bir başarı göstermiş; aynı araştırma grubunun yürüttüğü zaman serisi analizini içeren sonraki çalışmada da benzer sonuçlar elde edilmiştir.[13,14] Öte yandan İsveç'te ilk kez YBÜ'ye kabul edilen 200.000'den fazla hastada yapay sinir ağlarının uygulandığı bir başka sistem, SAPS-3 ile kıyaslandığında ölüm riskini tahmin etmede daha üstün performans sergilemiştir.[15]

Yapılan bir çalışmada YZ'nin hekimlerin işine etkisi ele alınmıştır. Katılımcılar sağlık hizmetlerinde YZ kullanımının hekimlerin bilgisayar sistemlerine bağımlılığını artıracağını düşünmektedir (%88,1, 267/303). Bunun yanı sıra YZ tabanlı karar destek sistemlerinin hekimlerin çalışma biçimini değiştireceği görüşü de yaygındır (%87,1, 264/303). Çoğunluk YZ'nin hekimlerin iş gereksinimlerinde değişikliğe neden olacağını öngörmüştür (%83,2, 252/303). Öte yandan "*YZ kullanımı, doktorların bir hastayı doğru şekilde değerlendirmeyi öğrenmelerini engeller*" ifadesi için verilen yanıtlar neredeyse eşit dağılmıştır (katılıyorum: %48,2, 146/303; katılmıyorum: %47,5, 144/303).[6] Çalışmamızdaki sonuçlar da hekimlerin bu teknolojilere temkinli yaklaştığını ve kendi klinik becerilerinin yerini almasını istemediklerini göstermektedir. Özellikle YZ'nin işlevsel bir yardımcı rol üstlenmesi gerektiği ve hekimlerin nihai karar verici olarak konumlarını koruma isteği vurgulanmıştır.

Görüntüleme işlemleri için YZ başlığındaki kategoride, hekimlerin büyük bir kısmı, önerilen tüm uygulamaların gelecekte hasta bakımını önemli ölçüde iyileştirebileceği görüşünde birleşmiştir. Özellikle YZ'nin röntgen, bilgisayarlı tomografi, manyetik rezonans tomografi ve ultrasonografi analizini geliştirme potansiyeline yönelik yüksek bir fikir birliği vardır (%86,8, 263/303). Bununla birlikte, endoskopik görüntü ve videoların analizinde YZ'nin gelecekteki potansiyeline yönelik fikir birliği, diğer uygulamalara kıyasla daha düşük bir oranla sınırlı kalmıştır (%64,0, 194/303).[6] Bu bulgu çalışmamızdaki hekimlerin tanı süreçlerinde YZ kullanımını destekleyen görüşleriyle paralellik göstermektedir. Özellikle YZ'nin görüntüleme analizindeki doğruluğu artırma potansiyeli klinik pratikte değerli bir araç olarak görülmektedir. Ancak, daha karmaşık analizlerdeki çekinceler, bu teknolojilerin hala geliştirilmesi gerektiğine işaret etmektedir.

YZ'nin tıbbi tedavi üzerindeki etkisi ile alakalı soruda katılımcıların büyük çoğunluğu ''*Tıbbın geleceği, insan zekası ve YZ'nin bir birleşimiyle şekillenecek*'' ifadesine katıldığını belirtmiştir (%90,1, 273/303). Ayrıca, çoğu hekim YZ'nin tıbbi hataları azaltacağını düşündüğünü ifade etmiştir (%67,3, 204/303). Bununla birlikte, katılımcıların çoğu YZ'nin kendilerine hastalarına daha fazla zaman ayırma olanağı sunacağını düşünmediklerini (%67,0, 203/303) veya hasta tedavisinde daha az rol üstleneceklerini beklemediklerini (%72,3, 219/303) ifade etmiştir.[6] Benzer şekilde çalışmamızda hekimlerin önemli bir kısmı, YZ'nin iş yüklerini tamamen hafifletmeyeceğini ifade etmişlerdir. Bu durum, YZ'nin klinik işleyişte tamamlayıcı bir araç olarak algılandığını ve hekimlerin bireysel sorumluluklarının önemini koruduğunu göstermektedir.

Yapılan bir çalışmada yoğun bakımda MÖ, enteral beslenme intoleransını, diyareyi ve yeniden beslenme hipofosfatemisini öngörmeyi mümkün kılmıştır. Ayrıca, bu yöntemler kanser hastalarının tedavi sonuçlarını iyileştirme potansiyeline sahiptir.[16] Çalışmamızda, beslenme kararlarının YZ ile verilmesine ilişkin soruya doktorların %46,02'si ''*katılıyorum*'' şeklinde yanıt vermiştir.

Yoğun bakım ünitesindeki hastalar, giyilebilir sensörler, ışık ve ses sensörleri ile kameralar kullanılarak detaylı ve otomatik olarak izlenmiştir. Yapılan analizlerde, deliryum yaşayan hastalar ile deliryum yaşamayan hastalar arasında yüz ifadeleri, hareketler ve çevresel faktörler açısından önemli farklılıklar olduğu tespit edilmiştir. Bu yöntem, kritik bakımda deliryumu erken öngörme ve yönetme konusunda faydalı bir tutum sunmaktadır.[17] Bu yöntem çalışmamızdaki erken tanı araçlarının önemini destekler niteliktedir.

Yoğun bakım ünitesinde YZ kullanım alanları; erken uyarı sistemleri, prognoz araçları, tedavi öneri modelleri, hastalık fenotiplemesi ve kaynak yönetimi olarak özetlenebilir. 2021'de yapılan bir sistematik derleme, çalışmaların en çok komplikasyon (%22,2) ve mortalite (%20,6) öngörmeye odaklandığını, yalnızca 18'inin prospektif tasarlandığını göstermiştir. 2020 itibarıyla, YBÜ'deki MÖ modellerinin %93'ü hal prototipleme-aşamasında (aşama 3-4) olup, yalnızca %1'i gerçek zamanlı model testine (aşama 6) ulaşabilmiştir.[18,19]

Yoğun bakım ve anestezi alanında YZ uygulamaları ile alakalı soruda hekimlerin büyük çoğunluğu, tüm uygulamaların hasta bakımını iyileştirme potansiyeline sahip olduğu konusunda hemfikirdir. Ancak, otomatik anestezi yönetiminin potansiyeline yönelik kabul oranı (%56,8, 172/303), YZ'nin hastanın durumunun kötüleşmesini erken tespit eden alarm sistemleri için kullanımına yönelik kabul oranından (%88,1, 267/303) belirgin şekilde daha düşük bulunmuştur.[6] Bu durum, çalışmamızda da gözlemlenmiş olup, hekimlerin belirli kritik müdahalelerde YZ'ye temkinli yaklaştığını göstermektedir. Özellikle hasta güvenliği ile doğrudan ilişkili süreçlerde, YZ'nin performansı hakkında daha fazla doğrulama ihtiyacı duyulduğu tespit edilmiştir.

Başka bir çalışmada hekimlerin büyük bir kısmının tıpta YZ'ye karşı olumlu veya çok olumlu bir tutuma sahip olduğunu göstermiştir. Hekimler YZ'nin klinik uygulamalarda çeşitli alanlarda kullanılacağını ve hasta bakımını büyük ölçüde iyileştireceğini öngörmektedir. Çoğunluk YZ'nin hekimlerin çalışma biçimini değiştireceği konusunda hemfikirdi. Ayrıca, katılımcılar tıbbi uygulamalara yönelik algoritmaların geliştirilmesinde anonimleştirilmiş hasta verilerinin araştırma amaçlı kullanımını olumlu karşılamıştır. Ancak, günümüzde Almanya'daki hastaneler ve sağlık hizmetlerinde YZ'nin klinik kullanımına nadiren rastlanmaktadır.[6] Bu sonuç çalışmamızdaki hekimlerin YZ'nin faydalarını genel olarak desteklediğini, ancak pratikte entegrasyon konusunda çekinceleri olduğunu ortaya koymaktadır. Özellikle

altyapı eksiklikleri ve kullanım kolaylığı konularındaki endişeler dikkat çekicidir. Bu nedenle insan ve YZ'nin hibrit bir çözüm oluşturması, simbiyotik bir ilişki sağlayabilir. Hekimler YZ'nin günlük çalışmalarını önemli ölçüde etkileyeceğini ve mesleklerinde değişikliklere yol açacağını beklemektedir. Bu durum, hekimlerin bilgisayar sistemlerine olan bağımlılığını ve yeni iş gereksinimlerini de kapsamaktadır. Yu ve ark. YZ'nin insan hatalarını azaltarak ve rutin klinik işlerden kaynaklanan yorgunluğu hafifleterek bakım kalitesini artırabileceğini ifade etmiştir. Ancak, tıbbi kılavuzların hassas hastalar için daha sık muayene önerme olasılığı göz önüne alındığında, YZ hekimlerin iş yükünü azaltmayabilir.[6,20] Bu görüşler çalışmamızda YZ'nin günlük pratikte yardımcı bir araç olarak rol oynayabileceği ancak insan faktörünün vazgeçilmez olduğunu vurgulayan katılımcıların görüşleri ile örtüşmektedir.

Hekimler tıbbın geleceğini insan ve YZ'nin bir kombinasyonunun şekillendireceğini öngörmekte ve YZ uygulamalarının hasta bakımını önemli ölçüde iyileştireceğini düşünmektedir. En yüksek potansiyel, sürekli veri toplayan sensör tabanlı uygulamalar (EKG, EEG, yoğun bakım izleme), tanısal görüntüleme ve ilaç etkileşimlerinin belirlenmesi alanlarında görülmektedir. Gelecekte YZ uygulamalarının sağlık hizmetlerinde yaygın şekilde kullanılmaya başlanacağı öngörülmektedir.[6] Bu durum, çalışmamızdaki bulgularla da uyumlu olup, katılımcıların büyük bir kısmı özellikle yoğun bakım gibi veri yoğun alanlarda YZ'nin destekleyici rolünü olumlu değerlendirmiştir.

Yoğun bakımda YZ'nin kullanımı yeni bir alan olduğu için karşılaşılacak etik sorunlar henüz tam olarak öngörülememektedir. Ancak, temel etik sorunlar arasında veri gizliliği ve paylaşımı ile klinik güvenlik yer almaktadır. Yapay zeka modellerinde veri sızıntısı riski, özellikle veri işleme ve doğrulama süreçlerinde ortaya çıkabilir. Federated learning gibi yeni yöntemler bu riski azaltabilir. Klinik uygulamalarda YZ çözümleri genellikle insan denetimini gerektiren otomasyon seviyesinde olup, güvenlik ve karar verme sorumluluğu hala klinisyenlere aittir. Ayrıca, hasta otonomisi ve bilgilendirilmiş onam süreçleri önem taşımakta, YZ önerilerinin her zaman hasta tercihlerine uyumlu olmayabileceği belirtilmektedir. Bu etik sorunların fark edilmesi ve çözümler geliştirilmesi, daha güvenli ve etik YZ uygulamalarını mümkün kılabilir.[21] Bu sorunlar çalışmamızdaki klinik verilerin korunmasına yönelik endişeler ve etik kaygılarla uyumludur.

Yapay zekanın yoğun bakım alanında giderek artan kullanımının en önemli gerekliliği, önyargı kaynaklarını belirlemek ve bunları en aza indirmektir. Yapay zeka yaşam döngüsünün tüm aşamalarında görülebilen ve önlenebilir nitelikte olan önyargı, klinik uygulamada göz ardı edildiğinde hastaların adaletsiz ve eşitsiz muamele görmesine yol açabilir. Bu nedenle önyargı kaynaklarını tanıyıp uyum sağlayabilen, çeşitli disiplinlerden uzmanları bir araya getiren ekipler, YZ'de önyargıyı azaltmak konusunda en etkili çözümleri sunma potansiyeline sahiptir.[22]

Bu çalışmanın bazı önemli kısıtlılıkları bulunmaktadır. Çalışma yalnızca yoğun bakım ünitesinde görev yapan doktorlarla sınırlı olduğu için elde edilen sonuçlar genel sağlık profesyonellerine genellenemeyebilir. Verilerin katılımcıların öznel beyanlarına dayanması, yanıtların objektifliğini etkileyebilecek bir unsur olarak değerlendirilmektedir. Ayrıca, anketin çevrimiçi olarak uygulanması, teknolojik erişim kısıtlamaları veya dijital platformlara aşinalık düzeyindeki farklılıklar nedeniyle katılım oranını sınırlamış olabilir. Bu kısıtlılıklar çalışmanın sonuçlarının daha geniş bir bağlamda yorumlanırken dikkate alınmasını gerektirir.

Çalışmamız yoğun bakım ünitelerinde görev yapan doktorların YZ teknolojileri konusundaki bilgi düzeylerini, bu teknolojilere yönelik tutumlarını ve görüşlerini değerlendirmek için gerçekleştirilmiştir. Elde edilen bulgular YZ'nin sağlık hizmetlerinde kullanımına yönelik genel bir olumlu tutum olduğunu, ancak uygulama sırasında yasal ve etik sorumluluklar, veri güvenliği ve teknik sorunlar gibi endişelerin de önemli bir yer tuttuğunu göstermektedir. Doktorların YZ uygulamalarını etkin bir şekilde kullanabilmesi için bu teknolojilere dair bilgi düzeylerinin artırılması ve bu endişelere yönelik çözümler geliştirilmesi gerektiği vurgulanmaktadır. Çalışma YZ'nin yoğun bakım süreçlerinde verimliliği artırma ve hasta bakımını iyileştirme potansiyelini ortaya koyarken, sağlık hizmetlerinde bu teknolojilerin entegrasyonunun desteklenmesinin önemini bir kez daha gözler önüne sermiştir.

Etik Standartlara Uygunluk

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Yazar Katkısı

KU: Konsept; KU: Tasarım; KU: Veri Toplama ve İşleme; KU: Analiz ve Yorumlama; KU: Literatür Taraması; KU: Yazım: Gözden Geçirme ve Düzenleme; Yazar son metni okuyup onaylamıştır.

Kaynaklar

1. Tobin JM, Lusczek E, Bakker J. Artificial intelligence and machine learning in critical care research. J Crit Care. 2024;82:154791. doi:10.1016/j.jcrc.2024.154791
2. Uluç K. Yoğun Bakımda Yapay Zekanın Kullanımı. Ayvat, Pınar (ed.). Anestezide İnovatif Teknolojiler. *Akademisyen Kitabevi*; 2022:93-104.

3. Reddy S, Fox J, Purohit MP. Artificial intelligence-enabled healthcare delivery. *J R Soc Med.* 2019;112(1):22-28. doi:10.1177/0141076818815510
4. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data.* 2018;5:180178. doi:10.1038/sdata.2018.178.
5. Tang R, Zhang S, Ding C, Zhu M, Gao Y. Artificial Intelligence in Intensive Care Medicine: Bibliometric Analysis. *J Med Internet Res.* 2022;24(11):e42185. doi: 10.2196/42185
6. Maassen O, Fritsch S, Palm J, et al. Future medical artificial intelligence application requirements and expectations of physicians in german university hospitals: Web-based survey. *J Med Internet Res.* 2021; 23(3):e26646. doi:10.2196/26646
7. van der Meijden SL, de Hond AAH, Thoral PJ, et al. Intensive Care Unit Physicians' Perspectives on Artificial Intelligence–Based Clinical Decision Support Tools: Preimplementation Survey Study. *JMIR Hum Factors.* 2023;10:e39114. doi:10.2196/39114.
8. Wadhwa V, Alagappan M, Gonzalez A, et al. Physician sentiment toward artificial intelligence (AI) in colonoscopic practice: a survey of US gastroenterologists. *Endosc Int Open.* 2020;8(10):E1379-E1384. doi:10.1055/a-1223-1926
9. Sarwar S, Dent A, Faust K, et al. Physician perspectives on integration of artificial intelligence into diagnostic pathology. *NPJ Digit Med.* 2019;2:28. doi:10.1038/s41746-019-0106-0
10. Oh S, Kim JH, Choi SW, Lee HJ, Hong J, Kwon SH. Physician confidence in artificial intelligence: An online mobile survey. *J Med Internet Res.* 2019;21(3):e12422. doi:10.2196/12422
11. Scheetz J, Rothschild P, McGuinness M, et al. A survey of clinicians on the use of artificial intelligence in ophthalmology, dermatology, radiology and radiation oncology. *Sci Rep.* 2021;11(1):5193. doi:10.1038/s41598-021-84698-5
12. Koyner JL, Carey KA, Edelson DP, Churpek MM. The development of a machine learning inpatient acute kidney injury prediction model. *Crit Care Med.* 2018;46(7):1070-1077. doi:10.1097/CCM.0000000000003123
13. Awad A, Bader-El-Den M, McNicholas J, Briggs J, El-Sonbaty Y. Predicting hospital mortality for intensive care unit patients: Time-series analysis. *Health Informatics J.* 2020;26(2):1043-1059. doi:10.1177/1460458219850323.
14. Awad A, Bader-El-Den M, McNicholas J, Briggs J. Early hospital mortality prediction of intensive care unit patients using an ensemble learning approach. *Int J Med Inform.* 2017;108:185-195. doi:10.1016/j.ijmedinf.2017.10.002
15. Holmgren G, Andersson P, Jakobsson A, Frigyesi A. Artificial neural networks improve and simplify intensive care mortality prognostication: A national cohort study of 217,289 first-time intensive care unit admissions. *J Intensive Care.* 2019;7:44. doi:10.1186/s40560-019-0393-1
16. Singer P, Robinson E, Raphaeli O. The future of artificial intelligence in clinical nutrition. *Curr Opin Clin Nutr Metab Care.* 2024;27(2):200-206.
doi:10.1097/MCO.0000000000000977
17. Davoudi A, Malhotra KR, Shickel B, et al. Intelligent ICU for Autonomous Patient Monitoring Using Pervasive Sensing and Deep Learning. *Sci Rep.* 2019;9(1):8020. doi:10.1038/s41598-019-44004-w
18. Fleuren LM, Thoral P, Shillan D, Ercole A, Elbers PWG. Right Data Right Now Collaborators. Machine learning in intensive care medicine: ready for take-off? *Intensive Care Med.* 2020;46(7):1486-1488. doi:10.1007/s00134-020-06045-y
19. van de Sande D, van Genderen ME, Huiskens J, Gommers D, van Bommel J. Moving from bytes to bedside: a systematic review on the use of artificial intelligence in the intensive care unit. *Intensive Care Med.* 2021;47(7):750-760. doi:10.1007/s00134-021-06446-7
20. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. *Nat Biomed Eng.* 2018;2(10):719-731. doi: 10.1038/s41551-018-0305-z
21. Yoon JH, Pinsky MR, Clermont G. Artificial Intelligence in Critical Care Medicine. *Crit Care.* 2022;26(1):75. doi: 10.1186/s13054-022-03915-3
22. Ranard BL, Park S, Jia Y, et al. Minimizing bias when using artificial intelligence in critical care medicine. *J Crit Care.* 2024;82:154796. doi:10.1016/j.jcrc.2024.154796

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Olgu Sunumu | Case Report

NADİR BİR KARIN AĞRISI NEDENİ: MİDENİN GLOMUS TÜMÖRÜ

A RARE CAUSE OF ABDOMİNAL PAİN: GASTRİC GLOMUS TUMOR

Mehmet Fatih Özsaray[1*], Turgay Şimşek [1] Nuh Zafer Cantürk[1]

[1]Kocaeli Üniversitesi, Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Kocaeli, Türkiye.

ÖZ

Glomus tümörleri genellikle ekstremitelerde yer alan, iyi huylu yumuşak doku tümörleridir; ancak gastrointestinal sistem (GİS), ürogenital ve solunum sistemi gibi vücudun diğer bölgelerinde de nadiren görülebilir. GİS'teki glomus tümörlerinin çoğunluğu mide antrumunda bulunur. Bu tümörler genellikle küçük çaplıdır (<4 cm), ancak bazen daha büyük boyutlara ulaşabilirler. Bu yazıda mide karın ağrısı şikayeti ile gelen ve tetkikler sonucunda mide glomus tümörü tanısı alan bir olgu üzerinde durulacaktır. Bu yazıda, iki aydır aralıklı olarak karın ağrısı bulantı, kusma şikayetleri olan ve bu şikayetlerle kliniğimize başvuran 48 yaşındaki kadın hastada saptanan mide glomus tümörü olgusu sunulmuştur. Üst GİS endoskopisinde mide küçük kurvaturda, submukozal bir lezyon tespit edilmiştir. Hastaya, lezyonu kapsayan bir parsiyel gastrektomi ameliyatı yapılmıştır. Glomus tümörünün teşhisi, immünohistokimyasal inceleme ile doğrulanmıştır. Glomus tümörleri genellikle benign olup, radikal cerrahi gerektirmez; bu nedenle en önemli husus, histolojik tanının kesin olarak konulması ve midenin daha sık görülen diğer lezyonlarından, özellikle de malign tümörlerden ayırt edilmesidir.

Anahtar Kelimeler: Glomus tümörü, mide, kanser

ABSTRACT

Glomus tumors are typically benign soft tissue tumors located in the extremities; however, they can also rarely occur in other parts of the body, such as the gastrointestinal (GI), urogenital, and respiratory systems. In the GI system, the majority of glomus tumors are found in the gastric antrum. These tumors are generally small in size (<4 cm) but may occasionally reach larger dimensions. This report focuses on a case of a gastric glomus tumor in a patient presenting with abdominal pain. This report presents a case of a 48-year-old female patient who visited our clinic with complaints of intermittent abdominal pain, nausea, and vomiting over a two-month period. Upper GI endoscopy revealed a submucosal lesion located on the lesser curvature of the stomach. The patient underwent partial gastrectomy encompassing the lesion. The diagnosis of a glomus tumor was confirmed through immunohistochemical examination. Glomus tumors are generally benign and do not require radical surgery. The most critical aspect is ensuring a definitive histological diagnosis and distinguishing these tumors from other more common gastric lesions, particularly malignant tumors.

Keywords: Glomus Tumor, Gastric, Cancer

***İletişim kurulacak yazar/Corresponding author:** Mehmet Fatih Özsaray; Kocaeli Üniversitesi, Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Umuttepe, 41001, Kocaeli, Türkiye.
Telefon/Phone: +90 (505) 7750110 **e-posta/e-mail:** f_ozsaray@hotmail.com
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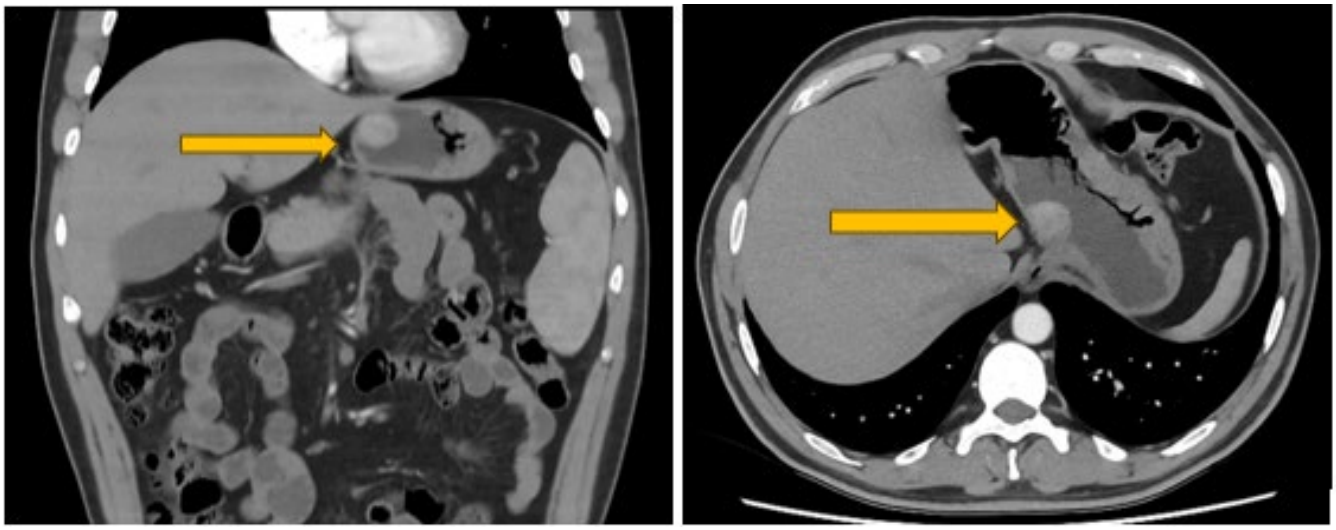
Giriş

Glomus tümörleri, ısı düzenlemesiyle ilgili glomus cisimciğinden kaynaklanan, mezenkimal kökenli, genellikle dermis ve ekstremitelerin subkutis tabakasında yer alan küçük ve iyi huylu lezyonlardır. Bu nedenle en sık el ve ayak tırnak yataklarında görülürler.[1,2]
Glomus tümörleri vücudun herhangi bir bölgesinde ortaya çıkabilir, ancak gastrointestinal sistemde (GİS) son derece nadirdir ve görüldüğünde genellikle midenin distal kısmında bulunur. Genellikle benign seyirlidir ve çoğu zaman belirti vermezler; ancak ülserleşmeleri durumunda üst gastrointestinal kanamalara neden olabilirler.[1,3] Çoğunlukla endoskopik veya radyografik incelemelerde submukozal bir kitle olarak tanımlanırlar ve sıkça diğer mide tümörleriyle karıştırılırlar. Kesin tanı, histopatolojik inceleme ile mümkündür.[1,2]

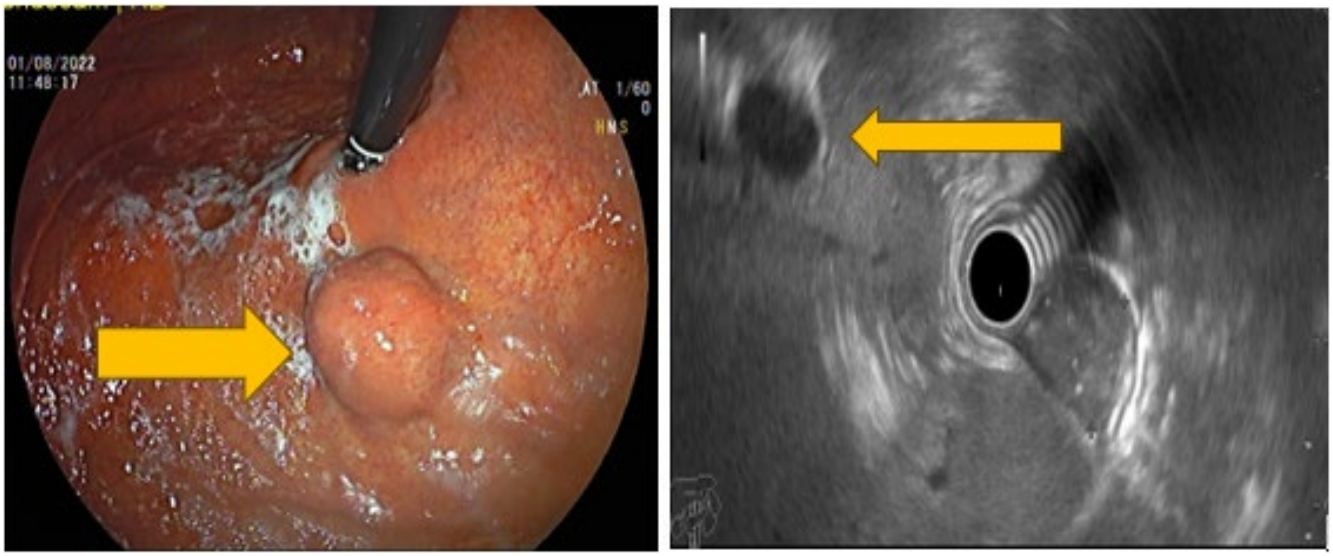
Bu yazıda, klinikte karın ağrısı ile ortaya çıkan mide glomus tümörü vakası sunulmuştur.

Olgu Sunumu

Kırk sekiz yaşında erkek hasta son iki aydır başlayan ara ara olan karın ağrısı, bulantı, kusma şikayetleri ve istemsiz kilo kaybı nedeniyle kliniğimize başvurdu. Yapılan batın ultrasonografide hepatosplenomegali, safra kesesinde milimetrik boyutlu kolesterol kristallerine ait olarak değerlendirilen birkaç adet ekojenite dışında ek patoloji izlenmedi. Ardından yapılan batın tomografisinde; mide küçük kurvaturda 2 cm kalınlığa ulaşan, çevre yağlı dokuya minimal uzanımı bulunan fokal duvar kalınlık artışı izlendi. Daha sonra hastaya gastroskopi planlandı ve yapılan gastroskopide korpus küçük kurvatur proksimalde üzeri mukoza intakt, biyopsi forcepsı ile dokunmakla yastık bulgusu vermeyen, yaklaşık 20 mm SML izlendi.



Şekil 1. Bilgisayarlı Tomografide ok ile işaretli alanlarda görülen lezyon



Şekil 2. Gastroskopi ve Endoluminal Ultrasonografide ok işaretli alanlarda görülen lezyon

Daha sonra yapılan endoskopik ultrasonografide Mide kardia küçük kurvatur tarafında yaklaşık 19,9 x 19,6 mm ebatında muskularis propria'dan köken alan, içerisinde hiperkojen noktalanmalar barındıran düzgün sınırlı hipoekejen lezyon olarak değerlendirildi. Mevcut bulgularla hastaya operasyon planlanarak pre-operatif

gastroskopi eşliğinde laparoskopik wedge rezeksiyon yapıldı. Hasta post-operatif dönemde komplikasyonsuz bir şekilde taburcu edilerek evine yollandı.

Makroskopik incelemede, submukozal yerleşimli, 2 cm çapında total eksize görünümde kesit yüzü bej homojen tümöral alan izlendi. Lezyonun immünhistokimyasal çalışmalarda tümör hücrelerinde; SMA ile diffüz kuvvetli sitoplazmik boyanma izlenmiştir. Vimentin ile diffüz kuvvetli sitoplazmik boyanma izlenmiştir. Calponin ile diffüz kuvvetli sitoplazmik boyanma izlenmiştir. CD56 ile fokal seyrek sitoplazmik boyanma izlenmiştir. Bu bulgularla hastaya midenin glomus tümörü tanısı konuldu. Hasta yaklaşık 6 ay sonra kontrole çağırıldı. Şikâyeti olmayan hastanın yapılan tetkikleri de normal sınırlarda idi.

Tartışma

Gastrik glomus tümörü ilk olarak 1948 yılında De Busscher tarafından tanımlanmıştır.[2] Bu tümörler, oldukça nadir görülen, solid, hipervasküler, intramural yerleşimli tek ve genellikle iyi huylu olan lezyonlardır.[1,2] Ancak, birden fazla glomus tümörünün bulunduğu vakalar da bildirilmiştir.[4] Özellikle leiomiyom, lipom, leiomiyosarkom gibi diğer submukozal mide lezyonları ile karışabilir. Hem erkek hem de kadınlarda eşit sıklıkta görülür. Mide içinde en sık antrum bölgesinde bulunur. Yumuşak kıvamlı ve değişen boyutlarda olabilir. Büyük kurvatur boyunca birkaç reaktif lenfadenopati görülebilir. Genellikle çapı 4 cm'den küçük olup, ortalama 2-2,5 cm arasında değişir, ancak nadiren daha büyük boyutlara ulaşabilir. Çoğunlukla semptom vermezler fakat bazen karın ağrısına neden olabilirler. Fakat bu ağrı genelde şiddetli bir ağrı değil ara ara olan hafif şiddette bir ağrıdır.[5]

Tanı genellikle endoskopik inceleme veya GİS pasaj grafilerinde submukozal bir lezyon olarak konulur. Bazen laparotomi sırasında ya da hastanın farklı şikayetlerinin incelenmesi esnasında rastlantısal olarak tespit edilebilir.[6] Endoskopik biyopsiyle alınan örnekler genellikle tanı için yetersizdir. Baryumlu grafilerde, tipik olarak iyi huylu submukozal lezyonlar, normal mukoza altında düz bir hat olarak görünür ve ülserleşmişse bu ülser de görülebilir. Endolüminal ultrasonografi (EUS) ile mide duvarındaki submukozal lezyonlar tanınabilir; dahası, literatürde EUS eşliğinde yapılan ince iğne aspirasyon biyopsilerinde glomus tümörü tanısı için yeterli materyal elde edilebildiği rapor edilmiştir.[2,7,8] Bazı araştırmacılar ise daha önce endoskopi ile tespit edilen gastrik submukozal kitlelerin, yüksek çözünürlüklü transabdominal ultrasonografi ile %93 oranında görüntülenebileceğini belirtmişlerdir.[9]

Bilgisayarlı tomografide (BT), glomus tümörleri genellikle iyi sınırlı, kontrast tutmayan lezyonlar olarak görünür. Bazı çalışmalarda bu tümörlerin yerleşimi ve kontrast tutulum farklılıkları sayesinde leiomiyom, lipom ve ektopik pankreas gibi diğer lezyonlardan ayırt edilebileceği öne sürülmüştür.[3]Bizim vakamızda, kitle ameliyat öncesi radyografik incelemelerde tespit edildi ve endoskopik incelemede submukozal bir lezyon olarak tanımlandı.

Glomus tümörleri tanısında endoskopi, BT, manyetik rezonans görüntüleme (MRG) ve EUS gibi modaliteler kullanılabilir. Ancak kesin tanı histopatolojik ve immünhistokimyasal inceleme ile konulur. Ayırıcı tanıda GIST, leiomiyom ve nöroendokrin tümörler yer alır. Glomus tümörleri çoğunlukla benign seyirlidir, ancak nâdiren malign olgu bildirimleri de vardır. Bu tümörlerin ayırt edilmesi, tedavi ve prognoz açısından kritik öneme sahiptir. GIST'ler, gastrointestinal sistemin en yaygın mezenkimal tümörleridir ve sıklıkla mide (%40-60) ve ince bağırsaklarda (%25-30) bulunurlar. Bu tümörler, genellikle KIT (CD117) veya PDGFRA gen mutasyonlarına sahiptir ve immünohistokimyasal olarak CD117 ve DOG1 pozitifliği gösterirler. GIST'ler, benign veya malign potansiyele sahip olabilir ve tedavi genellikle cerrahi rezeksiyonla birlikte imatinib gibi tirozin kinaz inhibitörlerinin kullanımını içerir. Leiomyomlar, düz kas hücrelerinden kaynaklanan benign tümörlerdir ve gastrointestinal sistemde en sık özofagus ve mide gibi organlarda bulunurlar. İmmünohistokimyasal olarak SMA ve desmin pozitifliği gösterirler, ancak CD117 ve DOG1 negatiftirler. Leiomyomlar genellikle asemptomatiktir ve küçük boyutlu olduklarında tedavi gerektirmeyebilirler; ancak semptomatik veya büyüyen lezyonlar cerrahi olarak çıkarılabilir. NET'ler, nöroendokrin hücrelerden kaynaklanan ve hormon üretebilen tümörlerdir. Mide de dahil olmak üzere gastrointestinal sistemin çeşitli bölgelerinde bulunabilirler. İmmünohistokimyasal olarak kromogranin A ve sinaptofizin pozitifliği gösterirler. NET'ler, biyolojik davranışlarına göre benign veya malign olabilir ve tedavi seçenekleri tümörün derecesine, yayılımına ve hormon üretimine bağlı olarak değişir.[11] Bu tümörlerin ayırıcı tanısında, histopatolojik ve immünohistokimyasal incelemeler büyük önem taşır. Doğru tanı, uygun tedavi planlaması ve prognozun belirlenmesi açısından kritiktir.

Glomus tümörleri en sık olarak muskularis propria tabakasında yer alır ve kollajenden zengin yalancı bir kapsül ile sınırlıdır.[1,6] Temel histolojik özellikleri arasında ince duvarlı, düzensiz yapıda kan damarları ve karakteristik glomus hücreleri bulunur. Glomus hücreleri, belirgin sınırları, kaba kromatinli ve yuvarlak çekirdekleri ile tanınır; mitoz ve nekroz gözlenmez. Ayırıcı tanıda immünohistokimyasal yöntemler kullanılabilir. Bu hücreler, vimentin, düz kas aktini ve kas spesifik antijen gibi düz kas belirteçlerine pozitif yanıt verirken, sinaptofizin ve kromogranin gibi nöroendokrin belirteçler ile LCA (leukocyte common antigen) negatif sonuç verirler.[1,6] Bu sayede, glomus tümörleri karsinoid ve lenfomadan ayırt edilebilir.

Gastrik glomus tümörleri genellikle benign seyirli olmakla birlikte, literatürde agresif seyir gösteren bazı vakalar da bildirilmiştir.[1,9] Bazı yazarlar, mide glomus tümörlerinin benign lezyonlar olduğunu ve sınırlı konservatif rezeksiyonla tedavi edilebileceğini bildirmişlerdir.[10] Kötü huylu formlarının muhtemelen epiteloid leiomiyosarkom veya epiteloid leiomiyoma benzer bir davranış sergilediğini öne süren yazarlar da vardır.[6] Ameliyat sırasında frozen inceleme ile glomus tümörü tanısının konulması, daha radikal bir girişimi önlemek açısından önemlidir.[7]

Ülkemizde tıp alanındaki gelişmeler ve endoskopik yöntemlerin yaygınlaşması ile bu tür submukozal lezyonların tanısında bir artış olacağı kesindir. Mide glomus

tümörünün oldukça nadir görülmesine rağmen, karın ağrısı ayırıcı tanısında dikkate alınması gereken bir lezyon olduğunu düşünüyoruz. Literatürde bildirilen vaka sayısının azlığı, glomus tümörlerinin genellikle daha konservatif bir cerrahi müdahale gerektirmesi nedeniyle malign tümörlerden ayrımının önemini vurgulayan önemli noktalardır.

Mide glomus tümörleri nadir olup, genellikle insidental olarak saptanır ve ayırıcı tanıda zorluk yaratabilir. Kesin tanı histopatolojik ve immünhistokimyasal inceleme ile konur. Cerrahi rezeksiyon hem tanı hem de tedavi açısından en uygun yaklaşımdır. Minimal invaziv cerrahi yöntemler, hastalar için daha az morbidite ile etkili bir tedavi seçeneği sunmaktadır.[8]

Etik Standartlara Uygunluk

Çalışmada gönüllü olur formu onayı alınmıştır

Çıkar Çatışması

Yazarlar arasında çıkar çatışması bulunmamaktadır.

Yazar Katkısı

MFÖ: Literatür taranması, Veri analizi; TŞ: Olgu sunumunun yazımı, Verilerin düzenlenmesi; NZC: Revizyon ve düzenlemelerin yapılması

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Kaynaklar

1. Ortenzi M, Ghiselli R, Cardinali L, Guerrieri M. Surgical treatment of gastric stromal tumors: laparoscopic versus open approach. *Ann Ital Chir*. 2017;88:S0003469X17026112.
2. Guvendir I, Zemheri IE, Altundal K, Ozdil K, Kahraman R, Tosun I. Ossified uncertain malignant potential gastric glomus tumor with tumor thrombus. *Indian J Pathol Microbiol*. 2021;64(2):369-372. doi:10.4103/IJPM.IJPM_374_20
3. Tsagkataki ES, Flamourakis ME, Gkionis IG, et al. Gastric glomus tumor: a case report and review of the literature. *J Med Case Rep*. 2021;15(1):415. Published 2021 Aug 16. doi:10.1186/s13256-021-03011-0
4. Frosio F, Petruzziello C, Poiasina E, Pisano M, Lucianetti A. Locally Advanced Glomus Tumor of the Stomach With Synchronous Liver Metastases: Case Report and Literature Review. *Cureus*. 2023;15(12):e51041. Published 2023 Dec 24. doi:10.7759/cureus.51041
5. Xing JJ, Huang WP, Wang F, Chai YR, Gao JB. Computed tomography features and clinicopathological characteristics of gastric glomus tumor. *BMC Gastroenterol*. 2022;22(1):174. doi:10.1186/s12876-022-02241-w
6. Lee HW, Lee JJ, Yang DH, Lee BH. A clinicopathologic study of glomus tumor of the stomach. *J Clin Gastroenterol*. 2006;40(8):717-720. doi:10.1097/00004836-200609000-00011
7. Wang X, Hanif S, Wang B, Chai C. Management of gastric glomus tumor: A case report. *Medicine (Baltimore)*. 2019;98(38):e16980. doi:10.1097/MD.0000000000016980
8. Zhang Y, Zhou P, Xu M, et al. Endoscopic diagnosis and treatment of gastric glomus tumors. *Gastrointest Endosc*. 2011;73(2):371-375. doi:10.1016/j.gie.2010.10.023
9. Deng M, Luo R, Huang J, et al. Clinicopathologic features of gastric glomus tumor: A report of 15 cases and literature review. *Pathol Oncol Res*. 2023;28:1610824. doi:10.3389/pore.2022.1610824
10. Kato S, Kikuchi K, Chinen K, Murakami T, Kunishima F. Diagnostic utility of endoscopic ultrasound-guided fine-needle aspiration biopsy for glomus tumor of the stomach. *World J Gastroenterol*. 2015;21(22):7052-7058. doi:10.3748/wjg.v21.i22.7052
11. Wang ZB, Yuan J, Shi HY. Features of gastric glomus tumor: a clinicopathologic, immunohistochemical and molecular retrospective study. *Int J Clin Exp Pathol*. 2014;7(4):1438-48.

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Case Report | Olgu Sunumu

EXPERIENCE WITH ADJUNCTIVE BREXPIPRAZOLE TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER AT A UNIVERSITY CLINIC: A CASE SERIES

BİR ÜNİVERSİTE KLİNİĞİNDE İZLENEN TEDAVİYE DİRENÇLİ MAJÖR DEPRESİF BOZUKLUK HASTALARINDA BREKSİPİPRAZOL EKLEME TEDAVİSİ DENEYİMİ: OLGU SERİSİ

Aila Gareayaghi[1*], Ezgi Sisman[2], Mert Turksoy[1], Aslihan Ozlem Polat Isik[1]

[1]Kocaeli University, Faculty of Medicine, Department of Psychiatry, Kocaeli, Türkiye. [2]Kocaeli City Hospital, Kocaeli, Türkiye.

ABSTRACT

This case series aims to evaluate the efficacy and tolerability of brexpiprazole as an adjunctive treatment in patients with treatment-resistant major depressive disorder (TRD) at a university clinic. Nine cases diagnosed with TRD, defined as insufficient response to at least two antidepressant therapies, were included. Patients were treated with brexpiprazole (0.5–3 mg/day) in combination with ongoing antidepressants. Treatment responses were assessed based on improvements in depressive symptoms, functionality, and tolerability. Brexpiprazole addition resulted in significant symptomatic improvement in seven cases, with reductions in depressive symptoms such as anhedonia, guilt, and psychomotor agitation. Specific cases highlighted brexpiprazole's potential in managing complex conditions such as borderline personality disorder and post-traumatic stress disorder. Most patients experienced enhanced daily functionality and social interactions. Mild weight gain and transient dizziness were the only side effects reported, with no treatment discontinuation due to adverse effects. Brexpiprazole demonstrates efficacy and tolerability in managing TRD, particularly as part of a personalized treatment approach. These findings align with existing literature, underscoring brexpiprazole's role in improving outcomes in resistant and comorbid depressive syndromes. Further studies are needed to confirm these results in larger patient populations.

Keywords: Major depressive disorder, treatment resistent, brexpiprazole

ÖZ

Bu olgu serisi, bir üniversite kliniğinde tedaviye dirençli majör depresif bozukluk (TR-MDB) hastalarında breksipiprazolün ek tedavi olarak etkinliğini ve tolere edilebilirliğini değerlendirmeyi amaçlamaktadır. En az iki antidepresan tedavisine yetersiz yanıt veren TR-MDB tanılı dokuz hasta çalışmaya dahil edilmiştir. Hastalara, mevcut antidepresan tedavilerine ek olarak breksipiprazol (0.5–3 mg/gün) uygulanmıştır. Tedavi yanıtları, depresif semptomlarda iyileşme, işlevsellik artışı ve tolere edilebilirlik açısından değerlendirilmiştir. Breksipiprazol ek tedavisi, yedi vakada belirgin semptomatik iyileşme sağlamış, anhedoni, suçluluk ve psikomotor ajitasyon gibi depresif semptomların azalmasına katkıda bulunmuştur. Özellikle, breksipiprazolün borderline kişilik bozukluğu ve travma sonrası stres bozukluğu gibi karmaşık durumlarda da etkili olduğu gözlenmiştir. Çoğu hastada günlük işlevsellik ve sosyal etkileşimlerde artış rapor edilmiştir. Hafif kilo artışı ve geçici baş dönmesi dışında kayda değer bir yan etki görülmemiş, tedaviye bağlı bırakma olmamıştır. Breksipiprazol, TR-MDB'nin yönetiminde, özellikle bireyselleştirilmiş tedavi yaklaşımlarının bir parçası olarak etkili ve tolere edilebilir bir seçenek sunmaktadır. Bu bulgular, breksipiprazolün dirençli ve eşlik eden depresif sendromlarda sonuçları iyileştirmedeki rolünü desteklemekte olup, daha geniş hasta popülasyonlarında doğrulayıcı çalışmalar gereklidir.

Anahtar Kelimeler: Majör depresif bozukluk, tedavi direnci, breksipiprazol

***Corresponding author/İletişim kurulacak yazar:** Aila Gareayaghi; Kocaeli University, Faculty of Medicine, Department of Psychiatry, Kocaeli, Türkiye.
Phone/Telefon: +90 (262) 303 75 75 **e-mail/e-posta:** aila.gareayaghi@kocaeli.edu.tr
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Introduction

Major Depressive Disorder (MDD) is a psychiatric condition characterized by persistent depressive mood, anhedonia (inability to experience pleasure), lack of energy, impaired concentration, feelings of guilt or worthlessness, and changes in sleep and appetite. According to the DSM-5, a diagnosis requires the presence of at least five of these symptoms for a minimum of two weeks, with one of them being either a depressed mood or anhedonia. If left untreated, MDD can persist for 6-12 months and lead to serious complications, including a high risk of suicide. Effective management of the disorder requires an interdisciplinary healthcare team approach and the inclusion of patient and family education.[1] According to the World Health Organization (WHO), MDD ranked third in the global disease burden in 2008 and is projected to rise to the top position by 2030.[2]

There is no universal consensus on the definition of treatment-resistant depression (TRD); however, it is generally described as the lack of response to two or more adequate antidepressant treatments.[3] In the literature, Thase and Rush proposed a classification system for TRD based on different stages. According to this system, Stage 0 represents the absence of any adequate antidepressant trial in terms of dose and duration. Stage 1 involves the failure of one antidepressant from a primary class, such as SSRIs, despite sufficient dose and duration. Stage 2 is defined by the failure of two antidepressants from different classes, such as an SSRI and a TCA. Stage 3 includes the failure of a tricyclic antidepressant (TCA) in addition to Stage 2. Stage 4 adds the failure of a monoamine oxidase inhibitor (MAOI), and Stage 5 includes the failure of bilateral electroconvulsive therapy (ECT) beyond Stage 4. Notably, this model does not incorporate mood stabilizers or antipsychotics in adjunctive treatments. However, a recent meta-analysis indicates that antipsychotics and mood stabilizers play a significant role in the management of TRD, demonstrating efficacy superior to placebo.[4]

Brexpiprazole has been approved by the U.S. Food and Drug Administration (FDA) since 2015 for use as an adjunctive treatment in treatment-resistant depression. According to the prescribing information, the starting dose is 0.5-1 mg/day, the recommended dose is 2 mg/day, and the maximum dose is 3 mg/day. A meta-analysis revealed that brexpiprazole treatment resulted in a significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores within the first week of initiation. From the second week onward, there was a statistically significant difference in response rates between treatment groups, and by the third week, a notable increase in remission rates was observed. These findings indicate that brexpiprazole effectively alleviates symptoms of Major Depressive Disorder (MDD) at an early stage.[5]

In this case series, we aimed to summarize the outcomes of brexpiprazole treatment applied in our clinic to patients with treatment-resistant depression who had received at least two different antidepressant treatments but did not achieve significant improvement in their depressive symptoms. To the best of our knowledge, no such case series has been reported following the introduction of brexpiprazole in our country. Therefore, through this case series, we aimed to contribute to the existing literature.

Case 1

A 39-year-old female patient, a primary school graduate, housewife, married, and mother of four, presented to the clinic nine years ago with complaints of irritability, unhappiness, inability to enjoy life, and frequent crying episodes. Her psychiatric symptoms were associated with her husband's extramarital affair and domestic violence, during which she had also attempted suicide. The patient did not benefit from previous interventions due to irregular medication use.

She was diagnosed with Major Depressive Disorder (MDD) in our clinic and treated with sertraline 50 mg/day, which was titrated to the maximum dose, but no sufficient response was achieved. Subsequently, fluoxetine was prescribed, but the patient discontinued it due to side effects. Duloxetine was started at 30 mg/day and increased to 60 mg/day, with alprazolam 1 mg/day added as an adjunct. However, since adequate improvement was not observed, duloxetine was tapered off and replaced with venlafaxine at 75 mg/day, gradually increased to 300 mg/day. Aripiprazole 5 mg/day was added as a supportive therapy. Despite regular use for one year, the patient reported only partial improvement and discontinued follow-up and treatment.

Three years later, the patient returned to our outpatient clinic with the same complaints, stating that none of the previous treatments had been effective. Paroxetine 20 mg/day and brexpiprazole 1 mg/day were initiated, with brexpiprazole increased to 2 mg/day as recommended after one week.

At the one-month follow-up, despite undergoing a divorce, the patient's depressive symptoms had subsided, and she reported no thoughts of self-harm or harm to others. The treatment was continued with paroxetine 20 mg/day and brexpiprazole 2 mg/day.

Case 2

A 58-year-old illiterate, married housewife presented nine years ago with complaints of reluctance to get out of bed, restlessness, and lack of motivation. Her first psychiatric consultation occurred in 1999 after she lost her husband and son in the Gölcük earthquake. She had been diagnosed with depression and received various treatments; however, her symptoms persisted and became resistant.

Following a one-month hospitalization with a diagnosis of MDD, her treatment regimen included paroxetine 60 mg/day, pregabalin 150 mg/day, and quetiapine 25 mg/day. During outpatient follow-ups, her symptoms worsened, leading to trials of different medication combinations (venlafaxine, aripiprazole, fluoxetine,

mirtazapine, lithium, bupropion, alprazolam). Despite irregular attendance at follow-ups, the patient claimed she used her medications regularly but never experienced complete symptom resolution.

During her most recent consultation, while on venlafaxine 150 mg/day, her lack of full recovery prompted an increase in venlafaxine to 225 mg/day, with brexpiprazole 1 mg/day added. At a one-week follow-up, brexpiprazole was titrated to 2 mg/day. The patient showed significant improvement in her symptoms, better self-care, and increased participation in household activities. Apart from weight gain following the addition of brexpiprazole, no side effects were reported. The final treatment regimen was adjusted to venlafaxine 225 mg/day and brexpiprazole 2 mg/day.

Case 3

A 24-year-old single female patient, a university graduate working as a makeup artist, presented five years ago with complaints of shortness of breath, heart palpitations, numbness, and loss of appetite. She was diagnosed with an anxiety disorder and started on paroxetine 20 mg/day, but due to side effects, her treatment was switched to sertraline 50 mg/day. Her history revealed impulsivity, sudden mood swings, social relationship losses, and a self-harm attempt two years earlier. Based on these findings, borderline personality disorder and major depressive disorder (MDD) were considered, and sertraline was increased to 100 mg/day with aripiprazole 5 mg/day added to the regimen.

During follow-ups, sertraline was further increased to 200 mg/day, while aripiprazole 5 mg/day was maintained. Although partial improvement in depressive symptoms was noted, self-harming behaviors and gambling addiction emerged. Lamotrigine 25 mg/day was added to the treatment; however, it had to be discontinued in the second week due to a skin rash.

As the patient's symptoms persisted, aripiprazole was replaced with brexpiprazole 1 mg/day, which was increased to 2 mg/day after one week, while sertraline 200 mg/day was continued.

At the latest follow-up, a significant reduction in depressive symptoms and gambling behavior was observed, although self-harming behaviors had not completely ceased. As the treatment was well-tolerated without side effects, brexpiprazole was increased to 3 mg/day, alongside sertraline 200 mg/day. The patient was monitored, and follow-ups revealed a marked decrease in self-harming behaviors.

Case 4

A 22-year-old single female university student presented four years ago with depressive complaints, including lack of motivation, loss of appetite, difficulty falling asleep, anhedonia, low self-confidence, and feelings of worthlessness. Since the age of 12, she had been under the care of child and adolescent mental health services, but her symptoms had not improved with previous treatments.

Her history revealed that at the age of five, following her parents' divorce, she moved to live with her father after her mother remarried. Initial treatment with fluoxetine 20 mg/day was started and titrated up to 60 mg/day, but no improvement was observed. Bupropion 150 mg/day was added but discontinued after triggering an epileptic seizure. Subsequently, venlafaxine was initiated and gradually increased to 300 mg/day; however, complete recovery was not achieved. Aripiprazole 10 mg/day, mirtazapine 15 mg/day, quetiapine 300 mg/day, and medazepam 10 mg/day were sequentially added, but the combination failed to produce sufficient benefits, and suicidal ideation emerged.

The patient was hospitalized in a psychiatric unit and received eight sessions of electroconvulsive therapy (ECT), resulting in improvement. She was discharged on venlafaxine 300 mg/day and quetiapine XR 300 mg/day.

After discharge, she resumed university but discontinued her medications due to weight gain despite feeling well. Two months later, her symptoms recurred, prompting her return to our clinic. Since she refused venlafaxine and quetiapine due to weight concerns, duloxetine 30 mg/day and brexpiprazole 1 mg/day were initiated. Duloxetine was discontinued due to daytime sedation, and sertraline 50 mg/day was started and gradually increased to 200 mg/day. Brexpiprazole, initiated as an adjunct, was titrated to 2 mg/day.

This treatment led to significant improvement, with no reported side effects. The patient has been stable on this regimen for six months.

Case 5

A 25-year-old married woman, a university graduate and housewife, presented to the clinic with complaints of inner distress, panic, persistent unhappiness, inability to experience pleasure, and feelings of guilt. Five months prior to her presentation, she was involved in a traffic accident, which, despite causing no physical injuries, resulted in re-experiencing the event and a fear of getting into a car.

The patient had been started on paroxetine 10 mg/day at an external center but experienced no improvement, leading her to seek treatment at our clinic. Diagnosed with Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD), her paroxetine dose was gradually increased to 40 mg/day. Trazodone 50 mg/day was added to address her insomnia, but her depressive symptoms did not fully resolve. Subsequently, paroxetine and trazodone were discontinued, and treatment was switched to sertraline 50 mg/day and brexpiprazole 0.5 mg/day. Follow-up evaluations resulted in adjustments to sertraline 100 mg/day and brexpiprazole 1 mg/day.

At the next follow-up, the patient reported a reduction in crying spells, psychomotor agitation, and insomnia. Given her partial response, brexpiprazole was increased to 2 mg/day, and sertraline was titrated to 150 mg/day. The patient did not report any side effects with this treatment.

Case 6

A 63-year-old widowed male, a retired laborer with a primary school education, presented with complaints of fear of death, feelings of worthlessness, social withdrawal, being unwanted by others, difficulty falling asleep, loss of appetite, and passive thoughts of death. He reported no benefit from previous treatments with various antidepressants and antipsychotics, including sertraline, valproic acid, carbamazepine, aripiprazole, risperidone, quetiapine, fluoxetine, olanzapine, and alprazolam, prescribed at an external center.

To rule out dementia, a Mini-Mental State Examination (MMSE) was performed, yielding a normal score of 29, and a neurology consultation also excluded dementia. His symptoms were considered related to treatment-resistant depression. Sertraline 50 mg/day and brexpiprazole 0.5 mg/day were initiated. Follow-ups led to dose adjustments to sertraline 100 mg/day and brexpiprazole 2 mg/day.

The patient reported dizziness after the increase in brexpiprazole dose, which resolved when the dose was reduced to 1 mg/day. During subsequent visits, the patient, who adhered to his medications, reported no side effects, showed improved appetite, and no longer experienced active or passive thoughts of death. Furthermore, his relationships with relatives improved. The final treatment regimen consisted of sertraline 100 mg/day and brexpiprazole 1 mg/day.

Case 7

A 56-year-old single woman, a primary school graduate who previously worked as a cleaner but had been unemployed for the past eight years, presented to the clinic with complaints of inner distress, restlessness, shortness of breath, and hearing voices. She had a prior diagnosis of psychotic major depressive disorder at an external center, had been hospitalized once, and had attempted suicide by jumping from a height.

At the time of her clinic visit, the patient was on venlafaxine 150 mg/day, lamotrigine 100 mg/day, quetiapine 400 mg/day, aripiprazole 10 mg/day, and diazepam 5 mg/day, but reported no benefit from these treatments. During her outpatient consultation, she described low mood, unhappiness, lack of pleasure in life, inner restlessness, and occasional urges to scream. She also reported pseudohallucinations, such as hearing her name being called. A diagnosis of major depressive disorder with pseudohallucinations was made. Her treatment was simplified to venlafaxine 300 mg/day and quetiapine 400 mg/day, with the addition of brexpiprazole 1 mg/day. A planned cross-tapering between quetiapine and brexpiprazole was implemented during follow-ups.

At subsequent check-ups, her screaming episodes and pseudohallucinations had decreased, and no self-harm behaviors were observed. Brexpiprazole was increased to 2 mg/day. At later follow-ups, her sleep patterns had normalized, and self-harm thoughts were absent. Her final treatment consisted of venlafaxine 300 mg/day, quetiapine 200 mg/day, and brexpiprazole 3 mg/day, with no reported side effects.

Case 8

A 31-year-old single male, a university graduate and computer engineer, presented with complaints of unhappiness, lack of motivation, inability to enjoy life, and difficulty falling asleep. He reported no benefit from previous treatments, including fluoxetine 40 mg/day and olanzapine 2.5 mg/day. His symptoms persisted despite being on venlafaxine 150 mg/day.

In our clinic, his treatment was adjusted to venlafaxine 225 mg/day, and brexpiprazole 0.5 mg/day was added, which was increased to 1 mg/day after one week. At follow-up, he reported a reduction in active symptoms but persistent insomnia, with no side effects. Mirtazapine 7.5 mg/day was added to his treatment alongside venlafaxine 225 mg/day and brexpiprazole 1 mg/day. With improvements in his sleep disturbances, the patient continued on this regimen during follow-up.

Case 9

A 31-year-old single female teacher with a university degree presented with complaints of lack of motivation, social withdrawal, difficulty concentrating, and chronic insomnia. She had previously been diagnosed with major depressive disorder at an external center and initially treated with sertraline 100 mg/day. After experiencing no benefit, her treatment was switched to paroxetine 30 mg/day and olanzapine 5 mg/day. Although her depressive symptoms improved, she experienced side effects such as increased sleep and appetite.

At our clinic, her treatment was adjusted by maintaining paroxetine 30 mg/day while discontinuing olanzapine. Brexpiprazole 1 mg/day was added to her regimen. At her follow-up, the patient reported satisfaction with the treatment, no side effects, increased social engagement with her family, and enjoyment from social activities. Her final treatment was continued as paroxetine 30 mg/day and brexpiprazole 1 mg/day.

A summary of the cases is given in Table 1.

Discussion

According to the World Health Organization (WHO) assessment report on the global burden of disease, depression was the second leading cause of disease burden and disability among all diseases as of 2020. Furthermore, it is projected to become the leading cause of global disease burden by 2030. A large meta-analysis indicates that only 50% of all depression cases achieve remission with antidepressant treatment.[6] Even when appropriate treatment is provided and remission is achieved, 25–40% of patients may experience a depressive episode within 2 years, 60% within 5 years, and 85% within 15 years.[7] Considering these statistics, the significance of incorporating options like brexpiprazole as an adjunctive treatment in managing a

condition that causes such substantial disability cannot be overstated.

Brexpiprazole acts as a partial agonist at D2 receptors rather than as an antagonist and also exhibits high affinity for 5HT2A, 5HT1A, and α1 receptors. Its antidepressant effect is based on its ability to modulate the balance of dopamine and serotonin through partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, as well as antagonist activity at 5-HT2A receptors.[3] Studies indicate that brexpiprazole does not have significant effects on receptors typically associated with sedation, weight gain, or increased cardiometabolic risk.

Table 1. Summary of the Cases

Case	Diagnosis	Complaints	Treatment	Side Effects
Case 1	Major depressive disorder	Irritability, unhappiness, crying, anhedonia	Brexpiprazole 2 mg/day, paroxetine 20 mg/day	Not reported
Case 2	Major depressive disorder	Inability to get out of bed, restlessness, lack of motivation	Brexpiprazole 2 mg/day, venlafaxine 225 mg/day	Weight gain
Case 3	Major depressive disorder + Borderline personality disorder	Impulsivity, sudden mood changes, gambling	Brexpiprazole 3 mg/day, sertraline 200 mg/day	Not reported
Case 4	Major depressive disorder	Lack of motivation, loss of appetite, difficulty falling asleep	Brexpiprazole 2 mg/day, sertraline 200 mg/day	Not reported
Case 5	PTSD + Major depressive disorder	Inner distress, panic, guilt feelings	Brexpiprazole 2 mg/day, sertraline 150 mg/day	Not reported
Case 6	Major depressive disorder	Fear of death, worthlessness, social withdrawal	Brexpiprazole 1 mg/day, sertraline 100 mg/day	Dizziness
Case 7	Major depressive disorder	Inner distress, restlessness, pseudohallucinations	Brexpiprazole 3 mg/day, venlafaxine 300 mg/day, quetiapine 200 mg/day	Not reported
Case 8	Major depressive disorder	Unhappiness, lack of motivation, insomnia	Brexpiprazole 1 mg/day, venlafaxine 225 mg/day, mirtazapine 7.5 mg/day	Not reported
Case 9	Major depressive disorder	Lack of motivation, social withdrawal, excessive sleep	Brexpiprazole 1 mg/day, paroxetine 30 mg/day	Not reported

The efficacy of brexpiprazole as an adjunctive treatment in cases of treatment-resistant depression has been demonstrated in various studies. Similarly, in our cases, the addition of brexpiprazole at varying doses to the treatment regimens of patients who had not responded or had shown insufficient response to at least two antidepressant treatments resulted in an increase in treatment response rates. As observed in Cases 1, 2, 4, 6, 7, 8, and 9, patients whose depressive symptoms persisted despite the use of multiple medications benefited from adjunctive brexpiprazole therapy. This finding is consistent with other brexpiprazole studies in the literature.[3,4,5]

A case series in the literature highlights the use of brexpiprazole in patients with borderline personality disorder. According to these findings, brexpiprazole reduces aggression, self-harming behaviors, and substance abuse in patients with borderline personality disorder.[8] In Case 3, a diagnosis of borderline personality disorder co-occurring with major depressive disorder was considered, and following treatment with brexpiprazole at 2 mg/day, the patient showed improvement in self-harming behaviors and gambling addiction.

According to a recently published study, the combination of sertraline and brexpiprazole has shown beneficial results in the treatment of post-traumatic stress disorder (PTSD).[9] In Case 5, a diagnosis of PTSD co-occurring with major depressive disorder was considered, and brexpiprazole 2 mg/day was added to sertraline 150 mg/day. Follow-up evaluations indicated that the patient benefited from the treatment.

In the literature, the most common side effects of brexpiprazole, such as weight gain and akathisia, are generally described as mild to moderate in severity.[10] Among our cases, no significant side effects were reported, except for mild weight gain in one case, which did not lead to treatment discontinuation, and dizziness in another case, which resolved with dose adjustment.

In conclusion, this case series demonstrates that brexpiprazole may be considered as an effective and well-tolerated option not only for treatment-resistant depression but also for the management of borderline personality disorder and post-traumatic stress disorder. In our cases, positive outcomes were achieved, including improvements in depressive symptoms, enhanced functionality, and reductions in aggression, self-harming behaviors, and pseudohallucinations. The efficacy and safety of brexpiprazole in various clinical conditions are supported by the literature, and our findings align with these results. The absence of severe side effects during the treatment process suggests that brexpiprazole offers an advantage in terms of patient adherence. Further exploration of brexpiprazole's role in individualized treatment approaches for depression and co-occurring psychiatric symptoms is warranted through larger case series and controlled studies.

Compliance with Ethical Standards

Ethical considerations have been observed while ensuring the patient's confidentiality.

Conflict of Interest

There is no conflict of interest among the authors. Informed consent was obtained from the patients before this case series was prepared.

Author Contributions

AG, EŞ, AP: Study idea; AG, EŞ, AP: Design; MT: Data collection; AG, EŞ, MT, AP Analysis; AG, EŞ: Literature review; AG, AP: Writing; AG, AP: Critical review.

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References

1. Curley LE, Lin JC, Chen TF. Major depressive disorder. *Encyclopedia of Pharmacy Practice and Clinical Pharmacy: Volumes 1-3*. 2023;1-3:672-685. doi:10.1016/B978-0-12-812735-3.00549-5
2. Malhi GS, Mann JJ. Depression. *Lancet*. 2018;392(10161):2299-2312. doi:10.1016/S0140-6736(18)31948-2
3. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*. 2023;22(3):394. doi:10.1002/WPS.21120
4. Nuñez NA, Joseph B, Pahwa M, et al. Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. *J Affect Disord*. 2022;302:385-400. doi:10.1016/j.jad.2021.12.134
5. Kishi T, Sakuma K, Nomura I, Matsuda Y, Mishima K, Iwata N. Brexpiprazole as adjunctive treatment for major depressive disorder following treatment failure with at least one antidepressant in the current episode: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*. 2019;22(11):698-709. doi:10.1093/IJNP/PYZ040
6. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia. *J Clin Psychiatry*. 2011;72(04):509-514. doi:10.4088/JCP.09m05949blu
7. Richards D. Prevalence and clinical course of depression: A review. *Clin Psychol Rev*. 2011;31(7):1117-1125. doi:10.1016/j.cpr.2011.07.004
8. Francis B, Ganasan VA, Sulaiman AR Bin. Brexpiprazole attenuates aggression, suicidality and substance use in borderline personality disorder: A case series. *Medicina.* 2024;60(2):283. doi:10.3390/MEDICINA60020283
9. Davis LL, Behl S, Lee D, et al. Brexpiprazole and sertraline combination treatment in posttraumatic stress disorder. *JAMA Psychiatry*. Published online December 18, 2024. doi:10.1001/jamapsychiatry.2024.3996
10. Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015;76(09):1224-1231. doi:10.4088/JCP.14m09688