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EDITORIAL

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A Global Public Health Threat: The Myopia Epidemic

Küresel Bir Halk Sağlığı Tehdidi: Miyopi Salgını

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Myopia, the most common refractive error affecting distance vision, was previously considered to be primarily related to genetic predisposition; however, today it has become a global silent epidemic directly linked to lifestyle, digitalization, environmental conditions, and rapid urbanization (1-4).

The term "myopia epidemic" covers two distinct but related issues. The first is an increase in the overall prevalence of myopia. The second is a rising prevalence of high myopia, which is associated with a higher rate of pathological outcomes (5).

According to projections by the World Health Organization and independent epidemiological research institutions, the global prevalence of myopia is expected to rise from 27% in 2010 to 52% by 2050 (a 2.6-fold increase). By 2050, myopia and high myopia (greater than -5.00 D or -6.00 D) are estimated to affect approximately five billion and one billion people, respectively. Currently, in East and Southeast Asian countries (including Singapore, Japan, South Korea, China, Hong Kong, Macau, and Taiwan), myopia and high myopia rates among adolescents and young adults have reached 70-90% and 10–20%, respectively. In European and North American countries, myopia prevalence remains in the 30-40% range (1-4).

Early educational onset, intensive academic programs, increased use of smartphones, tablets, and computers, along with prolonged near work (excessive accommodative load), trigger biochemical mechanisms that cause premature elongation of the eye's axial length (1-3).

One of the most critical factors in myopia development is sunlight exposure and time spent outdoors. Sunlight stimulates the retinal release of dopamine, a neurotransmitter that suppresses axial eye elongation. Conversely, increased indoor activity and insufficient sunlight exposure reduce retinal dopamine levels, promoting excessive ocular growth (1,3,6-9).

On the other hand, intense urbanization limits children's access to open spaces with a wide field of vision. Constantly being in enclosed and confined spaces eliminates the need to focus on distant objects, forcing the eye's refractive mechanism to adapt to near focus (1,6-9).

The fundamental dimensions of the myopia crisis encompass quality-of-life changes, psychosocial impacts, serious medical risks, and substantial global economic burdens. Unmanaged myopia—which disproportionately affects educated youth—can hinder academic progress. Furthermore, permanent vision loss from high myopia-related structural alterations may restrict career opportunities. Beyond functional limitations, individuals with severe refractive errors often experience psychological distress due to concerns over progressive vision loss, fear of dependence, and exclusion from social or physical activities (1,4,10,11).

High myopia significantly elevates the risk of secondary ocular pathologies, including cataracts, glaucoma, retinal detachment and myopic macular degeneration, all of which can lead to irreversible blindness (5).

The financial burden on the global economy is immense. It includes direct correction costs (standard or custom spectacles, contact lenses, pharmaceutical drops and solutions, and refractive surgery), management of high myopia complications, and complex surgical procedures. In Asian adults, the annual direct cost of myopia correction is estimated at US$328 billion (11).

Current options for controlling myopia progression include optical correction such as bifocal spectacle lenses, progressive addition spectacle lenses, undercorrection, orthokeratology, multifocal contact lenses; increased exposure to outdoor activities, the use of atropine eye drops and surgical techniques such as PRK, LASIK, SMILE, and ICL (these surgeries do not eliminate the underliying structural risks; they may increase them). In recent years,

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specialized myopia-control spectacle lenses utilizing myopic defocus technology (such as DIMS or HAL) have been clinically proven to retard axial elongation and are gaining widespread clinical adoption (1,12).

Behavioral modifications play a key supportive role. These include maintaining a reading distance of at least 30–40 cm, curbing digital device addiction, and adhering to the 20-20-20 rule—taking a 20-second break every 20 minutes of near work to look at an object at least 20 feet (approximately 6 meters) away to relax ocular accommodation (1,12,13).

Outdoor time is widely recognized as a critical factor in delaying myopia onset and slowing its progression. Encouraging children to spend at least two hours outdoors daily in natural sunlight has been shown in clinical studies to reduce the risk of developing myopia by 30–50% (1-3,12-14).

Consequently, key global public health policies targeting the myopia epidemic focus on reforming school curricula, incentivizing clinical interventions, and limiting screen exposure. Treating the issue as an urgent public health crisis, several East and Southeast Asian nations have instituted targeted regulations:

China: The National Health Commission mandated at least two hours of daily outdoor activity in schools and a 10-minute break for every 30 minutes of study. Schools with "glass classroom/transparent classroom/open classroom" architecture were built in pilot regions to maximize natural light. Under the 2021 "Double Reduction" policy, the government radically restructured the education system by restricting private tutoring to alleviate academic pressure, eliminating written exams for first- and second-graders, and capping homework loads. Additionally, the National Press and Publication Administration limited online gaming for minors under the age of 18 to three hours per week (specifically from 8 PM to 9 PM on Fridays, weekends, and public holidays), explicitly citing the protection of pediatric ocular health (9,13).

Taiwan: The "Tian-Tian 120" (Daily 120) initiative, jointly managed by the Ministries of Education and Health, mandates that elementary and preschool children spend at least 120 minutes outdoors every day (14).

Singapore: Under the Ministry of Health's National Myopia Prevention Programme, free annual eye screenings are conducted starting from kindergarten. Low-dose atropine drops (0.01%-0.05%) are subsidized for high-risk or rapidly progressing children, and advanced optical modalities (such as orthokeratology and specialized defocus lenses) are integrated into standard clinical pathways (15).

In Türkiye, while the Ministry of Health has established a "National Vision Screening Program," a holistic public health framework dedicated to combating the myopia epidemic has yet to be fully realized.

In conclusion, the myopia epidemic is a global public health threat that requires a collaborative approach involving not only the optical industry and ophthalmologists but also public health policies and education systems. Health and education policies should encompass active control systems that aim to mandate early childhood eye screenings and outdoor activities in schools, reduce or balance digital dependence, facilitate access to therapeutic eye drops and optical devices and develop a holistic approach and care model that also considers the psychological well-being of patients.

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ORIGINAL ARTICLE

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Follow-Up and Treatment Results in Penetrating Crohn's Disease

Penetran Crohn Hastalığında Takip ve Tedavi Sonuçları

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ABSTRACT

Background: To determine intestinal penetrating complications in patients with Crohn's disease (CD) and to retrospectively evaluate clinical characteristics, the frequency of accompanying stenosing and perianal complications, management strategies, and predictors of the need for surgical intervention.

Materials and Methods: Patients with CD complicated by penetrating intestinal manifestations, including sinus tracts, fistulas, phlegmon, and mesenteric or peritoneal abscesses, who were followed between 1986 and 2021, were included. Patients who developed penetrating complications after intra-abdominal interventions were excluded. Demographic, clinical, laboratory, and treatment data were recorded. Patients were classified into three groups: isolated abscess (IA), isolated fistula (IF), and an overlapping group (both an abscess and a fistula). Comparisons were performed among these groups.

Results: A total of 114 patients were evaluated: 18 (15.8%) had IAs, 35 (30.7%) had IFs, and 61 (53.5%) had both complications. Penetrating complications were detected in 84 of 114 patients during follow-up. Concomitant stenosis was more frequent in the overlapping group than in the other groups, although this difference did not reach statistical significance (80.3% vs. 55.6% and 65.7%; p = 0.075). The cut-off value of abscess size for predicting the need for surgical intervention was 2.75 cm. Patients with stenosis located in intestinal segments other than the fistula site had a 27.5-fold higher risk of requiring fistula surgery (p = 0.013). The rate of bowel resection was significantly higher in the overlapping group than in the IA and IF groups (70.5% vs. 27.8% and 28.6%, respectively; p < 0.001).

Conclusion: Penetrating complications occur frequently during follow-up in CD. Patients with both an abscess and a fistula have a worse prognosis, with a more severe clinical course and an increased likelihood of requiring surgical intervention.

Keywords: Abscess, complication, fistula, surgery

ÖZ

Amaç: Crohn hastalığı olan olgularda intestinal penetran komplikasyonların özelliklerini ortaya koymak ve klinik özellikleri, eşlik eden stenoz ve perianal komplikasyonların sıklığını, uygulanan tedavi yaklaşımlarını ve cerrahi gereksinimini öngören faktörleri retrospektif olarak değerlendirmek.

Gereç ve Yöntemler: Çalışmaya, 1986–2021 yılları arasında izlenen ve sinüs traktı, fistül, flegmon ile mezenterik veya peritoneal yerleşimli apse gibi intestinal penetran bulgularla komplike Crohn hastalığı tanısı olan hastalar dahil edildi. İntraabdominal girişimler sonrasında penetran komplikasyon gelişen olgular çalışma dışı bırakıldı. Hastaların demografik, klinik, laboratuvar ve tedaviye ilişkin verileri kaydedildi. Olgular üç grupta sınıflandırıldı: izole apse, izole fistül ve ortak grup (hem apse hem fistül bulunanlar). Gruplar arası karşılaştırmalar yapıldı.

Bulgular: Çalışmaya alınan 114 hastanın 18'inde (%15,8) sadece apse ve 35'inde (%30,7) sadece fistül saptanırken 61 hasta ortak gruptaydı. Yüz on dört hastanın 84'ünde penetran komplikasyonun takip sırasında ortaya çıktığı görüldü. Ortak gruptaki hastalarda, penetran komplikasyona eşlik eden darlık alanının varlığı diğer hastalık gruplarına kıyasla daha fazla olmakla birlikte, bu fark istatistiksel olarak anlamlı değildi (%80,3'e karşı %55,6 ve %65,7; p = 0,075). Apse açısından cerrahi operasyon için kesim noktası

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2,75 cm idi. Farklı segmentte darlık alanı olmasının fistül için cerrahi operasyon riskini 27,5 kat artırdığı istatistiksel anlamlılıkla gösterildi (p = 0,013). Ortak grupta bağırsak rezeksiyonu yapılma oranı diğer gruplara göre anlamlı derecede daha fazla saptandı (%70,5'e karşı %27,8 ve %28,6; p < 0,001).

Sonuç: Penetran hastalık çoğunlukla takip sırasında ortaya çıkmaktadır. Apse ve fistülün birlikte görüldüğü hastalar klinik gidiş ve cerrahi açısından daha kötü prognoza sahiptir.

Anahtar Kelimeler: Apse, komplikasyon, fistül, cerrahi

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that arises from dysregulated immune responses driven by the interaction of genetic susceptibility, environmental factors, and the intestinal microbiota (1). CD can involve any segment of the gastrointestinal tract in a discontinuous pattern and is characterized by recurrent transmural inflammation (2), which can lead to structural complications such as strictures, fistulas, and abscesses (3). Disease behavior is therefore classified according to the presence of these complications (4). The Montréal classification is widely used to define disease location and behavior, categorizing patients into inflammatory (B1), stricturing (B2), and penetrating (B3) phenotypes (5,6). Penetrating disease, which includes fistulas, intra-abdominal inflammatory masses, and abscesses, is reported to develop in approximately 40% of patients within five years of diagnosis (5,7).

Therapeutic goals extend beyond symptom control to include prevention of stricturing and/or penetrating complications that may necessitate surgical intervention (1,8). Thiopurines have not consistently reduced intestinal complication rates or the risk of surgical resection (9), whereas anti-tumor necrosis factor (anti-TNF) agents, owing to their superior effects on mucosal healing, have been associated with reduced rates of hospitalization and surgery (10). Infliximab has demonstrated efficacy in inducing and maintaining remission in both inflammatory and fistulizing diseases (11). These data emphasize the importance of identifying patients at increased risk for intestinal complications to guide timely treatment decisions (8).

In the penetrating phenotype, progressive transmural inflammation may result in sinus tracts or fistulas and evolve into phlegmon and, if infected, an abscess (12,13). Clinical manifestations vary by fistula location and the affected bowel segment (12,14). Non-perianal penetrating CD often requires complex management involving medical therapy, radiologically guided interventions, and surgery. However, evidence guiding the management of intestinal penetrating complications remains limited, and practice varies across inflammatory bowel disease (IBD) centers (12).

Accordingly, this study aimed to evaluate the frequency, spectrum, anatomical distribution, diagnostic approaches, and timing of non-perianal penetrating complications in CD; to identify risk factors independent of iatrogenic causes; to characterize management strategies; and to determine predictors of surgical intervention. Secondary aims were to examine the relationship between penetrating and stricturing disease and to determine the frequency of concomitant perianal disease in patients with intestinal fistulas.

Materials and Methods

Study Design

This retrospective cohort study was conducted at the IBD Outpatient Clinic of the Division of Gastroenterology, İstanbul University–Cerrahpaşa, Cerrahpaşa Faculty of Medicine. Medical records of patients with CD who were followed from 1986 to 2021 were reviewed by examining outpatient charts and the hospital information system. Adult patients (≥18 years) with a definite diagnosis of CD and at least one documented intestinal penetrating complication were eligible for inclusion. Patients were excluded if penetrating complications developed after intra-abdominal surgery, radiological drainage of an intra-abdominal abscess, or endoscopic balloon dilatation for strictures. Additional exclusion criteria were: a CD diagnosis of less than 6 months' duration, follow-up at our center shorter than 6 months, insufficient medical records prior to the development of penetrating complications, and follow-up shorter than 6 months after the diagnosis of penetrating complications.

Demographic and disease-related data were recorded. Disease location at diagnosis was classified according to the Montréal classification (L1–L4) and further detailed using endoscopic and radiological findings. The presence of perianal disease at diagnosis and during follow-up was also documented. Baseline laboratory parameters were obtained at diagnosis or, if initial data were unavailable, during a complication-free period. Colonoscopic findings, including ulcer morphology, fistula openings, and strictures, were reviewed. Ongoing and previous medical therapies during

the three months preceding the diagnosis of penetrating complications were recorded, together with subsequent changes in treatment and any surgical or radiological interventions. For the purposes of analysis, anti-TNF and other biologic agents were considered not to have been administered if induction therapy was not completed. Immunosuppressive agents used for less than three months were also classified as not administered.

Definitions and Classification of the Disease Groups

Mesenteric or peritoneal sinus tracts, fistulas, phlegmons, and abscesses were defined as penetrating complications in accordance with current guideline-based definitions (13-16). Obstructive complications were defined as fixed luminal narrowing with or without prestenotic dilatation. Penetrating and obstructive complications documented by radiological or endoscopic methods were systematically reviewed; fistulas diagnosed based on typical clinical features (e.g., vaginal, cutaneous, or vesical) were also included.

For time-based assessment, strictures detected within one month before or after a penetrating complication were classified as concomitant, whereas those identified more than one month before the penetrating complication were considered preceding. Localization of strictures and penetrating lesions was determined by computed tomography (CT), CT enterography, and endoscopy.

Patients were categorized into three groups: isolated abscess (IA), isolated fistula (IF), and an overlapping group (both an abscess and a fistula). Because fistulas that developed shortly after abscess diagnosis, without any intervention, were considered pathophysiologically related, these patients were further classified as the "abscess-associated fistula" subgroup. Accordingly, four groups (IA, IF, abscess-associated fistula, and others) were used for analysis of risk factors and prognosis. For abscess-related analyses, the IA and abscess-associated fistula groups were evaluated together.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± standard deviation or median (minimum–maximum), as appropriate. The Shapiro–Wilk test was used to assess normality. Categorical variables were compared using the Pearson chi-square, Fisher's exact, or Fisher–Freeman–Halton tests. Continuous variables were compared using the Student's t-test or the Mann–Whitney U test for two-group comparisons, and the Kruskal–Wallis test for multiple groups, with Dunn's test for post-hoc analyses. Variables significant in univariate analyses were included in multivariable binary logistic regression models. Model fit was assessed using the Hosmer–Lemeshow test and explanatory power was assessed using the Nagelkerke R^2. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of abscess size to predict the need for surgery by calculating the area under the curve (AUC). The optimal cut-off value was determined using the Youden index. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS software (version 28).

Ethic

Ethical approval was obtained from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (approval number: 189, approval date: 31.05.2022).

Results

Among 1,404 patients with CD followed at our center, penetrating complications were identified in 312. Of these, 112 patients with a history of intra-abdominal surgery or radiological intervention prior to the development of the fistula and 86 patients who met the exclusion criteria were excluded. Consequently, a total of 114 patients were included in the final analysis. Of the 114 patients included in the analysis, 59 were female and 55 were male. The mean age was 40.6 ± 13.1 years. At the time of CD diagnosis, penetrating complications were present in 30 patients (26.3%), and perianal disease was identified in 25 patients (21.9%). The mean interval from CD diagnosis to the development of penetrating complications was 39.7 ± 45.7 months. The demographic and clinical characteristics of the study population are summarized in Table 1.

Patients were categorized into three groups according to the type of penetrating complication: IA, IF, and an overlapping group with both an abscess and a fistula. The numbers of patients in these groups were 18 (15.8%), 35 (30.7%), and 61 (53.5%), respectively. Within the overlapping group, 26 patients who developed a fistula within three months of abscess diagnosis without intervention were further classified as the abscess-associated fistula subgroup.

Clinical Features of IA, IF, and Overlapping Groups

In the IA group (n = 18), 10 patients were female and 8 were male. The mean age was 42.9 ± 13 years (median 41; range 25–75), and the mean CD duration was 128 ± 68.5 months (median 114; range 24–252). The mean abscess size was 3.4 ± 1.7 cm (median, 3.4 cm; range, 1–7 cm). Abscesses were most frequently located in the ileocecal region (n = 11), followed by bowel-segment-related locations (n = 2), muscle-related locations (n = 2), pelvic locations (n = 1), combined ileocecal and muscle locations

(n = 1), and combined ileocecal and pelvic locations (n = 1). Concomitant obstructive complications were present in 10 patients (55.6%); in three of these patients, obstruction was detected concomitantly with the abscess, whereas in the remaining patients, it had been documented before the abscess diagnosis. Antibiotic therapy was administered to all but two patients, with a mean treatment duration of 5.1 ± 4.6 weeks (median, 3 weeks; range, 1–15 weeks). In addition to antibiotics, medical treatment was modified in 11 patients (61.1%): azathioprine was added to six patients, infliximab to one patient, adalimumab to one patient, combination therapy with azathioprine and an anti-TNF agent (adalimumab or certolizumab) to two patients, and oral mesalazine to one patient. Regarding interventional management, no invasive procedures were required for 10 patients, whereas three patients underwent surgery alone, three patients underwent radiological drainage alone, and two required both radiological drainage and subsequent surgery.

In the IF group (n = 35), 19 patients were female and 16 patients were male. The mean age was 41.6 ± 14.9 years (median 40 years; range 21–75 years), and the mean CD duration was 150.1 ± 74.6 months (median 144 months; range 24–324 months). Multiple fistulas were detected in six patients (17.1%). Regarding fistula types, enteroenteric fistulas were observed in 5 patients, enterocolic fistulas in 12 patients, colocolic fistulas in 4 patients, cutaneous fistulas in 1 patient, vesical fistulas in 1 patient, vaginal fistulas in 9 patients, ureteral fistulas in 1 patient, and combined enteroenteric and enterocolic fistulas in 2 patients. Fourteen patients (40%) underwent surgical intervention for fistula management. Among the 21 patients managed without surgery, medical therapy was modified in 12: anti-TNF treatment was initiated or intensified in nine, and azathioprine was added in three. Specifically, infliximab was initiated in four patients; certolizumab was used as monotherapy in one patient; infliximab or adalimumab were administered in combination with azathioprine in three patients; and infliximab dose escalation was performed in one patient. Risk factors for surgical intervention in patients with fistulizing CD were evaluated using univariate and multivariable analyses. In univariate analysis, increasing age and the presence of a stricture (either in the same or in a different intestinal segment from the fistula) were associated with a higher risk of surgery. Each one-year increase in age was associated with a 1.05-fold increase in surgical risk (p = 0.05); the presence of a stricture in a different segment was associated with a markedly increased risk (odds ratio

Table 1. Baseline demographic and clinical characteristics of patients with penetrating CD.

Baseline variables	Patients, n = 114
Gender, n (%) Female Male	 59 (51.8) 55 (48.2)
Age (years)	40.6 ± 13.1 (20–75)
Age at diagnosis (years)	29 ± 11.5 (14–72)
Disease duration (months)	143.9 ± 74.3 (16–420)
Time from symptom onset to CD diagnosis (months)	19.9 ± 36.9 (0–192)
Time from CD diagnosis to penetrating complication (months)	39.7 ± 45.7 (0–200)
Disease location at diagnosis (Montréal), n (%) Ileal (L1) Colonic (L2) Ileocolonic (L3) L4 (upper GI involvement)	 29 (25.4) 29 (25.4) 53 (46.5) 3 (2.6)
Smoking status, n (%) Never smoker Former smoker Current smoker	 49 (43) 23 (20.2) 42 (36.8)
Penetrating complication at diagnosis, n (%)	30 (26.3)
Perianal disease at diagnosis, n (%)	25 (21.9)
Perianal disease during follow-up, n (%)	24 (21.1)
Presence of obstructive segment, n (%) Absent prior to penetrating complication Present prior to penetrating complication Concomitant with penetrating complication	 32 (28.1) 53 (46.5) 29 (25.4)

Results are presented as mean ± standard deviation (range) or n (%), as appropriate. CD, Crohn's disease; GI, gastrointestinal.

[OR] = 27.5; p = 0.013). The presence of multiple fistulas was not significantly associated with surgical risk (OR 1.64; p = 0.585). Neither current nor prior use of azathioprine or corticosteroids was associated with the need for surgery. In multivariable binary logistic regression analysis, only the presence of strictures remained independently associated with surgical risk. A stricture located in a segment different from the fistula increased the risk of surgery 454.3-fold (p = 0.019), whereas a stricture located in the same segment increased the risk 70.7-fold (p = 0.042).

In the overlapping group (n = 61), 30 patients were female and 31 were male. The mean age was 39.2 ± 12.0 years (range, 20–71 years), and the mean CD duration was 145.1 ± 76.3 months (range, 16–420 months). Among these patients, 26 were classified as having an abscess-associated fistula. In this subgroup, 15 patients (57.7%) had a single fistula. Of the 26 patients with abscess-associated fistulas, seven did not undergo surgical intervention. Among these patients, medical therapy was modified in two patients by the addition of infliximab combined with azathioprine.

Comparison of Clinical Characteristics and Outcomes Between Groups

Clinical characteristics and outcomes were compared across the four groups—IAs, IFs, abscess-associated fistulas, and the remaining overlapping group—and are presented in detail in Table 2. Sex distribution, age at diagnosis, and disease duration were similar among groups (p = 0.24, p = 0.586, and p = 0.718, respectively). According to the Montréal classification, colonic involvement (L2) at diagnosis was significantly more frequent in the IF group than in the overlapping group–other subgroup (40% vs. 11.4%; p = 0.036). The presence of penetrating complications at diagnosis and the interval from CD diagnosis to the development of penetrating complications did not differ between groups (p = 0.484 and p = 0.521, respectively). Likewise, the prevalence of perianal disease and concomitant strictures at diagnosis were comparable across groups (p = 0.224 and p = 0.142). Baseline laboratory parameters were similar among groups (all p > 0.05). No significant differences were observed in colonoscopic findings, including ulcer morphology, strictures, and fistula openings (all p > 0.05).

Regarding prognosis, bowel resection rates were significantly higher in the abscess-associated fistula, overlapping, and other subgroups compared with the IA and IF groups (p < 0.001). The diverting ostomy rate was significantly lower in the abscess-associated fistula group (3.8%; p = 0.012) than in the other three groups, whereas the prevalence of permanent ostomy was similar across

Table 2. Comparison of clinical characteristics and outcomes across penetrating phenotypic groups.

	IA, n = 18	IF, n = 35	Abscess-associated fistula, n = 26	Overlapping group–others, n = 35	p-value
Gender, n (%) Female Male	 10 (55.6) 8 (44.4)	 19 (54.3) 16 (45.7)	 9 (34.6) 17 (65.4)	 21 (60) 14 (40)	0.24
Age (years)	42.9 ± 13 (25–75)	41.6 ± 14.9 (21–75)	38.3 ± 12.4 (20–62)	39.8 ± 11.7 (22–71)	0.759
Age at diagnosis (years)	32.8 ± 13.8 (17–72)	29.8 ± 13 (14–63)	27.3 ± 9.1 (14–51)	27.5 ± 9.9 (15–56)	0.586
Disease duration (months)	128 ± 68.5 (24–252)	150.1 ± 74.5 (24–324)	138.1 ± 77 (19–276)	150.2 ± 76.4 (16–420)	0.718
Time from symptom onset to CD diagnosis (months)	20.8 ± 32.8 (0–120)	15.6 ± 25.3 (0–120)	25.4 ± 51.6 (0–192)	19.9 ± 36.8 (0–180)	0.958
Smoking status, n (%) Never smoker Former smoker Current smoker	 7 (38.9) 6 (33.3) 5 (27.8)	 14 (40) 6 (17.1) 15 (42.9)	 12 (46.2) 6 (23.1) 8 (30.8)	 16 (45.7) 5 (14.3) 14 (40)	0.707
Family history of IBD, n (%)	0 (0)	5 (14.3)	2 (7.7)	5 (14.3)	0.346
Disease location at diagnosis (Montréal), n (%) Ileal (L1) Colonic (L2) Ileocolonic (L3) L4 (upper GI involvement)	 8 (44.4) 3 (16.7) 6 (33.3) 1 (5.6)	 4 (11.4) 14 (40) 16 (45.7) 1 (2.9)	 8 (30.8) 8 (30.8) 10 (38.5) 0 (0)	 9 (25.7) 4 (11.4) 21 (60) 1 (2.9)	**0.036**
Penetrating complication at diagnosis, n (%)	6 (33.3)	11 (31.4)	7 (26.9)	6 (17.1)	0.484

Table 2. Continued.

	IA, n = 18	IF, n = 35	Abscess-associated fistula, n = 26	Overlapping group–others, n = 35	p-value
Time from CD diagnosis to penetrating complication (months)	33.1 ± 50.5 (0–180)	38.6 ± 46.3 (0–200)	37.4 ± 40 (0–135)	45.8 ± 47.8 (0–200)	0.521
Perianal disease at diagnosis, n (%)	6 (33.3)	10 (28.6)	3 (11.5)	6 (17.1)	0.224
Development of perianal disease after diagnosis, n (%)	3 (16.7)	6 (17.1)	5 (19.2)	10 (28.6)	0.636
Concomitant stricturing disease, n (%)	10 (55.6)	23 (65.7)	20 (76.9)	29 (82.9)	0.142
Leukocyte count (10^3/μL)*	9.08 ± 2.76 (5.75–15.00)	10.16 ± 4.32 (4.30–21.80)	9.41 ± 2.96 (5.30–15.60)	9.90 ± 3.11 (5.20–16.37)	0.871
Hemoglobin (g/dL)*	11.1 ± 1.7 (8.5–14)	11.3±2.8 (8.3–14.8)	11.4 ± 1.4 (8.5–14.2)	11.7 ± 1.6 (8.6–14.3)	0.699
CRP (mg/L)[Δ]	59.3 ± 87 (8.7–318)	38.6±40.3 (1.2–157)	96.6 ± 104 (1.4–257.8)	55 ± 66.7 (4.4–247.7)	0.786
Albumin (g/dL)[Π]	3.5 ± 0.6 (2.3–4.4)	3.4±0.6 (2.4–4.4)	3.7 ± 0.7 (2–4.8)	3.3 ± 0.497 (2.5–4.2)	0.478
Colonoscopic findings, n (%)[•]					
Aphthous ulcers	3 (16.7)	5 (14.3)	2 (8)	10 (28.6)	0.212
Linear ulcers	2 (11.1)	4 (11.4)	1 (4)	7 (20)	0.344
Deep ulcers	3 (16.7)	1 (2.9)	0 (0)	2 (5.7)	0.123
Stricture	7 (38.9)	12 (34.3)	6 (24)	15 (42.9)	0.496
Fistula opening	0 (0)	3 (8.6)	1 (4)	0 (0)	0.227
Bowel resection performed, n (%)	5 (27.8)	10 (28.6)	20 (76.9)	23 (65.7)	**<0.001**
Diverting ostomy performed, n (%)	3 (16.7)	6 (17.1)	1 (3.8)	13 (37.1)	**0.012**
Permanent ostomy, n (%)	1 (5.6)	1 (2.9)	1 (3.8)	5 (14.3)	0.314
Organ-preserving surgery, n (%)	0 (0.0)	5 (14.3)	7 (26.9)	4 (11.4)	0.088
Recurrent intervention-unrelated penetrating events, n (%)	0 (0.0)	1 (2.9)	1 (3.8)	17 (48.6)	**<0.001**
Recurrent intervention-related penetrating events, n (%)	1 (5.6)	1 (2.9)	3 (11.5)	24 (68.6)	**<0.001**

*Leukocyte count and hemoglobin values were available for 11 of 18, 21 of 35, 12 of 26, and 18 of 35 patients in groups 1–4, respectively. [Δ]CRP values were available in 11/18, 19/35, 11/26, and 18/35 patients in groups 1–4, respectively. Values for [Π]-albumin were available in 10 of 18, 15 of 35, 10 of 26, and 13 of 35 patients in groups 1–4, respectively. [•]Endoscopic data were unavailable in one patient; analyses were based on 113 patients. Results are presented as mean ± standard deviation (range) or n (%), as appropriate. Statistically significant p-values (p < 0.05) are shown in bold. CD, Crohn's disease; CRP, C-reactive protein; GI, gastrointestinal; IBD, inflammatory bowel disease.

groups (p = 0.314). Organ-preserving surgical procedures were more frequently performed in the abscess-associated fistula group (26.9; n = 7), although this difference did not reach statistical significance (p = 0.088). Recurrent penetrating complications were evaluated separately as intervention-related and intervention-unrelated events. The rate of recurrence without interventional procedures was significantly higher in the overlapping group–other subgroup (48.6%, n = 17) than in the IA, IF, and abscess-associated fistula groups (p < 0.001). Similarly, recurrence following interventional procedures was most frequent in the overlapping group–other subgroup (68.6%, n = 24), and this rate was significantly higher than that in the other three groups (p < 0.001).

Factors Associated with Abscess Size and Surgical Outcomes in Patients with Abscess Complications

Among the 44 patients in the IA and abscess-associated fistula groups, abscess size data were available for 34 patients and were included in the analysis (Table 3). No significant associations were observed between abscess size and patient age, age at CD diagnosis, interval to abscess development, smoking duration, baseline CRP, hemoglobin, or albumin levels (all p > 0.05). In contrast, abscess size showed a significant positive correlation with disease duration (r = 0.384, p = 0.025) and with baseline leukocyte count (r = 0.535, p = 0.022). In addition, the mean abscess size was significantly larger in patients with a history of corticosteroid use than in those without prior corticosteroid exposure (5 ± 2.8 cm vs. 3.4 ± 1.8 cm, p = 0.05). Risk factors

Table 3. Factors associated with abscess size in patients with abscess complications.

Continuous variables (correlation analysis)	r	p-value
Disease duration (months)	0.384	0.025
Time to abscess development (months)	0.314	0.071
Age (years)	0.136	0.443
Age at diagnosis (years)	-0.067	0.706
Baseline leukocyte (10^3/μL)*	0.535	0.022
Baseline CRP (mg/L)$^{\Delta}$	0.194	0.456
Baseline hemoglobin (g/dL)*	-0.299	0.228
Baseline albumin (g/dL)$^{\Pi}$	-0.412	0.112
Categorical variables (group comparisons)	**Abscess size (cm)**	**p-value**
Sex Female Male	 3.5 ± 2.2 3.9 ± 2	0.457
Smoking status Never smoker Former smoker Current smoker	 3.8 ± 2 3.3 ± 2 4.2 ± 2.3	0.533
Disease location at diagnosis (Montréal) Ileal (L1) Colonic (L2) Ileocolonic (L3)	 3.3 ± 2.3 4.1 ± 2 3.9 ± 1.9	0.694
Perianal disease at diagnosis	3.4 ± 0.4	0.647
AZA use ⩽3 months	4.6 ± 2.9	0.539
CS use ⩽3 months	4.7 ± 2.3	0.163
Past AZA use	3.5 ± 1.6	0.969
Past CS use	5 ± 2.8	**0.05**

*Leukocyte and hemoglobin values were calculated based on available data from 18 patients. $^{\Delta}$CRP values were calculated based on available data from 17 patients. $^{\Pi}$Albumin values were calculated based on available data from 16 patients. Results are presented as mean ± standard deviation or as correlation coefficient (r), as appropriate. AZA, azathioprine; CRP, C-reactive protein; CS, corticosteroid.

for surgical intervention were further evaluated in the combined abscess cohort. In univariate analyses, no variable other than abscess size was significantly associated with the need for surgery. Active smoking status and corticosteroid use, whether within three months before abscess diagnosis or in the past, were not significantly associated with surgical risk (all $p > 0.05$). In multivariable logistic regression analysis, abscess size and the presence of multiple abscesses emerged as independent predictors of surgery. Each 1-cm increase in abscess size was associated with a 1.92-fold higher risk of surgical intervention ($p = 0.034$), and patients with multiple abscesses had a markedly higher risk of surgical intervention compared with those with a single abscess (OR = 16.02, $p = 0.042$). To further evaluate the discriminative ability of abscess size in predicting the need for surgical intervention, ROC curve analysis was performed. The optimal cut-off value for abscess size was identified as 2.75 cm based on the Youden index (0.393). The AUC was 0.721 ($p = 0.029$), indicating acceptable discriminatory performance. At this threshold, abscess size predicted the need for surgical intervention with a sensitivity of 86.7% and a specificity of 52.6%.

Discussion

In this study of patients with CD complicated by non-perianal penetrating manifestations, we comprehensively characterized the spectrum, management, and outcomes of penetrating complications at a large tertiary referral center. Our findings demonstrate that penetrating complications frequently develop during the disease course and are associated with substantial morbidity. Patients with combined abscess and fistula phenotypes exhibited a distinctly worse clinical course, with higher rates of bowel resection and recurrent penetrating events compared with those with an IA or an IF. In fistulizing disease, the presence of concomitant strictures—particularly in segments different from the fistula—emerged as a strong independent predictor of surgical intervention. Moreover, in patients with

abscess complications, larger and multiple abscesses were independently associated with the need for surgery; an abscess diameter of 2.75 cm provided a clinically relevant threshold for predicting that need. Collectively, these findings highlight key phenotypic features that may help identify high-risk patients and inform timely, individualized management strategies in non-perianal penetrating CD.

Population-based cohorts suggest that penetrating complications at diagnosis are relatively uncommon. Thia et al. (8) reported that 14% of 306 patients from Olmsted County, Minnesota had penetrating complications at diagnosis. In contrast, 26.3% of patients in our cohort already had penetrating complications at diagnosis, while the majority developed them during follow-up, reflecting both the dynamic evolution of disease behavior and the enrichment for severe phenotypes in a tertiary referral setting. Penetrating intestinal CD has been reported in approximately 16% of patients (15). In line with this, IAs accounted for 15.7% of cases in our study. However, we observed a substantial burden of fistulizing disease and a high frequency of combined abscess–fistula presentations, consistent with prior observations that fistulas often arise in association with adjacent inflammatory masses or abscesses (17).

Because postoperative intra-abdominal abscesses and enterocutaneous fistulas are recognized septic complications (18), careful differentiation between spontaneous penetrating disease and iatrogenic events is essential. To minimize confounding, we excluded patients whose penetrating complications followed intra-abdominal surgery or radiological intervention. Furthermore, among patients with both abscess and fistula, we defined the abscess-associated fistula subgroup as those who developed fistulas within three months of abscess diagnosis without any intervention. This approach allowed a pathophysiologically more homogeneous evaluation of spontaneous penetrating behavior and revealed that this subgroup carried a distinctly worse prognosis.

Disease location has been associated with complicated CD in several cohorts, with ileal involvement frequently reported among patients with penetrating disease (19,20). In our data, ileal involvement was more frequent in patients with IA than in those with IF, supporting a potential anatomical predisposition to abscess formation. Conversely, when comparing all four phenotypic groups, colonic involvement was more common in the IF group than in the overlapping group (other subgroup), suggesting that distinct anatomical distributions may contribute to different presentations of penetrating disease.

A persistent challenge in CD classification is the dynamic nature of disease behavior, with stricturing and penetrating phenotypes often evolving together over time (6). In a large multicenter study, Fan et al. (21) demonstrated that a substantial subset of patients ultimately develop both stricturing and penetrating complications, supporting the concept of a mixed phenotype. In our cohort, obstructive segments were common prior to or at the time of penetrating complications. Although stricture prevalence did not differ significantly among the four penetrating phenotypic groups, strictures were highly prognostically informative in fistulizing disease: their presence, particularly in segments distinct from the fistula, was independently associated with markedly increased surgical risk. This finding reinforces the central role of structural damage in guiding surgical decision-making and aligns with prior observations linking luminal narrowing to penetrating complications (22,23).

The relationship between intestinal fistulization and perianal disease remains debated. Tang et al. (24) reported a strong association between perianal and intestinal fistulas, whereas others have suggested that these may represent distinct clinical phenotypes (25). In our cohort, perianal disease at diagnosis was present in 21.9% of patients with penetrating complications, but this prevalence did not differ across phenotypic groups. However, the retrospective design and limited longitudinal data precluded a more definitive assessment of the temporal and causal relationship between perianal disease and intestinal penetrating complications.

Non-perianal intestinal fistulas occur in approximately 10–15% of CD patients, most commonly as enterocolic and enteroenteric fistulas (15). In our study, enterocolic fistulas were the most frequent subtype, consistent with prior reports. Evidence supporting medical therapy for fistulizing disease is largely derived from perianal cohorts, and intestinal fistulas are known to respond less favorably to anti-TNF therapy (12,26,27). Consistent with this, 40% of patients in our IF group ultimately required surgery despite frequent initiation or escalation of anti-TNF treatment. This finding supports the prevailing view that intestinal fistulas often necessitate surgical management (14,28). Notably, in our analyses, stricturing disease—rather than immunosuppressive exposure—was the dominant determinant of surgical risk, consistent with reports identifying strictures as key drivers of the need for surgery (23).

Intra-abdominal abscesses are frequent penetrating complications, reported in up to 30% of patients during the disease course (17). In our cohort, abscesses were most commonly localized to the ileocecal region, consistent with prior studies of spontaneous abscesses and phlegmon (13,29). The mean abscess size was comparable to values reported in other cohorts (30,31). Abscess size has direct implications for management: ECCO guidance cautions

against immunosuppression in large abscesses and notes the limited efficacy of antibiotics alone in some cases (32), while previous studies suggest that abscesses larger than 3–4 cm are more likely to require drainage or surgery (12,29,33). In our study, ROC analysis identified 2.75 cm as a practical threshold for predicting surgical need, with high sensitivity but moderate specificity. Furthermore, abscess size and multiplicity independently predicted surgical intervention, underscoring that abscess burden and morphology are central determinants of outcome. The association between prior corticosteroid exposure and larger abscess size observed in our cohort may reflect a more extensive inflammatory burden, although causality cannot be inferred.

Although predictors of developing penetrating CD are relatively well described, fewer data address the prognosis after penetrating complications have occurred (7,34). Prior studies have shown that penetrating behavior is associated with worse postoperative outcomes than inflammatory or stricturing phenotypes (35) and that the presence of abscesses increases the need for surgery in ileal penetrating disease (19). Consistent with this, we observed significantly higher bowel resection rates and recurrence rates of penetrating complications—both those unrelated to interventions and those occurring after radiologic or surgical procedures—in patients with combined phenotypes, particularly in the abscess-associated fistula and overlapping group–other subgroups. These findings emphasize that combined penetrating presentations represent a particularly high-risk subgroup requiring close surveillance and timely multidisciplinary management.

Study Limitations

The strengths of this study include the large cohort from a long-standing tertiary referral center, the extended observation period, and the detailed phenotypic characterization of non-perianal penetrating CD. Exclusion of postoperative and intervention-related cases and the subclassification of abscess-associated fistulas enabled a more homogeneous assessment of spontaneous penetrating behavior. The use of multivariable analyses and ROC methodology allowed identification of independent predictors of surgical risk and yielded a clinically applicable abscess size threshold. Several limitations should be acknowledged. The retrospective, single-center design may limit causal inference and generalizability, and may introduce referral bias toward more severe disease. A substantial proportion of patients were excluded based on predefined criteria to minimize iatrogenic confounding, which may have introduced selection bias. In addition, relatively small subgroup sizes may have limited the power of some comparisons, and incomplete longitudinal data onperianal disease activity and disease severity constrained more-detailed phenotypic analyses.

Conclusion

In conclusion, non-perianal penetrating CD represents a heterogeneous but clinically aggressive phenotype that develops during follow-up and is associated with substantial morbidity. Patients with combined abscess and fistula presentations experience the poorest outcomes, with higher rates of bowel resection and recurrent penetrating events, underscoring the need for close surveillance and multidisciplinary management in this subgroup. Concomitant strictures—when located in segments different from the fistula—emerge as the strongest determinants of surgical need in fistulizing disease, highlighting the pivotal role of structural damage in guiding therapeutic decisions. In patients with abscess complications, abscess size and multiplicity are key drivers of surgical risk, and an abscess diameter of 2.75 cm may serve as a practical threshold to identify patients unlikely to respond to conservative management. These findings emphasize the importance of detailed phenotypic assessment beyond traditional classifications and support an individualized, risk-adapted approach to the management of penetrating CD. Prospective multicenter studies incorporating standardized imaging and phenotyping are warranted to validate these observations and refine treatment algorithms for this challenging population.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (approval number: 189, approval date: 31.05.2022).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: A.P., T.E., Concept: O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Design: O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Data Collection or Processing: A.P., O.K.B., T.E., Y.E., A.F.Ç., A.İ.H., Analysis or Interpretation: O.K.B., Ö.P., A.F.Ç., A.İ.H., Literature Search: A.P., Ö.P., Writing: A.P., O.K.B.

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ORIGINAL ARTICLE

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Early-Career Publishing: Authorship Trends of Students and Residents in Anatomy

Erken Dönem Yayıncılık: Anatomi Alanında Öğrenci ve Asistan Yazarlık Eğilimleri

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ABSTRACT

Background: Participation of students and residents in academic publishing has gained attention across medical disciplines, yet little is known about their roles in anatomical research. This study aims to examine the frequency, authorship positions, and publication trends of student and resident authors (SRA) in anatomical journals.

Materials and Methods: Of the 36 anatomy journals reviewed, only Anatomical Sciences Education (ASE) provided identifiable author information. All articles published in ASE between January 2008 and December 2024 were retrospectively analyzed. Author roles were identified from author biographies, and authors were categorized as student author (SA), resident author (RA), both SRA, and non-SRA. Authorship positions, article types, number of citations, and annual trends were recorded.

Results: Among 4,920 authors across 1,223 articles, 8.5% were SAs and 3.2% were RAs. Over time, the number of SAs and RAs increased significantly; however, when expressed proportionally, only articles that included SRAs showed a significant increase. Articles with SA and/or RA had a higher number of authors and were most often research reports. SAs and RAs were primarily middle authors, with low rates of first- or last-author positions. Citation counts did not differ significantly across author groups; however, articles including SAs, RAs, or SRAs showed descriptively higher median citation values.

Conclusion: Early-career author numbers in ASE are increasing but remain limited in scope and role. Structured interventions such as mini-projects, mentorship programs, and writing workshops could enhance students' and residents' engagement and support their progression to lead authorship in anatomical scholarship.

Keywords: Student authorship, resident authorship, trainee authorship, early-career researcher, academic publishing trends

ÖZ

Amaç: Tıp alanında öğrenci ve asistan yazarların akademik yayınlardaki katılımı giderek daha fazla ilgi görmektedir; ancak bu grubun anatomik araştırmalardaki rolleri hakkında yeterli bilgi bulunmamaktadır. Bu çalışma, anatomi dergilerinde öğrenci ve asistan yazarların sıklığını, yazar sırasındaki konumlarını ve yıllara göre yayın eğilimlerini incelemeyi amaçlamaktadır.

Gereç ve Yöntemler: İncelenen 36 anatomi dergisinden yalnızca Anatomical Sciences Education (ASE) dergisi, yazar kimlik bilgilerini açıkça sunmaktaydı. Ocak 2008 ile Aralık 2024 arasında ASE'de yayımlanan tüm makaleler geriye dönük olarak analiz edildi. Yazar rolleri biyografi bilgilerinden belirlendi ve yazarlar şu şekilde sınıflandırıldı: öğrenci yazar (ÖY), asistan yazar (AY), hem öğrenci hem asistan yazar (ÖAY) ve öğrenci/asistan olmayan yazar. Yazar sıraları, makale türleri, atıf sayıları ve yıllara göre eğilimler kaydedildi.

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*The data of this investigation between 2008–2018 was presented as a poster presentation at the 19th Congress of the International Federation of Associations of Anatomists in London 2019.

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ÖZ

Bulgular: One thousand two hundred twenty-three makalede yer alan 4,920 yazarın %8,5'i öğrenci, %3,2'si asistan yazarlardan oluşmaktaydı. Zaman içinde ÖY ve AY sayıları artış göstermiş olsa da, makale sayısına göre oransal değerlendirme yapıldığında yalnızca ÖAY'li makalelerde belirgin bir artış gözlendi. ÖY ve/veya AY içeren makaleler daha fazla yazar sayısına sahipti ve en sık Araştırma Makalesi türündeydi. ÖY ve AY'ler çoğunlukla ortanca yazar konumunda yer almakta olup, ilk ya da son yazar olma oranları düşüktü. Atıf sayıları yazar grupları arasında istatistiksel olarak anlamlı bir farklılık göstermemiştir; ancak ÖY ve/veya AY içeren makalelerde ortanca atıf değerlerinin tanımlayıcı düzeyde daha yüksek olduğu gözlenmiştir.

Sonuç: ASE dergisinde erken dönem yazar sayısı artış göstermekte, ancak bu artış kapsam ve rol açısından sınırlı kalmaktadır. Mini projeler, mentorluk programları ve yazarlık atölyeleri gibi yapılandırılmış uygulamalar, öğrenci ve asistan katılımını artırarak bu grupların anatomik yayıncılıkta ilk yazar konumuna ilerlemesini destekleyebilir.

Anahtar Kelimeler: Öğrenci yazarlığı, asistan yazarlığı, eğitimci yazarlığı, genç araştırmacı, akademik yayıncılık eğilimleri

Introduction

The involvement of students and residents in scholarly publishing has expanded significantly over the past two decades, supported by formal research programs (1,2), mentorship initiatives (3,4), and academic development tracks (5,6). This shift reflects a growing emphasis on preparing early-career individuals for academic roles through meaningful engagement in research (1,3,5). Numerous studies have shown that such involvement contributes to long-term scholarly output, increased competitiveness for residency and fellowship positions, and a greater likelihood of pursuing careers in academic medicine (2,4).

Parallel to this trend is the evolving role of clinician-educators and physician-scientists, who serve as crucial links between patient care, teaching, and research. The demand for these dual-role professionals continues to rise, but concerns about their declining numbers and structural barriers to advancement remain well documented (7-9). Career development tracks and reform initiatives have been proposed to strengthen the physician-scientist pipeline and preserve academic medicine's research mission (10).

Clinician-educators, in particular, often play a central role in nurturing early-career researchers. Mentorship, whether through structured scholarly concentration programs or informal faculty guidance, has been repeatedly cited as a key determinant of publication success among trainees (11,12). Faculty commitment and institutional infrastructure, including academic medicine tracks and education fellowships, have also been shown to enhance student and resident engagement in research (13-15).

Despite the growing number of studies analyzing authorship by students and residents across fields such as general medical education (16), internal medicine (17,18), and surgery (19), similar investigations are absent in the anatomical sciences. This is a notable gap and a rich area for early-career contributions (20), especially considering the continuing shortage of anatomy educators (21). In this context, examining authorship trends in anatomy journals is particularly meaningful, as early-career engagement plays a critical role in sustaining the educational and academic capacity of the discipline. For this reason, the present study aimed to analyze the frequency, author positions, and annual trends among student and resident authors (SRA) in anatomical journals.

Materials and Methods

Within the scope of this study, 27 journals in the "Anatomy & Morphology" category of the Web of Science Master Journal List (22) and 21 journals listed in the Federative International Committee on Scientific Publications (FICSP) section of the International Federation of Associations of Anatomists website (23) were examined. Eleven of these journals appeared on both lists, and one was excluded from the study because it is no longer being published. To examine whether the remaining 36 journals regularly provided author information, a standardized and reproducible screening approach was applied across all journals. For each journal, the first issue published within the most recent 10-year period was examined to reflect current publication practices and to establish a comparable reference point across journals. The consistent inclusion of author biographies or contribution notes in the full-text articles of a given issue served as the criterion for determining whether a journal regularly provided author information. As a result, only one of these journals (Anatomical Sciences Education [ASE]) provided author information for full-text articles. Therefore, following this eligibility assessment, all articles published in ASE between January 2008 and December 2024 were included in the study. Full-text articles were collected from the website of ASE (24) between March and April 2025. Since this study was conducted using publicly available data, no ethics committee approval was obtained.

Article Evaluation

Published articles were classified according to ASE author guidelines (25) as: Research Report; Descriptive Article (renamed Discursive Articles from 2024); Viewpoint Commentary (renamed Viewpoint from 2024); Short Communication; Relevant Review (renamed Review from 2024); Letter to the Editor; and Editorial. Some ASE article categories underwent editorial renaming during the study period (from 2024 onward); however, these changes reflect terminology updates rather than structural differences. For consistency, the earlier category names were used throughout the analysis. Additionally, the number of citations was noted for each article on the Web of Science website between 7 and 9 April 2025.

Author Evaluation

The total number of authors and the author information were obtained from the Notes on Contributions (NoC) (renamed Author Biographies in 2024) section of full-text articles. Authors who were described as medical students, interns, bachelor's students, or undergraduate students (e.g., medical, dental, physiotherapy, psychology, and veterinary) were categorized as student authors (SA). Authors identified as clinical fellows, registrars, assistants, trainees or residents were categorized as resident authors (RA). Author roles such as healthcare staff (medical doctor, nurse, physical therapist, psychologist, midwife, etc.), academic (lecturer, assistant professor, associate professor, professor, emeritus prof, etc.), and non-medical roles (tutor, officer, librarian, statistician, etc.) were recorded as non-SRA (non-SRA). Additionally, authorships reported as research assistant, master's/MSc student, doctoral/PhD student, postdoctoral researcher/fellow, and teaching/research fellow were considered academic roles and included in the non-SRA group. This classification was based on the expectation that individuals in these positions are required to engage in scholarly publishing, either strategically or because it is compulsory, as part of their academic training or career development (26). Authorship positions of the SAs and RAs in the articles were recorded as first, middle, and last author positions. Middle authorship was only evaluated in articles with three or more authors.

Statistical Analysis

The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. For data not conforming to a normal distribution, non-parametric tests were used. The Mann–Whitney U test was performed for comparisons between two independent groups, and the Kruskal–Wallis H test was applied for comparisons among three or more groups. For post-hoc analyses following the Kruskal–Wallis H test, Dunn's test was performed. The relationships between categorical variables were examined using the chi-square test; when the assumptions of this test were not met, Fisher's exact test was used. For annual trend analyses, Spearman's rank correlation test (Spearman's rho, p) was applied, and results were reported as Spearman's rank correlation coefficients (p). To control for the increased risk of Type I error due to multiple comparisons, Bonferroni correction was applied in all post-hoc analyses. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 22 (IBM Corp., Armonk, NY).

Results

ASE published 1,280 articles between 2008 and 2024. Because the number of these article types was low, three perspective articles and one curriculum report were excluded from the analysis. In addition, articles classified as editorial (n = 42) did not provide adequate author information, and 3 research reports, 3 descriptive articles, 3 letters to the editor, 1 relevant review, and 1 viewpoint commentary without a NoC/Author Biography section were also removed from the analysis. The remaining 1,223 articles were included for further analysis (Figure 1). Included article types were research reports, descriptive articles, short communications, letters to the editor, relevant reviews, and viewpoint commentaries.

A total of 4,920 authors were identified, including 416 (8.5%) SAs and 158 (3.2%) RAs. The median number of authors per article was 4 (range: 1–47). Articles involving student and/or RAs had a higher median number of authors ($p < 0.001$): medians were 8 for articles with both SA and RA (SRA), 5 for articles with either SA or RA, and 3 for non-SRA articles (Table 1). A statistically significant difference in the number of authors was observed among the groups ($p < 0.001$); the number of authors in non-SRA articles was significantly lower than in the other groups ($p < 0.001$).

SAs and RAs were most frequently listed as contributors to research reports and were next most frequently listed as contributors to descriptive articles. Their involvement was lowest for letters to the editor (Table 1). A significant association was found between article type and author group ($p < 0.001$). Subgroup analyses revealed that SA involvement was higher in research reports, whereas non-SRA involvement was higher in letters to the editor ($p < 0.001$).

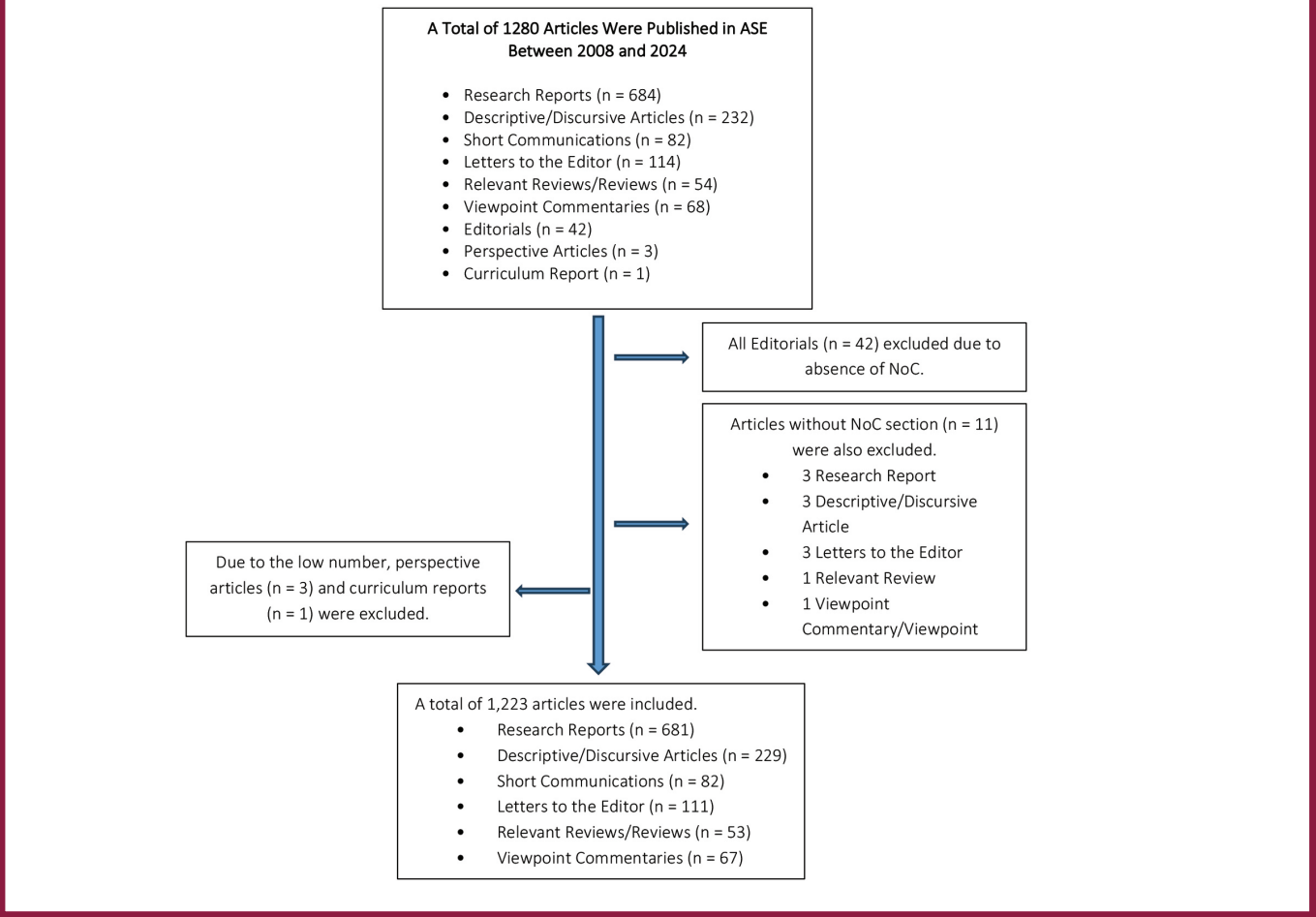

Figure 1. Identification of articles included and excluded in the analysis.
NoC, Notes on Contributions.

Of the published articles, 197 (16.1%) had one or more SA, 89 (7.3%) had one or more RA, 24 (2.0%) had one or more SRA, and 913 (74.7%) had non-SRA (Table 1). SA was the first author in 102 (8.3%), middle author in 164 (13.4%), and final author in 15 (1.2%) articles. Similarly, RA were first authors in 53 articles (4.3%), middle authors in 70 (5.7%), and last authors in 11 (0.9%). The positions of both SA and RA were significantly associated with article type (SA: $p < 0.001$; RA: $p = 0.015$). Specifically, SAs and RAs were more likely to be listed as first authors in research reports (SAs: $p < 0.001$; RAs: $p = 0.02$) and less likely to be listed as middle authors in letters to the editor (SAs: $p < 0.001$; RAs: $p < 0.001$).

The median number of citations per article was 14 (minimum: 0; maximum: 659). The median number of citations was lowest in non-SRA articles (13), compared with 15 in SA articles and 16 in RA and SRA articles (Table 1). However, no statistically significant differences in the number of citations were observed between author groups ($p = 0.629$) or between author positions (SA: $p = 0.700$; RA: $p = 0.774$).

Between 2008 and 2024, the numbers of both SAs ($p = 0.77$, $p < 0.001$) and RAs ($p = 0.56$, $p = 0.02$) increased significantly (Figure 2). Similarly, significant upward trends were observed in the numbers of articles classified as non-SRA ($p = 0.83$, $p < 0.001$), SA ($p = 0.68$, $p = 0.003$), and SRA ($p = 0.68$, $p = 0.003$). There was also an increase in the number of articles with RA, but this increase was not statistically significant ($p = 0.45$, $p = 0.072$). Regarding proportions, decreasing trends were observed in articles with non-SRA ($p = -0.34$, $p = 0.18$) and in those with RA ($p = -0.07$, $p = 0.79$), whereas an increasing trend was observed in articles with SA ($p = 0.33$, $p = 0.19$); however, none of these trends reached statistical significance (Figure 3). However, the proportion of articles with SRA ($p = 0.60$, $p = 0.011$) showed

Table 1. Distribution of authors by article types, citations, author numbers and positions.

		Author groups				
		non-SRA	SA	RA	SRA	p-value
Article types	Research Report	476 (38.9%)	130 (10.6%)	58 (4.7%)	17 (1.4%)	p < 0.001
	Discursive Article	179 (14.6%)	32 (2.6%)	15 (1.2%)	3 (0.2%)	
	Short Communication	60 (4.9%)	13 (1.1%)	8 (0.7%)	1 (0.1%)	
	Letter to the Editor	106 (8.7%)	4 (0.3%)	1 (0.1%)	0	
	Review	40 (3.3%)	10 (0.8%)	2 (0.2%)	1 (0.1%)	
	Viewpoint	52 (4.3%)	8 (0.7%)	5 (0.4%)	2 (0.2%)	
	Total articles: 1,223 (100%)	913 (74.7%)	197 (16.1%)	89 (7.3%)	24 (2%)	
Citation	Median (min–max)	13 (0–604)	15 (0–208)	16 (0–274)	16 (0–659)	p = 0.629
Author number	Median (min–max)	3 (1–47)	5 (1–27)	5 (1–12)	8 (3–14)	p < 0.001
Author positions	First author	NA	107 (2.2%)	53 (1.1%)	NA	NA
	Middle author		293 (6%)	94 (1.9%)		
	Last author		16 (0.3%)	11 (0.2%)		
	Total authors: 4,920 (100%)	4346 (88.3%)	416 (8.5%)	158 (3.2%)		

Data presented as number (%) or median (min–max).
min–max, minimum–maximum; NA, not applicable; non-SRA, non-student and resident author; RA, resident author; SA, student author; SRA, student and resident author.

a strong, statistically significant increasing trend over the years.

No significant change was observed in the proportion of SAs listed as first authors over time (p = 0.038, p = 0.188). However, the proportion of SAs as middle authors significantly increased (p = 0.079, p = 0.006), whereas their representation as last authors significantly decreased (p = −0.090, p = 0.002). No significant temporal trends were found in RA authorship positions (first: p = 0.007, p = 0.810; middle: p = 0.013, p = 0.648; last: p = −0.002, p = 0.934) for the entire study period.

Discussion

This study presents a comprehensive analysis of authorship by students and residents in the anatomical sciences, using a dataset of articles published in ASE (the only anatomy journal that includes complete author biographies) from January 2008 to December 2024. We assessed the frequency, placement, and academic impact of student and resident contributions by systematically examining author biographies, article types, authorship positions, and citation metrics. Our findings align with general trends reported in the literature for some topics, while revealing unique differences for others.

Student and Resident Authorship Rates and Trends

Author-Level Analysis

Among all authors analyzed in this study, 8.5% were students and 3.2% were residents. Although these groups represented a minority, the numbers of student and RAs showed a significant upward trend, reflecting the growing involvement of early-career individuals in anatomical science publications.

Similar patterns have been observed in other fields. Kan et al. (18) examined articles in JAMA Internal Medicine and found that 14.9% of authors were students, with SA increasing from 12.5% in 2010 to 19.3% in 2018. Likewise, Munzer et al. (16) reported cumulative SRA rates of 2.8% and 4.9%, respectively, in Academic Medicine, with residents contributing more frequently than students in nearly all years. In contrast, our findings show that SAs consistently outnumber RAs in ASE publications. Overall, authorship

patterns in the anatomical sciences are consistent with broader trends across medical disciplines, reflecting increasing early-career engagement.

Article-Level Analysis

Of the articles published in ASE, 25.4% included at least one early-career author, and increases in SA and SRA were observed across years. Notably, only SRA showed a statistically significant upward trend.

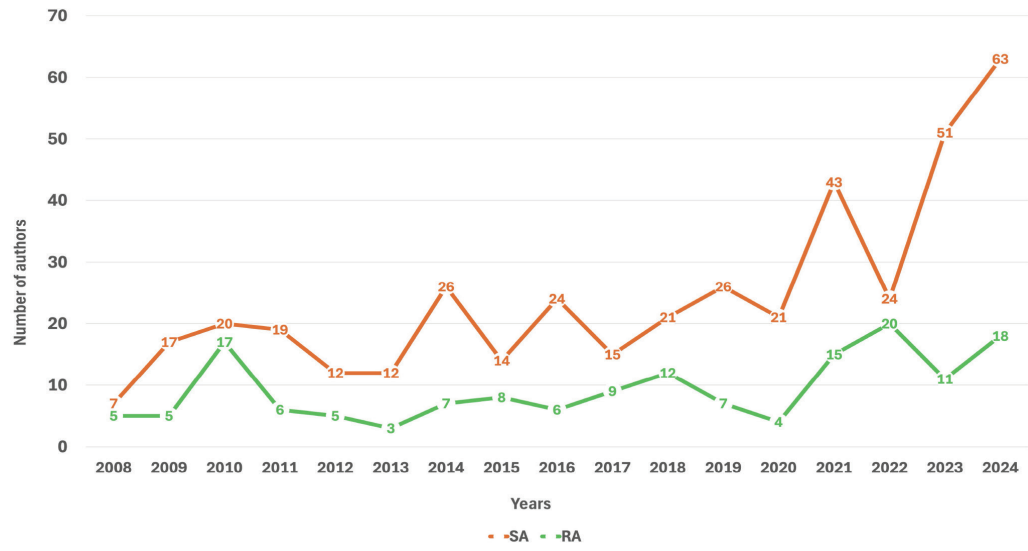

Figure 2. Annual trend in the number of student and RAs in ASE articles.
ASE, Anatomical Sciences Education; RA, resident author; SA, student author.

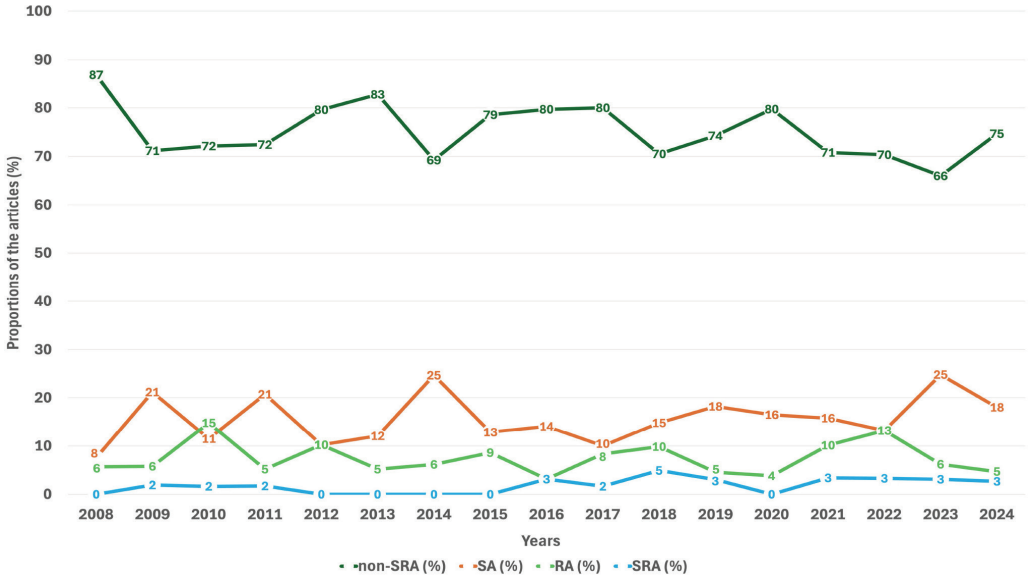

Figure 3. Annual trend of the proportion of articles by author groups.
non-SRA, non-student and resident author; RA, resident author; SA, student author; SRA, student and resident author.

Comparable findings have been reported elsewhere. Munzer et al. (16) recorded this rate as 14% (SA: 7.9%, RA: 7.7%) between 2002 and 2016. Kan et al. (18) reported that the percentage of articles with SA rose from 46.3% in 2010 to 58.0% in 2018, with a strong linear trend. Casciato et al. (19) noted that approximately 22% of articles published in the field of foot and ankle surgery were authored by residents. Wickramasinghe et al. (4) analyzed publications between 1980 and 2010 and reported an exponential increase in the number of articles including medical SA. Among these, the most represented fields were psychiatry (7.4%), general medicine (6.9%), and medical education (6%). Although anatomy shows lower early-career authorship rates than other disciplines, the upward trend in ASE indicates growing editorial and institutional support for these authors' involvement.

Number of Authors and Group-Based Variation

Our results indicate a clear relationship between the number of authors and early-career involvement. Non-SRA articles had the fewest authors (median = 3), followed by SA and RA articles (median = 5), and SRA articles (median = 8). This finding is consistent with studies showing that larger, collaborative teams often facilitate student participation (2,18,27).

Several mechanisms may explain this correlation. First, the inclusion of early-career authors often requires active mentorship within more complex research groups (28). Projects involving trainees commonly incorporate multiple contributors to support oversight and coordination (2,18). Second, student-involved research frequently takes place within structured educational frameworks such as scholarly concentration programs or departmental mentoring initiatives (5,6). Overall, these findings reflect a broader trend in which SRA articles typically emerge from larger, structured research teams.

Authorship Positions of Student and RAs

SAs and RAs were most frequently listed as middle authors. Students were middle authors in 13.4% of articles, first authors in 8.3%, and last authors in 1.2%; residents showed a similar pattern (middle: 5.7%, first: 4.3%, last: 0.9%). Middle authorship by students increased significantly over time, whereas their last authorship declined; no significant temporal changes were observed for residents. These findings mirror broader trends in the literature. Munzer et al. (16) reported that SAs are the most frequent first and middle authors, while RAs are the most frequent last authors, and that the rate of first and middle authorship increased over the years. Kan et al. (18) similarly noted an increase in first authorship among students. Across studies, last authorship remains rare for early-career contributors.

This distribution reflects typical authorship hierarchies in academic publishing. First authors commonly lead core research activities, middle authors often provide collaborative or supporting contributions, and last authorship usually denotes senior oversight or mentorship (14). Because students and residents rarely occupy supervisory roles, their limited last-author representation is expected. However, the predominance of middle authorship may reflect more limited opportunities for leadership roles among students and residents in academic publishing. In this context, mentorship programs may be a mechanism to support early-career contributors in progressing toward first authorship and, eventually, last authorship with faculty guidance.

Article Types

Students and residents contributed most frequently to research reports (66.1%), followed by descriptive articles, short communications, viewpoint commentaries, and relevant reviews. This pattern is consistent with previous studies reporting that full-length empirical manuscripts are the most accessible pathway to authorship for early-career researchers (2,18). Amgad et al. (2) similarly found that student research commonly results in cross-sectional studies, case reports, and reviews, as these formats are feasible within training timelines. Scholarly Concentration programs also support this model by offering structured mentorship and opportunities for data-driven projects (13).

Early-career contributors were less frequently involved in shorter or more conceptual formats, such as letters or brief commentaries—a trend also reported in prior studies (2,13,16). Increasing exposure to a wider range of scholarly genres, including opinion pieces or education briefs, may help diversify the types of contributions trainees are prepared to make.

Citation Analysis and Academic Impact of Student and Resident Authorship

In our ASE dataset, the median number of citations per article was 14, and no statistically significant differences were found between author groups. Articles with SA had a median of 15 citations, those with RA and SRA had a median of 16, and those with non-SRA had a median of 13, indicating that the inclusion of early-career authors does not reduce citation performance.

Findings in the literature are mixed. Wickramasinghe et al. (4) reported that 59.1% of SA articles received no citations, raising concerns about reach and visibility. In contrast, van Eyk et al. (29) ound that medical student publications had higher citation averages than articles in their respective fields. Beyond the number of citations, H-index comparisons

have been examined: Kan et al. (18) reported no significant differences between SAs and other authors. Overall, these results indicate that student or RA does not diminish the academic impact of publications and may, in some contexts, be associated with comparable or even higher citation performance.

Barriers to Early-Career Authorship and Strategies for Improvement

Student and resident involvement in academic publishing is widely recognized as valuable, yet participation remains limited due to several persistent challenges. Our findings provide empirical context for these barriers, particularly with respect to authorship positions, article types, and patterns of early-career participation. Both our findings and the broader literature consistently highlight similar barriers and potential strategies to address them.

First, limited training in research methodology and scientific writing is one of the most consistently reported barriers to early-career authorship (2,7,18). Students and residents often receive minimal formal instruction in study design, data analysis, manuscript preparation and submission, and the peer review process (2,7), which can discourage active participation. In our study, the predominance of middle authorship among early-career contributors may partly reflect limited methodological and writing autonomy during training. Proposed solutions include embedding compulsory or elective research components into medical curricula, since such participation is associated with greater academic output and satisfaction (2). Scholarly Concentration programs provide structured, mentored research experiences that support confidence, productivity, and long-term engagement (13,17). Additional approaches include skill-building workshops (11,30), field-specific training programs (31,32), and journal-led initiatives such as manuscript-writing resources or dedicated sections for trainee contributions (33).

Second, time constraints represent another major barrier, especially for residents balancing clinical duties and students managing academic workloads (8,9). This constraint may help explain why early-career contributors in our dataset were most frequently involved in full-length research reports rather than shorter or conceptual formats that require different writing competencies. Small-scale, well-scoped mini-project modules have been recommended to facilitate participation in research.

Third, limited access to committed mentorship further restricts early-career authorship. Many trainees struggle to find mentors with adequate time, expertise, or institutional support (7,10,12). Our observation that articles involving early-career authors were typically produced by larger, structured research teams is consistent with the central role of mentorship in enabling trainee participation. Strengthening mentorship networks and intentional mentor–mentee matching—approaches already emphasized in Scholarly Concentration programs—may support progression from passive involvement to meaningful intellectual contribution (11,15,19,23).

Fourth, students and residents do not have equal experience in authorship positions. Students and residents often report restricted contributions, being under-credited, or being assigned primarily technical tasks (3,34). Our findings mirror this pattern, with middle authorship far more common than first or last authorship among early-career contributors. This may explain students' perceptions of being used as "free labor" (3). Concerns about SA being used as a symbolic or superficial gesture rather than genuine inclusion have also been raised (35). Addressing these issues requires early authorship planning, transparent task delegation, and rotational opportunities that allow trainees to experience a range of authorship roles (2).

Fifth, limited exposure to short-form scholarly formats—such as letters, viewpoints, or brief commentaries—may reduce early-career participation. Consistent with this finding, our dataset showed that Letters to the Editor had the lowest participation by student and RAs. Targeted workshops and short-form writing assignments within research teams may help increase familiarity with these genres.

In summary, these challenges represent interconnected barriers to early-career authorship. With coordinated efforts from institutions (15), mentors (10,28,34), and journals and editors (33) (focused on training, mentorship, structure, and inclusion), early-career scholars can be better prepared to take on leadership roles in publishing and contribute to the long-term vitality of academia. In the context of the anatomical sciences, early-career authorship may play a particularly important role in sustaining the academic workforce, given the well-documented shortage of anatomy educators and the long training pathway required for academic careers in this field. From this perspective, authorship patterns observed in anatomical journals may also serve as indirect indicators of the state of anatomy education and the strength of the academic pipeline. Monitoring these trends may therefore provide insight into future workforce needs and the capacity of the discipline to support and retain early-career academics.

Study Limitations

This study has several methodological limitations, which also point toward future research directions. The analysis was restricted to ASE because of limited data availability.

This restriction reflects heterogeneity in journal publication policies regarding the reporting of author biographical information rather than a limitation of the study design itself. Accordingly, journal selection was limited to journals indexed in Web of Science and those identified through the IFAA/FICSP list; journals published by local anatomy associations outside these frameworks could not be systematically identified and were therefore not included. This may limit the generalizability of the findings to all anatomy journals and restrict insights into SRA in cadaver-based, radiologic, or clinical anatomy research. Future studies could expand these findings by including additional anatomy journals once author-level data become available.

Another limitation is the reliance on self-reported author roles, which introduces subjectivity. To overcome this and improve data reliability, journals could adopt standardized author contribution categories during manuscript submission. The inclusion of detailed contributor notes and the establishment of standardized author categories would provide more reliable metadata for future bibliometric studies. This would enable educators to establish longitudinal tracking of authorship trends, perform robust curricular performance analyses, and assess whether SAs remain academically active post-graduation.

Citation analysis was limited to the Web of Science database, which may have excluded citations from other indexing platforms. Additionally, the number of citations for recent articles is inherently lower due to limited time for accumulation; however, this limitation applies equally across all author groups and is not expected to bias comparisons. Lastly, excluding articles with incompletely declared author roles may have affected the reported contribution rates for student and RAs.

Conclusion

This study provides a comprehensive overview of student and resident contributions to research published in ASE between 2008 and 2024. The findings indicate a growing trend in SRA, reflecting broader shifts in academic medicine. Over this 17-year period, SA consistently outnumbered RAs.

Students and residents were more frequently listed as middle authors than as first or last authors, highlighting their active roles in conducting research while underscoring the mentorship-dependent nature of senior authorship. The increased number of co-authors on papers involving students or residents often indicates a collaborative, team-based research culture. Furthermore, although differences in citation counts were not statistically significant, articles with student and/or RAs demonstrated a higher median number of citations.

While these findings affirm the value of engaging early-career researchers in scholarly publishing, structural and educational strategies, such as mini-project modules, authorship rotation systems, targeted workshops, and certificate programs in anatomical research, could further promote equitable authorship opportunities and diversify the types of contributions available to trainees.

Increasing the involvement of students and residents in anatomical research not only supports their academic development but also contributes to the vitality, inclusivity, and sustainability of scholarship in the anatomical sciences. Strengthening mentorship, training, and infrastructure will be essential to ensure continued progress in the years ahead.

Ethics

Ethics Committee Approval: Since this study was conducted using publicly available data, no ethical committee approval was obtained.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: B.N.Ç.G., F.T.K., İ.A.G., Design: B.N.Ç.G., F.T.K., İ.A.G., Data Collection or Processing: B.N.Ç.G., F.T.K., Analysis or Interpretation: B.N.Ç.G., İ.A.G., Literature Search: B.N.Ç.G., F.T.K., Writing: B.N.Ç.G., İ.A.G.

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ORIGINAL ARTICLE

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Bridging Knowledge Gaps: Primary Healthcare Workers' Understanding of Breastfeeding During Pregnancy and Tandem Breastfeeding

Bilgi Eksikliklerinin Giderilmesi: Birinci Basamak Sağlık Çalışanlarının Gebelikte Emzirme ve Tandem Emzirme Hakkındaki Bilgi ve Görüşleri

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ABSTRACT

Background: Breastfeeding during pregnancy and tandem breastfeeding are challenging for both mothers and healthcare professionals, because societal taboos and lack of information often create uncertainty about whether to continue breastfeeding. This study aims to evaluate the knowledge and attitudes of primary healthcare workers, who play a key role in health counseling, regarding breastfeeding during pregnancy and tandem breastfeeding.

Materials and Methods: A cross-sectional study was conducted with 209 primary care providers (family physicians, nurses, midwives, paramedics). A 36-question survey was administered to participants. The questionnaire included items on demographic data, knowledge of and attitudes toward breastfeeding during pregnancy and tandem breastfeeding.

Results: The participants' mean age was 34.9 ± 6.4 years, and 60.3% were female. The majority (68.9%, n = 144) reported being knowledgeable about breastfeeding during pregnancy and tandem breastfeeding; most of this knowledge was acquired through in-service training (66.7%, n = 96). Approximately half of the participants (52.6%, n = 110) considered themselves sufficiently informed about breastfeeding during pregnancy, while only 28.2% (n = 59) felt knowledgeable about tandem breastfeeding. On the knowledge test, the highest rates of correct responses were observed for statements known to be false in the literature—namely, "Breastfeeding during pregnancy increases the risk of miscarriage" (74.2%, n = 155) and "Continuing breastfeeding during pregnancy causes low birth weight" (69.9%, n = 146). However, 45% (n = 95) of participants most frequently answered incorrectly to the statement known to be true in the literature: "The composition of breast milk changes in women who become pregnant while breastfeeding." Knowledge scores ranged from 0 to 9 (mean: 4.62 ± 2.14). Knowledge scores increased significantly with age (p = 0.027) and prior breastfeeding training (p = 0.003), but were not significantly associated with gender, marital status, professional role, or experience in family medicine.

Conclusion: Knowledge and attitudes regarding pregnancy and tandem breastfeeding vary among primary care workers. Targeted educational interventions and curriculum development are needed to strengthen competence in this area.

Keywords: Breastfeeding, child health, maternal health, pregnancy, family practice

ÖZ

Amaç: Gebelikte emzirme ve tandem emzirme, hem anneler hem de sağlık profesyonelleri için zorlu süreçlerdir; toplumsal tabular ve bilgi eksikliği, emzirmenin devamı konusunda çoğunlukla belirsizliğe yol açmaktadır. Bu çalışma, sağlık danışmanlığında kilit rol oynayan birinci basamak sağlık çalışanlarının gebelikte emzirme ve tandem emzirme konusundaki bilgi ve tutumlarını değerlendirmeyi amaçlamaktadır.

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ÖZ

Gereç ve Yöntemler: Kesitsel tipteki bu çalışma, 209 birinci basamak sağlık çalışanı (aile hekimi, hemşire, ebe, paramedik) ile gerçekleştirilmiştir. Katılımcılara 36 sorudan oluşan bir anket uygulanmıştır. Anket; demografik veriler ile gebelikte emzirme ve tandem emzirme konusundaki bilgi ve tutuma yönelik maddeleri içermektedir.

Bulgular: Katılımcıların yaş ortalaması 34,9 ± 6,4 yıl olup %60,3'ü kadındır. Çoğunluğu (%68,9, n = 144) gebelikte emzirme ve tandem emzirme konusunda bilgi sahibi olduğunu belirtmiş; bu bilgi çoğunlukla hizmet içi eğitim yoluyla (%66,7, n = 96) edinilmiştir. Katılımcıların yaklaşık yarısı (%52,6, n = 110) gebelikte emzirme hakkında yeterince bilgi sahibi olduğunu düşünürken, yalnızca %28,2'si (n = 59) tandem emzirme konusunda bilgili olduğunu düşünmektedir. Bilgi testinde, literatürde yanlış olduğu bilinen ifadeler—"Gebelikte emzirme düşük riskini artırır" (%74,2, n = 155) ve "Gebelikte emzirmeye devam etmek düşük doğum ağırlığına neden olur" (%69,9, n = 146)—ifadeleri için en yüksek doğru cevap oranları bulunmuştur ancak katılımcıların %45'i (n = 95) literatürde doğru olduğu bilinen "Emzirme döneminde gebe kalan kadınlarda anne sütünün bileşenleri değişir" ifadesini en yüksek oranda yanlış cevaplamıştır. Bilgi puanları 0 ile 9 arasında değişmektedir (ortalama: 4,62 ± 2,14). Bilgi puanları yaşın yükselmesi (p = 0,027) ve daha önce emzirme eğitimi almış olma ile (p = 0,003) anlamlı olarak artarken, cinsiyet, medeni durum, görev veya aile hekimliği deneyimiyle anlamlı ilişki göstermemiştir.

Sonuç: Birinci basamak sağlık çalışanlarının gebelikte ve tandem emzirme konusundaki bilgi ve tutumlarında değişkenlik gözlenmiştir. Bu alanda yetkinliği artırmak için hedefe yönelik eğitim müdahaleleri ve müfredat geliştirilmesine ihtiyaç vardır.

Anahtar Kelimeler: Emzirme, çocuk sağlığı, anne sağlığı, gebelik, aile hekimliği

Introduction

Breast milk is the optimal source of nutrition for newborns and plays a crucial role in strengthening the immune system, protecting against infections, and supporting healthy growth and development. The World Health Organization and other international pediatric organizations recommend exclusive breastfeeding for the first six months of life and continued breastfeeding alongside complementary foods for at least two years or beyond (1,2). In this context, breastfeeding during pregnancy and tandem breastfeeding—the practice of breastfeeding two children of different ages simultaneously—have gained increasing attention in recent years (3,4).

Despite these well-established benefits, breastfeeding during pregnancy and tandem breastfeeding are often surrounded by misconceptions and cultural taboos rather than evidence-based guidance. These practices are frequently perceived as unsafe, leading to uncertainty among both mothers and healthcare professionals. Such concerns may result in premature weaning and inconsistent counseling practices, ultimately affecting maternal and child health outcomes (3,4).

Recent studies have demonstrated that breastfeeding during an uncomplicated pregnancy is generally safe and not associated with an increased risk of spontaneous abortion, preterm birth, or low birth weight, provided that the mother is healthy and adequately nourished (3,5,6). However, in high-risk pregnancies or cases of maternal malnutrition, individualized assessment and monitoring are advised, with clinical decisions guided by a careful evaluation of potential risks and benefits. Studies examining tandem breastfeeding further indicate that the macronutrient composition and immunological quality of human milk remain appropriate for both the newborn and the older child, suggesting that breastfeeding can safely continue with adequate maternal support (7,8).

Although the clinical evidence regarding the safety of breastfeeding during pregnancy and of tandem breastfeeding has expanded in recent years, research focusing on healthcare workers' knowledge and attitudes toward these practices remains limited and heterogeneous, both nationally and internationally. Existing studies suggest that gaps in knowledge and persistent misconceptions among physicians and other healthcare providers may lead to inaccurate or misleading counselling practices (9,10).

Given that healthcare providers play a central role in providing evidence-based counseling, their knowledge and attitudes directly affect breastfeeding continuation and maternal confidence. Qualitative research indicates that mothers who receive supportive, evidence-based counseling from healthcare providers are more likely to continue tandem breastfeeding without anxiety, whereas misinformation or discouragement remains a leading cause of premature weaning (9-11).

Primary healthcare workers—including family physicians, nurses, and midwives—are often the first point of contact for pregnant and lactating women, placing them in a key position to influence maternal decision-making. However, recent surveys across different settings, including Türkiye, reveal significant knowledge gaps concerning breastfeeding during pregnancy and tandem breastfeeding, with many healthcare workers relying on outdated beliefs rather than current scientific evidence (9,11,12). These findings highlight the need to better understand not only healthcare workers'

knowledge and attitudes, but also how these factors may shape counseling practices in primary care settings.

Given limited data addressing the knowledge, attitudes, and misconceptions of primary healthcare professionals regarding breastfeeding during pregnancy and tandem breastfeeding, it is important to clarify the current situation and identify areas requiring educational support. Therefore, this study aimed to assess primary healthcare workers' knowledge and attitudes regarding breastfeeding during pregnancy and tandem breastfeeding, and to identify gaps that may affect evidence-based counseling and educational needs in primary care.

Materials and Methods

Study Design and Participants

This cross-sectional, descriptive study was designed to assess the knowledge and attitudes of family physicians and family health workers regarding breastfeeding during pregnancy and tandem breastfeeding. The study was conducted in family health centers across Yozgat, with the study population comprising all family physicians and family health workers employed in the province. Yozgat has 145 family medicine units, staffed by 134 family physicians and 134 family health workers. This study employed census (whole-population) sampling to include all family physicians and family health workers employed in family health centers across Yozgat province. Family physicians and family health workers who volunteered for the study were included; those who declined or withdrew were excluded. The study involved 209 participants, accounting for 77.9% of all primary healthcare workers.

Participants were contacted by telephone through their family health centers, data were collected online at their convenience. Prior to the initiation of the study, informed consent was secured from all participants, thereby guaranteeing voluntary participation.

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Yozgat Bozok University prior to study initiation (protocol number: 2017-KAEK-189_2023.10.26_04, dated: 26.10.2023).

Data Collection Tools

The data collection tool was a 36-item questionnaire developed by the researchers following an extensive review of relevant national and international literature, including previous studies and guidelines on breastfeeding during pregnancy and on tandem breastfeeding (3,5,7-9). The initial draft of the questionnaire was reviewed by three academic experts (two family physicians and one pediatrician) for content validity, relevance, and clarity. Based on their feedback, minor revisions were made to ensure conceptual consistency and clarity of wording. A pilot test was then conducted with 20 family physicians and family health workers who were not included in the main study to assess the comprehensibility of the survey and the time required to complete it. Feedback from this pilot group led to slight modifications in the wording and sequencing of several items. The final version consisted of three sections: (1) sociodemographic and professional characteristics (fourteen questions); (2) knowledge statements (nine items) regarding breastfeeding during pregnancy and tandem breastfeeding; (3) attitude statements (thirteen items) regarding breastfeeding during pregnancy and tandem breastfeeding. The knowledge section of the questionnaire consisted of nine statements, with response options of "true," "false," and "no idea." Correct responses were scored 1 point; incorrect and "no idea" responses were scored 0 points. Total knowledge scores, therefore, ranged from 0 (no correct answers) to 9 (all correct). The attitude section included 13 statements that participants could respond to with "agree," "neutral," or "disagree. The internal consistency coefficient for the knowledge items was found to be 0.715, while for the attitude items, it was calculated as 0.721.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.). Data normality was assessed using Skewness and Kurtosis coefficients, Q-Q plots, and histograms. Descriptive statistics, including percentages and frequencies, were used to summarize participants' demographic information and questionnaire responses. Independent-samples t-tests, one-way analysis of variant, Kruskal–Wallis tests were used to compare continuous variables between groups. A p-value <0.05 was considered statistically significant. A post-hoc power analysis indicated that the study had 86% power (n = 209, $\alpha = 0.05$, two-tailed) to detect a medium effect size (Cohen's d = 0.42).

Results

A total of 209 primary healthcare workers participated in the study, of whom 60.3% (n = 126) were female. The mean age of the participants was 34.92 ± 6.36 years. Nearly half of the participants were family physicians (49.3%), followed by nurses (30.1%), midwives (18.7%), and paramedics (1.9%).

The majority of participants had more than one year of overall professional experience (n = 204, 97.6%), and most had at least one year of experience working in family medicine (n = 181, 86.6%).

Regarding awareness of breastfeeding during pregnancy and tandem breastfeeding, 68.9% (n = 144) of the participants reported being familiar with these concepts.

Among those who were aware, the majority had obtained this information through in-service breastfeeding training. While more than half of participants (52.6%) considered themselves sufficiently knowledgeable about breastfeeding during pregnancy, only 28.2% reported adequate knowledge of tandem breastfeeding. In addition, 27.8% reported that insufficient knowledge of these topics caused anxiety. A high proportion of participants expressed interest in further education, with 84.7% willing to attend scientific meetings and 88% supporting the inclusion of these topics in healthcare curricula.

Participants demonstrated varying levels of knowledge regarding specific statements related to breastfeeding during pregnancy and tandem breastfeeding. The statements "Breastfeeding during pregnancy increases the risk of miscarriage" and "Continuing breastfeeding during pregnancy causes low birth weight in newborns" were answered correctly by the majority of participants. In contrast, the statement "The chemical composition of breast milk changes in women who become pregnant while breastfeeding" was the most frequently answered incorrectly (Table 1).

Analysis of attitudes and knowledge revealed significant differences between groups for most statements ($p < 0.05$). The lowest levels of awareness were observed for the statements "The mother should decide whether to continue breastfeeding her older child during pregnancy" (27.8%) and "If intrauterine growth restriction is present, I would recommend that the mother stop breastfeeding" (26.8%) (Table 2).

Knowledge scores ranged from 0 to 9, with a mean score of 4.62 ± 2.14; only two participants achieved the maximum score (Table 3). No significant associations were found between knowledge scores and gender, marital status, years of experience in family medicine, or professional role ($p > 0.05$). However, knowledge scores were significantly higher among older participants ($p = 0.027$) and among those who had received breastfeeding training compared with those who had not ($p = 0.003$) (Table 4).

Discussion

This study assessed family physicians' and family health workers' knowledge and attitudes regarding breastfeeding during pregnancy and tandem breastfeeding. Although most participants were familiar with the general concept of breastfeeding during pregnancy, overall knowledge levels were moderate and misconceptions remained common, particularly regarding physiological changes in breast milk composition. While statements related to miscarriage and low birth weight were frequently answered correctly, misunderstandings about breast milk composition during pregnancy reflected persistent gaps in professional knowledge.

Previous studies have shown that breastfeeding during a healthy, low-risk pregnancy does not increase the risk of miscarriage, preterm labor or low birth weight, provided the mother is well-nourished and monitored (13-17). Oxytocin release during breastfeeding in healthy pregnancies is generally insufficient to trigger uterine contractions due to decreased receptor sensitivity (14-16).

Table 1. Distribution of participants according to their knowledge levels about breastfeeding during pregnancy and tandem breastfeeding.

Statements	True		False		No idea	
	n	%	n	%	n	%
Breastfeeding during pregnancy increases the risk of miscarriage in the mother.	20	9.6	155	74.2	34	16.2
The chemical composition of breast milk changes in women who become pregnant during the breastfeeding period.*	82	39.2	94	45	33	15.8
The amount of milk decreases at the beginning of pregnancy in women who become pregnant during the breastfeeding period.	99	47.4	77	36.8	33	15.8
Continuing breastfeeding during pregnancy may lead to low birth weight in the newborn.	25	12	146	69.9	38	18.2
Uterine contractions may occur more commonly in women who breastfeed during pregnancy.*	77	36.8	78	37.4	54	25.8
Preterm labor is more commonly observed in women who breastfeed during pregnancy.	53	25.3	113	54.1	43	20.6
Tandem breastfeeding may lead to the newborn not being adequately nourished.	89	42.5	104	49.8	16	7.7
The stool of the older child may be yellowish/mustard in color while tandem breastfeeding.*	89	42.6	11	5.2	109	52.2
The decision to wean from tandem breastfeeding should be made independently of the children's ages.*	122	58.4	31	14.8	56	26.8

*Symbol represents the information that is correct according to the literature.

Table 2. Association between knowledge scores and attitudes regarding breastfeeding during pregnancy and tandem breastfeeding.

Statements	Agree		Neutral		Don't agree		p-value
	n	%	n	%	n	%	
I recommend that a mother without any additional risk factor to discontinue breastfeeding if she becomes pregnant.	41	19.6	28	13.4	140	67	<0.001 KW: 61.93
I conduct pregnancy follow-ups more frequently for mothers who breastfeed while pregnant.	103	49.3	42	20.1	64	30.6	<0.001 F(2, 98.77) = 14.10
I would schedule more frequent prenatal check-ups for a mother breastfeeding during pregnancy if she has additional risk factors.	171	81.8	17	8.1	21	10	0.055 KW: 5.80
I do not recommend breastfeeding during pregnancy for mothers with risk factors.	64	30.6	52	24.9	93	44.6	<0.001 F(2, 206) = 24.90
I recommend that the mother discontinue breastfeeding if the baby has intrauterine growth retardation.	80	38.3	56	26.8	73	34.9	<0.001 F(2, 124.17) = 19.46
I recommend that the mother discontinue breastfeeding if she has anemia.	31	14.8	39	18.7	139	66.5	<0.001 F(2, 60.74) = 14.39
I recommend that the mother to continue breastfeeding if her weight gain during pregnancy is adequate.	143	68.4	31	14.8	35	16.8	<0.001 F(2, 206) = 30.30
I recommend that the mother continue breastfeeding if she is motivated to feed her older child while pregnant.	27	12.9	31	14.9	151	72.2	<0.001 F(2, 206) = 42.87
I would closely monitor the newborn baby of a mother who is breastfeeding during pregnancy and practicing tandem breastfeeding.	41	19.6	15	7.2	153	73.2	<0.001 KW: 26.85
Healthcare professionals should encourage the mother to continue breastfeeding while pregnant.	32	15.3	43	20.6	134	64.1	<0.001 F(2, 206) = 49.78
Healthcare professionals should encourage the mother to continue tandem breastfeeding after birth.	23	11	45	21.5	141	67.5	<0.001 KW: 76.79
The mother should make her own decision regarding breastfeeeding during pregnancy.	60	28.7	58	27.8	91	43.5	<0.001 F(2, 109.55) = 9.90
The mother should make her own decision regarding tandem breastfeeding.	97	46.4	53	25.3	59	28.3	<0.001 F(2, 113) = 9.90

KW, Kruskal–Wallis Test; F, one-way analysis of variance.

Table 3. Descriptive statistics for breastfeeding during pregnancy and tandem breasfeeding knowledge scores.

	Mean ± standard deviation	Median	Minimum–maximum
Knowledge scores	4.62 ± 2.14	5.0	0-9

Table 4. Evaluation of participants' knowledge scores with various variables.

		n	Mean ± SD	Min.-max.	p-value
Gender	Female Male	126 83	4.59 ± 1.99 4.67 ± 2.36	1–8 0–9	0.774[a]
Age	<35 years ≥35 years	108 101	4.31 ± 2.13 4.83 ± 2.21	0–8 0–9	**0.027[a]**
Experince in family medicine	≤5 years >5 years	106 103	4.42 ± 2.06 4.81 ± 2.21	0–8 0–9	0.158[a]
Profession	Family physician Family health worker	103 106	4.55 ± 2.24 4.69 ± 2.06	0–9 1–8	0.650[a]
Previously having education on breastfeeding during pregnancy and tandem breastfeeding	Yes	98	5.09 ± 1.95	0–8	**0.003[a]**
	No	111	4.21 ± 2.22	0–9	

[a]Independent samples t-test. Min-max, minimum-maximum; SD, standard deviation.

Nevertheless, in pregnancies complicated by malnutrition, bleeding or preterm contractions, breastfeeding should be evaluated on an individual basis. The present study supports these findings, suggesting that healthcare professionals' understanding aligns partially with current scientific evidence.

Misconceptions regarding changes in breast milk composition during pregnancy appear to be widespread among both healthcare workers and mothers. Although compositional changes occur, breast milk continues to meet the nutritional and immunological needs of both the newborn and the older child during tandem breastfeeding (5,18). Inaccurate counseling may contribute to unnecessary early weaning, underscoring the need for clearer differentiation between normal physiological changes and clinical risk factors requiring intervention (16,19,20).

Another important finding was that a substantial proportion of participants expressed uncertainty regarding maternal decision-making about breastfeeding during pregnancy. This suggests limited awareness of the importance of maternal autonomy in breastfeeding counseling. Healthcare professionals should provide individualized, evidence-based guidance while supporting mothers in making informed decisions based on their own circumstances, consistent with mother-centered counseling principles (7,11,21,22).

Consistent with previous research, counseling about breastfeeding during pregnancy and tandem breastfeeding was perceived as challenging, and many participants reported anxiety due to insufficient knowledge. Participants who had received prior training demonstrated significantly higher knowledge levels, emphasizing the role of structured education in improving counseling confidence and accuracy. Although breastfeeding is included in undergraduate curricula, complex scenarios such as tandem breastfeeding are often insufficiently addressed, highlighting the need for enhanced coverage in both undergraduate and continuing professional education (7,9,11,23).

In this study, age was significantly associated with knowledge levels. This finding contrasts with several previous studies (24,25). The fact that this association is not commonly observed in the literature may be explained by differences in sample characteristics and the measurement tools used.

Given the limited number of studies focusing on healthcare providers rather than maternal experiences, this study contributes valuable insights from a primary healthcare perspective and highlights the need for standardized, evidence-based guidance. Future research should prioritize evaluating the effectiveness of targeted educational interventions and exploring counseling practices using qualitative approaches.

Study Limitations

Due to the cross-sectional design of the study, the results are applicable only to the study population, and causality cannot be established. Another limitation is that the study relied on self-reported survey data, which may have led to social desirability bias. In addition, the questionnaire used in the study was developed by the researchers, although content validity and internal consistency were evaluated, more advanced psychometric validation was not performed. Finally, as the study was conducted in a single province, the generalizability of the findings to other regions and healthcare settings may be limited.

Although descriptive and group comparison analyses were appropriate for the study objectives, the absence of multivariable analyses may limit the ability to conduct a more comprehensive assessment of factors associated with healthcare workers' knowledge and attitudes.

Conclusion

Healthcare workers who had received prior breastfeeding training demonstrated higher knowledge levels regarding breastfeeding during pregnancy and tandem breastfeeding. This finding highlights the need for targeted, evidence-based educational programs for primary healthcare workers to address misconceptions and improve counselling practices. Improving healthcare workers' knowledge may enhance maternal confidence and support the continuation of breastfeeding through informed decision-making.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Yozgat Bozok University prior to study initiation (protocol number: 2017-KAEK-189_2023.10.26_04, dated: 26.10.2023).

Informed Consent: Prior to the initiation of the study, informed consent was secured from all participants, thereby guaranteeing voluntary participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.U.Z., F.S.Z., Concept: K.U.Z., F.S.Z., Design: K.U.Z., F.S.Z., Data Collection or Processing: F.S.Z., Analysis or Interpretation: K.U.Z., Literature Search: K.U.Z., F.S.Z., Writing: K.U.Z., F.S.Z.

Conflict of Interest: No conflict of interest was declared by the author(s).

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A Comparative Analysis of Lateral Suspension Techniques and Sacrocolpopexy for Pelvic Organ Prolapse Repair in a Tertiary Care Center

Pelvik Organ Prolapsusu Cerrahisinde Üçüncü Basamak Bir Merkezde Yapılan Sakrokolpopeksi ile Lateral Süspansiyon Tekniklerinin Karşılaştırılması

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ABSTRACT

Background: Pelvic organ prolapse (POP) is a common condition in elderly women and has an enormous quality-of-life impact. Various surgical techniques, including vaginal, abdominal, open (laparotomy), and laparoscopic approaches, are utilized based on patient symptoms and clinical presentation. This study aimed to compare the perioperative outcomes and clinical results of laparotomic sacrocolpopexy (L-SCP), considered the gold standard for POP repair, with those of laparoscopic lateral suspension (LLS).

Materials and Methods: A retrospective analysis was conducted of 186 POP surgeries performed at a tertiary care center between 2022 and 2024. Patients who met the inclusion criteria were divided into two groups. 24 of these patients underwent L-SCP, and 25 underwent LLS. The parameters compared included age, body mass index, operative time, length of postoperative hospital stay, perioperative hemoglobin change, postoperative POP stage, and recurrence and complication rates. The primary outcome was the objective anatomical success rate, assessed using the POP Quantification system.

Results: The mean operative time was significantly longer in the L-SCP group than in the LLS group. Duration of hospital stay and perioperative hemoglobin changes were similar between the two groups. Preoperative POP-Q stage distribution differed significantly between the groups, with Stage 4 prolapse being more frequent in the L-SCP group and Stage 3 prolapse in the LLS group. At 12 months postoperatively, POP-Q stage distribution was comparable between the groups, with no significant difference ($p = 0.196$). In the L-SCP group, complications included one common iliac vein injury (4.1%), one ureteral injury (4.1%), and three surgical-site infections (12.5%). In the LLS group, two bladder injuries (8%), one ureteral injury (4%), two mesh-related inflammatory reactions (8%), and one surgical-site infection (4%) were observed.

Conclusion: Laparotomic and laparoscopic approaches showed similar short-term anatomical outcomes and recurrence rates. Laparotomic SCP was associated with longer operative time and higher infection risk, while laparoscopic LS had a different complication profile. The surgical approach should be guided by patient characteristics and the surgeon's experience, rather than by presumed superiority.

Keywords: Pelvic organ prolapse, sacrocolpopexy, lateral suspension

ÖZ

Amaç: Pelvik organ prolapsusu (POP), özellikle ileri yaş kadınlarda sık görülen ve yaşam kalitesini düşüren klinik bir durumdur. Hastaların semptom ve şikayetlerine göre farklı tekniklerle hastalara uygun cerrahi yapılmaktadır. Vajinal, abdominal, laparatomik ya da laparoskopik cerrahi teknikler kullanılabilir. POP'da altın standart teknik olan laparotomik sakrokolpopeksi (L-SCP) ile son yıllarda popüler olan laparoskopoik lateral süspansiyon (LLS) yapılan hastalar karşılaştırılmıştır.

Gereç ve Yöntemler: 2022 – 2024 yılları arasında üçüncü basamak bir hastanede gerçekleştirilen 186 POP cerrahi vakaları retrospektif olarak değerlendirildi. Yirmidört tane L-SCP ve 25 tane LLS cerrahi teknik olmak üzere iki gruba ayrıldı. Yaş, vücut kitle indeksi, operasyon süresi, postoperatif hastanede kalış süresi, perioperatif hemoglobin değişimi, postoperatif prolapsus evresi, nüks sayısı

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ÖZ

ve komplikasyon oranları karşılaştırıldı. Çalışmanın birincil sonucu olarak Pelvik Organ Prolapsusu Kantifikasyon sistemine göre objektif kür sağlama oranı değerlendirildi.

Bulgular: Ortalama ameliyat süresi L-SCP grubunda LLS grubuna kıyasla anlamlı olarak daha uzundu. Hastanede yatış süresi ve perioperatif hemoglobin değişimi iki grup arasında benzerdi. Preoperatif POP-Q evre dağılımı gruplar arasında anlamlı farklılık gösterdi; Evre 4 prolapsus L-SCP grubunda, Evre 3 prolapsus ise LLS grubunda daha sık görüldü. Postoperatif 12. ayda POP-Q evre dağılımı iki grup arasında benzerdi ve anlamlı farklılık saptanmadı (p = 0,196). L-SCP grubunda bir common iliak ven yaralanması (%4,1), bir üreter yaralanması (%4,1) ve üç cerrahi alan enfeksiyonu (%12,5) görüldü. LLS grubunda ise iki mesane yaralanması (%8), bir üreter yaralanması (%4), iki mesh ile ilişkili inflamatuvar reaksiyon (%8) ve bir cerrahi alan enfeksiyonu (%4) gözlendi.

Sonuç: L-SCP ve laparoskopik lateral süspansiyon kısa dönem anatomik sonuçlar ve nüks oranları açısından benzer gözlemsel sonuçlar göstermiştir. Bununla birlikte, cerrahi yaklaşım farklılığı ve gruplar arasındaki preoperatif prolapsus şiddeti eşitsizliği nedeniyle bu bulgular dikkatle yorumlanmalıdır. L-SCP daha uzun ameliyat süresi ve enfeksiyon riski ile ilişkiliyken, LLS farklı bir komplikasyon profili sergilemiştir. Bu nedenle cerrahi teknik seçimi, yöntemlerin mutlak üstünlüğü yerine hasta özellikleri ve cerrah deneyimi doğrultusunda bireyselleştirilmelidir.

Anahtar Kelimeler: Pelvik organ prolapsusu, sakrokolpopeksi, lateral süspansiyon

Introduction

Pelvic organ prolapse (POP) is a clinical syndrome in which pelvic organs sag into or below the vaginal canal, typically resulting in vaginal bulging and pelvic pressure. It results primarily from a defect or weakness within the connective tissue and supporting structures of the pelvic floor. POP most often occurs in women aged 45–85 years (1). It has been estimated that nearly 13% of women will require surgical correction for POP at some stage in their lives (2). As life expectancy increases, the prevalence of symptomatic POP among women is projected to rise to 46% by 2050 (3).

Although several factors associated with POP have been ascertained, the precise associations between these factors and established risk factors remain to be identified (4). Known risk factors include menopause, increased parity, obesity, advanced age, genetic predisposition, and connective tissue disorders.

Diagnosis of prolapse is based on patient history and physical examination, with the physical examination assessing the anterior vaginal wall, vaginal apex, and posterior vaginal wall. POP staging is performed based on these findings, typically using the POP Quantification (POP-Q) system. When surgery is indicated, the surgical approach (transvaginal, laparoscopic, or open laparotomy) and the choice between native-tissue repair and mesh use are determined by the patient's overall health status and specific characteristics. The vaginal route is less invasive and is associated with lower morbidity than laparotomy and laparoscopy (5).

In recent years, increasing complication rates associated with mesh use have been reported (6). These complications include vaginal mucosal erosion, pain, infection, prolapse recurrence, and bladder or bowel injury during mesh implantation (7). Even in carefully selected patients, judicious use of mesh prevents recurrence of prolapse and improves long-term quality of life by ensuring pelvic floor support (8). Effective treatment of POP development and postoperative recurrence requires careful preoperative counseling, understanding patient expectations, and individualized surgical planning (9).

Abdominal sacrocolpopexy (SCP) involves attaching the vaginal apex to the anterior longitudinal ligament using mesh (10). This procedure, described by DeLancey (11), is indicated for all POP patients with level 1 defects. In young, sexually active women, SCP remains the gold standard for apical prolapse repair. However, data on its short- and long-term success rates and complication rates are conflicting. SCP demands extensive pelvic dissection and advanced suturing skills. To mitigate the risk of complications, a less complex lateral suspension (LS) technique was developed. LS is performed by placing a T-shaped mesh in the vesicovaginal space and securing it with sutures to the anterior vaginal wall, cervix, and isthmus (12). Over the past decade, multiple studies have assessed the efficacy and complication profile of this technique.

The present study aims to compare the short-term outcomes of abdominal SCP, the gold standard for POP and apical prolapse repair, with those of laparoscopic LS, a technically less demanding procedure with a potentially lower risk of complications.

Materials and Methods

A retrospective review was conducted of 186 POP cases performed at a tertiary care hospital between January 2022 and January 2024. Twelve cases were excluded due to vaginal cuff prolapse, 42 due to isolated anterior colporrhaphy, 24 due to isolated posterior colporrhaphy, and 59 due to incomplete data (Figure 1).

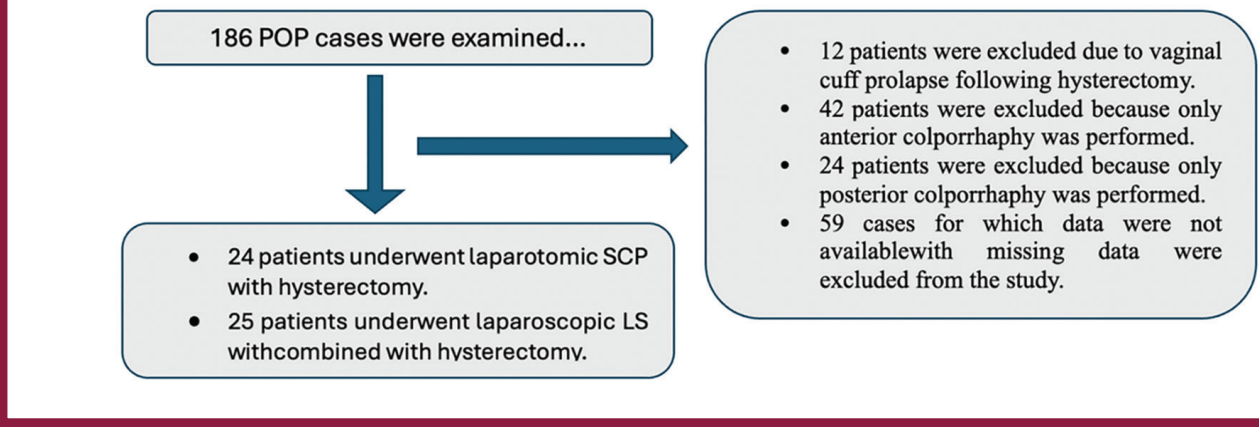

Figure 1. Study design.
POP, pelvic organ prolapse; SCP, sacrocolpopexy; LS, lateral suspension.

Due to the limited number of surgeons experienced in performing laparoscopic SCP at our center, various suspension techniques were compared across different surgical approaches.

The final analysis included 25 patients who underwent laparoscopic LS with hysterectomy and 24 who underwent open SCP with hysterectomy, constituting a retrospective cohort. Patients who underwent a hysterectomy planned for prolapse were included in the study. Patients who underwent a hysterectomy for myoma uteri or other indications were excluded.

The demographic and clinical variables compared included age, operative time, body mass index (BMI), postoperative hospital stay, postoperative change in hemoglobin, postoperative prolapse stage, and recurrence and complication rates. Patients with preoperative apical prolapse stage 2 or higher, according to the POP-Q system, were included. Recurrences were defined as stage III or higher prolapse occurring within one year postoperatively. The primary outcome was the objective cure rate evaluated by the POP-Q system.

The study protocol was approved by the Scientific Research Ethics Committee of Giresun Training and Research Hospital (decision number: 30.10.2024/04, dated: 04.11.2024). All procedures were conducted in accordance with the Ethical Principles for Medical and Health Research Involving Human Subjects.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables that were not normally distributed were summarized as medians and interquartile ranges while categorical variables were presented as numbers and percentages (n, %). Comparisons between the two groups were performed using the Mann–Whitney U test for non-normally distributed continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Preoperative and postoperative POP-Q stages were treated as ordinal variables and summarized using the median (range) and frequencies for each stage. A p-value <0.05 was considered statistically significant. Due to the retrospective nature of the study and the small sample size, no formal post hoc power analysis was performed; however, the effect sizes were calculated where relevant to assess clinical relevance.

Results

This retrospective cohort study included 49 patients with POP who underwent either laparotomic SCP (L-SCP) (n = 24) or laparoscopic LS (n = 25), all of whom underwent concomitant hysterectomy (Figure 1). Baseline characteristics, including age (median 60.5 vs. 63.5 years), duration of menopause, BMI, gravidity, parity, and comorbidities such as hypertension and diabetes, did not differ significantly (all $p > 0.05$). Operative time was significantly shorter in the LS group than in the SCP group (median 150 vs. 177.5 minutes, $p = 0.002$), reflecting the minimally invasive nature of the laparoscopic approach. Preoperative hemoglobin levels were slightly higher in SCP patients (13.45 vs. 12.65 g/dL, $p = 0.033$), and postoperative values were also higher (11.95 vs. 11.20 g/dL, $p = 0.012$); however, the magnitude of the hemoglobin drop and transfusion rates did not differ significantly (Table 1).

Preoperative POP-Q stage distribution differed significantly between the groups (p = 0.027). Stage 4 prolapse was more frequent in the L-SCP group (54.1% vs. 28.0%), whereas Stage 3 prolapse was more common in the laparoscopic LS group (68.0% vs. 41.6%). At the 12-month postoperative assessment, POP-Q stage distribution did not differ significantly between the groups (p = 0.196). Stage 1–2 prolapse was observed in the majority of patients in both groups, while Stage 3–4 prolapse was uncommon. These findings indicate that, despite differences in the distribution of baseline POP-Q stages, postoperative anatomical stage distributions were comparable between the two surgical groups at 12 months (Table 2).

Complication profiles were comparable, though bladder injury (8%) and mesh-related inflammatory reaction (8%) occurred exclusively in the LS group, whereas vascular injury (4.1%) and higher surgical-site infection rates (12.5%) occurred in the SCP group. Length of hospital stay and rates of injury to adjacent organs were similar between the groups (Table 3). Collectively, these data support the conclusion that

Table 1. Comparison between groups.

	L-SCP (n = 24)	Laparoscopic LS (n = 25)	p-value
Age (years), median (IQR)	60.5 (54–67)	63.5 (55–71)	0.441
Menopause Duration (years), median (IQR)	12 (6–18)	14 (7–21)	0.507
BMI (kg/m²), median (IQR)	26.15 (24–31)	28.3 (25–31)	0.395
Gravidity, median (IQR), median (IQR)	3 (2–4)	4 (2–5)	0.975
Parity, median (IQR)	2 (2–3)	3 (2–4)	0.819
Normal vaginal delivery, median (IQR)	2.5 (2–3)	3 (2–4)	0.758
Cesarean delivery, median (IQR)	0 (0–0)	0 (0–0)	0.584
Operative time (minutes), median (IQR)	177.5 (160–210)	150.00 (120–180)	0.002*
Hospital stay (days), median (IQR)	3 (3–4)	3 (3–4)	0.078
Preoperative hemoglobin (g/dL), median (IQR)	13.45 (12.5–14.2)	12.65 (11.9–13.4)	0.033*
Postoperative hemoglobin (g/dL), median (IQR)	11.95 (10.8–12.6)	11.20 (10.5–12.0)	0.012*
Hemoglobin change (g/dL), median (IQR)	1.45 (1.0–2.0)	1.3 (1.0–2.1)	0.489
Blood transfusion, n (%)	1 (4.1%)	3 (12%)	0.301
Adjacent organ injury, n (%)	2 (8.3%)	3 (12%)	0.673
Hypertension, n %	14 (58.3%)	11 (44%)	0.199
Diabetes mellitus, n (%)	10 (41.6%)	12 (48%)	0.880
Smoking, n (%)	9 (37.5%)	6 (24%)	0.474

Data are presented as median (IQR) or number (%). p-values calculated using Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Statistically significant p-values are shown in bold. BMI, body mass index; IQR, interquartile range; L-SCP, laparotomic sacrocolpopexy; LS, lateral suspension; n, number of patients.

Table 2. Preoperative and 12-month postoperative POP-Q stages in L-SCP and laparoscopic LS groups.

POP-Q stage	Laparotomic SCP (n = 24)	Laparoscopic LS (n = 25)	p-value
Preoperative POP-Q stage			
Stage 1	0 (0%)	0 (0%)	**0.027***
Stage 2	1 (4.1%)	1 (4.0%)	
Stage 3	10 (41.6%)	17 (68.0%)	
Stage 4	13 (54.1%)	7 (28.0%)	
Postoperative POP-Q stage (12 months)			
Stage 1	14 (58.3%)	13 (52.0%)	0.196
Stage 2	8 (33.3%)	9 (36.0%)	
Stage 3	1 (4.1%)	2 (8.0%)	
Stage 4	1 (4.1%)	1 (4.0%)	

p-values calculated using Fisher's exact test. L-SCP, laparotomic sacrocolpopexy; LS, lateral suspension; n, number of patients; POP-Q, Pelvic Organ Prolapse Quantification.

Table 3. Postoperative complications and perioperative outcomes.

	Laparotomic SCP (n = 24)	Laparoscopic LS (n = 25)
Vascular injury (common iliac vein)	1(4.1%)	0 (0%)
Bladder injury	0 (0%)	2 (8%)
Ureteral damage	1 (4.1%)	1 (4%)
Mesh-related inflammatory reaction	0 (0%)	2 (8%)
Surgical site infection	3 (12.5%)	1 (4%)

LS, lateral suspension; n, number of patients; SCP, sacrocolpopexy.

both SCP and LS are effective and safe for POP correction, with the laparoscopic approach associated with reduced operative time and slightly lower perioperative blood loss without increasing the risk of complications.

Discussion

The clinical management of POP remains challenging, with varying success rates reported among different surgical approaches. Minimally invasive techniques have gained popularity because they reduce operative morbidity, shorten hospital stays, and accelerate recovery. In our study, LS demonstrated significantly shorter operative times than abdominal SCP, consistent with the literature (13,14). Despite these differences, 12-month postoperative prolapse descent was comparable between LS and SCP, regardless of preoperative POP severity. Several studies support the efficacy of LS. One series reported 92% anterior compartment and 100% apical compartment recovery at 12 months post-laparoscopic LS (13). For an inexperienced surgeon, laparoscopic LS takes approximately 184 minutes (14). Learning-curve analyses indicate that LS is technically less demanding than laparoscopic SCP, while achieving similar objective success at 12 months (LS 89.1% vs. SCP 90.7%) (14). Laparoscopic LS is a less complex procedure to learn, and its success rate matches that of SCP. The degree of descent was the same for both procedures when compared at the 12-month postoperative follow-up in our study. Laparoscopic LS and SCP have equal efficacy and success rates in the management of POP (15). In another study, the primary cure rate of apical prolapse after laparoscopic LS was 87.5%, and after laparoscopic SCP was 100%. Laparoscopic LS, as a procedure with a low-risk of complications and short-term objective outcomes, may be an alternative to laparoscopic SCP (16). In our study, both techniques demonstrated similar effectiveness and short-term success. Our finding that LS was associated with shorter operative time and higher 12-month success rate is fully consistent with the literature. While some literature favors SCP for apical support, the findings of the present study suggest that LS does not compromise anatomical success despite its technical simplicity. While SCP remains a robust technique for advanced prolapse, LS offers a shorter operative duration and comparable short-term objective success. Given its shorter learning curve and equivalent efficacy at 1 year, LS should be considered a first-line minimally invasive option, particularly in surgical settings where reducing anesthesia time and technical complexity is prioritized. LS is a strong, reliable, and minimally invasive alternative to SCP, with its advantages in learning curve and operative time.

Comparing abdominal SCP and abdominal LS, apical prolapse repair rates were 94% and 92%, respectively, with both being equally effective at 12-month follow-up for severe apical prolapse (17). Anatomical success rates of 81.8% for SCP and 90% for LS were reported in a series of 93 patients; the treatments were considered equally effective (18). In our cohort, two patients in the SCP group and three patients in the LS group developed stage 3–4 prolapse at 12 months postoperatively, underscoring comparable success between the groups in managing advanced apical prolapse. The success rates in the literature parallel our low recurrence counts: 2 patients in SCP and 3 patients in LS. The primary finding is that the minimally invasive nature of LS does not compromise anatomical success. Since both techniques show similar efficacy in advanced apical prolapse, the choice should be based on logistical considerations and safety, rather than on success rates. The choice between SCP and LS may be guided more by surgical logistics and perioperative safety profiles than by differences in anatomical success, as both procedures offer high efficacy for long-term management of prolapse.

Pelvic dissection, particularly in the presacral region, carries inherent risks due to the proximity of critical structures. Previous studies report a 1.0% risk of ureteral injury and a 4.4% risk of vascular damage during pelvic surgery, with complications potentially exacerbated by anatomical variations, such as the more medial course of the left iliac vessels (19). Consistent with this, in our SCP cohort, vascular and ureteral injuries occurred in 4.1% of patients, highlighting the inherent intraoperative risks of the open approach. Wound-related complications, including surgical site infections and intra-abdominal abscesses, are also well-documented, with reported rates ranging from 2–12.5% for infections and 8% for abscesses (20). Bladder injury appears less common; a meta-analysis found no significant difference in bladder perforation rates between obese and non-obese patients undergoing SCP (21), and similarly, no bladder perforation was observed in non-obese women in our series. Surgical wound infection rates are

typically lower with laparoscopy because tissue damage is reduced and immune function is preserved (22). Our findings corroborate this, as the laparoscopic LS group demonstrated lower surgical site infection rates than SCP, supporting the advantages of minimally invasive techniques. Beyond surgical technique, patient-related factors also influence POP outcomes. Hormonal changes in menopause reduce estrogen levels, which, in turn, alter the collagen content and compromise pelvic tissue strength (23). Additionally, comorbidities such as diabetes mellitus and hypertension contribute to POP pathogenesis (24). In our study, a similar prevalence of these comorbidities in both groups suggests that the observed differences in complications were largely attributable to the surgical approach rather than to patient baseline characteristics. Overall, these findings emphasize the importance of surgical technique in minimizing perioperative complications and highlight the role of patient factors in POP management. Laparoscopic LS appears to offer a safer perioperative profile without compromising anatomical outcomes, particularly in patients with comparable comorbidity profiles.

Laparoscopic LS provides a safer perioperative profile than L-SCP, with lower rates of surgical site infections and major vascular or ureteral injuries. Both techniques achieve comparable 12-month anatomical success, making LS a highly effective and less invasive alternative for POP management. While LS is technically less demanding, it carries a distinct complication profile, including a higher risk of bladder injury and mesh-related inflammatory reactions, whereas SCP carries inherent risks of vascular and ureteral injury. The lower infection rates with LS and a similar distribution of comorbidities suggest that these outcomes primarily reflect the surgical approach rather than patient-related factors.

Study Limitations

This study has several important limitations. Its retrospective design and relatively small sample size restrict causal inference and the generalizability of the findings. The comparison of an open surgical approach (L-SCP) with a minimally invasive technique (laparoscopic LS) introduces potential confounding related to surgical access, rather than to the suspension method itself. Additionally, the limited number of experienced surgeons performing laparoscopic SCP at our center necessitated using different surgical approaches for the various suspension techniques, which represents a notable limitation. Preoperative hemoglobin levels differed significantly between groups; however, perioperative hemoglobin changes were analyzed without adjustment. This factor should be considered when interpreting the results and acknowledged as a limitation of the study.

Conclusion

In this retrospective cohort study, L-SCP and laparoscopic LS demonstrated comparable short-term anatomical outcomes and recurrence rates for POP surgery. L-SCP was associated with longer operative time and higher infectious morbidity, whereas laparoscopic LS showed a different complication profile, including mesh-related events. Given the methodological limitations and differences in surgical approach, no definitive superiority can be inferred. Surgical technique selection should, therefore, be individualized based on patient characteristics, disease severity, and the surgeon's experience. Prospective, approach-matched studies are needed to further clarify comparative effectiveness.

Ethics

Ethics Committee Approval: The study protocol was approved by the Scientific Research Ethics Committee of Giresun Training and Research Hospital (decision number: 30.10.2024/04, dated: 04.11.2024).

Informed Consent: Retrospective cohort study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.T., S.K., Ö.T., Concept: D.T., S.O.T., Design: D.T., S.K., Data Collection or Processing: D.T., S.O.T., Ö.T., Analysis or Interpretation: D.T., S.K., Literature Search: D.T., S.O.T., Ö.T., Writing: D.T., S.O.T., Ö.T.

Conflict of Interest: No conflict of interest was declared by the author(s).

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Analyzing COVID-19 Deaths by Weekday: A Four-Year Statistical Review (2020–2023)

Haftanın Günlerine Göre COVID-19 Ölümlerinin Analizi: Dört Yıllık İstatistiksel Bir İnceleme (2020–2023)

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ABSTRACT

Background: Earlier studies have suggested that the mortality rate of Coronavirus Disease-2019 (COVID-19) may vary by day of the week, possibly due to variations in healthcare system workflows or reporting delays. This study aimed to assess whether such day-of-week effects exist in COVID-19 death data from 2020 to 2023 in the United States.

Materials and Methods: We extracted nationwide United States COVID-19 mortality data from the Centers for Disease Control and Prevention WONDER database, grouping deaths by weekday for each year from 2020 to 2023. Negative binomial regression and Tukey's Honest Significant Difference test were used to assess differences in daily death counts. Additional comparisons were made between aggregated weekday (Monday–Friday) and weekend (Saturday–Sunday) totals.

Results: No statistically significant differences were observed in the number of deaths across individual weekdays in any year analyzed (p = 0.905 for all years combined). Post-hoc testing confirmed that all pairwise comparisons between weekdays were non-significant. Sub-analyses of early (2020–2021) and late (2022–2023) pandemic periods also showed no significant variation (all p-values >0.05). The average number of deaths was slightly higher on weekdays throughout the study period in the weekday-versus-weekend analysis; however, the combined difference did not reach statistical significance (p = 0.947).

Conclusion: Official COVID-19 mortality data from 2020 to 2023 in the United States show no evidence of a "weekend effect," indicating that the day of the week did not significantly influence reported deaths.

Keywords: Coronavirus Disease-2019, COVID-19, SARS-COV-2, mortality, weekend effect

ÖZ

Amaç: Önceki çalışmalar, Koronavirüs Hastalığı-2019 (COVID-19) mortalitesinin haftanın günlerine göre değişebileceğini; bunun da sağlık sistemi iş akışları veya bildirim gecikmelerinden kaynaklanabileceğini öne sürmüştür. Bu çalışmanın amacı, 2020–2023 yılları arasında Amerika Birleşik Devletleri'ne ait COVID-19 ölüm verilerinde haftanın gününe bağlı bir etkinin olup olmadığını değerlendirmektir.

Gereç ve Yöntemler: Amerika Birleşik Devletleri genelindeki COVID-19 mortalite verileri Hastalık Kontrol ve Önleme Merkezleri WONDER veri tabanından elde edilmiş ve 2020–2023 yıllarının her biri için ölümler haftanın günlerine göre gruplandırılmıştır. Günlük ölüm sayılarındaki farklılıkları değerlendirmek için negatif binom regresyonu ve Tukey'nin Dürüstçe Anlamlı Fark testi kullanıldı. Ayrıca, hafta içi (Pazartesi–Cuma) ve hafta sonu (Cumartesi–Pazar) toplamları arasında karşılaştırmalar yapılmıştır.

Bulgular: İncelenen hiçbir yılda haftanın bireysel günleri arasında ölüm sayıları açısından istatistiksel olarak anlamlı bir fark saptanmamıştır [tüm yıllar birleştirildiğinde (p = 0,905)]. Post-hoc analizler, haftanın günleri arasındaki tüm ikili karşılaştırmaların anlamsız olduğunu doğrulamıştır. Pandeminin erken (2020–2021) ve geç (2022–2023) dönemlerine yönelik alt analizlerde de anlamlı bir değişkenlik gözlenmemiştir (tüm p-değerleri >0,05). Hafta içi–hafta sonu karşılaştırmasında, çalışma dönemi boyunca ortalama ölüm sayılarının hafta içi günlerde hafif düzeyde daha yüksek olduğu gözlenmiş; ancak toplam fark istatistiksel anlamlılığa ulaşmamıştır (p = 0,947).

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ÖZ

Sonuç: Amerika Birleşik Devletleri'nde 2020–2023 yıllarına ait resmi COVID-19 mortalite verileri, haftanın gününe bağlı bir "hafta sonu etkisi" olduğuna dair kanıt sunmamaktadır. Bu bulgular, bildirilen ölüm sayılarının haftanın günlerinden anlamlı düzeyde etkilenmediğini göstermektedir.

Anahtar Kelimeler: Koronavirüs Hastalığı-2019, COVID-19, SARS-CoV-2, mortalitesi, hafta sonu etkisi

Introduction

Understanding the temporal distribution of mortality due to Coronavirus Disease-2019 (COVID-19) is critical for effective public health planning and response (1). Epidemiologists and health authorities have relied extensively on mortality data to track disease progression, allocate healthcare resources, and evaluate the impact of interventions such as vaccination campaigns and preventive (even restrictive) measures (2). However, fluctuations in reported deaths are shaped not only by the biological course of COVID-19 but also by administrative practices and the timing of data collection and reporting. Consequently, determining whether observed trends in mortality reflect genuine epidemiological patterns or are artifacts of reporting and operational cycles is essential (3).

The influence of the day of the week on reported COVID-19 deaths is a frequently examined aspect. Although viral transmission is not expected to follow a weekly rhythm, healthcare and reporting systems often do. Many hospitals and public health institutions operate on weekends with reduced staffing levels, which can delay diagnoses and treatments and potentially increase mortality rates. This operational pattern has been associated with the so-called "weekend effect"—a phenomenon where patients admitted during weekends experience worse outcomes, potentially due to limited access to specialized care, diagnostics, or senior medical staff. In 2018, Honeyford et al. (4) published a meta-analysis encompassing 39 studies and 57 separate analyses and found a 7% increased risk of death for weekend admissions (odds ratio [OR]: 1.07; 95% confidence interval [CI]: 1.03–1.12). Similarly, a subsequent meta-analysis by Chen et al. (5) in 2019, which included 68 studies and over 640 million hospital admissions, reported an even greater weekend-associated mortality risk of 16% (OR: 1.16; 95% CI: 1.10–1.23), with the highest effect observed among patients undergoing elective surgical procedures (OR: 1.70; 95% CI: 1.08–2.52)

In the context of COVID-19, care-seeking behavior delays during weekends could intensify disease outcomes, contributing to variations in mortality data. Evaluating whether such temporal effects are observable at a population level can offer insights for optimizing healthcare delivery and preparedness in future pandemics. Accordingly, this study aimed to assess whether statistically significant differences exist in the number of reported COVID-19 deaths by day of the week, including distinctions between weekdays and weekends, in the United States between 2020 and 2023.

Materials and Methods

Mortality data for COVID-19 were obtained from the United States Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. National Vital Statistics System, Mortality 2018–2023 on CDC Wide-Ranging, Online Data for Epidemiologic Research Online Database, released in 2024 (6). These data were extracted from the latest available Multiple Cause of Death Files at the time of our search (years 2018–2023), as compiled from records provided by 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Data extraction was performed on June 20, 2025. The search criteria used for this analysis included selecting the "Multiple Cause of Death, 1999–2023" database and filtering for the underlying cause of death coded as U07.1, which corresponds to COVID-19. The data were grouped by year and weekday to capture the total number of deaths recorded on each day of the week—Monday through Sunday—for 2020, 2021, 2022, and 2023. No age adjustment or demographic stratification was applied because such variables are not available in the dataset when mortality data are grouped by day of the week. The extracted results provided the raw death counts.

To evaluate differences in the total number of deaths across individual weekdays, a negative binomial regression was conducted for each year, after normality was verified using the Shapiro–Wilk test. Tukey's Honest Significant Difference (HSD) test was used as a post-hoc method to assess pairwise differences between all weekday combinations. Separate negative binomial regression and Tukey HSD tests were performed to compare aggregate weekday (Monday through Friday) and weekend (Saturday and Sunday) data, assessing broader temporal patterns.

Statistical Analysis

All statistical analyses were performed using the scipy.stats and statsmodels libraries in Python version 3.11 (Python Software Foundation, Wilmington, United States of America). Because the CDC WONDER is a publicly available,

anonymized, and freely searchable database, this study was exempt from approval by the ethics committee.

Results

Table 1 summarizes the total number of COVID-19 deaths recorded on each day of the week across the first four pandemic years. Visual inspection suggests relatively consistent totals across weekdays in each year. No obvious or systematic peak or flex is apparent on any specific day, even in years with higher overall deaths (e.g., 2020 and 2021). Although there was a slight trend toward reduced death counts on weekends (Saturday and Sunday), this pattern was neither pronounced nor consistent across years.

Figure 1 shows an improved visualization of data, showing the proportion of weekday deaths relative to the total weekly deaths for each year, expressed as percentages.

A negative binomial regression was applied to weekday totals for each year to assess whether any day of the week was significantly associated with different death totals compared to others, yielding a p-value of 0.905. Although the negative binomial regression did not reveal significant differences, the Tukey's honestly significant difference test was performed to explore potential pairwise differences between individual weekdays. The test results confirmed that none of the day-to-day comparisons were statistically significant, as all pairwise comparisons yielded adjusted p-values well above the threshold of 0.05, and no confidence intervals for mean differences were excluded. The largest observed mean difference (e.g., between Fridays and Sundays) was not statistically significant. Notably a sub-analysis with negative binomial regression limited to weekly data on a monthly basis of the individual pandemic years also yielded non-statistically significant differences across the different days of the week, as follows: 2020: p = 1.000; 2021: p = 1.000; 2022: p = 1.000; and 2023: p = 1.000.

To explore broader temporal contrasts, in a secondary analysis, total deaths were averaged across weekdays (Monday through Friday) and weekends (Saturday and Sunday) (Table 2).

The data revealed that weekdays were generally associated with slightly higher average deaths in all years. However, these differences were minimal and non-statistically significant, as confirmed by the negative binomial regression comparing the two groups across the four-year period, which again yielded a non-statistically significant difference (p = 0.947).

A negative binomial regression limited to monthly data for the individual pandemic years also yielded a non-statistically significant difference between weekdays and weekends, as follows: 2020: p = 0.895; 2021: p = 0.937; 2022: p = 0.986; and 2023: p = 0.985. Figure 2 shows a visual comparison of annual death counts on weekdays and weekends, expressed as percentages of the weekly total deaths.

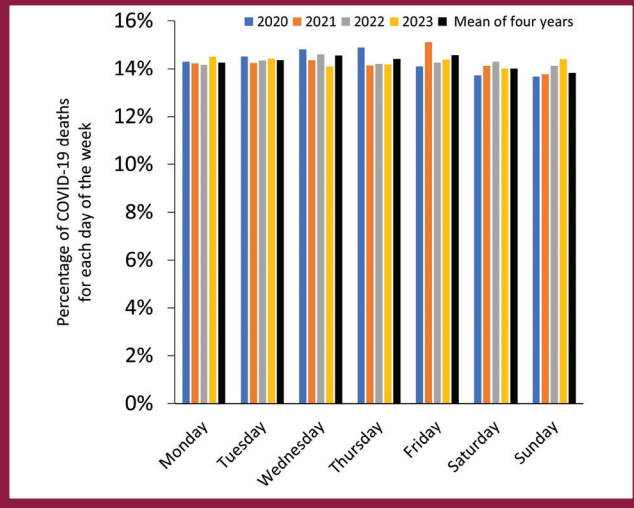

Figure 1. Deaths due to COVID-19 (% of all weekly deaths) recorded on each day of the week across the first four pandemic years in the United States.
COVID-19, Coronavirus Disease-2019.

Table 1. Total number of deaths from COVID-19 recorded on each day of the week across the first four years of the pandemic in the United States.

Year	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
2020	50,156	50,922	51,973	52,255	49,476	48,127	47,922
2021	59,353	59,359	59,890	58,928	62,998	58,922	57,441
2022	26,433	26,760	27,244	26,512	26,590	26,668	26,345
2023	7,239	7,203	7,041	7,083	7,183	6,995	7,188
Total	143,181	144,244	146,148	144,778	146,247	140,712	138,896

COVID-19, Coronavirus Disease-2019.

Table 2. Sum of annual averages of deaths for COVID-19 weekdays (Monday through Friday) and weekends (Saturday and Sunday).

Year	Weekdays (average)	Weekends (average)
2020	50,956	48,024
2021	60,106	58,182
2022	26,708	26,507
2023	7,150	7,092
Total	144,920	139,804

COVID-19, Coronavirus Disease-2019.

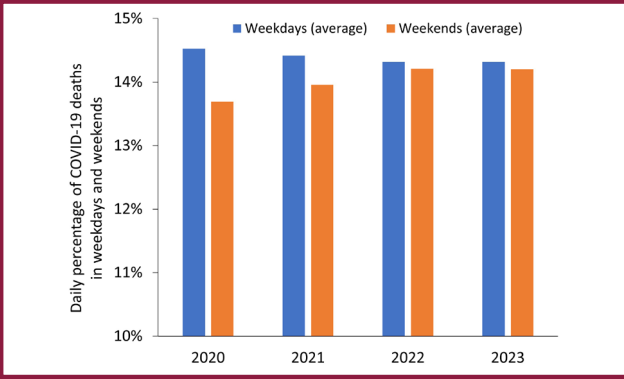

Figure 2. Deaths due to COVID-19 (% of all weekly deaths) recorded during weekdays or weekends across the first four pandemic years in the United States.
COVID-19, Coronavirus Disease-2019.

Discussion

The results of our study, encompassing both a detailed weekday-level analysis and a comparative assessment between weekdays and weekends, reveal no statistically significant differences in the total number of COVID-19 deaths by day of the week across the analyzed pandemic years (2020–2023). These findings suggest that the temporal pattern of COVID-19 mortality has remained consistent across weekdays and weekends in the United States across the first four years of the pandemic despite potential variations in healthcare resource availability, institutional workflows, or potential reporting delays. This consistency supports the hypothesis that the day of the week may not have a meaningful impact on the mortality rates of COVID-19 patients.

Our results do not align with those reported by Manzoor and Redelmeier (7), who analyzed COVID-19 mortality data from the World Health Organization database across 10 countries between March 7, 2020, and March 7, 2022. Their analysis identified a modest but significantly higher average daily death count on weekends (Saturdays and Sundays) than on weekdays (8,532 vs. 8,083; $p < 0.001$), corresponding to an approximately 6% relative increase. The largest absolute differences were observed in the United States (+22%) and Brazil (+29%), with such a "weekend effect" persisting throughout various pandemic phases. Consistent with these findings, Aly surveyed COVID-19-related deaths in the United States using Worldometer data from March to October 2020 (8) and found that weekends (Saturdays and Sundays) were associated with lower COVID-19 mortality than the rest of the week ($Z = 3.527$, $p = 0.0004$). However, these findings are challenged by data published by Bergman et al. (9), who demonstrated that the reporting artifacts in several studies may have substantially influenced the apparent oscillations in United States COVID-19 mortality. In their analysis, the "weekend effect" disappeared when COVID-19 death data were organized by episode rather than by report date, thus confirming the potential influence of uncontrolled confounding factors on the epidemiology of COVID-19 (10). An additional retrospective observational study by González-Gancedo et al. (11) investigated nearly 2,000 patients with COVID-19 admitted to the emergency departments of a private Spanish hospital network between February and April 2020. Although this study reported a significant association between the day of admission and survival—indicating lower survival rates for patients admitted on weekends—the authors defined the weekend as Friday, which is not considered a weekend day. Consequently, their findings are not directly comparable to those of other studies because the definition of "weekend" was different.

Conclusion

This nationwide analysis of COVID-19 mortality data from 2020 to 2023 in the United States reveals no statistically significant differences in death counts by day of the week or between weekdays and weekends. Despite prior studies suggesting a "weekend effect," our findings indicate a consistent mortality pattern across weekdays and weekends, even during peak pandemic periods. These results support the interpretation that temporal fluctuations in reported deaths are not indicative of systematic disparities in care or outcome but are more likely attributable to logistics of reporting. Our work aligns with prior analyses that identified reporting artifacts as important drivers of perceived variation in mortality, underscoring the importance of methodological rigor in epidemiological surveillance. When evaluating temporal patterns in health outcomes, future analyses should prioritize episode-based datasets and carefully account for administrative confounders.

Ethics

Ethics Committee Approval: Ethical approval was not required due to the use of publicly available web resources.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: G.L., C.M., Design: G.L., Data Collection or Processing: G.L., Analysis or Interpretation: G.L., C.M., Literature Search: G.L., Writing: G.L., C.M.

Conflict of Interest: No conflict of interest was declared by the author(s).

Financial Disclosure: The author(s) declared that this study received no financial support.

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ORIGINAL ARTICLE

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Relationship of Periapical and Periodontal Pathologies of Maxillary First Molars with Maxillary Sinus Membrane Thickness: A Retrospective CBCT Analysis

Maksiller Birinci Molarların Periapikal ve Periodontal Patolojilerinin Maksiller Sinüs Membran Kalınlığı ile İlişkisi: Retrospektif Bir KIBT Analizi

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ABSTRACT

Background: This study aimed to assess the association between periapical lesions (PLs), periodontal bone loss (PBL), and maxillary sinus mucosal thickness (SMT) in the maxillary first molar (M1) region using cone-beam computed tomography (CBCT).

Materials and Methods: In this retrospective cross-sectional study, 240 maxillary sinuses adjacent to the M1 were examined using CBCT images from 140 patients (mean age: 32.62 ± 12.22 years). SMT values were measured perpendicular to the sinus floor, with values exceeding 2 mm defined as pathological. PL size, PL-sinus distance, and PBL severity were categorized according to CBCT-based criteria. Statistical analysis was performed using non-parametric tests, and intra-observer reliability was evaluated using the intraclass correlation coefficient (ICC).

Results: Statistical analysis revealed excellent measurement reliability (ICC: 0.96). While gender had no significant impact on SMT ($p > 0.05$), increased SMT was clearly correlated with odontogenic pathologies, specifically PL and advanced PBL associated with the M1. This association was observed to intensify when lesions were closer to the sinus floor or directly affected its integrity.

Conclusion: CBCT findings demonstrate an association between periapical and periodontal pathologies in the M1 region and maxillary sinus mucosal thickening, supporting odontogenic effects on the Schneiderian membrane. A detailed CBCT evaluation of the relationship between dental pathologies and the maxillary sinus may enhance the accuracy of radiological diagnosis and contribute to improved clinical decision-making and appropriate referral planning.

Keywords: Cone-beam computed tomography, maxillary sinus, sinus mucosal thickness

ÖZ

Amaç: Bu çalışmanın amacı; maksiller birinci molarlara (M1) komşu periapikal lezyonlar (PL) ve periodontal kemik kaybı (PK) ile maksiller sinüs mukoza kalınlığı (SMK) arasındaki ilişkinin konik ışınlı bilgisayarlı tomografi (KIBT) aracılığıyla değerlendirilmesidir.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışma kapsamında 140 hastanın (yaş ortalaması: 32,62 ± 12,22) KIBT görüntüleri üzerinden M1 komşuluğundaki 240 maksiller sinüs incelendi. Sinüs tabanına dik ölçülen SMK değerlerinde 2 mm eşik kabul edilerek üzerindeki ölçümler patolojik olarak tanımlanmıştır. PL boyutu, PL-sinüs mesafesi ve PK şiddeti KIBT kriterlerine göre sınıflandırılırken, verilerin analizinde parametrik olmayan testler ve gözlemci içi güvenilirlik için ICC analizi kullanıldı.

Bulgular: Ölçüm güvenilirliği mükemmel düzeydeydi (ICC: 0,96). Cinsiyetin SMK üzerinde anlamlı bir etkisi saptanmazken ($p > 0,05$), artmış SMK'nin M1 kaynaklı PL'ler ve ileri derece PK ile korelasyon gösterdiği belirlenmiştir. Özellikle sinüs tabanı ile doğrudan temas kuran veya tabanı etkileyen lezyonlarda bu patolojik ilişkinin şiddetlendiği saptandı.

Sonuç: Bu KIBT bulguları, M1 bölgesindeki periapikal ve periodontal patolojiler ile maksiller sinüs mukozal kalınlığı arasındaki ilişkiyi açıkça ortaya koymakta ve Schneiderian membranı üzerindeki odontojenik etkileri desteklemektedir. Dental patolojiler ile maksiller sinüs arasındaki ilişkinin KIBT ile ayrıntılı değerlendirilmesi, radyolojik tanının doğruluğunu artırarak klinik karar verme sürecine ve uygun sevk planlamasına katkı sağlayabilir.

Anahtar Kelimeler: Konik ışınlı bilgisayarlı tomografi, maksiller sinüs, sinüs mukozal kalınlığı

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Introduction

Because of the well-known anatomical proximity between the root apices of maxillary posterior teeth and the maxillary sinus floor, odontogenic infections originating from these teeth may directly affect the Schneiderian membrane and contribute to inflammatory changes within the sinus cavity, potentially leading to odontogenic maxillary sinusitis (1,2). This anatomical relationship is of particular clinical importance in the maxillary first molar (M1) region, where the distance between the root apices and the sinus floor is often minimal (1,2). Several odontogenic factors, most notably periapical lesions (PLs) and advanced periodontal bone loss (PBL), have been associated with maxillary sinus mucosal thickening, while deep carious lesions and inadequate endodontic treatment may further contribute to this process (1-3). Chronic inflammatory conditions of odontogenic origin are thought to induce reactive changes in the Schneiderian membrane, which may range from mild mucosal thickening to clinically relevant sinus pathology (3-5).

Conventional two-dimensional imaging techniques, including periapical and panoramic radiographs, are limited by anatomical superimposition, magnification, and geometric distortion, which may obscure the true extent of periapical pathology and hinder accurate assessment of the spatial relationship between odontogenic lesions and the maxillary sinus (2,6). Cone-beam computed tomography (CBCT), however, allows three-dimensional and multiplanar visualization of dental structures, alveolar bone, and the maxillary sinus with high spatial resolution, making it particularly suitable for evaluating odontogenic sinus involvement and lesion-sinus relationships (7-9). For this reason, CBCT has increasingly been adopted as the imaging modality of choice in the assessment of odontogenic maxillary sinus pathology (4,10).

Several CBCT-based investigations have demonstrated an association between apical periodontitis and increased maxillary sinus mucosal thickness (SMT), reporting a significantly higher prevalence of mucosal thickening in teeth affected by PL compared with healthy teeth (1,2,8). In addition, periodontal disease involving maxillary posterior teeth has been shown to influence sinus mucosal health, supporting the concept that both endodontic and periodontal inflammatory processes may affect the maxillary sinus (3,11). Nevertheless, comparisons between studies remain challenging because lesion size thresholds, definitions of mucosal thickening, and criteria used to describe lesion-sinus relationships are not uniform across the literature (7). While many studies have primarily focused on the presence or absence of periapical pathology, fewer investigations have evaluated PL size, lesion–sinus spatial relationship, severity of PBL, and SMT simultaneously using standardized classification systems within a single analytical model (8). This limitation is particularly relevant for M1, whose anatomical characteristics predispose them to odontogenic sinus involvement and whose pathological conditions may therefore have a greater impact on sinus health (1,2).

Recent studies suggest that larger PL, particularly those in direct contact with or extending into the maxillary sinus floor, are associated with more marked mucosal thickening and an increased risk of odontogenic maxillary sinusitis (12). Findings from meta-analyses and contemporary CBCT-based studies further highlight the significant role of odontogenic factors in the development of maxillary sinus pathology and emphasize the importance of thorough radiological evaluation in affected individuals (6,13).

Although numerous studies have investigated the relationship between periapical pathologies and maxillary sinus mucosal thickening, a substantial proportion of these studies did not simultaneously evaluate PL size, the distance between the lesion and the sinus floor, PBL, and SMT using detailed, standardized classification systems. Accordingly, this study aims to clarify the role of odontogenic factors in sinus pathology and to support more-informed clinical decision-making in dental and maxillofacial practice by analyzing PL characteristics, PBL severity, and SMT.

Materials and Methods

Study Design and Sample Selection

The patient sample was obtained from the archives of the Department of Oral and Dentomaxillofacial Radiology, Faculty of Dentistry, Erzincan Binali Yıldırım University. CBCT images of patients acquired between January 2025 and October 2025 were included. These scans had originally been taken for routine clinical purposes, including evaluation of impacted teeth, orthodontic treatment planning, and implant assessment. The study included CBCT scans of individuals aged 18 years and older who had a clearly visible maxillary sinus floor and Schneiderian membrane adjacent to at least one M1. We excluded scans indicating a history of regional surgery (such as maxillary sinus surgery or root resections), trauma, or incomplete root development. Additionally, cases involving fixed prosthetics, extensive artifacts, or poor diagnostic quality were excluded from the analysis.

Acquisition of CBCT Images

All CBCT images were acquired using the PlanMeca ProMax® 3D Classic CBCT, with 0.2 mm section thickness, operating parameters of 90 kVp and 6.3 mA, an 8 x 8 cm

field of view, a 12.1-second acquisition time, and a voxel size of 200 µm. Image analysis was performed with Romexis 6.2.1 (R® software, Planmeca, Helsinki, Finland) on a 24-inch Dell LCD screen (Dell, TX, USA) with a resolution of 1920 × 1080 pixels.

Assessment of CBCT Images

This retrospective study analyzed CBCT scans to evaluate the relationship between the M1 and the adjacent Schneiderian membrane. The study focused exclusively on the M1 region due to its anatomical significance and high frequency of sinus floor involvement (12). Thickening of the maxillary sinus mucosa was measured along the long axis of M1, perpendicular to the maxillary sinus floor, using the measuring tool in Romexis software. The presence of mucosal thickening on the floor of the maxillary sinus was evaluated on coronal and sagittal CBCT images. The membrane was classified as "thickened" if its thickness exceeded 2 mm. In accordance with the comprehensive review by Psillas et al. (6) and the CBCT-based analysis by Capelli and Gatti (14), maxillary SMT greater than 2 mm was considered indicative of pathologic SMT. This measurement was taken from the sinus floor immediately superior to the M1 root apices, extending to the highest point of the mucosa. PL-sinus floor relationships were classified as follows: lesions distant from the sinus floor, lesions in contact with the sinus floor, and lesions penetrating the sinus floor (Figure 1).

For each category, the prevalence of sinus mucosal thickening ⩾2 mm was calculated and expressed as frequencies and percentages. PL size was assessed on CBCT images by measuring the maximum linear diameter of each lesion on the section in which it appeared largest. Lesion size thresholds were based on the CBCT-periapical index (CBCT-PAI) system described by Estrela et al. (15) and defined according to the maximum linear diameter of the lesion measured in millimeters on CBCT images. For exploratory analyses, CBCT-PAI scores were collapsed into three categories: small (⩽2 mm), medium (>2-⩽4 mm), and large (>4 mm) (15). PBL was evaluated on sagittal images by measuring the mesial and distal alveolar bone levels of maxillary first molars and expressing the loss as a percentage of the normal periodontal bone height. Normal periodontal bone height was defined as the distance from the physiologic bone level, located 2 mm apical to the cemento-enamel junction, to the root apex. PBL was classified as severe when >50% bone loss was present at any tooth surface, moderate when 25%-50% bone loss was observed, and normal to mild when bone loss was <25% (16). All SMT measurements were performed by a single observer (M.A.), an oral and maxillofacial radiologist with 3 years of clinical experience. To assess intra-observer reliability, all measurements were repeated by the same observer at two time points, with a minimum interval of two weeks between sessions.

Ethical Approval

This retrospective, cross-sectional study was conducted in compliance with the ethical standards of the Declaration of Helsinki (1964, and subsequent revisions) and was approved by the Non-Invasive Clinical Research Ethics Committee of Erzincan Binali Yıldırım University (decision number: 2025-18/04, date: 25.12.2025). Informed consent was waived by the Ethics Committee due to the retrospective design of the study.

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation, median, and minimum–maximum values for continuous variables, and as frequencies and percentages for categorical variables. Continuous variables were tested for normality using the Shapiro-Wilk test and were found to be non-normally distributed; non-parametric tests were applied. Comparisons of SMT between two independent groups were performed using the Mann-Whitney U test, while comparisons among more than two groups were

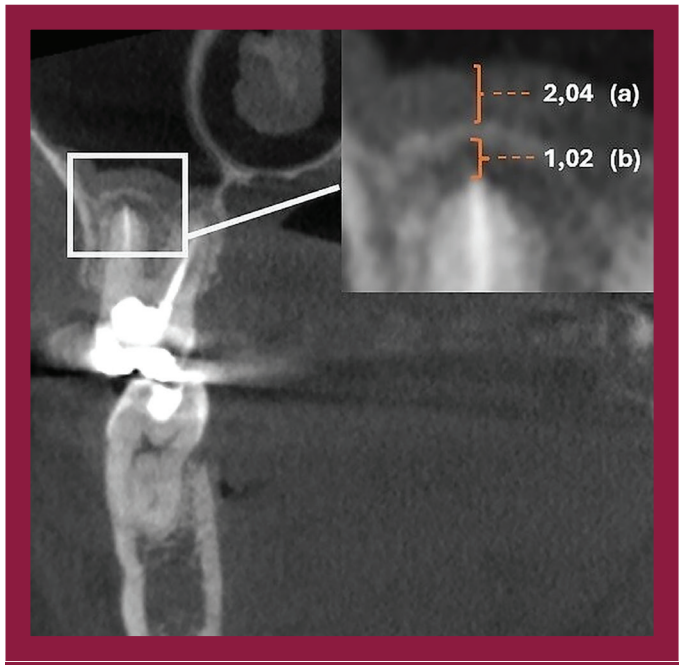

Figure 1. Representative CBCT images demonstrating sinus mucosal thickening associated with odontogenic factors. (a) Coronal CBCT section showing increased maxillary SMT adjacent to a maxillary first molar with periapical pathology, (b) sagittal CBCT image illustrating localized sinus mucosal thickening related to a root canal–treated maxillary first molar. CBCT, cone-beam computed tomography; SMT, sinus mucosal thickness.

conducted using the Kruskal-Wallis test with Bonferroni correction for post-hoc analyses. Associations between categorical variables were assessed using the chi-square test. Correlations between age and SMT were evaluated using Spearman's rank correlation coefficient. The agreement between repeated measurements was evaluated using the intraclass correlation coefficient (ICC). All analyses were performed in IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) with a significance level of $p < 0.05$. Although no a priori sample size calculation was performed given the retrospective design, a post-hoc power analysis confirmed that the study achieved adequate statistical power (>80%) for the primary comparisons (α: 0.05).

Results

A total of 140 patients met the inclusion criteria, (70 females, 70 males) with a mean age of 32.62 ± 12.22 years (females: 32.16 ± 11.73; males: 33.09 ± 12.77). Because maxillary molars were present unilaterally in some patients, a total of 240 maxillary sinuses were evaluated. Intra-class correlation coefficient analysis demonstrated excellent agreement between repeated measurements, with an ICC of 0.96, indicating high measurement reproducibility. There was no statistically significant difference in SMT between genders (male: 1.48 ± 2.00 mm; female: 1.65 ± 2.47 mm; $p = 0.742$). Clinical status of the 240 evaluated M1s, 145 (60.4%) were clinically normal, 48 (20.0%) were endodontically treated, and 47 (19.6%) were carious. The prevalence of PL was 23.8% (n = 57), and that of PBL was 19.2% (n = 46). A progressive increase in SMT was observed with increasing PL size. Teeth without PLs had minimal mucosal thickness, whereas teeth with small, medium, and large PLs had progressively higher median mucosal thickness. Differences among lesion size categories were statistically significant (Kruskal-Wallis test, $p < 0.001$; Table 1). The proximity of PLs to the sinus floor significantly increased the prevalence of SMT ≥2 mm (chi-square test, $p < 0.001$) (Table 2).

While the prevalence was 18.6% in sinuses without lesions, it increased markedly to 79.5-83.3% in sinuses with lesions, regardless of their specific relationship (distant, contacting, or penetrating) to the sinus floor. When PBL severity was analyzed, SMT differed significantly among the three categories (<25%, 25-50%, and >50% bone loss) (Kruskal-Wallis, $p = 0.008$) (Figure 2).

Sinuses associated with severe PBL (>50%) showed the greatest mucosal thickness (median: 3.86 mm), whereas those with mild bone loss (<25%) showed relatively limited mucosal changes. Furthermore, the prevalence of SMT >2 mm increased progressively with PBL severity (33.3%, 58.8%, and 86.7%, respectively), and this trend was statistically significant (chi-square test, $p < 0.001$).

Discussion

The present study utilized CBCT imaging to investigate the influence of periodontal and periapical conditions of M1 on SMT. The measurements demonstrated excellent reproducibility with an ICC of 0.96, underscoring the high reliability of the radiographic assessments. In our study, no statistically significant effect of gender on SMT was found ($p = 0.742$). These findings are consistent with Janner et al. (17), who suggested that gender is not a determining factor for mucosal thickness. However, this contrasts with other studies, such as those by Phothikhun et al. (16) and Shanbhag et al. (1), which reported a higher prevalence of mucosal thickening in males. A notable outcome of this investigation is the substantial influence of PL on SMT. We observed a significant contrast in pathological mucosal thickening (>2 mm): 18.6% in teeth without lesions versus more than 80% in those with lesions ($p < 0.001$). These observations corroborate the findings of Lu et al. (2) and Shanbhag et

Table 1. Comparison of maxillary sinus mucosal thickness according to periapical lesion size.

Periapical lesion size	Teeth (n)	Median mucosal thickness (IQR), mm	p-value
No periapical lesion	183	0.00 (0.00-1.46)	0.000..*
Small lesion	24	2.41 (1.88-3.12)	
Medium lesion	21	2.95 (2.26-3.81)	
Large lesion	12	3.88 (2.94-6.21)	

*Kruskal-Wallis test, $p < 0.001$. IQR, interquartile range.

Table 2. Prevalence of maxillary sinus mucosal thickening (≥2 mm)according to the proximity of periapical lesions to the sinus floor.

Lesion–sinus floor relationship	Teeth (n)	Mucosal thickness ≥2 mm, n (%)	p-value
No periapical lesion	183	34 (18.6)	0.000..*
Lesion distant from sinus floor	12	10 (83.3)	
Lesion contacting sinus floor	39	31 (79.5)	
Lesion penetrating sinus floor	6	5 (83.3)	

*Chi-square test, $p < 0.001$.

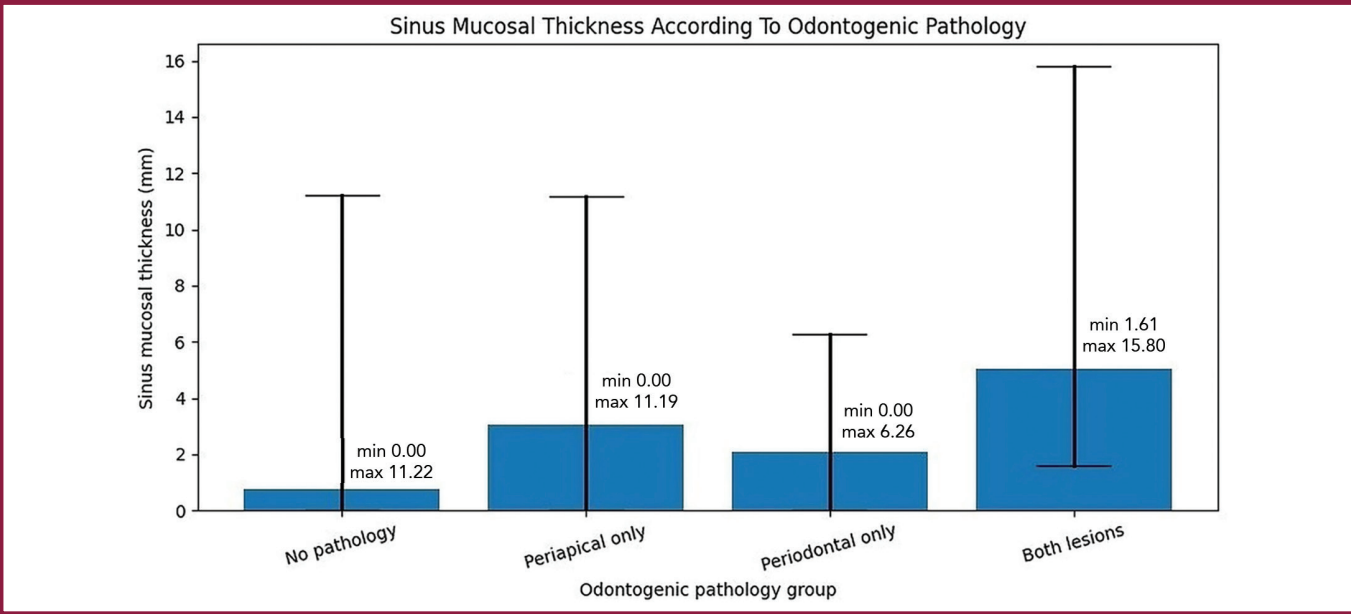

Figure 2. Sinus mucosal thickness according to odontogenic pathology. Bar chart illustrating mean sinus mucosal thickness according to odontogenic pathology. Bar heights represent mean values, while vertical whiskers with terminal caps indicate the minimum and maximum measurements for each group. (Kruskal-Wallis test, $p < 0.001$).

al. (1). Lu et al. (2), for instance, demonstrated that the prevalence of mucosal thickening rises from 41.5% to 100% in correlation with the severity of apical periodontitis. Furthermore, studies by Simuntis et al. (8) identify periapical pathology as a leading factor causing reactive hyperplasia of the sinus mucosa. Gomes et al. (18) reported that teeth exhibiting combined periodontal and periapical pathology were associated with the greatest SMT values, supporting the concept of a cumulative inflammatory burden. This observation aligns closely with our findings, in which the highest SMT values were recorded in M1 with severe PBL. We also observed a progressive increase in SMT with increasing PL ($p < 0.001$). This supports the findings of Oliveira et al. (4) and Goller-Bulut et al. (19) regarding the positive correlation between lesion volume and mucosal thickness. Our evaluation of lesion proximity revealed a significant link between lesion presence and mucosal thickening ⩾2 mm. Regardless of whether the lesions were distant from, in contact with, or penetrating the sinus floor, all groups demonstrated markedly higher rates of thickening than the control group. This finding suggests that the mere existence of periapical pathology is the dominant factor affecting the sinus mucosa, rather than its exact spatial relationship.

Phothikhun et al. (16) demonstrated a significant association between severe PBL and SMT, reporting that sinuses adjacent to teeth with advanced periodontal destruction were approximately three times more likely to exhibit mucosal thickening. Similarly, Zhang et al. (10) used CBCT to assess the periodontal condition of M1 and revealed a significant correlation between PBL and SMT; they also noted greater thickness in older age groups. Supporting this, Sheikhi et al. (11) evaluated 180 CBCT images (patients aged 13-81) and established a similar relationship, reporting that both PBL and SMT increase with age. In contrast, Çakır et al. (20) did not find a statistically significant relationship between age and SMT. Similarly, Shanbhag et al. (1), in a study involving 243 patients (485 CBCT images, aged 15-90), found no correlation between PBL and SMT, which aligns with the lack of significant associations reported by Çakır et al. (20). A statistically significant positive correlation was observed between the severity of PBL and SMT ($p < 0.001$). Our results demonstrated a progressive increase in SMT values corresponding to the extent of bone destruction. Specifically, teeth with severe bone loss (>50%) were associated with the highest mean mucosal thickness (6.11 mm) and the highest prevalence of pathological thickening (86.7%), whereas teeth with mild bone loss (<25%) showed relatively limited mucosal changes (mean: 2.02 mm). Furthermore, we observed a significant positive correlation between age and SMT (Spearman's rho: 0.33, $p < 0.001$). This indicates that mucosal thickness increases with advancing age, a finding that is compatible with the results reported by Zhang et al. (10) and Sheikhi et al. (11).

Study Limitations

This study has limitations. First, it was retrospective and performed at a single center, and only maxillary first molars were evaluated; therefore, the findings may not fully apply to other posterior teeth or to different patient groups. Second, we did not have clinical information, such as sinonasal symptoms, endoscopic findings, or microbiological results; therefore, mucosal thickening on CBCT cannot be directly interpreted as clinical sinusitis. Third, some subgroups were small (e.g., those with severe bone loss or lesions penetrating the sinus floor), which may have reduced statistical power. In addition, no a priori sample size calculation was performed. Although all eligible images were included and the post-hoc analysis demonstrated adequate statistical power (>80%), a prospectively calculated sample size would have strengthened the methodological rigor. Furthermore, statistical analyses were limited to univariate comparisons, restricting the ability to identify independent predictors of SMT in the presence of potential confounders. Finally, some patients' bilateral sinus measurements were analyzed without adjusting for within-patient correlation, which may have introduced partial non-independence into the dataset.

Conclusion

This CBCT-based study demonstrates that dental pathology adjacent to the maxillary first molar is associated with increased maxillary SMT. Both PLs and PBL were independently related to greater mucosal thickening; larger PLs and more severe bone loss were associated with proportionally greater mucosal changes. Lesions in closer proximity to the sinus floor were also associated with higher rates of SMT ⩾2 mm. Overall, careful CBCT evaluation of teeth and supporting tissues adjacent to the sinus may help avoid missed odontogenic causes and support more appropriate management.

Ethics

Ethics Committee Approval: This retrospective, cross-sectional study was conducted in compliance with the ethical standards of the Declaration of Helsinki (1964, and subsequent revisions) and was approved by the Non-Invasive Clinical Research Ethics Committee of Erzincan Binali Yıldırım University (decision number: 2025-18/04, date: 25.12.2025).

Informed Consent: Informed consent was waived by the Ethics Committee due to the retrospective design of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.O., Concept: A.O., Design: A.O., Data Collection or Processing: M.A., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: A.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Cardiopulmonary Bypass Induces Differential Neuroregenerative, Inflammatory, and Oxidative Stress Responses

Kardiyopulmoner Baypasın Nörorejeneratif, Enflamatuvar ve Oksidatif Stres Yanıtları Üzerindeki Farklılaştırıcı Etkileri

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ABSTRACT

Background: Cardiopulmonary bypass (CPB) is a fundamental technique in cardiac surgery; however, it is associated with systemic inflammation, oxidative stress, and adverse postoperative outcomes, including cognitive dysfunction. The pathophysiological mechanisms underlying these complications are not fully understood. Although both traditional and newly identified inflammatory markers have been studied, data on perioperative changes in neuronal plasticity and regeneration markers, such as growth-associated protein 43 (GAP43) and neuregulin-1 (NRG1), remain limited. This study aimed to evaluate preoperative and postoperative levels of GAP43 and NRG1 in patients undergoing CPB and to compare them with markers of oxidative stress, systemic inflammation, and neurological inflammation.

Materials and Methods: A total of 41 patients (32 males, 9 females) undergoing elective cardiac surgery with CPB were enrolled. Peripheral blood samples were collected pre- and postoperatively. Serum levels of GAP43, NRG1, brain-derived neurotrophic factor, and osteoprotegerin (OPG) were measured by enzyme-linked immunosorbent assay. Oxidative stress was assessed using total oxidant status (TOS) and total antioxidant status (TAS). Protein expression of sirtuin 2 (SIRT2) and C-X3-chemokine ligand 1 (CX3CL1) was analyzed by Western blotting. Data normality was evaluated with the Shapiro-Wilk test, and appropriate parametric or non-parametric tests were used for paired comparisons.

Results: Postoperative GAP43 levels decreased ($p < 0.05$), and the decrease was more pronounced in males. NRG1 showed no overall change but exhibited sex-specific trends, decreasing in females and increasing in males. OPG increased only in males, while TOS increased and TAS remained unchanged in both groups. Western blot analysis showed a loss of SIRT2 expression and an induction of CX3CL1.

Conclusion: CPB induces oxidative stress, neuroinflammation, and disruption of neuroregenerative processes. GAP43, a marker of neuronal plasticity, decreases postoperatively, particularly in males, whereas NRG1 shows a sex-dependent response. Combined assessment of GAP43, NRG1, and inflammatory and oxidative-stress markers may help predict postoperative neurological dysfunction and guide future protective strategies.

Keywords: Cardiopulmonary bypass, GAP43, NRG1, oxidative stress, neuroregeneration, biomarkers

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ÖZ

Amaç: Kardiyopulmoner baypas (KPB), kalp cerrahisinde yaygın olarak kullanılmakla birlikte, oksidatif stres, enflamasyon ve nörolojik komplikasyonlarla ilişkilidir. Bu çalışmada, nöronal plastisite ile ilişkili büyüme ile ilişkili protein 43 (GAP43) ve neuregulin-1 (NRG1) düzeylerindeki perioperatif değişimlerin, oksidatif stres ve enflamatuvar belirteçlerle birlikte değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: KPB uygulanan 41 hasta (32 erkek, 9 kadın) çalışmaya dahil edildi. Ameliyat öncesi ve sonrası alınan kan örneklerinde GAP43, NRG1, beyin kaynaklı nörotrofik faktör (BDNF) ve osteoprotegerin (OPG) düzeyleri enzime bağlı immünosorbent analiz ile ölçüldü. Toplam oksidan durum (TOS) ve toplam antioksidan durum (TAS) değerleri spektrofotometrik yöntemlerle değerlendirildi. Sirtuin 2 (SIRT2) ve C-X3-C motifli kemokin ligand 1 (CX3CL1) ekspresyonları Western blot ile analiz edildi. İstatistiksel değerlendirmede uygun parametrik ve non-parametrik testler kullanıldı.

Bulgular: GAP43 düzeylerinde ameliyat sonrası anlamlı azalma saptandı ($p < 0,05$) ve bu değişimin erkek hastalarda daha belirgin olduğu görüldü. NRG1 düzeylerinde genel olarak anlamlı fark izlenmezken, kadınlarda azalma, erkeklerde artış eğilimi dikkat çekti. Erkek hastalarda OPG düzeyleri artış gösterdi. TOS düzeyleri her iki cinsiyette artarken, TAS düzeylerinde değişiklik gözlenmedi. Western blot analizinde SIRT2 ekspresyonunun kaybolduğu, CX3CL1'in ise ameliyat sonrası belirgin olarak arttığı saptandı. Bu bulgular, KPB'nin oksidatif stres ve enflamasyonla birlikte nöronal yanıtları da etkilediğini göstermektedir.

Sonuç: Bu bulgular, kardiyopulmoner baypasın nörorejeneratif ve enflamatuvar süreçler arasındaki dengeyi bozabileceğini ve bunun postoperatif nörokognitif disfonksiyona katkıda bulunabileceğini düşündürmektedir. Gözlenen biyobelirteç değişimleri, erken risk değerlendirmesi ve hedefe yönelik nöroprotektif stratejilerin geliştirilmesi için potansiyel bir temel sunmaktadır.

Anahtar Kelimeler: Kardiyopulmoner baypas, GAP43, NRG1, oksidatif stres, nörorejenerasyon, biyobelirteçler

Introduction

Cardiopulmonary bypass (CPB) is a critical component of most heart surgery procedures, allowing surgeons to work on a "still heart." While essential for the surgical treatment of heart disease, postoperative complications such as systemic inflammation, oxidative stress, and neurocognitive dysfunction can occur in patients undergoing CPB (1-3). The clinical manifestations of neurocognitive disturbance after cardiac surgery include persistent decline in cognitive function, stroke, as well as more subtle neuropsychological changes that can affect a patient's quality of life after discharge from the hospital and impact postoperative outcome (4,5).

The biological response to CPB includes an inflammatory response, endothelial damage and increased production of reactive oxygen species (1-3). Levels of several inflammatory markers have been studied, but changes in neurobiological parameters are not completely understood, especially early changes (6,7). This is especially true for markers of neuronal plasticity or regeneration (8).

Growth-associated protein 43 (GAP43) is known to be associated with neuronal growth and plasticity, thus may serve as a marker of neuronal plasticity (9,10). Neuregulin-1 (NRG1) has been demonstrated to modulate neuronal survival, calcium signaling, neurovascular and autonomic nervous system interactions, and modulate cardiovascular functions (11,12). An understanding of the neurovascular modifications occurring during CPB and of the perioperative variations in these proteins in adult CPB patients has not been well elucidated.

In addition to affecting neuroregenerative factors, CPB alters oxidative-antioxidative balance and the inflammatory response (2,13,14). We therefore determined the following biomarkers as indicators of vascular inflammation, neurovascular regulation, immune cell recruitment, and oxidative stress defense: osteoprotegerin (OPG), brain-derived neurotrophic factor (BDNF), C-X3-chemokine Ligand 1 (CX3CL1)/fractalkine, and the sirtuins, particularly sirtuin 2 (SIRT2), which are part of cellular defense against oxidative stress (15-18).

Beyond experimental measurements, integrating biomarker data with *in silico* approaches may help contextualize molecular interactions and functional pathways associated with CPB-related neurovascular alterations (19,20).

The aim of this study was to determine GAP43 and NRG1 levels in patients undergoing CPB and to compare them with markers of oxidative stress and inflammation. An *in silico* analysis of the obtained results was performed to predict potential interactions among the studied biomarkers and to identify relevant biological pathways. The goal of this work was to combine experimental data with *in silico* analysis to provide a systems-level view of neurovascular changes caused by CPB at the molecular level.

Materials and Methods

Study Population and Sample Collection

A total of 41 patients (32 males and 9 females) undergoing elective cardiac surgery with CPB were included in this study. Peripheral blood samples were collected preoperatively and postoperatively. Serum samples were obtained by centrifugation and stored at -80 °C until further analysis.

The study was approved by the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Ethics Committee (approval number: 24/727; decision number: 14/16, date: 28.11.2024). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment in the study.

Biochemical Analysis

Serum levels of GAP43, BDNF, OPG, and NRG1 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. GAP43 levels were measured using an ELISA kit (Catalog No: YLA2806HU, YL Biont, Shanghai, China). NRG1 levels were determined using a human Neuregulin-1 ELISA kit (Catalog No: YLA1122HU, YL Biont, Shanghai, China). BDNF levels were measured using a commercial ELISA kit (Catalog No: E1302Hu, BT Lab, China). OPG levels were measured using a commercially available ELISA kit (Catalog No. E1558Hu; BT Lab, China).

Serum total antioxidant status (TAS) and total oxidant status (TOS) levels were quantified using fully automated colorimetric assays as described in previously published method (21,22). The TAS method relies on the capacity of antioxidants in the sample to neutralize the $ABTS^{+}$ radical cation, resulting in reduced color intensity. In contrast, TOS measurement is based on the oxidation of the ferrous ion-o-dianisidine complex by oxidant molecules in the sample. TAS results were expressed as mmol Trolox equivalents per liter, whereas TOS results were expressed as μmol H_2O_2 equivalents per liter. All measurements were performed in duplicate to ensure accuracy.

Western Blot Analysis

Serum samples stored at -80 °C were processed prior to analysis. High-abundance proteins were depleted using a Top14 depletion resin (Thermo Scientific, USA) according to the manufacturer's instructions. Total protein concentrations were determined using the Bradford assay.

Equal amounts of protein (50 μg) were denatured, separated by SDS-PAGE, and transferred to PVDF membranes. Membranes were blocked with 3% bovine serum albumin and incubated overnight at 4 °C with primary antibodies against SIRT2 (1:1000, ABclonal, A-0273, USA) and fractalkine (CX3CL1) (1:1000, Abcam, ab25088, UK). After washing, membranes were incubated with HRP-conjugated anti-rabbit secondary antibody (1:5000, Cell Signaling Technology, 7074, USA).

Protein bands were visualized using chemiluminescence and imaged with a ChemiDoc imaging system (Bio-Rad, USA). Band intensities were assessed using ImageJ software (NIH, USA). No housekeeping-protein normalization was performed; equal protein loading was ensured by Bradford-based protein quantification and loading 50 μg of total protein per lane. Uniform contrast adjustments were applied to entire blots without altering individual bands.

In Silico Network and Functional Enrichment Analysis

To explore potential functional relationships among the studied biomarkers, an *in silico* analysis was conducted using GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2 as input genes. Protein-protein interaction networks were constructed using the STRING database (version 12.0), incorporating both experimentally validated and predicted interactions.

Functional enrichment analysis was performed using g:Profiler to identify significantly overrepresented Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes pathways. Multiple testing correction was applied using the false discovery rate, and pathways with an adjusted p-value < 0.05 were considered statistically significant.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro-Wilk test. Because most variables did not meet the criteria for a normal distribution, analyses were primarily conducted using non-parametric approaches.

Paired comparisons between preoperative and postoperative values were conducted using the Wilcoxon signed-rank test. For normally distributed variables, paired t-tests were applied when appropriate. Differences between independent groups were assessed using the Mann-Whitney U test or the independent samples t-test, as appropriate. Data were presented as median with interquartile range or mean ± standard error/standard deviation, depending on distribution characteristics. A p-value < 0.05 was considered statistically significant.

Results

Study Population

A total of 41 patients undergoing CPB were included in the study, comprising 32 males and 9 females. Biochemical analyses were performed on the entire cohort, whereas Western blot analyses were performed on a subgroup of two patients (one female and one male). Preoperative and postoperative measurements were obtained for all evaluated parameters. Detailed descriptive data for all biomarkers are presented in Table 1.

Table 1. Perioperative changes in the evaluated serum biomarkers.

	OPG (pg/mL)	GAP43 (pg/mL)	TOS (μmol H_2O_2 equiv./L)	TAS (mmol Trolox equiv./L)	NRG1 (pg/mL)	BDNF (ng/mL)
Female preop (n = 9)	109.44 (182.18)	10065.0 (41.25)	0.67 (0.13)	3.22 (0.45)	19.86 (34.35)	0.31 (0.45)
Female postop (n = 9)	117.58 (235.71)	8100.0 (4068.53)	0.9350 (0.31)*	3.17 (0.15)	19.0 (20.67)	0.55 (0.84)
Male preop (n = 32)	101.68 (289.76)	6639.56 (5302.0)	0.62 (0.11)	3.17 (0.38)	3.57 (11.02)	0.68 (1.54)
Male postop (n = 32)	126.25 (344.47)*	6723.9 (4564.03)*	1.14 (0.61)*	3.15 (0.48)	5.00 (4.61)	1.14 (1.77)

Perioperative changes in serum levels of OPG (pg/mL), GAP43 (pg/mL), TOS (μmol H_2O_2 equiv./L), TAS (mmol Trolox equiv./L), NRG1 (pg/mL), and BDNF (ng/mL) in female and male patients undergoing CPB. Data are presented as median (IQR). Preoperative and postoperative values are shown separately for each sex. *p < 0.05 compared with preoperative values. IQR, interquartile range; GAP43, growth-associated protein 43; OPG, osteoprotegerin; TOS, total oxidant status; TAS, total antioxidant status; NRG1, neuregulin-1; BDNF, brain-derived neurotrophic factor; CPB, cardiopulmonary bypass.

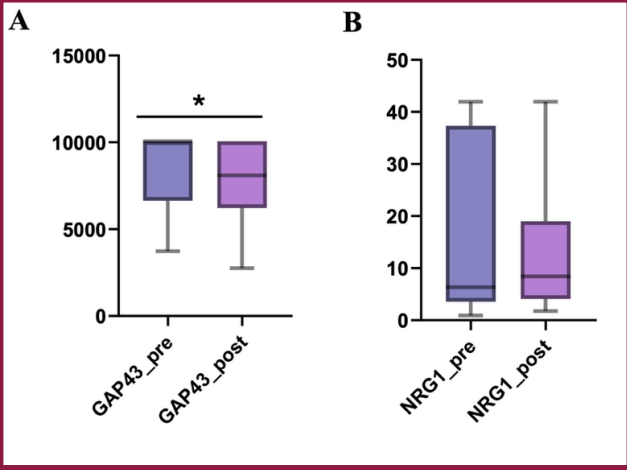

Figure 1. Perioperative alterations in serum GAP43 and NRG1 levels following CPB. (A) GAP43 levels were significantly reduced postoperatively compared to preoperative values. (B) NRG1 levels did not exhibit a statistically significant overall change, although distribution patterns differed between pre- and postoperative measurements. Data are presented as median (IQR) for the overall cohort (n = 41). *p < 0.05. Paired statistical analyses were performed to assess perioperative differences. IQR, interquartile range; GAP43, growth-associated protein 43; CPB, cardiopulmonary bypass; NRG1, neuregulin-1.

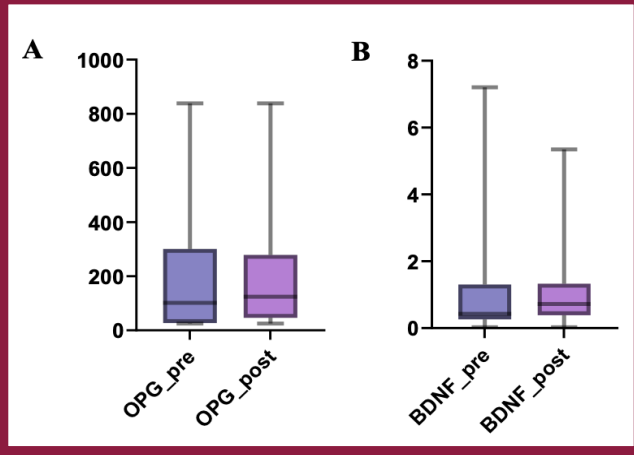

Figure 2. Perioperative alterations in inflammatory and neurotrophic biomarkers following CPB. (A) OPG levels did not differ significantly between preoperative and postoperative measurements in the overall cohort, although a significant postoperative increase was observed in male patients in the sex-stratified analysis. (B) BDNF levels did not differ significantly between pre- and postoperative measurements; however, opposite directional trends were observed between the sexes. Data are presented as median (IQR) for the overall cohort (n = 41). Paired statistical analyses were used for comparisons. CPB, cardiopulmonary bypass; OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; IQR, interquartile range.

Serum GAP43 levels decreased significantly following CPB in the overall cohort (p = 0.046). Sex-stratified analysis demonstrated that this reduction was more pronounced in male patients, whereas no significant change was observed in females (Table 1, Figure 1).

In the overall cohort, NRG1 levels did not differ significantly between preoperative and postoperative measurements (p = 0.438). However, after surgery, distinct sex-specific patterns were observed: NRG1 levels decreased in female patients and increased in male patients (Table 1).

Inflammatory and Neurotrophic Markers

Serum OPG levels increased postoperatively in male patients (p = 0.04), whereas no significant change was observed in female patients (Figure 2A). BDNF levels did not show statistically significant differences between pre- and postoperative measurements in either sex; however, opposite trends were observed, with an increase in females and a decrease in males (Figure 2B).

Oxidative Stress Parameters

TOS levels increased significantly after CPB in both female and male patients ($p = 0.0088$ and $p = 0.0009$, respectively), indicating elevated oxidative stress. In contrast, TAS levels remained unchanged in both groups (female: $p = 0.36$; male: $p = 0.35$) (Figure 3, Table 1).

Western Blot Findings

Western blot analysis demonstrated that SIRT2 expression was present in preoperative samples but undetectable postoperatively. In contrast, CX3CL1 expression was absent before surgery and became clearly detectable following CPB (Figure 4).

In Silico Network and Functional Enrichment Analysis

Protein-protein interaction analysis using the STRING database (version 12.0) demonstrated that GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2 were functionally connected in a common interaction network (Figure 5A).

Subsequent functional enrichment analysis showed that these proteins were significantly associated with pathways related to neuronal signaling, inflammatory response, and oxidative stress, including neurotrophin, TNF, chemokine, and cyclic adenosine monophosphate (cAMP) signaling pathways (Figure 5B).

Discussion

Changes in molecular markers of neuroregeneration, as well as in some inflammatory and oxidative stress molecules, occur before, during, and after clinical CPB. We investigated these changes in 41 adult patients undergoing cardiac surgery with CPB. Blood samples obtained before and after CPB were analyzed. A decrease in GAP43 levels was found in all samples, and NRG1 levels showed a sex-dependent pattern in blood samples. Our results provide new insights into the neurobiological changes associated with CPB.

GAP43 is a protein critical for axonal growth, synaptic plasticity, and neuronal repair, and is therefore a marker of neuronal plasticity. GAP43 remains a key molecule associated with axonal growth, regeneration, and injury-induced neuronal plasticity, supporting its relevance as a marker of altered neuroplastic responses after CPB (23). A postoperative reduction in GAP43 suggests an impairment of neuronal plasticity following CPB. Most studies investigating CPB-induced inflammation have not considered markers of neuronal regeneration. Notably, the decrease in GAP43 was greater in men, suggesting that the neurobiological response to CPB may be modulated by sex-related differences in hormonal regulation, vascular response, and cellular resilience.

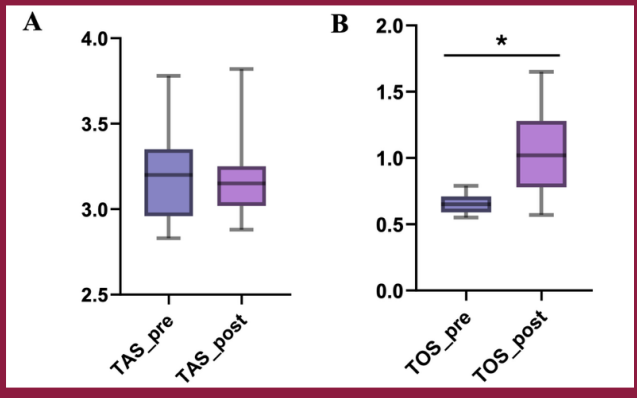

Figure 3. Perioperative changes in oxidative stress parameters following CPB. (A) TAS levels did not differ significantly between preoperative and postoperative measurements. (B) TOS levels increased significantly in the postoperative period compared with preoperative values. Data are presented as median (IQR) for the overall cohort (n = 41). *p < 0.05. Paired statistical analyses were used to evaluate perioperative differences. CPB, cardiopulmonary bypass; TOS, total oxidant status; TAS, total antioxidant status; IQR, interquartile range.

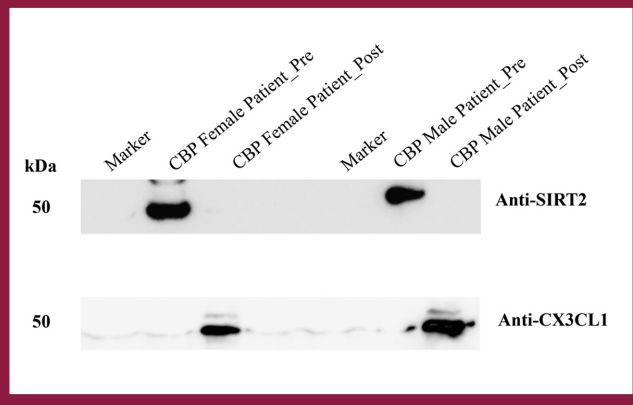

Figure 4. Representative Western blots showing SIRT2 and CX3CL1 protein expression in paired preoperative and postoperative serum samples from a subgroup of two patients (one female and one male). Molecular-weight marker lanes were included to indicate the approximate sizes of the detected proteins. SIRT2 was detectable in the preoperative samples but not in the corresponding postoperative samples, whereas CX3CL1 became detectable postoperatively. SIRT2, sirtuin 2; CX3CL1, C-X3-C motif chemokine ligand 1; CPB, cardiopulmonary bypass.

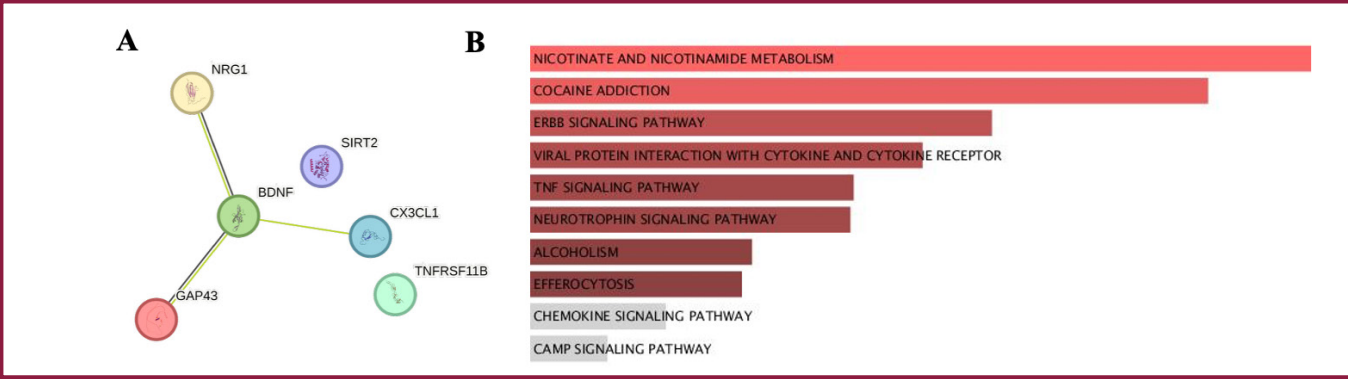

Figure 5. Integrated in silico analysis of the studied biomarkers. (A) A protein-protein interaction network was constructed using the STRING database (version 12.0), demonstrating functional connectivity among GAP43, NRG1, BDNF, TNFRSF11B (OPG), CX3CL1, and SIRT2. (B) KEGG pathway enrichment analysis identifying pathways associated with neuronal signaling, inflammatory response, and cellular stress regulation, including neurotrophin, TNF, chemokine, and cAMP signaling pathways. The analysis highlights coordinated interactions linking neuroregeneration, inflammation, and oxidative stress-related processes. GAP43, growth associated protein 43; NRG1, neuregulin-1; BDNF, brain-derived neurotrophic factor; TNFRSF11B, tumor necrosis factor receptor superfamily member 11B; OPG, osteoprotegerin; CX3CL1, C-X3-chemokine Ligand 1; SIRT2, sirtuin 2; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; KEGG, Kyoto Encyclopedia of Genes and Genomes; TNF, tumor necrosis factor; cAMP, cyclic adenosine monophosphate.

NRG1 did not show an overall significant change, but exhibited different trends in males and females, both of which are biologically significant. An increase in NRG1 in males may reflect up-regulation of a protein that helps cells survive under stress, compensating for the effects of surgery, whereas a decrease in females may indicate a different mechanism. NRG1 signals through the ErbB family of receptor tyrosine kinases and is involved in calcium homeostasis; thus, these findings support the hypothesis that sex-specific modulation of neuroprotective signaling pathways that can impact recovery from surgery.

Elevated OPG levels in the male patients studied suggest increased vascular inflammation following CPB. OPG has been shown to be involved in endothelial dysfunction and vascular remodelling; thus, its elevation could be an early marker of inflammation related to extracorporeal circulation. Interestingly, the trends in BDNF levels are opposite to those of OPG and suggest that neurotrophic support is complex and highly regulated in this context. Although the sex differences were not significantly increased, they may still be important.

In addition to neuroinflammation, CPB-induced brain injury likely involves oxidative stress. Recent experimental studies have further demonstrated that CPB-induced neuroinflammation contributes to persistent deficits in neurogenesis and cognitive function (24). The TOS increased severalfold, whereas the TAS remained unchanged. This increase in TOS relative to TAS is expected to promote cellular injury and impair neuroregenerative processes, consistent with the postoperative decrease observed in GAP43, a protein involved in neuronal sprouting and synaptic plasticity.

The brain exhibited signs of a disrupted cellular response following recovery from CPB. SIRT2 was downregulated post-CPB, which may suggest a loss of neuroprotective pathways involved in metabolic and stress responses that enable cells to resist oxidative stress and maintain cellular homeostasis. SIRT2 has emerged as an important regulator of oxidative stress, mitochondrial homeostasis, and neuroinflammatory signaling, although its functional effects appear to depend on the specific cellular and pathological context (25). Conversely, increased expression of CX3CL1 suggests activation of inflammatory signaling, alteration of neuron-immune communication, and chemotaxis of immune cells to the brain, all of which may contribute to neuroinflammation. CX3CL1 signaling is increasingly recognized as a central regulator of neuron–microglia communication and a critical mediator of neuroinflammatory responses (26,27).

The identified molecular changes were incorporated into an *in silico* analysis of alterations occurring during recovery from hypothermic CPB. A protein-protein interaction network was built using the subset of markers GAP43, NRG1, BDNF, OPG, CX3CL1, and SIRT2 identified as altered during recovery from hypothermic CPB (Figure 5). The network revealed numerous interactions among the identified markers, including several that potentially play a central role in recovery from hypothermic CPB, notably GAP43, which is implicated in neuronal plasticity, inflammation, and oxidative stress. An *in silico* pathway enrichment analysis revealed that major pathways that changed during

recovery from hypothermic CPB included those related to neurotrophin signaling, TNF signaling, chemokine signaling, and cAMP signaling. In parallel with the hypothesis, the results also claim that CPB induces a series of changes that link neuroregenerative, inflammatory, and stress responses. However, these results must be confirmed by experimental analysis.

In addition to inducing oxidative stress and a whole-body inflammatory response, the surgical stress associated with CPB could modulate positive neuroregenerative signals. The loss of GAP43, a marker of enhanced neuronal plasticity, might signal a postoperative shift toward decreased plasticity.

Overall, our results suggest that CPB is accompanied by integrated alterations in neuroregenerative, inflammatory, and oxidative stress-related processes. The integration of GAP43 and NRG1 with conventional biomarkers provides a more comprehensive framework for understanding CPB-related neurobiological changes and may contribute to the identification of novel targets for early intervention and risk stratification.

Study Limitations

This study has certain limitations. Notably, the relatively limited sample size—especially within sex-based subgroups—may have reduced the statistical power and reliability of subgroup analyses. The lack of long-term neurological follow-up prevents establishing a direct correlation between biomarker alterations and clinical neurocognitive outcomes. Additionally, Western blot analyses were performed in an exploratory subgroup of two patients and were interpreted qualitatively without densitometric or statistical comparison. Therefore, these representative findings should be considered preliminary and require confirmation in a larger cohort. Although *in silico* analyses provided insights into potential molecular interactions, these findings require further experimental validation.

Conclusion

CPB induces a complex biological response characterized by oxidative stress, inflammation, and altered neuroregenerative signaling. The postoperative decrease in GAP43 suggests impaired neuronal plasticity, whereas the sex-dependent behavior of NRG1 indicates differential neurobiological adaptation.

The combined evaluation of neuroregenerative, inflammatory, and oxidative stress markers provides a more integrated view of CPB-related changes. Additionally, *in silico* analyses support the notion that these biomarkers are functionally interconnected, linking neuronal, immune, and stress-response pathways.

Overall, GAP43 and NRG1 may serve as promising candidates for early detection of CPB-associated neurobiological alterations, although larger and longitudinal studies are needed to confirm their clinical utility. These results underscore the potential value of combined neuroregenerative and inflammatory biomarkers as early indicators of CPB-associated neurovascular alterations and may contribute to improved perioperative monitoring strategies.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine Ethics Committee (approval number: 24/727; decision number: 14/16, date: 28.11.2024).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: D.S.A., A.K., Design: D.S.A., Data Collection or Processing: N.H.K., Y.G., N.O., R.N.B., D.E., Analysis or Interpretation: D.S.A., N.H.K., A.K., F.C., Ü.Ç., Literature Search: D.S.A., N.O., Writing: D.S.A., N.H.K., A.K., Y.G., N.O., R.N.B., D.E., F.C., S.A., Ü.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Diagnostic Challenges in Fumarate Hydratase-Deficient Leiomyomas: Report of Two Cases

Fumarat Hidrataz-Defektif Leiomyomlarda Tanısal Zorluklar: İki Olgunun Sunumu

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ABSTRACT

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant syndrome caused by germline mutations in the fumarate *hydratase* (FH) gene, which encodes the FH enzyme. Most women with HLRCC develop uterine leiomyomas, typically during the second and third decades of life. Patients may also present with cutaneous leiomyomas, which generally manifest in the fourth decade of life. Pathological features—such as staghorn vasculature, alveolar-pattern edema, eosinophilic cytoplasmic inclusions, ovoid nuclei, bizarre, dispersed nuclei, and large eosinophilic nucleoli with perinucleolar halos—are suggestive but not definitive. Immunohistochemically, FH staining has high specificity, whereas 2-succinocysteine (2SC) staining demonstrates both high sensitivity and specificity. Although molecular testing is the diagnostic gold standard, it is not widely available. We present two patients diagnosed with FH-deficient leiomyoma (FH-dUL). The first is a 52-year-old woman who previously underwent nephrectomy for renal cell carcinoma. A subsequent positron emission tomography scan revealed high fluorine-18 fluorodeoxyglucose uptake in a uterine myoma, prompting hysterectomy. The second case involves a 34-year-old woman who underwent myomectomy due to a rapidly enlarging uterine myoma. Histopathological evaluation in both cases confirmed FH-dUL. FH-deficient uterine leiomyomas present diagnostic challenges due to overlapping morphological and immunohistochemical (IHC) findings. FH loss does not always indicate HLRCC, underscoring the need for careful evaluation. Although FH and 2SC IHC analyses are useful screening tools, molecular testing remains the gold standard for definitive diagnosis, requiring multidisciplinary assessment for optimal patient management and follow-up.

Keywords: Fumarate hydratase-deficient leiomyoma, 2-succinocysteine, fumarate hydratase, immunohistochemical analysis

ÖZ

Kalıtsal leiomyomatozis ve renal hücreli karsinom (HLRCC), fumarat hidrataz (FH) genindeki germline mutasyonlardan kaynaklanan otozomal dominant kalıtılan bir sendromdur ve bu gen FH enzimini kodlar. HLRCC'li kadınların çoğunda, genellikle ikinci ve üçüncü dekatta uterin leiomyomlar gelişir. Hastalar ayrıca kutanöz leiomyomlarla da başvurabilir ve yaklaşık %15'inde genellikle dördüncü dekatta agresif bir renal hücreli karsinom gelişir. Patolojik özellikler—staghorn benzeri damar yapıları, alveoler patern ödemi, eozinofilik sitoplazmik inklüzyonlar, ovoid nükleuslar, dağınık bizar nükleuslar ve perinükleer halo ile çevrili büyük eozinofilik nükleoller—önerici olup kesin tanı için yeterli değildir. İmmünohistokimyasal olarak, FH ve 2-süksinosistein (2SC) boyamaları FH-defektif tümörlerin tanımlanmasında yaygın olarak kullanılmaktadır; FH yüksek spesifiteye sahipken, 2SC hem yüksek sensitivite hem de yüksek spesifite gösterir. Moleküler testler tanısal altın standart olmasına rağmen, yaygın olarak erişilebilir değildir. FH-defektif leiomyoma tanısı alan iki hasta sunulmaktadır. İlk olgu, daha önce RCC nedeniyle nefrektomi geçirmiş 52 yaşındaki bir kadındır. Takipte yapılan pozitron emisyon tomografisi taramasında uterin myomda yüksek flor-18 florodeoksiglukoz tutulumu saptanmış ve buna bağlı olarak histerektomi uygulanmıştır. İkinci olgu, hızlı büyüyen uterin bir myom nedeniyle myomektomi yapılan 34 yaşındaki bir kadındır. Her iki hastanın histopatolojik değerlendirmesi FH-defektif leiomyoma olarak doğrulanmıştır. FH-defektif uterin leiomyomlar, morfolojik ve immünohistokimyasal bulguların örtüşmesi nedeniyle tanısal zorluklar oluşturur.

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ÖZ

FH kaybı her zaman HLRCC anlamına gelmez; bu durum dikkatli değerlendirme gerektirir. FH ve 2SC immünohistokimyasal analizler yararlı tarama araçları olsa da kesin tanı için moleküler test altın standarttır ve optimal hasta yönetimi ile takibi için multidisipliner yaklaşım gereklidir.

Anahtar Kelimeler: Fumarat hidrataz-defektif leiomyom, 2-süksinosistein, fumarat hidrataz, immünohistokimyasal analiz

Introduction

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant syndrome caused by germline mutations in the fumarate *hydratase* (FH) gene (1,2). Women with HLRCC develop multiple symptomatic uterine leiomyomas and cutaneous leiomyomas at a young age and are at risk for aggressive renal tumors that can metastasize even when small (1). FH-deficient leiomyomas (FH-dUL) exhibit variable morphological features that are not specific in isolation (2). Although FH loss and 2-succinocysteine (2SC) positivity provide diagnostic clues, molecular analysis is required for a definitive diagnosis; however, this method is not readily available in all centers (3). This case report aims to emphasize the diagnostic challenges in morphological and immunohistochemical (IHC) analysis of rare FH-dUL, to demonstrate that FH negativity is not always associated with HLRCC, and to discuss the diagnostic approach through two different clinical examples in light of the literature.

Case Report

Case 1

The patient, who underwent nephrectomy for renal cell carcinoma (RCC), was referred to the gynecology clinic two months after nephrectomy due to intense ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake in the uterus on positron emission tomography (PET) imaging. The 52-year-old patient, in menopause for three years, had no history of disease other than RCC. Her children had no history of disease or cancer. Her mother had endometrial cancer, one sister had breast cancer, the other sister had stomach cancer, and her nephew had cervical cancer. Gynecological examination revealed a 3-cm degenerated myoma. Due to intense FDG uptake on PET (standardized uptake value maximum: 31.5), laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed. Gastroscopy and colonoscopy were performed simultaneously. Macroscopic examination revealed multiple intramural myomas. Histopathology showed focal alveolar edema, staghorn- or hemangiopericytoma-like vessels, spindle or epithelioid cells with ovoid nuclei, and prominent eosinophilic nucleoli surrounded by perinuclear halos; focal multinucleated and bizarre cells were also observed (Figure 1). In IHC, CD34 was positive in vascular structures, CD117 in mast cells, and desmin in neoplastic cells; FH was negative. CD10 was negative; caldesmon and ER were positive, Ki67 was 2–3%. Based on morphological and IHC findings, the case was diagnosed as FH-dUL. The patient was discharged without complications and received genetic counseling due to high-risk for HLRCC. Genetic analysis revealed only a somatic FH defect. The patient has been under regular medical oncology follow-up for two years, including three-monthly magnetic resonance imaging/computed tomography imaging and routine biochemical surveillance, as well as annual PET imaging. No pathological findings have been detected to date, and no systemic oncological treatment has been required. Written informed consent was obtained from the patient for publication of this case report.

Case 2

A 34-year-old patient with one normal delivery and a body mass index of 39.6 presented for myoma follow-up. Her past and family history were otherwise unremarkable except for a 12-cm myoma detected during an examination two years earlier. The patient had no personal or family history of cancer. Examination revealed a giant myoma measuring 14 × 20 cm with indistinct borders from the uterus. Due to rapid growth and the patient being of reproductive age, myomectomy was performed. Macroscopic examination showed a hard myoma measuring 20 × 14 cm with a hemorrhagic nodular cut surface. Histopathology revealed focal spindle or epithelioid cells with ovoid nuclei and prominent eosinophilic nucleoli surrounded by perinuclear halos. IHC showed FH (–), CD10 (–), and Ki67 3–5%. The pathology report diagnosed FH-dUL (Figure 2). Following the pathological diagnosis, renal screening with ultrasonography was performed one month after surgery, revealing no renal pathology. Although genetic testing was not performed in this patient, the absence of a personal or family history of cancer and the unremarkable renal screening findings were taken into consideration in the clinical assessment. The patient was followed for one year post-myomectomy without any complications. She had a desire for fertility and is currently maintaining a healthy pregnancy in the third trimester. Written informed consent was obtained from the patient for publication of this case report.

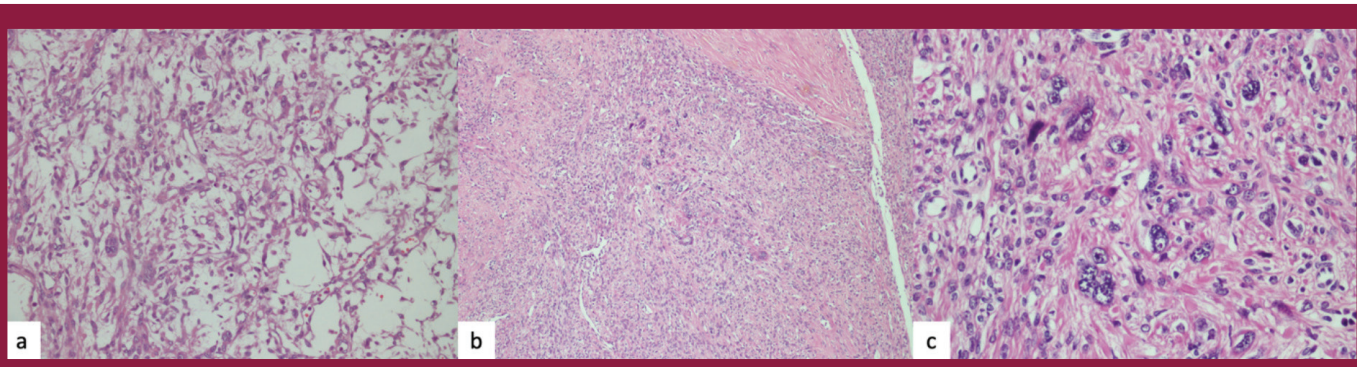

Figure 1. On microscopic examination, focal alveolar edema (H&E, 200x) (a), spindle or epithelioid cells with oval nuclei and prominent eosinophilic nucleoli surrounded by perinucleolar halos were observed in the cases examined (H&E, 100x) (b). Focal multinucleated and bizarrely nucleated cells were observed (H&E, 400x; c).
H&E, hematoxylin and eosin.

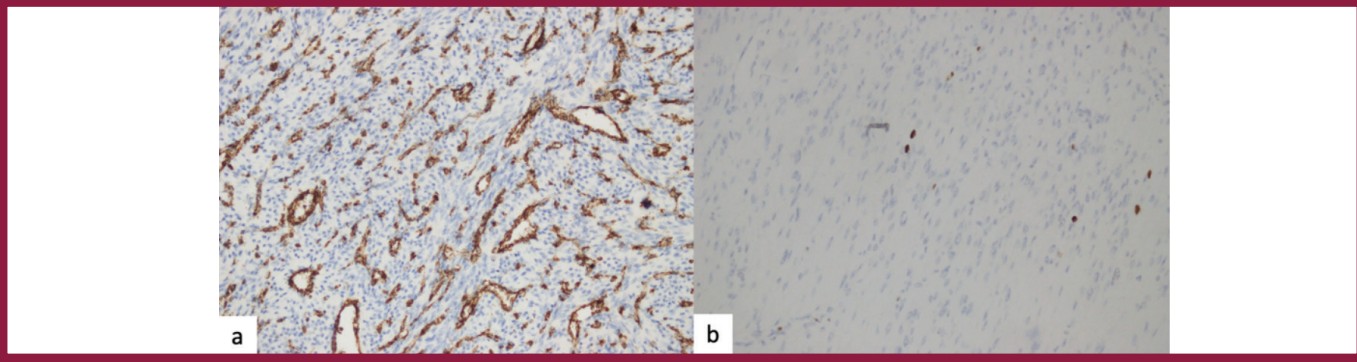

Figure 2. On immunohistochemical examination, atypical cells do not show reactivity for FH, whereas FH reactivity is present in the vascular structures (FH, 200x) (a). In the Ki67 index evaluation, very low reactivity was observed (Ki67, 200x) (b).
FH, fumarate hydratase.

Discussion

This study presents two FH-negative cases: an elderly woman with RCC and FH-negative myoma, and a young woman with a giant FH-negative myoma. The *FH* gene is located on chromosome 1q42.3-43 and encodes a common mitochondrial enzyme (1). HLRCC syndrome arises from germline mutations in the *FH* gene, placing carriers at risk for renal carcinoma and cutaneous and uterine leiomyomas (4). Somatic mutations in the *FH* gene may also occur and have been reported in cutaneous and uterine smooth muscle tumors (5). While sporadic FH mutations are predominant in FH-dUL, FH-deficient renal carcinomas are generally associated with germline FH mutations (1). Consequently, fumarate and succinate accumulation in tumor cells promotes oncogenic effects by stabilizing hypoxia-inducible proteins and causing their overexpression (4). In our RCC patient with FH-dUL and a family history of cancer, genetic counseling was recommended, and a somatic FH mutation was detected.

FH-dULs are typically large and numerous, with non-specific symptoms, and usually require early surgery (1). While sporadic leiomyomas are diagnosed in the fourth decade, FH-dUL patients are diagnosed in the second decade and undergo surgery in the third decade. Women with HLRCC have an 8–9-fold higher risk of developing uterine leiomyomas compared to the general population (5). FH-dULs are known for a high recurrence rate of 35.2–52.8% after myomectomy (6). Cutaneous leiomyomas are the most specific and sensitive clinical marker of HLRCC. When genetic testing is unavailable, dermatologic examination for cutaneous leiomyomas can help identify high-risk HLRCC women (7). HLRCC-associated renal carcinomas are clinically aggressive regardless of tumor type and often

present at an advanced stage, causing significant morbidity and mortality (8). The lifetime incidence of RCC in HLRCC patients is 15–20% (4). Renal tumors may occur at an early age (10–44 years), although the average age at diagnosis is in the fourth decade (2,9,10). Poor prognosis and syndrome-related mortality are associated with high-grade RCCs, which frequently present with advanced metastatic disease at diagnosis (8), and metastasis can occur even at small sizes (1). HLRCC-associated renal tumors typically exhibit type 2 papillary architecture but can also be cystic, tubulopapillary, tubular, or solid, and may be bilateral or multifocal (8,9).

Characteristic morphologic features of FH deficiency include staghorn-like vessels, focal alveolar stromal edema, ovoid nuclei arranged in chains, eosinophilic cytoplasmic inclusions, and perinuclear haloed eosinophilic macronuclei (2). A "schwannoma-like" growth pattern with nuclear palisading has also been described. Among these findings, staghorn vasculature is the strongest morphologic indicator for FH-dUL. Additional features, such as alveolar edema and nuclear chain formation, may not be evident in every tumor. However, due to variable FH-dUL morphology, definitive diagnosis based solely on histology is challenging (1). IHC, FH loss, and 2SC positivity serve as widely used screening methods for tumors associated with FH deletion; FH shows high specificity, while 2SC shows both high sensitivity and specificity (1,3). FH IHC is not fully sensitive for FH deficiency, as missense mutations in the *FH* gene may produce a non-functional protein detectable by IHC. The 2SC stain appears sensitive and specific for FH deficiency, but its clinical use is limited due to unavailability (2). Molecular genetic testing remains the gold standard for confirming HLRCC syndrome, but limited access in many centers represents a significant diagnostic constraint (3). However, 2SC immunohistochemistry could not be performed in our cases because this staining is not routinely available in our institution.

These two cases provide important contributions to the literature. First, they illustrate that FH-dUL can occur in both elderly and young women, and FH negativity does not always indicate HLRCC, emphasizing the importance of thorough clinical evaluation. Second, our cases demonstrate that characteristic morphologic and IHC features can support diagnosis even in the absence of genetic testing, providing practical guidance for centers with limited molecular resources. Finally, the long-term clinical follow-up and reproductive outcomes of our second case highlight that conservative management and fertility preservation are feasible in selected FH-dUL patients, information that is currently scarce in the literature.

Conclusion

This case report highlights the diagnostic challenges of the rare FH-dUL in terms of morphology and IHC. Demonstrating that FH negativity is not always associated with HLRCC emphasizes the need for careful clinical and genetic evaluation in diagnostic approaches. While IHC, showing FH loss and 2SC positivity, serves as a useful screening tool for FH-dUL diagnosis, molecular genetic testing remains the gold standard for definitive diagnosis. Therefore, multidisciplinary assessment and genetic counseling, when indicated, are important for patients suspected of FH-dUL.

Ethics

Informed Consent: Written informed consent was obtained from both patients for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö., E.A., Concept: G.Ö., Design: G.Ö., E.A., Data Collection or Processing: G.Ö., Analysis or Interpretation: G.Ö., E.A., Literature Search: G.Ö., Writing: G.Ö., E.A.

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