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*Değerli **'Tıp Fakültesi Klinikleri Dergisi'** okuyucuları,*

2026 yılının Temmuz sayısında, temel ve klinik bilimler olmak üzere farklı disiplinlerden beş araştırma makalesi ve bir derleme ile toplam altı çalışma ile karşınızdayız.

Bu sayımızda, yer alan makaleler kendi alanlarında yeni bilgiler içermekte ve okuyucuların eksikliklerini tamamlayacak niteliktedir.

Yazarlar, kendi alanlarında yaptıkları çalışmalarıyla aydınlatıcı, yön verici ve hastaların tedavi süreçlerine katkı sunabilecek bulguları içeren değerli makalelerini dergimizde paylaşmışlardır.

Siz değerli okurlarımıza yeni ve özenle yaptığımız hakem değerlendirmeleriyle kaliteli makaleleri sunmak başlıca amacımızdır. Nitelikli ulusal ve uluslararası dizinlerde yer alabilmek için titizlikle sürdürdüğümüz gayretlerimizin devam etmektedir. Dergimiz hakemli olup ulusal ve uluslararası dizinlerde taranmaktadır. Dergimiz ulusal dizinlerden; Türk Eğitim İndeksi, Türkiye Atıf Dizini ve ASOS indeksinde ve uluslararası dizinlerden; EBSCOhost, Google Scholar ve Central and Eastern European Academic Source (CEEAS)'da yer almaktadır.

Dergimize büyük emek harcayarak hazırladıkları bilimsel makalelerini gönderen yazarlarımıza ve bu makalelerin daha nitelikli hale getirilmesinde tecrübelerini ve bilgi birikimlerini ortaya koyan ve bizimle paylaşan değerli hakemlerimize teşekkür ederiz.

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Yeni sayımızın bilime katkı sağlaması dileğiyle…

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ARAŞTIRMA MAKALESİ RESEARCH ARTICLE

Severity of Obstructive Sleep Apnea and Its Impact on Retinal Ganglion Cell Complex and Retinal Nerve Fiber Layer

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Abstract

Aim: To evaluate whether systemic hypoxia associated with obstructive sleep apnea syndrome (OSA) is related to structural changes in the retinal ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL).

Materials and Methods: SThis cross-sectional, observational case–control study included 49 OSA patients and 20 age- and sex-matched healthy controls with a normal apnea–hypopnea index (AHI <5). Participants were aged 30–65 years. Exclusion criteria included systemic or ocular disease, prior ocular surgery, smoking, and alcohol use. Only participants with refractive errors between −5.00 and +3.00 diopters were included. All subjects underwent overnight polysomnography. Spectral-domain optical coherence tomography (SD-OCT; Optovue RTVue) was performed in the morning (09:00–11:00) to measure average and sectoral GCC and RNFL thickness. Recorded sleep parameters included AHI, mean oxygen saturation (SpO^2), nadir SpO^2, duration of sleep with SpO^2 between 80–90%, and the percentage of total sleep time spent in this range.

Results: No statistically significant differences were observed between the OSA and control groups for average or sectoral GCC and RNFL thickness (all $p>0.05$). Correlation analyses showed no significant associations between GCC or RNFL thickness and AHI, mean SpO^2, nadir SpO^2, duration of SpO^2 at 80–90%, or the percentage of sleep time spent in this range (all $p>0.05$). Sector-based analyses revealed no focal retinal thinning.

Conclusion: GCC and RNFL thickness were not significantly associated with OSA severity or nocturnal hypoxemia parameters. These findings suggest that global hypoxic burden alone may not be sufficient to drive early retinal neurodegeneration. However, given the limited statistical power of the study, the results should be interpreted with caution. Larger, well-powered longitudinal studies are needed to confirm these findings.

Keywords: *Obstructive sleep apnoea, Ganglion cell complex, Retinal nerve fibre layer, Hypoxia, Optical coherence tomography*

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Obstrüktif Uyku Apnesinin Şiddeti ve Bunun Retina Ganglion Hücre Kompleksi ile Retina Sinir Lifi Tabakası Üzerindeki Etkisi

Özet

Amaç: AObstrüktif uyku apne sendromunda (OUAS) kronik sistemik hipoksinin retina gangliyon hücre kompleksi (GCC) ve retina sinir lifi tabakası (RNFL) kalınlıkları ile ilişkisini değerlendirmek.

Gereç ve Yöntem: Bu kesitsel, gözlemsel vaka-kontrol çalışmasına, 49 OSA hastası ve normal apne-hipopne indeksi (AHI <5) olan, yaş ve cinsiyet açısından eşleştirilmiş 20 sağlıklı kontrol katılımcısı dahil edildi. Katılımcıların yaşları 30–65 arasındaydı. Dışlama kriterleri arasında sistemik veya göz hastalıkları, daha önce geçirilmiş göz ameliyatı, sigara kullanımı ve alkol kullanımı yer alıyordu. Sadece −5,00 ile +3,00 diyoptri arasında refraktif kusuru olan katılımcılar çalışmaya dahil edildi. Tüm deneklere gece boyunca polisomnografi uygulandı. Ortalama ve sektörel GCC ve RNFL kalınlığını ölçmek için sabah (09:00–11:00) spektral alan optik koherens tomografi (SD-OCT; Optovue RTVue) yapıldı. Kaydedilen uyku parametreleri arasında AHI, ortalama oksijen satürasyonu (SpO^2), en düşük SpO^2, SpO^2'nin %80–90 arasında olduğu uyku süresi ve toplam uyku süresinin bu aralıkta geçirilen yüzdesi yer almıştır.

Bulgular: OUAS ve kontrol grupları arasında GCC ve RNFL kalınlıkları açısından anlamlı fark saptanmadı. Ayrıca GCC ve RNFL kalınlıkları ile AHI ve oksijen satürasyon parametreleri arasında anlamlı ilişki bulunmadı.

Sonuç: GCC ve RNFL kalınlığı, OUAS şiddeti veya gece hipoksemi parametreleriyle anlamlı bir ilişki göstermedi. Bu bulgular, genel hipoksik yükün tek başına erken dönem retina nörodejenerasyonunu tetiklemek için yeterli olmayabileceğini düşündürmektedir. Ancak, çalışmanın istatistiksel gücünün sınırlı olduğu göz önüne alındığında, sonuçlar dikkatli bir şekilde yorumlanmalıdır. Bu bulguları doğrulamak için daha geniş kapsamlı ve istatistiksel gücü yeterli uzunlamasına çalışmalar gereklidir.

Anahtar Kelimeler: *Obstrüktif uyku apnesi, Ganglion hücre kompleksi, Retina sinir lifi tabakası, Hipoksi, Optik koherens tomografi*

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INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder characterized by recurrent upper airway collapse during sleep, resulting in intermittent hypoxia and sleep fragmentation. It affects approximately 13% of middle-aged men and 5% of women, and chronic nocturnal oxygen desaturation is known to contribute to metabolic, cardiovascular, and neurocognitive morbidity (1). Increasing evidence suggests that OSA may also have important ocular implications. Intermittent hypoxemia and hemodynamic fluctuations associated with OSA can induce oxidative stress, inflammation, and endothelial dysfunction, ultimately impairing optic nerve head perfusion and predisposing to retinal nerve fiber layer (RNFL) thinning (1).

OSA has been associated with several ophthalmic conditions, including floppy eyelid syndrome, retinal vascular occlusions, and glaucoma. When the optic nerve is involved, hypoxia-related vascular dysregulation and impaired autoregulation may lead to retinal ganglion cell apoptosis, resulting in progressive RNFL loss (2). These mechanisms support a potential link between OSA and glaucomatous optic neuropathy, independent of intraocular pressure elevation.

OSA is known to be associated with a wide range of systemic disorders, including cardiovascular, metabolic, and neurocognitive diseases, reflecting its multisystem impact (3). Several epidemiological studies have examined the relationship between OSA and glaucoma. A large meta-analysis including 46 studies demonstrated that OSA is associated with an approximately 40% increased risk of glaucoma, even after adjustment for confounding factors (4). In addition to clinical data, optical coherence tomography (OCT)-based imaging studies have provided further structural evidence

supporting this association. Reduced peripapillary RNFL thickness has been reported in OSA patients compared with controls, particularly in those with moderate to severe disease, suggesting a role of chronic intermittent hypoxia in optic nerve vulnerability (1, 2).

Despite these observations, findings regarding OSA-related RNFL changes remain inconsistent. While some studies have reported focal or sectoral RNFL thinning, others have failed to demonstrate significant structural differences between OSA patients and healthy individuals (1). Such discrepancies may be attributed to variations in study design, disease severity, duration of hypoxic exposure, and imaging methodology, indicating that the retinal impact of OSA has not yet been fully clarified.

Another important issue is whether OSA-related retinal alterations are reversible with treatment. Continuous Positive Airway Pressure(CPAP) is the first-line therapy for OSA and effectively reduces nocturnal hypoxia. Previous studies have shown that CPAP therapy may lead to improvements in RNFL thickness and visual function, particularly in patients with more severe disease (5). These findings suggest that at least some OSA-related retinal changes may be partially reversible with timely intervention.

Based on the conflicting evidence in the literature, the present study was designed to evaluate the relationship between OSA severity and RNFL and GCC thickness prior to treatment initiation. By correlating OCT-derived retinal measurements with Polysomnography (PSG) parameters, we aimed to clarify whether increasing OSA severity is associated with detectable structural retinal changes and to better characterize the link between OSA and optic nerve vulnerability.

MATERIALS AND METHODS

This cross-sectional, observational case–control study was conducted between 1 June and 1 December 2022 to evaluate the relationship between OSA severity and RNFL and ganglion cell complex (GCC) thickness before treatment. The study was approved by the XXX Clinical Research Ethics Committee (Approval No. 2022-5, dated 9 October 2022), and written informed consent was obtained from all participants. The study included 49 newly diagnosed, untreated OSA patients and 20 age- and sex-matched healthy controls with Apnea–Hypopnea Index (AHI) <5 confirmed by full-night PSG. Participants were aged 30–65 years, had Best Corrected Visual Acuity (BCVA) ≥20/20, and a spherical equivalent between –5.00 and +3.00 Diopter (D). Only non-smokers without alcohol use were included. Individuals with systemic disease, ocular disease, previous ocular surgery or trauma, glaucoma or suspected glaucoma, Intraocular Pressure (IOP) >20 mmHg, poor-quality OCT images, or use of medications affecting IOP or retinal structures were excluded. PSG was performed using the Alice 6 system (Philips Respironics). OSA severity was classified according to AASM criteria as mild (AHI 5–14.9), moderate (AHI 15–29.9), or severe (AHI ≥30). Recorded parameters included AHI, mean SpO2, lowest SpO2, duration of SpO2 between 80–90%, and the percentage of total sleep time spent within this range.

All participants underwent a comprehensive ophthalmological examination between 09:00 and 11:00 by a single masked ophthalmologist. Spectral-domain optical coherence tomography (SD-OCT) imaging was performed using the RTVue system (Optovue Inc., Fremont, CA, USA). Average peripapillary RNFL thickness and average macular GCC thickness were used for analysis, as no significant sectoral differences were observed. Only high-quality OCT images were included; images with a signal strength index (SSI) <40, motion artifacts, segmentation errors, or poor centration were excluded. Data were analyzed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD. Group comparisons were performed using the Mann–Whitney U test, and associations between OCT and PSG parameters were assessed using Spearman's correlation analysis. A post hoc power analysis (G*Power 3.1) demonstrated a statistical power of 47% to detect a medium effect size ($r = 0.3$) at $\alpha = 0.05$.

This study protocol was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Mardin Artuklu University (Approval No. 2022-5, dated 9 October 2022).

RESULTS

A total of 49 patients with newly diagnosed OSA and 20 healthy control subjects were included in the study. The demographic and clinical characteristics of the participants are presented in Table 1.

Table 1. A total of 49 patients with newly diagnosed OSAS and 20 healthy controls were included in the study. The demographic and clinical characteristics of the study population is summarized.

Parameter	Total (n=69)	OSAS Group (n=49)	Control Group (n=20)	P value
Age (years), mean ± SD	46.3 ± 10.1	47.1 ± 9.8	44.0 ± 10.5	0.28
Female, n (%)	44 (63.3%)	31 (63.3%)	13 (65.0%)	0.89
BMI (kg/m²), mean ± SD	32.5 ± 6.4	33.6 ± 5.9	29.8 ± 7.1	0.03*
AHI, mean ± SD	28.0 ± 23.6	37.8 ± 22.1	3.2 ± 1.5	<0.001*
Mean SpO2 (%), mean ± SD	90.6 ± 2.8	89.9 ± 2.9	92.5 ± 2.1	0.001*
Lowest SpO2 (%), mean ± SD	76.8 ± 10.1	73.4 ± 9.8	85.0 ± 6.1	<0.001*
80–90% SpO2 duration (min), mean ± SD	92.9 ± 91.7	118.5 ± 95.6	25.1 ± 15.4	<0.001*
% Sleep time at 80–90% SpO2, mean ± SD	24.4 ± 22.2	31.0 ± 22.5	6.9 ± 5.8	<0.001*

BMI: Body Mass Index; AHI: Apnea-Hypopnea Index; SpO2: Oxygen saturation.

The mean age of the study population was 46.3 ± 10.1 years (range: 30–65 years), and 63.3% of the participants were female. The mean body mass index was 32.5 ± 6.4 kg/m², with values ranging from 19.0 to 48.5 kg/m². None of the participants had a history of systemic comorbidities such as diabetes mellitus, hypertension, renal failure, or other chronic systemic diseases. Correlation analyses demonstrated no significant associations between AHI and RNFL or GCC thickness in either eye. Similarly, mean oxygen saturation, lowest oxygen saturation, total duration of desaturation between 80% and 90%, and the percentage of time spent within this saturation range were not significantly correlated with RNFL or GCC measurements (all $p > 0.05$). These results are presented in Table 2.

Table 2. *The correlation analysis between sleep parameters and OCT measurements.*

Parameter	GCC OD (μm)	GCC OS (μm)	RNFL OD (μm)	RNFL OS (μm)
AHI	r = -0.08, p = 0.51	r = -0.10, p = 0.43	r = -0.12, p = 0.35	r = -0.09, p = 0.49
Mean SpO2 (%)	r = 0.11, p = 0.39	r = 0.09, p = 0.47	r = 0.08, p = 0.51	r = 0.10, p = 0.44
Lowest SpO2 (%)	r = 0.14, p = 0.27	r = 0.12, p = 0.34	r = 0.15, p = 0.23	r = 0.13, p = 0.31
80–90% SpO2 duration (min)	r = -0.07, p = 0.56	r = -0.09, p = 0.47	r = -0.11, p = 0.39	r = -0.10, p = 0.45
% Sleep time at 80–90% SpO2	r = -0.09, p = 0.48	r = -0.11, p = 0.38	r = -0.10, p = 0.44	r = -0.12, p = 0.34

GCC: Ganglion Cell Complex; RNFL: Retinal Nerve Fiber Layer; OD: Right Eye; OS: Left Eye; BMI: Body Mass Index; AHI: Apnea-Hypopnea Index; SpO2: Oxygen Saturation.

The mean AHI was 28.0 ± 23.6, with values ranging from 1.2 to 109.0. According to AASM criteria, 20 participants were classified as normal (AHI <5) and served as the control group, while 10 participants had mild OSA, 14 had moderate OSA, and 25 had severe OSA. The mean oxygen saturation during sleep was 90.6% ± 2.8%, and the lowest recorded oxygen saturation was 76.8% ± 10.1%. Participants spent an average of 92.9 ± 91.7 minutes with oxygen saturation between 80% and 90%, corresponding to 24.4 ± 22.2% of total sleep time. When patients with severe OSA were compared directly with the control group, no statistically significant differences were observed in average GCC thickness (97.65 ± 9.14 µm vs. 95.31 ± 2.44 µm, p = 0.32) or average RNFL thickness (102.47 ± 13.32 µm vs. 105.17 ± 7.97 µm, p = 0.56). The mean GCC thickness was 97.5 ± 7.6 µm in the right eye and 97.5 ± 8.1 µm in the left eye. The mean RNFL thickness was 104.9 ± 12.1 µm in the right eye and 107.0 ± 10.9 µm in the left eye.

Sectoral analyses of RNFL and GCC thickness did not reveal any statistically significant differences across OSA severity groups (p > 0.05), as summarised in Table 3.

Table 3. *Comparison of OCT parameters between OSAS and Control groups*

Parameter	OSAS (n=49) Mean ± SD	Control (n=20) Mean ± SD	p-value
Average GCC (µm)	97.03 ± 8.97	95.31 ± 2.44	0.32
Average RNFL (µm)	103.94 ± 12.36	105.17 ± 7.97	0.56

DISCUSSION

In this study, we evaluated the relationship between OSA severity, nocturnal hypoxemia parameters, and retinal structural measurements. No significant associations were found between polysomnography-derived indices, including AHI and oxygen saturation parameters, and OCT-derived GCC and RNFL thickness. In addition, retinal structural parameters did not differ significantly between OSA patients and healthy controls or within the severe OSA subgroup. These findings suggest that systemic hypoxemia alone may not be sufficient to explain early retinal structural changes.

Instead, local microvascular or perfusion-related factors may play a more important role. Our cross-sectional study did not find a significant correlation between the severity of OSA and the thickness of the RNFL or GCC. Several prior studies, however, have reported structural retinal changes in OSA. For instance, Shiba et al. found that nasal RNFL thickness decreases as OSA severity increases (6). Likewise, a meta-analysis by Yu et al. concluded that OSA patients had significantly thinner average RNFL than healthy controls, particularly in cases of moderate to severe disease (7). In contrast, other cross-sectional investigations have not observed consistent retinal thinning. Ferrández et al. reported no significant difference in GCC (ganglion cell layer + inner plexiform layer) thickness between OSA patients and controls (8) , although OSA patients in that study did show reduced retinal sensitivity on perimetry. Similarly, Moyal et al.(2018) found no significant differences in peripapillary or macular perfusion density between OSA patients and healthy individuals (9). Taken together, these conflicting results highlight the variability of findings across cross-sectional studies and suggest that the impact of OSA on retinal structure may be influenced by differences in study design, disease duration at the time of evaluation, comorbid conditions, or measurement techniques.

Intermittent hypoxemia is a hallmark feature of OSA and has been proposed as a potential mechanism for neural stress. Repeated cycles of oxygen desaturation and reoxygenation at night are thought to generate oxidative stress and inflammatory mediators. Experimental work by Kaur et al. demonstrated that hypoxia–ischemia in the retina can induce overexpression of hypoxia-inducible factor (HIF-1α) and downstream targets such as vascular endothelial growth factor (VEGF) and nitric

oxide synthase (10). Excess VEGF may disrupt the blood–retinal barrier, while increased nitric oxide and glutamate release have been associated with excitotoxicity and calcium influx, potentially leading to retinal ganglion cell (RGC) injury. These pathways have therefore been discussed in the literature as contributors to RGC loss during chronic intermittent hypoxia. RGCs are considered particularly sensitive to even short-term oxygen deprivation – Kergoat et al. reported that acute, transient hypoxic stress was sufficient to cause measurable RGC damage. Acute hypoxia tends to produce rapid energy failure and cell death, whereas chronic hypoxia might allow partial cellular adaptation. It has been hypothesized that prolonged low-grade hypoxia could trigger protective metabolic or mitochondrial adaptations in retinal neurons (11). Ferrández et al. suggested this as a possible explanation for why some OSA patients in their cross-sectional study did not exhibit RNFL thinning. In the context of our own cross-sectional findings, the absence of significant RNFL/GCC thinning despite OSA may indicate that intermittent hypoxia alone was not strongly associated with detectable retinal structural changes. The balance between potentially injurious effects of intermittent hypoxia and possible compensatory mechanisms may vary between individuals, but longitudinal studies would be needed to clarify this.

The relationship between OSA and glaucoma has been widely debated, with some epidemiological studies reporting a higher prevalence of glaucoma in patients with severe OSAS, potentially related to hypoxia-induced vascular dysregulation rather than intraocular pressure elevation (12). In this context, OSA has been proposed as a contributing factor to an optic neuropathy resembling normal-tension glaucoma, possibly mediated by vascular insufficiency and oxidative stress (13).

However, the present study focused primarily on early retinal structural changes rather than glaucomatous damage. In our cohort, none of the participants demonstrated manifest glaucoma, and no significant differences in RNFL or GCC thickness were observed across OSA severity groups. These findings suggest that OSA alone may not be sufficient to induce detectable structural retinal changes, at least in a cross-sectional setting. Consistent with previous reports, including Ferrández et al. (8), the relationship between OSA and ocular involvement appears to be heterogeneous and likely influenced by additional systemic and microvascular factors.

Interestingly, our cross-sectional results indicated that local retinal vascular factors may have a closer association with retinal status than systemic oxygen metrics. It has been hypothesised that ischaemia at the level of the retinal microcirculation could have a stronger influence on retinal ganglion cells (RGCs) than intermittent systemic hypoxaemia alone. Recent optical coherence tomography angiography (OCTA) studies have reported microvascular alterations in eyes with OSA, lending support to this idea. Ucak and Ünver (2020), for example, demonstrated reduced vessel densities in the superficial capillary plexus and radial peripapillary capillaries in OSA patients, which correlated with disease severity (14). Findık et al. observed significantly higher resistance in the posterior ciliary arteries that supply the optic nerve in OSA patients, which was accompanied by thinner RNFL measurements and a higher frequency of optic nerve ischaemic changes in those with severe OSA (12). Similarly, other investigators have described associations between reduced retinal perfusion and thinner retinal layers. In healthy individuals, a positive correlation has been documented between retinal capillary perfusion and inner retinal thickness (15), suggesting that chronic blood flow reduction may contribute to retinal thinning. Within this context, it is plausible that OSA-related ocular changes are more strongly linked to cumulative microvascular insufficiency rather than to systemic hypoxaemia indices such as AHI or average oxygen saturation. This interpretation may help explain why we did not observe direct correlations between systemic polysomnographic parameters and GCC/RNFL thickness in our study: these systemic metrics may not fully capture the nuances of ocular perfusion at a single time point.

Our observations are consistent with previous

cross-sectional studies suggesting that retinal vascular impairment may be an important mediator of structural changes in eyes with OSA (13). Indeed, OCTA has been identified as a valuable tool for detecting early microvascular alterations in glaucoma and other optic neuropathies, and it may also provide useful information in the assessment of OSA patients who could be at risk of optic nerve compromise (16).

The methods we used to assess retinal structure are worth noting. We employed the Optovue SD-OCT, which includes a dedicated GCC analysis. The GCC represents the combined thickness of the RNFL, the ganglion cell layer (GCL), and the inner plexiform layer (IPL) in the macula (17). This metric is clinically useful because glaucoma and other optic neuropathies tend to affect these inner retinal layers earlier and more prominently than the outer layers. By measuring the GCC in addition to the peripapillary RNFL, our aim was to provide a more comprehensive evaluation of RGC integrity. This constitutes an advantage over earlier OCT devices that reported only peripapillary RNFL thickness.

In our cross-sectional cohort, neither average RNFL thickness nor macular GCC thickness demonstrated significant reduction or correlation with OSA severity metrics. This finding may appear unexpected given the numerous mechanisms proposed for hypoxia-related retinal injury. One possible explanation is that many of our patients were newly diagnosed and had not yet developed long-standing OSA, meaning that structural degeneration may require a longer disease duration to become detectable. Another explanation is that subtle functional changes might precede structural alterations, which were not captured in our measurements. Importantly, our study design provides only a snapshot of baseline retinal status in untreated OSA, and does not allow conclusions about disease progression or causality.

Another important consideration in the interpretation of our findings is the difference in body mass index (BMI) between the groups. Increased BMI has been associated with systemic inflammation, endothelial dysfunction, and impaired microvascular circulation, all of which may potentially influence ocular structures and retinal integrity. Previous studies have suggested that obesity-related vascular dysregulation may affect retinal nerve fiber layer thickness and ocular perfusion. Therefore, the observed BMI difference in our cohort may have acted as a confounding factor, potentially masking or modulating the relationship between OSA severity and retinal parameters and increasing the risk of residual confounding. Although this variable was acknowledged as a limitation, its potential impact should be considered when interpreting the results. Future studies with better-controlled BMI distribution or adjusted analyses are warranted to clarify the independent effects of OSA on retinal structures.

Several limitations of this cross-sectional study should be acknowledged. The duration of OSA prior to diagnosis was unknown, preventing estimation of cumulative hypoxic exposure, which may partly explain the absence of consistent retinal structural changes. Retinal function was not assessed using visual field or electrophysiological tests, and subtle functional impairment may therefore have been missed. The relatively low statistical power (47% for a medium effect size) increases the risk of a type II error, and the lack of significant associations should be interpreted with caution. In addition, higher BMI in the OSA group represents a potential confounding factor, as obesity may independently affect vascular and ocular circulation. Finally, the limited sample size, particularly after stratification by OSA severity, and the reliance on static OCT measurements may have reduced sensitivity for detecting small or dynamic retinal changes, highlighting the need for larger longitudinal studies incorporating structural, functional, and vascular assessments.

The strengths of this study include the use of standard polysomnography for the confirmation of OSA in all participants, the performance of OCT measurements by a single masked examiner, and the inclusion of a treatment-naïve patient population.

CONCLUSION

In conclusion, this cross-sectional study did not demonstrate a significant association between OSA severity and retinal neurodegenerative parameters, including RNFL and GCC thickness. These findings suggest that systemic hypoxaemia or global hypoxic burden alone may be insufficient to explain early retinal structural changes. Retinal involvement may vary among individuals and could be influenced by additional factors, particularly local microvascular or ocular perfusion abnormalities. However, given the limited statistical power of the study, these results should be interpreted with caution. Larger, well-powered longitudinal studies incorporating both structural and functional retinal assessments are needed to confirm these findings and to further clarify the underlying pathophysiological mechanisms.

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ARAŞTIRMA MAKALESİ RESEARCH ARTICLE

Phytochemical Characterization and Preliminary In Vitro Cytotoxic Activity of the Endemic Plant *Cousinia birecikensis Hub.-Mor.**

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Abstract

Aim: This study aimed to characterize the phytochemical composition of the endemic plant Cousinia birecikensis and to evaluate its antioxidant capacity and preliminary in vitro cytotoxic activity.

Materials and Methods: Sequential extracts (hexane, dichloromethane, methanol, and aqueous) were prepared. Total phenolic and flavonoid contents were determined, and antioxidant capacity was evaluated using DPPH, ABTS, FRAP, and CUPRAC assays. LC-MS/MS analysis was performed for phytochemical profiling. Cytotoxic effects were assessed using the MTT assay on A549 and BEAS-2B cell lines, and apoptosis was evaluated using Annexin V-FITC/PI staining.

Results: Methanol and aqueous extracts exhibited higher phenolic content and antioxidant activity ($p<0.05$). LC-MS/MS analysis revealed fumaric acid and vanillic acid as major compounds. The methanol extract showed dose-dependent cytotoxic activity on A549 cells (IC^{50}: 89.67 µg/mL), while lower toxicity was observed in BEAS-2B cells. Annexin-V analysis indicated increased apoptotic cell populations.

Conclusion: The findings demonstrate that *Cousinia birecikensis* possesses significant antioxidant capacity and preliminary in vitro cytotoxic activity. Further in vivo and mechanistic studies are required to validate these findings.

Keywords: *Cousinia birecikensis, Antioxidant, Biochemical contents, Cytotoxic activity, Nutraceutical*

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Endemik Bitki Cousinia birecikensis'in Fitokimyasal Karakterizasyonu ve Ön İn Vitro Sitotoksik Aktivitesi

Özet

Amaç: Bu çalışma, endemik bitki *Cousinia birecikensis*'in fitokimyasal bileşimini karakterize etmeyi ve antioksidan kapasitesini ve ön in vitro sitotoksik aktivitesini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Ardışık ekstraktlar (heksan, diklorometan, metanol ve sulu) hazırlandı. Toplam fenolik ve flavonoid içerikleri belirlendi ve antioksidan kapasitesi DPPH, ABTS, FRAP ve CUPRAC testleri kullanılarak değerlendirildi. Fitokimyasal profilleme için LC-MS/MS analizi yapıldı. Sitotoksik etkiler, A549 ve BEAS-2B hücre hatlarında MTT testi kullanılarak değerlendirildi ve apoptoz, Annexin V-FITC/PI boyama yöntemi kullanılarak değerlendirildi.

Bulgular: Metanol ve sulu ekstraktlar daha yüksek fenolik içerik ve antioksidan aktivite sergiledi ($p<0,05$). LC-MS/MS analizi, fumarik asit ve vanilik asidin ana bileşikler olduğunu ortaya koydu. Metanol ekstresi, A549 hücrelerinde doza bağımlı sitotoksik aktivite gösterdi (IC^{50}: 89,67 µg/mL), BEAS-2B hücrelerinde ise daha düşük toksisite gözlendi. Annexin-V analizi, apoptotik hücre popülasyonlarında artış olduğunu gösterdi.

Sonuç: *Cousinia birecikensis*'in önemli antioksidan kapasiteye ve ön in vitro sitotoksik aktiviteye sahip olduğunu göstermektedir. Bu bulguları doğrulamak için daha ileri in vivo ve mekanistik çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: *Cousinia birecikensis, Antioksidan, Biyokimyasal içerikler, Sitotoksik aktivite, Nutrasötik*

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Abbreviations: TPC: Total Phenolic Content, **TFC:** Total Flavonoid Content, **DPPH:** 1,1-Diphenyl-2-picrylhydrazyl, **ABTS:** 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid), **FRAP:** Ferric Reducing Antioxidant Power, **CUPRAC:** Cupric Ion Reducing Antioxidant Capacity, **GAE:** gallic acid equivalent, **QE:** quercetin equivalent, **TE:** Trolox equivalent

INTRODUCTION

Plants play a central role in both modern and traditional medical practices and are at the forefront of pharmacological research. The phytochemicals they contain serve as a rich reservoir of molecular structures with healing properties. In addition to their contributions to the management and treatment of various diseases, these plants are also valuable components of defense mechanisms developed against global health challenges (1).

When examined from a technical perspective in the literature, medicinal plants are defined as biological resources that, thanks to the pharmacologically active molecules they contain, offer the possibility of therapeutic intervention—either directly or indirectly—in the prevention or treatment of specific pathologies (2).

Numerous studies aimed at determining the pharmacological potential of plants have examined the medical characteristics of these natural sources across a wide range, from their anti-inflammatory effects to their antitumor properties, and from their ability to combat diabetes to their components that combat oxidative stress (3).

Antioxidants are molecules that sacrifice themselves in the reduction process of free radicals, thereby oxidizing themselves and protecting neutral substrates. To halt the oxidation of biological structures, this defense mechanism must enter into a rapid reaction cycle with free radicals. The radical form resulting from the oxidation of the antioxidant must generate stable derivatives to disrupt the radical production mechanism within the system (4).

When the body's natural enzymatic defense cannot completely neutralize the radical species produced, oxidative stress develops. Identifying new antioxidant sources to bolster these defense mechanisms is of great importance in this context. Today, a wide variety of analytical methods are utilized to determine the efficacy of these potential sources and manage their development processes. In general, antioxidant compounds that enhance the body's resistance to free radicals are often obtained externally through dietary intake (5).

Pharmacologically active compounds isolated from natural sources play a strategic role in chemotherapeutic processes due to their greater compatibility with human physiology and relatively low side effect profiles. These plant-derived agents stand out for their potential to minimize the severe complications associated with conventional treatment methods (6).

Extracts derived from taxa belonging to the Asteraceae (Compositae) family exhibit a strong radical scavenging capacity due to their phenolic compound composition and other bioactive substances. These phenolic derivatives demonstrate therapeutic efficacy by stimulating endogenous antioxidant defense mechanisms, inactivating transition metal ions through chelation, and inhibiting free radical production pathways (7).

The primary objective of this study is to characterize the pharmacological properties of the endemic plant *Cousinia birecikensis* (*C. birecikensis*) (Asteraceae) is a species native to Türkiye and represents a valuable source of bioactive compounds. During the study, the antioxidant potential of the plant extracts (using ABTS, CUPRAC, FRAP, and DPPH methods), their metabolomic content (amino acids, carnitine, and vitamins), the structure of phenolic compounds, and trace element levels were characterized in detail. Additionally, the plant's in vitro activity against cancer cell lines was tested.

MATERIALS AND METHODS

Collection of Plants and Preparation of Solutions from Plant Samples

C. birecikensis plant material was collected from its natural habitats in the Atatürk Dam Lake basin (Euphrates River) within the province of Şanlıurfa. The plants were collected during the period when the taxon was most suitable for pharmacological analysis. After the *C. birecikensi*s plant samples used in the study were collected, they were left to dry in a shaded environment, away from direct sunlight, to preserve their phytochemical content. The dried plant material (flowers, leaves, and roots) was ground into a homogeneous powder using a mechanical grinder.

Portions of 100 grams were weighed from the powdered samples and, in the first stage, left to macerate in hexane at room temperature overnight. Following the incubation period, the mixtures were homogenized using an ultrasonicator for 15 minutes to enhance extraction efficiency. The resulting suspensions were filtered using Whatman filter paper, and the filtrate was concentrated using a rotary evaporator to remove the solvent, yielding the crude extract.

The plant residues separated from the solvent were dried in a freeze-dryer in preparation for the next step. The same extraction procedure was repeated using dichloromethane, methanol, and distilled water as solvents, in that order. Thanks to this stepwise solvent system, four distinct fractions with varying levels of polarity (hexane, dichloromethane, methanol, and aqueous) were obtained from the plant.

Total phenolic content determination

The total amount of phenolic compounds in the extracts was determined spectrophotometrically using the Folin-Ciocalteu reagent in accordance with the established methodology (8). Gallic acid was selected as the standard for quantitative analysis in this study. The absorbance values of the prepared standard series and samples were measured at a wavelength of 760 nm against a blank solution using a spectrophotometer. The obtained data were calculated using the gallic acid standard curve.

Total Flavonoid Content Determination

The total flavonoid content of the samples was determined using a colorimetric method (9). The intensity of the resulting chromogenic complex is directly proportional to the flavo-

noid concentration of the sample and was analyzed spectrophotometrically at a wavelength of 510 nm. The obtained absorbance data were calculated using a calibration curve established with quercetin as the standard.

FRAP Method (Ferric Reducing Antioxidant Power Analysis)
To determine the total reducing capacities of the extracts, fresh FRAP reagent was first prepared during the analysis process. A homogeneous mixture was obtained by adding 1 mL of plant extract and 2 mL of FRAP reagent to test tubes. The mixtures were incubated at room temperature for 30 minutes to allow the reaction to complete. At the end of the incubation period, the color intensity of the formed complex was measured spectrophotometrically at a wavelength of 593 nm (10, 11). Troloks was used as the standard for quantitative evaluation, and the entire procedure was repeated for the standard series.

Determination of ABTS Radical Scavenging Activity
The ABTS radical scavenging capacities of the extracts were determined by measuring the absorbance values of the samples and standard solutions spectrophotometrically at a wavelength of 734 nm. As a control group, a reaction mixture containing pure solvent (methanol) instead of plant extract was used (12). The radical scavenging percentage for each sample was calculated using the following formula:

ABTS (%) = [(C0-C1) / C0] x 100
C0 = Control absorbance value
C1 = Absorbance value of the sample and standard

Concentration-activity curves were plotted based on the calculated percentage inhibition values for the plant extracts and standards. The resulting curves were correlated with data from Troloks, which was used as a standard, and the results were reported in terms of Troloks equivalents.

CUPRAC method
To determine the copper-reducing antioxidant capacities of the extracts, 40 µL of a plant extract sample was added to the prepared reagent mixture and incubated at room temperature for 30 minutes. At the end of the incubation period, the absorbance values of the resulting colored complex were measured spectrophotometrically at a wavelength of 450 nm. Concentration-absorbance curves were plotted using the data obtained for both plant extracts and standard solutions, and the total reducing capacities of the samples were calculated (13,14).

DPPH Method
The free radical scavenging capacities of the extracts were determined using the stable DPPH radical. As part of the analysis, the absorbance values of the samples and standard solutions were measured spectrophotometrically at a wavelength of 517 nm (15). The radical scavenging activities of the samples were calculated as a percentage of inhibition using the following formula, compared to the negative control:

DPPH (%) = [(C0-C1) / C0] x 100
C0 = Control absorbance value
C1 = Absorbance value of the sample and standard

Concentration-activity graphs were constructed using the percentage values obtained for the plant extracts and standards. The data obtained from these graphs were correlated with the Troloks curve used as a standard, and the results were quantified in Troloks equivalent units.

Content Analyses of Plant Extracts
Advanced analytical techniques were employed to determine the phytochemical composition of methanol extracts obtained from the aboveground parts of the *C. birecikensis* plant. In this context, the phenolic compound profile, free amino acid content, and carnitine levels of the extracts were characterized using a high-sensitivity Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) system.

The trace element content of the samples was determined using the Inductively Coupled Plasma (ICP) method, a plasma-based ionization technique. Additionally, the concentrations of glucose, vitamin B12, and folic acid—which are of critical biochemical importance—were

quantified using the chemiluminescence method, which provides high specificity. This integrated analytical approach enabled the comprehensive mapping of both the organic and inorganic components of the plant extract.

Trace Element Content Analysis

The Inductively Coupled Plasma (ICP) method, a highly sensitive analytical technique, was used to determine the trace element composition in plant extracts. The ICP method is considered the gold standard in trace element analysis due to its low limits of detection (LOD), wide dynamic measurement range, and ability to simultaneously quantify multiple elements (multielemental analysis). In this study, the quantification of metals and metalloids in the extracts was performed within the framework of the high reproducibility and accuracy parameters provided by this method.

Investigation of the cytotoxic Activities of Plant Extracts

Cell culture

We would like to inform you that the cell lines used in this study are sourced and certified by the American Type Culture Collection (ATCC), and therefore do not require ethical committee approval. In this study, lung cancer epithelial (A549) and normal lung epithelial (BEAS-2B) cell lines were used. The cell lines used in the study were cultured by thawing samples stored under cryopreservation (stock) conditions in liquid nitrogen. For cell maintenance, appropriate culture media (RPMI-1640) enriched with 10% Fetal Bovine Serum (FBS) and supplemented with streptomycin and penicillin to prevent contamination were used.

Following the incubation process, cells that reached appropriate confluence (surface coverage density) on the plate surface within approximately 24 hours were detached from the surface using trypsinization, an enzymatic method. After centrifugation and counting, the cells were seeded onto plates at appropriate densities for the experimental groups and prepared for in vitro analysis.

Determination of cytotoxic effects using the MTT assay

The effects of plant extracts on cell viability were determined using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, which is based on mitochondrial metabolic activity. The basic principle of this method is that succinate dehydrogenase enzymes present in the mitochondria of live cells reduce the yellow-colored tetrazolium salt, converting it into purple-colored, water-insoluble formazan crystals. As part of the experimental procedure, normal and cancer cells in the logarithmic growth phase were seeded into 96-well microplates at a density of 1×10^4 cells per well and incubated for 24 hours. Following incubation, the existing culture medium was removed, and extracts at varying concentrations ranging from 0 to 200 µg/ml were applied to the cells. Wells containing only culture medium and no other substances were designated as "blank," while wells containing only cells and culture medium were designated as the "negative control" group. After a 24-hour incubation following the application, 10 µL of MTT solution was added to each well, and the plates were incubated in the dark for 4 hours. At the end of the incubation period, 100 µL of DMSO was added to the wells to dissolve the formed formazan crystals. The absorbance values of the resulting colored complex were measured at a wavelength of 570 nm using a microplate reader. Assuming the viability of the control group was 100%, the relative cell viability percentages (%) were calculated based on the absorbance values of the samples. Cell viability ratios in the experimental groups were calculated based on the normalization of the optical density (OD) data obtained from spectrophotometric analyses relative to the control group. Accordingly, the relative cell viability (viability) was determined by dividing the absorbance value of each sample by the average absorbance of the untreated control group and then converting it to a percentage:

([{Sample OD} / {Control OD}] × 100). These percentage values were used to quantitatively demonstrate the inhibitory effect of *C. birecikensis* extracts on cell proliferation and their cytotoxic potential.

Annexin V-FITC/PI flow cytometry analysis

The determination of cell death pathways (ap-

optotic or necrotic) was performed using the Annexin V-FITC and Propidium Iodide (PI) double-staining method. The principle of this method is based on the detection of Annexin V-FITC, a calcium-dependent fluorescent dye that binds to phosphatidylserine (PS) molecules, which translocate from the inner to the outer surface of the cell membrane during the early stages of apoptosis. FITC generates green fluorescence in cells bound to Annexin V, thereby identifying the early apoptotic population.

To identify dead or late apoptotic/necrotic cells, the PI dye was used, which intercalates into the nucleic acids of cells with disrupted membrane integrity and emits red fluorescence. The cells were analyzed using flow cytometry based on their fluorescence intensity and classified into four main populations: live, early apoptotic, late apoptotic, and necrotic.

Statistical Analysis

All experiments were performed in triplicate (n=3) and results are presented as mean ± standard deviation (SD). Statistical analyses were carried out using GraphPad Prism software (version XX). Differences between groups were evaluated using one-way ANOVA followed by Tukey's post hoc test. A *p*-value <0.05 was considered statistically significant.

IC_{50} Calculation

The half-maximal inhibitory concentration (IC_{50}) values were determined using nonlinear regression analysis (log(inhibitor) vs. normalized response) in GraphPad Prism. The SC_{50} values (the concentration required to scavenge 50% of free radicals) for DPPH and ABTS assays were calculated using nonlinear regression analysis based on concentration–inhibition curves. GraphPad Prism software was used for these calculations.

Solvent Control

All extract solutions were prepared in DMSO, and the final DMSO concentration in cell culture did not exceed 0.1%. A vehicle control group containing the same concentration of DMSO was included in all experiments.

RESULTS

Total phenolic content determination

For the determination of total phenolic content (TPC) in plant extracts, a calibration curve was established using gallic acid as the standard. The phenolic content values calculated based on the obtained data were standardized in mg GAE/g. When *C. birecikensis* flower extracts were analyzed, the most pronounced TPC values were observed in the methanol fraction, followed by the dichloromethane, water, and hexane extracts, respectively (183.06 ± 9.15; 52.3 ± 2.61; 51.95 ± 2.59; 31.95 ± 1.59 mg GAE/g). In leaf extracts, the hierarchy was methanol > water > dichloromethane > hexane, with numerical values recorded as 88.55 ± 4.42; 80.56 ± 4.02; 12.44 ± 0.62; and 12.02 ± 0.60 mg GAE/g, respectively. Similarly, in root extracts, the highest phenolic content was observed in the methanol phase (133.06 ± 6.65 mg GAE/g), while the efficiency of the other solvents was ranked as water (79.45 ± 3.97), dichloromethane (29.04 ± 1.45 mg GAE/g), and hexane (3.69 ± 0.18 mg GAE/g). The TPC results of the extracts are shown in Table 1.

Total flavonoid content determination

The total flavonoid contents (TFC) of the analyzed plant extracts were determined using a linear regression equation established with quercetin as the standard. The results are expressed in mg quercetin equivalent (mg QE/g). When the flavonoid contents of *C. birecikensis* flower extracts were examined, the highest values were observed in the methanol fraction (528.44 ± 26.42 mg QE/g). This was followed, in order, by the dichloromethane (261.08 ± 13.05 mg QE/g), water (25.52 ± 1.27 mg QE/g), and hexane (24 ± 1.2 mg QE/g) extracts.

In leaf samples, however, the hierarchy changed depending on solvent polarity; with the highest content detected in the water extract (166.63 ± 8.33 mg QE/g), while methanol (140.25 ± 7.01 mg QE/g), dichloromethane (33.16 ± 1.65 mg QE/g), and hexane (19.97 ± 0.99 mg QE/g) exhibited lower concentrations. In the data obtained from root extracts, the methanol phase (197.33 ± 9.86 mg QE/g) stood out; the water, dichloromethane, and hexane extracts, on the

other hand, completed this ranking with values of 163.86 ± 8.19; 132.61 ± 6.63, and 13.3 ± 0.66 mg QE/g, respectively. The TFC results of the extracts are shown in Table 1.

Table 1. Total phenolic content and total flavonoid content of *C. birecikensis* extracts

Plant part	Solvent	TPC (mg GAE/g)	TFC (mg QE/g)
Flowers	Water	51.95 ± 2.59	25.52 ± 1.27
	Dichloromethane	52.30 ± 2.61	261.08 ± 13.05
	Hexane	31.95 ± 1.59	24.00 ± 1.20
	Methanol	183.06 ± 9.15	528.44 ± 26.42
Leaves	Water	80.56 ± 4.02	166.63 ± 8.33
	Dichloromethane	12.44 ± 0.62	33.16 ± 1.65
	Hexane	12.02 ± 0.60	19.97 ± 0.99
	Methanol	88.55 ± 4.42	140.25 ± 7.01
Roots	Water	79.45 ± 3.97	163.86 ± 8.19
	Dichloromethane	29.04 ± 1.45	132.61 ± 6.63
	Hexane	3.69 ± 0.18	13.30 ± 0.66
	Methanol	133.06 ± 6.65	197.33 ± 9.86

Values are expressed as mean ± standard deviation (SD) of three independent experiments (n = 3).

DPPH assay

The free radical scavenging potentials of the extracts were determined using the DPPH method, and their antioxidant capacities were calculated in terms of the standard Trolox equivalent (mg Trolox/g). The strongest antioxidant activity observed in *C. birecikensis* flower extracts was detected in the methanol fraction (SC_{50} 45.66 ± 4.38 µg/mL), followed by the hexane, dichloromethane, and water extracts, which exhibited values of 67.06 ± 6.20; 62.17 ± 6.10, and 55.66 ± 5.88 µg/mL, respectively.

When the findings from leaf samples were examined, the SC_{50} values were as follows: methanol (56.38 ± 4.31 µg/mL), water (55.46 ± 4.27 µg/mL), hexane (64.85 ± 5.24 µg/mL), and dichloromethane (63.21 ± 5.16 µg/mL) extracts showed a similar yet hierarchical activity pattern. A similar pattern was observed for root extracts, with the highest scavenging effect SC_{50} recorded in the methanol extraction (52.44 ± 3.32 µg/mL). The other activity values for the root region were ranked as follows: water (54.06 ± 4.20 µg/mL), dichloromethane (62 ± 5.20 µg/mL), and hexane (68.51 ± 6.17 µg/mL). The DPPH results of the extracts are shown in Table 2.

ABTS assay

Troloks was used as the standard in the ABTS radical scavenging activity assay conducted as part of this study. When the antioxidant capacities of extracts obtained from different parts of the *C. birecikensis* plant were examined, the order of activity in the flower extracts was methanol > water > dichloromethane > hexane (SC_{50} 40.03 ± 3.80; 45.94 ± 4.74; 58.68 ± 5.43; 160.1 ± 12.80 µg/mL).

In leaf extracts, the highest activity values were observed in the water fraction, followed by methanol, dichloromethane, and hexane (SC_{50} 45.69 ± 4.78; 47.26 ± 5.71; 84.67 ± 9.23; 112.83 ± 11.64 µg/mL, respectively). Similarly, in root extracts, solvents with higher polarity (water and methanol) were found to exhibit stronger antioxidant potential (SC_{50} 42.48 ± 3.77; 45.26 ± 3.91; 77.05 ± 6.85; 124.94 ± 11.74 µg/mL). The ABTS results of the extracts are shown in Table 2.

FRAP assay

The iron-reducing antioxidant capacity (FRAP) of the extracts was determined using the standard compound Trolox (mg TE/g). As a result of the analyses, the antioxidant potential of *C. birecikensis* flower extracts was determined using methanol, dichloromethane, water, and hexane solvents in that order (1061.96 ± 53.09; 543.39 ± 27.16; 332.14 ± 16.60; 49.82 ± 2.49

mg TE/g). In leaf samples, the most pronounced activity was measured in the water extract, followed by the methanol, dichloromethane, and hexane fractions (507.85 ± 25.39; 472.85 ± 23.64; 117.5 ± 5.87; 41.07 ± 2.05 mg TE/g). In root extracts, the highest FRAP values were obtained in the methanol and water extracts, while dichloromethane and hexane exhibited lower capacity (683.75 ± 34.18; 641.07 ± 32.05; 196.96 ± 9.84; 42.5 ± 2.12 mg TE/g). The FRAP results of the extracts are shown in Table 2.

CUPRAC assay

The copper (II) reducing antioxidant capacities (CUPRAC) of the extracts were determined using analyses conducted with Troloks (mg TE/g) as the standard. The hierarchy of antioxidant activity observed in *C. birecikensis* flower extracts showed a sequence of methanol, water, dichloromethane, and hexane (202.82 ± 11.14; 127.16 ± 6.35; 36.3 ± 1.81; 32.75 ± 1.63 mg TE/g).

Upon examining the findings from leaf samples, it was determined that the highest values were again concentrated in the methanol extract, followed by the water, dichloromethane, and hexane fractions (200.12 ± 10.03; 143.82 ± 9.12; 48.04 ± 2.40; 17.6 ± 0.88 mg TE/g). A similar trend was observed in root extracts, with the strongest reducing capacity measured in the methanol fraction (176.22 ± 9.18 mg TE/g), while the lowest activity was detected in the hexane extract (11.22 ± 0.56 mg TE/g). The CUPRAC results of the extracts are shown in Table 2.

Table 2. Antioxidant activity results of *C. birecikensis* extracts

Plant part	Solvent	DPPH SC_{50} (µg/mL)	ABTS SC_{50} (µg/mL)	FRAP (mgTrolox/g)	CUPRAC (mgTrolox/g)
Flowers	Water	55.66 ± 5.88	45.94 ± 4.74	332.14 ± 16.60	127.16 ± 6.35
	Dichloromethane	62.17 ± 6.10	58.68 ± 5.43	543.39 ± 27.16	36.30 ± 1.81
	Hexane	67.06 ± 6.20	160.10 ± 12.80	49.82 ± 2.49	32.75 ± 1.63
	Methanol	45.66 ± 4.38	40.03 ± 3.80	1061.96 ±53.09	202.82 ± 11.14
Leaves	Water	55.46 ± 4.27	45.69 ± 4.78	507.85 ± 25.39	143.82 ± 9.12
	Dichloromethane	63.21 ± 5.16	84.67 ± 9.23	117.50 ± 5.87	48.04 ± 2.40
	Hexane	64.85 ± 5.24	112.83 ± 11.64	41.07 ± 2.05	17.60 ± 0.88
	Methanol	56.38 ± 4.31	47.26 ± 5.71	472.85 ± 23.64	200.12 ± 10.03
Roots	Water	54.06 ± 4.20	42.48 ± 3.77	641.07 ± 32.05	118.82 ± 9.11
	Dichloromethane	62.00 ± 5.20	77.05 ± 6.85	196.96 ± 9.84	52.45 ± 2.62
	Hexane	68.51 ± 6.17	124.94 ± 11.74	42.50 ± 2.12	11.22 ± 0.56
	Methanol	52.44 ± 3.32	45.26 ± 3.91	683.75 ± 34.18	176.22 ± 9.18

Values are expressed as mean ± standard deviation (SD) of three independent experiments (n = 3).

Phenolic Compound Profiles in Methanol Extracts of Plants

As part of this study, the phenolic composition of methanol extracts obtained from the above-ground parts of the *C. birecikensis* plant was analyzed qualitatively and quantitatively using the LC-MS/MS technique. Based on the chromatographic data obtained, the primary component identified in the methanol extract was fumaric acid (3398.75 µg/L). This primary component was followed by vanillic acid (2248.69 µg/L) and syringic acid (710.88 µg/L). Detailed phenolic profile distributions and quantitative values for the plant extracts in question are presented in Table 3.

Table 3. Phenolic contents of the *C. birecikensis* extract

Phenolic Compounds	Measure (µg/L)
Luteolin	390.35
Acetohydroxamic acid	116.80
Curcumin	4.08
Vanillic acid	2248.69
Naringenin	83.37
Syringic acid	710.88
Quercetin	86.78
Fumaric acid	3398.75
Ellagic acid	413.31
Caffeic acid	576.69
Oleuropein	18.51
Hydroxycinnamic	408.48
Salicylic acid	214.22
Hydroxybene	189.22

Additional Content Analysis of Plant Extracts

The levels of glucose, folic acid, and vitamin B12 in the methanol extracts were quantitatively determined using a chemiluminescence method. In the analyses conducted, glucose concentration in the aboveground parts of *C. birecikensis* was found to be 2.26 ng/mL, vitamin B12 0.048 ng/mL, and folic acid >24 ng/mL.

Upon examining the plant's basic elemental composition, it was observed that potassium (13,530 mg/kg) and calcium (10,820 mg/kg) were predominant in terms of mineral content; these elements were followed by sodium (1,293 mg/kg) and magnesium (591.3 mg/kg), respectively.

When the amino acid profile was analyzed, proline (4,600.45 µmol/L) and alanine (682.774 µmol/L) emerged as the most abundant components in the *C. birecikensis* methanol extract. In terms of essential amino acids, valine (434.149 µmol/L) has the highest concentration, followed by threonine, isoleucine, leucine, and phenylalanine. At lower levels, lysine (50.225 µmol/L), histidine (25.954 µmol/L), methionine (0.989 µmol/L), and tryptophan (0.168 µmol/L) were detected.

Furthermore, in the analysis of carnitine derivatives, free carnitine (2.65 µmol/L) and acetylcarnitine (1.26 µmol/L) were found to be the most prominent quantitative fractions in the extract.

Investigation of the Cytotoxic Activities of Plant Extracts

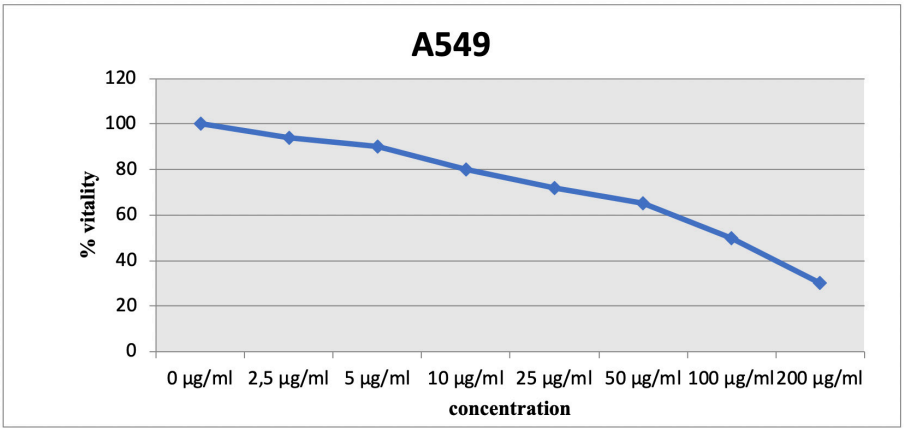
The cytotoxic potential of methanol extracts prepared from the aboveground parts of the *C. birecikensis* plant on cancerous and healthy cell lines was analyzed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and evaluated based on IC_{50} values.

When cell line-specific responses were examined, it was determined that *C. birecikensis* extracts exhibited significant antitumor activity against the A549 (lung adenocarcinoma) cell line. In comparative analyses with normal lung epithelial cells (BEAS-2B), it was determined that the extract's cytotoxic effect manifested at much higher doses in healthy cells compared to cancer cells.

As a result of the dose-response analyses conducted, it was determined that the inhibitory effect of the *C. birecikensis* extract on the proliferation of A549 lung cancer cells became evident at concentrations of 50 µg/mL and above.

This trend of decreased cell viability continued in parallel with increasing doses, and the half-maximal inhibitory concentration of the extract on the relevant cell line was calculated to be IC_{50} 89.67 µg/mL. This is shown in Figure 1.

Figure 1. Percentage viability graph of *C. birecikensis* extract on A549 cell line.



Investigation of the apoptotic effects of plant extracts using the Annexin-V method

The results of the Annexin-V analysis conducted on A549 cell lines quantitatively demonstrated the effect of *C. birecikensis* extract on programmed cell death. Under standard normoxic incubation conditions—37°C, 5% carbon dioxide, and 21% oxygen—the viability rate of untreated control group cells was determined to be 93.8%; the proportion of apoptotic and necrotic cells within the total population remained at 6.2%.

In contrast, in the experimental group treated with *C. birecikensis* extract at a concentration of 100 µg/mL, a significant decrease in cell viability was observed, dropping to 63.5%. At the same dose, the proportion of cells undergoing apoptotic and necrotic processes was found to rise to 36.6%. These data confirm that the applied extract significantly triggered cell death mechanisms (apoptosis/necrosis) in A549 lung cancer cells. This is shown in Figure 2 and Figure 3.

Figure 2. Annexin-V Result of A549 Cell Line

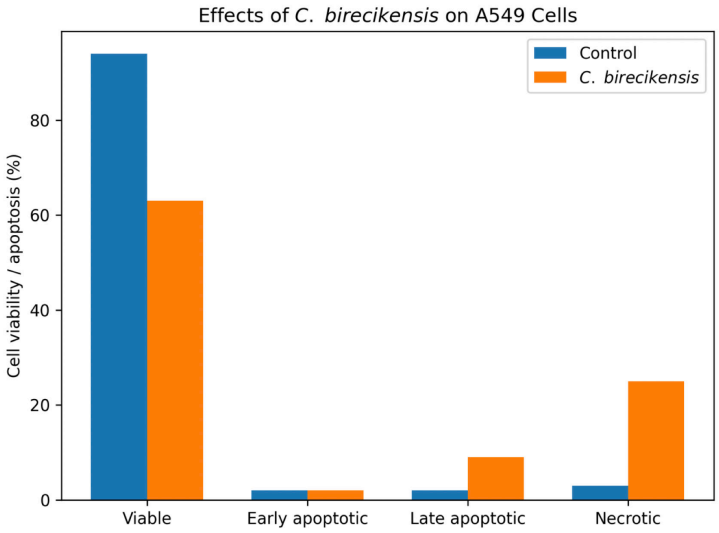
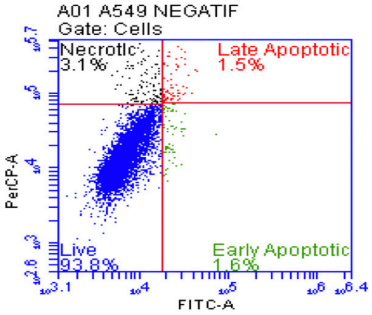
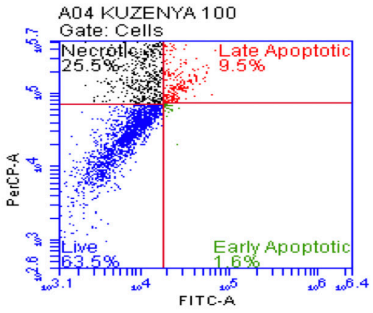


Figure 3. Demographic graph of Annexin-V Result of A549 Cell Line



Negative



C. birecikensis

DISCUSSION

The primary focus of this study is to identify the biological activities of the *C. birecikensis* plant with the aim of providing new natural resources for the treatment of cytotoxic activity and similar complex diseases.

In the extraction processes conducted on the flower, leaf, and root tissues of the *C. birecikensis* plant, it was observed that the phytochemical distribution varied depending on the polarity of the solvent. It was determined that the total phenolic content reached its highest values in methanol extracts in all three plant parts. When examining flavonoid distribution, methanol proved to be the most effective solvent in the flower and root sections, while water provided a more efficient extraction in the leaf tissue. A study conducted in the literature examining the Baccaurea angulata species supports our findings; as that study also reported that methanolic extracts possess the highest polyphenolic content and significant antiradical activity. This can be explained by methanol's selective success in extracting phenolic compounds and carotenoids, which exert an inhibitory effect on free radicals due to their ability to donate hydrogen (16).

A similar trend was also observed in a previous study. When the phytochemical profile of the Centaurea lycaonica species was examined, it was reported that methanol extracts exhibited high total phenolic and flavonoid concentrations, a finding that showed a strong correlation with the data from our study (17).

Based on radical scavenging activity (DPPH), the most pronounced activity values for all three morphological parts of the *C. birecikensis* taxon were recorded in the methanol extracts. Methanol has once again proven to be the most efficient solvent for the extraction of antioxidant components in flower, leaf, and root samples. Lower SC_{50} values observed in methanol extracts further support their strong antioxidant capacity, consistent with their higher phenolic content. The radical scavenging results we obtained for *C. birecikensis* are consistent with the data presented here. Researchers have determined that methanol and water fractions of the Centaurea lycaonica species exhibit significant antioxidant potential; this parallels the solvent efficacy observed in our study (17).

When examining the inhibitory effects of *C. birecikensis* samples on the ABTS radical, methanol extracts stood out in the flower parts, while aqueous extracts were observed to offer a more dominant antioxidant profile in the leaf and root sections. Lower SC_{50} values observed in methanol extracts further support their strong antioxidant capacity, consistent with their higher phenolic content. A study in the literature aligns with our findings that the activities of methanol and water solvents in ABTS analysis are comparable. Although methanol demonstrated slightly higher performance in the study in question, it was emphasized that both solvents were effective (18). Furthermore, the data obtained confirm the effectiveness of these two polar solvents in radical scavenging capacity, thereby reinforcing the validity of our study (17).

When the antioxidant potential of different morphological parts of *C. birecikensis* was examined using the FRAP method, it was observed that methanol was the most effective extraction solvent in flower and root samples, while water was the most effective in leaf samples. These data from our study are consistent with the results presented by Fatullayev et al. The researchers confirmed that the FRAP-based antioxidant levels in the methanol extracts of the plant species in question were superior to those of other solvent groups (17).

When the antioxidant potential of extracts obtained from the morphological parts of *C. birecikensis* was examined using the CUPRAC method, it was observed that methanol was the most effective solvent in all flower, leaf, and root samples. These results align with the data from the study conducted by Kubik et al. on taxa belonging to the Centaurea genus. The researchers emphasized that combinations of methanol and water also offer high reducing capacity, thereby confirming the solvent efficacy observed in our study (19).

An analysis of the compositional profile of the methanolic extracts revealed that *C. birecikensis* contains high levels of fumaric acid and vanillic acid. These findings are consistent with those of Boussoussa et al., who identified vanillic and syringic acids as the primary antioxidants in Rhanterium adpressum extracts (20). The roles of these phenolic compounds in vital processes—such as the regulation of endothelial function, the suppression of inflammation, and the balancing of blood pressure as an ACE inhibitor—have previously been reported by Liu et al. (21). Therefore, our study demonstrates that *C. birecikensis* is a strategic candidate as a botanical raw material for the production or supplementation of these biologically active molecules.

sis within the scope of the study revealed that *C. birecikensis* is source of potassium, calcium, and sodium. As emphasized by Baj et al. in the literature, the importance of calcium in bone development and neural regulation, the cardiovascular protective effect of potassium, and the vital role of sodium in electrolyte balance enhance the pharmaceutical value of this plant (22). The mineral profile data obtained from our study are consistent with the findings of Kovacik et al. (23).

Our research findings have revealed that the *C. birecikensis* taxon possesses an amino acid profile rich in proline and alanine. As emphasized by Raza and Linju in the literature, proline enhances the plant's resistance to environmental stressors through its ability to maintain cellular integrity and regulate oxidative stress pathways (24, 25). From a pharmacological perspective, it is essential for connective tissue health and collagen production. Similarly, alanine content plays a strategic role in regulating liver functions and the activity of aminotransferase enzymes through enzyme-substrate interactions in the body (26).

Carnitine, a key component of fatty acid metabolism in human physiology, plays critical roles in establishing hormonal balance and energy storage processes. This compound is primarily obtained exogenously through animal-based foods (meat, milk, and dairy products). Although animal sources are predominant, Jacques et al. have demonstrated the presence of carnitine in plant tissues and its biological significance through their studies on various plant species (27). In this study, the levels of free carnitine and acetyl carnitine detected in the *C. birecikensis* extract were recorded as the highest values among the measured parameters. The presence of free carnitine in the mitochondrial matrix enables the synthesis of acetyl-L-carnitine, which results in the reduction of acetyl-CoA, while also supporting the production of free CoA, which is essential for the continuity of the glycolytic pathway (28). Additionally, according to our analysis results, glucose, folic acid, and vitamin B12 were detected in the *C. birecikensis* extract. A deficiency in folic acid, which plays an active role in cellular growth, development, and amino acid metabolism cycles, can pave the way for serious pathologies such as anemia and carcinogenesis. Similarly, in cases of deficiency in components such as vitamin B12—which is of vital importance for maintaining the integrity of the nervous system and cell proliferation—replacement

through diet or dietary supplements is necessary (29).

As part of our studies, the cytotoxic potential of *C. birecikensis* extract on A549 and BEAS-2B cell lines was evaluated. The findings revealed that the extract exhibited significant cytotoxicity on both cell lines. Importantly, it was determined that the concentration required for the *C. birecikensis* extract to exert a cytotoxic effect on BEAS-2B cells was higher compared to that required for the A549 cell line. This indicates that the extract's inhibitory effect on the cancer cell line (A549) occurs at lower doses compared to BEAS-2B cells, which can be considered a control line.

According to the results of the Annexin-V analysis, the viability rate in the control group of A549 cells under normoxic conditions was 93.8%, while the total percentage of apoptotic and necrotic cells was recorded as 6.2%. In contrast, in the group treated with a 100 µg/mL dose of *C. birecikensis* extract, cell viability was found to have dropped to 63.5%, while the total proportion of apoptotic and necrotic cells rose to 36.6%.

All these findings demonstrate that the extracts possess biological cytotoxicity against lung cancer cell lines. Upon reviewing similar studies in the literature, it is observed that the results of the research conducted by Al Sharie et al. are consistent with our data. In the aforementioned study, it was reported that zinc oxide nanoparticles synthesized using the methanolic extract inhibited the proliferation of A549 human alveolar basal epithelial adenocarcinoma cells in a dose-dependent manner. MTT assays revealed that the methanolic extract exhibited preliminary cytotoxic activity against the A549 cell population (30). The results obtained in our study also support the therapeutic potential of plant extracts against lung cancer.

This study has several limitations. First, the cytotoxic activity was evaluated using only a single cancer cell line (A549), which limits the generalizability of the findings. Second, the molecular mechanisms underlying the observed cytotoxic effects were not investigated. Additionally, no in vivo validation was performed. Therefore, the present results should be considered as preliminary findings, and further studies involving multiple cancer models, mechanistic analyses, and in vivo experiments are required.

CONCLUSION

Within the scope of this study, the phytochemical profile, antioxidant capacity, and cytotoxic potential of plant extracts from *C. birecikensis*, an endemic species, were comprehensively analyzed.

Methanol and water extracts were found to exhibit high activity in DPPH, ABTS, FRAP, CUPRAC, TPC, and TFC assays. These data confirm that *C. birecikensis* possesses radical scavenging potential. In the conducted content analyses, fumaric acid and vanillic acid emerged as the primary components. Due to its rich phenolic and flavonoid content, it is anticipated that this plant could be utilized as a natural antioxidant source in the pharmaceutical or food industry by neutralizing free radicals. While the concentrations of potassium (K), calcium (Ca), and sodium (Na) in the plant are measured at the highest levels, the absence of heavy metals with toxic properties is critical for the plant's safety profile.

Proline and alanine were identified as the predominant components in the amino acid profile. Additionally, the detection of high levels of free carnitine and acetyl carnitine in the extracts indicates the plant's importance in metabolic processes. The presence of glucose, as well as vital micronutrients such as folic acid and vitamin B12, in the extracts enhances the plant's nutraceutical value.

It has been found that *C. birecikensis* extract exhibits a preliminary cytotoxic effect on lung cancer cell lines. The biomolecular richness of this endemic species highlights its potential for use in disease prevention or as a supportive therapy. Additionally, it possesses the potential to serve as a value-added commercial product for the regional economy.

In conclusion, *C. birecikensis* exhibits notable antioxidant capacity and preliminary in vitro

cytotoxic activity against A549 lung cancer cells. However, these findings are limited to in vitro conditions and a single cell model. Further studies, including mechanistic investigations and in vivo validation, are necessary to clarify its potential biological and pharmacological relevance.

Author's contributions: Methodology: V.A., I.K.; Software: M.M.B.; Validation: V.A., I.K.; Formal Analysis: V.A., F.Z.A.; Investigation: V.A., M.M.B.; Resources: V.A.; Data Curation: V.A.; Writing-Original Draft Preparation: V.A.; Writing-Review-Editing: V.A., I.K., F.Z.A.; Visualization: V.A.; Supervision: I.K.

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Ethics approval: Ethics approval was not applicable, as the study was performed solely on herbal/plant material.

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ARAŞTIRMA MAKALESİ **RESEARCH ARTICLE**

Asırlık bir Hekimin Gözlemlerinden Tıbbın 100 Yılı: Tıp Eğitim Tarihi Portre Biyografi Araştırması

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Özet

Amaç: Cumhuriyetle yaşıt bir hekim olarak son yüzyılın tıbbi gelişmelerine yakından tanıklık edip katkı veren Prof. Dr. Osman Akata'nın tıbbın ve tıp eğitiminin son 100 yılına ilişin gözlemlerinin araştırılmasıdır.

Gereç ve Yöntem: Ankara Tıp Fakültesi Genel Cerrahi emekli Anabilim Dalı Başkanı Akata araştırma konusu olarak seçilmiş 2019 yılı sonunda bir "görüşme" gerçekleştirilmiş ve konuyla ilişkin kaynakların "metin analiz yönetimi" ile değerlendirilmesiyle "Tıp Eğitim Tarihi Portre Biyografik Araştırması" gerçekleştirilmiştir.

Bulgular: Prof. Dr. Osman Akata 100 yaşında bir hekim olarak Cumhuriyet Dönemi tıp eğitiminin gelişmelerine tanıklık edip katkıda bulunmuştur. 1933 Üniversite Reformuyla ülkemize gelen bilim insanlarının eğittiği Akata; gerçekleştirdiği ülkemiz cerrahisinde bir devrim olan abdominal aorta anevrizması ameliyatıyla sentetik damar yaması graft uygulamasını "Tarihte Bireyin Rolü" ilkesi doğrultusunda bu ameliyat için tıbbi yetkinliği ile uygulayabilecek cesareti olduğu ve ameliyatı gerektiren koşullar da işlemi yapmasına imkan verdiğinden **"**Etkenler Kuramı" bağlamında gerçekleştirebilmiştir. Prof. Dr. Osman Akata; 100 yıllık yaşamında ülkemizde yeni tıp fakültelerinin kuruluşuna, tıp eğitiminde genel cerrahiden diğer cerrahi dallarının ayrılmasına, ameliyahane hizmetleriyle teknolojisinin gelişmesine ve cerrahi uygulamaların ilerlemesine de tanıklık etmiştir.

Sonuç: "Tarih Yöntem Bilgisi"; olayların analizinde "Tarihte Bireyin Rolü" ilkesiyle kişilerin katkılarının tanımlanmasıdır. "Tarihte Bireyin Rolü" kitabında **"**Etkenler Kuramı"nda Phlehanov:"olayların gelişimi kaçınılmazsa kişi olayların ilerlemesine yardımcı olan veya olayın gelişimine karşı bir eylem gerçekleştirir" görüşünü savunmaktadır. Prof. Dr. Osman Akata gerçekleştirdiği ülkemiz cerrahisinde bir devrim niteliğindeki abdominal aorta anevrizması ameliyatında sentetik damar yaması uygulamasını "Tarihte Bireyin Rolü" doğrultusunda bu ameliyat uygulayabilecek cerrahi yetkinliği ile işlemi uygulayabilecek cesareti olduğu ve ameliyatı gerektiren tarihsel koşullar da bu cerrahi işlemi yapmasına imkan verdiği için **"**Etkenler Kuramı" bağlamında gerçekleştirebilmiştir.

Anahtar Kelimeler: *Tıp eğitimi, Üniversite reformu,Cerrahi, Anevrizma, Tıp tarihi*

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100 Years of Medicine from a Century-Old Physician's Observations: Medical Education History Portrait Biographical Research

Abstract

Aim: Researching the observations of Prof. Dr. Osman Akata, a century old physician who witnessed the medical developments and contributed to advancements of the last 100 years was aimed.

Material and Methods: Prof. Dr. Osman Akata, a retired chairman of Ankara University Medical Faculty General Surgery Clinics was selected as the subject, an "interview" was conducted at the end of 2019, and a "Medical Education History Portrait Biographical Research" was carried out by evaluating the relevant literature sources using "text analysis methodology".

Results: Prof. Dr. Osman Akata, a century old physician, was educated by scientists who came to Turkey with the 1933 University Reform, witnessed and contributed to the Republican Era's medical education advancements. Akata, performed a revolutionary abdominal aortic aneurysm surgery by synthetic vascular graft in accordance with the "Individual's Role in History". His competence, courage and also circumstances enabled him within the "Theory of Factors". He has witnessed new medical faculties' establishments, branching off surgery medical education, operational technological developments, and surgical practices advancements throughout his century old life.

Conclusion: "Individual's Role in History" is an analysis of events and individual's contributions in the "Methodology of History". Phlekhanov in "Individual's Role in History" book defined it as: "if events are inevitable, a person will either helps or halts their progress by his actions". Prof. Dr. Osman Akata performed a revolutionary abdominal aortic aneurysm surgery by using a synthetic vascular graft within the context of the "Theory of Factors" as his competence and courage within "Individual's Role in history" and the circumstances also permitted him to act.

Keywords: *Medical education, University reform, Surgery, Aneurysm, Medical history*

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GİRİŞ

Atatürk Türkiyesi'nin 1933 üniversite reformu ile kesişen Akata'nın yaşam öyküsü

Dar-ül Fü'nun 06 Haziran 1933 tarihinde 2252 sayılı kanunla kapatılmış, İstanbul Üniversitesi kurulmuş; Atatürk'ün davetiyle Nazi Almanyası'ndan kaçan öğretim üyeleri Türkiye'ye gelmişlerdir. Ankara Tıp Fakültesi de 9 Haziran 1937'de 3328 sayılı yasayla kurulmuş ancak İkinci Dünya Savaşı nedeniyle ertelenen açılışını 19 Ekim 1945'de İsmet İnönü gerçekleştirmiştir. Ankara Fen Fakültesinde temel tıp eğitimi; Cebeci Kampüsündeki hastanede ve Numune Hastanesinde klinik staj eğitimi verilmiştir. Ankara Üniversitesi ise 18 Haziran 1946'da 4936 sayılı yasayla Cumhuriyetin ilk ve Türkiye'nin İstanbul Üniversitesi ve İstanbul Teknik Üniversitesi ardından üçüncü üniversitesi olarak kurulmuştur (1, 2, 3, 4, 5, 6, 7).

Almanya'dan 1933 yılında gelen öğretim üyeleri: Ankara Hukuk Fakültesi'nde: Ernest Hirsch, İstanbul Hukuk Fakültesi'nde: Gerhard Kessler ve Fritz Nuemark, İstanbul İktisat Fakültesi'nde: Alexander Rustow ve Wilhelm Röpke, Cumhurbaşkanlığı Senfoni Orkestrası'nda: Paul Hindenmith ve Ernst Praetorius, Devlet Tiyatrosu'nda: Carl Ebert, Devlet Konservatuvarı'nda: Eduard Zuckmayer, Devlet Güzel Sanatlar Akademisi'nde: Bruno Taut, Mülkiye Mektebi'nde: Ernest Reuter, İstanbul Teknik Üniversitesi Mimari'de: Clemens Holzmeister, Ankara Dil-Tarih-Coğrafya Fakültesi Arkeoloji'de: Hans Gustav Güterbock, Ankara Fen Fakültesi'nde: Freundlich ve Gleissberg, İstanbul Fen Fakültesi'nde yazarların büyükhalaları Prof. Dr. Neriman Konoralp Ozban'ı biliminsanı olarak yetiştiren Kurt Kosswig, İstanbul Tıp Fakültesi'nde: Nissen, Liepmann ve Igersheimer; Numune Hastanesi'nin Kulak-Burun-Boğaz Kliniği'nde: Max Meyer, Fizik Tedavi Kliniği'nde: August Laquer, Dahiliye Kliniği'nde: Ernst Magnos Alsleben, Genel Cerrahi Kliniği'nde: Edward Melchior

ve Çocuk Hastalıkları Kliniği'nde yazarların anneleri ile büyükannesi olan Ankara Tıp Fakültesi Çocuk Hastalıkları Kliniği'nden 1966 yılında uzmanlık alan Uzm. Dr. Tülay Konoralp Kılıçaslan'ın da hocası Prof. Dr. Bahtiyar Demirağ'ı yetiştiren Dr. Albert Eckstein idi. Bu hocalardan beklenen öğrencileri yetiştirmeleri, konularında bilimsel makaleler ve ders kitapları hazırlamalarıydı (1, 2, 3, 4).

Osman Akata ise Ordu ilinde 1923'de doğmuş, o dönem Türkiye'nin tek tıp fakültesi olan İstanbul Tıp Fakültesi'ni 1941'de başlayıp 1948'de bitirmiştir. Türkiye'nin ikinci ve Cumhuriyet'in ilk tıp fakültesi olan Ankara Tıp Fakültesi'nin II.Genel Cerrahi Kliniği Numune Hastanesi'nde Dr. Edward Melchior'un yanında 1950-1953 yılları arasında uzmanlık eğitimi alıp New York Colombia ve Baltimor Maryland Üniversiteleri'ne 1957-1959 yılları arası vasküler cerrahi uzmanlığı için gönderilmiştir. Akata; Baltimore'daki hastanede yaşlı bir meslektaşının Dr. Melchior'un öğrencisi olduğu kendisine güven duyduğunu ve Atatürk'ün "1933 Üniversite Reformu"nun ne denli isabetli olduğunu bu surette anladığını görüşmede belirtmiştir (8).

Akata; Türkiye'ye 1959'da dönüp 4 Mart 1960'da "teflon sentetik greft ile Abdominal Aorta Anevrizması ameliyatı" yaparak Türk Tıp Tarihi'ne geçmiştir. Ankara Tıp Fakültesi Genel Cerrahi Kliniği'nde 1961'de doçent, 1966'da profesör olmuş; 1974-1990 yılları arası Genel Cerrahi Anabilim Dalı Başkanlığı'nı üstlenip, 1974-1979 yılları arasında Ankara Tıp Fakültesi Genel Cerrahi Anabilim Dalı ile birleştirilen Tıp Tarihi ve Etik Anabilim Dalı Başkanlığı'nı yürütmüştür. Genel Cerrahi Anabilim Dalı'ndan Ortopedi ve Travmatoloji, Göğüs Cerrahi, Kalp ve Damar Cerrahisi, Çocuk Cerrahisi, Plastik ve Rekonstrüktif Cerrahi Anbilim Dalları'nın ayrıldığını görüp Vasküler Cerrahi Bilim Dalı'nın kurulmasını sağlamış ve 1990'da emekli olmuştur (8, 9, 10).

GEREÇ ve YÖNTEM

"Tıp Eğitim Tarihi Portre Biyografik Araştırması" için Ankara Tıp Fakültesi Genel Cerrahi emekli Anabilim Dalı Başkanı Prof. Dr. Osman Akata seçilmiştir. Akata; 100 yıllık yaşamında tıbbın ve tıp eğitiminin gelişimine tanıklık etmiştir.

"Tarih Yöntem Bilgisi" açısından "Tarihte Bireyin Rolü" konusu tarihi olayların analizinde bireysel katkı, başarı ve emeklerin aslına uygun olarak tanımlanıp; "biyografik tarih araştırması" ile tarihsel arka plan önünde kişilerin katkılarının gerçekçi olarak ifade edilmesidir. Phlehanov'un "Tarihte Bireyin Rolü" kitabındaki "Etkenler Kuramı"nda: "kişinin eylemleri zorunlu olaylar sıralamasında yer alan etkense olayların gelişiminin kaçınılmaz olduğuna ilişkin genel kanı oluştuğunda kişi ya eylemini gerçekleştirmek için yardımcı olan veya olayın gelişimine karşı olan bir eylem gerçekleştirir" denilmektedir.

Akata; devrim niteliğindeki abdominal aorta anevrizması ameliyatıyla sentetik yama uygulamasını tıbbi yetkinliği ve bunu uygulayabilecek cesareti olduğu için yine ameliyatı gerektiren şartlar işlemi yapmasına imkan verdiğinden eylemi gerçekleştirebilmiştir (11, 12).

Ankara Tıp Fakültesi Genel Cerrahi öğretim üyesi Prof. Dr. Uğur Bengisun aracılığıyla Akata ve ailesinden izin alınıp "yüzyüze görüşme metodu" ile "Helsinki Deklarasyon Prensipleri'ne uygun" bir "nitel araştırma" gerçekleştirilmiştir. Bu "Tıp Eğitim Tarihi Portre Biyografik Araştırması" 1933 Üniversite Reformu'nu yaşayan Akata'nın hatıralarının değerlendirilmesi amacıyla Covid-19 salgını öncesi 2019 yılı sonunda yapılmıştır. "Tarih Yöntem Bilgisi" metodolojisiyle ilgili süreç araştırılıp Ankara'daki üniversite kütüphanelerinden konuyla ilişkin kaynakların bulunup ayrıştırılıp "metin analiz yönetimi" ile değerlendirilmesiyle gerçekleştirilmiştir.

BULGULAR

Osman Akata'nın tıp ve cerrahi'deki gelişim sürecine tanıklığı

Akata; 1942 yılında İstanbul Tıp Fakültesi'ne başladığında Atatürk Türkiye'sinde "1933 Üniversite Reformu" yeni yapılmıştı. Reformun amacı çağdaş bilim standartlarına ulaşılıp ülkemize bilim insanlarının kazandırılmasıydı (1, 2, 3, 4).

İstanbul Tıp Fakültesi'nde öğrenci olduğu 1942-1948 arası dönemi izlenimlerini anlatırken Akata; Almanya'dan gelen profesörlerin Türkiye için bir fırsat olduğunu ilerleyen yıllarda bu hocaların kendilerine çok avantajlar sağladığını belirtmektedir. Akata; İstanbul Tıp Fakültesi öğrenciliği döneminde bu hocaların asistanları da olan Türk tercümanlarla ders yaptıklarına tanıklık etmiştir. O dönem hakim olan dilin Almanca ve Fransızca olduğunu; kitaplar Türkçe'ye çevrildiği için kitap sıkıntısı çekmediklerini de belirtmektedir (8).

Akata'nın Genel cerrahi uzmanlık eğitimine 1950 yılında başladığı dönemde abdominal aorta anevrizması ameliyatı dünyada ilk kez 29 Mart 1951 yılında Paris'de Fransız albayı Dr. Charles Dubost tarafından gerçekleştirilmiştir. Dubost; 50 yaşında erkek hastada abdominal aorta anevrizmasını çıkarıp bir kadavranın Torasik Aorta'sını hastasının Sağ Arteria Illiaca Comunis'ine anastomoz yapmış ve bu girişim tarihe geçmiştir (6, 7, 13).

Akata'nın ülkemizde ilk kez gerçekleştirdiği ameliyat ve önemi

Akata; 1953'de genel cerrahi uzmanı olarak vasküler cerrahi deneyimi için New York Columbia ve Baltimore Maryland Üniversitesi'ne gönderilmiş, ülkemize 1959'da donüp 4 Mart 1960'da Ankara Tıp Fakültesi'nde Türkiye'nin ilk abdominal aorta anevrizması ameliyatını gerçekleştirip sentetik damar yaması Polivinil Klorid yapılı "Vinyon-N" grefti kullanarak 60 yaşındaki bir erkek hastasını opere etmiştir. Akata; bu ameliyatın en önemli noktasının: "organik bir yapı olan insan vücuduna yerleştirilen inorganik sentetik bir madde" olduğu belirtmekte; ameliyatın olanaklılığını ise: "kullanılacak sentetik inorganik maddenin temini kolay, ucuz ve dayanıklı, tüm damarlarıda uygulanabilir olması" gerekliliğine bağlamaktadır (8).

Akata; geçen yarım yüzyıla rağmen ülkemizin halen bu materyallerin üretmekte güçlük çekildiğini, daha ucuz ithal greftlerinin tercih edildiğini belirtmektedir. Bunu: "teknoloji transferine açık bir ülke olmamıza" bağlayıp; bağımlılığın önlenebilmesinde üretimde istenen düzeye gelinemediğini belirtip durumu: "ben ameliyatı yapıp damarı değiştirebilirim ama bu damarı üretemem" sözleriyle tıbbın gelişmesi için mühendisliğin gelişmesi gerekliliğine değinip; "eğer bunlar gelişmez ise ancak kopyasının çekilebileceğine" vurgu da yapmaktadır (8).

Akata'nın gözünden yıllar içinde tıp ortamının değişimi ve ileriye yönelik düşünceleri

Akata; İstanbul Tıp Fakültesi'ne 1942'de başlarken Rektör Cemil Birsel'in evraklarını imzalayıp ellerini sıktığını anlatıp o dönem üniversite okumanın nadir bir iş olduğunu ifade etmiştir. Ülkemize 1933'de gelen bilim insanlarının İstanbul Tıp Fakültesi'nde de bulunduğunu belirten Akata: "ilk sene fizik-kimya-biyolojiden son sınıfa kadar meşhur hocalarla okuduk" diyerek: "tabi o zaman kıymetini bilebildik mi bilemiyorum ama şimdi düşünüyorum da o adamlar hakikaten dünyanın en kıymetli adamlarıymış" sözleriyle dönemi tanımlamıştır (8).

Ankara Tıp Fakültesi'ne bağlı Numune Hastanesi'nin Genel Cerrahi Kliniği Direktörlüğüne getirilen Dr. Edward Melchior'un yanına uzmanlık eğitimi aldığı beliriten Akata hocasını: "gayet disiplinli bir hocaydı. Türkiye'ye 1934'de gelmişti. Çok çalışkan ve örnek bir hocaydı. Hergün evinin olduğu Yenişehir'den yürüyerek saat 07.00'da, tatiller hariç, hiç aksatmadan Numune Hastanesi'ne gelirdi" sözleriyle anmaktadır (8). Akata; 1957'de eğitim için gönderildiği Baltimor'daki bir Amerikalı cerrahın kendisine Heidelberg'li Prof. Dr. Melchior'un yanında yetişmiş hekim olarak güvenebileceğini söylediğini belirterek: "bu hocanın yanında yetişmek bana avantaj oldu." sözleriyle bu hocaların değerini de ifade etmiştir (8). Akata; Dr. Melchior'un geldiği ortamı anlatırken: "hoca bana demişti ki 1934'de Ankara'ya geldim. Bir appandisit paniği vardı"; Dr. Melchior'un sözleriyle konuyu açarak: "Perfore Appandist'ten gelen hastalar peritonitten ölüyorlardı, çünkü teşhis koyamıyorlardı. Rebound Tenderness muayene bulgusunu hekimleriniz bilmiyorlardı. İyi hekimler yetişmemişti o zamana dek dedi." şeklinde açıklamış; Dr. Melchior'un yorumlarını aktararak: "Rebound Tenderness Apandist'te tanı koydurucudur. Bunu dahi bilmiyorlardı. Akut Karında ya bir davranışta bulunmaktan korkuyorlardı ya da 1934'de Ankara'da herkes korkudan appen-

dektomi yapıyordu. Ben regule ettim bunu ve lüzümsuz appendektomilere mani oldum." hatıralarıyla 1933'de gelen hocaların katkılarını tanımlamıştır (8). Akata'nın öğrenciliği ve asistanlığında ülkemizde hastane sayısı, hasta yatağı sayısı ve hekim sayısı yetersizdir. Ameliyatta intratrakeal anestezi yoktur. Ameliyathanede tamponlar defalarca kullanılmakta, cerrahi iplikler piyasadan toplanıp sterilize edilmekte, cerrahi eldivenler kaynatılıp yeniden kullanılmaktadır. Akata yatak yetersizliğini şöyle ifade etmiştir: "125 yataklı Cerrahi Kliniğinin 200'den fazla hastası olurdu ve yerlerde yatılırdı. Peritoniti olan veya kanayan hastayı geri gönderemezsin biz de ameliyat yapar yere yatırırdık." (8). Anestezi'nin cerrahiye getirdiği yenilikleri açıklarken Osman Akata durumu söyle ifade etmiştir: "narkoz vermek lazımdı ama asistanlığım devrinde açık eterle hastayı uyutuyorduk. Anestezi için tüpü koyacaksınız ki göğüsünü açacaksınız. Biz ancak yaralanıp göğüsü açılmışlar ile ampiyem vak'alarına müdahale edebiliyorduk; yoksa regüler bir lobektomi, pnömonektomi yapılamıyordu. Asıl cerrahi ise narkoz mütehassısları yetişip, 1952-1953'de Narkoz aletleri Türkiye'ye gelmeye başlayınca mümkün oldu, zaten Göğüs Cerrahi de ondan sonra ayrıldı. Cerrahinin gelişmesi teknolojiyle olmuştur." Nitekim bu dönemde ileri eğitim için üniversite tarafından Almanya'ya gönderilmiş sorumlu yazarın kayınpederi Uzm. Dr. Fikret Çakmaklı'nın da aralarında bulunduğu anestezi uzmanları dönüşlerinde Ankara Tıp Fakültesi'nde intratreakeal anestezi uygulamaya başlamışlardır (8).

Akata; teçhizat yetersizliği bahisle: "kanı durdurmak için kullandığımız gazlı tamponları su dolu kovaya ayırıyorduk orada yıkanınca tekrar kullanıyorduk. Eldivenleri kaynatıp kullanıyorduk. O devrin ipek iplikleri cerrahi iplikler değildi. Piyasadan topluyorduk, makara iplikleri, sağlam keten iplikler kullanıyorduk" sözcükleriyle tanımlamış; transfüzyon ve sıvı replasmanı yapılamadığını ise: "serum intravenöz replasman yapılmıyordu. Kendi imal ettiğimiz serumları takıyorduk ki onlardan da iki tanesinden biri titretiyordu. Transfüzyon çok enderdi ancak 1950'den sonra gelişip kan bankaları kuruldu" sözleriyle ifade etmiştir (8). Akata; cerrahinin nasıl dallara ayrıldığına değinirken: "genel cerrahiye başladığımda beyin cerrahisi, göğüs cerahisi, plastik cerrahi yoktu; hepsini biz genel cerrahlar yapıyorduk. Kalp ameliyatları da bizden sonradır. Göğüs-kalp-damar cerrahi için genel anestezi lazımdı." diyerek tıbbi gelişimine tanıklığını şöyle ifade etmiştir: "intratrakeal anestezi sonrası cerrahi gelişti. Bizden sonra 15-20 yılda Türkiye'de ve dünyada cerrahi çok üst seviyelere gelmiştir." Nitekim yazarların baba ve büyükbabası 1954 Ankara Tıp Fakültesi ve 1963 Gülhane Askeri Tıp Akademisi mezunu Opr. Dr. Mehmet Yaşar Kılıçaslan'ın genel cerrahi tıpta uzmanlık kitapları içinde damar cerrahi, göğüs cerrahi operasyonları mevcut olduğu saptanmış olup o dönem genel cerrahlar ortopedi ampütasyonlarını da uygulamakta olduğu da kaynaklarımızdan tespit edilmiştir (8).

Akata; öğrencilik döneminde hekim eksikliğine değinerek:"bugün memleketin her ilinde bir tıp fakültesi var. Bu tenkit edilebilir ama benim asistanlığımda Anadoludan otobüs dolusu insan gelirdi, Numune Hastanesinin kapısına sabah dökülürlerdi. Anadolu hekimsizdi. Türkiye'de 4,000-4,500 hekim vardı; üçte ikisi İstanbul, İzmir ve Ankara'da yoğunlaşmıştı." ifadelerini kullanmış tıp eğitiminde yeni tıp fakülteleri lehinde tutum sergilemiştir (8). Eğitimde teknolojik gelişimle bilgiye ulaşmanın kolaylaştığına da değinerek: "bilgisayar her şeyi değiştirdi ve artık öğrenmek kolay, dünyanın her yerindeki bilgiye elinizdeki küçücük aletle ulaşabiliyorsunuz." diyen Akata; dönemlerinde bilgiye ulaşmanın ancak basılı yayınlarla mümkün olduğunu, dergilerin uzun yazışma süreçlerine tabi olduğunu hatırlatıp: "bilgi alacağız diye mecmuaya yazardık. Cevap gelemesi haftalar sürüyordu, sonra biz ondan istifade edecektik korkunç vakit kaybı vardı. Tıp talebesi bir torunum var, bir şey sordum geçende hemen cep telefonundan okudu." yorumunu getirmiş tıpta eğitiminde teknolojinin önemini vurgulamıştır (8).

Akata; tıp eğitiminde geleceğe dair öngörülerini ifade ederken yaklaşık yüz yıllık yaşamında atomun parçalanmasına, aya ulaşılmasına şahit olduğunu, eğitim için 3 ayda gemiyle gittiği Amerika'ya artık uçakla 10 saatte gidildiğini hatırlatıp; gelecekte tıp eğitiminde her organın

bir cerrahı olacağını öngörerek el cerrahisini örnek göstermiştir. Temennisini ise: "hastalıkları cerrahisiz tedavisinin mümkün olabileceği olan bir dünya" olarak belirtse de Akata cerrahiden vazgeçilemeyeceğini düşünmektedir (8).

TARTIŞMA

Cumhuriyetimiz Atatürk Dönemi'nde 1933 yılında bir üniversite reformu gerçekleştirerek Dar-ül Fü'nun'u yeniden yapılandırmak üzere kapatmış; İstanbul Üniversitesi'ni kurmuştur. Bu üniversitenin ve modern Türkiye'nin diğer akademik kurumlarının eğitici gereksinimi ise Nazi Almanyası'ndan kaçan profesörlerin Atatürk tarafından Türkiye'ye davetiyleriyle sağlanmıştır. Bu hocalardan beklenen de öğrencileri ve asistanları eğitmeleri, bilimsel makale ile literatür geliştirmeleri ve ders kitaplarını hazırlamalarıydı (1, 5, 10).

Ankara'ya bir üniversite kurulması Atatürk Dönemi'nde planlamış olsa da bu girişim İkinci Dünya Savaşı sonrası gerçekleştirilebilmiş ve ilkin Ankara Tıp Fakültesi ardından da Ankara Üniversitesi kurulmuştur. Almanya'dan gelen öğretim elemanlarının bazıları bu yeni üniversitede görev almışlardır. Osman Akata ise Türkiye'nin ikinci ve Cumhuriyet'in ilk tıp fakültesi Ankara Tıp Fakültesi II. Genel Cerrahi Kliniği olan Numune Hastanesi'nde 1933 Üniversite Reformu ile Atatürk Türkiye'sine gelen Dr.Edward Melchior'un yanında 1950-1953 yılları arasında genel cerrahi tıpta uzmanlık eğitimi almıştır (2, 3, 4, 5, 6, 7).

"Tıp Eğitim Tarihi Portre Biyografik Araştırması" olan çalışmamızda cumhuriyetimizle yaşıt olan Prof. Dr. Osman Akata'nın ülkemiz tıp tarihi ile tıp eğitimindeki gelişmeler tanıklığı ve süreci dair açıklamaları "yüzyüze görüşme metodu" ve ardından dönemi anlatan kaynaklar "metin analizi" ile taranıp araştırılmıştır (8). Bilimin ilerlemesinin tıp eğitimi alanındaki yansımaları sonucu önceden yapılması dahi düşünülemeyen operasyonların yapılabilir olması yanında; tıp eğitiminde bilgi birikimin artışıyla işyükü artan genel cerrahi içinden farklı uzmanlıkların çıkışına tanık olan bir hekimin anlatımlarıyla "Tarih Yöntem Bilgisi" açısından literatürdeki bulgular "Metin Analizi Niteliksel Araştırması" ile karşılaştırılmıştır (5, 8, 9, 10).

"Tarih Yöntem Bilgisi" açısından "Tarihte Bireyin Rolü" ilkesi olayların analizinde kişilerin katkı, başarı ve emeklerinin tanımlanmasıdır. Phlehanov "Tarihte Bireyin Rolü" kitabındaki **"**Etkenler Kuramı"nda: "kişinin eylemleri zorunlu olaylar sıralamasında yer alan bir etkense kişi ya o eylemini gerçekleştirmek için olayların ilerlemesine yardımcı olacak veya olayın gelişimine karşı bir eylem gerçekleştirir" denilmektedir (11, 12).

Prof. Dr. Osman Akata gerçekleştirdiği ve ülkemiz cerrahisinde bir devrim niteliğinde olan Vaskluer Greft yani damar yaması kullanarak yaptığı Aorta Anevrizması ana atar damar balonlaşması ameliyatını "Tarih Yöntem Bilgisi" içindeki "Tarihte Bireyin Rolü" ilkesi doğrultusunda bu işlem için bilimsel yetkinliği ve gerçekleştirecek cesareti olduğundan; ayrıca o esnadaki koşullar bu işleme imkan verdiğinden **"**Etkenler Kuramı" bağlamında yaptığı cerrahi girişimini gerçekleştirebilmiştir (11, 12).

SONUÇ

Prof. Dr. Akata; 100 yıllık yaşamı süresince tıbbi gereç ve sağlık elemanı yokluklarından teknoloji çağına dek bilimsel gelişmelere tanık olmuş; Türkiye'de ilk damar yaması cerrahi uygulamasını da yapmış, öğretim üyeliği döneminde bilimin ilerlemesiyle genel cerrahiden ayrılan anabilim dallarına da tanık olmuştur. Akata; Feridun Nafiz Uzluk'un emekliliği ardından bir dönem Ankara Tıp Fakültesi Genel Cerrahi ile Tıp Tarihi ve Deontoloji Anabilim Dalları ortak yöneticiliğini de yapmış olup; daha sonra Tıp Tarihi ve Etik Anabilim Dalı Başkanlığı olan Fuat Aziz Göksel ve Yaman Örs'ün Ankara Tıp Fakültesi'ne kazandırılmasını sağlamıştır. Akata; 1923 doğumlu Cumhuriyetle yaşıt bir hekim olarak 1942'de başlayan tıp ve 1950'de başlayan genel cerrahi tıpta uzmanlık eğitimleri sırasında Atatürk'ün 1933 Üniversite Reformuyla Türkiye'ye gelen bilim insanlarının ülkemiz tıp eğitimine katkılarını gözlemleyip Türk Tıbbının gelişimine tanık olmuştur (14, 15). Bugün artık devlet ve vakıf üniversite hastanelerimiz bünyesinde güvenle yapılabilen laparoskopik tüm cerrahi ve laparoskopik cerrahi onkoloji girişimleri ise Akata gibi öncü cerrahlar sayersinde mümkün olabilmiştir (16).

Teşekkür
Ankara Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı Vasküler Cerrahi Bilim Dalı Öğretim Üyesi Prof. Dr. Uğur Benginsun'a ve Ankara Üniversitesi Tıp Fakültesi Tıp Tarihi ve Etik Anabilim Dalı Başkanı Prof. Dr. Berna Arda'ya teşekkür ederiz.

Yazarların katkıları: Kavramsallaştırma, denetim, yazma, inceleme, düzenleme, orijinal taslak hazırlama: RLK, EY, YDK.

Çıkar çatışması: Yazarlar bu araştırmada herhangi bir çıkar çatışması olmadığını beyan ederler. Tüm yazarlar yazının yayınlanmış versiyonunu okudu ve kabul etti. Yazarlar bu araştırmada herhangi bir fonlama ve mali destek olmadığını beyan ederler.

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ARAŞTIRMA MAKALESİ **RESEARCH ARTICLE**

Clinical Outcomes of Purse-String Versus Linear Skin Closure After Stoma Reversal: A Retrospective Comparative Study

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Abstract

Aim: This study aimed to compare the clinical outcomes of purse-string (PS) and linear skin closure (LS) techniques following stoma reversal.

Materials and Methods: Patients who underwent stoma reversal between January 2020 and January 2025 were retrospectively review ed. Patients were divided into PS and LS groups according to the skin closure technique used. Demographic characteristics, clinical variables, operative findings, and postoperative outcomes were compared between the groups.

Results: A total of 209 patients were included, of whom 68 (32.5%) underwent PS closure and 141 (67.5%) underwent LS closure. The groups were comparable regarding age, sex, body mass index, Charlson Comorbidity Index, and comorbidity profile. ASA score distribution differed significantly between the groups (p=0.039). The distribution of colostomy locations was significantly higher in the LS group (p=0.026). Midline incision use (29.8% vs. 7.4%, p<0.001), drain placement (61.0% vs. 35.3%, p<0.001), and operative time (115.1±65.7 vs. 88.8±44.2 minutes, p=0.003) were significantly greater in the LS group. No significant differences were observed in wound healing time (p=0.340), length of hospital stay (p=0.815), overall morbidity (31.9% vs. 38.2%, p=0.366), reoperation rate (7.8% vs. 10.3%, p=0.547), or mortality (2.1% vs. 1.5%, p=1.000).

Conclusion: PS and LS skin closure techniques provide comparable clinical outcomes following stoma reversal. Although operative time, midline incision use, and drain placement were higher in the LS group, postoperative outcomes did not differ significantly between the two techniques.

Keywords: *Stoma reversal, Ileostomy, Colostomy, Purse-string closure, Linear skin closure, Surgical wound infection*

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Stoma Kapatılması Sonrası Kese Ağzı (Purse-String) ile Doğrusal Cilt Kapatmanın Klinik Sonuçları: Retrospektif Karşılaştırmalı Bir Çalışma

Özet

Amaç: Bu çalışma, stoma kapatılması sonrasında uygulanan kese ağzı (purse-string, PS) ve doğrusal cilt kapatma (linear skin closure, LS) tekniklerinin klinik sonuçlarını karşılaştırmayı amaçlamıştır.

Gereç ve Yöntem: Ocak 2020 ile Ocak 2025 tarihleri arasında stoma kapatılması uygulanan hastalar retrospektif olarak incelendi. Hastalar, kullanılan cilt kapatma tekniğine göre PS ve LS gruplarına ayrıldı. Demografik özellikler, klinik değişkenler, ameliyat bulguları ve postoperatif sonuçlar gruplar arasında karşılaştırıldı.

Bulgular: Toplam 209 hasta çalışmaya dahil edildi; bunların 68'ine (%32,5) PS kapatma, 141'ine (%67,5) ise LS kapatma uygulandı. Gruplar yaş, cinsiyet, vücut kitle indeksi, Charlson Komorbidite İndeksi ve komorbidite profili açısından benzerdi. ASA skoru dağılımı gruplar arasında anlamlı farklılık gösterdi (p=0,039). Kolostomi yerleşimlerinin dağılımı LS grubunda anlamlı olarak daha yüksekti (p=0,026). Orta hat insizyonu kullanımı (%29,8'e karşı %7,4; p<0,001), dren yerleştirilmesi (%61,0'a karşı %35,3; p<0,001) ve ameliyat süresi (115,1±65,7'ye karşı 88,8±44,2 dakika; p=0,003) LS grubunda anlamlı olarak daha yüksekti. Yara iyileşme süresi (p=0,340), hastanede kalış süresi (p=0,815), genel morbidite (%31,9'a karşı %38,2; p=0,366), yeniden ameliyat oranı (%7,8'e karşı %10,3; p=0,547) veya mortalite (%2,1'e karşı %1,5; p=1,000) açısından gruplar arasında anlamlı farklılık saptanmadı.

Sonuç: PS ve LS cilt kapatma teknikleri, stoma kapatılması sonrasında benzer klinik sonuçlar sağlamaktadır. LS grubunda ameliyat süresi, orta hat insizyonu kullanımı ve dren yerleştirilmesi daha yüksek olmasına rağmen, postoperatif sonuçlar açısından iki teknik arasında anlamlı bir farklılık bulunmamıştır.

Anahtar Kelimeler: *Stoma kapatılması, İleostomi, Kolostomi, Büzgü dikişi ile kapatma, Lineer cilt kapatılması, Cerrahi yara enfeksiyonu.*

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INTRODUCTION

Temporary stomas are commonly created in colorectal surgery to protect the anastomosis and minimize the clinical consequences of anastomotic leakage (1). Although stoma reversal is generally considered a safe procedure, it remains associated with various postoperative complications, particularly surgical site infection (SSI) (2).

SSI following stoma reversal is one of the most frequently encountered complications, largely due to chronic bacterial contamination of the peristomal skin and subcutaneous tissues (2). Consequently, the impact of different skin closure techniques on postoperative wound-related outcomes has been the subject of considerable investigation.

Linear skin closure has traditionally been the most widely adopted technique; however, purse-string closure has emerged as an alternative approach in recent years. By allowing continuous drainage through a small central opening, purse-string closure is thought to reduce the risk of SSI (3). Current evidence indicates that the advantages of purse-string closure may be confined primarily to infection-related outcomes. Beyond SSI prevention, no clear differences have been established between purse-string and linear closure with respect to recovery and postoperative morbidity, including wound healing time, operative duration, hospital stay, and incisional hernia occurrence (4, 5). In light of these findings, we sought to investigate the clinical outcomes associated with purse-string (PS) and linear skin closure (LS) in patients undergoing stoma reversal.

MATERIALS AND METHODS

Study Design and Patient Selection

Medical records of consecutive patients who underwent stoma reversal at the General Surgery Department of our institution between

January 2020 and January 2025 were retrospectively evaluated. Only adult patients (≥18 years) were considered eligible for inclusion. Cases with missing clinical information and those undergoing simultaneous major abdominal procedures were excluded from the analysis.

Based on the method of skin closure performed at the time of stoma reversal, patients were allocated to either the purse-string closure (PS) or linear skin closure (LS) group. Clinical information was extracted from both institutional electronic databases and archived patient files. Variables of interest included demographic characteristics, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index (CCI), coexisting medical conditions, indication for the index operation, stoma characteristics, neoadjuvant and adjuvant treatment history, preoperative computed tomography (CT) and colonoscopy findings, anal sphincter tone, operative details, wound healing time, duration of hospitalization, need for reoperation, postoperative morbidity, and mortality.

Wound healing time was defined as the interval until complete epithelialization of the wound and the absence of any further need for wound dressing. This information was obtained retrospectively from wound assessment records documented by the operating surgeon during routine outpatient follow-up visits. Complete epithelialization was defined as the first follow-up visit at which the wound surface was fully epithelialized and no further wound dressing was required. Morbidity was defined as the occurrence of any postoperative complication, including surgical site infection (SSI), ileus, anastomotic leakage, hematoma, seroma, fistula, incisional hernia, and other postoperative adverse events.

Surgical Technique

All stoma reversals were performed according to standard surgical principles. The choice of skin closure technique was based on the operating surgeon’s preference. No institutional protocol or predefined patient selection criteria were used for choosing the skin closure technique. The decision was made according to the operating surgeon's routine clinical practice and intraoperative judgment.

In the LS group, the stoma was dissected free from the abdominal wall through an elliptical peristomal skin incision. Following restoration of bowel continuity, anastomosis was performed. Intestinal continuity was re-established using a stapled anastomosis in most patients, whereas hand-sewn anastomosis was reserved for selected cases when stapling was not feasible. Fascial closure was performed using absorbable multifilament sutures, and the skin was closed primarily in a linear fashion with nonabsorbable monofilament sutures. Subcutaneous drains were placed selectively when deemed necessary.

In the PS group, a circular skin incision was made around the enterocutaneous junction. Intestinal anastomosis and fascial closure were performed in the same manner as in the LS group. Skin closure was achieved using the purse-string technique, approximating the skin circumferentially while leaving a central opening of approximately 1 cm to facilitate drainage. Absorbable monofilament sutures were used for skin closure. No subcutaneous drains were placed in this group.

Postoperative SSI, wound-related complications, and other postoperative adverse events were assessed using patient records and follow-up data.

Statistical Analysis

Continuous variables were summarized using means with standard deviations (SDs), medians, and ranges, whereas categorical data were expressed as frequencies and percentages. The normality of data distribution was evaluated using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons of continuous variables that did not follow a normal distribution were performed using the Mann–Whitney U test. Differences between categorical variables were assessed using either the chi-square test or Fisher's exact test, depending on the distribution of the data. All statistical analyses were conducted using SPSS Statistics for Win-

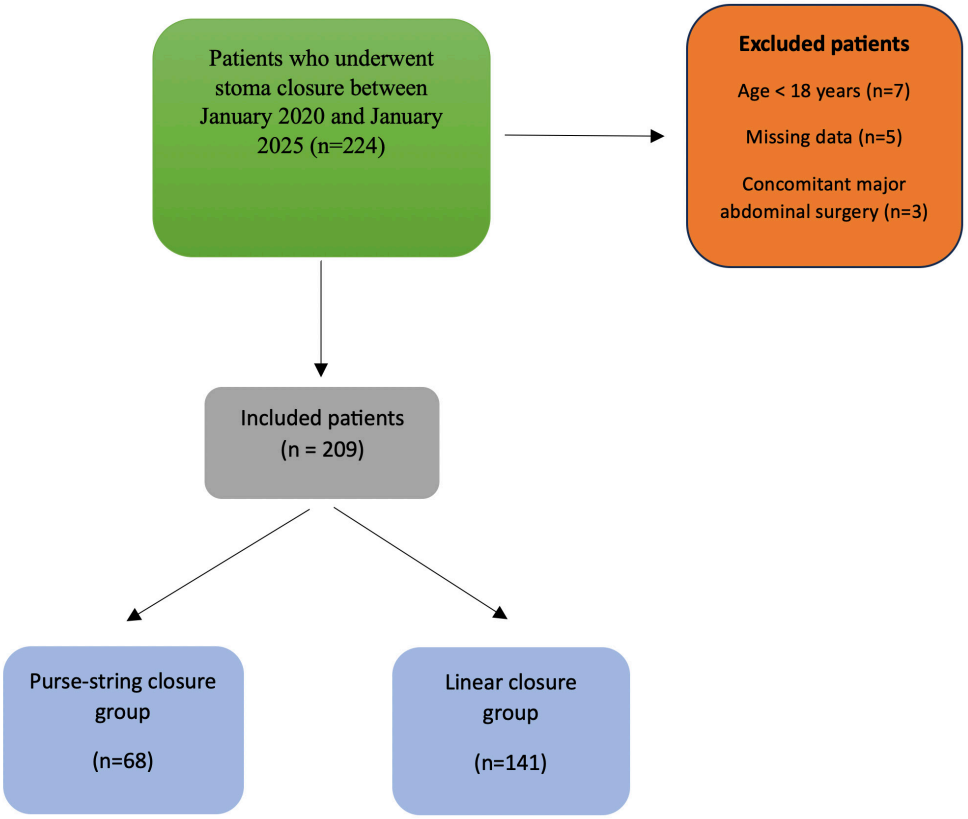
dows, version 27.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-tailed p-value of less than 0.05.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Local Ethics Committee (Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Bilimsel Araştırmalar Etik Kurulu) prior to the initiation of the study (Date: 09.04.2025; Decision No: 2025-07-10).

RESULTS

A total of 224 patients underwent stoma reversal during the study period from January 2020 to January 2025. After excluding five patients with missing clinical information, seven patients younger than 18 years, and three patients who had simultaneous major abdominal procedures, 209 patients remained eligible for analysis. The process of patient selection and allocation into the study groups is depicted in Figure 1.

Figure 1. Flowchart of patient selection and allocation into the purse-string and linear closure groups.



The study cohort had a mean age of 55.7 ± 14.5 years, ranging from 18 to 84 years. Female patients accounted for 35.9% of the population (n=75), whereas 134 patients (64.1%) were male. The average body mass index (BMI) was 26.4 ± 5.0 kg/m². The majority of patients belonged to the ASA II category (68.4%), and the mean Charlson Comorbidity Index (CCI) was 3.1 ± 2.7. At least one comorbidity was present in 55.0% of patients. The most common comorbid conditions were hypertension (22.5%), diabetes mellitus (19.6%), and cardiovascular disease (12.0%).

The index operation had been performed electively in 57.9% of patients and under emergency conditions in 42.1%. Surgical approaches for the index procedure included open surgery

in 49.8%, laparoscopic surgery in 33.5%, and robotic surgery in 16.7% of patients. The underlying pathology was malignant in 57.4% and benign in 42.6% of cases. Loop ileostomy was the most frequently constructed stoma type (57.9%). Most patients had not received neoadjuvant therapy (83.7%) or adjuvant therapy (77.0%). The mean interval between the index operation and stoma reversal was 11.4 ± 8.9 months. Among patients with an ileostomy, the mean distance between the ileostomy and the ileocecal valve was 38.8 ± 21.0 cm. Among patients with a colostomy, the most common locations were the descending colon (14.8%) and sigmoid colon (10.0%). Table 1 provides an overview of the demographic profile, clinical features, characteristics of the index procedure, and stoma-related variables of the study cohort.

Table 1. Baseline demographic, clinical and stoma-related characteristics of the study population (n=209)

		Min-Max	Median	Mean±SD/n-%
Age (years)		18.0 - 84.0	58.0	55.7 ± 14.5
Sex	Female			75 35.9%
	Male			134 64.1%
BMI		16.4 - 47.3	25.8	26.4 ± 5.0
ASA score	I			7 3.3%
	II			143 68.4%
	III			57 27.3%
	IV			2 1.0%
CCI score		0.0 - 12.0	3.0	3.1 ± 2.7
Comorbidity	None			94 45.0%
	Present			115 55.0%
Comorbid conditions	Hypertension			47 22.5%
	Diabetes mellitus			41 19.6%
	Cardiovascular disease			25 12.0%
	Neurological disease			15 7.2%
	Pulmonary disease			11 5.3%
	Chronic kidney disease			10 4.8%
	Urological disease			7 3.3%
	Malignancy			5 2.4%
	Hematological disease			2 1.0%
	Others			24 11.5%
Index surgery	Emergency			88 42.1%
	Elective			121 57.9%
Initial Surgical Approach	Laparoscopic			70 33.5%
	Open			104 49.8%
	Robotic			35 16.7%
Type of stoma	Loop ileostomy			121 57.9%
	End ileostomy			10 4.8%
	Loop coloctomy			14 6.7%
	End colostomy			41 19.6%
	Ileostomy with mucous fistula			19 9.1%
	Jejunostomy			6 2.9%

Pathological diagnosis at initial surgery	Benign			89	42.6%
	Malignant			120	57.4%
Neoadjuvant therapy	None			175	83.7%
	Chemotherapy			5	2.4%
	Radiotherapy			16	7.7%
	Chemoradiotherapy			13	6.2%
Adjuvant therapy	None			161	77.0%
	Chemotherapy			42	20.1%
	Radiotherapy			1	0.5%
	Chemoradiotherapy			5	2.4%
Distance between ileostomy and ileocecal valve (cm)		10.0 - 100.0	30.0	38.8 ± 21.0	
Colostomy site	None			148	70.8%
	Ascending colon			2	1.0%
	Transverse colon			7	3.3%
	Descending colon			31	14.8%
	Sigmoid colon			21	10.0%
Interval between initial surgery and stoma closure (months)		1.0 - 57.0	9.0	11.4 ± 8.9	

ASA: *American Society of Anesthesiologists;* ***CCI****: Charlson Comorbidity Index;* ***BMI:*** *Body Mass Index;* ***SD:*** *Standard deviation.*

According to the skin closure technique, 68 patients (32.5%) underwent purse-string closure (PS) and 141 patients (67.5%) underwent linear skin closure (LS). No significant differences were observed between the groups regarding age, sex distribution, BMI, CCI, or the presence of comorbidities. However, ASA score distribution differed significantly between the groups (p=0.039). No significant differences were found in the prevalence of diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease, neurological disorders, renal disease, or other comorbid conditions (all p>0.05). The demographic and clinical characteristics of the two groups are presented in Table 2.

Table 2. Comparison of baseline characteristics between the purse-string and linear closure groups

		Purse-string group (n=68)		Linear group (n=141)			
		Mean±SD/n-%	Median	Mean±SD/n-%	Median		
Age (years)		54.1 ± 15.4	56.5	56.5 ± 14.1	59.0	0.296	m
Sex	Female	27 39.7%		48 34.0%		0.424	X^2
	Male	41 60.3%		93 66.0%			
ASA score	ASA I	2 2.9%		5 3.5%		0.039	X^2
	ASA II	49 72.1%		94 66.7%			
	ASA III	16 23.5%		42 29.8%			
	ASA IV	1 1.5%		1 0.7%			
BMI		26.5 ± 5.2	25.6	26.3 ± 4.9	26.1	0.971	m
CCI score		3.0 ± 2.5	3.0	3.2 ± 2.7	3.0	0.893	m

Comorbidity	None	29	42.6%	65	46.1%	0.638	X²
	Present	39	57.4%	76	53.9%		
Diabetes mellitus		16	23.5%	25	17.7%	0.323	X²
Hypertension		17	25.0%	30	21.3%	0.546	X²
Cardiovascular disease		12	17.6%	13	9.2%	0.079	X²
Pulmonary disease		3	4.4%	8	5.7%	0.702	X²
Neurological disease		6	8.8%	9	6.4%	0.522	X²
Urological disease		3	4.4%	4	2.8%	0.553	X²
Malignancy		2	2.9%	3	2.1%	0.661	X²
Chronic kidney disease		4	5.9%	6	4.3%	0.606	X²
Hematological disease		1	1.5%	1	0.7%	0.546	X²
Other		7	10.3%	17	12.1%	0.708	X²

[m] Mann-Whitney U test / [X²] Chi-square test (Fischer's exact test)
***ASA:** American Society of Anesthesiologists; **CCI**: Charlson Comorbidity Index; **BMI:** Body Mass Index;*
***SD:** Standard deviation.*

Preoperative characteristics were comparable between the groups with respect to the urgency of the index operation, surgical approach, underlying pathology, receipt of neoadjuvant or adjuvant therapy, and the interval between the index operation and stoma reversal (all p>0.05). Among patients with ileostomies, the distance between the stoma and the ileocecal valve was similar between groups (p=0.745). The distribution of colostomy locations differed significantly between the groups (p=0.026). No significant differences were observed regarding the rates and findings of preoperative colonoscopy, CT findings, or anal sphincter tone (all p>0.05). A comparison of preoperative and stoma-related characteristics is presented in Table 3.

Table 3. Comparison of preoperative and stoma-related characteristics between the purse-string and linear closure groups

		Purse-string group (n=68)			Linear group (n=141)			
		Mean±SD/n-%		Median	Mean±SD/n-%		Median	
Index surgery	Emergency	23	33.8%		65	46.1%		0.092 X²
	Elective	45	66.2%		76	53.9%		
Initial Surgical Approach	Laparoscopic	27	39.7%		43	30.5%		0.414 X²
	Open	31	45.6%		73	51.8%		
	Robotic	10	14.7%		25	17.7%		
Pathological diagnosis at index surgery	Benign	30	44.1%		59	41.8%		0.755 X²
	Malignant	38	55.9%		82	58.2%		
Neoadjuvant therapy	None	55	80.9%		120	85.1%		0.438 X²
	Chemotherapy	1	1.5%		4	2.8%		
	Radiotherapy	7	10.3%		9	6.4%		
	Chemoradiotherapy	5	7.4%		8	5.7%		

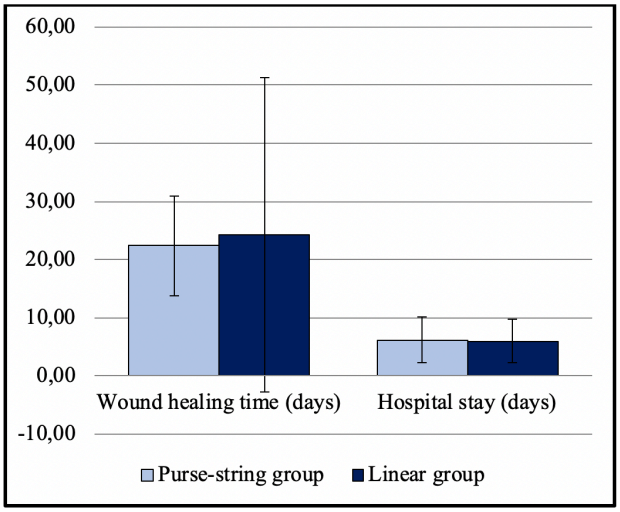
Adjuvant therapy	None	56	82.4%		105	74.5%		0.204 X^2
	Chemotherapy	10	14.7%		32	22.7%		
	Radiotherapy	0	0.0%		1	0.7%		
	Chemoradiotherapy	2	2.9%		3	2.1%		
Interval between index surgery and stoma closure (months)		11.2 ± 9.3		9.0	11.4 ± 8.7		10.0	0.670 m
Distance between ileostomy and ileocecal valve (cm)		39.0 ± 22.6		30.0	38.7 ± 20.1		30.0	0.745 m
Colostomy site	None	55	80.9%		93	66.0%		0.026 X^2
	Ascending colon	0	0.0%		2	1.4%		
	Transverse colon	3	4.4%		4	2.8%		
	Descending colon	6	8.8%		25	17.7%		
	Sigmoid colon	4	5.9%		17	12.1%		
Preoperative colonoscopy	No	7	10.3%		12	8.5%		0.674 X^2
	Yes	61	89.7%		129	91.5%		
Colonoscopy findings	Normal	26	42.6%		59	45.7%		0.591 X^2
	Abnomal	35	57.4%		70	54.3%		
Preoperative CT	No	5	7.4%		8	5.7%		0.638 X^2
	Yes	63	92.6%		133	94.3%		
CT findings	Normal	48	76.2%		100	75.2%		0.960 X^2
	Abnomal	15	23.8%		33	24.8%		
Preoperative anal sphincter tone	Normal	67	98.5%		136	96.5%		0.666 X^2
	Decreased	1	1.5%		5	3.5%		

^{m} Mann-Whitney U test / $^{X^2}$ Chi-Square test (Fisher' exact test)

***CT:** Computed Tomography; **SD:** Standard deviation*

With respect to operative variables, no significant difference was observed in the anastomotic technique, and stapled anastomosis was used in the vast majority of patients. With regard to operative characteristics, patients in the LS group underwent midline incision more often than those in the PS group (29.8% vs. 7.4%, p<0.001). Likewise, the use of subcutaneous drains was more prevalent among LS patients (61.0% vs. 35.3%, p<0.001). The frequency of concomitant hernia repair and the need for postoperative blood transfusion did not differ significantly between the two groups. The mean operative duration was greater in the LS group compared with the PS group (115.1 ± 65.7 vs. 88.8 ± 44.2 minutes, p=0.003). Conversely, no between-group differences were observed in wound healing time or length of hospitalization (p=0.340 and p=0.815, respectively) (Figure 2).

Figure 2. Comparison of wound healing time and length of hospital stay between the purse-string and linear closure groups.



Overall postoperative morbidity affected 38.2% of patients in the PS group and 31.9% of those in the LS group (p=0.366). Similarly, reoperation rates (10.3% vs. 7.8%, p=0.547) and mortality rates (1.5% vs. 2.1%, p=1.000) remained comparable between the groups. A detailed comparison of operative and postoperative outcomes is provided in Table 4.

Table 4. Comparison of operative and postoperative outcomes between the purse string and linear closure groups

		Purse-string group (n=68)			Linear group (n=141)				
		Mean±SD/n-%		Median	Mean±SD/n-%		Median		
Anastomotic technique	Hand-sewn	0	0.0%		2	1.4%		0.324	X^2
	Stapled	68	100.0%		139	98.6%			
Incision type	Stoma-site incision	63	92.6%		99	70.2%		*<0.001*	X^2
	Midline incision	5	7.4%		42	29.8%			
Hernia repair	No	59	86.8%		126	89.4%		0.581	X^2
	Yes	9	13.2%		15	10.6%			
Drain placement	No	44	64.7%		55	39.0%		*<0.001*	X^2
	Yes	24	35.3%		86	61.0%			
Postoperative blood transfusion requirement	No	68	100.0%		139	98.6%		1.000	X^2
	Yes	0	0.0%		2	1.4%			
Operative time (min)		88.8 ± 44.2		80.0	115.1 ± 65.7		99.0	*0.003*	m
Wound healing time (days)		22.4 ± 8.6		20.5	24.3 ± 27.0		19.0	0.340	m
Length of hospital stay (days)		6.2 ± 3.9		5.0	6.0 ± 3.7		5.0	0.815	m

Reoperation	No	61	89.7%	130	92,2%	0.547	X²
	Yes	7	10.3%	11	7,8%		
Morbidity	No	42	61.8%	96	68,1%	0.366	X²
	Yes	26	38.2%	45	31,9%		
Mortality	No	67	98.5%	138	97,9%	1,000	X²
	Yes	1	1.5%	3	2,1%		

ᵐ Mann-Whitney U test / X² Chi-Square test (Fisher's exact test)

***SD:** Standard deviation*

Analysis of postoperative complications revealed that SSI, ileus, and incisional hernia were the most frequently encountered adverse events. SSI occurred in 13.2% of patients in the PS group and 7.8% in the LS group, whereas ileus was observed in 13.2% and 6.4% of patients, respectively. Incisional hernia developed in 8.8% of patients in the PS group and 9.2% of those in the LS group. Hematoma, seroma, fistula, anastomotic leakage, subcutaneous abscess, evisceration, and perforation were uncommon in both groups. The overall distribution of complications was comparable between the groups. As some patients experienced more than one complication, the total number of complications exceeded the number of patients with postoperative morbidity. Detailed postoperative complication profiles are presented in Table 5.

Table 5. Comparison of postoperative complications between the purse-string and linear closure groups

Postoperative complications	Purse-string group (n=68)		Linear group (n=141)	
	n	%	n	%
Surgical site infection	9	13.2%	11	7.8%
Hematoma	1	1.5%	6	4.3%
Seroma	0	0.0%	4	2.8%
Fistula	0	0.0%	2	1.4%
Ileus	9	13.2%	9	6.4%
Anastomotic leakage	3	4.4%	3	2.1%
Incisional hernia	6	8.8%	13	9.2%
Subcutaneous abscess	0	0.0%	1	0.7%
Evisceration	1	1.5%	3	2.1%
Perforation	1	1.5%	0	0.0%

Some patients experienced more than one postoperative complication; therefore, the sum of complications may exceed the total number of patients with morbidity.

DISCUSSION

The present study compared the clinical outcomes of purse-string (PS) and linear skin closure (LS) techniques following stoma reversal. The principal finding was the absence of significant differences between the two techniques with respect to wound healing time, reoperation, overall morbidity, and mortality. In contrast, midline incision use, drain placement, and operative time were significantly higher in the LS group. These findings suggest that postoperative outcomes following stoma reversal are influenced not only by the skin closure technique itself but also by patient characteris-

tics, stoma-related factors, and the overall complexity of the procedure.

Although stoma reversal is generally considered a relatively minor surgical procedure, it may still be associated with clinically relevant complications, including surgical site infection (SSI), ileus, anastomotic leakage, incisional hernia, and the need for reoperation (6, 7). The prolonged exposure of the peristomal skin and subcutaneous tissues to fecal contamination contributes substantially to wound-related complications (8). Consequently, the optimal method of skin closure after stoma reversal has become one of the most extensively investigated technical aspects of the procedure.

The purse-string closure technique was first described by Banerjee and was designed to reduce the risk of SSI by permitting continuous drainage through a small central opening in the wound (3). By avoiding complete skin closure, this technique may limit the accumulation of fluid and bacterial contamination within the subcutaneous space (1, 6). A substantial body of evidence supports the potential benefit of PS closure in reducing SSI rates. In a meta-analysis of randomized controlled trials, Hsieh et al. demonstrated significantly lower infection rates with PS closure compared with conventional linear closure (4). Similar findings were reported by Rondelli et al., who observed a significant reduction in wound infections associated with the PS technique (9). More recent systematic reviews and meta-analyses, including a Cochrane review and contemporary analyses published in 2024–2025, have largely confirmed these findings (10, 11).

Despite these observations, no significant difference in overall morbidity was identified between the two groups in the present study. Although this may initially appear inconsistent with reports demonstrating lower SSI rates after PS closure, overall morbidity encompasses a broad spectrum of postoperative events, including ileus, anastomotic leakage, incisional hernia, hematoma, seroma, and other complications. Indeed, several meta-analyses have reported that while PS closure may reduce SSI rates, it has not consistently translated into lower overall morbidity, reduced reoperation rates, or shorter hospital stays (4–11). Therefore, the beneficial effect of PS closure on SSI may not necessarily be reflected in analyses of overall postoperative morbidity.

One noteworthy finding of the current study was the higher proportion of colostomies in the LS group. Compared with ileostomy reversal, colostomy closure may involve a greater bacterial burden, increased fecal contamination, and more extensive tissue dissection. Liang et al. identified colostomy as an independent risk factor for SSI following stoma reversal (6). Likewise, recent meta-analytic evidence has suggested that colostomy closure may be associated with a higher risk of wound-related complications (12). Nevertheless, despite a greater proportion of colostomies in the LS group, no significant differences in morbidity or mortality were observed. This finding highlights the difficulty of evaluating the isolated impact of skin closure techniques independent of patient selection and stoma-related characteristics.

Another important observation was the significantly higher rate of midline incision use in the LS group. These baseline differences indicate that complete homogeneity between the study groups could not be achieved. Colostomy closure, the need for a midline incision, and drain placement may all reflect greater operative complexity. Therefore, the longer operative time observed in the LS group should not be attributed solely to the skin closure technique. Our findings suggest that operative duration and postoperative outcomes may also be influenced by patient- and procedure-related factors. Midline access is often required in patients with dense adhesions, colostomies, concomitant pathology, or technically demanding operative conditions. Such cases frequently necessitate more extensive dissection, potentially resulting in longer operative times and a greater need for drain placement. The higher rates of both midline incision and drain use observed in the LS group suggest that these patients may have represented a more surgically complex population. This may also explain the longer operative times recorded in the LS group, as skin closure itself constitutes only a small component of

the overall procedure. Previous meta-analyses have generally reported no significant differences in operative duration between PS and LS techniques (5,9,10). Although operative time was longer in the LS group in our cohort, this difference is more likely attributable to procedural complexity than to the skin closure technique itself.

No significant difference was observed in wound healing time between the two groups. While the open central defect inherent to the PS technique might theoretically prolong secondary wound healing, wound infections and fluid collections following LS closure may similarly delay recovery. Consequently, each technique possesses distinct advantages and disadvantages that may ultimately balance one another. Although some studies have reported longer wound healing times after PS closure, long-term clinical outcomes have generally remained comparable between the two approaches (5, 13). The absence of a significant difference in wound healing time in the present study supports the notion that the biological advantages of each technique may result in similar overall clinical outcomes.

Reoperation rates were also comparable between groups. Reoperation is typically required for major complications such as anastomotic leakage, severe ileus, evisceration, or significant wound-related problems. Previous studies have not demonstrated a consistent effect of skin closure technique on reoperation rates (9, 14). Accordingly, the comparable reoperation rates observed in our study suggest that both techniques provide an acceptable safety profile. Analysis of individual complications revealed SSI, ileus, and incisional hernia to be the most common adverse events, a finding consistent with previous reports (6, 12, 15). Although SSI appeared numerically more frequent in the PS group, the number of events was insufficient to permit meaningful subgroup analysis. Furthermore, several patients experienced more than one complication, complicating interpretation of complication-specific outcomes. Therefore, these findings should be interpreted with caution.

Incisional hernia rates were similar between the two groups. Previous meta-analyses have likewise reported no significant difference in incisional hernia development between PS and LS closure techniques (8,10,14). Factors such as fascial closure technique, wound infection, obesity, and duration of follow-up are likely to play a more important role in incisional hernia formation than the method of skin closure itself (6).

Several limitations of this study should be acknowledged. First, the retrospective single-center design may limit the generalizability of the findings. Second, the lack of randomization introduces the potential for selection bias. Third, cosmetic outcomes, patient satisfaction, and quality-of-life measures were not assessed. Finally, significant differences in ASA score distribution, colostomy rate and location, midline incision, and drain placement indicate that complete baseline homogeneity between the study groups could not be achieved. These baseline imbalances may have acted as potential confounding factors, particularly with respect to operative time and postoperative outcomes. In addition, several postoperative complications occurred infrequently; therefore, separate statistical comparisons for individual complications were not performed. Consequently, complication-specific findings should be interpreted with caution. Nevertheless, the inclusion of a contemporary five-year patient cohort and the comprehensive evaluation of both operative and postoperative outcomes represent important strengths of the present study.

CONCLUSION

No significant differences were observed between purse-string and linear skin closure techniques with respect to wound healing time, length of hospital stay, reoperation, overall morbidity, or mortality following stoma reversal. Although midline incision use, drain placement, and operative time were more frequent in the LS group, these differences did not translate into inferior postoperative outcomes. The present findings suggest that both techniques are safe and feasible options for skin closure after stoma reversal. However, postoperative outcomes appear to be influenced not only by

the skin closure technique but also by patient characteristics, stoma type, and operative complexity. Therefore, these factors should be considered collectively when selecting the most appropriate skin closure method. The choice of closure method should be individualized according to stoma characteristics, procedural complexity, and surgeon preference. Larger prospective randomized studies are warranted to further validate these findings.

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Ethics approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Local Ethics Committee (Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Bilimsel Araştırmalar Etik Kurulu) prior to the initiation of the study (Date: 09.04.2025; Decision No: 2025-07-10).

Artificial intelligence statement: No artificial intelligence–based tools or algorithms were used in the conduct, analysis, or writing of this study.

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ARAŞTIRMA MAKALESİ **RESEARCH ARTICLE**

Comparison of Early- and Mid-Term Outcomes of Surgical Treatment and Laser Ablation for Pilonidal Sinus Disease

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Abstract

Aim: This study aimed to compare the early- and mid-term outcomes of different surgical and minimally invasive treatment methods for pilonidal sinus disease in terms of wound healing, postoperative complications, chronic postoperative pain, and recurrence.

Materials and Methods: Data from 173 patients operated on for sacrococcygeal pilonidal sinus disease between July 2021 and May 2025 were retrospectively evaluated. Patients were divided into Karydakis flap, primary closure, and laser ablation groups according to the surgical method performed. Demographic characteristics, wound healing, complications, chronic pain, and recurrence rates were compared. Subgroup analyses were also performed in primary cases without previous abscess attacks or prior surgery.

Results: Karydakis flap was performed in 96 (55.5%) patients, primary closure in 42 (24.3%), and laser ablation in 35 (20.2%). Mean hospital stay was shorter in the laser group ($p=0.0002$). Complete wound healing time was significantly longer in the laser group ($p<0.001$). The overall recurrence rate was 9.8%, with recurrence rates of 4.2% in the Karydakis group, 14.3% in the primary closure group, and 20.0% in the laser group ($p=0.014$). However, subgroup analysis in primary cases showed no significant difference between groups ($p=0.118$). Chronic pain and recurrence rates were higher in patients with early wound complications.

Conclusion: Minimally invasive methods may provide advantages such as shorter hospital stay and lower wound dehiscence rates. However, patient selection, disease severity, and wound healing process play an important role in long-term outcomes.

Keywords: *Pilonidal sinus, Karydakis flap, Laser ablation, Recurrence, Wound healing*

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Pilonidal Sinüs Hastalığında Cerrahi Tedavi ve Lazer Ablasyonun Erken ve Orta Dönem Sonuçlarının Karşılaştırılması

Özet

Amaç: Bu çalışmada pilonidal sinüs hastalığında farklı cerrahi ve minimal invaziv tedavi yöntemlerinin yara iyileşmesi, postoperatif komplikasyonlar, kronik postoperatif ağrı ve nüks açısından erken ve orta dönem sonuçlarının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Temmuz 2021-Mayıs 2025 tarihleri arasında sakrokoksigeal pilonidal sinüs hastalığı nedeniyle opere edilen 173 hastanın verileri retrospektif olarak değerlendirildi. Hastalar uygulanan yönteme göre Karydakis flep, primer kapama ve lazer ablasyon gruplarına ayrıldı. Demografik veriler, yara iyileşmesi, komplikasyonlar, kronik ağrı ve nüks oranları karşılaştırıldı. Ayrıca geçirilmiş abse veya önceki cerrahi öyküsü olmayan primer olgularda alt grup analizi yapıldı.

Bulgular: Hastaların 96'sına (%55,5) Karydakis flep, 42'sine (%24,3) primer kapama ve 35'ine (%20,2) lazer ablasyon uygulandı. Ortalama yatış süresi lazer grubunda daha kısa bulundu (p=0,0002). Tam yara iyileşme süresi lazer grubunda anlamlı olarak daha uzundu (p<0,001). Toplam nüks oranı %9,8 idi ve nüks oranı Karydakis grubunda %4,2, primer kapama grubunda %14,3 ve lazer grubunda %20,0 olarak saptandı (p=0,014). Ancak primer olgular üzerindeki alt grup analizinde gruplar arasındaki fark anlamlılığını kaybetti (p=0,118). Erken yara komplikasyonu gelişen hastalarda kronik ağrı ve nüks oranları daha yüksekti.

Sonuç: Minimal invaziv yöntemler kısa yatış süresi ve düşük yara ayrışması oranı gibi avantajlar sağlayabilir. Bununla birlikte hasta seçimi, hastalık şiddeti ve yara iyileşme süreci uzun dönem sonuçlar üzerinde önemli rol oynamaktadır.

***Anahtar Kelimeler**: Pilonidal sinüs, Karydakis flep, Lazer ablasyon, Nüks, Yara iyileşmesi*

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INTRODUCTION

Pilonidal sinus disease (PSD) is a chronic inflammatory disease located in the sacrococcygeal region, particularly common in young adult men. Hair penetration, local trauma, the deep gluteal groove structure, and hygiene factors play a role in the etiopathogenesis of the disease. PSD remains a significant clinical problem due to recurrent infections, pain, discharge, and loss of work capacity (1, 2).

Different surgical and minimally invasive methods have been described for the treatment of pilonidal sinus disease, and there is still no complete consensus on the ideal treatment method. Classical surgical approaches include total excision and primary closure, as well as off-midline flap techniques (such as Karydakis flap and Limberg flap). It has also been reported that flap techniques that shift the midline are associated with lower recurrence rates (3, 4).

However, these methods may be associated with longer operating times, more tissue dissection, and postoperative morbidity. In recent years, minimally invasive approaches to pilonidal sinus disease have gained increasing importance. Methods such as laser ablation offer advantages such as being less invasive, shorter hospital stays, faster recovery, and earlier return to work. However, data on the long-term effectiveness and recurrence rates of these techniques are limited (5).

While some studies report that minimally invasive methods provide the advantage of low morbidity and rapid recovery, other studies have reported higher recurrence rates and the need for re-intervention, especially in long-term follow-ups (6, 7).

In addition, it is thought that different surgical techniques may have different clinical outcomes not only in terms of recurrence rates but also in terms of wound healing process, postoperative complications, and long-term patient comfort (8).

The impact of early wound complications on long-term recurrence and chronic symptom development is not sufficiently clarified in the literature. Therefore, it is important to comparatively evaluate the effects of different surgical and minimally invasive treatment methods in pilonidal sinus disease not only in terms of recurrence but also on wound healing, postoperative complications, and long-term patient comfort.

This study aimed to compare the early and mid-term outcomes of different treatment methods in patients who underwent surgical treatment for pilonidal sinus disease, in terms of wound healing, postoperative complications, development of chronic symptoms, and recurrence.

MATERIALS AND METHODS

Patient Selection and Study Design

This study was planned as a single-center comparative cohort study retrospectively examining the data of patients who underwent surgical treatment for pilonidal sinus disease. Data from patients operated on for sacrococcygeal pilonidal sinus disease at the General Surgery Clinic of Istanbul Aydın University Faculty of Medicine between July 2021 and May 2025 were retrospectively evaluated. A total of 173 adolescent and adult patients who were diagnosed with pilonidal sinus disease and underwent Karydakis flap procedure, total cyst excision and primary closure or laser ablation during the specified period, and for whom regular postoperative follow-up data were available, were included in the study. Patients were divided into Karydakis flap procedure, total cyst excision and primary closure, and laser ablation groups according to the surgical method applied. Demographic data, disease characteristics, operation records, and postoperative follow-up data were evaluated from patient files and the electronic record system. Patients with incomplete clinical data, unavailable follow-up information, incomplete postoperative follow-up process, or pathology results inconsistent with pilonidal sinus disease were excluded from the study.

Patient Assessment

The variables examined included age, gender, duration of symptoms, history of abscess attacks, previous surgical history, type of anesthesia, drain use, and length of hospital stay. Additionally, the time to return to work or school, complete wound healing time, suture removal time, early complications, development of chronic pain or discharge, presence of recurrence, time of recurrence, and need for re-intervention were evaluated in the postoperative period. Early complications were defined as wound infection, wound dehiscence, and seroma. Clinically, recurrence was defined as the development of a new sinus or the need for re-surgery/intervention. Chronic postoperative symptoms included pain or persistent discharge exceeding the normal wound healing time and lasting at least 2 months. A subgroup analysis was also performed on primary cases without a history of previous abscess attacks or previous surgery.

Surgical Techniques and Follow-up

In the presence of an infected wound, patients were treated with antibiotic therapy appropriate to their age and clinical condition. Surgical treatment was applied after the local and systemic infection signs subsided. Patients presenting with pilonidal sinus abscesses underwent local abscess drainage and were re-evaluated by being were followed up in the outpatient clinic every two days after the procedure. Definitive surgery was planned after complete healing was achieved.

All surgical procedures were performed by the same surgical team. The surgical methods applied were:

1. Total cyst excision and primary closure
2. Karydakis flap procedure
3. Laser ablation

Laser ablation was preferentially offered to patients without evidence of chronic infection, with limited disease extent, and who preferred a minimally invasive treatment after being informed about the available treatment options. Conversely, Karydakis flap or primary closure was preferred in patients presenting with persistent chronic discharge, recurrent disease, relatively extensive pilonidal sinus disease, lateral secondary sinus openings, or in patients

who declined laser ablation. The final treatment decision was made based on both clinical suitability and patient preference.

Total cyst excision was defined as a surgical method based on the principle of completely removing the cystic area with minimal loss of healthy tissue through an incision made to include all sinus openings and tracts in the sacrococcygeal region, and then primary closure without midline shifting. The Karydakis flap procedure is defined as a surgical method based on the complete excision of pilonidal sinus tracts through an asymmetric elliptical incision in the sacrococcygeal region, followed by sliding the gluteal flap to lateralize the midline, thereby moving the wound away from the midline and performing primary closure. Laser ablation is defined as a surgical method performed without extensive tissue excision, where the pilonidal sinus tracts are cleaned using a minimally invasive approach, and epithelialized tracts are destroyed by thermal ablation using a radial laser probe placed inside the sinus cavity. During this procedure, continuous energy is applied to the laser probe placed inside the sinus cavity from distal to proximal, and the probe is withdrawn at approximately 1 mm per second to achieve thermal ablation throughout the entire sinus tract. Cold compression was applied to the surgical area for 5 minutes after the procedure. Surgical procedures were performed under local, spinal, or general anesthesia. All patients were prescribed oral antibiotics and nonsteroidal anti-inflammatory drugs in the postoperative period. Patients who underwent surgical excision and had drains placed were called for outpatient follow-up visits every two days to monitor the drains. Drains were removed when the 24-hour drainage volume fell below 25 cc. All patients, with or without drains, were called for outpatient follow-up visits on the 10th postoperative day for suture evaluation, and the decision regarding suture removal was made based on the wound condition.

Patients who underwent laser ablation were called for outpatient follow-up visits every two days for wound monitoring during the first two weeks. After the second week, weekly follow-up visits continued, and follow-ups were maintained until the wound was completely closed. In patients who underwent surgical excision, complete wound healing was defined as the removal of sutures and the absence of infection or dehiscence at the wound site; in patients who developed wound infection or dehiscence, complete wound healing was defined as the complete closure of the wound site without discharge.

All materials obtained from patients who underwent excision were sent for histopathological examination, and all samples were reported as consistent with benign pilonidal sinus disease. All patients were followed up for at least 12 months. Follow-up of patients was carried out through outpatient follow-up visits and telephone calls. Recurrence was primarily confirmed by clinical examination during outpatient follow-up visits. For patients who could not attend outpatient visits, recurrence status was assessed by structured telephone interviews, and those with suspected recurrence were invited for clinical evaluation.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were expressed as median (minimum–maximum). Categorical variables were presented as numbers and percentages. Student t-test or Mann–Whitney U test was used to compare continuous variables between two groups, while One-Way ANOVA or Kruskal–Wallis test was preferred for comparisons between three groups when appropriate. Chi-square test or Fisher exact test was used to compare categorical variables. In addition, subgroup analyses were performed on primary cases without a history of previous abscess attack or previous surgery. A p value <0.05 was considered statistically significant.

This study was approved by the Istanbul Aydın University Faculty of Medicine Clini-

cal Research Ethics Committee (Decision no: 155/2026, Date: 15.04.2026). The requirement for informed consent for patient inclusion in the study was waived by the ethics committee due to the retrospective design.

RESULTS

A total of 173 patients were included in the study. The mean age of the patients was 30.3±9.6 years, with 140 (80.9%) being male and 33 (19.1%) being female. The median duration of symptoms was 2 months (0.5–36 months). Karydakis flap procedure was performed on 96 (55.5%) patients, total cyst excision and primary closure on 42 (24.3%) patients, and laser ablation on 35 (20.2%) patients. 131 (75.7%) patients were operated on under general anesthesia, 37 (21.4%) under spinal anesthesia, and 5 (2.9%) under local anesthesia. 41 (23.7%) patients had a history of previous pilonidal abscess, and 11 (6.4%) had a history of recurrence after previous surgery. Histopathological examination of all excision materials was reported as consistent with benign pilonidal sinus disease. The overall median follow-up duration was 14 months (range, 12–48 months). The median follow-up duration was 14 months (range, 12–48 months) in the Karydakis group, 15 months (range, 12–23 months) in the primary closure group, and 15 months (range, 12–24 months) in the laser ablation group. The demographic characteristics, operative data, and postoperative outcomes of the patients are summarized in Table 1.

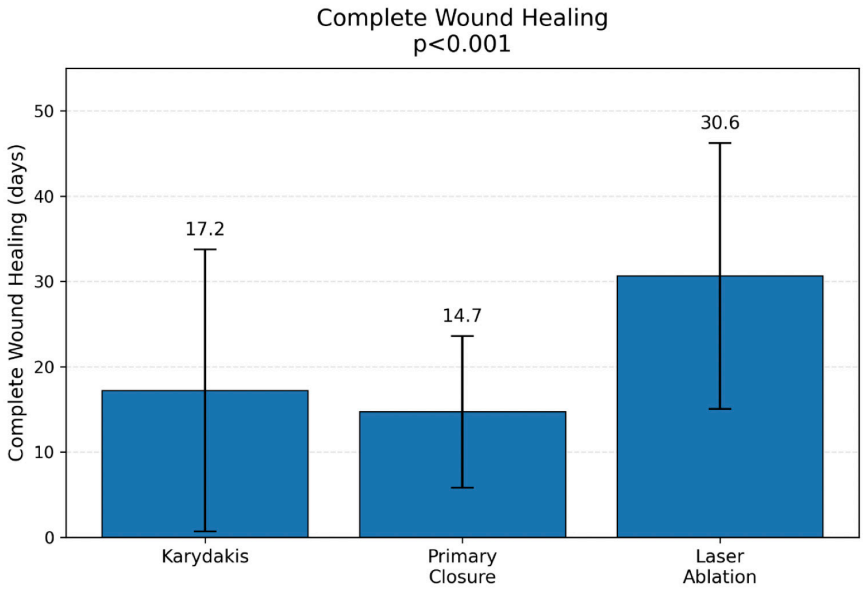
Table 1. Comparison of demographic, operative, and postoperative outcomes according to surgical technique

Variable	**Karydakis (n=96)**	**Primary Closure (n=42)**	**Laser Ablation (n=35)**	**p**
Age (years)	31.31±9.13	31.02±9.67	26.69±10.41	**0.044**
Male sex, n (%)	80 (83.3)	32 (76.2)	28 (80.0)	**0.610**
Symptom duration (months)	2.0 (0.2–24.0)	3.0 (0.5–42.0)	2.0 (0.5–12.0)	**0.002**
Previous abscess history, n (%)	16 (16.7)	12 (28.6)	13 (37.1)	0.028
Previous surgery/recurrence history, n (%)	2 (2.1)	3 (7.1)	6 (17.1)	0.006
General anesthesia, n (%)	69 (71.9)	39 (92.9)	23 (65.7)	**<0.001**
Spinal anesthesia, n (%)	27 (28.1)	3 (7.1)	7 (20.0)	**<0.001**
Local anesthesia/sedoanalgesia, n (%)	0 (0.0)	0 (0.0)	5 (14.3)	**<0.001**
Drain use, n (%)	91 (94.8)	11 (26.2)	0	<0.001
Length of hospital stay (days)	1.07±0.29	1.00±0.00	0.86±0.35	0.0002
Return-to-work time (days)	12.56±3.65	11.76±3.06	10.83±4.41	0.058
Complete wound healing time (days)	17.20±16.53	14.71±8.89	30.63±15.57	<0.001
Suture removal time (days)	11.74±2.09	11.24±1.59	—	0.251
Early complications, n (%)	26 (27.1)	10 (23.8)	4 (11.4)	0.169
Wound dehiscence, n (%)	12 (12.5)	6 (14.3)	0	0.074
Seroma, n (%)	3 (3.1)	0	0	
Chronic pain, n (%)	5 (5.2)	1 (2.4)	3 (8.6)	0.476
Recurrence, n (%)	4 (4.2)	6 (14.3)	7 (20.0)	0.014
Follow-up duration (months), median (range)	**14 (12–48)**	**15 (12–23)**	**15 (12–24)**	**0.155**

The mean length of hospital stay was found to be shorter in the laser group. The mean length of hospital stay was 1.07±0.29 days in the Karydakis group, 1.00±0.00 days in the primary closure group, and 0.86±0.35 days in the laser group (p=0.0002). Patients operated on under local anesthesia or sedoanalgesia were discharged on the same day. Drains were used in 91 (94.8%) of the patients who underwent the Karydakis flap procedure and in 11 (26.2%) of the patients who underwent primary closure. The duration of drain placement in patients with drains was found to be 4.05±1.46 days on average in the Karydakis group and 3.55±1.21 days in the primary closure group; No statistically significant difference was found between the groups in terms of drain dwell time (p=0.281).

No statistically significant difference was found between the groups in terms of return-to-work or school time (p=0.058). Return-to-work/school time was found to be an average of 12.56±3.65 days in the Karydakis group, 11.76±3.06 days in the primary closure group, and 10.83±4.41 days in the laser group. Complete wound healing time was significantly longer in the laser group (p<0.001). The average complete wound healing time was found to be 17.20±16.53 days in the Karydakis group, 14.71±8.89 days in the primary closure group, and 30.63±15.57 days in the laser group. Suture removal time was evaluated only in patients who underwent excision. The mean suture removal time was 11.74±2.09 days in the Karydakis group and 11.24±1.59 days in the primary closure group, with no significant difference between the groups (p=0.251). Complete wound healing times according to surgical techniques are shown in Figure 1.

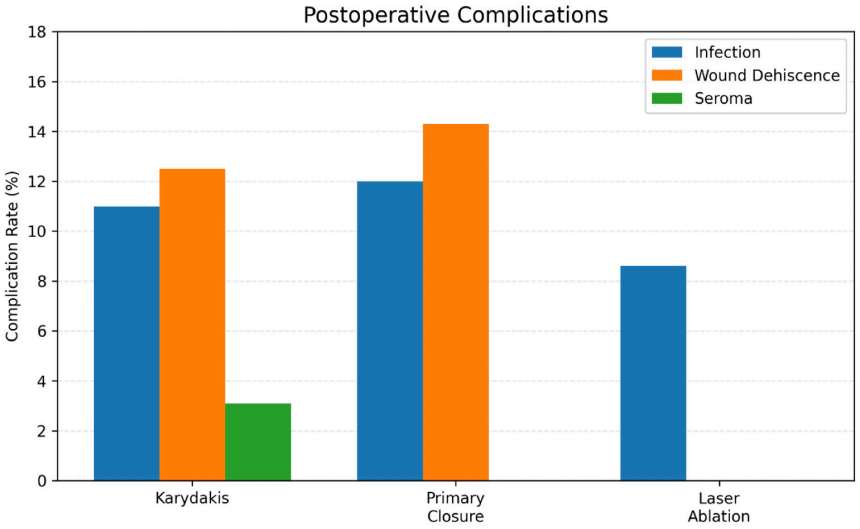
Figure 1. Complete wound healing times according to surgical technique and comparison of complete wound healing durations among different treatment methods.



A total of 40 patients (23.1%) developed early complications. Early complication rates were 27.1% in the Karydakis group, 23.8% in the primary closure group, and 11.4% in the laser group; however, no statistically significant difference was observed between the groups (p=0.169). Wound infection occurred in 19 patients (11.0%), wound dehiscence in 18 patients (10.4%), and seroma in 3 patients (1.7%). Wound infection rates were similar among surgical methods (p=0.941). Wound dehiscence was observed in 12.5% of the Karydakis group and 14.3% of the primary closure group, while no wound dehiscence was observed in the la-

ser group. Although the difference between the three groups was not statistically significant (p=0.074), wound dehiscence was significantly lower when the laser method was compared with other surgical methods (p=0.026). Seroma was observed only in the Karydakis group. The distribution of postoperative complications according to surgical techniques is shown in Figure 2.

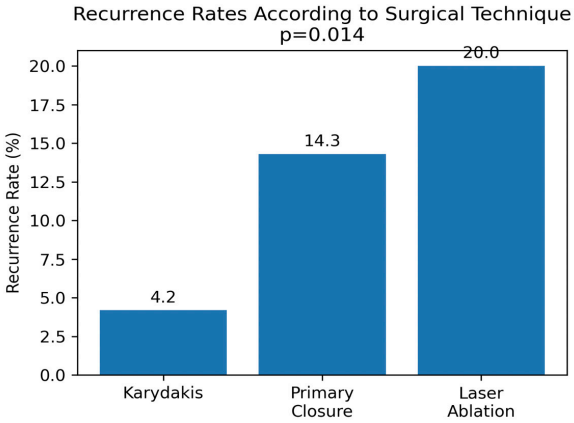
Figure 2. Distribution of postoperative complications according to surgical technique and comparison of wound infection (p = 0.941), wound dehiscence (p = 0.074), and overall postoperative complication rates (p = 0.169) among treatment groups. Comparisons were performed using the Chi-square test.



A total of 9 patients (5.2%) developed chronic postoperative pain. The rates of chronic postoperative pain were found to be 5.2% in the Karydakis group, 2.4% in the primary closure group, and 8.6% in the laser group, and no significant difference was observed between the groups (p=0.476). The median duration of symptoms in patients who developed chronic postoperative pain was 3 months (2–6 months). The rate of chronic postoperative pain was significantly higher in patients who developed early complications (12.5% vs. 3.0%; p=0.032). Similarly, chronic postoperative pain was significantly more frequent in patients who developed wound infection (21.1% vs. 3.2%; p=0.009).

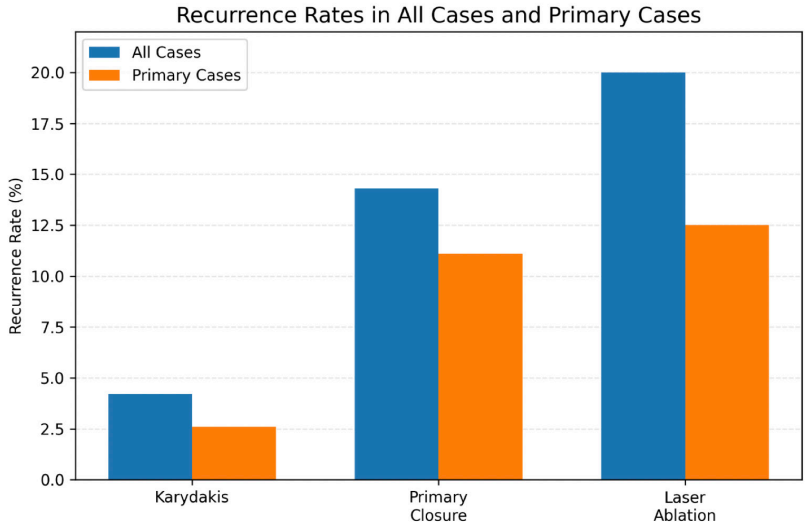
Recurrence was detected in a total of 17 patients (9.8%). Recurrence was observed in 4 patients (4.2%) in the Karydakis group, 6 patients (14.3%) in the primary closure group, and 7 patients (20.0%) in the laser group, with a significant difference between the groups (p=0.014). The median time to recurrence was 10 months (2–52 months). The recurrence rate was significantly higher in patients who developed wound infection (26.3% vs. 7.8%; p=0.025). The recurrence rate was also significantly higher in patients who developed chronic postoperative symptoms (44.4% vs. 7.9%; p=0.006). The distribution of recurrence rates according to surgical techniques is shown in Figure 3.

Figure 3. Recurrence rates according to surgical technique and comparison of recurrence rates among Karydakis flap, primary closure, and laser ablation groups.



A history of previous pilonidal abscess was more frequent in the laser group (37.1%) compared to the Karydakis (16.7%) and primary closure (28.6%) groups, with a significant difference between the groups (p=0.028). Similarly, the rate of recurrent cases after previous surgery was significantly higher in the laser group (17.1% vs. 7.1% and 2.1%; p=0.006). In subgroup analysis performed on primary cases without a history of previous abscess attack or previous surgery, recurrence rates were found to be 2.6% in the Karydakis group, 11.1% in the primary closure group, and 12.5% in the laser group; however, no statistically significant difference was found between the groups (p=0.118). Comparison of recurrence rates in all cases and primary cases is shown in Figure 4.

Figure 4. Comparison of recurrence rates between all cases and primary cases according to surgical technique. The recurrence rates differed significantly among all cases (p = 0.014), whereas no significant difference was observed after excluding patients with previous abscess history or recurrent disease (primary cases, p = 0.118). Comparisons were performed using the Chi-square test.



DISCUSSION

Recurrence rates after surgical and minimally invasive treatment of pilonidal sinus disease worldwide have been reported as variable (7,9). While Bi et al. reported that flap techniques were associated with lower recurrence rates in their network meta-analysis, it was emphasized that minimally invasive methods offer advantages in terms of short-term patient comfort, but long-term recurrence results are still controversial(10).

In our study, consistent with the literature, the recurrence rate was lower after the Karydakis flap procedure than after primary closure. Although the laser ablation group demonstrated a shorter hospital stay and lower wound dehiscence rates, the crude recurrence rate was higher. Although the difference in hospital stay was statistically significant, the absolute difference was relatively small and its clinical relevance should be interpreted with caution. Subgroup analysis showed that a considerable proportion of patients who developed recurrence after laser ablation had a history of previous abscess episodes or prior surgery at the time of initial presentation. This finding suggests that patient selection and baseline disease severity may have substantially influenced the observed outcomes. Indeed, the loss of statistical significance after excluding complicated cases indicates that the higher crude recurrence rate may not be attributable solely to the surgical technique itself. This imbalance in baseline characteristics represents a potential source of selection bias. Therefore, the higher crude recurrence rate observed in the laser ablation group should be interpreted with caution and may partly reflect the greater proportion of patients with previous abscess episodes or recurrent disease rather than the treatment modality itself. Furthermore, follow-up duration did not differ significantly among the three treatment groups ($p = 0.155$), suggesting that the observed differences in recurrence rates were unlikely to be explained by unequal follow-up periods. Consequently, the outcomes of minimally invasive techniques should be interpreted with careful consideration of patient selection, particularly in patients with more advanced or recurrent disease.

Laser ablation has gained attention due to its simple and minimally invasive technique. In fact, it has been shown to be easily repeatable in well-selected cases of relatively less severe recurrence. There are studies showing that better healing results are obtained in studies where multiple sessions are applied (11, 12). In our study, we performed a single session of laser ablation on patients in the laser ablation group. Also, compared to other groups, the rate of patients with a history of abscess and recurrence was higher in this group. Therefore, the use of a single-session laser protocol should be considered when interpreting our findings, as it may have contributed to the observed recurrence rates and represents a limitation of the present study.

Although the suture removal time was similar between the Karydakis and primary closure groups in patients who underwent excision in our study, the complete wound healing time showed a more variable distribution. This situation can be explained by the fact that suture removal time is mostly a procedure dependent on the standard postoperative follow-up protocol, while complete wound healing is affected by clinical factors such as wound infection, wound dehiscence, seroma, and delayed epithelialization. Indeed, while suture removal time is generally reported to be between 10–15 days in the literature, it has been shown that wound healing time can vary over a wider range depending on surgical technique, development of complications, and open/closed wound management (13-15).

In minimally invasive methods such as laser ablation, suture removal is not necessary, but complete wound healing or time to complete closure without discharge should be evaluated as a separate clinical healing parameter. Therefore, the different results of suture removal time and complete wound healing time in our study are not a methodological discrepancy, but a natural consequence of the two evaluated parameters reflecting different clinical processes. In our study, it was observed that chronic postoperative pain and recurrence rates were significantly higher in patients who developed early wound complications. The significantly

increased rates of both chronic pain and recurrence, particularly in patients who develop wound infection, suggest that early wound healing problems may have an impact on long-term clinical outcomes. Some recent studies have reported that wound healing problems and postoperative infections may be associated with recurrence after pilonidal sinus surgery (6, 16, 17).

However, while most studies in pilonidal sinus surgery focus on comparing surgical techniques, the number of studies evaluating the relationship between wound complications and long-term outcomes is limited. Therefore, we believe that our study can contribute to the literature in this respect. Overall, our findings highlight that careful patient selection remains a key determinant of successful outcomes following minimally invasive treatment for pilonidal sinus disease and should be carefully considered when interpreting the results of laser ablation.

Study Limitations

Due to the retrospective and single-center design of our study, selection bias cannot be completely ruled out. The choice of surgical method was not randomized and may have been influenced by clinical factors such as disease extent, previous abscess attack, and previous surgical history. Nevertheless, the fact that all patients were operated on by the same surgical team, had a follow-up period of at least 1 year, and underwent regular outpatient follow-ups can be considered among the strengths of the study. In addition, the relatively small number of recurrence and chronic pain events may have limited the statistical power of some subgroup analyses.

CONCLUSION

In conclusion, minimally invasive techniques may provide advantages such as shorter hospital stay and lower wound dehiscence rates in appropriately selected patients with pilonidal sinus disease. However, patient selection, baseline disease severity, and postoperative wound healing appear to play a significant role in long-term outcomes. Careful patient selection should therefore remain a fundamental consideration when choosing minimally invasive treatment, particularly in patients with recurrent or more extensive disease. Furthermore, early wound complications may be associated with an increased risk of long-term recurrence and chronic postoperative pain.

Authorship contributions: Surgical and Medical Practices: S.B., Y.E.A.; Concept: S.B., Y.E.A.; Design: S.B., Y.E.A.; Data Collection or Processing: S.B., Y.E.A.; Analysis or Interpretation: S.B., Y.E.A.; Literature Search: S.B., Y.E.A.; Literature Search: S.B., Y.E.A.; Writing: S.B., Y.E.A.

Conflict of interest: No conflict of interest was declared by the authors. The authors declared that this study received no financial support.

Ethical approval: This study was approved by the Istanbul Aydın University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 155/2026, Date: 15.04.2026). The requirement for informed consent for patient inclusion in the study was waived by the ethics committee due to the retrospective design, and the study was conducted in accordance with the principles of the 1967 Declaration of Helsinki**.**

Informed consent: Informed consent was obtained from all adult patients and from the legal guardians of patients under 18 years of age, after providing information about all procedures.

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DERLEME **REVIEW**

Emerging Roles of miR-146a-5p in Multiple Sclerosis: Evidence from Recent Studies

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Abstract

Multiple sclerosis is a complex neuroimmune disorder characterized by chronic inflammation, demyelination, and neurodegeneration. Among the various molecular players, microRNA-146a-5p has emerged as a critical, albeit complex, regulator of the neuroimmune landscape in MS. This review brings together current evidence highlighting the dual role of miR-146a-5p, which, while primarily functioning as an anti-inflammatory regulator, is also thought to respond as part of compensatory mechanisms depending on cell type and context. Its expression is dynamically regulated in the central nervous system, cerebrospinal fluid, and blood, correlating with disease activity, treatment response, and clinical metrics such as the Expanded Disability Status Scale (EDSS). We explore its compartmentalized dysregulation, notably in active gadolinium-enhancing lesions, and its potential as a sensitive diagnostic and prognostic biomarker. The involvement of miR-146a-5p in key cellular processes -including microglial activation, oligodendrocyte maturation, and astrocyte pathology- underscores its therapeutic relevance. Furthermore, we discuss its interaction with environmental factors like Vitamin D and its role in exosome-mediated intercellular communication. Preclinical studies demonstrating that manipulating miR-146a-5p levels can ameliorate neuroinflammation and promote remyelination its potential as a novel therapeutic target. Future research should focus on clarifying the context-specific regulatory roles of miR-146a-5p and on developing safe, targeted delivery strategies to support its therapeutic potential.

Keywords: *Multiple Sclerosis, miR-146a-5p, Biomarker, MicroRNA, Neuroinflammation*

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Multiple Sklerozda miR-146a-5p'nin Ortaya Çıkan Rolleri: Güncel Çalışmalardan Kanıtlar

Özet

Multipl skleroz, kronik inflamasyon, demiyelinizasyon ve nörodejenerasyon ile karakterize karmaşık bir nöroimmün hastalıktır. Çeşitli moleküler düzenleyiciler arasında, mikroRNA-146a-5p, MS'te nöroimmün ortamın kritik ancak kompleks bir düzenleyicisi olarak öne çıkmıştır. Bu derleme, esas olarak anti-inflamatuvar bir düzenleyici olarak işlev görmesine rağmen, hücre tipine ve bağlama bağlı olarak kompansatuar mekanizmaların bir parçası olarak da yanıt verebileceği düşünülen miR-146a-5p'nin çift yönlü rolünü vurgulayan güncel çalışmaları bir araya getirmektedir. miR-146a-5p'nin ekspresyonu merkezi sinir sistemi, beyin omurilik sıvısı ve kanda dinamik olarak düzenlenmekte; hastalık aktivitesi, tedavi yanıtı ve Genişletilmiş Engellilik Durum Ölçeği (EDSS) gibi klinik göstergelerle ilişki göstermektedir. Aktif gadolinyumla zenginleşmiş lezyonlarda belirgin olan bölgesel düzensizliği ve duyarlı bir tanısal ve prognostik biyobelirteç olarak potansiyeli ele alınmıştır. miR-146a-5p'nin mikroglia aktivasyonu, oligodendrosit olgunlaşması ve astrosit patolojisi gibi temel hücresel süreçlerdeki rolü, terapötik önemini vurgulamaktadır. Ayrıca, D vitamini gibi çevresel faktörlerle etkileşimi ve eksozom aracılı hücreler arası iletişimdeki rolü de tartışılmıştır. miR-146a-5p düzeylerinin düzenlenmesinin nöroinflamasyonu hafiflettiğini ve remiyelinizasyonu desteklediğini gösteren preklinik çalışmalar, bu molekülün yeni bir terapötik hedef olarak potansiyelini vurgulamaktadır. Gelecekteki araştırmaların, miR-146a-5p'nin bağlama özgü düzenleyici rollerini netleştirmeye ve bu molekülün terapötik potansiyelini destekleyecek güvenli ve hedefe yönelik taşıma stratejileri geliştirmeye odaklanması önemlidir.

Anahtar Kelimeler: *Multipl Skleroz, miR-146a-5p, Biyobelirteç, MikroRNA, Nöroinflamasyon*

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INTRODUCTION

1. Multiple Sclerosis and miR-146a-5p

1.1. Multiple Sclerosis and miRNAs

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system (CNS), with numerous genetic risk factors contributing to its pathogenesis (1). The disease is marked by demyelination and relapsing attacks, where reduced neuronal repair mechanisms and progressive neurodegeneration amplify neuroinflammation, further dysregulating the inflammatory milieu of surrounding CNS cells (2, 3). The majority (85%) of cases initially present as relapsing-remitting MS (RRMS), characterized by acute inflammatory attacks causing neurological dysfunction followed by partial or complete remission. Over time, typically within 20 years, most RRMS patients transition to secondary progressive MS (SPMS), marked by continuous neurological deterioration independent of relapses (4, 5).

MicroRNAs (miRNAs) are small non-coding RNAs that serve as critical regulators of diverse biological processes (6, 7). miRNAs regulate gene expression post-transcriptionally by mostly binding to complementary sequences in the 3'-UTRs of target mRNAs, leading to mRNA degradation or translational repression (8, 9). Figure 1 details the miRNA biogenesis pathway (10, 11). This process requires miRNA incorporation into the RNA-induced silencing complex (RISC), where the mature miRNA guides Argonaute proteins -the core catalytic component of RISC- to its target mRNA to execute silencing. Although miRNAs predominantly target 3′UTRs to promote mRNA degradation or translational repression, they can also bind to coding sequences (CDS) or 5′-UTRs or other non-canonical regions to inhibit protein expression. Similar to their interactions with 3′-UTRs, binding to these non-canonical sites contribute to miRNAmediated gene silencing (12).

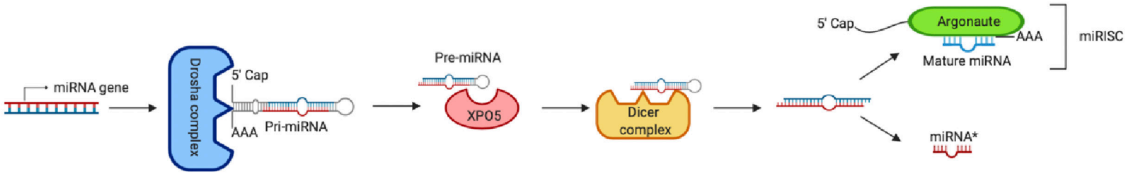

Figure 1: miRNA Biogenesis (10, 11)

1.2. miR-146a-5p

The dysregulation of neuroimmune responses is a hallmark of neuroinflammatory disorders, and miR-146a-5p has emerged as a critical post-transcriptional regulator of this process. By fine-tuning key pathogenic signaling pathways, miR-146a-5p represents a novel and promising therapeutic target and biomarker for these diseases (13). Endogenous miR-146a-5p is a promising, yet complex, inflammatory biomarker with expression that shifts with disease chronicity. Evidence indicates lower or stable levels during acute neuroinflammation, contrasting with a progressive increase in chronic settings. This later upregulation may represent a compensatory anti-inflammatory response aimed at resolving inflammation and restoring neuronal homeostasis (14).

In the following sections, we systematically evaluate recent evidence regarding miR-146a-5p in MS, focusing on its biomarker potential, compartment-specific regulation, therapeutic implications, and cell-type specific mechanisms.

2. Clinical and Mechanistic Dimensions of miR-146a-5p in Multiple Sclerosis

2.1. Vitamin D and Its Influence on miR-146a-5p in Multiple Sclerosis

Vitamin D is vital for maintaining bone integrity and also contributes to immune regulation as well as regulating cell growth and division (15). It has been shown to attenuate inflammation by reducing pro-inflammatory markers and increasing anti-inflammatory cytokines (16). Moreover, its status seems to be associated with both MS incidence and disease activity, with deficiency correlating to higher risk of development and worse clinical outcomes (17). Another study shows that Vitamin D may mitigate EAE, an animal model of MS, by suppressing pro-inflammatory Th17 cell differentiation and IL-17 production. This effect involves upregulation of specific microRNAs that regulate the Th17 transcription factor RORγ-t (18).

One study reported a possible association between altered miR-146a-5p expression, low vitamin D levels, and increased disease burden in individuals with RRMS. miR-146a-5p expression was found significantly lower in RRMS patients compared to healthy individuals. miR-146a-5p, known for its anti-inflammatory function, initially showed increased expression with rising vitamin D levels, suggesting a potential protective response. However, the finding that miR-146a-5p's expression declined when vitamin D levels exceeded 40 ng/ml (19) may reflect a regulatory shift towards immune balance once sufficient Vitamin D status is achieved. Additionally, miR-146a-5p was downregulated in patients with higher EDSS scores, indicating a possible link between reduced anti-inflammatory regulation and increased disease severity (19). Given the central role of neuroinflammation in MS pathogenesis, these findings may have broader implications, supporting the potential of vitamin D-miR-146a-5p interactions as a therapeutic avenue in MS as well.

2.2. Compartmentalized Dysregulation: miR-146a-5p as a CSF Biomarker for Active MS Lesion

To assess and characterize active lesions in MS patients, gadolinium-enhanced magnetic resonance imaging (MRI) can be used. Its mechanism lies in enhancing areas at which the integrity of the BBB has been compromised due to an inflammation caused by immune-related responses (20). Recent evidence suggests that certain miRNAs may show localized expression in MS, with cerebrospinal fluid (CSF) often presenting a more disease-relevant profile than peripheral compartments.

A recent study reported that differentially expressed miR-146a-5p in the CSF was noticed in RRMS patients. miR-146a-5p was significantly upregulated in cerebrospinal fluid, a differential expression pattern that effectively distinguishes RRMS from controls (21). In RRMS patients, cerebrospinal fluid analysis revealed that miR-146a-5p expression was elevated in those who were untreated or receiving first-line therapy, and was higher compared to patients receiving second-line treatment. Moreover, its expression was upregulated in gadolinium-enhancing (Gd+) active white matter lesions in the brain, suggesting a link between miR-146a-5p dysregulation and MRI detectable inflammation (22) . Additionally, Muñoz-San Martín et al. found an overexpression of miR-146a-5p in the CSF of gadolinium-enhancing MS lesions, which shows a similar pattern to the previous study. There was also a correlation between this miRNA and the CSF neurofilament light chain, which is reported as one of the biomarkers for axonal damage in MS. However, while an increased regulation of miR-146a-5p was detected in the CSF, no difference between its regulation in plasma was noticed between Gd+ and Gd- patients again pointing to the compartmentalized nature of regulation (23).

2.3. miR-146a-5p as a Biomarker for Treatment Response and Disease Course

The clinical relevance of miR-146a-5p in MS appears to be linked to its association with treatment response and longitudinal disease activity rather than serving as a static marker of tissue damage. Evidence suggests that miR-146a-5p may function as a context-dependent indicator of ongoing inflammatory dynamics and compensatory regulatory mechanisms. In patients treated with Glatiramer Acetate (GA), serum levels of miR-146a-5p were elevated in those who experienced confirmed disability progression at two years, indicating an association with continued disease activity (24). This observation aligns with findings from Dominguez-Mozo et al., who reported a positive correlation between miR-146a-5p levels and EDSS scores. The authors proposed that this upregulation likely reflects a compensatory anti-inflammatory response rather than a direct pathogenic effect, where higher levels correspond to a greater underlying disease burden (25).

The sensitivity of miR-146a-5p to different therapeutic mechanisms is further evidenced by studies on Dimethyl Fumarate and intensive immunomodulation. While plasma levels may be lower at baseline compared to healthy controls, longitudinal analysis under Dimethyl Fumarate treatment revealed that higher miR-146a-5p levels correlated with lower disability severity (ARMSS and EDSS scores) over time (26). This pattern may reflect stabilization of anti-inflammatory regulatory capacity under treatment. In contrast, downregulation of miR-146a-5p in whole blood and fecal samples has been reported in patients with RRMS compared to both healthy controls and CIS, suggesting a potential role in disease differentiation (27). Furthermore, the downregulation of miR-146a-5p in extracellular vesicles has been linked to cognitive decline and EDSS progression, providing a potential predictor for treatment non-responders (28).

This compartmentalized dysregulation is most clearly observed following high-efficacy interventions like autologous hematopoietic stem cell transplantation (aHSCT). In patients undergoing aHSCT, miR-146a-5p levels in the cerebrospinal fluid showed a significant decrease, approaching levels comparable to healthy controls (22). This reduction suggests that miR-146a-5p may respond to intensive immunomodulatory therapy and could potentially reflect changes in neuroinflammatory activity. Taken together (Table 1), these findings indicate that monitoring miR-146a-5p across different biological compartments may provide complementary information regarding a patient's response to specific Disease Modifying Therapies.

Table 1: Clinical and Compartment-Specific Expression Profiles of miR-146a-5p in MS

Clinical Context/ Therapy	Sample Source	Direction of Change	Interpretation	Ref.
Glatiramer Acetate (GA)	Serum	Increase	Associated with ongoing disease activity and possible compensatory anti-inflammatory response.	(24,25)
Dimethyl Fumarate	Plasma	Higher levels during treatment	Longitudinal elevation correlates with clinical stability and lower disability (EDSS).	(26)
aHSCT (Stem Cell Trans.)	CSF	Decrease (approaching HC levels)	Marked reduction suggesting resolution of active neuroinflammation	(22)
RRMS vs. CIS Diagnosis	Blood / Feces	Decrease	Associated with transition from CIS to established RRMS	(27)
Neurodegenerative Decline	Extracellular Vesicles	Decrease	Associated with cognitive decline and poor therapeutic response	(28)

2.4. miR-146a-5p in Oligodendrocytes: Modulating Remyelination and Repair

Oligodendrocytes play a crucial role in producing the myelin sheath that facilitates rapid signal conduction within the central nervous system (CNS). Disruptions in their development, survival, or functional maturation are linked to a range of neurological conditions -including both developmental defects and neurodegenerative disorders- and may also limit the CNS's capacity for regeneration after damage (30). One study has demonstrated that increasing miR-146a-5p levels enhances oligodendrocyte progenitor cell differentiation and remyelination in an EAE model, suggesting that miR-146a-5p may serve as a promising therapeutic target for demyelinating diseases such as multiple sclerosis (31). Interestingly, while the absence of miR-146a-5p was broadly protective against demyelination and inflammation, it also led to a slightly lower number of oligodendrocyte progenitor cells during remyelination, suggesting a complex, dual role for this microRNA in repair processes (32).

2.5. Microglial Modulation: miR-146a-5p in M1/M2 Polarization and Neuroprotection

As the resident macrophages of the central nervous system, microglia play a dual role in multiple sclerosis, mediating both neurotoxic and neuroprotective effects through their cytokine secretion, which makes them a promising therapeutic target (33). Microglia-mediated neuroinflammation plays a dual role in neurodegenerative diseases: while pro-inflammatory M1 microglia drive neurotoxicity, anti-inflammatory M2 microglia promote neuroprotection. Therefore, modulating M1/M2 polarization represents a promising therapeutic approach (34). One study demonstrates that microglia are the primary source of miR-146a-5p in the CNS, and its absence alters microglial function and protein expression, highlighting miR-146a-5p's key role in regulating gene expression in active multiple sclerosis lesions (35). Furthermore, miR-146a-5p can inhibit the apoptosis of hippocampal neurons induced by microglial activation, revealing a molecular basis for its neuroprotective effect (36).

2.6. Bridging the Evidence Gap: miR-146a-5p's Potential in Astrocyte Pathology

Astrocytes are increasingly recognized as active participants in the pathogenesis of multiple sclerosis, rather than passive or merely reactive components. A research group initially reported elevated miR-146a-5p expression in macrophages and later found its levels to be reduced in astrocytes from active MS lesions, suggesting cell type-specific regulation of this miRNA (37).

Laser microdissection of astrocytes from chronic active MS lesions has revealed decreased miR-146a expression compared to controls, while no similar reduction was ob-

served in microglia, suggesting a disrupted astrocyte-specific anti-inflammatory regulatory mechanism in chronic neuroinflammation (38). In a separate experimental study, fumarate treatment was shown to reduce miR-146a-5p expression in astrocytes in parallel with attenuated inflammatory signaling. Given that miR-146a-5p is typically upregulated in MS lesions as a compensatory response to neuroinflammation, this decrease may reflect treatment-associated normalization of the inflammatory milieu rather than a loss of regulatory capacity, suggesting a shift toward astrocytic homeostasis (39). While direct evidence for miR-146a-5p in astrocytes in MS is limited, findings from other neurodegenerative diseases underscore its critical role in glial pathology. For instance, in Amyotrophic Lateral Sclerosis (ALS), the restoration of miR-146a-5p in astrocytes reversed their pathological phenotype and mitigated the neurotoxic effects of their secretome on motor neurons and microglia (40). This compelling evidence from ALS, coupled with the related role of miR-146b-5p in modulating astrocyte-mediated inflammation in MS (41), strongly warrants further investigation into this miRNA family in the MS context.

2.7. Intercellular Communication: Exosomal miR-146a-5p and its Role in MS

Exosomes have recently gained attention as critical mediators of intercellular communication in the central nervous system. Because they can cross the blood-brain barrier and remain stable in peripheral fluids, exosomes are considered promising biomarkers and potential therapeutic vehicles in multiple sclerosis (42).
One study demonstrated that miR-146a-5p was significantly downregulated in the serum exosomes of IFN-β-treated RRMS patients compared to untreated individuals (43). In cerebrospinal fluid-derived exosomes from untreated relapsing-remitting MS patients, miR-146a-5p expression, which is known to be stimulated during Epstein-Barr virus (EBV) infection, was significantly upregulated compared to the healthy control (HC) group (21). Functional studies done with exosomes derived from bone marrow mesenchymal stem cells have highlighted the immunomodulatory role of miR-146a-5p, showing that it can influence microglial activation towards anti-inflammatory M2 polarization and may hold therapeutic potential in conditions involving neuroinflammation (44).

Conclusion and Future Perspectives

In conclusion, recent evidence solidifies miR-146a-5p as a central, yet complex, regulator in the neuroimmune landscape of multiple sclerosis. Its expression is dynamically regulated across different CNS compartments and cell types, reflecting a dual nature where it can exert both anti-inflammatory, protective functions, while context-dependent dysregulation may accompany ongoing pathogenic processes. Indeed, it is predominantly considered an anti-inflammatory molecule, and its observed increase in more severe disease states is often interpreted as a compensatory, yet ultimately insufficient, feedback response to counteract chronic inflammation. The consistent dysregulation of miR-146a5p in the CSF and blood of MS patients, its correlation with disease activity and treatment response, and its critical roles in modulating microglial activation, oligodendrocyte maturation, and astrocyte pathology collectively underscore its significant potential as a diagnostic and prognostic biomarker, with its utility also suggested in contexts like Vitamin D status and exosomal delivery. Furthermore, preclinical studies demonstrating that manipulating miR-146a-5p levels can ameliorate neuroinflammation and promote remyelination highlight its promise as a novel therapeutic target. Notably, the heterogeneous expression patterns reported across studies likely reflect differences in disease stage, cellular compartment, and therapeutic exposure, emphasizing the importance of contextual interpretation when considering miR-146a-5p as a biomarker. Future research should focus on resolving the cell-type and context-specific actions of miR-146a-5p and developing efficient delivery strategies to harness its therapeutic potential, ultimately paving the way for miR-146a-5p-based interventions in MS.

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YAZAR KILAVUZU

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Tıp Fakültesi Klinikleri dergisi, İstanbul Aydın Üniversitesi Tıp Fakültesinin bilimsel içerikli, resmi yayınıdır. Mart, Temmuz, Kasım aylarında olmak üzere yılda 3 sayı olacak şekilde yayımlanır.

Tıp Fakültesi Klinikleri Dergisi, tıbbın tüm alanlarında, klinik ve temel bilim orijinal araştırma makaleleri, derlemeler, editör görüşleri ve olgu sunumları yazılarının yayımlandığı "çift-kör" hakemlik (peer-review) ilkelerine dayanan uluslararası bir dergidir.

Tıp Fakültesi Klinikleri Dergisi'nde makale başvuru veya işlem ücreti uygulanmamaktadır. Yayınlanan yazılar için herhangi bir ücret ya da karşılık ödenmez.

Dergi; temel tıp bilimleri ve klinik branşlarda ulusal ve uluslararası düzeyde katkı yapan araştırma, özgün çalışma, derleme, olgu bildirimleri yayımlamayı hedeflemektedir.

2. Yayın Değerlendirme Politikası

Makaleler dergimize gönderilmeden önce etik uygunluğu açısından yazar tarafından "intihal.net"den kontrol taramasından geçirilmesi gerekmektedir.

Dergiye gönderilen yazıların, ulusal ya da uluslararası bir dergide yayımlanmamış, yayına Kabul edilmemiş ya da yayın için değerlendirme aşamasında olmaması gerekir. Bu gereklilik bilimsel toplantılarda bildiri olarak sunulmuş ve özeti yayınlanmış yazıları kapsamaz ancak bu durumda bildirinin sunulduğu toplantı adı, tarihi ve yeri belirtilmelidir. Eğer makalede daha önce yayımlanmış; alıntı yazı, tablo, resim vs. mevcut ise makale yazarı, yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu makalede belirtmek zorundadır.

Tıp Fakültesi Klinikleri Dergisi'nin uluslararası indekslerde ve veritabanında, İngilizce adı "Journal of Medical Clinics"dir, ve kaynaklarda belirtilirken "J Med Clin" olarak yazılmalıdır.

Makalelerin formatı "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications (www.icjme.org) kurallarına göre düzenlenmelidir.

Yazıların bilimsel ve etik sorumlulukları yazarlara, telif hakkı ise İstanbul Aydın Üniversitesi'ne aittir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur. Yazarlar, yayın haklarının devredildiğini belirten onay belgesini (Yazarlık Katkıları, Yayın Hakkı Devri, Maddi Yardım ve Teşekkür-Kabul İzin Formu) uygun biçimde doldurarak dergi editörlüğüne göndermelidir. Bu forma dergi web adresinden (http://www.iautipklinikleri.com) ulaşılabilir. Bu belgenin tüm yazarlar tarafından imzalanarak dergiye gönderilmesi ile birlikte yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermiş, bilimsel katkı ve sorumluluklarını beyan etmiş sayılırlar. Bu aşamadan sonra makaleye yeni yazar eklenemez veya yazar isim sıralamasında değişiklik yapılamaz.

Tıp Fakültesi Klinikleri Dergisi'nde yayınlanmak amacıyla gönderilen ve Etik Kurul onayı alınması zorunluluğu olan deneysel, klinik ve ilaç araştırmaları için Helsinki Bildirisi'ne uygun Etik Kurul Onay Raporu gereklidir https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf

Deneysel hayvan çalışmalarında ise yazarlar, "Guide for the care and use of laboratory animals" (http://oacu.od.nih.gov/regs/guide/guide.pdf) yönergesi kapsamında hayvan haklarını koruduklarını belirtmeli ve kurumlarından Etik Kurul Onay Raporu almalıdır. Etik Kurul onayı ve "Bilgilendirilmiş Gönüllü Onam Formu" alındığı araştırmanın "Gereç ve Yöntem" bölümünde mutlaka (etik onay numarası ile birlikte) belirtilmelidir. Makalelerin etik kurallara uygunluğu yazarların sorumluluğundadır.
Değerlendirme sürecinde gerek görülürse editör tarafından Etik Kurul onayının bir örneği yazarlardan istenebilir.

Yazılar değerlendirme sürecinde aşırma, yanıltma ve kopya yayın açısından denetlenecek ve etik dışı durumların tespit edilmesi halinde yaptırım uygulanacaktır. Yaptırımlar Committee on Publication Ethics (COPE) kuralları kapsamında belirlenecektir. Bunun yanı sıra, intihali önlemek için yayın öncesinde tüm yazıların intihal araştırma programları ile taraması yapılmaktadır.

3. Makale Başvurusu

Yazarlar makale gönderimlerini derginin online makale kabul sistemi üzerinden yaparlar (http://www.iautipklinikleri.com). Bütün başvurularda Yazarlık Katkıları, Yayın Hakkı Devri, Maddi Yardım ve Teşekkür-Kabul İzin Formu doldurularak gönderilmelidir. Yazarlar onay formunu doldurarak, makalelerinin telif hakkını Tıp Fakültesi Klinikleri''ne bıraktıklarını, bilimsel katkı ve sorumluluklarını ve çıkar çatışmasına yol açabilecek mali ya da diğer ilişkilerini açıklamalıdır. Gönderilen yazıda yazışma yapılacak yazar elektronik posta adresi ve yazının tipi (araştırma, derleme, olgu sunumu vs.) belirtilmelidir.
Tüm yazarlar bilimsel katkı ve sorumluluklarını ve çıkar çatışması olmadığını bildiren toplu imza ile yayına katılmalıdır. Araştırmalara yapılan kısmi de olsa nakdi ya da aynı yardımların hangi kurum, kuruluş, ilaç-araç-gereç firmalarınca yapıldığı dipnot olarak bildirilmelidir. Yayına kabul edilmeyen yazılar yazarlara geriye yollanmaz.

4. Hakem Değerlendirmesi

Tıp Fakültesi Klinikleri Dergisi bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan süreli bir yayın organıdır. Editör yayın koşullarına uymayan yazıları; düzeltmek üzere yazarına geri gönderme, biçimce düzenleme veya reddetme yetkisine sahiptir. Gönderilen yazılar, editör ve editör yardımcıları ile en az iki hakem incelemesinden geçip, gerek görüldüğü takdirde, istenen değişiklikler yazarlarca yapıldıktan sonra yayımlanır.
Hakem belirleme yetkisi tamamen editör ve yayın kuruluna aittir. Hakemler belirlenirken derginin ulusal veya uluslararası yayın danışma kurulundan isimler seçilebileceği gibi yazının konusuna göre ihtiyaç duyulduğunda, yurtiçi veya yurtdışından bağımsız hakemler de belirlenebilir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör, editör yardımcıları, düzeltme yapmalarını kabul etmiş sayılır.

5. Yazım Kuralları

Yazar Sorumluluğu

Makaleler dergimize gönderilmeden önce etik uygunluğu açısından yazar tarafından "intihal.net"den kontrol taramasından geçirilmesi gerekmektedir.

Makalelerin bilimsel kurallara uygunluğu yazarların sorumluluğundadır. Tüm yazarların gönderilen makalede akademik veya bilimsel olarak doğrudan katkısı olmalıdır.

Yazar(lar) olarak belirlenen isim aşağıdaki özelliklere sahip olmalıdır:

(1) Makaledeki çalışmanın fikir, planlama, yöntem, veri toplama, veri analizi/yorumlama, yazı taslağını oluşturma, içeriğin eleştirel incelenmesi, son onay ve sorumluluk aşamalarında görev almış olmalıdır.

(2) Makalenin son halini kabul etmelidir.

Yayın, direkt ya da indirekt ticari bağlantı içeriyorsa veya çalışmaya materyal desteği veren bir kuruluş varsa, yazarlar kullanılan ticari ürün, ilaç, firma vs. ile ticari hiçbir ilişkisinin olmadığını ya da var ise nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar) editöre sunum sayfasında belirtmek zorundadır. İncelemeye sunulan araştırmada olası bir bilimsel hata, etik ihlal şüphesi veya iddiasıyla karşılaşılırsa, dergi verilen yazıyı destek kuruluşların veya diğer yetkililerin soruşturmasına sunma hakkını saklı tutar. Dergi, sorunun düzgün biçimde takip edilmesi sorumluluğunu kabul eder ancak gerçek soruşturmayı veya hatalar hakkında karar verme yetkisini üstlenmez.

Kısaltmalar
Makalede kullanılan kısaltmalar uluslararası kabul görmüş şekilleriyle kullanılmalı, ilk kullanıldıkları yerde açık olarak yazılmalı ve parantez içinde kısaltılmış şekli gösterilmelidir. İlaç adları kullanımında ilaçların jenerik adları Türkçe okunuşlarıyla yazılır. Laboratuvar ölçümleri Uluslararası Sistem (US; Systéme International: SI) birimleri ile bildirilmelidir.

İstatistik Değerlendirme
Makalelerin biyoistatistiksel kurallara uygunluğu yazarların sorumluluğundadır. Tüm retrospektif, prospektif ve deneysel araştırma makaleleri biyoistatistiksel olarak değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Makalelerde p değerleri açık olarak verilmelidir.

Yazım Dili
Derginin yayın dili Türkçe ve İngilizce olup, Türkçe makalelerde Türk Dil Kurumu'nun Türkçe Sözlüğü veya Yazım Kılavuzuna uygun yazım (www.tdk.gov.tr) geçerlidir.

İngilizce makalelerin ve özetlerin, dergiye gönderilmeden önce gerek duyulduğunda, dil bilgisi kuralları yönünden profesyonelce gözden geçirilmesi sağlanmalıdır. Ayrıca gönderilmiş olan makalelerdeki yazım ve dilbilgisi hataları, makalenin içeriğine dokunmadan, redaksiyon komitemiz tarafından düzeltilmektedir. Makalelerin yazım ve dil bilgisi kurallarına uygunluğu yazarların sorumluluğundadır.

6. Dergiye Gönderilecek Yazı Türleri ve Özellikleri
Tıp Fakültesi Klinikleri Dergisi "Vancouver stili" diye anılan kurallara göre düzenlenmiş yazıları yayınlar (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. New England Journal of Medicine, 1997; 336:309-315).

Yazıların formatı şu şekildedir:

Dergiye gönderilecek makaleler "Kapak Sayfası", "Ana Metin", "İntihal Raporu (%20'yi aşmamalıdır.)", "Etik Onay Yazısı", "Telif Hakkı Formu" ve gerektiğinde "Ek" kısımlarından oluşmalıdır.

Bilimsel araştırmaya dayalı özgün nitelikteki araştırma makalelerinde "Başlık" "Özet/Abstract", "Anahtar Kelimeler", "Giriş", "Gereç ve Yöntem", "Bulgular", "Tartışma", "Sonuç" ve "Kaynakça" kısımları mutlaka bulunmalıdır. Gerektiğinde Bulgular ile Tartışma kısımları birleştirilebilir (Bulgular ve Tartışma).

1) Makale Başlığı: Makale başlığı metnin içeriğini yansıtmalı, kelimelerin sadece baş harfi büyük olacak şekilde yazılmalı, 14 punto, Times new roman yazı formatında, ortalanmış ve koyu yazılmalı, başlık sonrası 2 satır boşluk konmalıdır.

2) Türkçe-İngilizce Özet ve Anahtar Kelimeler: Türkçe hazırlanmış eserlerde öncelikle Türkçe başlık ve özet; ardından makalenin İngilizce başlığı ve özeti (Abstract) yazılmalıdır. İngilizce olarak hazırlanmış eserlerde ise Türkçe başlık ve özet zorunluluğu yoktur. Makalenin özeti, konunun amacını, yöntemini ve kapsamını net olarak, en az 100 en fazla 250 kelime ile ifade edecek şekilde, 10 punto, Times new roman yazı formatında olarak yazılmalıdır.

Türkçe ve İngilizce özetlerin bir satır altına, sayısı en az 3, en fazla 5 olacak şekilde, çalışmayla doğrudan ilgili anahtar kelimeler/keywords yazılmalıdır. Makalenin başlığında bulunan kelimeler yerine mümkün olduğunca alternatif kelimeler üretilmeli, başlığı tamamlayan kelimelerden oluşturulmalıdır. Başlıktaki kelimelerin eş anlamlıları veya benzerleri de anahtar kelime olarak kullanılabilir. Anahtar kelimeler normal, küçük harfle (ilk anahtar kelimenin ilk harfi büyük) yazılmalı ve aralarına virgül konulmalıdır.

3) Metin: A4 kâğıda (210 x 297 mm), sayfa kenar boşlukları soldan, sağdan, alttan ve üstten 2.5'er cm olacak şekilde, 1.5 satır aralığıyla, "Times new roman" yazı formatında 12 punto büyüklükte Microsoft Word ile yazılmalıdır. Satırbaşlarında boşluk olmamalıdır. Metin iki yandan hizalanmış olmalıdır. Metin içinde sık tekrarlanan ve birçok kelimeden oluşan, makalenin çalışma konusuna özgü isimler için kısaltma yapılabilir. Kısaltılacak isim ilk kullanıldığı yerde açık bir şekilde yazılmalı ve parantez içinde kısaltılmış hali belirtilmelidir. Daha sonraki kullanımlarda sadece kısaltılmış hali kullanılmalıdır. Başlık (title) ve özet (abstract) bölümlerinde mümkün olduğunca kısaltmalardan kaçınılmalıdır. Kesirli sayıların belirtilmesinde ondalık ayıracı olarak Türkçe metinde virgül, İngilizce metinde ise nokta işareti kullanılmalıdır. Yüzde işaretleri yazılırken sayılarla işaret arasında boşluk bırakılmamalıdır (Örnek: Türkçe metin için %25, İngilizce metin için 25%). Metnin genel kullanımında parantezden önce boşluk konulmalıdır. Makalede yer alan başlıkların tümü sola yaslanmış olarak koyu harfle yazılmalıdır. Başlık ve alt başlıklar numarasız olarak verilmelidir. Mümkün olduğunca kısa olmalıdır. Birinci düzey başlıklarda bütün kelimelerin ilk harfleri büyük yazılmalıdır. İkinci ve üçüncü düzey başlıkların sadece ilk kelimenin baş harfi büyük olmalı; üçüncü düzey başlıklar italik yazılmalıdır. Dördüncü düzey başlık kullanılmamalıdır. Latince isimler italik yazılmalıdır. Sayfa sayısı kaynaklar hariç 5'ten az 12'dan fazla olmamalıdır (Kapsamı geniş makalelerde yayın kurulunun onayı alındıktan sonra sayfa sayısında artış yapılabilir).

4) Kaynaklar ve Dipnotlar: Kaynaklar metin içerisinde cümle sonunda parantez içi numaralandırma yöntemi ile verilmeli ve Kaynaklar bölümünde numaralandırılarak yazılmalıdır.

5) Tablo ve/veya Şekiller: Tabloların numarası ve başlığı bulunmalı, ayrı ayrı sıra sayısı verilerek numaralandırılmalıdır. Sola yaslanmış olarak tablo numarası kalın, tablo adı normal ve 10 punto büyüklükte Times new roman yazı tipinde yazılmalıdır. Sonuna nokta konulmamalıdır. Metinde kullanılan fotoğraflar, resimler, grafikler, haritalar, şemalar, çizimler vb basım karakterinde yazılamayan bütün görseller şekil adı ile kullanılmalıdır. Tablo ve şekil başlıkları, tablo ve şeklin üst bölümünde yer almalıdır. Başlıklar, tablo ve şekil numarasının altına gelecek şekilde ayrı bir satırda yer almalıdır. Tablo içi başlıklar düz ve sadece ilk kelimenin baş harfi büyük olmalıdır. Kullanılan kısaltmalar ve gerekli açıklamalar çizelge ve şekil altında verilmelidir. Tablolarda punto büyüklüğü en az 9, en fazla 12 olmalıdır. Şeklin içerisinde herhangi bir metnin yer alması durumunda 9 ile 12 punto arasında bir punto büyüklüğünde, Times new roman yazı tipi kullanılmalıdır. Şekilde yer alan verilerin daha anlaşılır olmasını sağlamak için ekstra bilgiler verilmesinin gerekmesi durumunda bu bilgiler şeklin altına eklenmelidir. Başka bir kaynaktan alıntı yapılan (yapılan çalışmadan üretilmeyen) tablo ve şekillerde, tablo ve şekil başlığının sonunda kaynak referans gösterilmeli; kaynakça listesinde yer almalıdır. Makalede kullanılan tablo ve şekillere metin içinde atıf yapılmalıdır. Atıf yapılırken dizgi esnasında oluşabilecek sayfa değişiklikleri ve kaymalar dikkate alınarak "yukarıda/aşağıda" ya da "sayfa X'te yer alan tabloda/şekilde" gibi ifadeler yerine "Tablo /Şekil 2'de yer alan verilere göre..." örneğinde olduğu gibi tablo/şekil numaraları kullanılmalıdır. Cümle sonunda verilen atıflarda nokta, atıf parantezinden sonra konulmalıdır.

6) Kapak Sayfası: Kapak sayfası sırasıyla ortalanmış olarak makale başlığını, yazarlara ait bilgileri (yazarlar sıralı olarak alt alta yazılmalı, her bir yazarın altına çalıştığı kurum, e-posta adresi ve ORCID numarası belirtilmelidir) içermeli; yazışmadan sorumlu yazarın isim ve iletişim bilgilerini ayrıca belirtilmelidir. Yüksek lisans ve doktora öğrencileri lisansüstü eğitim gördükleri üniversite, enstitü ve ana bilim dallarını belirtmelidirler. Çalışma, daha önce bir kongre ya da sempozyumda bildiri olarak sunulmuş ise veya yazarlardan birisinin yüksek lisans veya doktora tez çalışmasından üretilmişse bu sayfada belirtilmelidir.

7) Yazarların katkıları: Kavramsallaştırma, denetim, yazma, inceleme, düzenleme, orijinal taslak hazırlama. (İlgili katkıların yanlarına sadece yazar isim ve soyisimlerinin baş harfleri, büyük harflerle yazılacak. Örneğin; Kavramsallaştırma; AB, KL, Yazma; KL, BH.) Devamında da "Tüm yazarlar yazının yayınlanmış versiyonunu okudu ve kabul etti." yazısı eklenecektir.

Conceptualization, supervision, writing, review, editing, original draft preparation. (Only the initials of

the authors' names and surnames will be written in capital letters next to the relevant contributions. For example; Conceptualization; AB, KL, Writing; KL, BH.) It continued: "All authors have read and agreed to the published version of the manuscript." text will be added.

Makale Türleri
A. Araştırma Makaleleri

Bu yazılar daha önce yayınlanmamış, özgün araştırma yazılardır.

Araştırma yazıları;
- Türkçe ve İngilizce başlık,
- Türkçe ve İngilizce 250 kelimeyi geçmeyecek şekilde özet

Türkçe Özet

Amaç
Gereç ve yöntem
Bulgular
Sonuç
Anahtar Kelimeler

Türkçe Makale Metni

Giriş
Gereç ve yöntem
Bulgular
Tartışma
Sonuç
Teşekkür (İsteğe bağlı)
Yazarların katkıları
Çıkar çatışması
Etik Kurul Onayı (Hücre çalışmaları hariç)
Kaynaklar

İngilizce Özet

Aim
Materials and Methods
Results
Conclusion
Keywords

İngilizce Makale Metni

Introduction
Materials and methods
Results
Discussion
Conclusion
Acknowledgments (If desired)
Author's Contribution
Conflict of interest
Ethical committee approval (Except for cell studies)
References

B. Olgu Sunumları

Bir ya da daha fazla olgunun klinik değerlendirme açısından bilimsel önemini belirten yazılardır.

Olgu sunumları;
- Türkçe ve İngilizce başlık,
- Türkçe ve İngilizce özetler,
- Türkçe ve İngilizce anahtar kelimeler
- Ana metin (Giriş, Olgu Sunumu ve Tartışma bölümlerini içermelidir),
- Kaynaklar (En fazla 15 kaynak gösterilebilir),
- Tablo/şekil/resim bölümlerinden oluşur.

Olgu sunumlarının özeti bölümlere ayrılmış olmayıp 250 kelimeyle, yazının ana metni de 1500 kelimeyle sınırlıdır.

C. Derleme

Belirli bir konuyu tanımlamak, ana hatlarıyla özetlemek, alanyazındaki boşlukları vurgulamak gibi amaçlarla yazılan alanla ilgili yeni ve güncel bilgileri içeren derleme makalelerinde "Giriş" bölümünden sonra ana ve alt başlıklar halinde konu detaylandırılır. Derleme makalelerde "Sonuç" bölümü mutlaka yer alır. Derleme makalelerde incelenen kaynakların ağırlıklı olarak son 5 yıla ait olması gerekir. Derleme çalışmalarında "iyi bir tarama yapılması, tarafsız bir gözle değerlendirilmesi, belirli bir analiz ve sentez yapılması" gereklidir.

Tıp Fakültesi Klinikleri Dergisi'nde doğrudan veya davet ile gönderilen bilimsel yazılardır. Uzmanlık derneklerinin hazırladıkları ve derlemelerden oluşan sayılarda "Konuk Editör" sistemi vardır.

Derlemeler:
-Türkçe başlık
-Türkçe özet
-Türkçe anahtar kelimeler
-İngilizce başlık
-İngilizce özet
-İngilizce anahtar kelimeler
bölümlerinden oluşur ve yazar sayısı en fazla beş, metin dosyası en fazla 4000 kelime, kaynak sayısı da 40 ile sınırlıdır.

D. Editöre Mektup

Son bir yıl içinde dergide yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelime içeren yazılar olup kaynak sayısı 5 ile sınırlıdır. Başlık ve özet bölümleri yoktur. Hangi makaleye (sayı, tarih verilerek) ithaf olunduğu belirtilmeli ve sonunda yazarın ismi, kurumu, adresi bulunmalıdır. Mektuba cevap verildiği takdirde, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

E. Kaynaklar

1. TFK dergisinde yer alan makalelerden en az 1 tane atıf yapılmalıdır. (At least one citation must be made from the articles in the TFK journal/Journal of Medical Clinics)
2. Tüm kaynaklar yazı içinde sıralı olarak belirtilmelidir.
3. Dörtten fazla yazarı olan yazılarda ilk üç isimden sonra "et al." ibaresi kullanılmalıdır.
4. Dergi isimleri Index Medicus'da kullanılan biçimde kısaltılmalıdır.

Dergi: Yazar A, Yazar B, Yazar C. Makalenin başlığı. Dergi adının kısaltılması Yıl; Cilt: Sayfa(lar).
Kitap: Yazar A, Yazar B, Yazar C. Bölüm başlığı. In: Editör A, Editör B, Editör C, eds. Kitabın adı. Kaçıncı baskı olduğu. Yayınlanma yeri: Yayınevi; Yıl. Sayfa(lar).

Dergi Yazıları

Dergi: Knyazev GG, Bocharov AV, Levin EA, Savostyanov AN, Slobodskoj-Plusnin JY. Anxiety and oscillatory responses to emotional facial expressions. Brain Res 2008 28;1227:174-88. doi: 10.1016/j.brainres.2008.06.108.

Kitaplar

Kitap bölümü: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, Diagnosis, and Management içinde. 2nd Ed. New York: Raven Press; 1995. p. 465-478.

Kitap: Eyre HJ, Lange DP, Morris LB. Informed decisions: the complete book of cancer diagnosis, treatment, and recovery. 2nd ed. Atlanta: American Cancer Society; c2002. p.768.

Web Örneği

Hunzeker CM, Fangman W, Latkowski JM. Folliculotropic mycosis fungoides. Dermatology Online Journal. Available at:http://dermatology.cdlib.org/131/.

Yazışma
Tıp Fakültesi Klinikleri Dergisi

Editör

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AUTHOR GUIDELINES

1. Scope and Purpose

The Journal of Medical Clinics is the scientific publication of Istanbul Aydın University School of Medicine. It is published three times a year, in March, July, and November.

The Journal of Medical Clinics is an international journal based on the principles of "double-blind" peer review, publishing original research articles, reviews, editorials, and case presentations in all fields of medicine, both clinical and basic sciences.

There are no submission or processing fees for articles submitted to the Journal of Medical Clinics. No fees or compensation are required for published articles.

The journal aims to publish research, original studies, reviews, and case reports contributing to the national and international level in basic medical sciences and clinical specialties.

2. Publication Evaluation Policy

Before submission to our journal, articles must undergo a plagiarism check by the author through "intihal.net" for ethical compliance. This requirement does not include papers presented at scientific meetings and published as abstracts; however, in such cases, the name, date, and location of the conference where the paper was presented must be specified. If the article includes previously published material such as quoted text, tables, or images, the author must obtain written permission from the copyright holder and acknowledge this in the article.

In international indexes and databases, the English name of Tıp Fakültesi Klinikleri Dergisi is "Journal of Medical Clinics."

The format of the articles should be prepared according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications" rules (www.icjme.org).

The scientific and ethical responsibilities of the articles belong to the authors, while the copyright belongs to Istanbul Aydın University. Authors are responsible for the content of the articles and the accuracy of the sources. Authors must submit the consent form indicating the transfer of publication rights (Authorship Contributions, Publication Rights Transfer, Financial Assistance, and Acknowledgment-Acceptance Permission Form) to the journal editorial office properly filled out. This form can be accessed from the journal's website (http://www.iautipklinikleri.com). By signing and submitting this document to the journal, all authors guarantee that the submitted work has not been published in or is under review for publication in another journal, and they declare their scientific contribution and responsibility. After this stage, new authors cannot be added to the article, and changes cannot be made to the order of author names.

For experimental, clinical, and drug research submitted for publication in Journal of Medical Clinics that require approval from an Ethics Committee, an Ethics Committee Approval Report in accordance with the Helsinki Declaration is necessary. https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf)

In experimental animal studies, authors must declare that they have protected animal rights in accordance with the "Guide for the care and use of laboratory animals" (http://oacu.od.nih.gov/regs/guide/guide.pdf) and obtain Ethics Committee Approval from their institutions. The Ethics Committee approval and "Informed Consent Form" must be explicitly stated in the "Materials and Methods" section of the research (along with the ethics approval number). The compliance of articles with ethical rules is the responsibility of the authors. During the evaluation process, if deemed necessary, the editor may request a copy of the

Ethics Committee approval from the authors.
Articles will be checked for plagiarism, misleading information, and duplicate publication during the evaluation process, and sanctions will be applied if unethical situations are detected. Sanctions will be determined in accordance with the rules of the Committee on Publication Ethics (COPE). In addition, to prevent plagiarism, all articles undergo plagiarism screening using plagiarism detection software before publication.

3. Article Submission
Authors submit their articles through the journal's online article submission system (http://www.iautipklinikleri.com). In all submissions, the Authorship Contributions, Publication Rights Transfer, Financial Assistance, and Acknowledgment-Acceptance Permission Form must be completed and submitted. By filling out the consent form, authors declare that they transfer the copyright of their articles to Journal of Medical Clinics, disclose their scientific contributions and responsibilities, and disclose any financial or other relationships that may lead to conflicts of interest. The corresponding author's email address and the type of the article (research, review, case presentation, etc.) should be indicated in the submitted manuscript. All authors must participate in the publication with a collective signature declaring their scientific contributions and responsibilities and stating that there is no conflict of interest. Even if partial financial or similar assistance is provided to the research, the institutions, organizations, or pharmaceutical/medical equipment companies providing such assistance should be acknowledged in a footnote. Articles that are not accepted for publication will not be returned to the authors.

4. Peer Review
Journal of Medical Clinics is a periodic publication that adheres to the principles of independent, unbiased, and double-blind peer review. The editor has the authority to return articles that do not comply with publication conditions to the author for correction, formatting, or rejection. Submitted articles undergo review by the editor, associate editors, and at least two reviewers, and they are published after any necessary revisions have been made by the authors.

The authority to select reviewers lies entirely with the editor and the editorial board. Reviewers may be selected from the national or international advisory board of the journal, or independent reviewers from domestic or foreign sources may be chosen based on the subject matter of the article. Authors are considered to have accepted the revisions made by the editor, associate editors, or reviewers in accepted articles, provided that no fundamental changes are made to the text.

Writing Rules

Author Responsibilities
Before the articles are sent to our journal, they must be scanned by the author on "intihal.net" for ethical compliance.

The adherence of articles to scientific standards is the responsibility of the author(s). All author(s) should have a direct academic or scientific contribution to the submitted article.

The author(s) identified for a manuscript must possess the following qualifications:

(1) They should have been involved in the conception, planning, methodology, data collection, data analysis/interpretation, drafting of the manuscript, critical review of the content, final approval, and accountability stages of the research presented in the article.

(2) They must approve the final version of the article.

If the publication contains any direct or indirect commercial connections or if the research received material support from an organization, the author(s) must disclose in the submission page to the editor whether they have any commercial relationships with the products, drugs, companies, etc., used in the study or if such relationships exist (e.g., consulting, other agreements). In case of possible scientific errors or allegations

of ethical violations encountered during the review of the submitted research, the journal reserves the right to submit the manuscript to investigations conducted by supporting institutions or other authorities. The journal accepts the responsibility for ensuring proper follow-up of the issue but does not assume the authority to make decisions regarding the actual investigation or errors.

Abbreviations

Abbreviations used in the article should be in internationally accepted forms, written out in full at their first occurrence, and followed by the abbreviated form in parentheses. Drug names should be written in their generic names with Turkish pronunciation. Laboratory measurements should be reported using the International System of Units (SI units).

Statistical Evaluation

The adherence of articles to bio-statistical rules are the responsibility of the author(s). All retrospective, prospective, and experimental research articles should be bio-statistically evaluated and appropriately planned, analyzed, and reported. P-values should be clearly stated in the articles.

Language

The publication language of the journal is Turkish and English. For Turkish articles, writing should follow the guidelines of the Turkish Language Institution's Turkish Dictionary or Writing Guide (www.tdk.gov.tr).

English articles and abstracts should be professionally proofread for grammar rules before submission to the journal. Additionally, any writing and grammar errors in the submitted articles are corrected by our editorial committee without touching the content of the article. The compliance of articles with writing and grammar rules are the responsibility of the authors.

The Types and Characteristics of Articles to be Submitted to the Journal

The Journal of Medical Clinics publishes articles prepared according to the rules known as the ''Vancouver style'' (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. New England Journal of Medicine, 1997;336;309-315).

The format of the articles should consist of the following sections:

"Cover Page," "Main Text," "Plagiarism Report (should not exceed 20%)," "Ethical Approval Letter," "Copyright Form," and if necessary, "Appendices."
Scientific research-based original articles must include the following sections: "Title," "Abstract," "Keywords," "Introduction," "Materials and Methods" "Results," "Discussion," "Conclusion," and "References." The "Results" and "Discussion" sections can be combined if necessary (Results and Discussion).

1) Article Title: The article title should reflect the content of the text. It should be written in sentence case, with only the first letter of each major word capitalized. The font size should be 14 points, in Times New Roman font, centered and in bold. There should be a 2-line space after the title.

2) Turkish-English Abstract and Keywords: For articles written in Turkish, the Turkish title and abstract (özet) should be provided first, followed by the English title and abstract. For articles written in English, there is no requirement for a Turkish title and abstract. The abstract of the article should clearly and concisely express the aim, method and scope of the subject, comprising a minimum of 100 and a maximum of 250 words. It should be written in 10-point font, Times New Roman, format.

Underneath the Turkish and English abstracts, at least 3 and up to 5 keywords relevant to the study should be written. Whenever possible, alternative keywords should be generated instead of using words from the article title. The keywords can include synonyms or similar terms related to the words used in the title. Keywords should be written in lowercase (with the first letter of the first keyword capitalized) and separated by commas.

3) Text: The text should be written in Microsoft Word, using A4 paper size (210 x 297 mm) with 2.5 cm margins on the left, right, bottom, and top. The font size should be 12 points, and the font type should be "Times New Roman." The text should have a line spacing of 1.5, and there should be no extra space between paragraphs. The text should be justified on both sides. In the text, abbreviations can be used for frequently repeated and long names specific to the subject of the article. The first use of an abbreviation should be spelled out clearly, followed by the abbreviation in parentheses. In subsequent uses only, the abbreviation should be used. However, in the title and abstract sections, abbreviations should be avoided as much as possible.

For fractional numbers, use a comma as the decimal separator in Turkish text and a period in English text (e.g., 25,25 for Turkish, 25.25 for English). Percentages should be written without a space between the number and percentage sign (e.g., 25% for both Turkish and English).

In general usage throughout the text, a space should be placed before parentheses. Headings in the article should all be left-aligned and written in bold font. Headings and subheadings should not be numbered. They should be as concise as possible. In the first-level headings, the initial letter of each Word should be capitalized. Second and third-level headings should have only the first Word capitalized, with third-level headings in italics. Fourth-level headings should not be used. Latin names should be written in italics.The total number of pages, excluding references, should be between 5 and 12. In articles with extensive content, an increase in the page count may be allowed with the approval of the editorial board.

4) References and Footnotes: References should be provided in the text using the parenthetical numbering method, and they should be listed and numbered in the "References" section

5) Tables and/or Figures: Tables should have a number and a title, and they should be numbered separately, with each having its own sequence number. The table number should be bold, the table title should be in normal font, and both should be written in 10-point Times New Roman font aligned to the left. No period should be placed at the end. Photographs images, graphs, maps, diagrams, drawings, or any other visuals that cannot be reproduced in typesetting should be referred to as "Figure" and used with a figure title in the text. Table and figure titles should be located at the top of the table or figure. The titles should be on a separate line below the table or figure number. Table headers should be plain, and only the first letter of each word should be capitalized. Abbreviations used and necessary explanations should be provided below the table or figure. The font size in tables should be at least 9 and at most 12 points. If any text is included within a figure, a font size between 9 and 12 points in Times New Roman font should be used. If additional information is needed to make the data in the figure clearer, it should be added below the figure. In tables and figures taken from another source (not created by the current study), a reference to the source should be provided at the end of the table or figure title and included in the reference list. Tables and figures used in the article should be cited in the text. When citing them, instead of using expressions like "above/below" or "in the table/figure on page X," use the table/figure numbers, such as "According to Table/Figure 2…" as an example. In-text citations at the end of sentences should have the period placed after the citation in parentheses.

Cover Page

The cover page should contain, in the following order and centered, the article title, information about the authors (authors should be listed one below the other, and each author's affiliated institution, email address, and ORCID number should be provided), and the name and contact information of the corresponding author. Master's and doctoral students should also indicate the university, institute, and department of heir graduate studies. If the study has been previously presented at a conference or symposium or if it is derived from a master's or doctoral thesis of one of the authors, this should be specified on this page.

Contributions of Authors

Conceptualization; AB, KL, Writing; KL, BH, Review; [Author Initials], Editing; [Author Initials], Preparation of Original Draft; [Author Initials]. (Author initials should be written in capital letters next to the relevant contributions. For example; Conceptualization; AB, KL, Writing; KL, BH.) Following that, the statement "All authors read and approved the published version of the article." will be added.

Types of Articles

1.Research Articles

These articles are original research articles that have not been published before.
Research articles should include;

Turkish and English Titles
Abstracts in Turkish and English, not exceeding 250 words

Turkish Abstract

Amaç
Gereç ve yöntem
Bulgular
Sonuç
Anahtar Kelimeler

Turkish Article Text

Giriş
Gereç ve yöntem
Bulgular
Tartışma
Sonuç
Teşekkür (İsteğe bağlı)
Yazarların katkıları
Çıkar çatışması
Etik Kurul Onayı (Hücre çalışmaları hariç)
Kaynaklar

English Abstract

Aim
Materials and Methods
Results
Conclusion
Keywords

English Article Text

Introduction
Materials and methods
Results
Discussion
Conclusion
Acknowledgments (If desired)
Author's Contribution
Conflict of interest
Ethical committee approval (Except for cell studies)
References

2.Case Reports
Case reports are papers that emphasize the scientific importance of one or more cases from a clinical evaluation perspective.

Case reports should include the following sections:
- Turkish and English titles
- Turkish and English abstracts
- Turkish and English keywords
- Main text (including Introduction Case Presentation and Discussion sections)
- References (up to 15 references)
- Consists of Tables/Figures/Images Sections.

The main text of case reports should not exceed 1500 words, and the abstract should be in a single paragraph with a word limit of 250 words.

3. Review Articles
Review articles are written with the aim of defining a specific topic, summarizing it with an overview, and highlighting gaps in the existing literature. They include new and up-to-date information related to the field. In review articles, after the "Introduction" section, the topic is detailed with main and subheadings. Review articles must include a "Conclusion" section. The majority of the sources examined in review articles should be from the last 5 years. A good review article requires a comprehensive search, unbiased evaluation, and specific analysis and synthesis.

In the Journal of Medical Clinics, review articles are either directly submitted or invited by the editorial board. Special issues consisting of reviews prepared by professional organizations follow the "Guest Editor" system.

Review articles include the following sections:
- Turkish title
- Turkish abstract
- Turkish keywords
- English title
- English abstract
- English keywords

The number of authors should not exceed five, the text file should be limited to 4000 words, and the number of references should be limited to 40.

4. Letter to the Editor
"Letters to the Editor" are articles of up to 500 words that contain readers' different opinions, experiences, and questions related to the articles published in the journal within the last year. The number of references is limited to 5. There are no title and abstract sections. The letter should specify which article it is dedicated to (with issue number and date) and end with the author's name, institution, and address. If a response to the letter is given, it will be published in the journal, either by the editor or the author(s) of the article.
References
1. At least one citation must be made from the articles in the TFK journal/Journal of Medical Clinics.
2. All references should be listed in the text in sequential order.
3. For articles with more than four authors, the abbreviation "et al." should be used after the first three names.
4. Journal names should be abbreviated as used in Index Medicus.
Journal: Author A, Author B, Author C. Title of the article. Abbreviation of the Journal name Year; Volume: Page(s)

Book: Author A, Author B, Author C. Title of the chapter. In: Editor A, Editor B, Editor C, eds Title of the book. Edition number. Place of publication: Publisher; Year. Page(s)

Examples

Journal Articles:

Journal: Knyazev GG, Bocharov AV, Levin EA, Savostyanov An, Slobodskoj-Plusnin JY. Anxiety and oscillatory responses to emotional facial expressions. Brain Res. 2008 Oct 28; 1228:174-99. DOI: 10.1016/j.brainres.2008.07.108.

Books:

Book Chapter(s): Phillips SJ, Whisnant JP. Hyper tension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, Diagnosis and Management. 2nd Ed. New York: Raven Press; 1996. P. 465-478.

Book: Eyre HJ, Lange DP, Morris LB. Informed decisions: the complete book of cancer diagnosis, treatment, and recovery. 2nd ed. Atlanta: American Cancer Society; c2002. P.768.

Web Example

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