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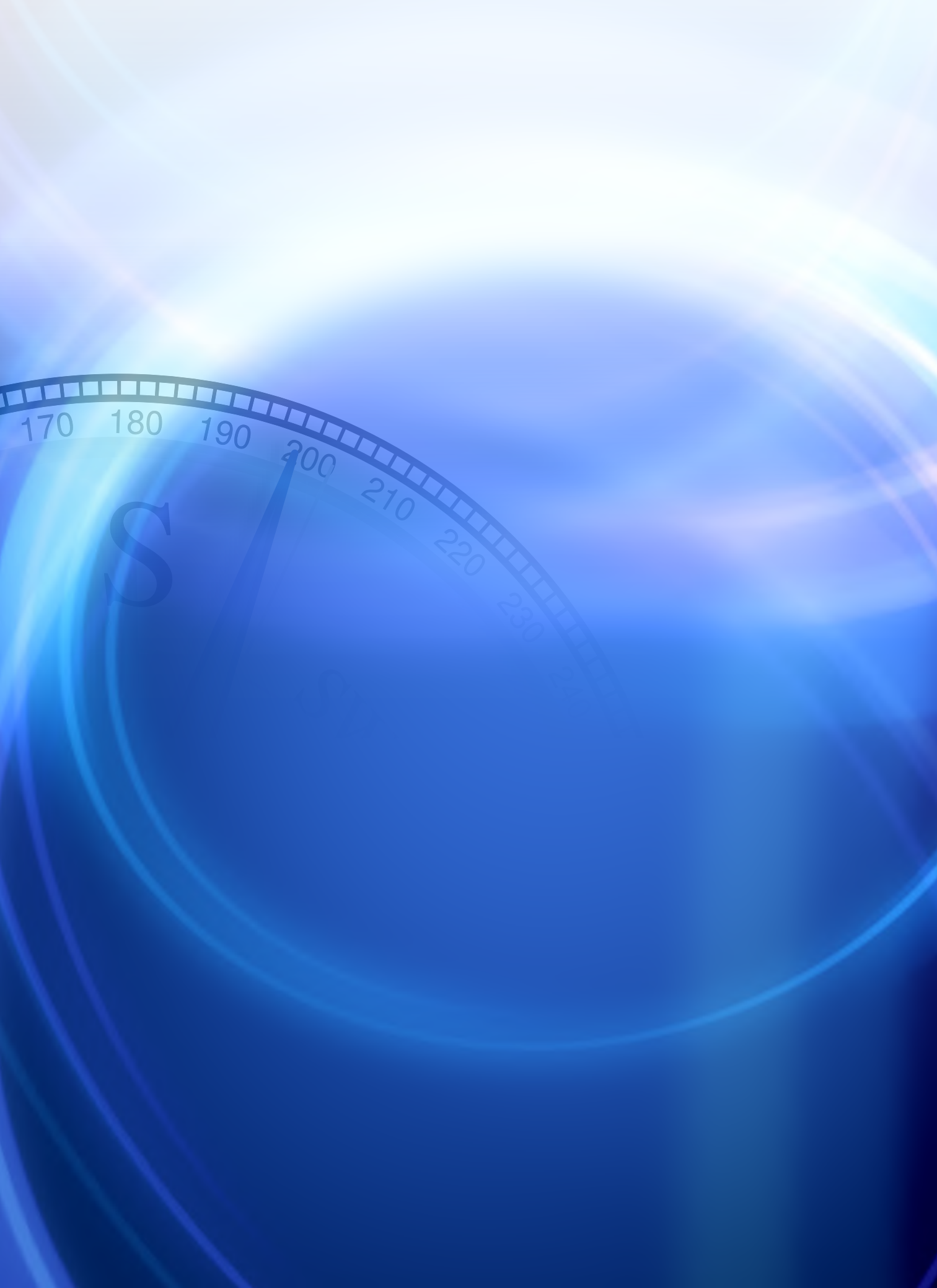
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ORIGINAL ARTICLES

REVIEW

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Original Article

Methylene Blue–Guided Localization to Improve Accuracy and Safety in Pulmonary Nodule Resection

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Keywords: CT-guided localization; methylene blue; minimally invasive surgery; pulmonary nodule; VATS; video-assisted thoracoscopic surgery.

ABSTRACT

Objective: The increasing detection of small and non-palpable pulmonary nodules through low-dose computed tomography (CT) screening has highlighted the need for reliable intraoperative localization, particularly during video-assisted thoracoscopic surgery (VATS). CT-guided methylene blue marking is a simple, rapid, and widely accessible technique that facilitates minimally invasive resection. This study aimed to evaluate the technical success, safety profile, and determinants of outcomes in CT-guided methylene blue localization of pulmonary nodules.

Methods: This retrospective study included 49 consecutive patients who underwent preoperative CT-guided methylene blue localization followed by thoracic resection, predominantly via VATS, between 2020 and 2025. Demographic characteristics, nodule morphology, procedural parameters, surgical details, and postoperative outcomes were analyzed. Categorical variables were compared using Chi-square or Fisher-based tests, and continuous variables using the Mann–Whitney U test.

Results: Localization was successful in 47 of 49 patients, yielding a technical success rate of 95.9%. Two unsuccessful localizations (4.1%) occurred, both in lower-lobe lesions and both associated with complications. Localization-related adverse events developed in nine patients (18.4%), most commonly pneumothorax (12.2%) and parenchymal hemorrhage (6.1%). The median patient age was 63 years, and the median nodule diameter was 9 mm. Malignancy was identified in 69.4% of nodules. No significant associations were found between localization success and nodule type, FDG uptake, lobar distribution, resection type, or procedural parameters. Tumor size showed a non-significant trend toward association with malignancy.

Conclusion: CT-guided methylene blue localization is a safe, highly effective, and practical technique for facilitating thoracoscopic resection of small pulmonary nodules. Technical success is consistently high and appears largely independent of radiological, anatomical, or procedural factors. These findings support the use of methylene blue marking as a reliable adjunct to minimally invasive thoracic surgery.

INTRODUCTION

Lung cancer remains one of the most common causes of cancer-related mortality worldwide.[1] With the increasing use of low-dose computed tomography (CT), clinicians encounter an increasing number of small and indeterminate pulmonary nodules in routine practice.[2,3] Some of these nodules prove to be early primary lung cancers, whereas others represent metastatic deposits from extrathoracic malignancies.[4] In selected patients, limited surgical resection offers both definitive diagnosis and, when appropriate, a potentially curative treatment option.[5,6]

The expansion of video-assisted thoracoscopic surgery (VATS) has improved perioperative outcomes, but small or deep pulmonary nodules can be difficult to detect intraoperatively because the surgeon lacks the ability to palpate the lung.[7] This limitation led to the development of preoperative localization techniques. One of the earliest practical approaches was described by Lenglinger et al.[8] in 1994, who reported CT-guided methylene blue injection for marking pulmonary nodules. Its simplicity, low cost, and ability to provide direct visual guidance during thoracoscopy facilitated its widespread clinical adoption.

Since then, several alternative localization techniques—

including hook-wire, microcoil, lipiodol, radiotracers, and fluorescent dyes—have been introduced.[9-12] Despite these options, methylene blue remains widely used because it does not require specialized equipment or advanced imaging facilities and can be readily implemented in most centers.

Although high technical success rates have been reported for methylene blue localization,[13-15] factors influencing its performance remain inconsistent across studies. The impact of anatomical and radiological features on localization success is particularly unclear, especially for small, subpleural, or ground-glass lesions.

The present study aims to evaluate the technical success, complication profile, and factors associated with CT-guided methylene blue localization of pulmonary nodules in a retrospective cohort from our institution.

MATERIALS AND METHODS

This retrospective cohort comprised 49 consecutive patients who underwent CT-guided methylene blue localization and thoracic resection at our thoracic surgery unit between January 2020 and May 2025. All patients had pulmonary nodules that were radiologically suspicious for malignancy or represented indeterminate lesions requiring surgical diagnosis. Localization was performed for small or impalpable nodules expected to be difficult to identify intraoperatively, particularly in cases with multiple nodules of varying sizes.

Demographic characteristics (age, sex, smoking history), prior cancer history, nodule features (size, morphology, FDG uptake, and lobar location), procedural parameters (needle gauge, marking-to-surgery time, number of punctures, marking-to-lesion distance, and pleural distance), and postoperative outcomes were retrospectively reviewed.

Ethical approval was obtained from the Istanbul University Ethics Committee (No: 2025/2027, Date: 31/10/2025) and the requirement for informed consent was waived due to the retrospective nature of the study. The study was conducted according to the Helsinki Declaration.

All localizations were performed by experienced thoracic radiologists using a 64-slice CT scanner without contrast enhancement and with a 2.5-mm slice thickness. Patients were positioned prone to ensure consistent access to posterior and basal lung segments. After sterile preparation and local anesthesia with 1% lidocaine, a 16-, 20-, or 22-gauge Chiba needle was inserted percutaneously under intermittent CT guidance. Needle gauge selection was based on radiologist preference, lesion depth, and anticipated trajectory.

Once the needle tip was confirmed adjacent to or within the lesion, a mixture of 1.0 ml autologous blood and 1.0 ml methylene blue (total 2.0 ml) was injected. The addition of autologous blood was intended to reduce dye diffusion and enhance intraoperative visibility, consistent with previously described dye-blood mixture techniques. A final CT scan was performed immediately afterward to confirm accurate staining and to assess for complications such as pneumothorax or pulmonary hemorrhage.

For patients with multiple nodules, only those anticipated to be difficult to detect intraoperatively—typically smaller or deeper lesions—were marked. Continuous communication between the radiologist and thoracic surgeon was maintained throughout the procedure to optimize the localization trajectory and ensure intraoperative accuracy.

Following localization, all patients were transferred directly to the operating room. General anesthesia with single-lung ventilation was achieved using either a double-lumen endotracheal tube or an endobronchial blocker. All operations were performed on the same day as the localization. Dye-marked lesions were identified thoracoscopically based on the blue-stained pleural surface, and resection depth was guided by preoperative CT findings. Surgical resections were performed using uniportal, biportal, or triportal VATS, depending on lesion location and surgeon preference.

Wedge resection was the primary technique and was performed with an endoscopic stapler to secure adequate parenchymal margins. Segmentectomy was preferred when the lesion was poorly visible or when wedge resection was deemed insufficient. Thoracotomy was performed when

Figure 1. Intraoperative and specimen findings of CT-guided methylene blue-localized pulmonary nodules. **(a)** Thoracoscopic view showing blue-stained pleural surface marking the target lesion; **(b)** Wedge resection performed under direct visualization of the dye-marked parenchyma; **(c)** Resected specimens demonstrating clear methylene blue staining, confirming precise localization during VATS resection.

additional large or central lesions required simultaneous resection; in these cases, smaller nodules in the same lung were localized preoperatively to facilitate detection.

Localization was defined as technically successful when the dye-marked area was clearly visible intraoperatively and the target lesion was completely resected, as confirmed by gross examination or frozen-section analysis. All specimens underwent pathological evaluation to determine lesion type, margin status, and final diagnosis (Fig. 1)

Patient demographics, nodule characteristics, and procedural details were summarized using descriptive statistics. Categorical variables were reported as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQR) due to non-normal distribution. Group comparisons for categorical variables were performed using the Chi-square test, Fisher's exact test, or Fisher–Freeman–Halton exact test, as appropriate. Continuous variables were analyzed with the Mann–Whitney U test.

A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 49 patients were included in the analysis. The median age was 63 years (IQR: 52-68), and 51.0% were female. A smoking history was present in 55.1% of the cohort, while 57.1% had a previous diagnosis of malignancy. The most common lesion location was the right upper lobe (40.8%), followed by the left lower lobe (24.5%). Part-solid nodules represented the dominant morphological subtype (44.9%), and FDG uptake on PET/CT was positive in 44.9% of cases.

The median tumor size was 9 mm (IQR: 6–10). Localization was performed with a median of 2 punctures (IQR: 2–4). The median pleura-to-lesion distance was 9 mm (IQR: 4.5–15.9), the marking-to-lesion distance was 3.7 mm (IQR: 1.3–7.3), and the median interval between localization and surgery was 25 minutes (IQR: 25–30).

Biportal VATS was the predominant surgical approach (83.8%), followed by uniportal VATS (12.2%), triportal VATS (2.0%), and thoracotomy (2.0%). The patient who underwent thoracotomy was also marked preoperatively because the deeply located target nodule was not expected to be reliably identified by palpation alone. Wedge resection was performed in 40 patients (81.6%), and anatomical segmentectomy in 9 patients (18.4%). One planned segmentectomy was converted to lobectomy based on frozen-section findings; this case was documented separately and not included in the primary resection-type analysis.

Localization-related adverse events occurred in nine patients (18.4%). Pneumothorax was the most common complication (12.2%), followed by parenchymal hemorrhage (6.1%) and subcutaneous emphysema (2.0%). Most pneumothoraces were radiologic and required no intervention. Postoperative complications occurred in 12 patients (24.5%), most frequently prolonged air leak (16.3%) and pneumonia (8.2%).

Table 1. Demographics, nodule characteristics, procedural parameters, surgical details, complications, and final pathology (n=49)

Variable	n (%) or Median (IQR)
Demographics	
Age, years	63 (52–68)
Female sex	25 (51.0)
Smoking history	27 (55.1)
Prior malignancy	28 (57.1)
Nodule characteristics	
Tumor size, mm	9 (6–10)
FDG uptake positive	22 (44.9)
Nodule type	
- Solid	14 (28.6)
- Part-solid	22 (44.9)
- Pure ground-glass	12 (24.5)
Lobar distribution	
RUL	20 (40.8)
LLL	12 (24.5)
Other lobes	17 (34.7)
Procedural details	
Number of punctures	2 (2–4)
Pleura–lesion distance, mm	9 (4.5–15.9)
Marking–lesion distance, mm	3.7 (1.3–7.3)
Marking–surgery time, min	25 (25–30)
Surgical approach	
Biportal VATS	41 (83.8)
Uniportal VATS	6 (12.2)
Triportal VATS	1 (2.0)
Thoracotomy	1 (2.0)
Resection type	
Wedge	40 (81.6%)
Segmentectomy	9 (18.4%)
Localization-related adverse events	
Pneumothorax	6 (12.2)
Parenchymal hemorrhage	3 (6.1)
Subcutaneous emphysema	1 (2.0)
Patients with ≥1 adverse event	9 (18.4)
Postoperative complications	
Prolonged air leak	8 (16.3)
Pneumonia	4 (8.2)
Renal dysfunction	2 (4.1)
Pancytopenia	1 (2.0)
Patients with ≥1 postoperative complication	12 (24.5)
Final pathology	
Malignant	34 (69.4)
Benign	15 (30.6)

VATS: Video-assisted thoracoscopic surgery; RUL: Right upper lobe; LLL: Left lower lobe.

Table 2. Relationship of nodule type and FDG uptake with malignancy

Variable	Category	Benign n (%)	Malignant n (%)	Total	p-value
Nodule Type	Solid	3 (21.4)	11 (78.6)	14	0.617
	Part-solid	9 (40.9)	13 (59.1)	22	
	Pure GGO	3 (25.0)	9 (75.0)	12	
	Mixed	0 (0.0)	1 (100.0)	1	
	Total	15 (30.6)	34 (69.4)	49	
FDG Uptake	Negative	10 (37.0)	17 (63.0)	27	0.358
	Positive	5 (22.7)	17 (77.3)	22	
	Total	15 (30.6)	34 (69.4)	49	

FDG: 18F-fluorodeoxyglucose.

Table 3. Association between marking success and localization-related complications

Marking success	No complication n (%)	Complication n (%)	Total	p-value
Unsuccessful	0 (0.0%)	2 (22.2%)	2	
Successful	40 (100.0%)	7 (77.8%)	47	
Total	40 (81.6%)	9 (18.4%)	49	0.077

Table 4. Association between marking success and lobar distribution

Lobe	Unsuccessful n (%)	Successful n (%)	Total	p-value
RUL	0 (0.0)	20 (42.6)	20	
RML	0 (0.0)	4 (8.5)	4	
RLL	1 (50.0)	5 (10.6)	6	
LUL	0 (0.0)	7 (14.9)	7	
LLL	1 (50.0)	11 (23.4)	12	
Total	2 (4.1)	47 (95.9)	49	0.210

RUL: Right upper lobe; LLL: Left lower lobe; LUL: Left upper lobe; RML: Right middle lobe; RLL: Right lower lobe.

Malignancy was identified in 34 patients (69.4%), including primary lung adenocarcinoma (34.7%), metastatic tumors (30.6%), and other malignant histologies (4.1%). Benign pathology was present in 15 patients (30.6%).

A detailed summary of all demographic, radiologic, procedural, surgical, and outcome variables is presented in Table 1.

There was no statistically significant association between malignancy and either nodule type (p=0.617) or FDG uptake (p=0.358). Solid, pure GGO, and FDG-positive nodules showed numerically higher malignancy rates, although these differences were not statistically significant (Table 2).

There was no statistically significant association between marking success and the occurrence of localization-related complications (p=0.077). Both unsuccessful localizations occurred in patients who developed complications, whereas seven of the 47 successful cases also experienced minor adverse events (Table 3).

There was no statistically significant association between marking success and lobar distribution (p=0.210). Both unsuccessful localizations occurred in lower-lobe lesions (one in the right lower lobe and one in the left lower lobe), whereas all upper-lobe and middle-lobe lesions were successfully localized (Table 4).

There was no statistically significant association between marking success and the type of surgical resection performed (p=0.999). Both unsuccessful localizations occurred in patients undergoing wedge resection, whereas all segmentectomy procedures achieved successful marking. These findings indicate that resection type did not influence the likelihood of localization success.

Posterolateral thoracotomy was required in 2.0% of patients (1/49), primarily for the resection of large or deep lesions, synchronous nodules, or when formal mediastinal

Table 5. Association between marking success and resection type

Resection type	Unsuccessful n (%)	Successful n (%)	Total	p-value
Wedge	2 (5.0%)	38 (95.0%)	40	
Segmentectomy	0 (0.0%)	9 (100.0%)	9	
Total	2	47	49	0.999

lymph node dissection was indicated. Wedge resection was the most frequently performed procedure (81.6%, 40/49), followed by segmentectomy (18.4%, 9/49). In 11 patients (22.4%), an intraoperative frozen-section–guided completion procedure was required, including 5 completion lobectomies, 4 completion segmentectomies, and 2 extended wedge resections. These were performed either for positive/suspicious margins or oncologic optimization after the initial wedge resection. The mean number of staplers used per resection was 2.4±0.9.

Histopathological evaluation demonstrated a wide spectrum of pulmonary lesions, including primary malignancies, metastatic tumors, and benign or pre-invasive entities. Primary lung adenocarcinoma was the most common malignant diagnosis (34.7%), exhibiting diverse histologic subtypes such as lepidic, acinar, mucinous, enteric, and minimally invasive adenocarcinoma. Metastatic tumors accounted for 30.6% of cases, most frequently originating from colorectal carcinoma, followed by breast carcinoma, pleomorphic sarcoma, and synovial sarcoma. Benign or pre-invasive lesions represented 30.6% of the cohort and included hamartoma, organizing pneumonia, atypical adenomatous hyperplasia (AAH), necrotizing granulomatous inflammation, fibrotic nonspecific interstitial pneumonia (NSIP), and meningothelial-like nodules.

Three patients presented with mixed or dual malignancies within the same lung, highlighting the biological complexity of multifocal pulmonary disease. One patient with a history of soft-tissue sarcoma harbored both metastatic sarcoma and a synchronous primary adenocarcinoma. Another patient previously diagnosed with adenoid cystic carcinoma exhibited a metastatic lesion alongside a separate primary lung adenocarcinoma. The third patient demonstrated anatomically distinct typical and atypical carcinoid tumors, indicating simultaneous dual neuroendocrine differentiation. These cases underscore the diagnostic challenges associated with small pulmonary nodules and emphasize the utility of CT-guided localization in ensuring accurate, tissue-preserving resection in anatomically complex or multifocal disease.

DISCUSSION

CT-guided methylene blue localization continues to be a practical, widely accessible, and safe technique for guiding minimally invasive resection of small or impalpable pulmonary nodules. In the present study, the overall technical success rate was 95.9%, comparable to the success rates reported in previous methylene blue and other dye-based localization series.[16-18] The overall complication rate was 18.4%, with pneumothorax and minor pulmonary hemorrhage being the most common events, in line with the established safety profile of dye, microcoil, and hook-wire localization methods.[19-22] Notably, none of the complications required additional intervention.

The two unsuccessful localizations in our cohort occurred in lower-lobe lesions, both of which exhibited extensive dye spread or insufficient intraparenchymal deposition. Similar patterns have been described in cases where steep needle angulation or increased pleura-to-lesion distance reduces dye concentration at the target site.[23,24] Although these trends did not reach statistical significance, they highlight known limitations of methylene blue, particularly in deeper lesions or those requiring oblique needle trajectories.

All segmentectomy cases in our series achieved successful localization, and wedge resections accounted for both unsuccessful attempts. However, resection type itself showed no statistical association with marking success, suggesting that localization feasibility is primarily determined by radiologic characteristics rather than the extent of surgical resection. This finding is consistent with recent data supporting the reliability of dye-based localization even in anatomic segmentectomy, including lymphadenectomy cases.[25]

A technical modification used in our practice—injecting 1 mL methylene blue mixed with 1 mL autologous blood—has been reported to reduce diffusion and create a more compact stain, at the expense of slightly decreased color intensity.[26] This approach appeared beneficial in emphysematous or anthracotic lungs, in which excessive diffusion may otherwise obscure the staining pattern.

Our cohort contained a high proportion of part-solid nodules and FDG-avid lesions, features frequently associated with malignancy. The malignancy rate of 69.4% aligns with reports from oncologic referral centers and screening programs. Several patients demonstrated dual or synchronous primaries, including combinations of metastatic sarcoma with primary adenocarcinoma and simultaneous typical and atypical carcinoid tumors. Such cases underscore the biological complexity of multifocal pulmonary disease and emphasize the importance of accurate lesion targeting to avoid sampling errors, preserve lung parenchyma, and en-

sure complete treatment of each suspicious focus.[27]

Although none of the radiologic parameters—including nodule type, FDG uptake, pleura-to-lesion distance, or marking-to-lesion distance—showed a statistically significant association with marking success, deeper lesions demonstrated numerically lower success, consistent with prior observations that depth increases dye dispersion and reduces localization accuracy.[28] Tumor size showed a borderline trend toward malignancy prediction, in agreement with established size-based malignancy models.[29]

When comparing localization techniques, hook-wire marking carries a higher risk of dislodgement (2.4-7.5%) and higher pneumothorax rates.[19] Microcoil localization provides reliable intraoperative fluoroscopic guidance but increases radiation exposure.[20] Lipiodol offers excellent radiopacity but includes the potential risk of embolization and requires specialized imaging capabilities.[21] Indocyanine green (ICG) is safe and increasingly utilized, though its fluorescence penetration is limited to shallow depths (<20-24 mm) and requires near-infrared equipment.[22] Bronchoscopic technologies such as electromagnetic navigation (EMN) and VAL-MAP are promising but require hybrid operating conditions, experienced operators, and higher costs.[30] Compared with these modalities, methylene blue remains a cost-effective, rapid, and widely available technique that can be performed in standard CT suites without additional equipment.

This study has limitations, including its retrospective design, potential selection bias due to selective marking criteria, and the absence of a non-localization control group. The single-center setting and operator-dependent variability may also limit generalizability. Nevertheless, the study provides valuable real-world data reflecting contemporary VATS practice, including cases requiring anatomic segmentectomy, lymphadenectomy, and frozen-section–guided completion resections.

Future prospective, multicenter studies directly comparing methylene blue with ICG fluorescence, hybrid-room intraoperative CT, and advanced bronchoscopic localization techniques are needed to determine standardized localization strategies tailored to lesion morphology, depth, and surgical approach.

Conclusion

CT-guided methylene blue localization is a safe, efficient, and widely accessible method for the intraoperative identification of small, deep, or subsolid pulmonary nodules. In this study, the technique achieved a high marking success rate (95.9%) with a low incidence of complications, the majority of which were minor and self-limited. Successful localization facilitated precise intraoperative identification of target lesions and supported both diagnostic wedge resections and therapeutic anatomic resections, including segmentectomy and, when indicated, frozen-section–guided completion procedures.

Even when selectively applied to challenging cases—such as patients with prior malignancy, multifocal nodules, or part-solid lesions—the technique maintained reliable performance. Its low cost, rapid execution, and compatibility with all surgical approaches, including both VATS and thoracotomy, underscore its practicality across centers with variable technical resources.

Accurate preoperative localization enhances operative planning by enabling targeted resections, minimizing unnecessary parenchymal loss, and improving diagnostic yield. Given these advantages, our findings support the continued, judicious use of CT-guided methylene blue marking as a valuable adjunct in the surgical management of pulmonary nodules, particularly in oncologic populations in whom lesion multiplicity, anatomic complexity, and histologic heterogeneity are common.

Ethics Committee Approval

The study was approved by the Istanbul University Hospital Ethics Committee (Date: 31.10.2025, Decision No: 2025/2027).

Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.D.; Design: S.D., R.K.; Supervision: S.D.; Fundings: S.D.; Materials: C.C.E.; Data collection &/or processing: S.D., B.O.; Analysis and/or interpretation: S.D., R.K.; Literature search: B.O., M.K.; Writing: S.D., A.D.; Critical review: S.D.

Conflict of Interest

None declared.

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Pulmoner Nodül Rezeksiyonunda Doğruluk ve Güvenliği Artırmak için Metilen Mavisi Rehberli Lokalizasyon

Amaç: Düşük doz bilgisayarlı tomografi (BT) taramalarıyla küçük ve palpabl olmayan pulmoner nodüllerin giderek daha fazla saptanması, özellikle video yardımlı torakoskopik cerrahi (VATS) sırasında güvenilir intraoperatif lokalizasyon ihtiyacını artırmıştır. BT eşliğinde metilen mavisi ile işaretleme; basit, hızlı ve yaygın olarak erişilebilir bir yöntem olup minimal invaziv rezeksiyonu kolaylaştırmaktadır. Bu çalışma, pulmoner nodüllerin BT kılavuzluğunda metilen mavisi ile işaretlenmesinin teknik başarısını, güvenlik profilini ve sonuçlara etki eden belirleyicileri değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, 2020-2025 yılları arasında preoperatif BT eşliğinde metilen mavisi ile işaretleme yapıldıktan sonra çoğunlukla VATS ile torasik rezeksiyon uygulanan ardışık 49 hasta dahil edildi. Demografik özellikler, nodül morfolojisi, işlemle ilişkili parametreler, cerrahi detaylar ve postoperatif sonuçlar analiz edildi. Kategorik değişkenler Ki-kare veya Fisher testi ile, sürekli değişkenler ise Mann–Whitney U testi ile karşılaştırıldı.

Bulgular: İşaretleme 49 hastanın 47'sinde başarılıydı ve teknik başarı oranı %95.9 olarak saptandı. Başarısız olan iki işaretleme (%4.1) alt lob nodüllerinde ve komplikasyon gelişen olgularda görüldü. İşaretleme ilişkili komplikasyon oranı %18.4 olup en sık pnömotoraks (%12.2) ve parankimal kanama (%6.1) izlendi. Hastaların medyan yaşı 63 yıl, medyan nodül çapı 9 mm idi. Nodüllerin %69.4'ü malign olarak raporlandı. Lokalizasyon başarısı ile nodül tipi, FDG tutulumu, lobar yerleşim, rezeksiyon tipi veya işlem parametreleri arasında anlamlı bir ilişki bulunmadı. Tümör boyutu, malignite ile ilişki açısından anlamlı olmayan bir eğilim gösterdi.

Sonuç: BT eşliğinde metilen mavisi ile işaretleme, küçük pulmoner nodüllerin torakoskopik rezeksiyonunu kolaylaştıran güvenli, etkili ve pratik bir yöntemdir. Teknik başarı oranı yüksek olup radyolojik, anatomik veya işlemle ilişkili değişkenlerden büyük ölçüde bağımsız görünmektedir. Bulgularımız, metilen mavisi ile işaretlemenin minimal invaziv göğüs cerrahisinde güvenilir bir yardımcı yöntem olarak kullanılmasını desteklemektedir.

Anahtar Sözcükler: Metilen mavisi; minimal invaziv cerrahi; pulmoner nodül; VATS; video yardımlı torakoskopik cerrahi.

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Original Article

Garré's Sclerosing Osteomyelitis of Long Bones in Children: Clinical Features, Diagnosis, and Treatment Outcomes

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Keywords: Chronic sclerosing osteomyelitis; Garré's osteomyelitis; pediatric bone infection; long bone inflammation.

ABSTRACT

Objective: To evaluate the presentation, diagnosis, and outcomes of pediatric Garré's sclerosing osteomyelitis of long bones.

Methods: We retrospectively reviewed 11 pediatric cases of long bone Garré's osteomyelitis treated between 2011 and 2019. Clinical, imaging, laboratory, microbiological, and out-come data were recorded, and all patients underwent biopsy for definitive diagnosis

Results: The 11 patients (ages 1–18 years) typically presented with chronic bone pain and minimal or no systemic symptoms. The femur was most commonly affected (5 cases), followed by the tibia (4 cases). Radiographs showed cortical thickening and periosteal new bone formation without osteolysis or abscess. Biopsy confirmed chronic osteomyelitis in all cases with no malignancy. Cultures identified a pathogen in 7 patients (64%): Staphylococcus aureus was most frequent (5 cases), with one Salmonella and one M. tuberculosis. All patients were treated with prolonged antibiotics; 6 also underwent surgical debridement. At follow-up, infection resolved in all patients. One staphylococcal humerus case had a late recurrence requiring repeat surgery, but was ultimately cured. No long-term functional deficits were observed.

Conclusion: Garré's chronic sclerosing osteomyelitis of long bones is an important consideration in children with atypical chronic bone lesions to avoid misdiagnosis as malignancy. Imaging alone can be misleading, and confirmatory biopsy is essential. Appropriate antibiotic therapy combined with surgical intervention when needed results in excellent outcomes, with most patients achieving full recovery. Early recognition and a multidisciplinary approach are key to successful management.

INTRODUCTION

Garré's sclerosing osteomyelitis is a rare chronic form of osteomyelitis characterized by a non-pyogenic, insidious infection that leads to diffuse sclerosis and thickening of bone. First described by Carl Garré in 1893, this condition involves a chronic inflammatory process without pus, sequestrum or fistula formation.[1] It predominantly affects children and adolescents and classically involves the jaw (mandible) in the context of odontogenic infection.[2,3] However, Garré's osteomyelitis is not confined to craniofacial bones; it can also occur in the long bones of the appendicular skeleton, albeit much more infrequently.[4] The most commonly reported sites outside the jaw are the metaphyseal regions of long bones such as the femur, tibia, fibula, humerus, and clavicle.[4] Radiologically, the hallmark is periosteal new bone proliferation – often described as an "onion skin" layering in mandibular cases – along with cortical hyperostosis and medullary canal narrowing. Unlike acute osteomyelitis, the sclerosing form typically lacks overt suppuration or abscess formation.

Clinically, patients with chronic sclerosing (Garré's) os-

teomyelitis usually present with chronic bone pain and swelling, but minimal systemic signs of infection. The indolent nature of the disease, coupled with prominent bony sclerosis on imaging, means it is often mistaken for other pathologies. In particular, the radiographic appearance can mimic bone tumors (such as osteoid osteoma, osteosarcoma or Ewing's sarcoma) or other chronic bone disorders like fibrous dysplasia.[5] Misdiagnosis can lead to unnecessary delays or interventions; therefore, recognizing this entity is important for both radiologists and treating physicians. A definitive diagnosis of Garré's osteomyelitis requires histopathological confirmation of chronic osteomyelitis and exclusion of malignancy. Biopsy is thus an indispensable step whenever imaging features are ambiguous.[5,6]

The exact etiopathogenesis of Garré's osteomyelitis remains a subject of discussion. Many cases have no organism isolated, and some authors have considered them as a subset of chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) – autoinflammatory bone conditions.[7] Nonetheless, in other cases a bacterial pathogen is identified, suggesting a low-grade infection as the inciting cause. Staphylococcus aureus is frequently implicated in chronic osteomyelitis in general and has been reported in Garré-type osteomyelitis as well.[5] Less common organisms, including Mycobacterium tuberculosis and atypical bacteria, have also been associated with sclerosing osteomyelitis in isolated reports. The resulting bone reaction is thought to stem from a prolonged smoldering infection that triggers persistent periosteal and endosteal bone formation.

Because of its rarity, most of the literature on Garré's sclerosing osteomyelitis consists of individual case reports or small series. There is a particular paucity of data on long bone involvement in the pediatric population.[8] Here, we present our experience with 11 pediatric patients diagnosed with chronic sclerosing osteomyelitis of the long bones. We describe their clinical and radiologic features, the process of diagnosis (often requiring differentiation from neoplasms), the microbiological findings, and the treatment approaches used. Our aim is to enhance understanding of this uncommon condition and highlight strategies to improve its diagnosis and management. This case series is, to our knowledge, among the largest collections of Garré's osteomyelitis in long bones reported in children, and it provides insights into the outcomes of contemporary treatment in such patients.

MATERIALS AND METHODS

Study Design and Patients: We conducted a retrospective review of all pediatric patients diagnosed with chronic sclerosing osteomyelitis (Garré's osteomyelitis) of the long bones at our tertiary care hospital between 2011 and 2019. The study included patients up to 18 years of age who had clinical and radiological findings suggestive of chronic osteomyelitis and in whom the diagnosis was confirmed by histopathology. A total of 11 patients met these inclusion criteria. Patients with acute (suppurative) osteomyelitis or those with jaw (mandibular/maxillary) involvement were excluded to focus on long bone, nonsuppurative cases. Ethical approval for this study was obtained from the institutional review board of Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethical Committe (No: 2025/010.99/18/4, Date: 20/07/2025). The study was conducted according to the Helsinki Declaration.

Data Collection: Using hospital records and imaging archives, we collected detailed information for each patient. Demographic data (age and sex) were recorded, as well as any relevant history of trauma, recent infections, or underlying medical conditions (e.g. immunodeficiency or autoinflammatory disorders). Clinical presentation was assessed, including duration of symptoms and key signs/symptoms such as pain, swelling, erythema, fever, or limp. Laboratory values at presentation were noted (white blood cell count, erythrocyte sedimentation rate, C-reactive protein). Imaging studies (plain radiographs for all patients, with MRI in 8 and CT in 3) were reviewed for features like cortical thickening, periosteal reaction, sclerosis, lytic lesions, or abscess (Fig. 1). The initial radiologic impression or differential diagnosis was recorded.

All patients underwent a bone biopsy of the lesion. Intraoperative findings and histopathology reports were reviewed for evidence of chronic osteomyelitis (e.g. chronic inflammatory infiltrate, fibrosis, new bone formation) and to confirm the absence of malignancy. Biopsy samples were also sent for microbiological culture (aerobic, anaerobic, fungal, and mycobacterial cultures as indicated). Culture results were recorded, including any organisms isolated and their antibiotic sensitivities. In cases with prior antibiotic use, we noted that cultures might be affected.

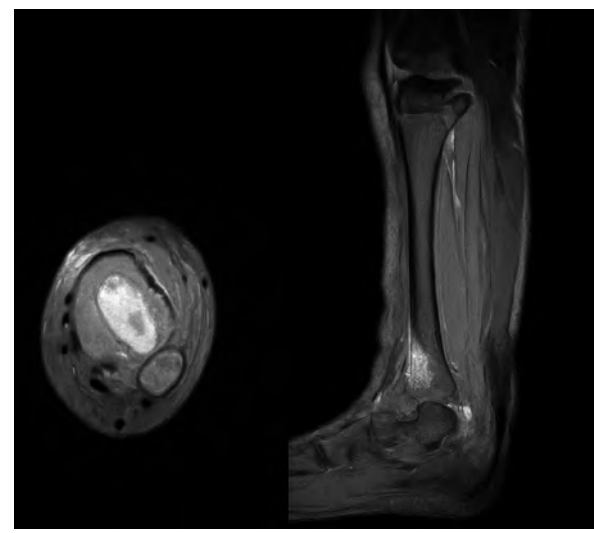

Figure 1. Left side: Axial T1-weighted MRI image, Right side: Sagittal PD-weighted MRI image. This visual illustrates the typical MRI features of sclerosing osteomyelitis including cortical thickening and periosteal reaction, predominantly visible in long bones of pediatric patients.

Treatment and Follow-Up: The treatment modalities for each patient were documented. We noted whether management was medical (antibiotics) alone or combined medical-surgical. For surgical treatment, the type of intervention was recorded – e.g. fenestration (cortical window and intramedullary debridement), curettage, sequestrectomy, or segmental resection. Antibiotic therapies were recorded including agents and total duration. In culture-proven infections, targeted antibiotic regimens were given (for example, anti-staphylococcal antibiotics for S. aureus or multidrug therapy for tuberculosis); in culture-negative cases, broad-spectrum empiric regimens were used covering likely bacteria. Follow-up data were collected to assess outcomes, including resolution of infection (clinical and radiological), any recurrences, and complications such as fracture or growth disturbance. The length of follow-up for each case was also noted.[9]

Data Analysis: This being a descriptive case series, results are presented as counts, percentages, and medians as appropriate. No statistical comparisons were performed given the small sample size. A summary of patient characteristics is provided in Table 1.

RESULTS

Patient Demographics and Presentation: Eleven patients (6 male, 5 female) were identified. Ages ranged from 1 year to 18 years (median ~10 years). Seven patients (64%) were adolescents (≥10 years old) and four were under 10 (including one infant). All patients had an insidious onset of localized bone pain that persisted for weeks to months (median symptom duration 3 months) before diagnosis. Pain was the predominant symptom in every case, often with mild tenderness or swelling over the involved site. Classic signs of acute infection (high fever, erythema, abscess or draining sinus) were absent in all but one case. The exception was the 1-year-old patient, who presented with fever and irritability in addition to limb pain; this patient was later found to have Salmonella osteomyelitis. Two patients had notable comorbid conditions: One had familial Mediterranean fever (an autoinflammatory disease) and another had a history of Henoch-Schönlein purpura. These conditions occasionally contributed to episodic limb pains or inflammatory markers, which initially confounded the clinical picture. A history of antecedent trauma was noted in one case (a 14-year-old boy had a motorcycle accident injuring his leg several months prior), but no other patients had significant trauma before symptom onset.

Anatomical Distribution and Imaging: The distribution of affected bones is summarized in Table 1. The long bones of the lower extremity were most frequently involved. The femur was the single most common site, affected in 5 of 11 cases (45%). Four of these involved the distal femoral metaphysis or metadiaphysis, and one was in the mid-diaphysis. The tibia was the second most common site, in 4 cases (36%). Two tibial lesions were diaphyseal and two were in the distal metaphysis (one of which extended into the adjacent distal fibula). Additionally, 1 case involved the diaphysis of the humerus, and 1 case involved the calcaneus (heel bone). All lesions were unifocal; we did not observe multifocal disease in any patient.

On radiographic examination, all cases showed the characteristic features of chronic sclerosing osteomyelitis. Plain X-rays demonstrated diffuse sclerosis and cortical thickening of the affected bone, often with fusiform enlargement of the shaft and obliteration of the normal medullary canal. Periosteal new bone formation was present in the majority of cases, appearing as layered or solid periosteal reaction along the cortex. For example, one femoral lesion exhibited an "onion-skin" type periosteal layering reminiscent of that seen in Ewing sarcoma or chronic os-

Table 1. Summary of patient characteristics and outcomes

Case	Age (y)	Sex	Bone (site)	Microorganism	Treatment (Abx=antibiotics)	Outcome (follow-up)
1	16	F	Humerus (diaphysis)	*S. aureus* (MSSA)	Abx (8 wk) +fenestration	Recurrence (2y; re-debrided), cured
2	18	M	Femur (mid-diaphysis)	*S. aureus* (MRSA)	Abx (8 wk) + segmental resection/graft	Cured (24 mo)
3	14	M	Tibia (distal) + fibula	*S. aureus* (MSSA)	Abx (6 wk) + fenestration	Cured (18 mo)
4	15	F	Femur (distal metaphysis)	No organism isolated	Abx (6 wk) only	Cured (12 mo)
5	10	M	Femur (distal metaphysis)	*M. tuberculosis*	Anti-TB therapy (6 mo)	Cured (48 mo)
6	13	F	Femur (metaphysis)	No organism isolated	Abx (6 wk) only	Cured (36 mo)
7	17	M	Tibia (diaphysis)	*S. aureus* (MSSA)	Abx (8 wk) + fenestration	Cured (9 mo)
8	7	F	Tibia (diaphysis)	No organism isolated	Abx (6 wk) only	Cured (12 mo)
9	8	F	Calcaneus	*S. aureus* (MSSA)	Abx (6 wk) + curettage	Cured (12 mo)
10	9	M	Femur (metaphysis)	No organism isolated	Abx (6 wk) + fenestration	Cured (6 mo)
11	1	M	Tibia (proximal)	*Salmonella* spp.	Abx (8 wk) only	Cured (6 mo)

MSSA: Methicillin-sensitive Staphylococcus aureus; MRSA: Methicillin-resistant S. aureus. Fenestration: Surgical cortical window and intramedullary debridement. Anti-TB therapy: Standard multi-drug tuberculosis treatment. Follow-up duration is given as months (mo) or years (y).

teomyelitis. Importantly, there were no osteolytic defects, sequestra, or periosteal bone sequestra noted. MRI findings (available in 8 patients) included low to intermediate signal intensity of the marrow on T1-weighted images, high T2 signal with periosteal elevation, and patchy gadolinium enhancement, but no fluid collections or abscesses. These imaging characteristics, although consistent with a chronic osteitic process, led to diagnostic confusion. In 6 patients (55%), the initial radiology interpretation raised suspicion for a neoplasm rather than infection. Differential considerations included osteosarcoma, Ewing sarcoma, osteoid osteoma or osteoblastoma, and in one case, stress fracture. In two instances, radiologists did consider osteomyelitis but recommended biopsy to exclude malignancy. Consequently, all 11 patients underwent bone biopsy for definitive diagnosis.

Laboratory Findings: Laboratory evaluation at presentation was largely unremarkable or only mildly inflammatory in most cases. Inflammatory markers were generally normal or only modestly elevated, consistent with a low-grade infection. CRP and WBC were within normal limits in about half of the patients and only slightly elevated in the others, while ESR was often moderately elevated (typically 30–85 mm/hour). Notably, the infant with Salmonella osteomyelitis had a markedly high CRP (>150 mg/L) during the acute febrile phase. No patients had severe leukocytosis or other laboratory evidence of acute infection. These findings reflect the indolent nature of Garré's osteomyelitis.

Histopathology and Microbiology: Biopsy histopathology in all cases confirmed chronic osteomyelitis, showing dense lymphoplasmacytic infiltrates, marrow fibrosis, and reactive new bone formation. No malignant cells or granulomas (except in one case) were present. In one patient (a 10-year-old boy with a distal femur lesion), histology revealed granulomatous inflammation with caseation necrosis, suggestive of tuberculosis; subsequent cultures and PCR confirmed Mycobacterium tuberculosis in this case.

Microbiological cultures of the biopsy specimens identified an organism in 7 out of 11 cases (64%). Staphylococcus aureus was the most common pathogen, isolated in 5 patients (all methicillin-sensitive except one MRSA). In several of these staphylococcal cases, there was a history of prior transient bone pain or an "acute osteomyelitis" episode that resolved with initial treatment, implying that S. aureus infection had persisted at a low level. One patient (the infant) grew a non-typhoidal Salmonella species on culture – an uncommon cause of osteomyelitis in immunocompetent children. The tuberculous case, as noted, was culture-positive for M. tuberculosis. Four patients had negative cultures. Two of the culture-negative patients had received antibiotics before biopsy, likely contributing to sterile cultures, and the other two may represent either undetected bacterial infection or a non-bacterial osteomyelitic process. Blood cultures (performed in 3 patients who had fevers) were all negative.

Treatment: All patients received appropriate antibiotic therapy. In culture-confirmed cases, targeted antibiotics were administered for approximately 6–8 weeks (e.g. anti-staphylococcal antibiotics for S. aureus, multi-drug therapy for tuberculosis). In culture-negative cases, broad-spectrum empirical regimens were used to cover staphylococci (including MRSA) and Gram-negative organisms for a similar duration. Six patients (55%) underwent adjunct surgical intervention in addition to antibiotics. The most common procedure was a limited cortical fenestration with intramedullary debridement (performed in 4 cases), which involves creating a small cortical window and reaming or curetting out the sclerotic, avascular bone within the medullary cavity. This serves to decompress the bone and improve antibiotic penetration.[5] One patient with an extensive femoral diaphyseal lesion underwent a segmental resection of approximately 4 cm of diseased bone followed by fibular strut grafting to reconstruct the defect. Another patient with a calcaneal lesion had surgical curettage of the sclerotic focus through a small window. The remaining 5 patients improved with antibiotic therapy alone (though all had a diagnostic biopsy, which in some cases may have also provided therapeutic decompression). All surgeries were uncomplicated; notably, no frank pus was encountered intraoperatively, consistent with the non-suppurative nature of these infections.

Outcomes: After a mean follow-up of about 2 years (range 6 months to 4 years), all patients achieved resolution of their osteomyelitis. Clinically, bone pain and any swelling resolved within the initial weeks to months of therapy in every case. By final follow-up, all patients had returned to normal daily activities without pain or functional limitation. In those patients who were athletes or active, full sports participation was resumed with no issues. Inflammatory markers (CRP, ESR) returned to normal in all cases after treatment. Follow-up radiographs demonstrated gradual remodeling of the affected bones. Over 1–2 years, the cortical thickening partially regressed and medullary cavities began to reappear, indicating new healthy bone formation. Some residual sclerosis persisted but was expected to remodel further during the child's growth. Importantly, no progressive bone destruction or new lesions were seen post-treatment.

One patient experienced a recurrence of osteomyelitis. This was a 16-year-old female with a chronic sclerosing lesion of the humerus (Case 1 in Table 1). She initially responded to antibiotics and a fenestration surgery (culture grew MSSA). About 2 years later, she developed pain again in the same site. Imaging showed renewed periosteal reaction and sclerosis. She underwent a repeat surgical debridement; cultures at the second surgery grew Staphylococcus epidermidis (a skin commensal, possibly a new low-grade infection). She was treated with another course of antibiotics and has remained asymptomatic for 18 months since. Aside from this case, no other patient had a recurrence. There were no long-term sequelae observed. No pathologic fractures occurred, and there were no growth disturbances or limb deformities in any patient

(the lesions were largely diaphyseal or metaphyseal and our surgical approaches preserved the growth plates). In summary, all 11 children attained full recovery with resolution of infection and return to normal function.

DISCUSSION

Our case series highlights key features of Garré's sclerosing osteomyelitis in children and contributes new data on its involvement in long bones. Although rare, this condition deserves clinical attention as it can mimic more serious diagnoses, including bone malignancies. Consistent with previous literature, our patients were predominantly school-aged children and adolescents (median age around 10 years) with a balanced sex distribution.[10] They presented with localized, indolent bone pain of several weeks to months' duration, often without systemic symptoms. This subtle clinical course frequently delays diagnosis, as pain without fever may be mistaken for benign musculoskeletal complaints.[4]

Radiographically, the femur and tibia were the most frequently involved bones, in keeping with previously reported extragnathic Garré's osteomyelitis. Though the mandible remains the classical site due to odontogenic infections, long bones such as the femur, tibia, humerus, fibula, and clavicle have been increasingly reported in children.[11] In our series, the femur and tibia accounted for 9 out of 11 cases, supporting their predominance among long bone sites. One case involved the humerus, and another the calcaneus, which is rarely affected in this entity. Importantly, all cases were unifocal. No patient exhibited multifocal lesions, which distinguishes Garré's osteomyelitis from chronic recurrent multifocal osteomyelitis (CRMO) or SAPHO syndrome—conditions typically associated with sterile, autoinflammatory bone lesions.[12]

A major clinical challenge in Garré's osteomyelitis is its radiologic resemblance to malignant bone tumors. Over half of our cases were initially misinterpreted as neoplasms based on radiographs or MRI findings, with differential diagnoses including Ewing sarcoma, osteosarcoma, or osteoid osteoma. Features such as layered periosteal reaction and bone sclerosis are not specific and may overlap with neoplastic conditions. Therefore, histopathological confirmation is essential. In our series, biopsy not only confirmed chronic osteomyelitis in all cases but also excluded malignancy. Additionally, biopsy allowed for culture sampling, aiding in targeted antibiotic therapy. We echo the consensus in the literature that early biopsy is critical in evaluating sclerotic lesions of unclear etiology in children to avoid both overtreatment and delayed care.

Microbiological findings in our study shed light on the underlying pathogenesis. In 64% of cases, we isolated a pathogen, with Staphylococcus aureus being the most frequently identified organism. This supports the view that Garré's osteomyelitis often stems from a low-grade bacterial infection rather than a purely sterile inflammatory process. The presence of methicillin-resistant S. aureus (MRSA) in one case demonstrates that even antibiotic-resistant pathogens can manifest as indolent disease. Our culture-positive rate was relatively high compared to prior reports, likely due to adequate biopsy technique and culture protocols.

We also observed two atypical pathogens. One infant had non-typhoidal Salmonella osteomyelitis, an uncommon finding in children without hemoglobinopathies. This highlights the possibility of hematogenous spread from subclinical gastrointestinal sources. Another patient's biopsy revealed granulomatous inflammation with caseation, and culture confirmed Mycobacterium tuberculosis. Although tuberculosis typically causes lytic bone lesions, our patient exhibited mainly sclerotic changes, reinforcing that TB should remain in the differential diagnosis for chronic bone lesions, especially in endemic areas.

Four patients had negative cultures. In two of these, prior antibiotic use may have sterilized the biopsy samples. The remaining two may represent either low-virulence bacterial infections undetected by standard cultures or non-bacterial autoinflammatory osteitis. Interestingly, one of the culture-negative patients had a known autoinflammatory disorder (familial Mediterranean fever), which may have predisposed him to sterile bone inflammation. Nevertheless, all culture-negative cases responded favorably to antibiotic treatment, suggesting that an occult infectious etiology was still likely. In the future, molecular tools such as broad-range PCR or next-generation sequencing could help detect fastidious organisms in similar patients.

Treatment was tailored to each case but followed general principles of chronic osteomyelitis management.[6] All patients received prolonged antibiotic therapy. In bacterial cases, this involved 6–8 weeks of targeted antibiotics. The tuberculosis case received standard 6-month antitubercular treatment. Culture-negative patients were treated empirically with broad-spectrum regimens aimed at S. aureus and Gram-negative organisms. Clinical and radiographic resolution in all patients confirmed the effectiveness of this approach.

Surgical intervention was performed in 6 of 11 patients (55%). The majority underwent fenestration with intramedullary debridement—a technique shown to relieve intraosseous pressure and improve antibiotic penetration. In one severe femoral case, we performed segmental bone resection with fibular graft reconstruction due to near-total medullary obliteration. Another patient underwent curettage of a calcaneal lesion through a small cortical window. In all surgically treated patients, no abscess or frank pus was encountered intraoperatively, consistent with the non-suppurative character of the disease. The remaining five patients improved with antibiotics alone, though they also had biopsy procedures that may have contributed therapeutically through decompression.

None of our patients required multiple surgeries, long-term suppressive antibiotics, or advanced reconstructive procedures beyond a single autograft. This suggests that

Garré's osteomyelitis, while potentially radiographically alarming, generally responds well to timely and targeted treatment. In particular, our use of conservative surgical approaches—limited debridement rather than extensive resection—proved effective and spared children from more invasive interventions.

Outcomes in our series were excellent. At a mean follow-up of two years, all 11 children were symptom-free, functionally normal, and had returned to age-appropriate activities. Radiographs showed gradual remodeling of the affected bones, with partial resolution of sclerosis and reconstitution of the medullary canal in most cases. Importantly, there were no pathological fractures, limb length discrepancies, or angular deformities. The growth plates were preserved in all cases, likely due to the predominantly diaphyseal location of lesions and careful surgical planning. One patient experienced a late recurrence at the original lesion site two years after initial treatment. She underwent repeat debridement and recovered without further relapse, confirming that even recurrences can be successfully managed.

These findings align with other reports in the literature, which describe chronic sclerosing osteomyelitis as a disease with a favorable prognosis once properly diagnosed and treated.[4] Our recurrence rate of 9% (1 of 11 patients) is within the range reported in similar pediatric case series. The indolent course of the disease typically allows sufficient time for diagnosis before complications such as fracture occur, and the natural healing potential in children facilitates bone remodeling after infection resolution.

There are some limitations to this study. As a retrospective single-center series with a small sample size, our findings may not be generalizable. We also lacked genetic or molecular testing in culture-negative cases to definitively distinguish infectious from autoinflammatory etiologies. However, the uniform treatment response supports a shared clinical pathway and reinforces the utility of our management algorithm in similar clinical settings.

Conclusion

In conclusion, Garré's sclerosing osteomyelitis of the long bones should be considered in the differential diagnosis of chronic bone pain with radiologic sclerosis in children. Early histopathological evaluation and microbiological culture are essential to differentiate it from neoplasia and identify causative organisms. The combination of appropriate antibiotics and surgical intervention when indicated leads to excellent outcomes. A multidisciplinary approach—engaging radiology, orthopedics, pathology, and infectious diseases—is vital to the timely and accurate diagnosis of this rare but treatable condition.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Hospital Ethics Committee (Date: 20.07.2025, Decision No: 2025/010.99/18/4).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.S.A.; Design: E.B.; Supervision: E.E.; Materials: E.B.; Data collection &/ or processing: M.S.A.; Analysis and/or interpretation: E.B.; Literature search: M.S.A.; Writing: H.B.C.; Critical review: E.B.

Conflict of Interest

None declared.

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Çocuklarda Uzun Kemiklerin Garré Tipi Sklerozan Osteomiyeliti: Klinik Özellikler, Tanı ve Tedavi Sonuçları

Amaç: Çocukluk çağında uzun kemikleri tutan Garré'nin sklerozan osteomiyelitinin klinik bulgularını, tanı sürecini ve tedavi sonuçlarını değerlendirmek.

Gereç ve Yöntem: 2011 ile 2019 yılları arasında tedavi edilen uzun kemik Garré osteomiyeliti tanılı 11 pediatrik olgu geriye dönük olarak incelendi. Klinik, görüntüleme, laboratuvar, mikrobiyolojik ve sonuç verileri kaydedildi; tüm hastalara kesin tanı için biyopsi yapıldı.

Bulgular: Yaşları 1–18 arasında değişen 11 hastanın tümü kronik kemik ağrısı ile başvurdu; sistemik semptomlar yoktu veya çok hafifti. En sık tutulan kemik femur (5 olgu), ardından tibia (4 olgu) idi. Radyografilerde kortikal kalınlaşma ve periosteal yeni kemik oluşumu izlendi; osteolitik lezyon veya apselere rastlanmadı. Biyopsilerde tüm olgularda malignite olmaksızın kronik osteomiyelit doğrulandı. Kültürlerde 7 hastada (%64) etken saptandı: 5 olguda en sık Staphylococcus aureus, 1'er olguda Salmonella ve Mycobacterium tuberculosis izole edildi. Tüm hastalara uzun süreli antibiyotik tedavisi uygulandı; 6 hastaya cerrahi debridman yapıldı. Takiplerde tüm hastalarda enfeksiyonun düzeldiği görüldü. Humerus tutulumu olan bir S. aureus vakasında geç nüks görülüp tekrar cerrahi gerekmiş, ancak başarıyla tedavi edilmiştir. Uzun vadeli fonksiyonel kayıp izlenmedi.

Sonuç: Uzun kemiklerde görülen Garré tipi kronik sklerozan osteomiyelit, malignite ile karıştırılmaması için atipik kemik lezyonu olan çocuklarda mutlaka düşünülmelidir. Görüntüleme yeterli olmayabilir; tanı için biyopsi şarttır. Uygun antibiyotik tedavisi ve gerektiğinde cerrahi müdahale ile hastaların büyük çoğunluğu tamamen iyileşmektedir. Erken tanı ve multidisipliner yaklaşım başarılı tedavi için kritik öneme sahiptir.

Anahtar Sözcükler: Garré osteomiyeliti; kronik sklerozan osteomiyelit; pediatrik kemik enfeksiyonu; uzun kemik inflamasyonu.

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Original Article

Intrahepatic Cholestasis of Pregnancy and Neonatal Acidemia: A Retrospective Analysis of Perinatal Outcomes

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Keywords: Bile acids; fetal cord blood pH; intrahepatic cholestasis of pregnancy; neonatal outcomes; perinatal morbidity.

ABSTRACT

Objective: This study aimed to evaluate the incidence of neonatal acidemia and its association with fasting bile acid levels in pregnancies diagnosed with intrahepatic cholestasis.

Methods: This retrospective cohort study included pregnant women who delivered at the Department of Obstetrics and Gynecology of our institution between January 2020 and March 2025. Patients diagnosed with intrahepatic cholestasis of pregnancy (ICP) were enrolled.Maternal and neonatal data were collected from hospital records, including demographic characteristics, laboratory values, treatment regimens, delivery details, and neonatal outcomes. Statistical analysis was conducted using SPSS version 24.0.

Results: A total of 58 women with intrahepatic cholestasis of pregnancy (ICP) were included. Based on serum bile acid levels at diagnosis, patients were divided into two groups: <40 μmol/L (n=41) and ≥40 μmol/L (n=17). No significant differences were observed between the groups regarding maternal demographics, gestational age, birth weight, or history of ICP (p>0.05). Preterm birth rates were similar in both groups (48.8% vs. 47.1%, p=1.000). NICU admissions were more common in the ≥40 μmol/L group (70.6% vs. 53.7%), but not statistically significant (p=0.36). Incidences of neonatal jaundice, tachypnea, and respiratory distress syndrome showed no significant group differences (p>0.05). Neonatal acidemia, defined as umbilical cord pH <7.20 or <7.10, occurred at comparable rates across both bile acid groups, without statistically significant differences. The mean pH was 7.29±0.11 in the <40 μmol/L group and 7.28±0.11 in the ≥40 μmol/L group (p=0.856). No correlation was observed between maternal bile acid levels and neonatal umbilical cord pH (r=–0.02, p=0.884).

Conclusion: No significant association was found between maternal bile acid levels and neonatal acidemia. Further prospective studies are needed to clarify this relationship in intrahepatic cholestasis of pregnancy.

INTRODUCTION

Intrahepatic cholestasis of pregnancy is the most commonly diagnosed liver disorder during pregnancy, particularly in the second and third trimesters. The condition is characterized by widespread pruritus, which typically intensifies at night, along with elevated liver transaminase levels (AST, ALT) and increased serum bile acid concentrations.[1] The prevalence of ICP shows significant variation across different geographic regions and ethnic groups, with reported rates ranging from 0.4% to 10%.[2] A range of risk factors including metabolic and hepatobiliary conditions like gestational diabetes, obesity, hepatitis C, and a previous ICP diagnosis have been linked to the emergence of this disorder.[3]

The diagnosis is made on the basis of a serum bile acid level of ≥10 μmol/L in patients presenting with pruritus.[4] Some guidelines recommend ≥19 μmol/L as the diagnostic threshold; however, a level of ≥10 μmol/L is generally accepted.[5,6] While the collection of fasting samples is considered the optimal method for measuring serum bile acids, recent clinical guidelines also accept postprandial samples as valid for diagnostic purposes.[4,6]

The pathophysiology of intrahepatic cholestasis of pregnancy involves impaired bile acid transport across the hepatocellular membrane due to hormonal, genetic, and environmental factors. Elevated estrogen and progesterone metabolites are thought to inhibit bile acid excretion, leading to intrahepatic accumulation. This accumulation increases the permeability of the placental barrier and

may cause fetal cardiotoxicity, vasoconstriction of placental vessels, and arrhythmias, which together contribute to adverse fetal outcomes such as hypoxia and sudden intrauterine death.[7]

It has been reported that fetal complications are associated with serum bile acid levels. Consequently, the severity of the disease is categorized as mild (10-40 µmol/L), moderate (40-100 µmol/L), and severe (>100 µmol/L) based on the bile acid level. This classification system serves as a clinical guide, informing the monitoring of disease progression and the determination of delivery timing.[8]

Although elevated maternal bile acid levels in intrahepatic cholestasis of pregnancy have been linked to various neonatal complications such as meconium stained amniotic fluid and preterm birth, objective data on neonatal acidemia, particularly based on umbilical cord blood gas analysis, remain sparse and inconsistent.

Based on previous studies reporting associations between bile acids and adverse fetal outcomes, we hypothesized that elevated maternal bile acid levels would correlate with neonatal acid-base disturbances, particularly acidemia.

This study aimed to assess perinatal outcomes in pregnancies complicated by intrahepatic cholestasis and to explore the relationship between maternal bile acid concentrations and neonatal acidemia.

MATERIALS AND METHODS

Study Design and Setting

The present study was designed as a retrospective cohort analysis. All women who delivered at the Department of Obstetrics and Gynecology of our institution between January 2020 and March 2025 were screened; those with a confirmed diagnosis of intrahepatic cholestasis of pregnancy (ICP) were included in the study. Approval for the study was provided by the Institutional Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital, and all procedures adhered to the ethical principles outlined in the Declaration of Helsinki (No: 2025/010.99/16/6, Date: 27/05/2025).

Patient Selection and Exclusion Criteria

ICP was diagnosed based on the presence of maternal pruritus and fasting serum bile acid levels ≥10 µmol/L, following the exclusion of other hepatic and dermatologic conditions. As per institutional protocol, all patients received ursodeoxycholic acid (UDCA) treatment.

Exclusion criteria included cases with incomplete neonatal outcome data or missing cord blood gas values, maternal age below 18 or above 45 years, and pregnancies complicated by fetal anomalies. As this was a retrospective study, informed consent was not required; however, patients with inaccessible or incomplete medical records were excluded from the analysis.

Data Collection

Maternal and neonatal data were retrospectively collected from the electronic medical records. The collected maternal variables included demographic characteristics such as maternal age, gravida and parity, as well as medical history including any comorbidities during pregnancy. Detailed information regarding the gestational week at the time of ICP diagnosis was recorded, along with laboratory parameters such as fasting serum bile acid levels at the time of diagnosis and again prior to delivery. Furthermore, an assessment was conducted to determine the presence of hepatic involvement. This assessment entailed the observation of liver enzyme levels, encompassing alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Information regarding the use of medical treatment, particularly ursodeoxycholic acid (UDCA), was documented in detail. The administered UDCA dose ranged between 10 and 15 mg/kg/day, divided into two or three doses per day. The duration of therapy was calculated from the date of diagnosis until delivery. Dose adjustments were made based on symptom severity and serum bile acid levels, in accordance with institutional protocol.

Abdominal ultrasound findings were evaluated for the presence of hepatobiliary abnormalities, including hepatomegaly, biliary sludge, gallstones, and intrahepatic ductal dilatation, as well as any other significant anatomical or pathological findings. Obstetric outcomes included mode of delivery, indication for cesarean delivery if applicable, and gestational age at the time of birth.

Neonatal outcomes included neonatal birth weight and sex, need for neonatal intensive care (NICU), duration of NICU stay, umbilical cord blood pH, and the presence of respiratory distress syndrome, tachypnea, or neonatal jaundice.

Statistical Analysis

For the purpose of all statistical analyses, the IBM SPSS Statistics for Mac version 24.0 software was employed. In this study, we utilized the Kolmogorov–Smirnov test and employed visual inspection of histograms to assess the normality of continuous variables. Variables with a parametric distribution were expressed as the mean (standard deviation), and comparisons between groups were performed using the independent samples t-test. In cases where the data were found to be non-normally distributed, a logarithmic transformation was first applied, and the parametric test was subsequently employed if the data were found to be normally distributed following this transformation. For variables that did not follow a normal distribution, the Mann-Whitney U test served as the appropriate statistical tool. These variables were described using the median and minimum–maximum values. Categorical comparisons were conducted via chi-squared or Fisher's exact tests, depending on the distribution of data in contingency tables. Results were deemed statistically significant when the p-value was below 0.05.

RESULTS

This study involved a total of 58 pregnant women diagnosed with Intrahepatic Cholestasis of Pregnancy (ICP). Patients were categorized into two groups according to their serum bile acid levels at diagnosis: Group 1 (<40 µmol/L, n=41) and Group 2 (≥40 µmol/L, n=17). Maternal and perinatal characteristics of the two groups are presented in Table 1.

A statistically significant disparity was not observed between the groups with regard to maternal age, gravidity, parity, gestational age at diagnosis, gestational age at delivery, birth weight, or history of cholestasis in a previous pregnancy (p>0.05 for all). Alanine aminotransferase (ALT) levels were significantly higher in Group 2 than in Group 1 (197.2=127.6 vs. 121.2=121.3 U/L, p=0.045).

Although bile acid concentrations are presented as medians in Table 1 due to non-normal distribution, the mean (±SD) serum bile acid level for the entire cohort was 31.7=32.2 µmol/L. In subgroup analysis, the mean (±SD) values were 17.4=5.9 µmol/L in Group 1 and 66.0=42.9 µmol/L in Group 2.

Neonatal outcomes were compared between patients with bile acid levels <40 µmol/L (Group 1) and those with levels ≥40 µmol/L (Group 2). The rate of preterm birth was similar between Group 1 and Group 2 (48.8% vs. 47.1%, p=1.00). The rate of NICU admission was higher in Group 2 (70.6%) than in Group 1 (53.7%), but the difference was not statistically significant (p=0.23) (Table 2).

Neonatal jaundice was observed in 58.8% of Group 2 and 36.6% of Group 1 (p=0.15). Similarly, rates of tachypnea (36.6% vs. 29.4%, p=0.51) and respiratory distress syndrome (RDS) (9.8% vs. 11.8%, p=1.00) were comparable between groups, with no statistically significant differences observed in any of the evaluated neonatal outcomes (Table 2).

Neonatal acidemia was assessed using two different pH thresholds. When defined as a pH<7.20 (mild acidemia), it was observed in 14.6% of newborns in Group 1 and 17.6%

Table 1. Comparison of maternal and perinatal characteristics according to bile acid levels

	Group 1 (<40 µmol/L, n=41)	Group 2 (≥40 µmol/L, n=17)	p-value
Maternal age (years)	30.6 (5.4)	31.0 (7.0)	p=0.97*
Gravidity	3 (1-6)	2 (1-6)	p=0.51**
Parity	1 (0-4)	0 (0-3)	p=0.90**
ALT (U/L)	121.2±121.3	197.2±127.6	p=0.045***
AST (U/L)	82.6±92.4	168.3±185.2	p=0.085***
GA at diagnosis (weeks)	34 (26-38)	32 (18-38)	p=0.64**
Bile acid level at diagnosis (µmol/L)	18 (10.4-31.2)	52 (40-219)	p<0.001**
History of ICP in previous pregnancy (%)	7 (17.1)	3 (17.6)	p=0.95****
GA at delivery (weeks)	37 (27-39)	37 (32-40)	p=0.50**
Birth weight (g)	2842.3 (677.9)	2860.9 (628.5)	p=0.92***
Cesarean section (%)	22 (53.7)	8 (47.0)	p=0.48****

ALT: Alanine aminotransferase; AST = Aspartate aminotransferase; GA: Gestational age; ICP: Intrahepatic cholestasis of pregnancy; µmol/L: Micromoles per liter; g: grams. Data are presented as mean (SD) for parametric variables, median (min-max) for nonparametric variables, and frequency (percentage) for categorical variables. *Independent samples t-test after logarithmic transformation. **Mann-Whitney U test. ***Independent samples t-test. ****Chi-square test. p<0.05 was considered statistically significant.

Table 2. Neonatal outcomes according to bile acid groups

	Group 1<40 µmol/L (n=41)	Group 2 ≥40 µmol/L (n=17)	p-value
Preterm birth n (%)	20 (48.8)	8 (47.1)	1.00
NICU admission n (%)	22 (53.7)	12 (70.6)	0.23
Jaundice n (%)	15 (36.6)	10 (58.8)	0.15
Tachypnea n (%)	15 (36.6)	5 (29.4)	0.51
RDS n (%)	4 (9.8)	2 (11.8)	1.00
Mild acidemia (pH<7.20) n (%)	6 (14.6)	3 (17.6)	1.00
Severe acidemia (pH<7.10) n (%)	2 (4.9)	2 (11.8)	0.70

NICU: Neonatal Intensive Care Unit; RDS: Respiratory Distress Syndrome; n: Number of cases. Categorical variables are presented as frequency (percentage) and compared using the Chi-square test. p<0.05 is considered statistically significant. No statistically significant differences were found.

Table 3. Comparison of umbilical cord blood gas parameters according to bile acid levels

	Group 1<40 µmol/L (n=41)	Group 2 ≥40 µmol/L (n=17)	p-value
pH	7.30 (6.80-7.43)	7.28 (7.06-7.44)	0.797*
pCO_2 (mmHg)	48.91 (13.81)	50.33 (11.84)	0.591**
pO_2 (mmHg)	33.63 (11.17)	30.82 (11.88)	0.410***
HCO_3 (mmol/L)	20.80 (9-27.4)	21.60 (7-27.6)	0.885*
Base Excess (BE)	3.50 (0.1-13)	4.20 (0.3-9.3)	0.771*

pCO_2: Partial pressure of carbon dioxide; pO_2: Partial pressure of oxygen; HCO_3^-: Bicarbonate; BE: Base excess; SD: Standard deviation. Data are presented as mean (SD) for parametric variables, median (min–max) for nonparametric variables. *Mann-Whitney U test. **Independent samples t-test after logarithmic transformation. ***Independent samples t-test. p<0.05 was considered statistically significant.

in Group 2 (p=1.00). Using a stricter definition (pH<7.10, severe acidemia), the rates were 4.9% and 11.8% for Group 1 and Group 2, respectively (p=0.70). In both definitions, the differences between the bile acid groups were not statistically significant (Table 2).

The comparison of umbilical cord blood gas parameters between the two bile acid groups is presented in Table 3. No statistically significant differences were observed in any of the measured parameters, including pH, pCO_2, pO_2, bicarbonate (HCO_3^-), or base excess (BE), between Group 1 (<40 µmol/L) and Group 2 (≥40 µmol/L). Median cord blood pH values were 7.30 and 7.28 in Group 1 and Group 2, respectively (p=0.797). Similarly, other gas parameters showed comparable distributions across groups, suggesting no association between bile acid levels and cord blood gas status at birth.

Additionally, Pearson correlation analysis showed no statistically significant relationship between maternal bile acid levels and neonatal cord pH (r=–0.02, p=0.884).

DISCUSSION

Intrahepatic cholestasis of pregnancy is one of the most common liver-related disorders occurring during pregnancy. Serum bile acid levels are widely accepted as the primary parameter for both diagnosis and monitoring of the condition. In the evaluation of ICP severity, bile acid levels are classified as mild if between 10-40 µmol/L, moderate if between 40-100 µmol/L and severe if above 100 µmol/L.[5,6,9] In the present study, due to the distribution of the number of patients, the grouping was made in two categories: <40 µmol/L and ≥40 µmol/L. However, the limited number of patients with concentrations ≥100 µmol/L precluded triple classification and constrained the statistical power of subgroup analyses.

The impact of intrahepatic cholestasis on obstetric outcomes has been extensively documented in the extant literature. The most frequently reported complications include preterm labour, meconium-stained amniotic fluid, fetal distress, fetal asphyxia and intrauterine fetal death. These findings suggest that the disease may have serious effects on fetal well-being.[10,11]

In the study conducted by Brouwers et al.,[12] it was reported that bile acid may increase the risk of preterm labour by causing toxic effects on placental membranes. It has been hypothesised that this mechanism may be responsible for the early degeneration of amniotic membranes and the acceleration of cervical maturation. In our study, preterm labour occurred in 48.3% of 58 patients diagnosed with intrahepatic cholestasis. This rate is significantly higher compared with the frequency of preterm labour of approximately 11% reported in the general obstetric population.[13] The present study is consistent with earlier research[12,14] and demonstrates that intrahepatic cholestasis is a high-risk condition for preterm delivery. In a subgroup analysis, a higher rate of preterm delivery was observed in pregnant women with serum bile acid levels ≥40 µmol/L. However, this difference was not statistically significant. This may be attributable to the inability of the analyses to attain sufficient statistical power due to the constrained sample size.

The necessity for the utilisation of the Neonatal Intensive Care Unit (NICU) is a prevalent neonatal outcome in pregnancies accompanied by cholestasis and prematurity. The development of this condition is hypothesised to be facilitated by fetal distress and respiratory system problems. In the present study, the necessity for NICU was found to be elevated in the group with a serum bile acid level of 40 µmol/L and above. However, this discrepancy was not statistically significant.

In this study cohort, neonatal jaundice occurred in 44.6% of newborns, and tachypnea was identified in 35.7% of cases. While the incidence of jaundice was consistent with the overall neonatal population, the prevalence of tachypnea was found to be higher than the averages reported in existing studies.[15,16] However, later subgroup analyses did not show a statistically significant link between these neonatal complications and serum bile acid levels. Therefore, these results should be interpreted cautiously, and further research with larger sample sizes is needed to explore possible associations.

Another important issue pertaining to ICP is fetal acidosis and postnatal acid-base balance. In the present study, neonatal acidosis was objectively evaluated by umbilical

cord blood gas analysis. Acidemia, defined as a pH below 7.20, was identified in 15.5% of cases, with more severe acidemia (pH <7.10) present in 6.9%. However, no significant relationship was found between bile acid level and pH value. In a prospective case-control study, Futterman et al.[17] investigated troponin I levels to assess fetal myocardial injury potentially associated with sudden fetal death. Troponin I levels were found to be significantly elevated in the group with intrahepatic cholestasis of pregnancy. In their secondary analysis, cord blood pH and base excess were assessed to investigate neonatal acidosis. Consistent with our results, the study found no meaningful differences between the ICP and control groups. The results indicate that maternal bile acids might exert minimal influence on the acid-base balance of the fetus. It has been hypothesised that the protective effect of the placental barrier, fetal compensatory mechanisms, or treatments such as UDCA, may weaken this relationship.

Specifically, the placenta may limit the transplacental passage of toxic bile acids through active transport systems such as the bile salt export pump, thereby reducing fetal exposure.[18] Additionally, the fetal acid–base balance may be buffered by endogenous compensatory mechanisms including bicarbonate and protein buffering systems.[19] Recent investigations such as Tosun et al.[20] have explored endoplasmic reticulum stress–related biomarkers as novel predictors of placental dysfunction in ICP, providing new insights beyond conventional bile acid measurement. UDCA treatment, commonly used in intrahepatic cholestasis of pregnancy, has been reported to improve certain aspects of placental function, which may help support fetal well-being and contribute to a more stable intrauterine environment.[21] These factors, alone or in combination, may contribute to the lack of a clear association between maternal bile acid levels and neonatal acidosis observed in this study.

Clinically, our findings suggest that while bile acid levels remain a key diagnostic marker in ICP, they may not directly reflect the degree of fetal acid-base impairment. This suggests that fetal risk in cholestasis of pregnancy is multifactorial. In addition to bile acid concentration, many factors such as placental perfusion, maternal liver function, and response to treatment also contribute to fetal risks. Therefore, when assessing perinatal risk, bile acid measurement should be interpreted in conjunction with other maternal and fetal parameters.

The main limitations of our study are its small sample size, the low number of patients in the group with high bile acid levels, and its single-center, retrospective design. These factors may limit the generalizability of our findings and constrain our ability to establish causal relationships. In addition, due to the retrospective nature of the study, certain confounding variables such as genetic predisposition and medication compliance could not be fully controlled. The small number of patients with severe cholestasis also reduced the statistical power for subgroup analyses. Therefore, multicenter prospective studies with larger patient populations are needed to validate and expand upon these findings.

Conclusion

This study found no evidence to suggest that there is a significant association between maternal serum bile acid levels and neonatal acidemia. Although our findings suggest no direct relationship, the limited number of patients with high bile acid levels may have restricted the power to detect such an association. Therefore, larger-scale, prospective studies are needed to better clarify this potential relationship and its clinical implications.

Ethics Committee Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 27.05.2025, Decision No: 2025/010.99/16/6).

Informed Consent

Not required due to the retrospective design of the study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.Y., D.K.; Design: A.Y.; Supervision: D.K.; Funding: A.Y.; Materials: A.Y.; Data collection and/or processing: D.K.; Analysis and/or interpretation: D.K.; Literature search: A.Y., D.K.; Writing: A.Y., D.K.; Critical review: A.Y.

Conflict of Interest

None declared.

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Gebeliğin İntrahepatik Kolestazı ve Yenidoğan Asidemisi: Perinatal Sonuçların Retrospektif Analizi

Amaç: Çalışmamızın amacı intrahepatik kolestaz tanısı almış gebeliklerde yenidoğan asidemisi insidansını saptamak ve bunun açlık safra asidi düzeyleri ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: Kurumumuz Kadın Hastalıkları ve Doğum Kliniği'nde Ocak 2020 ile Mart 2025 tarihleri arasında doğum yapan ve intrahepatik kolestaz (İHK) tanısı konan gebelerin dosyaları retrospektif olarak tarandı ve çalışmamıza dahil edildi. Anne ve yenidoğana ait veriler; demografik özellikler, laboratuvar değerleri, tedavi protokolleri, doğum bilgileri ve yenidoğan sonuçları hastane kayıtlarından toplanmıştır. İstatistiksel analizler SPSS 24.0 programı kullanılarak yapıldı.

Bulgular: Toplam 58 İHK tanılı gebe çalışmaya dahil edilmiştir. Hastalar, serum safra asidi düzeylerine göre <40 µmol/L (n=41) ve ≥40 µmol/L (n=17) olmak üzere iki gruba ayrılmıştır. Gruplar arasında maternal demografik özellikler, gebelik haftası, doğum ağırlığı ve önceki kolestaz öyküsü açısından anlamlı fark bulunmamıştır (p>0.05). Preterm doğum oranları her iki grupta benzer bulunmuştur (%48.8 vs. %47.1; p=1.000). Yenidoğan yoğun bakım ünitesine (YYBÜ) yatış oranı ≥40 µmol/L grubunda daha yüksek saptanmakla birlikte (%70.6 vs. %53.7), bu fark istatistiksel olarak anlamlı değildir (p=0.36). Yenidoğan sarılığı, takipne ve solunum sıkıntısı sendromu insidansları da gruplar arasında benzer bulunmuştur (p>0.05). Yenidoğan asidemisi (göbek kordonu pH <7.20 ya da <7.10 olarak tanımlanan olgular) her iki grupta benzer oranlarda gözlenmiş, gruplar arasında anlamlı fark saptanmamıştır. Ortalama pH değerleri <40 µmol/L grubunda 7.29±0.11≥40 µmol/L grubunda ise 7.28±0.11 olarak hesaplanmıştır (p=0.856). Maternal serum safra asidi düzeyi ile göbek kordonu pH değeri arasında anlamlı bir korelasyon bulunmamıştır (r=–0.02; p=0.884).

Sonuç: Gebelik kolestazı olan hasta grubunda, maternal safra asidi düzeyleri ile yenidoğan asidemisi arasında anlamlı bir ilişki saptanmamıştır. Bu ilişkinin daha iyi anlaşılabilmesi için ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: FGL-2 düzeyi; nonalkolik steatohepatit; prognostik önem.

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Original Article

Determinants of Types of Aortic Arch and Bovine Aortic Arch in Thrombectomy and Intraarterial Thrombolytic Procedures in Acute Ischemic Stroke

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Keywords: Arch; aorta; intra-arterial thrombolysis; stroke; thrombectomy.

ABSTRACT

Objective: Complex aortic arch anatomy increases technical difficulties in acute ischemic stroke interventions. We hypothesized that aortic arch variations correlate with patient age and atherosclerotic burden in thrombectomy and intraarterial thrombolytic therapy (IAT) patients.

Methods: This retrospective study analyzed aortic arch morphology in 63 consecutive patients (39 males, 24 females; median age 72 years) who underwent thrombectomy and IAT for acute ischemic stroke. Aortography was systematically performed before intervention to classify arch types (I, II, III) and identify bovine arch variants. Statistical analysis examined relationships between arch variations, patient demographics, and risk factors.

Results: Type II arch was most prevalent (37 patients, 58.7%), followed by Type I (13 patients, 20.6%) and Type III (13 patients, 20.6%). Bovine arch occurred in 16 patients (25.4%). Patients with Type II/III arches were significantly older than those with Type I ($p=0.028$). Aortic plaque presence strongly correlated with arch type ($p<0.001$), with 92.3% of Type III patients having plaques versus 7.7% of Type I patients. Procedural success was achieved in 59/63 cases (93.7%).

Conclusion: This retrospective analysis demonstrates that aortic arch variations increase with age and correlate with atherosclerotic burden. Type II and III arches predominate in stroke intervention patients, requiring specialized catheter techniques while maintaining high procedural success rates.

INTRODUCTION

The brain receives blood supply through supraaortic vessels. The aortic arch generates the supraaortic arteries, often called the great vessels. Types of aortic arch have been described in humans, namely type I, II and III (Fig. 1). Classification of the aortic arch is determined by measuring the gap from its peak to the innominate artery's origin (Fig. 2).[1] The most frequent structural form of the aortic arch in humans is the standard type. This common structure is estimated to appear in nearly 70% of individuals. The Bovine arch is the second most frequent variant of the aortic arch (Fig.3). When the left CCA emerges from the innominate artery, it is identified as a 'Bovine origin'.

In proximal intracranial occlusion affecting the anterior circulation, intraarterial intervention within six hours and stent retriever thrombectomy are proven to be both safe and effective.[2,3] For intracranial and extracranial interventional procedures, the first stage is the passage of catheters through the aortic arch. Endovascular interventions using

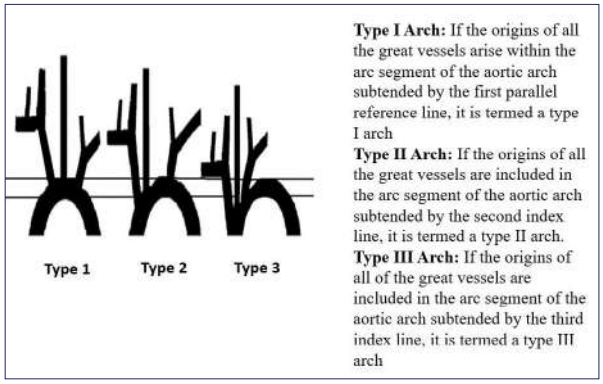

Figure 1. Aortic arch classification system. Type I: normal anatomy suitable for standard catheters; Type II: moderate elongation requiring modified approach; Type III: severe angulation creating technical challenges for endovascular procedures.

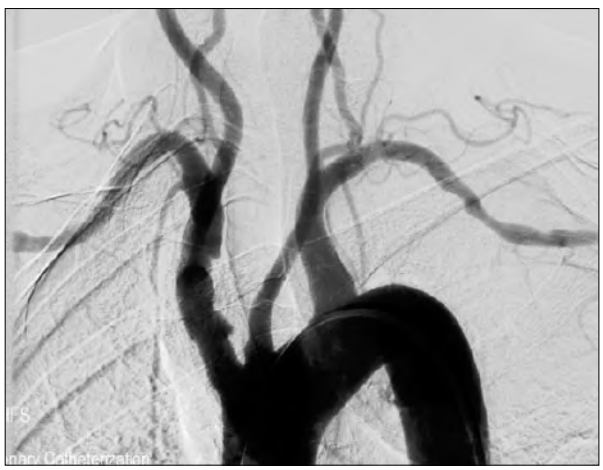

Figure 2. Type III aortic arch showing severe angulation between arch apex and innominate artery. This configuration complicates catheter navigation and requires specialized techniques during stroke interventions.

stents and coils for carotid stenosis and aneurysms are established treatment modalities with demonstrated positive outcomes and durable results.[4]

The congenitally variable anatomy of the supraaortic vessels increases the complications of endovascular interventions (carotid artery stenting, thrombectomy, IAT, etc.).[5,6] In addition to extending the processing time. Type I arc is normal and suitable for intervention while type II, III and Bovine arch are difficult for endovascular intervenions. Thus, recognizing aortic arch classification is essential for intervention planning. Aortography can identify different aortic arch variations before intervention. So that appropriate materials can be selected. Anatomical differences in the aortic arch arise from congenital or acquired influences. The exact causes of these anatomical variations remain undetermined in research. All individuals are initially born possessing a Type I arch.[7]

We analyzed aortic arch variations and their risk factors in patients who underwent thrombectomy and intra-arterial

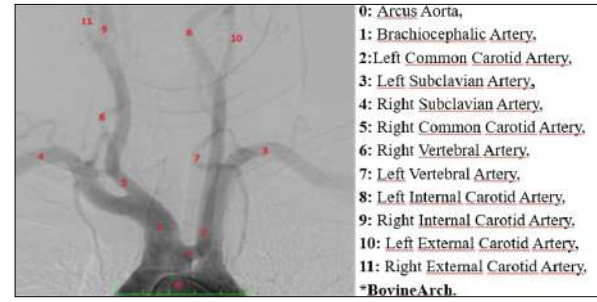

Figure 3. Bovine arch variant with common origin of innominate and left carotid arteries. Present in 25.4% of our cohort, this anatomy alters standard catheter approach during emergency procedures.

(IA) thrombolysis for acute ischemic stroke, drawing from our own experience.

MATERIALS AND METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki. Approval was obtained for retrospective analysis of patient data from the Zonguldak Bulent Ecevit University Ethics Committee (No: 2025/01, Date: 08/01/2025).

This retrospective study analyzed 63 consecutive patients who underwent thrombectomy and intraarterial (IA) therapy for acute ischemic stroke in our hospital's catheter lab. This was a single-center retrospective observational study. All interventions and imaging procedures were performed as part of standard clinical care for acute stroke management. Patient data were collected retrospectively from medical records and our catheter lab database

Patients were transported to the hospital by air or ground ambulance and received IA-tPA treatment within the 6-hour therapeutic window and patients who received thrombectomy were taken within 8 hours (Fig. 4; Fig. 5). All patients routinely were received aortograph before the thrombectomy and IAT.

Inclusion criteria for IA fibrinolytic therapy: Moderate benefits observed in those with severe deficiencies in the 0 to 6 hour window and minor or branch of large artery (large arteries: ICA, middle cerebral artery and basilar artery) cerebral thrombotic occlusions.

Inclusion criteria for thrombectomy: In the 0- to 8-hour window moderate net benefits when applied to all patients with potentially disabling deficits and large artery cerebral thrombotic occlusions. Exclusion criteria for IA fibrinolytic therapy and thrombectomy: Patients with imaging evidence of extensive ischemic damage, absence of salvageable ischemic penumbra, and standard contraindications for angiography (e.g., severe contrast allergy, severe renal dysfunction, inability to obtain vascular access).

All patients underwent risk factors evaluation prior and after thrombectomy or IAT in the hospital. Plaques in the

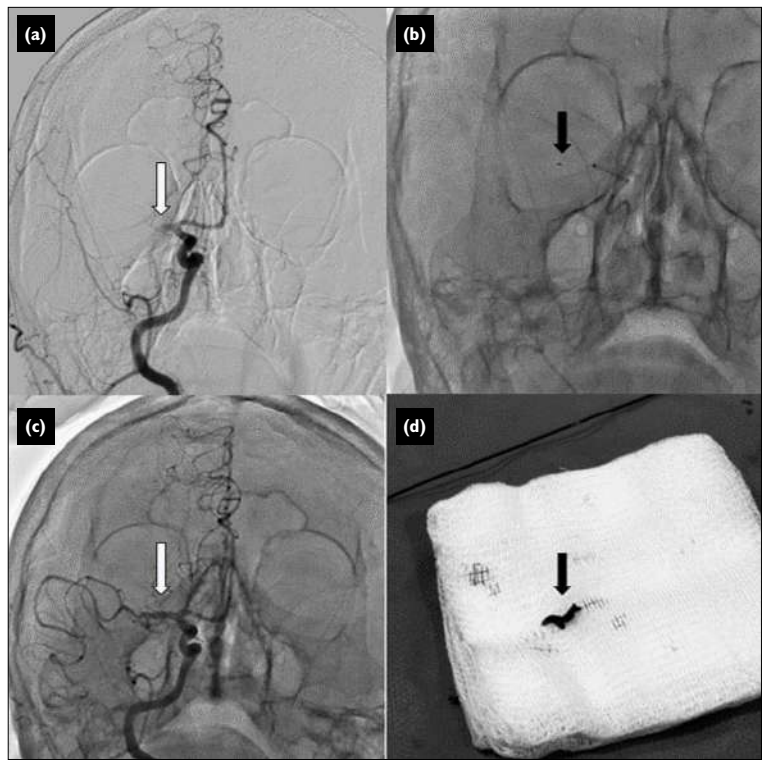

Figure 4. Mechanical thrombectomy procedure. **(a)** Right MCA occlusion (white arrow); **(b)** Stent retriever deployment (black arrow); **(c)** Complete recanalization (white arrow); **(d)** Retrieved clot material (black arrow). Demonstrates successful endovascular technique.

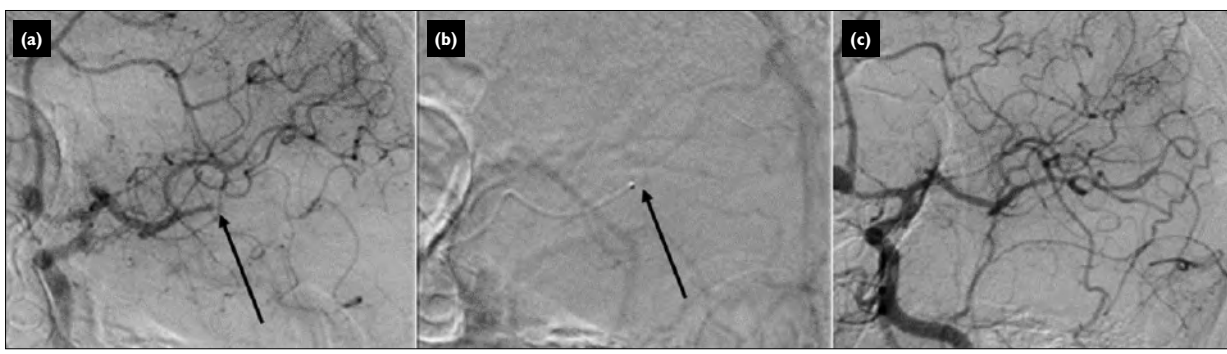

Figure 5. Intraarterial thrombolysis procedure. **(a)** Inferior MCA division occlusion (black arrow); **(b)** Alteplase administration via microcatheter (black arrow); **(c)** Post-treatment recanalization. Shows effective pharmacological intervention for branch vessel occlusions.

aorta and large arteries were recorded during angiography. The relationship between the types of aortic arch, Bovine aortic arch and plaques was studied in digital subtraction angiography (DSA). Additionally, we studied the relationship with risk factors.

Power Analysis: Sample size calculation was performed using G*Power 3.1.9.7. With an alpha level of 0.05, power of 80%, and expected effect size of 0.5 based on preliminary data, the minimum required sample size was calculated as 52 patients. Our study included 63 patients, providing adequate power (84%) for detecting clinically meaningful differences between arch types.

Aortography procedure

Transfemoral access was utilized for angiographic imaging. After administering 2% lidocaine or xilocaine, the common femoral artery was punctured, and a 6F or 7F sheath was positioned. A pigtail catheter (6F) over a 0.035-inch, hydrophilic or non-hydrophilic guidewire was advanced for cannulation of the arcus aorta target was performed.

Arch angiography was performed with the patient's head turned right and chin elevated. The view was aligned to include the arch peak and carotid arteries up to the mandible. Each patient received 30 mL contrast at 15 mL/

min under 700 psi pressure, with no increase rate.

This retrospective analysis included 63 patients who underwent aortography during acute ischemic stroke interventions. The study population comprised 39 males and 24 females, with a median age of 72 years. DSA classified aortic arch forms, including the Bovine type. Arch variations, including Bovine type, were compared with prior studies and their clinical impact assessed.

"The manuscript is entered in the system under "Clinical Trial Registration" as being a clinical trial that does not require registration. Because the treatments are performed on a routine basis. But The World Medical Association (WMA) Helsinki Declaration has been evaluated."

Statistical Analysis

PASW 18.0for Windows program was used for statistical analysis. Descriptive statistics, average for numeric variables, standard deviation, median, percentile 25 (Q1), percentile 75 (Q3) was presented as minimum and maximum. Normal distribution of variables were examined using visual (histogram and probability graphics) and analytical (Kolmogorov-Smirnov / Shapiro-Wilk tests) methods. Mann Whitney U Test was used in two independent group comparison analyzes where no normal distribution condition was provided for numerical variables. Kruskal Wallis Test in multiple group comparisons; Chi-square test for binary and multiple comparisons for categorical variables, Fisher's Exact Test for binary comparisons not provided with chi-square condition, and Fisher's Exact Test for multiple comparisons was used. The level of statistical significance was accepted as the value of p less than 0.05.

Table 1. Main clinical characteristics of our study population

	Overall (n=63)
Age (years)	72 (64-76)
Age group, n (%)	
(45-59 years)	10 (15.9)
(60-69 years)	15 (23.8)
(70-79 years)	29 (46.0)
(80≤ years)	9 (14.3)
Female gender, n (%)	24 (38.1)
Types of aortic arch, n (%)	
Type I	13 (20.6)
Type II	37 (58.7)
Type III	13 (20.6)
Bovine aortic arch, n (%)	16 (25.4)
Plaque, n (%)	31 (49.2)
Risk factors	
Diabetes mellitus, n (%)	14 (22.2)
Current smoker, n (%)	16 (25.4)
Hyperlipidemia, n (%)	14 (22.2)
Hypertension, n (%)	45 (71.4)
Heart diseases, n (%)	45 (71.4)

RESULTS

Baseline characteristics and demographics are shown in Table 1. 63 patients were studied (39 men and 24 women), there were 13 type I arch, 37 type II arch and 13 type III arch. The mean age of participants was 72 (64-76) years undergoing thrombectomy or IAT were included in the

Table 2. Relationship between arch types and demographic and clinical features

	Types of Aortic Arch			
	Type I	**Type II**	**Type III**	**p**
Bovine, n (%)	1 (7.7)	12 (32.4)	3 (23.1)	0.244
Plaque, n (%)	1 (7.7)	18 (48.6)	12 (92.3)	**<0.001**
Gender, n (%)				
Male	9 (69.2)	20 (54.1)	10 (76.9)	
Female	4 (30.8)	17 (45.9)	3 (23.1)	0.324
Age, median(Q1-Q3)	64 (51-73)	72 (66-76)	74 (67-83)	0.689
Age group, n (%)				
45-59 years	5 (38.5)	4 (10.8)	1 (7.7)	
60-69 years	2 (15.4)	10 (27.0)	3 (23.1)	**0.028**
70-79 years	5 (38.5)	20 (54.1)	4 (30.8)	
80≤ years	1 (7.7)	3 (8.1)	5 (38.5)	
Risk factors, n (%)				
Hypertension	7 (53.8)	28 (75.7)	10 (76.9)	0.313
Hyperlipidemia	3 (23.1)	5 (13.5)	6 (46.2)	0.055
Diabetesmellitus	3 (23.1)	8 (21.6)	3 (23.1)	1.000
Current smoker	4 (30.8)	6 (16.2)	6 (46.2)	0.095
Heart diseases	6 (46.2)	29 (78.4)	10 (76.9)	0.088

Table 3. Association between bovine arch variant and patient characteristics

	Bovine Arch (-)	Bovine Arch (+)	p
Types of Aortic Arch, n (%)			
Type I	12 (25.5)	1 (6.3)	0.251
Type II	25 (53.2)	12 (75.0)	
Type III	10 (21.3)	3 (18.8)	
Plaque, n (%)	20 (42.6)	11 (68.8)	0.070
Gender, n (%)			
Male	32 (68.1)	7 (43.8)	0.083
Female	15 (31.9)	9 (56.3)	
Age, median (Q1-Q3)	72 (64-77)	75 (68-76)	0.575
Age group, n (%)			
45-59 years	7 (14.9)	3 (18.8)	0.658
60-69 years	13 (27.7)	2 (12.5)	
70-79 years	20 (42.6)	9 (56.3)	
80 ≤ years	7 (14.9)	2 (12.5)	
Risk factors, n (%)			
Hypertension	31 (66.0)	14 (87.5)	0.121
Hyperlipidemia	11 (23.4)	3 (18.8)	1.000
Diabetesmellitus	12 (25.5)	2 (12.5)	0.487
Current smoker	13 (27.7)	3 (18.8)	0.740
Heart diseases	32 (68.1)	13 (81.3)	0.522

study. Procedural failure occurred in four patients (three patients had type III aorta and one patient had type II aorta), three patients were then referred for the intravenous thrombolytic therapy. One patient was not eligible for this treatment. All remaining procedures were successfully completed.

Patients with "type II and III," compared to those with type I, exhibited a significantly higher aging (p=0,028) (Table 2). In the whole patients, Bovine aortic arch was present in 16 cases (25.4%): 1 (7.7%) patient had a type I arch, 12 (32.4%) patients had a type II arch, 3 (23.1%) patients had type III arch (p=0.244) (Table 3). Patients with plaque in aortic arch were comparable in types of aortic arch. The difference is statistically significant (p<0.001) (Table 4). There were no statistically significant difference in the types of the aortic arch types among the genders, risk factors (hypertension, hyperlipidemia, diabetes, smoking, heart diseases).

DISCUSSION

Endovascular stroke interventions including thrombectomy and IAT comprise three critical phases: Vascular access, supraaortic navigation, and clot retrieval using mechanical devices. Cannulation of the supraaortic arteries is crucial for procedural success. Variations in the arch or branches may complicate routine angiography. Awareness of aortic arch structure and its variants is vital for procedures. Conventional angiography begins with aortic arch imaging to determine optimal catheter selection, thereby reducing procedure time and contrast material usage. Subsequently, this facilitates appropriate device selection for the planned intervention. Types of aortic arch and Bovine arch have been presented by some other authors but has not been studied during acute ischemic stroke therapy.[8-10] Most studies have been performed on carotid artery stenting (CAS). Macdonald et al.[11] developed a scoring framework for anatomical assessment. CAS assessment considers anatomical aspects like access (short or tortuous CCA, occluded ECA), arch structure (severe atheroma, vessel origin disease, type III or Bovine arch), and target vessel traits (pinhole narrowing, ICA angulation, circumferential calcification).

Thrombectomy and IAT are growing interventions for acute stroke, but feasibility depends on patient factors like arch anatomy. Previous studies reported for unfavorable anatomic variants an overall increased risk of procedural failure and neurological complications in the course of supraaortic interventionals.[5,6,12] These studies, however, were focused on carotid artery stending. This study retrospectively examined aortic structure using pre-thrombectomy or IAT digital subtraction angiography, categorizing aortic anatomy and Bovine type. The time is very important in acute ischemic stroke. Late treatment results in high morbidity and mortality. Type III arch is associated with challenging supraaortic access. In this study, Type II was most prevalent (58.7%), followed by Type I (20.6%) and Type III (20.6%).

This research indicates an association between older age and Type II/III arches. These rates surpass earlier findings, likely due to no preprocedural screening and an older population.[9,13] Specialized techniques and tools are needed

Table 4. Correlation between aortic arch morphology and atherosclerotic plaque burden

	Plaque (-)	Plaque (+)	p
Types of Aortic Arch, n (%)			
Type I	12 (37.5)	1 (3.2)	**<0.001**
Type II	19 (59.4)	18 (58.1)	
Type III	1 (3.1)	12 (38.7)	
Bovine, n (%)	5 (15.6)	11 (35.5)	0.070
Gender, n (%)			
Male	21 (65.6)	18 (58.1)	0.537
Female	11 (34.4)	13 (41.9)	
Age, median (Q1-Q3)	71 (61-75)	75 (67-79)	**0.026**
Age group, n (%)			
45-59 years	8 (25.0)	2 (6.5)	0.064
60-69 years	6 (18.8)	9 (29.0)	
70-79 years	16 (50.0)	13 (41.9)	
80 ≤ years	2 (6.3)	7 (22.6)	
Risk factors, n (%)			
Hypertension	21 (65.6)	24 (77.4)	0.300
Hyperlipidemia	5 (15.6)	9 (29.0)	0.201
Diabetesmellitus	11 (34.4)	3 (9.7)	**0.018**
Current smoker	6 (18.8)	10 (32.3)	0.218
Heart diseases	19 (59.4)	26 (83.9)	0.031

for aortic arch anomalies. Various methods have been suggested to aid supraaortic artery access in cases of aortic arch anomalies.[14]

This study confirms thrombectomy and IAT feasibility across different aortic arch anomalies, with only 4 failures in 63 cases. These high success rates align with expertise and likely result from meticulous planning tailored to aortic anatomy. In this experience, using a dedicated guiding catheter without a diagnostic one facilitated quicker supraaortic artery access, reducing fluoroscopy and total procedure time.

Aortic arch anomalies can elevate the risk of neurological and local complications due to the increased technical challenge of supraaortic access. We had three patients who developed transient vasospasm during ICA intervention.

There were no statistically significant relationship between gender, risk factors and arch types. There was no significant difference between sexes. Standard Aortic Arch is the most common anatomic appearance in humans. Here, the innominate artery splits into the right carotid and subclavian arteries. The Bovine configuration is the most common variant of the aortic arch. In a Bovine arch, the innominate and left common carotid arteries originate from the same point. As a result, two primary vessels emerge from the aortic arch. This pattern of branching is seen in approximately 13% of patients.[15]

Changes in the development of aortic arch arteries during embryogenesis likely cause variations in the branching pattern of the arch. Our study supported this with its results. In our study, no significant difference was observed between the different age groups with the cattle belt.

There are some studies in literature that aortic arch variations lead to cerebrovascular diseases.[16-19] Patil et al.[16] investigated seventy-five aortic arches from adult cadavers of Indian origin. In this study, the usual three-branched aortic arch was found in 58 cadavers (77.3%), 7 (12%) were diagnosed with cerebrovascular disease, while in the case of variant branching pattern, type II and type III, 4 (23.5%) cadavers out of 17 had cerebrovascular disease. Our study supported these claims. Because only 20.6% of patients had a type I aorta.

A significant correlation was found between aortic plaque presence and age groups in the aortic arch. This is particularly true for patients with type 3 aorta who are older than 80 years. This research represents the experience of a single center. A major limitation of this research is the limited sample size. Because of the stroke is seen in older ages, another limitation of this study is the age of patients is advanced. More studies with a bigger sample and multicenter randomized trials are essential.

Complex arch anatomy creates intervention obstacles through sharp angulation and altered vessel origins. Type II/III configurations necessitate alternative catheter designs, extending procedure duration and radiation exposure.[20,21] Our data demonstrates higher procedural complexity correlates with patient age and atherosclerotic disease burden.

Contemporary studies report similar arch distribution

patterns in stroke populations compared to our findings.[20-22] The elevated bovine variant frequency in our cohort suggests anatomical predisposition among intervention candidates. Despite these challenges, our success metrics remain comparable to established benchmarks.

Conclusion

Immediate improvements include: Enhanced pre-intervention imaging protocols, specialized equipment availability, and operator skill development for complex cases. Institutions should establish arch-specific procedural pathways and monitor outcomes accordingly. Future efforts should focus on technique standardization and technology advancement for challenging anatomical scenarios.

Ethics Committee Approval

This retrospective study was conducted in accordance with the Declaration of Helsinki. Approval was obtained for retrospective analysis of patient data from the Zonguldak Bulent Ecevit University Ethics Committee (Date: 08.01.2025, Decision No: 2025/01).

Informed Consent

Individual informed consent was waived due to the retrospective nature of the study and anonymous data analysis.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: G.Ö.; Design: G.Ö., E.K.; Supervision: G.Ö., E.A.; Fundings: G.Ö., M.S.G.; Materials: E.A.; Data: G.Ö., E.K.; Analysis: M.S.G., E.K.; Literature search: E.A., E.K.; Writing: G.Ö., E.K.; Critical revision: E.A.

Conflict of Interest

None declared.

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Akut İskemik İnmenin Endovasküler Tedavisinde Aort Ark Varyasyonları ve Belirleyicileri

Amaç: Karmaşık aort arkı anatomisi, akut iskemik inme müdahalelerinde teknik zorlukları artırmaktadır. Trombektomi ve intraarteriyel trombolitik tedavi (İATT) uygulanan hastalarda aort arkı varyasyonlarının hasta yaşı ve aterosklerotik yük ile ilişkili olduğu hipotezini öne sürdük.

Gereç ve Yöntem: Bu retrospektif çalışmada, akut iskemik inme nedeniyle trombektomi ve İATT uygulanan 63 ardışık hastada (39 erkek, 24 kadın; ortanca yaş 72) aort ark morfolojisi analiz edildi. Ark tiplerini (I, II, III) sınıflandırmak ve sığır ark varyantlarını belirlemek için müdahaleden önce sistematik olarak aortografi yapıldı. İstatistiksel analizde ark varyasyonları, hasta demografisi ve risk faktörleri arasındaki ilişkiler incelendi.

Bulgular: Tip II ark en yaygın olanıydı (37 hasta, %58.7), bunu Tip I (13 hasta, %20.6) ve Tip III (13 hasta, %20.6) izledi. Sığır arkı 16 hastada (%25.4) meydana geldi. Tip II/III arkı olan hastalar, Tip I olanlardan anlamlı derecede daha yaşlıydı ($p=0.028$). Aort plak varlığı ark tipiyle güçlü bir korelasyon gösterdi ($p<0.001$), Tip III hastaların %92.3'ünde plak bulunurken, Tip I hastaların %7.7'sinde plak vardı. İşlem başarısı 63 vakanın 59'unda (%93.7) sağlandı.

Sonuç: Bu retrospektif analiz, aort ark varyasyonlarının yaşla birlikte arttığını ve aterosklerotik yük ile ilişkili olduğunu göstermektedir. İnme müdahalesi yapılan hastalarda tip II ve III arklar baskın olup, yüksek işlem başarı oranları korunurken özel kateter teknikleri gerektirmektedir.

Anahtar Sözcükler: Arkus; aorta; inme; intraarteriyel trombolitik; trombektomi.

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Original Article

Auditory Evaluation of Three Most Commonly Used Anti-Seizure Medications Valproate (VPA), Carbamazepine (CBZ) and Levetiracetam (LEV) in School-Aged Children: A Single Center Prospective Study with Extensive Auditory Test Design in a Small Epileptic Cohort

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Keywords: Anti-seizure medications; auditory brainstem response; distortion-product otoacoustic emissions; ototoxicity; pediatric epilepsy; pure-tone audiometry.

ABSTRACT

Objective: This study aimed to assess the effects of commonly used anti-seizure medications (ASMs)—valproate (VPA), carbamazepine (CBZ), and levetiracetam (LEV)—on hearing function in school-aged children with newly diagnosed epilepsy.

Methods: A prospective study was conducted on 16 treatment-naive children (mean age 11.5±3.7 years) diagnosed with idiopathic generalized or self-limited focal epilepsy per 2017 ILAE criteria. Patients received VPA (n=12), CBZ (n=2), or LEV (n=2), titrated to therapeutic levels within one month. Audiological assessments—including pure-tone audiometry (0.25–8 kHz), tympanometry with acoustic reflexes, distortion-product otoacoustic emissions (DPOAE), and auditory brainstem response (ABR)—were performed before treatment and after a mean follow-up of 10 months. Paired t-tests compared baseline and follow-up results (significance set at $p<0.05$).

Results: All baseline hearing thresholds were ≤25 dB HL. Post-treatment thresholds were unchanged except for a slight increase at 4 kHz in the right ear (+3.8 dB HL, p=0.009). ABR latencies and inter-peak intervals remained stable. Tympanometry and acoustic reflexes were unchanged. DPOAE amplitudes declined at 2 kHz (−7.3 dB, p=0.001) and 6 kHz (−4.7 dB, p=0.006) in the right ear, while left-ear measures remained stable. No auditory symptoms or adverse events were reported.

Conclusion: Monotherapy with VPA, CBZ, or LEV over ~10 months did not result in clinically significant hearing impairment in children. However, minor frequency-specific reductions in cochlear emissions were noted. Further large-scale, drug-specific studies are needed to validate these preliminary findings.

INTRODUCTION

Epilepsy is one of the most common neurological diseases in childhood with an incidence rate of 0.5 to 8 per 1000 person-years.[1,2] Considering the chronic nature of the disease and the need for long-term treatment, the possible side effects of the drugs should be taken into consideration at the beginning of the treatment.[1] It is widely recognized that certain medications can have ototoxic (cochleotoxic or vestibulotoxic) effects, which may be either temporary or permanent.[3]

Anti-seizure medications (ASM) are the mainstay of epilepsy treatment.[4] Approximately 80% of children with epilepsy have seizure control with an appropriate medical treatment.[5,6] However, 20% of patients fail to respond to antiepileptic drugs and belong to the drug-resistant epilepsy group in which more than two antiepileptics are used. Side effects of the medications used are very important, especially in this particular epilepsy group.[7]

Generally known side effects of most commonly used antiepileptic drugs are headache, nausea, dizziness, a tendency to sleep, liver dysfunction, pancreatitis, kidney stones, visual disturbances, allergic reactions, hyperlipidemia, thyroid dysfunctions, cognitive dysfunction; and the patients are regularly monitored for these side effects by the clinician who initiates the treatment(3). Cognitive and language dysfunctions can be comorbid conditions related to the underlying etiology of epilepsy as well as complications of long-term antiepileptic drug use.[8,9]

Auditory symptoms like sound or voice hallucinations and tinnitus are known ictal manifestations of some epilepsy types (temporal, temporal-parietal-occipital epilepsies) and have been related to the underlying genetic etiology but could also be the result of ototoxic side effects of antiepileptic drugs used.[9,10]

Considering the fact that the highest incidence of childhood epilepsy is reported in the first year of life, possible deleterious side effects of antiepileptics on the auditory system need to be taken into special consideration and precautions and careful monitoring should be performed to prevent any long-term language and cognitive delay related with auditory dysfunction.[11,12] And also long-term use of antiepileptic drugs can affect central nervous system (CNS) functions even in the absence of clinical neurotoxicity symptoms.[3]

Tinnitus, disturbed pitch perception, reversible sensorineural hearing loss, and vestibular dysfunction are the auditory problems reported in the literature which have been attributed to side effects of some widely used anti-seizure medications like carbamazepine, oxcarbazepine, valproic acid, phenytoin, gabapentin and vigabatrin.[13,14] Pitch perception abnormalities have been reported by carbamezapine (CBZ) but not by valproic acid (VPA) or levetirasetam (LEV).[15] CBZ is also reported to inhibit the neural activity.[3]

There are proposed pathophysiological mechanisms for demonstrated auditory side effects associated with the main mechanisms of actions of the drugs in case series but still randomized controlled prospective studies are lacking in the literature.

CBZ, VPA, and LEV are the most commonly used and studied anti-seizure medications in childhood epilepsy, while the first two are old-generation drugs with well-documented side effects, LEV is among new-generation drugs with similar effects but with the least documented side effects related with auditory system.[5,16,17]

The aim of this prospective study was to detect any possible effects of the most commonly used antiepileptics carbamazepine, valproic acid, and levetirasetam on the auditory system by the extensive diagnostic evaluation.

MATERIALS AND METHODS

Participants and Treatment Protocol

This study included patients aged 6 to 18 years who were newly diagnosed with either focal or generalized seizures, in accordance with the 2017 International League Against Epilepsy (ILAE) classification system. Only individuals classified under idiopathic generalized epilepsy or self-limited focal epilepsy subgroups were considered for inclusion.[18] Eligible participants were those for whom initiation of monotherapy with valproic acid (VPA), carbamazepine (CBZ), or levetiracetam (LEV) was planned. None of the included patients had previously received any antiepileptic drug (AED) therapy.

Exclusion criteria comprised the presence of neurocognitive delay or autistic features that could impair the individual's ability to cooperate with audiological testing procedures.

Initial antiepileptic drug dosing was standardized as follows:

Valproic acid (VPA): 10 mg/kg/day divided into two doses

Carbamazepine (CBZ): 5 mg/kg/day divided into two doses

Levetiracetam (LEV): 10 mg/kg/day divided into two doses

Titration schedules were individualized, with the goal of achieving therapeutic target doses by the end of the first month. This approach was guided by established pediatric epilepsy management protocols.[19,20] At the time of the second audiological assessment, all participants were receiving effective therapeutic doses below the maximum allowable thresholds. No participants reported adverse effects attributable to the medications during the course of the study.

The maximum accepted daily doses were as follows:

VPA: up to 60 mg/kg/day, not exceeding 2.5 g/day
CBZ: up to 40 mg/kg/day, not exceeding 2 g/day
LEV: up to 60 mg/kg/day, not exceeding 3 g/day

Patients who were unable to tolerate the prescribed medication or who demonstrated poor adherence, resulting in failure to reach therapeutic levels, were excluded from final analysis.

Patients previously diagnosed with hearing loss attributable to other causes including craniofacial malformation, middle ear disease, craniofacial surgery, history of meningitidis, other ototoxic drug exposure and/or those using any other medication for any chronic disease were excluded. Patients with neuromotor retardation or who could not cooperate to hearing tests were also not included. This study included patients with normal hearing with pure tone audiometry thresholds better than 25 dB HL.

All the patients underwent a basal audiological evaluation before they started to use the prescribed medication and a second audiological evaluation including the same tests was performed to the patients after minimum 6 month of ongoing treatment with an average of 10 months.

Audiological evaluation

The hearing was evaluated by pure-tone audiometry, acoustic immitancemetry, otoacoustic emissions and auditory brainstem response (ABR).

All equipment used in the audiological evaluation was calibrated before the research according to the American National Standards Institute/Acoustical Society of America (ANSI/ASA S3.6-2010). Pure tone audiometry is a behavioral test that assesses air and bone conduction proccesses of the auditory system and detects the auditory thresholds.[21,22]

All participants were evaluated with an AC-40 clinical audiometer (Interacoustics A/S, Audiometer Alle 1 5500 Middelfart, Denmark) in a soundproof booth. All participants completed an audiological evaluation consisting of air and bone-conducted pure-tone thresholds (0.25 to 8 kilohertz -kHz- octave frequencies for air conduction; 0.5 to 4 kHz for bone conduction) for both ears, using the American Speech and Hearing Association (ASHA) guidelines.[23]

Acoustic immitancemetry assesses the integrity of the middle ear.[24] Acoustic immittance assessment was conducted using the AT 235(Middelfart, Denmark) model device. The tympanometric assessment was conducted using a 226 Hz probe tone. Acoustic reflexes were assessed ipsilaterally at 0.5 kHz, 1 kHz, and 2 kHz. Tympanometry measurement results were evaluated based on Jerger's tympanogram classification system, ensuring standardized interpretation of middle ear function.

Distortion product otoacoustic emission (DPOAE) is a diagnostic tool used to assess outer hair cell integrity and cochlear function.[25] When applied correctly in audiology settings, they provide a reliable diagnostic method for accurately detecting hearing loss.[26] The test also enables us to assess the extent to which cochlear function is affected by the ototoxicity.

Distortion product otoacoustic emission (DPOAE) was examined with the ILO292 USB-I Otoacoustic Emissions Instrument (Otodynamics Ltd., Beaconsfield Road Hatfield, AL10 8BB, U.K.). Simultaneous pure-tone signals were presented to each ear at 2 different frequencies (f1 and f2) at different intensities (l1 and l2; 65 and 55 dB sound pressure level-SPL), where f2>f1 with an f1:f2 ratio of 1.22 was used to measure DPOAE. The f1-f2 intermodulation distortion-product component was measured as a function of f2 frequency at 1/3-octave frequency intervals and was recorded in the form of DP grams. According to the characteristics of the device in the clinic participating in the study 1, 1.5, 2, 3, 4, 6, 8 and 10 kHz responses were obtained. DPOAE amplitudes were recorded at each frequency, DPOAE responses were considered valid when at least the lowest amplitude of 0 dB was reached and the signal/noise ratio (SNR) was >6 dB for 3 frequencies.[27]

The auditory brainstem response (ABR) is a neurophysiological signal generated by the brainstem following an auditory stimulus.[28] It reflects the synchronous electrical activity of neural structures along the auditory pathway. The ABR waveform typically consists of five to seven distinct peaks, labeled waves I through VII, each representing successive activation of specific, although sometimes overlapping, anatomical sites within the auditory system.[29]

ABR was recorded using the Interacoustics Eclipse EP 25 system (Middelfart, Denmark) for auditory evoked potentials. Diagnostic assessment was conducted at 70 dB nHL utilizing CE-Chirp® LS stimulus, delivered via insert earphones (3M EARTONE Insert Earphone 3A BR, Littleton, Colorado, USA), ensuring precise evaluation of auditory pathway integrity.

The recording electrodes were gold cup surface electrodes with impedance <5 kΩ. The active electrode was positioned centrally at Cz, following the 10–20 electrode system, while the reference and ground electrodes were placed at the ipsilateral and contralateral mastoid, respectively. The responses were band-pass filtered within a frequency range of 100-3000 Hz, spanning a 12 ms post-stimulus period.

Peak latencies for waves I, III, and V were identified, with their absolute and interpeak latencies subsequently analyzed for further response evaluation.

All these tests were performed on the patients for the purpose of comparison in case of abnormality to choose the optimal screening test with the highest diagnostic yield for audiological evaluation in patients using antiepileptic drugs.

The second hearing evaluation was performed before the first year of the treatment, on the patients who did not discontinue the antiepileptic drug for a minimum 6 months.

The patients were checked to use their medication in optimal treatment dose ranges appropriate for age and weight. Patients who were using the medications in dosages apart from recommended dose ranges or those with a history of ear infection after initiation of antiepileptic treatment were excluded. Patients whose antiepileptic dosages were changed frequently or a second antiepileptic drug was added to the treatment were excluded as well.

Local ethics committee approval was obtained for the study and it's been conducted according to the Helsinki Declaration.

Statistical analyses were performed using IBM SPSS software (version 22, USA), ensuring rigorous and standardized data processing. Statistical analysis student's t-paired test used for statistical analyses

RESULTS

Out of 30 patients whose initial audiological evaluation were performed 16 patients who fulfilled the inclusion criteria for the second audiological evaluation were included in the study (9 females, 56%) Used drug distribution was as follows: VPA (n=12), CBZ (n=2), LEV (n=2)

The mean patient age at the time of study was 11.5±3.7 (6-17) years. The mean time passed after initiation of treatment for the second evaluation was 10.1±1.2 (6-12) months.

Mean pure tone audiometry measurements of all patients were found to be within normal values and there was no statistically significant difference between the two measurement values of the patients, except for 4 kHz of the right ears. (Table 1a-1b).

Table 1a. Pure tone audiometry-right ear (pre/post treatment)

Side	Test time	Mean	SD	t	df	P*
Right ear						
SSO	Pre	7.87	3.519	1.047	15	0.311
	Post	6.81	3.936			
250 Hz	Pre	11.25	5.916	-0.187	15	0.855
	Post	11.56	6.511			
500 Hz	Pre	8.43	4.732	0.643	15	0.530
	Post	7.50	6.055			
1000 Hz	Pre	6.56	4.366	-0.222	15	0.827
	Post	6.87	6.551			
2000 Hz	Pre	6.87	4.366	1.159	15	0.264
	Post	5.31	6.551			
4000 Hz	Pre	3.43	3.520	-3.000	15	0.009*
	Post	7.18	5.764			
6000 Hz	Pre	10.00	8.56	1.065	15	0.304
	Post	8.12	7.719			
8000 Hz	Pre	7.50	9.309	-1.496	15	0.155
	Post	10.31	9.74			

*paired samples t-test.

Table 1b. Pure tone audiometry-left ear (pre/post treatment) (pre/post treatment)

Side	Test time	Mean	SD	t	df	P*
SSO	Pre	7.00	5.513	0.000	15	1.000
	Post	7.00	5.440			
250 Hz	Pre	9.66	8.653	-0.745	15	0.468
	Post	11.25	5.322			
500 Hz	Pre	7.66	6.289	-0.833	15	0.418
	Post	9.37	6.291			
1000 Hz	Pre	6.33	7.180	-0.421	15	0.680
	Post	6.87	6.551			
2000 Hz	Pre	7.33	5.120	1.585	15	0.134
	Post	5.31	5.617			
4000 Hz	Pre	4.66	5.617	-1.348	15	0.198
	Post	6.87	6.551			
6000 Hz	Pre	8.66	9.030	0.451	15	0.658
	Post	7.50	6.324			
8000 Hz	Pre	13.00	16.30	-0.805	15	0.4337
	Post	13.00	6.29			

*paired samples t-test.

Table 2a. ABR results-right ear (pre/post treatment)

Side	Component	Test time	Mean	SD	t	df	P*
Right ear	I. wave	Pre	1.58	0.269	-0.982	15	0.341
(70 dB nHL)		Post	2.36	3.109			
	III. wave	Pre	3.66	0.432	-0.200	15	0.844
		Post	3.69	0.634			
	V. wave	Pre	5.59	0.451	0.179	15	0.860
		Post	5.56	0.637			
	I-III	Pre	2.15	0.226	-1.305	15	0.211
		Post	2.43	0.752			
	III-V	Pre	1.97	0.637	0.893	15	0.386
		Post	1.84	0.169			
	I-V	Pre	3.88	0.686	-0.408	15	0.689
		Post	3.98	0.657			

*paired samples t-test.

Table 2b. ABR results-left ear (pre/post treatment)

Side	Component	Test time	Mean	SD	t	df	P*
Left ear	I.wave	Pre	1.53	0.139	-0.730	15	0.477
(70 dB nHL)		Post	1.57	0.141			
	III.wave	Pre	3.68	0.174	-0.435	15	0.670
		Post	3.71	0.253			
	V. wave	Pre	5.51	0.270	-0.250	15	0.860
		Post	5.53	0.280			
	I-III	Pre	2.17	0.227	-0.380	15	0.709
		Post	2.20	0.259			
	III-V	Pre	1.93	0.644	0.550	15	0.591
		Post	1.82	0.178			
	I-V	Pre	3.98	0.197	0.054	15	0.957
		Post	3.97	0.363			

*paired samples t-test.

Table 3a. Acoustic immitance testing-right ear (pre/post treatment)

Frequency		Test time	Mean	SD	t	df	P*
Right ear	500 Hz	Pre	89.64	5.35	-0.486	13	0.635
Acustic		Post	90.35	5.35			
immitence	1000 Hz	Pre	93.00	6.21	-0.435	14	0.670
threshold		Post	93.66	6.11			
(ipsilateral)	2000 Hz	Pre	94.28	7.031	-1.058	14	0.869
		Post	94.36	5.061			

*paired samples t-test.

ABR absolute peak latencies and interpeak latencies results of all patients were found to be in within normal ranges and no statistical difference was found between the mean values of the the basal and control measures($p>0.05$) (Table 2a-2b).

Acoustic immittance testing values of all of the patients were found in normal limits and control values also were not statistically different compared to the basal values. Type A tympanograms were obtained in all subjects (Table 3a-3b)

Table 3b. Acoustic immitance testing-left ear (pre/post treatment)

Frequency		Test time	Mean	SD	t	df	p
Left ear	500 Hz	Pre	91.42	6.629	-0.862	13	0.404
Acustic		Post	93.21	7.992			
immitence	1000 Hz	Pre	93.92	5.941	-0.168	13	0.869
threshold		Post	94.28	7.032			
(ipsilateral)	2000 Hz	Pre	94.28	7.032	-1.047	13	0.314
		Post	96.78	5.041			

*paired samples t-test.

Table 4a. Distortion product otoacoustic emission (DPOAE)-right ear (pre/post- treatment)

Side		Test time	Mean	SD	t	df	p
Right ear	1000	Pre	9.61	6.61	-0.734	12	0.477
		Post	10.91	2.68			
	1500Hz	Pre	14.24	5.28	-0.380	13	0.710
		Post	14.73	4.20			
	2000Hz	Pre	12.66	4.37	5.491	14	0.00**
		Post	5.33	5.95			
	3000 Hz	Pre	14.88	5.75	0.616	13	0.548
		Post	13.89	4.97			
	4000 Hz	Pre	16.85	7.43	0.065	12	0.949
		Post	16.78	6.17			
	6000 Hz	Pre	20.97	6.36	3.331	12	0.006**
		Post	16.31	4.84			

*paired samples t-test.

Table 4b. Distortion product otoacoustic emission (DPOAE)-left ear (pre/post- treatment)

Side	Frequency	Test time	Mean	SD	t	df	p
Left ear	1000 Hz	Pre	11.58	6.36	0.516	11	0.616
		Post	10.65	4.77			
	1500Hz	Pre	16.83	7.22	0.563	11	0.585
		Post	15.64	6.92			
	2000Hz	Pre	15.64	5.95	0.925	11	0.375
		Post	14.12	6.45			
	3000 Hz	Pre	15.46	6.78	0.027	11	0.979
		Post	15.40	7.25			
	4000 Hz	Pre	17.67	6.84	-0.593	11	0.565
		Post	18.58	6.96			
	6000 Hz	Pre	19.82	7.61	1.327	10	0.214
		Post	16.45	5.82			

*paired samples t-test.

Distortion product otoacoustic emission (DPOAE) measurements only showed a statistically significant difference between the two values for the right ear in 2000 Hz and 6000 Hz.

DISCUSSION

Although with a limited number of patients, this study is unique in nature, as all components of the auditory system have been evaluated with the latest up-to-date diagnos-

tic tests. In our study, no statistically significant difference was observed between the hearing assessment results obtained before therapy and those recorded within the first year after minimum six months of follow-up.

All the studies evaluating the audiologic side effects performed so far have had conflicting results and have been performed with limited tests that evaluated only specific parts of the auditory system. Case reports are the major source of information related to autotoxic side effects of antiepileptic drugs.[30]

Conflicting results have been reported by studies that performed ABR to evaluate the impact of ASM on the brainstem and peripheral auditory pathways.[31] Yuksel et al.[32] applied ABR to all patients who started to use carbamazepine or valproate before and after 13 months of treatment. They reported abnormalities in both earlier and late components of ABR results in patients using CBZ but not in any with valproate. They interpreted their findings as a possible interference effect of CBZ on synaptic transmission of neuronal membranes. Two more similar studies in the literature verified these findings regarding CBZ.[33,34] Our results are not consistent with these findings but, a relatively lower number of patients in our study might be a confounding factor.

Conducted studies with patients diagnosed with epilepsy and control groups of adults, report that individuals with epilepsy exhibited abnormal immittance findings and prolonged ABR component latencies compared to the control groups. Additionally, they observed that increasing CBZ dosage was associated with further latency prolongation in ABR components.[31]

In a study conducted by Koçak et al.,[26] no prolongation was observed in the absolute interwave latencies between waves I and V of ABR in epilepsy patients using CBZ, compared to the control group.[35]

The study that performed only pure tone air and bone thresholds to evaluate the effects of valproate on hearing did not find any abnormalities after 6 months of valproate use.[36] Our pure tone audiometry results are consistent with these results. Drug level monitoring was not performed in our study however all the patients were on therapeutic recommended dosages according to pediatric guidelines and none of them reported any side effects attributed to the used drug. Some studies have reported auditory side effects of antiepileptic drugs even in therapeutic drug doses.[12]

CBZ has been reported to cause tinnitus, changes in pitch perception, reversible sensorineural hearing disruption, and abnormalities in ABR even in therapeutic plasma drug levels. The proposed mechanism for these deleterious effects was through sodium channel blockage however, prospective experimental animal studies for elucidating the possible pathophysiology are still lacking.(9) Reversible sensorineural hearing loss confirmed by audiogram has been reported 6 days after intake of very high dose CBZ and the late effect has been attributed to delayed clearance of the active metabolite of the drug.[14]

LEV is one of the second-generation anti-seizure medication with presumed fewer side effects. The number of studies investigating the effect of LEV on hearing is very limited. One animal study has revealed a slight decrease in DPOAE levels post-treatment with LEV however these results were not statistically significant.[37] The main known mechanism of LEV is the inhibition of calcium channels which possibly affects cochlear neural response by affecting neurotransmitter release. This mechanism has been proposed as a benefit of this drug to prevent audiogenic seizures in therapeutic doses.[37] Application of extremely high doses (100mg/kg) of LEV has shown to decrease cochlear action potentials (CAP) in rats by a proposed mechanism of L-type calcium and potassium channel suppression in neurons of hippocampus in addition to glutamate release inhibition however studies in the literature evaluating effects of LEV on the auditory system are still lacking and more experimental and clinical studies are needed for more precise conclusions.[38]

It is known that there is a stepwise continuous development of human auditory system development beginning with the embryonic period and not completed till the late ages of childhood. The myelination process of the neuronal axons is reported to be prolonged till around age 12 as well as and ongoing maturation has been reported till early adulthood.[39] This knowledge brings to mind the question of how the antiepileptics might be affecting the incompletely developed auditory system in terms of multiple functional components like hearing, receptive language, sound discrimination, and speech capacity.

As studies about the effects of anti-seizure medications on the auditory system accumulate, cumulative knowledge about the side effects of the drugs will increase the clinician's awareness about drug selection, especially in childhood epilepsy syndrome where accompanying neurodevelopmental abnormalities are very common. This clinical approach will provide additional contribution in the prevention of additional losses related to speech and cognition.

Limitations of the study

This prospective study was designed with the aim of evaluating all aspects of the auditory system in patients who started antiepileptic drugs. Because of the nature of some audiology tests, only the patients who were able to perform all the tests could be included in the study, so patients under age 6 and those with poor cooperation were excluded. This limited the number of patients included in the study. Future studies including audiologic tests appropriate for age covering all aspects of the auditory system could add further valuable contribution to the literature.

Valproic acid (VPA) was the most commonly prescribed medication among patients eligible for inclusion within the planned study timeline (n=12; 75%). However, the limited number of patients receiving carbamazepine (CBZ) or

levetiracetam (LEV) precluded a meaningful comparative analysis of audiological outcomes across the three treatment groups.

Our study does not demonstrate the potential long-term effects of these medications on hearing; however, conducting future studies in this area would be beneficial.

Conclusion

Childhood epilepsy is a very common disease that can be controlled to a large extent with proper symptomatic treatment. Antiepileptic drugs still constitute the mainstay of the treatment strategies. Auditory side effects of antiepileptic drugs need to be taken into consideration at the process of drug initiation to prevent further possible neurodevelopmental regression. Further studies focusing on age-based auditory side effects of antiepileptics are needed to be held in the future.

Ethics Committee Approval

The study was approved by the Marmara University Medical Faculty Clinical Research Ethics Committee (Date: 04.01.2019, Decision No: 09.2019.111).

Informed Consent

Prospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: G.B., N.O.A.; Design: G.B., N.O.A., N.H.; Supervision: D.T., O.U., A.C.; Fundings: G.O., N.O.A.; Materials: G.O., N.H., N.O.A.; Data collection &/or processing: G.O., O.U N.O.A.; Analysis and/or interpretation: D.T., A.C., O.U.; Literature search: D.T., A.C., O.U.; Writing: G.O., N.H., N.O.A.; Critical Review: D.T., O.U., A.C.

Conflict of Interest

None declared.

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Okul Çağındaki Çocuklarda En Sık Kullanılan Antiepileptik İlaçlardan Valproat (VPA), Karbamazepin (KBZ) ve Levetirasetam (LEV)'ın İşitsel Değerlendirmesi: Küçük Bir Kohortta Geniş Kapsamlı İşitsel Test Tasarımı ile Tek Merkezli Prospektif Çalışma

Amaç: Bu çalışmada, yaygın olarak kullanılan antiepileptik ilaçların (AEİ)—valproat (VPA), karbamazepin (KBZ) ve levetirasetamın (LEV)—yeni tanı konmuş epilepsili okul çağındaki çocukların işitme fonksiyonları üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2017 ILAE kriterlerine göre idiopatik jeneralize veya kendi kendini sınırlayan fokal epilepsi tanısı almış, tedavi almamış 16 çocuk (ortalama yaş 11.5±3.7 yıl) üzerinde prospektif bir çalışma yürütüldü. Hastalara VPA (n=12), CBZ (n=2) veya LEV (n=2) tedavisi başlandı ve ilaç dozları bir ay içinde terapötik düzeylere çıkarıldı. İşitsel değerlendirmeler; tedavi öncesi ve ortalama 10 aylık takip sonrasında, saf ses odyometrisi (0.25–8 kHz), timpanometri ve akustik refleksler, distorsiyon ürünü otoakustik emisyonlar (DPOAE) ve işitsel beyin sapı yanıtı (ABR) testleri ile gerçekleştirildi. Başlangıç ve takip sonuçları eşleştirilmiş t-testi ile karşılaştırıldı (anlamlılık düzeyi $p<0.05$).

Bulgular: Başlangıçta tüm işitme eşikleri ≤25 dB HL idi. Tedavi sonrası işitme eşikleri genel olarak değişmedi, ancak sağ kulakta 4 kHz frekansında hafif bir artış gözlendi (+3.8 dB HL, p=0.009). ABR latansları ve pikler arası süreler stabil kaldı. Timpanometri ve akustik reflekslerde değişiklik gözlenmedi. DPOAE amplitüdlerinde sağ kulakta 2 kHz (−7.3 dB, p=0.001) ve 6 kHz (−4.7 dB, p=0.006) frekanslarında azalma saptandı. Sol kulak ölçümleri ise sabit kaldı. Hiçbir hastada işitsel semptom veya advers etki bildirilmedi.

Sonuç: Yaklaşık 10 aylık monoterapi ile uygulanan VPA, CBZ veya LEV tedavisi, çocuklarda klinik olarak anlamlı bir işitme bozukluğuna yol açmamıştır. Bununla birlikte, kohlear emisyonlarda frekansa özgü küçük düşüşler gözlemlenmiştir. Bu ön bulguların doğrulanması için daha geniş örneklemli, ilaçlara özgü çalışmalar gerekmektedir.

Anahtar Sözcükler: Anti-nöbet ilaçlar; distorsiyon ürünü otoakustik emisyonlar; işitsel beyin sapı yanıtı; ototoksisite; pediatrik epilepsi; saf ses odyometrisi.

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Original Article

Investigation of Pregnancy Outcomes, Either Spontaneous or Through Assisted Reproductive Techniques, in Patients Undergoing Diagnostic Laparoscopy and/or Operative/Office Hysteroscopy

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ABSTRACT

Objective: The aim of this study was to investigate the pregnancy outcomes, either spontaneous or through assisted reproductive techniques, in patients who underwent diagnostic laparoscopy and/or operative/office ysteroscopy due to primary or secondary infertility.

Methods: The study included 144 patients diagnosed with primary or secondary infertility at the University Hospital, Department of Obstetrics and Gynecology, between January 2021 and May 2024, who underwent diagnostic laparoscopy (L/S) and, according to indications, office/operat e hysteroscopy (H/S) for adhesiolysis, chromotubation, cystectomy, cyst aspiration, etc., and for uterine cavity control or septum resection. For exclusion of intrauterine pathology, uterine cavity control was performed using offic hysteroscopy, and findings were recorded. Surgical interventions were performed in patients with adhesions, endometriosis, ovarian cysts, or tubal pathology.

Results: 76 (52.7%) patients had primary and 68 (47.2%) secondary infertility. Cyst was seen in 25% and 26.5% of primary and secondary infertile patients, respectively; septum in 27% and 26.5%; adhesion in 35.5% and 38.2%; endometriosis in 10.5% and 7.4%; and bilateral/unilateral tubal passage was seen in 94.7% of primary infertile patients and 92.6% of secondary infertile patients. β-hCG was observed to be positive in 42 (55.3%) and 37 (54.4%) of primary and secondary infertile patients, respectively. Of the primary infertile group with positive β-hCG, 3 (7.1%) had IUI, 12 (28.6%) had IVF, and 27 (64.3%) had spontaneous pregnancy. In both groups, higher rates of spontaneous pregnancy and cesarean delivery were observed after the operation.

Conclusion: We believe that the surgical correction of commonly detected pelvic and uterine pathologies in patients undergoing simultaneous laparoscopic and hysteroscopic surgery for infertility has positively contributed to pregnancy outcomes.

INTRODUCTION

Primary infertility is the failure to conceive despite 12 months of regular unprotected sexual intercourse, while secondary infertility is the failure to conceive despite a previous pregnancy (such as ectopic pregnancy, abortion, preterm/term pregnancy) and despite 12 months of regular unprotected sexual intercourse. The probability of pregnancy occurring in each menstrual cycle is called fecundability. Under normal conditions, this rate is 20-25% for each menstrual cycle. At the end of a one-year period, this rate increases to 80-85% in couples with normal fertility. If fecundability has abnormal for a year, this indicates that the couple should be investigated for infertility.[1] In light of the data in the literature, it has been revealed that the rate of primary infertility is higher than secondary infertility (57.5% vs. 42.5%).[2] Each gynecological pathology should be investigated to determine the cause of infertility. The most common causes of female infertility include polycystic ovary syndrome, uterine malformations, endometrial polyps, endometriosis, uterine fib oids and premature ovarian failure.[3] In cases of treatment failure

or assisted reproductive techniques (ART) failure in an infertile couple, secondary invasive diagnostic methods such as hysteroscopy and laparoscopy are generally preferred. [4] After several unsuccessful ovulation induction attempts, diagnostic laparoscopy allows the visual detection and treatment of a significant portion of the pelvic pathology that may cause infertility.[5] In addition, it has been shown that laparoscopic bilateral salpingectomy increases implantation and pregnancy rates in women with bilateral hydrosalpinx seen ultrasonographically, before IVF cycles to be attempted.[6] Hysteroscopy, one of the secondary invasive diagnostic methods in the surgical evaluation of pathologies that may cause infertility, allows visualization of the endocervical canal, uterine cavity, and tubal openings. In addition, simultaneous laparoscopy enables the examination and treatment of tubes, adhesions, endometriosis and pathological cystic and mass lesions in the ovaries. [7] The frequency of laparoscopic findings in primary and secondary infertility is higher than hysteroscopic findings [8] The combined use of laparoscopy and hysteroscopy in patients presenting with infertility diagnosis reduces the risk of recurrent surgery in terms of infertility diagnosis and treatment and shortens the time required for pregnancy after the operation. In light of all these, our study aims to investigate the pregnancy outcomes of patients who underwent diagnostic laparoscopy and/or operative/offic hysteroscopy with a diagnosis of primary or secondary infertility between January 2021 and May 2024 in a tertiary health center.

MATERIALS AND METHODS

In this study, patients who applied to the tertiary center between January 2021 and May 2024 due to primary or secondary infertility and underwent a history, physical examination and ultrasonographic evaluation, followed by advanced laboratory tests and imaging methods, were subjected to combined operative procedures such as laparoscopy alone or combined office/operat e hysteroscopy, uterine septum surgeries, and chromotubation with a preliminary diagnosis of primary/secondary infertility. The infertility diagnosis of the patients was made as patients over the age of 35 without additional risk who could not conceive despite 6 months of regular sexual intercourse and patients under the age of 35 who could not conceive despite 1 year of regular sexual intercourse. A total of 186 patients were found who underwent surgery in our clinic. 144 patients who underwent these procedures were reached. Approval was received from our hospital's ethics committee for our retrospective study dated 01.08.2024. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and prior to participation, informed consent was obtained from participants.

According to the evaluation results, patients with male infertility factors, any other medical or surgical disorders which precluded the use of hysterolaparoscopy as a diagnostic modality, history of significant illness affecting fertility, AMH <0.59, patients younger than 18 and older than 39 were excluded from the study. Patients aged 18-39 were included in the study. The patients' contact information was obtained from the hospital information system. The patients were informed by phone before being called to the hospital that there was no invasive procedure that could harm the patient and that no information that would harm the patient's rights would be shared. Questions were asked about the patients' preoperative age, gravida, parity, abortion, preterm birth, term birth, delivery method, number of living children, anti-müllerian hormone level, use of assisted reproductive techniques before the operation, presence of previous surgery and whether there was a positive β-hCG test after the surgical operation performed by us, whether pregnancy occurred spontaneously or using assisted reproductive techniques, methods of conception and whether they took a live baby home. Written consent forms were obtained from the patients before the operation. All patients included in the study were under general anesthesia and ventilation was provided with an endotracheal tube. Patients were stained with povidone iodine twice from bilateral areola level to perineum in dorsolitomy position. 16 French Foley catheter was inserted under sterile conditions. During hysteroscopy operation, 8 mm diameter resectoscope with 5 mm diameter 30 degree angle optic, monopolar coagulation electrode was used. During laparoscopy, 30° two dimensional 10 mm telescope with white LED light source was used. Abdominal entry was made with 1 10 mm and 2 5 mm trocars. A 3.5 mm trocar was placed from suprapubic region according to intraoperative adhesive conditions. Laparoscopy was used alone or combined laparoscopy and hysteroscopy according to preoperative indications of patients. Hysteroscopy was used in offic or operative form according to patient indication. During diagnostic hysteroscopy, saline was used as an expander solution, and during operative hysteroscopy, mannitol (resectol) infusion was used, while unipolar coagulation electrode was used. Intraoperative findings that were thought to be abnormal were noted. In combined procedures, uterine cavity was entered via cannula and methylene blue was administered to perform chromotubation to evaluate tubal patency, and findings were noted. Laparoscopic surgical intervention was performed in patients with adhesion, endometriosis, hydrosalpinx, ovarian cysts or tubal obstruction. Hysteroscopic excisional procedures were performed in patients with intrauterine septum, myoma, and polyp.

Statistical Analysis

Data were transferred to IBM SPSS.25 (IBM Inc., Chicago, IL, USA) program and evaluated with statistical analyses. Before proceeding with statistical analyses, checks were made regarding the absence of data entry errors and whether the parameters were within the expected range. Mean and standard deviation were given in descriptive statistics of continuous variables; number of patients and percentage values were given in definition of categorical vari-

ables. Chi-square test was used for comparisons between categorical variables. Kolmogrov Smirnov and Shapiro Wilk's normality tests were used to check whether continuous variables showed normal distribution; variance homogeneity was checked with Levene's test. In cases where normal distribution was not observed, Mann-Whitney U test was used to determine the diffe ence between the two groups. In all analyses, $p<0.05$ was accepted as the significance l vel.

Table 1. Number and percentage values of patient groups and pathologies included in the study

Patient group	n	%
Primer Infertility	76	52.8
Seconder Infertility	68	47.2
Ovarian Cyst		
+	37	25.7
-	107	74.3
Uterin Septum		
+	39	27.1
-	105	72.9
Adhesion		
+	53	36.8
-	91	63.2
Endometriosis		
+	13	9.1
-	131	90.9
Bilateral/Unilateral Tubal Patency		
+	135	93.7
-	9	6.3

Table 2. Evaluation of intraoperative pathologies in both infertility groups

	Patient group		
	Primer infertility	Seconder infertility	
Ovarian Cyst	n (%)		p
+	19 (25.0)	18 (26.5)	0.840
-	57 (75.0)	50 (73.5)	
Uterin Septum			
+	21 (27.6)	18 (26.5)	0.876
-	55 (72.4)	50 (73.5)	
Adhesion			
+	27 (35.5)	26 (38.2)	0.736
-	49 (64.5)	42 (61.8)	
Endometriosis			
+	8 (10.5)	5 (7.4)	0.507
-	68 (89.5)	63 (92.6)	
Tubal Patency			
+	72 (94.7)	63 (92.6)	0.605
-	4 (5.3)	5 (7.4)	

RESULTS

The youngest patient was 18 years old and the oldest was 39 years old, and the mean age of the patients was 28.31±5.37. The study was conducted on two patient groups. The first group was the primary infertile group, consisting of 76 (52.8%) patients, and the other was the secondary infertile group, consisting of 68 (47.2%) patients. Cyst was observed in 37 (25.7%) patients, septum in 39 (27.1%), adhesion in 53 (36.8%) and endometriosis in 13 (9%). Bilateral/unilateral tubal passage was observed in 135 (93.7%) patients. The mean AMH values were determined as 3.96±2.82 for both groups. It was observed that there was no statistically significant relationship between the intraoperatively detected pathologies of cyst, septum, adhesion, tubal passage status with both patient groups ($p>0.05$) (Table 1).

In the primary infertile group, cyst 25%, septum 27.6%, adhesion 35.5%, endometriosis 10.5%, and bilateral/unilateral tubal passage 94.7%. In the secondary infertile group, cysts were 26.5%, septum 26.5%, adhesions 38.2%, endometriosis 7.4%, and bilateral/unilateral tubal transition 92.6% (Table 2). There was no statistically significant relationship between both patient groups and postoperative β-hCG status ($p>0.05$) (Table 3).

The mean age and mean preoperative AMH value of patients in the primary infertility group was found to be statistically significant y lower than those in the secondary infertility group ($p<0.05$) (Table 4). In the primary infertility patient group who underwent surgery due to uterine

Table 3. Postoperative β-hCG negativity and positivity in infertility groups

	Primer infertility	Seconder infertility	
β-hCG	n (%)		p
-	34 (44.7)	31 (45.6)	0.918
+	42 (55.3)	37 (54.4)	

Table 4. Distribution of preoperative age and AMH values in infertility groups

	Primer infertility	Seconder infertility	
	Mean± SS		p
Age	27.04±4.83	29.72±5.63	0.005*
AMH	4.59±3.20	3.19±2.04	0.006*

*$p<0.05$; Chi-square test, Mann Whitney-U test.

Table 5. Comparison of β-hCG situations according to the results of intraoperative pathologies of patients who underwent surgery due to primary infertility

Primary infertility	β-hCG -	β-hCG +	
Ovarian Cyst	n (%)		p
+	11 (32.4)	8 (19.0)	0.183
-	23 (67.6)	34 (81.0)	
Uterin Septum			
+	4 (11.8)	17 (40.5)	0.004*
-	30 (88.2)	25 (59.5)	
Adhesion			
+	15 (44.1)	12 (28.6)	0.159
-	19 (55.9)	30 (71.4)	
Tubal Patency			
+	31 (91.2)	41 (97.6)	0.211
-	3 (8.8)	1 (2.4)	

*p<0.05; Chi-square test, Mann Whitney-U test.

Table 6. Comparison of β-hCG situations according to the results of intraoperative pathologies of patients who underwent surgery due to secondary infertility

Seconder Infertility	β-hCG -	β-hCG +	
Ovarian Cyst	n (%)		p
+	11 (35.5)	7 (18.9)	0.123
-	20 (64.5)	30 (81.1)	
Uterin Septum			
+	6 (19.4)	12 (32.4)	0.223
-	25 (80.6)	25 (67.6)	
Adhesion			
+	15 (48.4)	10 (27.0)	0.068
-	16 (51.6)	27 (73.0)	
Tubal Patency			
+	27 (87)	36 (97.3)	0.020*
-	4 (13)	1 (2.7)	

*p<0.05; Chi-square test, Mann Whitney-U test.

septum, β-hCG in postoperative follow-ups was negative in 11.8% and positive in 40.5% (p<0.05) (Table 5). In the patient group who underwent laparoscopic bilateral/unilateral tubal transition due to secondary infertility, 87% of them had negative β-hCG in their postoperative follow-up and 97.3% had positive β-hCG (p<0.05) (Table 6).

In the postoperative follow-up of patients who underwent surgery for secondary infertility, the mean age of patients with negative β-hCG was found to be statistically significantly higher than those with positive β-hCG (p<0.05). In the postoperative follow-up of patients who underwent surgery for secondary infertility, the mean preoperative AMH values of patients with negative β-hCG were found to be statistically significant y lower than those with positive β-hCG (p<0.05).

In the primary infertile group, 3 (7.1%) of 42 patients with β-hCG positive had IUI, 12 (28.6%) had IVF, and 27 (64.3%) had spontaneous pregnancy; in the secondary infertile group, 4 (10.8%) of 37 patients had IUI, 5 (13.5%) had IVF, and 28 (75.6%) had spontaneous pregnancy (Fig. 1). In the primary infertility group with β-hCG positive follow-up, 8 (19%) of 42 patients had spontaneous abortion, 23 (54.8%) had cesarean section, and 11 (26.2%) had normal spontaneous vaginal delivery. In the secondary infertility group, 8 (21.6%) of 37 patients had spontaneous abortion, 20 (54.1%) had cesarean section, and 9 (24.3%) had normal spontaneous vaginal delivery. Cesarean delivery rates were higher in both groups.

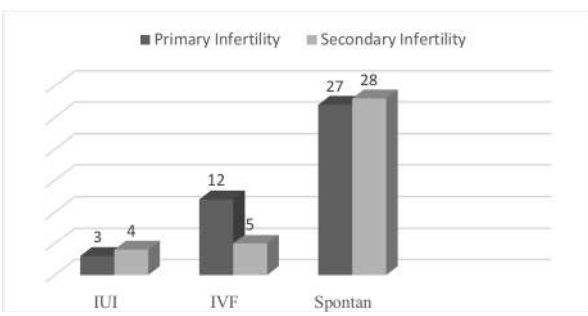

Figure 1. Postoperative pregnancy methods in both infertility groups.

DISCUSSION

In both groups, pregnancy rates after detection of tubal passage, separation of adhesions, evaluation of the uterine cavity and treatment of pathological conditions were similar, and the number of patients who conceived spontaneously after the operation was higher. As a result of applying L/S and H/S in the same session, the evaluation and treatment of many infertility factors, the expected time for pregnancy and, if necessary, the earlier application of ART were positively affec ed. In the study of Nayak et al.[9] including 300 patients who underwent combined laparoscopy and hysteroscopy with infertility diagnosis, 206 (69%) had primary infertility and the remaining 94 (31%) had secondary infertility. The patients in the secondary infertility group were slightly older compared to the primary group (28.8±3.7 years vs. 31.1±4.5 years). Laparoscopic abnormalities were observed more in the primary infertility group compared to hysteroscopy. (35% vs. 17%, P<0.0001). Endometriosis and adnexal adhesions detected by laparoscopy were the most common abnormalities in the both groups.[9] In the study of Chanu et al.,[10] 88 (58.28%) of 151 patients were in the primary and 63 (41.72%) were in the secondary infertility group. These patients underwent diagnostic hysterolaparoscopy to

investigate the etiology of infertility. In both primary and secondary infertility patients, intraoperatively detected laparoscopic abnormalities (37.5% and 49.2%) were more common than hysteroscopic abnormalities (7.95% and 14.29%). Laparoscopic abnormalities were significant in both groups. The most common abnormalities in the both infertility groups were adhesions and hydrosalpinx.[10] In our study, adhesions detected laparoscopically were 35.5% and 38.2% in patients with primary and secondary infertility, respectively, and are similar to other studies. The study group of Jain et al.[11] consisted of 121 women with primary and 82 women with secondary infertility. Tubal pathology was observed in 62.8% and 54.8% of primary and secondary infertile women who underwent laparoscopic chromotubation, respectively. Fallopian tubes (unilateral or bilateral) were observed to be blocked in 57% of women with primary and 51.2% of women with secondary infertility. Laparoscopically observed adhesions were seen in 33% of women with primary and 31% of women with secondary infertility. The incidence of dense adhesions was 13.2% and 6.1%, respectively.[11] In our study, laparoscopic chromotubation was applied to 72 (94.7%) out of 76 patients with primary infertility and 63 (92.6%) out of 68 patients with secondary infertility, and tubal passage was observed. Bilateral passage was not observed in 4 (5.3%) patients in the primary and in 5 (7.4%) patients in the secondary infertile group. The presence of unilateral passage was not examined separately in our study. The presence of dense adhesion secondary to endometriosis was seen in 8 (10.5%) patients in the primary and in 5 (7.4%) patients in the secondary infertile group. The frequency of dense adhesion is similar to other studies. In the study conducted by Shamim et al.,[12] 38 (70.4%) of the 54 patients included had primary infertility and 16 (29.6%) had secondary infertility. Pelvic adhesions were reported in 7 (18.4%) of the primary and in 3 (18.7%) of the secondary infertility group.[12] Since our patient population was larger compared to this study, intraoperatively detected adhesions were 27 (35.5%) in the primary infertility group and 26 (38.2%) in the secondary infertility group, which is more common. Stochino-Loi et al.[13] calculated the mean age of 180 patients with preoperative AMH values as 30±3.8 years and 31.2±3.6 years for AMH ≥2 ng/ml and <2 AMH ≥1 ng/ml, respectively. Of the 180 patients who underwent surgery for endometriosis or endometrioma after preoperative AMH values were seen, 100 (74.6%) out of 134 (74.4%) patients with preoperative AMH ≥2ng/ml achieved pregnancy in the postoperative period, 54% of these pregnancies were spontaneous and 46% with ART. Of the 46 patients with <2 AMH ≥1 ng/ml, 34 (73.9%) became pregnant, 20 of them (58.8%) spontaneously and 14 (41.2%) with ART.[13] The AMH of the patients included in our study was >0.59. 79 of the 144 patients included were able to become pregnant. Of these, 55 (69.6%) conceived spontaneously, 17 (21.5%) through IVF, and 7 (7.9%) through IUI. The included groups were not separated by AMH values, and assisted reproductive techniques were examined as IUI and IVF. In another study, 44 patients out of 176 had uterine septum, while 132 were in the control group. Pregnancy occurred in 17 (38.6%) of 44 patients who underwent surgery for uterine septum. Pregnancy occurred in 27 (20.4%) out of 132 patients in the control group. ($p<0.05$). Live birth rates were 34.1 and 18.9 in the septum and control groups, respectively.[14] Of the 76 patients in the primary infertility group included in our study, 42 (55.3%) achieved pregnancy, 11 (26.2%) had spontaneous vaginal delivery, 23 (54.8%) had cesarean section, and 8 (19%) had spontaneous abortion. In the study conducted by Pabuçcu et al.[15] with 61 patients aged ≤35 with primary infertility and uterine septum, 25 patients (41%) became pregnant after septum resection and 18 (29.5%) of them gave birth. 12 (66.6%) of these deliveries were by cesarean section. Spontaneous abortion occurred in 7 (11.5%) patients.[15] Although the number of patients included in our study was high, our spontaneous birth rate was high, but our miscarriage rate was similar to the other study.

In another study involving 360 patients, 19 (5.27%) of those who underwent laparoscopy and hysteroscopy due to infertility were found to have uterine anomalies. 7 (37.15%) of these were defined as septate uterus. Among the 360 women examined, 51 (14.16%) had endometriosis and 24 (6.66%) had ovarian cysts. Pelvic adhesions were identified as an infertility factor in 40 (11.11%) of our patients.[16] In addition to laparoscopy, hysteroscopy was performed in necessary patients in 144 patients with infertility diagnosis included in our study. Ovarian cysts were observed in 37 (25.7%) of the patients, uterine septum in 39 (27.1%), pelvic adhesion in 63 (43.7%), and endometriosis in 13 (9%). Bilateral tubal passage was not observed in 9 (6.3%) patients. The fact that our patient number is small but the pathologies obtained are close in number is due to the fact that we are a last-level health institution and we perform complicated cases. In our study, when pregnancy results after β-hCG positivity were examined, high values such as cesarean section rates were observed in both infertility groups, 54.8% in the primary infertility group and 54.1% in the secondary infertility group. In the study conducted by De Geyter et al.,[17] it was reported that cesarean section rates in pregnancies obtained with ART could exceed 40% due to multiple pregnancies and age-related complications. In this context, it can be said that cesarean section rates in our study are consistent with the values reported in the literature.[17] In the study conducted by Maheshwari et al.,[18] it is stated that IVF is an important treatment option for women over 35 years of age and is preferred due to the low spontaneous pregnancy rates in this age group. In our study, the reason for the relatively low use of IVF in women in the younger age group may be the higher spontaneous pregnancy rates. It was determined that IVF was used at a rate of 28.6% in the primary infertility group and 10.8% in the secondary infertility group. According to literature reviews, IVF has higher success rates, especially in advanced age and in the presence of serious tubal factors.[18] In another study, a total of 226 infertile patients diagnosed with both adenomyosis (AM) and en-

dometriosis (EM) underwent laparoscopic surgery. Forty-three patients were excluded based on predetermined criteria. Additionally, seven patients who became pregnant during the study period but did not deliver were excluded from the final analysis.To evaluate factors influencing pregnancies resulting in live birth, the remaining 176 women were divided into two groups: Group A (n=97) included women who achieved live birth after surgery (81 term and 16 preterm deliveries), while Group B (n=79) comprised those who failed to achieve live birth.The mean age of women in Group A was 32.52±3.20 years, whereas it was 33.53±3.95 years in Group B; patients with live births were significant y younger (p=0.046). Among the 183 patients who achieved clinical pregnancy, 135 conceived through assisted reproductive technology (ART) and 48 conceived spontaneously. In the ART group, 70 women achieved live birth, while 27 live births occurred in the spontaneous conception group.[19] In our study, among a total of 144 patients diagnosed with infertility, 79 (54.9%) had a positive clinical pregnancy test. Of these, 55 (69.9%) conceived spontaneously, while 24 (30.4%) achieved pregnancy through assisted reproductive techniques (ART). Regardless of the mode of conception, 63 out of 79 patients (79.7%) resulted in live births.

In a 2020 study involving 230 women who underwent combined hystero-laparoscopy, the participants' ages ranged from 21 to 46 years, with a mean age of 35.6±5.9 years. Among the cases, 106 (46.1%) had primary infertility and 124 (53.9%) had secondary infertility. Lesions detected during hystero-laparoscopy, regardless of infertility etiology, included intrauterine adhesions (41.3%; n=95), endometrial polyps (20.0%; n=46), submucosal fib oids (16.1%; n=37), and Müllerian duct anomalies (14.8%; n=34). The most common Müllerian anomaly was arcuate uterus (41.2%; n=14). Abnormal laparoscopic fin - ings were observed in 171 patients (74.4%), with tubal pathologies present in 161 (70.0%), predominantly tubal blockage (56.5%; n=130) and hydrosalpinx (41.7%; n=96). Bilateral tubal obstruction occurred in 46 cases (20.0%). Pelvic adhesions and endometriosis were detected in 91 (39.6%) and 19 (8.8%) women, respectively.[20]

In our study, a total of 144 patients were evaluated. The first group consisted of 76 women (52.8%) with primary infertility, and the second group included 68 women (47.2%) with secondary infertility. Among the overall cohort, 37 patients (25.7%) had ovarian cysts, 39 (27.1%) had uterine septum, 53 (36.8%) presented with pelvic adhesions, and 13 (9%) were diagnosed with endometriosis. Bilateral or unilateral tubal occlusion was noted in 9 patients (6.3%).

In our study, uterine anomalies were limited to uterine septum, and tubal pathology was restricted to bilateral occlusion.

The main limitation of this study is its retrospective design, which does not completely eliminate potential selection and information bias. In addition, the small sample size limits the generalizability of the findings

Only septate uterus cases were included, while other uterine anomalies were excluded. Since part of the data was based on patient self-report, there is a risk of recall bias.

Moreover, the absence of randomization and a control group prevents a defini ive causal interpretation between surgical intervention and pregnancy outcomes.

However, the strength of our study is that chromotubation is performed on patients with infertility diagnosis, tubal patency is demonstrated, tubal pathologies are evaluated and simultaneous treatment is provided. Since the cavity is checked with offic hysteroscopy during the case, the exclusion of uterine pathologies is defined during the intraoperative process. Nevertheless, the study provides valuable clinical insights into the potential benefits of simultaneous laparoscopic and hysteroscopic surgery in infertile women.

Conclusion

Most pelvic pathologies in infertile women often cannot be adequately evaluated with routine pelvic examinations and standard diagnostic methods, and additional diagnostic methods are needed. Hysterolaparoscopy, when performed with appropriate patient selection, can be accepted as a definiti e diagnosis and treatment method for comprehensive evaluation of female infertility. Prospective or retrospective studies to be conducted in the future will also be supportive of our study.

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Ethics Committee Approval

The study was approved by the Süleyman Demirel University Hospital Ethics Committee (Date: 01.08.2024, Decision No: 20).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: I.T., A.D.B.; Design: I.T., A.D.B., H.B.O.; Supervision: I.T., A.D.B.; Fundings: I.T., A.D.B.; Materials: I.T., A.D.B., H.B.O.; Data collection &/ or processing: I.T., A.D.B., H.B.O.; Analysis and/or interpretation: I.T.; Literature search: I.T., A.D.B.; Writing: I.T., A.D.B.; Critical review: I.T.

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Conflict of Interest

The authors did not present any potential conflicts of interest.

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Diagnostik Laparoskopi ve/veya Operatif/Ofis isteroskopi Uygulanan Hastaların Spontan/Yardımcı Üreme Teknikleri ile Gebelik Sonuçlarının Araştırılması

Amaç: Primer veya sekonder infertilite nedeniyle diagnostik laparoskopi ve/veya operatif/ofis histeroskopi uygulanan hastaların spontan veya yardımcı üreme teknikleri ile gebelik sonuçlarının araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmamız üçüncü basamak sağlık merkezine Ocak 202-Mayıs 2024 tarihleri arasında primer veya sekonder infertilite tanıları ile diagnostik laparoskopi (L/S) ve endikasyona göre ofis/operatif histeroskopi (H/S) eşliğinde adezyolizis, kromotubasyon, kistektomi, kist aspirasyonu vb. ve H/S ile kavite kontrolü, septum rezeksiyonu yapılan 144 hastadan oluşmaktadır. İntrauterin patoloji ekartasyonu nedeniyle hastalara ofis histeroskopi ile kavite kontrolü yapıldı. Bulgular not edildi. Adezyon, endometriozis, kist veya tubal patoloji izlenen hastalara cerrahi müdahaleler yapıldı.

Bulgular: 76 (%52.7)'sı primer, 68 (%47.2)'i sekonder infertiliteye sahip hasta saptandı. Primer ve sekonder infertillerin sırasıyla %25 ve %26.5'inde kist; %27 ve %26.5'inde septum; %35.5 ve %38.2'sinde adezyon; %10.5 ve %7.4'ünde endometriozis ve primer infertillerin %94.7'sinde, sekonder infertillerin %92.6'sında bilateral/unilateral tubal geçiş görüldü. β-hCG, primer ve sekonder infertil hastalarda sırasıyla 42 (%55.3)'sinde ve 37 (%54.4)'sinde pozitif izlenmiştir. β-hCG pozitif olan primer infertil grubun 3 (%7.1)'ünde IUI, 12 (%28.6)'sinde IVF, 27 (%64.3)'sinde spontan yollarla gebelik gerçekleşmiştir. İki grupta da operasyon sonrası spontan gebelik ve sezaryen ile doğum oranları daha yüksek gözlemlenmiştir.

Sonuç: İnfertilite nedeniyle eş zamanlı laparoskopik ve histeroskopik cerrahi yapılan hastalarda sık saptadığımız pelvik ve uterin patolojilerin opere edilmesi sonrası gebelik sonuçlarına olumlu katkıda bulunduğunu düşünmekteyiz.

Anahtar Sözcükler: Gebelik; histeroskopi; infertilite; laparoskopi; yardımcı üreme teknikleri.

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Original Article

The Impact of Mortality Conferences on Clinical Processes and Physician Awareness in the Emergency Department: A Single-Center Five-Year Analysis

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Keywords: Emergency department; mortality meetings; mortality rate; patient safety.

ABSTRACT

Objective: Emergency departments (EDs) have high patient volumes and elevated mortality rates. Mortality and Morbidity (M&M) conferences aim to identify causes of death and system deficiencies, thereby improving patient safety. This study retrospectively analyzed ED deaths between 2019 and 2023 and evaluated the impact of M&M conferences initiated in June 2022.

Methods: This single-center, retrospective study included 1,914 patients who died in the ED between January 2019 and December 2023. Demographic data, admission characteristics, triage area, and causes of death were collected. The study period was divided into pre-M&M (January 2019–June 2022) and post-M&M (June 2022–December 2023) phases.

Results: In the pre-M&M period, 1,334 deaths occurred among 1,565,124 ED visits (mortality rate: 8.47 per 10,000 visits). In the post-M&M period, 580 deaths were recorded among 1,306,517 visits (mortality rate: 4.17 per 10,000), corresponding to an approximately 51% relative reduction. The most pronounced decline was observed in the red triage area ($p<0.05$). The mean age of patients was lower in the post-M&M period ($p=0.002$). Non-traumatic deaths decreased, while trauma-related deaths significantly increased ($p<0.001$).

Conclusion: Implementation of structured M&M conferences in the ED was associated with reduced mortality rates and improvements in clinical processes. These conferences provide opportunities for case review, promote continuous learning, and strengthen patient safety culture.

INTRODUCTION

Adverse events caused by medical errors have emerged as a major patient safety concern in modern healthcare. Studies have shown that approximately 10% of hospitalized patients experience adverse events during care, and a substantial proportion of these events are preventable.[1] These findings highlight the importance of quality improvement and patient safety initiatives in healthcare systems and have accelerated the development of systematic approaches to reduce errors.

Morbidity and Mortality (M&M) conferences are among the longstanding initiatives designed to learn from medical errors and improve clinical practice. Historically, M&M conferences are considered to have been introduced in the early 20th century by surgeon Ernest Amory Codman at Massachusetts General Hospital in Boston.[2] Today, M&M conferences remain an integral part of specialty training programs and institutional quality improvement initiatives worldwide.[3]

Emergency departments (EDs) represent one of the most error-prone areas of healthcare due to high patient volumes, time pressure, and elevated mortality rates. In the literature, ED mortality has been reported at approximately 2.6 per 1,000 visits in several series.[4] This underscores the need for systematic evaluation mechanisms to improve

processes and reduce errors, particularly in the management of critically ill patients. Regular M&M conferences in EDs are valuable tools not only for clinical reflection and continuing education but also for strengthening multidisciplinary coordination.[5] These meetings address not only individual clinical errors but also systemic deficiencies, thereby contributing to the reorganization of processes.[6]

Recent studies have demonstrated that structured M&M conferences improve patient outcomes, enhance clinician awareness, and strengthen the culture of safety.[7,8] In surgical settings, comprehensive mortality review programs have been shown to improve observed-to-expected mortality ratios and significantly reduce hospital mortality.[9] In this context, investigating the impact of M&M conferences on clinical processes and mortality rates in the ED represents an important research area for both patient safety and healthcare quality.

MATERIALS AND METHODS

This study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (No: 2023/514/260/10, Date: 30/10/2023). Owing to the retrospective design, informed consent was waived; the study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

This was a single-center, retrospective analytical study conducted in the emergency department of Kartal Dr. Lütfi Kırdar City Hospital , between January 1, 2019, and December 31, 2023. M&M conferences were initiated on June 24, 2022. Accordingly, the study period was divided into pre-M&M (January 2019–June 2022) and post-M&M (June 2022–December 2023) intervals.

Participants

A total of 1,980 ED deaths were identified during the study period. After applying exclusion criteria, 1,914 patients were included in the final analysis. Patients aged ≥18 years who died within the ED were eligible. Cases with missing data or indeterminate cause of death were excluded.

Data Collection

Patient data were retrieved retrospectively from the hospital's electronic medical record system and transferred to Microsoft Excel. Variables included age, sex, time of presentation (daytime/nighttime), triage area (yellow, red, resuscitation), presenting complaint, and cause of death.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics were reported as mean ± standard deviation and percentages. The Kolmogorov-Smirnov test was used to assess normality. Student's t-test was used for two-group comparisons; ANOVA or Kruskal-Wallis tests were applied for comparisons involving more than two groups. Categorical variables were analyzed using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

During the five-year study period (January 2019–December 2023), a total of 1,914 deaths were recorded in the emergency department (ED) and included in the analysis. Annual mortality rates increased in 2020 and 2021 during the COVID-19 pandemic, followed by a gradual decline starting in 2022. The lowest mortality rate was observed in 2023 (1.18 per 10,000 visits) (Table 1). After the introduction of structured M&M conferences on June 24, 2022, a marked reduction in overall mortality rates was observed. In the pre-M&M period, 1,334 deaths occurred among 1,565,124 ED visits, corresponding to a mortality rate of 8.47 per 10,000 visits. In the post-M&M period, 580 deaths were recorded among 1,306,517 visits, corresponding to a rate of 4.17 per 10,000 visits. This corresponds to an approximate 51% relative reduction in overall mortality (Table 1). The decline was most pronounced in the red triage area, where mortality rates decreased from 43.3 to 37.7 per 10,000 visits (p<0.05). In the yellow triage area, the absolute number of deaths decreased, although

Table 1. Annual mortality rates (per 10,000 visits)

	2019	2020	2021	2022	2023
Mortality Rates	8.47	6.70	4.17	3.82	1.18

Table 2. Distribution of mortality cases by triage area before and after implementation of M&M conferences

Triage Area	Before (n, %)	After (n, %)	Mortality Rate (per 10,000 visits)	p-value
Red	1213 (91.0%)	540 (93.1%)	43.3 → 37.7	<0.05
Yellow	108 (8.1%)	40 (6.9%)	11.5 → 12.6	
Total	1334 (100%)	580 (100%)	55.0 → 41.0	<0.05

Table 3. Demographic characteristics of mortality cases before and after implementation of M&M conferences

Variable	Before (n=1334)	After (n=580)	Total (n=1914)	p-value
Gender				
Male	722 (54.2%)	306 (52.8%)	1028 (53.7%)	0.571
Female	611 (45.8%)	274 (47.2%)	885 (46.3%)	
Age (Mean±SD)	73.4±15.2	70.1±17.7	72.0±16.4	0.002

Table 4. Distribution of causes of death before and after implementation of M&M conferences

Cause of Death	Before (n, %)	After (n, %)	Total (n, %)	p-value
Acute abdominal pathology	11 (0.8%)	14 (2.7%)	25 (1.4%)	<0.001
Acute coronary syndrome	413 (31.0%)	146 (28.3%)	559 (30.2%)	
Acute cerebrovascular event	29 (2.2%)	18 (3.5%)	47 (2.5%)	
Acute respiratory failure	515 (38.6%)	152 (29.5%)	667 (36.1%)	
Acute vascular causes	39 (2.9%)	28 (5.4%)	67 (3.6%)	
Intoxication	8 (0.6%)	3 (0.6%)	11 (0.6%)	
Multiorgan dysfunction	204 (15.3%)	82 (15.9%)	286 (15.5%)	
Fluid-electrolyte disorder	60 (4.5%)	34 (6.6%)	94 (5.1%)	
Trauma-related death	55 (4.1%)	39 (7.6%)	94 (5.1%)	

the mortality rate showed a slight increase (from 11.5 to 12.6 per 10,000 visits) (Table 2). Male patients accounted for 53.7% of all deaths, with no significant difference between the pre- and post-M&M periods (p=0.571). The mean age of patients decreased from 73.4±15.2 years in the pre-M&M period to 70.1±17.7 years in the post-M&M period (p=0.002) (Table 3). Non-traumatic etiologies such as acute respiratory failure and acute coronary syndrome predominated overall, but their proportion declined following implementation of M&M conferences. Conversely, trauma-related deaths increased significantly in the post-M&M period (p<0.001) (Table 4).

DISCUSSION

This study demonstrated that regular M&M conferences implemented in the ED may contribute to improved quality of care and reduced mortality. Following the introduction of conferences in June 2022, a statistically significant decline in overall mortality was observed. The reduction in non-traumatic deaths suggests that M&M conferences may be effective in reducing preventable mortality.

Our findings are consistent with the literature. For instance, previous studies reported that the vast majority of ED deaths are unpreventable, with only a minority attributable to care deficiencies.[10] However, reductions in non-traumatic deaths observed in our study indicate that structured M&M conferences may influence preventable outcomes. Evidence from intensive care units has also demonstrated that regular M&M conferences reduce adverse events and mortality.[11] Similarly, surgical series have reported improvements in observed-to-expected mortality ratios and reductions in preventable deaths following structured mortality reviews.[9]

Beyond reducing mortality, M&M conferences contribute to professional development, system improvement, and the reinforcement of a safety culture. Systematic reviews have highlighted the positive impact of standardized M&M conferences on clinician engagement and patient safety.[12] Innovative formats, such as "Morbidity, Mortality, and Improvement" conferences, have shown promise in further strengthening safety culture.[13] In emergency medicine, residents perceive M&M conferences as valuable educational tools and emphasize their role in promoting a culture of safety.[14] In internal medicine, participants report learning not only clinical knowledge but also system-level insights and enhanced awareness of patient safety through M&M conferences.[15]

This study has several limitations. As a single-center, retrospective observational study, the observed mortality reductions cannot be attributed solely to M&M conferences. Changes in patient profiles and ED visit volumes following the COVID-19 pandemic may have influenced outcomes. Furthermore, the observational design precludes definitive causal inferences. Differences in the structure and implementation of M&M conferences across institutions may also limit generalizability.

Conclusion

Structured and regularly implemented M&M conferences in the ED were associated with improvements in clinical processes and reductions in non-traumatic mortality. These conferences provide continuous opportunities for

learning and self-reflection, thereby reinforcing a culture of patient safety.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Hospital Ethics Committee (Date: 30.10.2023, Decision No: 2023/514/260/10).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: R.I., A.U.S.; Design: R.I., A.U.S., E.Y. ; Supervision: R.A., N.B.; Fundings: R.I., A.U.S.; Materials: R.I.; Data collection &/or processing: R.I.; Analysis and/or interpretation: R.I., A.U.S., E.Y.; Literature search: R.A., A.U.S., N.B.; Writing: R.I., A.U.S., N.B., E.Y., R.A.; Critical review: R.I., A.U.S.

Conflict of Interest

None declared.

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Acil Serviste Mortalite Toplantılarının Klinik Süreçler ve Hekim Farkındalığı Üzerine Etkisi: Tek Merkezli Beş Yıllık Analiz

Amaç: Acil servisler (AS), yüksek hasta hacmi ve artmış mortalite oranları nedeniyle kritik birimlerin başında gelir. Morbidite ve Mortalite (M&M) toplantıları, ölüm nedenlerini ve sistemdeki eksiklikleri belirleyerek hasta güvenliğini artırmayı hedefler. Bu çalışma, 2019–2023 yılları arasında acil serviste gerçekleşen ölümleri geriye dönük olarak analiz etmiş ve Haziran 2022'de başlatılan M&M toplantılarının etkisini değerlendirmiştir.

Gereç ve Yöntem: Tek merkezli, retrospektif tasarıma sahip bu çalışmaya, 1 Ocak 2019-31 Aralık 2023 tarihleri arasında acil serviste hayatını kaybeden 1,914 hasta dahil edildi. Demografik veriler, başvuru özellikleri, triyaj alanı ve ölüm nedenleri kaydedildi. Çalışma dönemi, M&M toplantılarından önceki (Ocak 2019-Haziran 2022) ve sonraki (Haziran 2022-Aralık 2023) dönemler olarak ikiye ayrıldı.

Bulgular: M&M toplantılarından önce 1,565,124 acil servis başvurusunda 1,334 ölüm gerçekleşti (10,000 başvuruda mortalite: 8.47). Toplantılar sonrası 1,306,517 başvuruda 580 ölüm kaydedildi (10,000 başvuruda mortalite: 4.17) ve yaklaşık %51'lik göreceli azalma gözlendi. En belirgin düşüş kırmızı triyaj alanında izlendi ($p<0.05$). Hastaların ortalama yaşı toplantı sonrası dönemde daha düşüktü ($p=0.002$). Travma dışı ölümler azalırken travmaya bağlı ölümler anlamlı olarak arttı ($p<0.001$).

Sonuç: Acil serviste düzenli olarak uygulanan yapılandırılmış M&M toplantıları, mortalite oranlarının azalması ve klinik süreçlerin iyileşmesi ile ilişkili bulunmuştur. Bu toplantılar, olgu değerlendirmesi için fırsat sunar, sürekli öğrenmeyi destekler ve hasta güvenliği kültürünün güçlenmesine katkı sağlar.

Anahtar Sözcükler: Acil servis; hasta güvenliği; morbidite ve mortalite toplantıları; mortalite oranı.

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Original Article

Functional Outcomes, Complications and Reconstructive Strategies Following Internal Hemipelvectomy: A Single-Center Experience

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Keywords: Hemipelvectomy; pelvis; reconstruction strategy; resection; tumor.

ABSTRACT

Objective: Internal hemipelvectomy is a safe surgical method in the resection of pelvic sarcomas, although it has high complication rates. We aimed to evaluate the complications and functional outcomes of internal hemipelvectomy for malignant pelvic tumors. We also sought to determine the reconstruction strategies used and to identify factors influencing success rates.

Methods: A retrospective review was conducted on 43 patients who underwent internal hemipelvectomy between January 2010 and January 2023. Demographic data, tumor characteristics, resection types, reconstruction methods, perioperative variables, and oncological outcomes were analyzed. Surgical margins, complications, implant survival, and functional outcomes were recorded. Functional status was assessed using the Musculoskeletal Tumor Society (MSTS) scoring system. Kaplan–Meier survival analysis was used to estimate overall survival.

Results: The mean age was 40.9 years, and the average follow-up duration was 47.2 months. Chondrosarcoma was the most common diagnosis (48.9%). Type II and combined resections accounted for 55.8% of cases. Modular hemipelvic endoprostheses were used in 15 patients, while others underwent biological or cement-based reconstructions. The overall complication rate was 60.4%, with infections (27.9%) and dislocations (20.9%) being the most common. The mean MSTS score among survivors was 18.5, reflecting moderate functional outcomes. Local recurrence occurred in 17% and distant metastasis in 24.4% of patients. The overall survival rate at last follow-up was 51%, and worse outcomes may be associated with larger resections and implant-based reconstructions.

Conclusion: Internal hemipelvectomy is a viable limb-salvage option for pelvic tumors but is associated with substantial morbidity. Reconstruction type and resection extent significantly influence postoperative complications and functional outcomes. Careful patient selection and tailored reconstruction strategies are crucial for improving long-term results.

INTRODUCTION

Internal hemipelvectomy is a preferred but rarely performed procedure in the surgical treatment of orthopedic tumors in the pelvic region.[1,2] This approach aims to reduce local recurrence and metastasis rates, achieve wide resection of the tumor, preserve the functional integrity of the limb, and improve the patient's quality of life.[3,4] Unlike external hemipelvectomy, internal hemipelvectomy allows for regional tumor resection while preserving the limb.[1,2,5]

Pelvic resections are classified into four main types according to the Enneking classification system and can be performed in isolation or in combination.[3] The defects resulting from these resections often necessitate various reconstruction techniques.[5] The choice of reconstruction method depends on several factors, including the location and extent of the resection, the patient's general health status, age, and activity level.[3] Each of these factors must be carefully considered during the surgical planning and execution phases. The primary goals of reconstruction following hemipelvectomy include restoring pelvic stability, preserving limb length and joint function, and minimizing pain.[3,5] To achieve these objectives, various methods such as allografts, autografts, bone cement, implants, prosthe-

ses, and their combinations are utilized.[6]

Each of these techniques carries different implications in terms of postoperative complications, functional outcomes, and long-term durability. Due to the anatomical complexity and extensive nature of pelvic surgery, complications such as infection, wound dehiscence, neurovascular injury, implant failure, and local recurrence occur more frequently in pelvic sarcomas compared to other musculoskeletal tumors.[7,8] Furthermore, patient survival, recurrence rates, implant survival, and functional outcomes are of great importance in evaluating treatment success and guiding clinical decision-making.[9]

Despite advances in surgical techniques and adjuvant therapies, the literature reveals significant variability in outcomes among different reconstruction approaches.[3-5] Implant survival rates vary considerably; while prosthetic reconstructions are often associated with issues such as loosening and infection, biological reconstructions may encounter complications like nonunion or resorption.[4,10] Functional outcomes also vary depending on the extent of resection, type of reconstruction, and individual patient factors such as age and comorbidities.[5,8]

This study aims to evaluate the outcomes of resection and reconstruction strategies in patients who underwent internal hemipelvectomy for pelvic bone tumors at a tertiary referral center. A comprehensive analysis will be conducted in terms of postoperative complications, survival rates, local recurrence, implant survival, and functional outcomes. Through this analysis, we aim to contribute meaningfully to the existing literature by identifying optimal reconstruction strategies, improving treatment success, and enhancing patient outcomes in this challenging oncologic population.

MATERIALS AND METHODS

A total of 55 patients who underwent hemipelvectomy for pelvic bone tumors between January 2010 and January 2023 in our orthopedic oncology department were retrospectively reviewed. The study was approved by the Ethics Committee of Baltalimani Bone Diseases Education and Research Hospital (Date: 26/04/2025, No: 257) and conducted in accordance with the principles of the Helsinki Declaration. Inclusion criteria were patients who underwent internal hemipelvectomy with wide or marginal resection, had a pathological diagnosis of bone sarcoma, metastasis, or benign aggressive tumor, complete clinical, radiological, and histopathological records, and a minimum of 2 years of follow-up or until death. Twelve patients who underwent external hemipelvectomy due to unreconstructable pelvic tumors were excluded. The remaining 43 patients (29 males (67.4%) and 14 females (32.6%) were included in the study.

Patient age at the time of surgery, sex, postoperative follow-up duration, clinical characteristics, histopathological diagnosis, surgical margin status, type of resection, reconstruction methods, neoadjuvant and adjuvant therapies were evaluated using patient records, radiographs, magnetic resonance imaging (MRI) and computed tomography (CT). Tumor size was assessed based on preoperative MRI, and tumor volume was calculated by measuring the maximum diameter in the coronal, sagittal, and axial planes.

The need for blood products (red blood cell suspension, fresh frozen plasma), operative time, and length of hospital stay were obtained from operative and discharge notes. Postoperative complications (infection, wound necrosis, implant failure, prosthesis dislocation) were identified through clinical records. Infections were classified as early (within the first 30 postoperative days) or late (after 30 days), and further categorized as superficial or deep. Functional outcomes were evaluated using the Musculoskeletal Tumor Society (MSTS) scoring system.

The type of resection performed was classified according to the Enneking and Dunham system. Type I resection involved partial or complete removal of the ilium, Type II resection involved periacetabular resection, Type III resection involved resection of the ischium and pubis, and Type IV resection involved sacral resection.[11] Reconstruction methods (allograft, autograft, bone cement, endoprosthesis, spacer, or no reconstruction) were recorded. Neoadjuvant and adjuvant treatments (chemotherapy, radiotherapy, arterial embolization) were obtained from patient records.

Oncological outcomes were evaluated in terms of local recurrence, metastasis, or death. Surgical margins were classified according to the Enneking classification as intralesional, marginal, wide, or radical.

Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means and standard deviations or medians and min-max ranges, depending on the distribution of the data. Disease-free survival and overall survival rates were analyzed using the Kaplan–Meier survival method. Analyses were performed using SPSS software version 22.0 (SPSS Inc., Armonk, NY, USA).

RESULTS

The mean age at the time of surgery was 40.9 years (8–88). The mean follow-up was 47.2 months (4–148). Based on closed biopsy results, 21 patients (48.9%) were diagnosed with chondrosarcoma, 5 (11.6%) with pleomorphic sarcoma, 6 (14%) with Ewing sarcoma, 5 (11.6%) with metastasis, 3 (7%) with osteosarcoma, 1 (2.3%) with synovial sarcoma, 1 (2.3%) with giant cell tumor of bone, and 1 (2.3%) with aneurysmal bone cyst (Table 1).

According to the Enneking and Dunham classification system, multiple resection combinations were performed in 19 patients (44.2%). Ten patients (23.4%) underwent Type I hemipelvectomy, five (11.7%) Type II, three (6.9%) Type I–II, eight (18.6%) Type III, five (11.7%) Type I–II–III, seven (16.2%) Type II–III, one (2.3%) Type IV, two (4.6%) Type

Table 1. Study data

Variable	n (%)
Sex	
Male	29 (67.4)
Female	14 (32.6)
Age (years)	40.9 (8-88)
Follow-up (months)	47,2 (4-148)
Diagnosis	
Chondrosarcoma	21 (48.9)
Ewing	6 (14)
Pleomorphic Sarcoma	5 (11.6)
Metastasis	5 (11.6)
Osteosarcoma	3 (7)
Synovial Sarcoma	1 (2.3)
Giant Cell Tumor of the Bone	1 (2.3)
Aneurysmal Bone Cyst	1 (2.3)
Resection type	
Type 1	10 (23.4)
Type 2	5 (11.7)
Type 3	8 (18.6)
Type 4	1 (2.3)
Type 1-2	3 (6.9)
Type 1-2-3	5 (11.7)
Type 1-2-4	2 (4.6)
Type 1-2-3-4	2 (4.6)
Type 2-3	7 (16.2)
Adjuvant treatments	
Chemotherapy	18 (41.9)
Radiotherapy	12 (27.9)
Preoperative selective arterial embolization	1 (2.3)
Surgical insicion	
T incision	20 (46.5)
Ilioinguinal	23 (53.5)

I–II–IV, and two (4.6%) Type I–II–III–IV resections (Table 1). Wide en bloc resection was performed in 41 patients (95.3%), while marginal resection was performed in 2 patients (4.7%) diagnosed with giant cell tumor and aneurysmal bone cyst. Pathological examination of resected specimens revealed surgical margins less than 1 cm in 7 of the wide resection cases.

In two patients who underwent Type I hemipelvectomy, non-vascularized fibular grafting was performed (Fig. 1). One of these grafts had to be removed due to deep infection. In two patients with no resulting instability, reconstruction was performed with bone cement, and six patients did not require any reconstruction.

Due to the involvement of the acetabulofemoral joint and its impact on pelvic instability and poor functional outcomes, the 24 patients (55.8%) who underwent Type II resection or its variants were evaluated as a group. In one patient (2.3%) with sacral involvement, posterior lumbopelvic instrumentation with polyaxial screws and rods was performed. Fifteen patients (34.8%) underwent reconstruction with modular hemipelvic endoprostheses (Fig. 2). In the early postoperative period, infection and prosthetic dislocation occurred in two patients. One patient experienced recurrent dislocation and late infection. In three patients, the prosthesis was removed and a spacer was placed. External hemipelvectomy was performed in two patients due to local recurrence. In one patient, the prosthesis was removed and a spacer was placed due to both local recurrence and infection.

Among the eight patients who underwent Type III hemipelvectomy, one received a spacer, which was later removed due to early postoperative infection. In the remaining seven patients, no reconstruction was needed, and no postoperative complications were observed (Fig. 3).

Figure 1. (a) Conventional radiograph of the 13-year-old patient diagnosed with Ewing's sarcoma. (b) Preoperative coronal T2-weighted MR image. (c) Conventional radiograph taken following Type 1 internal hemipelvectomy and subsequent non-vascularized reconstruction.

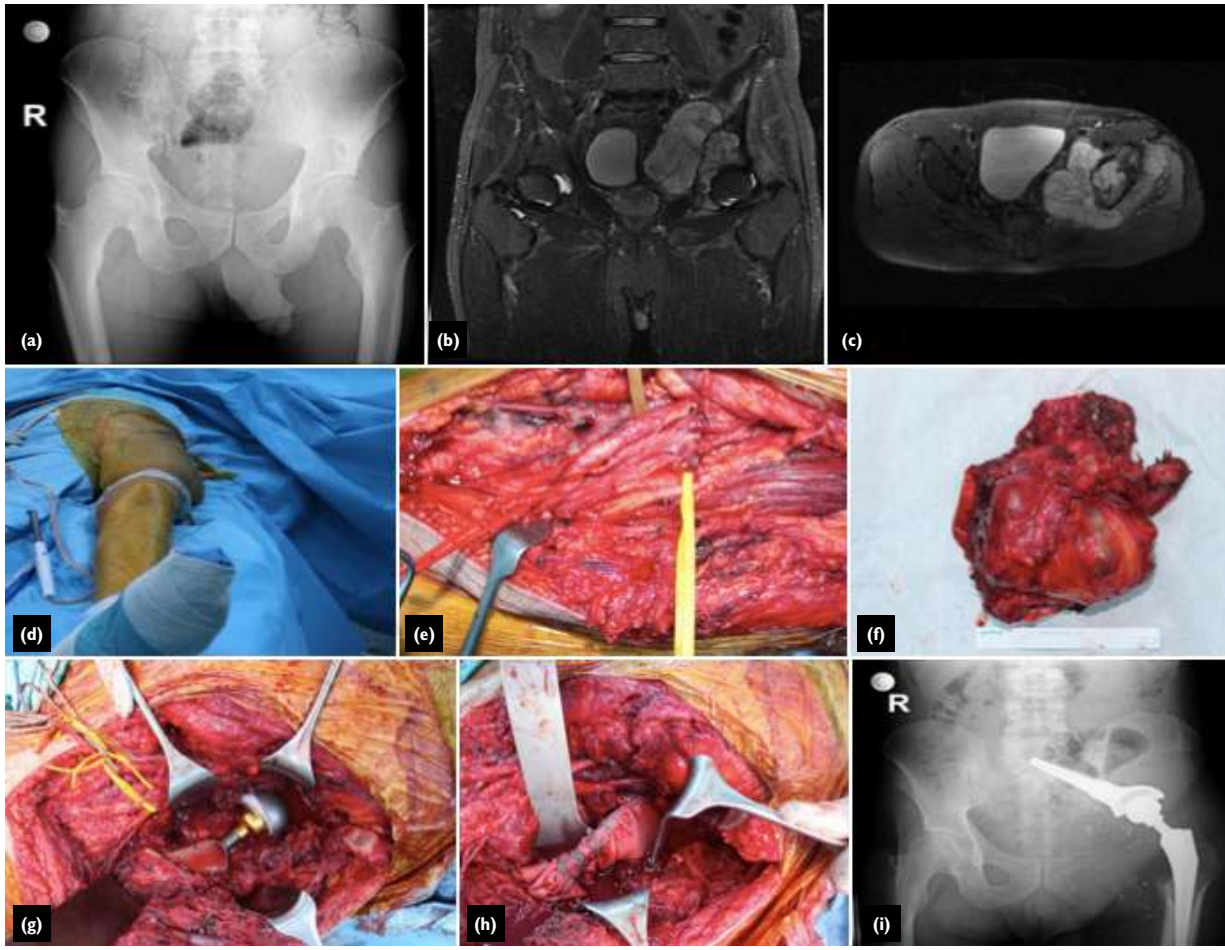

Figure 2. (a) Conventional radiograph of a 49-year-old patient diagnosed with chondrosarcoma in the left acetabulum. Preoperative **(b)** coronal and **(c)** axial T2-weighted MR images. **(d)** Iliofemoral incision of the patient in the supine position. **(e)** Femoral vein, artery and nerve dissected during surgery. **(f)** Resected tumor. **(g)** Appearance following application of the endoprosthesis. **(h)** Appearance following application of the Trevira tube. **(i)** Conventional radiograph taken following Type 2-3 internal hemipelvectomy and subsequent reconstruction.

In the single patient who underwent Type IV hemipelvectomy, lumbopelvic instrumentation was applied following sacral resection. This patient developed a superficial wound infection in the postoperative period, which was treated with wound debridement and antibiotic therapy (Fig. 4).

Table 2 summarizes the reconstruction methods and complications for each resection type.

Eighteen patients (41.9%) received chemotherapy, twelve (27.9%) received radiotherapy, and one patient (2.3%) underwent preoperative arterial embolization according to the histological tumor type (Table 1).

The mean postoperative transfusion requirements were as follows: Red blood cell suspension, 8.28 units (1–40; n=36); fresh frozen plasma, 4.14 units (1–13; n=28). The mean duration of surgery was 345 minutes (180–720), and the mean hospital stay was 22.2 days (10–98).

At final follow-up, 17 patients (39.5%) had died due to primary tumor or metastasis, and 4 patients (9.5%) due to systemic causes. Thus, 22 patients (51%) were alive at a mean follow-up of 64.7 months (24–148).

Distant metastases of malignant tumors were present in 10 patients (24.4%), while local recurrence was observed in 7 patients (17%). A high rate of morbidity was noted among the operated patients. The mean Musculoskeletal Tumor Society (MSTS) functional score of the 22 surviving patients after a mean follow-up of 64.7 months was 18.5 (10–25).

According to Kaplan–Meier analysis, the estimated mean overall survival was 76.4±8.5 months (95% CI: 33.4-176.5). Survival analysis by histological diagnosis showed a mean survival of 51.5±15.8 months for Ewing sarcoma, 82.1±12.3 months for chondrosarcoma, 58.8±21 months for pleomorphic sarcoma, and 16.3±9.8 months for osteosarcoma.

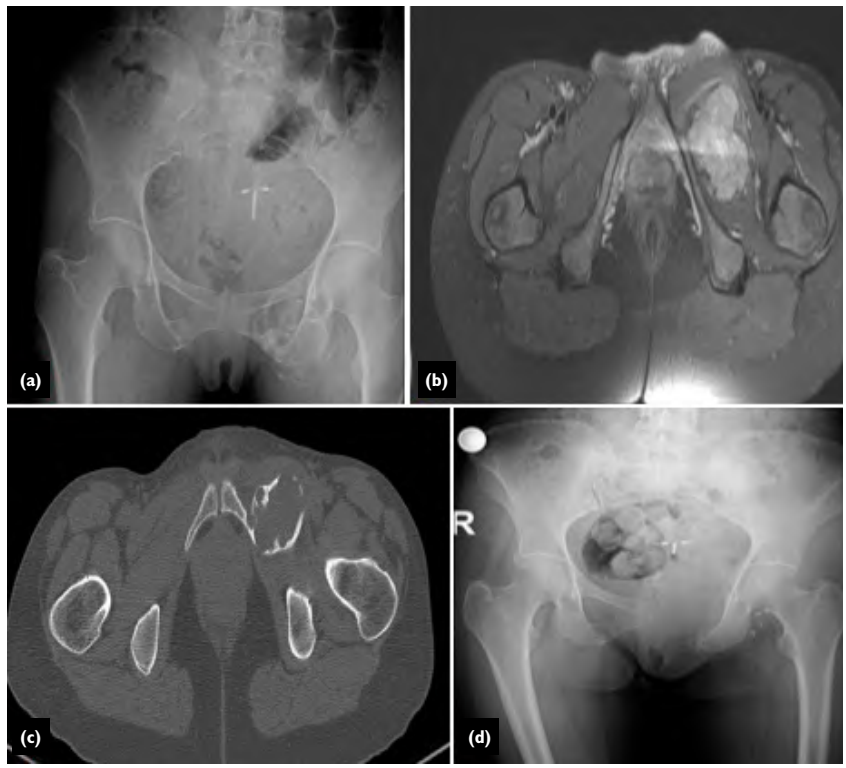

Figure 3. (a) Conventional radiograph of a 38-year-old patient diagnosed with chondrosarcoma of the pubic ramus. **(b)** Preoperative axial T2-weighted MR image. **(c)** CT scan displaying the axial plane. **(d)** Conventional radiograph taken following Type 3 internal hemipelvectomy.

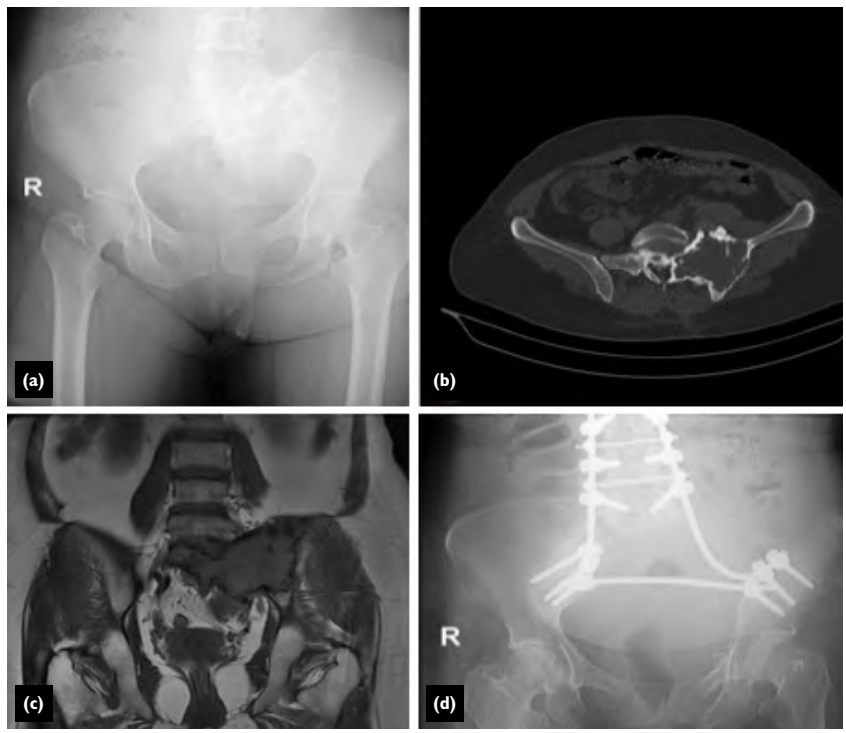

Figure 4. (a) Conventional radiograph of the 33-year-old patient diagnosed with giant cell tumor of the sacrum. **(b)** Preoperative CT scan displaying the axial plane. **(c)** Preoperative coronal MR image. **(d)** Conventional radiograph taken following Type 4 internal hemipelvectomy.

Table 2. Distribution of reconstruction methods and complications according to resection types

Resection Type	Reconstruction methods	Major complications	Minor comlications
Type I (n=10)	Non-vascularized fibular graft (n=2)	Early deep infection; graft extracted and follow with no reconstruction (n=1)	No complication
	Cementation (n=2)	No complication	Superficial wound infection (n=1)
	No reconstruction (n=6)	No complication	Wound dehiscence and superficial wound infection (n=1)
Type 2 (n=5)	LUMiC® endoprosthesis (n=2)	Recurrent dislocation and late deep infection, prosthesis extracted and follow with spacer (n=1)	No complication
	Spacer-vascularized fibular graft (n=1)	No complication	No complication
	Cementation (n=1)	No complication	No complication
	No reconstruction (n=1)	No complication	No complication
Type 1-2 (n=3)	LUMiC® endoprosthesis (n=1)	No complication	No complication
	Spacer (n=1)	No complication	No complication
	Partial Hip Endoprosthesis (n=1)	Limb length discrepancy (n=1)	Superficial wound infection (n=1)
Type 1-2-3 (n=5)	LUMiC® endoprosthesis (n=3)	No complication	Dislocation; treated with closed reduction (n=1)
	Spacer (n=1)	Late deep infection; spacer extracted and follow with no reconstruction (n=1)	No complication
	Partial Hip Endoprosthesis (n=1)	Limb length discrepancy (n=1)	No complication
Type 1-2-3-4 (n=2)	Spacer (n=2)	No complication	No complication
Type 2-3 (n=7)	LUMiC® endoprosthesis (n=7)	Local recurrence treated with external hemipelvectomy (n=2) Late deep infection treated with external hemipelvectomy (n=1) Early deep infection; extracted prosthesis and follow with spacer (n=1)	No complication
Type 1-2-4 (n=2)	LUMiC® endoprosthesis (n=2)	Dislocation and infection; extracted prosthesis and follow with spacer (n=1)	Marginal necrosis and superficial infection in incision site (n=1)
Type 3 (n=8)	No reconstruction (n=8)	Early deep infection treated with spacer (n=1)	No complication
Type 4 (n=1)	Lumbopelvic instrumentation (n=1)	No complication	Superficial wound infection (n=1)

DISCUSSION

This study evaluated patients who underwent internal hemipelvectomy for pelvic bone tumors over a 13-year period at a tertiary referral center and sheds light on several important findings. Over a mean follow-up of 47.2 months, the overall survival rate was 51%, with a local recurrence rate of 17% and a distant metastasis rate of 24.4%. Complications were common, particularly infections and implant-related issues, reflecting the complex nature of pelvic surgery. The mean Musculoskeletal Tumor Society (MSTS) score of 18.5 among surviving patients indicates moderate functional outcomes, highlighting the difficulty in balancing oncologic resection with limb preservation.

Resection of pelvic malignancies via internal hemipelvectomy carries risks of infection, soft tissue complications, prosthetic failure, and local recurrence. The risk of postoperative complications after pelvic resections is reported to range from 30% to 50%.[3,12,13] Appropriate reconstruction strategies are crucial to reduce these risks.[14] In our series, early infections were observed in three patients who underwent modular hemipelvic endoprosthesis reconstruction, while one developed late infection and recurrent dislocations, necessitating prosthesis removal and spacer placement. One patient underwent external hemipelvectomy due to persistent late infection. In another patient who received a non-vascularized fibular graft, the graft was removed due to deep infection. The high morbidity rate observed in our study, particularly infections and implant-related complications, is consistent with the literature.

[3,7,15] Our mean operative time of 345 minutes and mean red blood cell transfusion requirement of 8.28 units highlight how prolonged surgeries and blood loss may increase infection risk.[13,14]

Combined treatment involving internal hemipelvectomy and chemotherapy or radiotherapy has shown superior survival, lower local recurrence, and fewer complications compared to external hemipelvectomy in the surgical treatment of pelvic malignancies,[16,17] while also improving quality of life. External hemipelvectomy, which includes amputation of the pelvis and ipsilateral lower limb, may be necessary when limb-salvage is not feasible.[5] Although safe and wide tumor margins can be achieved through amputation, limb-sparing internal hemipelvectomy with pelvic reconstruction remains the standard approach to minimize the functional, cosmetic, and psychological impact.[18] Generally, survival in patients with pelvic tumors is worse than for those with extremity tumors,[19,20] likely due to delayed symptom onset, resulting in later diagnosis and larger tumors. Literature suggests no significant difference in survival between limb-sparing surgery and amputation for malignant bone tumors, supporting the use of limb-sparing procedures even in advanced-stage tumors.[21] In our series, 55 patients underwent hemipelvectomy between January 2010 and January 2023-12 received external and 43 internal (limb-sparing) procedures.

The T-incision approach during internal hemipelvectomy is recommended in pelvic sarcoma patients as it provides better exposure of venous, neural, and intrapelvic structures.[22] In our study, 20 of the 43 patients who underwent Type I or II hemipelvectomy or their variants received T-incision, while 23 underwent standard iliofemoral incision. No significant difference was observed between the two incision types in terms of exploration, postoperative complications, or wound healing, and thus the choice should depend on surgeon preference and experience.

Type I hemipelvectomy is commonly used in the surgical management of primary tumors located in the iliosacral region.[23] However, pelvic ring instability caused by wide bony resections often necessitates reconstruction.[23] Bone defects after Type I resection can be reconstructed with fibular autografts, cortical allografts, or bone cement to improve stability and functional outcomes.[16,24] In our series, only two of the ten patients who underwent Type I resection received fibular graft reconstruction. One of them required graft removal due to early postoperative infection, potentially related to prolonged operative time. No major complications occurred in the eight unreconstructed patients, likely due to smaller resection volumes. These findings suggest that with careful patient selection, non-reconstructed Type I resections may be followed safely while avoiding potential complications such as infection or reconstruction failure.

Type II resections (and variants) involving the periacetabular region are considered the most technically demanding and are associated with the highest complication rates.[25] Multiple reconstruction options exist.[26] In our study, 15 patients underwent modular hemipelvic endoprosthesis reconstruction following Type II or combined resections. Among these, early postoperative infection and dislocation were observed in two patients, while one developed chronic dislocation and late infection consistent with prior literature.[15,27] Endoprostheses were removed and spacers placed in five patients (11.6%).

The mean follow-up duration in our series was 47.2 months (4-148), and the average MSTS score was 18.5 (10-25), which is consistent with previously published data for hemipelvectomy patients.[21,28] Functional outcomes largely depend on the extent of resection and the reconstruction method used. For instance, Type II resections involving the acetabulum (55.8% of patients) were generally associated with lower functional scores due to pelvic instability and altered hip mechanics.

Type III resections, when performed in isolation, typically do not require reconstruction.[16] In our series, one of the eight patients who underwent isolated Type III resection received a spacer, which was later removed due to early infection, and no reconstruction was performed. The remaining seven patients also did not undergo reconstruction, and none developed postoperative complications. Thus, reconstruction may not be essential in isolated Type III resections.

Total sacrectomy is indicated for malignant or aggressive benign lesions of the sacrum.[29] Despite potential complications and the risk of neurological dysfunction, it can improve recurrence-free survival.[30] In our series, one patient underwent Type IV hemipelvectomy and posterior lumbopelvic instrumentation, and developed superficial wound infection, which was successfully managed with systemic antibiotics.

Moreover, we did not perform statistical comparisons between different resection types or reconstruction methods, which is a limitation that weakens conclusions about the optimal surgical approach. Additionally, outcomes based on incision type or specific reconstruction techniques were not systematically compared, representing another limitation of this study. We also acknowledge that our literature comparisons were not exhaustive; a more extensive review of reconstruction techniques in the literature could further contextualize our findings. Despite these limitations, our long-term observations with adequate follow-up provide valuable data to aid surgeons in predicting prognosis and planning appropriate strategies for managing pelvic malignancies. Future studies could focus on developing decision-making algorithms or guidelines to assist surgeons in selecting the most appropriate reconstruction method for each patient.

Conclusion

The high complication rate following pelvic tumor resection surgery is a major contributor to morbidity and mortality. Factors that may improve surgical outcomes include the surgeon's experience, reduced operative time, optimal soft tissue reconstruction to minimize dead space, meticulous wound care, and appropriate rehabilitation.

Additionally, the selection of the correct reconstruction strategy may significantly influence the success of internal hemipelvectomy.

Ethics Committee Approval

The study was approved by the Baltalimani Bone Diseases Education and Research Hospital Ethics Committee (Date: 26.04.2025, Decision No: 257).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: N.I., O.E.A., B.D.; Design: N.I., O.E.A., B.D.; Supervision: N.I., O.E.A.; Data collection &/ or processing: N.I., B.D.; Analysis and/or interpretation: N.I., O.E.A.; Literature search: N.I.; Writing: N.I.; Critical review: O.E.A.

Conflict of Interest

None declared.

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İnternal Hemipelvektomi Sonrası Fonksiyonel Sonuçlar, Komplikasyonlar ve Rekonstrüktif Stratejiler: Tek Merkezli Bir Deneyim

Amaç: İnternal hemipelvektomi, pelvik sarkomların rezeksiyonunda güvenli bir cerrahi yöntem olmakla birlikte, yüksek komplikasyon oranlarına sahiptir. Malign pelvik tümörler için internal hemipelvektominin komplikasyonlarını ve fonksiyonel sonuçlarını değerlendirmeyi amaçladık. Ayrıca kullanılan rekonstrüksiyon stratejilerini belirlemeyi ve başarı oranlarını etkileyen faktörleri tanımlamayı hedefledik.

Gereç ve Yöntem: Ocak 2010 ile Ocak 2023 tarihleri arasında internal hemipelvektomi uygulanan 43 hasta retrospektif olarak incelendi. Demografik veriler, tümör özellikleri, rezeksiyon tipleri, rekonstrüksiyon yöntemleri, perioperatif değişkenler ve onkolojik sonuçlar analiz edildi. Cerrahi sınırlar, komplikasyonlar, implant sağkalımı ve fonksiyonel sonuçlar kaydedildi. Fonksiyonel durum, Kas-İskelet Sistemi Tümör Derneği (MSTS) skorlama sistemi kullanılarak değerlendirildi. Genel sağkalım oranı Kaplan–Meier analiz yöntemi ile hesaplandı.

Bulgular: Ortalama yaş 40.9 yıl, ortalama takip süresi ise 47.2 aydı. En sık görülen tanı kondrosarkomdu (%48.9). Tip II ve kombine rezeksiyonlar olguların %55.8'ini oluşturdu. On beş hastada modüler hemipelvik endoprotez kullanılırken, diğer hastalarda biyolojik ya da çimentolu rekonstrüksiyon uygulandı. Genel komplikasyon oranı %60.4 olup, en sık enfeksiyon (%27.9) ve çıkık (%20.9) görüldü. Hayatta kalanlarda ortalama MSTS skoru 18.5 olarak bulundu ve bu orta düzeyde fonksiyonel sonuçlara işaret etti. Lokal nüks oranı %17, uzak metastaz oranı ise %24.4 olarak saptandı. Son takipte genel sağkalım oranı %51 idi; daha geniş rezeksiyonlar ve implant bazlı rekonstrüksiyonlar daha olumsuz sonuçlarla ilişkili olabilir.

Sonuç: İnternal hemipelvektomi, pelvik tümörler için ekstremite koruyucu uygulanabilir bir seçenek olmakla birlikte, önemli morbidite ile ilişkilidir. Rekonstrüksiyon tipi ve rezeksiyonun boyutu, postoperatif komplikasyonlar ve fonksiyonel sonuçlar üzerinde anlamlı etkiye sahiptir. Uzun dönem sonuçları iyileştirmek için dikkatli hasta seçimi ve kişiye özel rekonstrüksiyon stratejileri kritik öneme sahiptir.

Anahtar Sözcükler: Hemipelvektomi; pelvis; rekonstrüksiyon stratejisi; rezeksiyon; tümör.

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Original Article

Determinants of Postoperative Sleep Deterioration After Surgery for Gynecologic Malignancies

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Keywords: Gynecologic oncology; Pittsburgh Sleep Quality Index (PSQI); postoperative care; quality of life; sleep quality; surgical menopause.

ABSTRACT

Objective: This study aimed to prospectively evaluate the factors influencing sleep quality in patients undergoing surgical interventions for gynecological malignancies, with a particular focus on the impact of surgical menopause.

Methods: This prospective cohort study included 142 patients who underwent surgical procedures for endometrial, ovarian, or cervical cancer at a tertiary care institution. Participants were divided into two cohorts: Those who underwent surgical menopause (SM group, n=68) and those who did not (non-SM group, n=74). Sleep quality was assessed usingethe Pittsburgh Sleep Quality Index (PSQI) both preoperatively and three months postoperatively. Preoperative anxiety and depression levels were measured using the Hospital Anxiety and Depression Scale (HADS). Demographic, clinical, and surgical data were collected systematically. Multiple linear regression analysis was performed to identify independent associated factor of poor postoperative sleep quality, as indicated by changes in the PSQI score.

Results: The mean global PSQI score significantly worsened from 5.1±2.8 at baseline to 8.9±4.1 at 3 months postoperatively ($p<0.001$). The deterioration in sleep quality was significantly greater in the SM group than in the non-SM group (mean PSQI change: +5.6 vs. +2.1, $p<0.001$). In the multivariate regression model, surgical menopause ($\beta=3.12$, $p<0.001$), adjuvant chemotherapy ($\beta=1.89$, $p=0.002$), higher baseline HADS anxiety score ($\beta=0.25$, $p=0.005$), and higher postoperative pain score (VAS) ($\beta=0.31$, $p=0.018$) were identified as independent associated factor of a greater increase in the PSQI score (worse sleep quality).

Conclusion: Postoperative sleep quality significantly deteriorated following gynecologic cancer surgery, with surgical menopause identified as the most significant independent associated factor of this decline. Furthermore, pre-existing anxiety, adjuvant chemotherapy, and postoperative pain substantially contributed to this deterioration. These findings highlight the necessity of routine screening of sleep quality and the implementation of targeted interventions, including the management of menopausal symptoms, provision of psychological support, and effective pain control within this vulnerable patient cohort.

INTRODUCTION

Gynecologic malignancies pose a significant health challenge for women worldwide, with treatment protocols often encompassing aggressive surgical interventions, chemotherapy, and radiotherapy.[1] While oncologic outcomes remain the primary focus, there is increasing acknowledgment of the effects of these treatments on patients' quality of life (QoL).[2] Among the most common and distressing symptoms affecting QoL in cancer survivors is poorr sleep quality, which may present as insomnia, fragmented sleep, and nonrestorative rest.[3]

Sleep disturbances in patients with cancer are multifactorial, stemming from the psychological distress associated with the diagnosis, side effects of treatment such as pain and nausea, and direct physiological changes.[4,5] In gynecologic oncology, surgical menopause is a distinct and abrupt physiological stressor. The removal of both ovaries (bilat-

eral salpingo-oophorectomy) in premenopausal women induces an immediate and significant state of estrogen deficiency, which triggers severe vasomotor symptoms (hot flashes and night sweats), mood instability, and urogenital atrophy.[6,7] These symptoms are well-documented disruptors of sleep architecture and continuity.[8]

While the correlation between menopause and sleep disturbances is well established, the specific effects of iatrogenic surgically induced menopause, exacerbated by the stress of a cancer diagnosis and major surgery, remain less clearly defined. Previous research has often aggregated all gynecologic cancer patients or focused solely on vasomotor symptoms, without isolating the independent impact of surgical menopause from other significant variables such as preoperative psychological state, type of surgery, adjuvant therapy, and postoperative pain.[9,10] Understanding the hierarchy and interactions of these factors is crucial for developing targeted interventions.

This study aimed to address this gap by prospectively evaluating the factors influencing changes in sleep quality following surgical intervention for gynecological malignancies. The primary objective was to determine the independent effect of surgical menopause on postoperative sleep quality, considering other relevant clinical, surgical, and psychological variables.

MATERIALS AND METHODS

This prospective cohort study will be conducted at The Diyarbakır Gazi Yaşargil Training and Research Hospital, a tertiary referral center, from January 2024 to May 2025. This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Health Sciences University Gazi Yaşargil Training and Research Hospital Ethics Committee. (No: 525, Date: 27/06/2025) and all participants provided written informed consent.

The inclusion criteria were as follows: (a) Individuals aged ≥ 18 years; (b) A recent diagnosis of endometrial, ovarian, or cervical cancer with plans for primary surgical intervention; and (c) The capacity to comprehend and complete the study questionnaires. The exclusion criteria were as follows: (a) A pre-existing diagnosis of a primary sleep disorder, such as sleep apnea or narcolepsy; (b) Regular use of hypnotic medications at baseline; (c) Severe psychiatric disorders other than anxiety or depression; and (d) Metastatic disease that precludes surgery with curative intent.

A total of 158 patients were initially evaluated for their eligibility. After exclusions, 142 patients were enrolled in the study. For the primary analysis, the patients were divided into two groups:

1. Surgical Menopause (SM) Group: Premenopausal patients who underwent bilateral salpingo-oophorectomy.

2. Non-Surgical Menopause (non-SM) Group: Postmenopausal patients undergoing any type of surgery or premenopausal patients undergoing fertility-sparing surgery.

Data Collection and Measures: Data were collected at two time points: Baseline (within one week before surgery) and three months postoperatively during a follow-up visit.

1. Primary Outcome: Sleep Quality. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality over the preceding month.[11] The PSQI is a 19 item self-report instrument that generates seven component scores and a global score ranging from 0 to 21. A global score of >5 indicates poor sleep quality. The Turkish version of the PSQI has been shown to possess high reliability and validity.[12] The primary outcome was the change in the global PSQI score from baseline to three months postoperatively.

2. Psychological Distress: The Hospital Anxiety and Depression Scale (HADS) was employed at baseline to evaluate preoperative psychological conditions.[13] This instrument comprises 14 items and provides distinct scores for anxiety (HADS-A) and depression (HADS-D).

3. Postoperative Pain: At 3-month follow-up visit, patients rated their average pain over the preceding 7 days usingg a 10-cm Visual Analog Scale (VAS), where 0represenetds no pain and 10represenetds the worst imaginable pain. No discharge VAS was collected

4. Clinical and Demographic Data: Information on age, BMI, cancer diagnosis, FIGO stage, surgical approach (laparotomy vs. minimally invasive surgery, MIS), and planned adjuvant therapy (chemotherapy/radiotherapy) were collected from the patient records.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics. Paired t-tests were used to compare pre-and postoperative PSQI scores. Independent t tests or Mann Whitney U tests were used to compare continuous variables between groups, while Chi-square or Fisher's exact tests were used for categorical variables.

Multiple linear regression analysis was performed to identify independent associated factor of postoperative sleep disturbance. To control for baseline sleep quality and isolate the factors contributing to sleep deterioration, the change in the global PSQI score (ΔPSQI=postoperative PSQI, preoperative PSQI) was used as the dependent variable in the regression analysis. The independent variables included in the model were those found to be significant ($p<0.1$) in the bivariate analyses, including surgical menopause status, age, cancer stage, adjuvant chemotherapy, baseline HADS-A score, and postoperative VAS pain score. Statistical significance was set at $P<0.05$.

Table 1. Baseline demographic and clinical characteristics of participants (N=142)

Characteristic	Total Cohort (n=142)	SM Group (n=68)	Non-SM Group (n=74)	p-value
Age (years), mean±SD	55.2±10.1	48.5±5.2	61.3±8.9	<0.001
BMI (kg/m²), mean±SD	29.8±5.5	29.1±5.1	30.4±5.8	0.215
Cancer Type, n (%)				0.340
Endometrial	84 (59.1)	37 (54.4)	47 (63.5)	
Ovarian	41 (28.9)	22 (32.4)	19 (25.7)	
Cervical	17 (12.0)	9 (13.2)	8 (10.8)	
FIGO Stage, n (%)				0.002
Stage I-II	105 (73.9)	58 (85.3)	47 (63.5)	
Stage III-IV	37 (26.1)	10 (14.7)	27 (36.5)	
Surgical Approach, n (%)				0.411
MIS	65 (45.8)	33 (48.5)	32 (43.2)	
Laparotomy	77 (54.2)	35 (51.5)	42 (56.8)	
Adjuvant Chemo, n (%)	59 (41.5)	21 (30.9)	38 (51.4)	0.015
HADS-Anxiety, mean±SD	7.9±3.5	9.1±3.1	6.8±3.6	<0.001
HADS-Depression, mean±SD	6.5±3.1	6.8±2.9	6.2±3.3	0.288

Data are presented as mean±SD or n (%). SM: Surgical Menopause; non-SM: Non-Surgical Menopause; BMI: Body Mass Index; FIGO: International Federation of Gynecology and Obstetrics; MIS: Minimally Invasive Surgery; HADS: Hospital Anxiety and Depression Scale; PSQI: Pittsburgh Sleep Quality Index; VAS: Visual Analog Scale. p-values refer to between-group comparisons.

Table 2. Preoperative and postoperative PSQI scores

PSQI Score	Total Cohort (n=131)	SM Group (n=62)	Non-SM Group (n=69)	p-value (between groups)
Baseline Global PSQI	5.1±2.8	5.4±2.7	4.9±2.9	0.354
Post-op Global PSQI	8.9±4.1	11.0±3.5	7.0±3.4	<0.001
Mean Change (ΔPSQI)	+3.8±2.9	+5.6±2.9	+2.1±2.0	<0.001

Higher PSQI scores indicate worse sleep quality; ΔPSQI: postoperative minus preoperative global PSQI. PSQI: Pittsburgh Sleep Quality Index; SM: Surgical Menopause; non-SM: Non-Surgical Menopause. Independent tests were used for between-group comparisons, and paired tests were used for within-group changes.

RESULTS

Of the 142 enrolled patients, 131 completed the 3 month follow-up (92.3% follow-up rate). The baseline demographic and clinical characteristics are shown in Table 1. The mean age was 55.2±10.1 years old. The most common diagnosis was endometrial cancer (n=58.9%). The SM (n=68) and non-SM (n=74) groups were similar at baseline in terms of BMI, cancer type distribution, and HADS-D scores. However, the SM group was significantly younger, had a higher proportion of early stage disease, and had higher baseline HADS-A scores ($p<0.05$).

As shown in Table 2, the mean global PSQI score for the entire cohort significantly increased from 5.1±2.8 at baseline to 8.9±4.1 at 3 months postoperatively ($p<0.001$), indicating a clinically significant worsening of sleep quality. The percentage of patients classified as "poor sleepers" (PSQI score >5) increased from 40.1% to 71.0%. Deterioration was significantly more pronounced in the SM group than that in the control group. The mean change in PSQI score (ΔPSQI) was +5.6±2.9 in the SM group, compared to +2.1±2.0 in the Non SM group ($p<0.001$).

Multiple linear regression analysis identified four independent associated factor of worsened postoperative sleep quality (higher ΔPSQI score). The final model was statistically significant ($F(4, 126)=28.5$, $p<0.001$) and explained 47.5% of the variance in changes in sleep quality ($R^2=0.475$). As shown in Table 3, surgical menopause was the strongest independent associated factor. Adjuvant chemotherapy, higher baseline HADS anxiety score, and higher postoperative pain (VAS) were also significant independent associated factor. In the multivariable model, the effect sizes with 95% confidence intervals were as follows: Surgical menopause ($\beta=3.12$, 95% CI=2.15-4.09, $p<0.001$), adjuvant chemotherapy ($\beta=1.89$, 95% CI=0.72-3.06, $p=0.002$), baseline HADS-anxiety ($\beta=0.25$, 95% CI=0.07-0.43, $p=0.005$), and postoperative pain (VAS) ($\beta=0.31$, 95% CI=0.05-0.57, $p=0.018$).

Table 3. Multiple linear regression analysis predicting change in PSQI score (ΔPSQI)

Variable	Unstandardized Coefficient (B)	Standard Error (SE)	Standardized Coefficient (β)	95% Confidence Interval	p-value
(Constant)	-1.54	0.65		-2.82 to -0.26	0.019
Surgical Menopause (Yes)	3.12	0.49	0.45	2.15 to 4.09	<0.001
Adjuvant Chemotherapy (Yes)	1.89	0.59	0.23	0.72 to 3.06	0.002
Baseline HADS-Anxiety Score	0.25	0.09	0.20	0.07 to 0.43	0.005
Post-op Pain (VAS Score)	0.31	0.13	0.17	0.05 to 0.57	0.018

Dependent variable: ΔPSQI. Variables with p<0.10 in bivariate analyses were entered into the model. Abbreviations: B: Unstandardized coefficient; β: Standardized coefficient; CI: Confidence Interval; HADS: Hospital Anxiety and Depression Scale; VAS: Visual Analog Scale.

DISCUSSION

This prospective study offers essential insights into the significant impact of gynecological cancer surgery on sleep quality, identifying surgical menopause as the most critical associated factor of its decline. Our primary finding that sleep quality deteriorates markedly for all patients, with a particularly pronounced effect in those experiencing acute menopause, underscores a vital area for intervention in oncologic care.

The observed deterioration in sleep quality within our cohort, as evidenced by the increase in mean PSQI from 5.1 to 8.9, aligns with existing literature that reports high incidences of sleep disturbances among cancer survivors.[3,14] This decline can be attributed to a confluence of factors, including the psychological trauma associated with diagnosis, the physical stress of surgical interventions, and the adverse effects of subsequent treatments.[4] Our study effectively disentangled some of these contributing factors.

The significant independent effect of surgical menopause (β=3.12, p<0.001) corroborates our primary hypothesis. This result builds upon previous research by quantifying its impact in relation to other variables. It is particularly noteworthy that a substantial negative effect of surgical menopause on sleep quality was identified, despite this cohort being significantly younger and having a lower incidence of advanced-stage disease and adjuvant chemotherapy. This underscores the potent physiological impact of sudden estrogen withdrawal. The abrupt cessation of estrogen induces severe vasomotor symptoms, notably night sweats, which are known to cause frequent awakenings and fragmented sleep.[8,15] Beyond hot flashes, estrogen deficiency also directly influences central neurotransmitter systems that regulate the sleep-wake cycle, such as serotonin and norepinephrine, thereby contributing to primary insomnia.[16] Our findings strongly indicate that the physiological shock of surgical menopause is a more potent disruptor of sleep than the baseline menopausal status of older patients.

Our model has also identified adjuvant chemotherapy as independent associated factor of poor sleep quality. This finding is consistent with extensive research on "chemobrain" and cancer-related fatigue, wherein inflammatory cytokines, direct neurotoxicity, and corticosteroid use during treatment cycles disrupt normal sleep patterns.[17,18] It is imperative for clinicians to recognize that sleep disturbances in patients undergoing chemotherapy are not merely secondary symptoms of fatigue but constitute a distinct clinical entity that necessitates management. In subgroup analyses stratified by adjuvant chemotherapy status, the direction and significance of associations remained consistent.

The substantial association between preoperative anxiety and postoperative sleep quality highlights the critical mind-body connection in surgical recovery. Patients exhibiting elevated baseline anxiety levels are more susceptible to hyperarousal, which complicates the initiation and maintenance of sleep, a vulnerability further intensified by the stress associated with surgery.[19,20] This observation underscores a potential opportunity for preoperative psychological interventions, such as cognitive behavioral therapy (CBT) or mindfulness training, which may mitigate the decline in postoperative sleep quality.[21]

In conclusion, the identification of postoperative pain as an independent associated factor, persisting even at the three-month mark, underscores the critical need for effective and sustained analgesic interventions. Chronic post-surgical pain is an established syndrome, and our findings indicate that its effects extend beyond immediate discomfort, significantly disrupting essential restorative processes such as sleep.[22]

Clinical Implications The results of this study bear significant clinical implications. Firstly, they advocate for the incorporation of routine sleep assessments, utilizing validated instruments such as the PSQI, into the standard care protocol for gynecologic oncology. Secondly, patients identified as high-risk, particularly premenopausal women scheduled for bilateral oophorectomy, necessitate targeted preoperative and postoperative counseling. This counseling should encompass education regarding anticipated menopausal symptoms and their impact on sleep quality. Thirdly, the management of these patients should adopt a multidisciplinary approach, which includes proactive treatment of vasomotor symptoms, potentially employing hormone replacement therapy (HRT) in carefully selected patients with non-hormone-sensitive cancers,

following a comprehensive risk-benefit analysis, rigorous management of postoperative pain, and the provision of accessible psychological support.[23,24] While menopausal symptom control is pivotal, hormone replacement therapy (HRT) is not universally appropriate; contraindications include hormone-sensitive malignancies, a history of thromboembolic disease, active liver disease, or uncontrolled hypertension. In such cases, non-hormonal options (SSRIs/SNRIs, gabapentin, CBT-I, and lifestyle interventions) should be considered.The principal strengths of our study encompass its prospective design, which facilitates the evaluation of temporal changes, the employment of validated questionnaires, and the implementation of multivariate analysis to control for key confounding variables.

Nevertheless, it is imperative to acknowledge the limitations inherent in this study. Firstly, the study was conducted at a single center, which may constrain the generalizability of the findings. Additionally, this study was conducted at a single tertiary center, which may limit the generalizability of the findings. Objective sleep assessments such as actigraphy or polysomnography were not performed, and thus the results rely on self reported data. Secondly, the follow-up period was limited to three months, leaving the long-term trajectory of sleep quality unexplored. Thirdly, the study did not employ objective measures of sleep, such as polysomnography or actigraphy, relying instead on self reported data, which is susceptible to recall bias. Lastly, other potential confounding variables, including social support, physical activity levels, and dietary habits, were not assessed.

Future research should prioritize long term follow-up studies to enhance understanding of the chronic nature of these sleep disturbances. Additionally, there is an urgent need for randomized controlled trials to evaluate the efficacy of targeted interventions, such as cognitive behavioral therapy for insomnia (CBT-I), exercise programs, and various hormone replacement therapy (HRT) regimens, in improving sleep quality among gynecological cancer patients who undergo surgical menopause.[25,26]

Conclusion

In conclusion, the quality of sleep is a critical determinant in the outcomes of gynecological cancer surgery, with surgical menopause identified as the most significant and independent factor contributing to its deterioration. Additionally, preoperative anxiety, adjuvant chemotherapy, and postoperative pain are recognized as significant risk factors. Our research highlights the imperative for a paradigm shift in postoperative care, advocating for a comprehensive approach that incorporates proactive screening and management of sleep disturbances as an essential component of survivorship care.

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Ethics Committee Approval

The protocol was approved by the Institutional Review Board of (Health Sciences University Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: 27.06.2025, Decision No: 525).

Informed Consent

Written informed consent was obtained from all participants prior to enrollment.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: K.A.; Design: K.A., G.C.C.; Supervision: K.A., G.C.C.; Fundings: K.A.; Materials: P.B.I.; Data collection &/ or processing: K.A., G.C.C.; Analysis and/or interpretation: K.A., P.B.I.; Literature search: K.A., P.B.I.; Writing: K.A.; Critical review: K.A., G.C.C.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Jinekolojik Malignite Cerrahisi Sonrası Postoperatif Uyku Bozulmasının Belirleyicileri

Amaç: Bu çalışmanın amacı, jinekolojik maligniteler nedeniyle cerrahi müdahale geçiren hastalarda uyku kalitesinin belirleyicilerini, cerrahi menopozun etkilerine özel bir vurgu yaparak prospektif bir şekilde değerlendirmektir.

Gereç ve Yöntem: Bu prospektif kohort çalışmasına, bir üçüncü basamak sağlık kuruluşunda endometrium, over veya serviks kanseri nedeniyle cerrahi müdahale geçiren 142 hasta dahil edilmiştir. Katılımcılar, cerrahi menopoz yaşayanlar (SM grubu, n=68) ve yaşamayanlar (non-SM grubu, n=74) olmak üzere iki gruba ayrılmıştır. Uyku kalitesi hem preoperatif hem de postoperatif üçüncü ayda Pittsburgh Uyku Kalitesi İndeksi (PUKİ) kullanılarak değerlendirilmiştir. Preoperatif anksiyete ve depresyon düzeyleri, Hastane Anksiyete ve Depresyon Ölçeği (HADÖ) ile ölçülmüştür. Demografik, klinik ve cerrahi veriler sistematik olarak toplanmıştır. PUKİ skorundaki değişimlerle gösterilen kötü postoperatif uyku kalitesinin bağımsız belirteçlerini belirlemek amacıyla çoklu lineer regresyon analizi yapılmıştır.

Bulgular: Genel olarak, ortalama global PUKİ skoru başlangıçtaki 5.1±2.8'den postoperatif 3. ayda 8.9±4.1'e yükselerek anlamlı derecede kötüleşti ($p<0.001$). Uyku kalitesindeki bozulma, non SM grubuna göre SM grubunda anlamlı derecede daha fazlaydı (ortalama PUKİ değişimi: +5.6'ya karşılık +2.1, $p<0.001$). Çok değişkenli regresyon modelinde, cerrahi menopoz ($\beta=3.12$, $p<0.001$), adjuvan kemoterapi ($\beta=1.89$, $p=0.002$), daha yüksek başlangıç HADÖ-anksiyete skoru ($\beta=0.25$, $p=0.005$) ve daha yüksek postoperatif ağrı skoru (VAS) ($\beta=0.31$, $p=0.018$), PUKİ skorunda daha büyük bir artışın (daha kötü uyku kalitesi) bağımsız belirteçleri olarak tanımlandı.

Sonuç: Jinekolojik kanser cerrahisinin ardından postoperatif uyku kalitesinde belirgin bir azalma gözlemlenmiş olup, bu kötüleşmenin en önemli bağımsız öngörücüsü cerrahi menopoz olarak tanımlanmıştır. Ayrıca, önceden var olan anksiyete, adjuvan kemoterapi ve postoperatif ağrı da bu düşüşe önemli ölçüde katkıda bulunmuştur. Bu bulgular, bu hassas hasta kohortunda menopozal semptomların yönetimi, psikolojik destek sağlanması ve etkili ağrı kontrolü dahil olmak üzere, rutin uyku kalitesi taramasının ve hedefe yönelik müdahalelerin uygulanmasının gerekliliğini vurgulamaktadır.

Anahtar Sözcükler: Cerrahi menopoz; jinekolojik onkoloji; Pittsburgh Uyku Kalitesi İndeksi (PUKİ); postoperatif bakım; uyku kalitesi; yaşam kalitesi.

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Original Article

Comparison of Indications and Complications in Patients Undergoing Primary and Reoperative Thyroid Surgery

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Keywords: Hypocalcemia; hypoparathyroidism; total thyroidectomy; vocal cord paralysis.

ABSTRACT

Objective: Today, indications for thyroid surgery have significantly narrowed. Factors such as the increase in the number of experienced cytopathologists, the performance of biopsies by clinicians, and the significantly improved evaluation of ultrasound have contributed to this. Due to the increased reliability of needle aspiration biopsies, multiple biopsies can be performed, especially in patients with indications for re-operative surgery, and many patients can avoid re-operative surgery. We aimed to investigate the indications for re-operative thyroid surgery in our clinic by evaluating the pathology results and complications of patients who underwent re-operative thyroid surgery.

Methods: Primary (primary group) and re-operative thyroid patients (re-operative group) who underwent surgery in the Breast and Endocrine Surgery Unit of our hospital's General Surgery Clinic between February 2014 and August 2019 were included in the study. Patient characteristics and demographics, primary surgery, type of re-operative surgery, indication for primary surgery, indication for re-operative surgery, operation time, perioperative complications, and postoperative complications were used as evaluation parameters.

Results: 934 patients (93.6%) in the primary group and 64 patients (6.4%) in the re-operative group were compared in accordance with the study criteria. No significant differences were found in postoperative voice findings and vocal cord paralysis, while preoperative and postoperative hypocalcemia findings were significantly more common in the re-operative group across multiple criteria ($p<0.05$).

Conclusion: Indications and pathological examination results for primary and re-operative thyroid patients are similar according to current guidelines. While this reflects the accuracy of the indications, the high rates of hypocalcemia and persistent hypoparathyroidism in the re-operative patient group necessitate the restriction of indications. Prospective studies are needed for patients with narrower indications.

INTRODUCTION

In recent years, the indications for thyroid surgery have significantly narrowed. This has been attributed to several factors, including the addition of diagnoses such as Non-Invasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFT-P) to recent guidelines, the increase in the number of experienced cytopathologists, the performance of biopsies by shortage, and the substantial improvement in the use of ultrasonography for evaluation.[1,2] Despite these advances, the number of thyroid cancer surgeries has proportionally increased. Furthermore, a rise in aggressive variants of papillary carcinoma and an increased incidence of papillary carcinoma in younger populations have led to a higher mortality rate from thyroid cancer.[3]

In our country, as in the current ATA (American Thyroid Association) guidelines, the 2020 Thyroid Diseases Guideline published by the Turkish Society of Endocrinology and Metabolism does not include subtotal or near-total thyroidectomy procedures.[4] However, due to the widespread use of tissue-preserving surgeries up to 15 years ago, there is still a need for completion thyroidectomies.[5] Additionally, incomplete surgeries (such as missed mediastinal thy-

roid tissue), the necessity of lymph node dissections in thyroid cancers, or cases where the thyroid bed has been reopened for other reasons (such as extensive parathyroid exploration, esophageal surgery, or inadvertent entry into the thyroid bed during anterior cervical stabilization leading to iatrogenic thyroid injury) may require re-operative thyroid surgery. Like all secondary operations, re-operative thyroid surgery presents significant challenges. In particular, surgical adhesions around the recurrent laryngeal nerve, difficulties in identifying the parathyroid glands, and the risk of developing hypoparathyroidism can make these procedures highly demanding.[6]

Due to the increased reliability of fine-needle aspiration biopsies, multiple biopsies can be performed, particularly in patients considered for re-operative surgery, and most patients can thus be spared from reoperation. However, in patients whose cytology results include nondiagnostic material, atypia of undetermined significance, or follicular lesion of undetermined significance, the fact that postoperative pathological findings after repeated biopsies tend to favor benign pathologies according to guideline recommendations is noteworthy.[7]

The aim of this study is to evaluate the pathological results and complications of patients who underwent re-operative thyroid surgery in a high-volume center and to question the indications for such surgeries. By comparing the findings obtained in our clinical practice with the indications recommended by current guidelines, we aim to provide further data on the necessity of re-operative surgery and to shed light on future research in this field. In addition, by sharing our experience regarding postoperative complications and surgical challenges, we aim to contribute to the development of a more selective and effective approach to re-operative thyroid surgery.

MATERIALS AND METHODS

This study was designed as a retrospective analysis and conducted between February 2014 and August 2019 in the Breast and Endocrine Surgery Unit of the Department of General Surgery at our hospital. The study included patients who underwent either primary thyroid surgery (first surgical intervention) or re-operative thyroid surgery (patients with a previous thyroid operation requiring a second surgical procedure). Patients were divided into two groups: The Primary Group, consisting of patients who underwent thyroid surgery for the first time, and the Re-operative Group, consisting of patients who had previously undergone thyroid surgery and required a second surgical intervention.

Patients who underwent unilateral lobectomy without a surgical procedure on the contralateral lobe (i.e., lobectomy followed by completion thyroidectomy) were excluded, as surgical standardization could not be achieved in this group. Additionally, patients who were not followed up for at least one year after surgery or for whom permanent hypoparathyroidism could not be assessed were excluded from the study. Patients who failed to complete the required follow-up examinations or whose data were insufficient were also excluded from the analysis.

Demographic and clinical characteristics of the patients, types of primary and re-operative surgery, indications for both procedures, operative time, and intraoperative and postoperative complications were evaluated. All data were collected from the hospital database. Ethical approval for the study and data collection process was obtained from the Kartal Dr. Lütfi Kırdar Hospital Ethics Committee (Date: 25/09/2019, Approval No: 2019/514/162/2). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Study data were analyzed using descriptive statistical methods (mean, standard deviation, frequency, percentage, minimum, and maximum values). The distribution of variables between groups was assessed for normality using the Shapiro-Wilk test. For normally distributed quantitative variables, comparisons between two groups were performed using the independent samples t-test. Quantitative variables that did not follow a normal distribution were analyzed using the Mann-Whitney U test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test when appropriate. For multiple comparisons, the Bonferroni correction was applied. A p-value<0.05 was considered statistically significant.

RESULTS

Between February 2014 and August 2019, a total of 1,500 thyroid surgeries were performed in our clinic (Fig. 1). Of these patients, 1,321 (88.1%) underwent their primary surgery, while 179 (11.9%) underwent a re-operative procedure at our clinic. After excluding patients who underwent lobectomy-completion thyroidectomy, 998 patients meeting the study criteria were included. In the Primary group, 934 patients (93.6%) and in the Re-operative group, 64 patients (6.4%) were compared according to the study criteria.

The mean age in the Primary group was 50.8±12.9 years, and in the Re-operative group, it was 50.5±13.5 years, with no statistically significant difference between the groups (Fig. 2). In the Primary group, 717 patients (76.8%) were female, while in the Re-operative group, 56 patients (87.5%) were female. The proportion of female patients was significantly higher in the Re-operative group compared to the Primary group (p<0.05).

The distribution of surgical indications for patients in the Primary and Re-operative groups is shown in Table 1. The most common indication in all groups was compressive symptoms, and no significant difference in surgical indications was observed between the groups (p>0.05).

Preoperative evaluation of patients' calcium levels and thyroid function tests is presented in Table 2. There was a

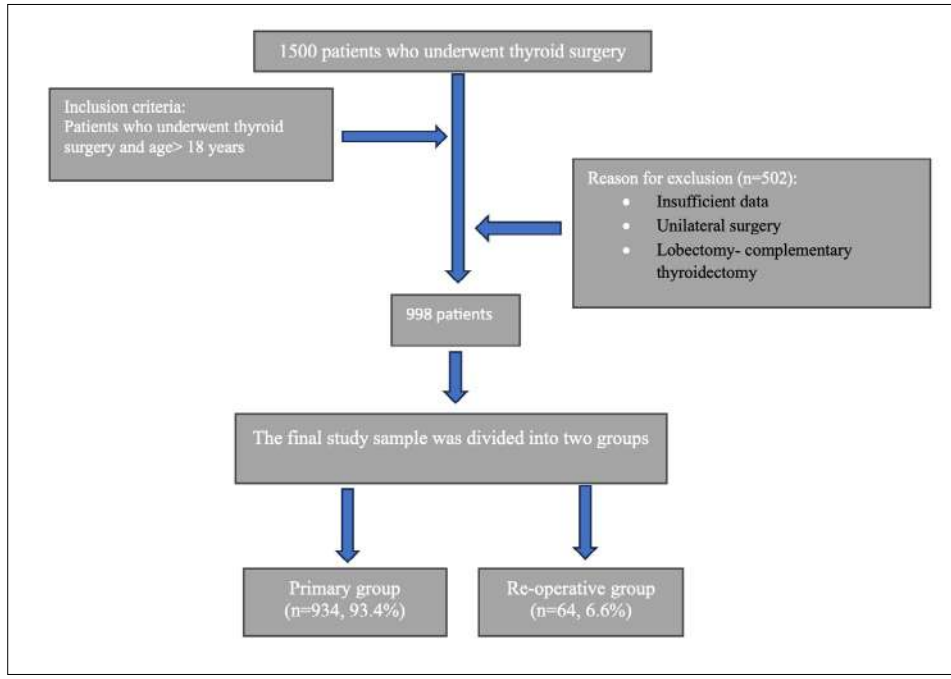

Figure 1. Flow chart of study population.

statistically significant difference between the two groups in terms of mean preoperative calcium levels (Fig. 3) ($p<0.001$). Additionally, statistically significant differences were observed between the groups regarding subclinical hyperthyroidism and subclinical hypothyroidism ($p<0.05$).

The distribution of surgical procedures in the Primary and Re-operative groups is presented in Table 3. Total thyroidectomy was the most commonly performed procedure in both groups, with a frequency comparable to that of total thyroidectomy combined with central neck dissection ($p>0.05$). However, it was performed significantly more often than other types of surgery ($p<0.05$).

Postoperative pathological results are presented in Table 4. The Primary and Re-operative groups showed similar pathological outcomes ($p>0.05$).

Voice hoarseness complications are presented in Table 5. The proportion of patients without voice/vocal cord pathology was significantly lower in the Re-operative group ($p<0.05$). Additionally, preoperative unilateral vocal cord paralysis was significantly more common in the re-operative group ($p<0.05$). However, postoperative voice hoarseness, independent of vocal cord paralysis, was ob-

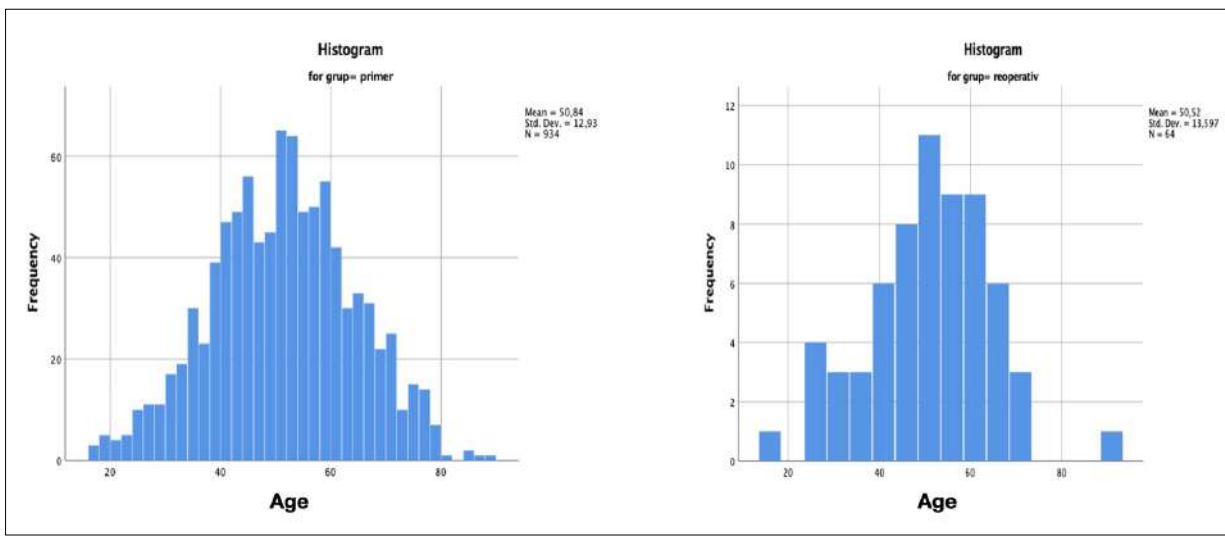

Figure 2. Age distribution of study population.

Table 1. Distribution of surgical ındications in primary and re-operative groups

Surgical Indications	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
Compression Symptom, n (%)	267 (28.6%)	22 (34.4%)
Toxic MNG, n (%)	193 (20.7%)	5 (7.8%)
Papiller Carsinom, n (%)	113 (12.1%)	11 (17.2%)
Suspicion of malignancy, n (%)	93 (10%)	10 (15.6%)
AUS twice, n (%)	82 (8.8%)	8 (12.5%)
Graves, n (%)	68 (7.3%)	0
Hurthle Cell Neoplasia, n (%)	50 (5.4%)	3 (4.7%)
Follicular Neoplasia, n (%)	34 (3.6%)	3 (4.7%)
Recurrent Nondiagnostic, n (%)	32 (3.4%)	2 (3.1%)
Thyroiditis, n (%)	2 (0.2%)	0

MNG: Multinodular goiter; AUS: Atypia of undetermined significance.

Table 2. Calcium and thyroid hormone evaluations of patients

	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
Calcium (mg/dl), mean±SD	9.54±0.61	9.24±0.64
Euthyroid, n (%)	660 (70.7%)	50 (78.1%)
Hypothyroidism, n (%)	11 (1.2%)	2 (3.1%)
Hyperthyroidism, n (%)	45 (4.8%)	0
Subclinical hypothyroidism, n (%)	22 (2.4%)	8 (12.5%)
Subclinical hyperthyroidism, n (%)	196 (21%)	4 (6.3%)

SD: Standard deviation.

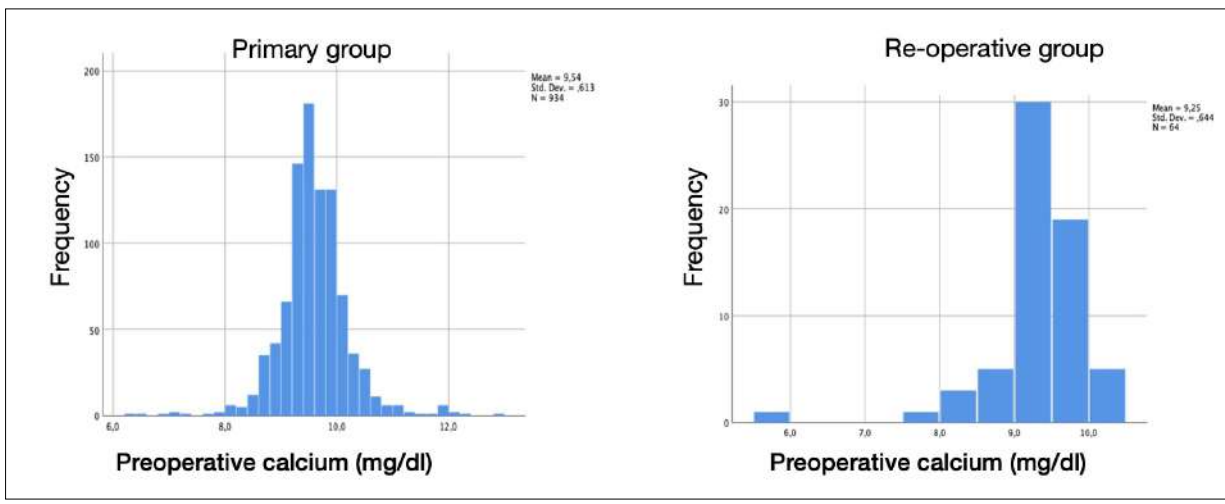

Figure 3. Preoperative mean calcium levels.

served at a similar rate in both groups. Although the only patient requiring tracheostomy was in the Primary group, there was no significant difference between the groups.

Postoperative bleeding findings are presented in Table 5. No statistically significant difference was observed between the two groups in terms of postoperative bleeding-related complications.

Postoperative hypocalcemia findings were evaluated according to biochemical parameters and are presented in Table 6. The number of patients with postoperative

Table 3. Surgery distribution of the groups

Type of Surgery	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
TT	894 (89.6%)	56 (5.6%)
TT+CCD	38 (3.8%)	5 (0.5 %)
TT+MRND	2 (0.2%)	2 (0.2%)
CCD	0	1 (0.1%)

TT: Total thyroidectomy; TT+CCD: Total thyroidectomy + central compartment dissection; TT+MRND: Total thyroidectomy + modified radical neck dissection; CCD: Central compartment dissection.

hypocalcemia was significantly higher in the Re-operative group ($p<0.05$). However, both groups were similar regarding patients with biochemical hypocalcemia without symptoms. Patients with hypocalcemia accompanied by low parathyroid hormone levels and clinical symptoms were significantly more frequent in the Re-operative group ($p<0.05$). Additionally, preoperative hypoparathyroidism was significantly more common in the Re-operative group ($p<0.05$).

The duration-based and permanent-versus-transient evaluation of hypocalcemia is presented in Table 6. The number of patients without hypocalcemia was significantly higher in the Primary group ($p<0.05$). Transient hypocalcemia lasting less than one month was significantly more frequent in the Re-operative group. Similarly, permanent hypoparathyroidism (>12 months) was significantly more common in the Re-operative group ($p<0.05$).

Table 4. Postoperative pathology results

	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
Benign, n (%)	513 (54.9%)	41 (64.1%)
Papillary Microcarcinoma, n (%)	190 (20.3%)	8 (12.5%)
Papillary Carcinoma, n (%)	213 (22.8%)	14 (21.9%)
Medullary Carcinoma, n (%)	6 (0.6%)	1 (1.6%)
Papillary + Medullary Carcinoma, n (%)	2 (0.2%)	0
NIFT-P, n (%)	6 (0.6%)	0
Poorly Differentiated Carcinoma, n (%)	4 (0.4%)	0

NIFT-P: Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features.

Table 5. Hoarseness and postoperative bleeding

	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
No features, n (%)	898 (96.1%)	57 (89.1%)
Voice is hoarse, vocal cords are normal, n (%)	17 (1.8%)	2 (3.1%)
Hoarse voice, vocal cord paralysis, n (%)	16 (1.7%)	3 (4.7%)
Preop vocal cord paralysis (one side), n (%)	2 (0.2%)	2 (3.1%)
Tracheostomy, n (%)	1 (0.1%)	0
No Bleeding, n (%)	906 (97%)	61 (95.3%)
Bleeding Yes - bleeding control, n (%)	3 (0.3%)	1 (1.6%)
Bleeding Yes - conservative, n (%)	25 (2.7%)	2 (3.1%)

DISCUSSION

One of the key priorities in the treatment of thyroid diseases is to protect patients from unnecessary surgery. The risk-benefit relationship should be carefully evaluated, and a comprehensive treatment plan should be provided, reserving surgery only when indicated.[8] The aim of surgical treatment for thyroid diseases is to achieve the most effective treatment with the lowest complication and recurrence rates. Numerous risk factors influence complication rates, including surgeon experience, patient sex, previous thyroid surgery, and anatomical variations.

In patients with thyroid cancer, total thyroidectomy is considered the standard approach.[9] Advances in surgical technique, nerve monitoring, and the limitations of subtotal thyroidectomy have led to total thyroidectomy being increasingly preferred even for some benign thyroid

Table 6. Postoperative hypocalcemia

	Primary (n=934, 93.6%)	Re-operative (n=64, 6.4%)
None, n (%)	682 (73%)	34 (53.1%)
Biochemical hypocalcemia, symptoms (-), n (%)	103 (11%)	12 (18.8%)
Biochemical hypocalcemia, symptoms (+), n (%)	35 (3.7%)	3 (4.7%)
PTH low, hypocalcemia, symptom (-), n (%)	45 (4.8%)	5 (7.8%)
PTH low, hypocalcemia, symptom (+), n (%)	68 (7.3%)	9 (14.1%)
Preoperative hypoparathyroidism patient, n (%)	1 (0.1%)	1 (1.6%)
Temporary, <1 month, n (%)	164 (17.6%)	18 (28.1)
Temporary, 1-3 months, n (%)	49 (5.2%)	4 (6.3%)
Temporary, 3-6 months, n (%)	10 (1.1%)	2 (3.1%)
Temporary, 6-12 months, n (%)	10 (1.1%)	1 (1.6%)
>12 months, n (%)	19 (2.0%)	5 (7.8%)

PTH: Parathyroid hormone.

conditions. Successful hormone replacement therapy also supports the choice of total thyroidectomy.[10]

Today, total thyroidectomy allows radical surgical treatment without leaving any residual thyroid tissue, effectively eliminating the risk of recurrent disease. Cappellani et al.[11] noted that preventing recurrent goiter is best achieved through primary total thyroidectomy. Total thyroidectomy is a safe procedure with a low incidence of permanent complications, thereby reducing the need for secondary surgery.[12]

Historically, many surgeons preferred bilateral subtotal thyroidectomy to minimize operative risk and preserve a small portion of functioning tissue.[13] However, subtotal thyroidectomy carries a lifelong risk of recurrence in some patients. After subtotal resection of multinodular goiter, recurrence rates of up to 40% have been reported in long-term follow-up.[14]

Differences in perioperative complication rates cannot justify performing less than total thyroidectomy, even in benign disease. The morbidity associated with repeat surgery alone is a strong reason to avoid conservative procedures. Furthermore, suppressive therapy with levothyroxine often fails to prevent recurrence and may induce morbidity in some cases.[15] Surgical treatment of recurrent disease carries higher morbidity than primary total thyroidectomy.[11] Scar tissue and altered anatomy from previous surgery complicate dissection and increase complication risk in re-operative procedures.

In a study by Osmólski et al.[16] approximately 850 thyroidectomies were retrospectively reviewed, showing that re-operative thyroidectomies had significantly higher rates of temporary and permanent recurrent laryngeal nerve injury compared to primary surgeries. Rates of hypoparathyroidism were also significantly higher after reoperation.

To ensure homogeneity in our sample, we included only total thyroidectomy patients. Although the proportion of female patients in the Primary group was lower than in the Re-operative group, this is likely explained by the fact that the re-operative cohort consisted predominantly of female patients.

When comparing indications, compressive symptoms were the most frequent. This refers to nodules >4 cm or nodules <4 cm causing respiratory compromise on imaging. Similar indications in both groups reflect adherence to ATA and TEMD guidelines . Likewise, the lack of statistical difference in pathological outcomes between groups supports the accuracy of these indications. Rates of total thyroidectomy and total thyroidectomy with central compartment dissection were similar and significantly higher than other procedures, consistent with shared indications.

As expected, mean preoperative calcium levels were higher in the Primary group, largely due to heterogeneous distribution in the Re-operative group. Hypocalcemia and subclinical hypothyroidism were more frequent in the Re-operative group, likely due to reduced or nonfunctional residual tissue.[4] Conversely, subclinical hyperthyroidism was more common in the Primary group , reflecting residual tissue with normal or excessive function.

Early complications were evaluated separately from late complications. Postoperative bleeding was similar between groups with no statistical difference. Early hypocalcemia was defined as occurring within the first 24-72 hours postoperatively, potentially prolonging hospital stay if symptomatic.[17] Postoperative hypocalcemia was more frequent in the Re-operative group, particularly symptomatic patients with concurrent low parathyroid hormone and calcium levels. Within the first month, the incidence of hypocalcemia and permanent hypoparathyroidism was significantly lower in the Primary group.

The primary goals of this study were to compare indications and complication rates. The lack of difference in indications validates the implementation of current guidelines in our clinic following subspecialization in 2013. Subspe-

cialization has likely contributed to the lower complication rates observed compared to historical data.[18] Although nerve monitoring is commonly used in current practice, its application during the study period was below 5%, limiting the assessment of its effect. The retrospective nature of the study is another limitation.

Despite similar indications, differences in complications were observed. The main complication remained calcium metabolism disturbances rather than vocal cord paralysis, even with limited nerve monitoring. As expected, the proportion of patients without preoperative voice or vocal cord pathology was lower, and the proportion with unilateral preoperative vocal cord paralysis was higher in the Re-operative group. Postoperative vocal cord paralysis and voice hoarseness were similar and low in both groups, likely due to increased surgical experience after subspecialization. However, experience alone did not reduce calcium metabolism complications.[18]

The higher rates of transient hypocalcemia and permanent hypoparathyroidism in the Re-operative group highlight the need to carefully evaluate surgical indications. Notably, 64.1% of re-operative patients had benign pathology. Patients with toxic goiter, compressive symptoms, repeated AUS, or recurrent nondiagnostic findings could be considered for alternative management such as radioactive iodine or repeat biopsy. Permanent hypoparathyroidism is difficult to manage, often inadequately treated, and significantly reduces quality of life. Its occurrence is largely unavoidable due to fibrosis and adhesions in re-operative fields and the low likelihood of preserving parathyroid function during surgery.[19]

Although recurrent laryngeal nerve preservation is enhanced by surgical expertise and stimulation techniques, parathyroid protection is not fully ensured.[20] Therefore, narrowing surgical indications in re-operative patients may reduce complication rates to levels similar to primary cases. Malignancy must still be excluded, which can often be achieved through repeat biopsies. The cumulative complication risk of multiple biopsies is likely lower than that of hypocalcemia. As subtotal or near-total thyroidectomies have been largely abandoned, the number of re-operative patients is gradually decreasing, and in the next 20 years, reoperation will primarily concern cancer recurrence.

Conclusion

Primary and re-operative thyroid patients show similar surgical indications and pathological outcomes when managed according to current guidelines. While this reflects the accuracy of the indications, the higher rates of hypocalcemia and permanent hypoparathyroidism in the re-operative group highlight the need to restrict surgical indications in these patients. Prospective studies are warranted to evaluate outcomes in patients managed with more selective, guideline-based indications.

Acknowledgement

I would like to sincerely thank Dr. Cemalettin Yılmaz for his kind help, guidance, and encouragement during the preparation of this work.

Ethics Committee Approval

The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Kartal City Hospital (Date: 25.09.2019, Decision No: 514/162/2).

Informed Consent

Due to the retrospective design of our study, informed consent was not obtained.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: O.A., H.E.S.; Design: O.A., H.E.S, H.F.K.; Supervision: H.E.S., H.F.K; Materials: O.A., M.K.B.; Data collection &/or processing: O.A., M.K.B.; Analysis and/or interpretation: O.A., H.E.S.; Literature search: O.A., M.K.B., H.E.S.; Writing: O.A., H.E.S.; Critical review: H.E.S., H.F.K.

Conflict of Interest

None declared.

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Primer ve Re-operatif Tiroid Cerrahisi Uygulanan Hastaların Endikasyon ve Komplikasyonlarının Karşılaştırılması

Amaç: Günümüzde tiroid ameliyat endikasyonları belirgin olarak daralmıştır. Deneyimli sitopatolog sayısında artış, biyopsilerin klinisyenler tarafından yapılması, ultrasonografinin belirgin olarak daha iyi şekilde değerlendirmede yer alması gibi faktörler bu hususta rol oynamıştır. İğne aspirasyon biyopsilerinde güvenilirliğin artması nedeniyle özellikle re-operatif cerrahi endikasyonu konulacak hastalarda multipl biyopsiler yapılabilmekte ve çoğu hasta reoperatif cerrahiden korunabilmektedir. Kliniğimizde re-operatif tiroid cerrahisi uygulanan hastaların patoloji sonuçları eşliğinde komplikasyonları da değerlendirerek re-operatif tiroid cerrahisi endikasyonlarını sorgulamayı amaçladık.

Gereç ve Yöntem: Şubat 2014-Ağustos 2019 tarihleri arasında hastanemizin Genel Cerrahi Kliniği Meme ve Endokrin Hastalıkları Cerrahisi Birimi' nde ameliyat edilen primer (Primer grup) ve re-operatif tiroid hastaları (Re-operatif grup) çalışmaya dahil edilmiştir. Hastaların karakteristik ve demografik özellikleri, primer ameliyat, re-operatif cerrahi tipi, primer cerrahi endikasyonu, re-operatif cerrahi endikasyonu, operasyon süresi, peroperatif komplikasyonlar, postoperatif komplikasyonlar değerlendirme parametreleri olarak işleme alınmıştır.

Bulgular: Primer grupta 934 (%93.6), re-operatif grupta ise 64 (%6.4) hasta çalışma kriterleriyle uyumlu olarak karşılaştırıldı. Postoperatif ses bulguları ve vokal kord paralizisi açısından anlamlı farklılık saptanmazken, preoperatif ve postoperatif hipokalsemi bulguları pek çok kriter değerlendirmesinde re-operatif grupta anlamlı olarak daha fazla saptandı ($p<0.05$).

Sonuç: Primer ve re-operatif tiroid hastaları güncel kılavuzlar eşliğinde endikasyonları ve patolojik inceleme sonuçları benzerlikler göstermektedir. Bu durum endikasyonların doğruluğunu yansıtmakla beraber re-operatif hasta grubunda hipokalsemi ve kalıcı hipoparatiroidi oranının yüksek olması nedeniyle re-operatif hasta grubunda endikasyon kısıtlamasının gerekliliği söz konusudur. Endikasyonların daraltılarak takip edildiği hastalarla ilgili prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Hipokalsemi; hipoparatiroidi; total tiroidektomi; vokal kord paralizisi.

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Original Article

Vancomycin Drug Levels and Clinical Correlations in Critical Pediatric Patients

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Keywords: Pediatrics; therapeutic drug monitoring; vancomycin.

ABSTRACT

Objective: Vancomycin is an antibiotic frequently used in the treatment of resistant gram-positive infections. Although data on its efficacy and safety in pediatric patients are limited, it is widely used in clinical practice. Recommended trough serum levels are 15–20 mg/L, and peak levels are 20–40 mg/L. To reach these targets, it is generally administered at a dose of 40–60 mg/kg/day depending on the infection type. Pediatric Intensive Care Unit (PICU) admissions frequently involve clinical complexity. In this study, we aimed to evaluate the serum levels of vancomycin in patients treated in our unit.

Methods: This retrospective study includes patients who were hospitalized in our PICU between 2015 and 2019, received vancomycin therapy, and had serum vancomycin levels measured.

Results: Data from 14 patients (median age: 45.4 months, 42.9% male) were evaluated. Sepsis (50%) and pneumonia (21.4%) were the leading indications. The median vancomycin dose was 50 mg/kg/day (40–60), with a treatment duration of 7 days (2–10). In total, 30 serum vancomycin levels were analysed. Trough levels were measured in 47.6% and peak levels in 52.4% of patients, respectively. Levels were within the target range in 44.4%, below in 44.4%, and above in 11.1%.

Conclusion: Optimal vancomycin levels in critically ill pediatric patients often necessitate individualized dosing strategies. Close monitoring remains essential to ensure both efficacy and safety.

INTRODUCTION

Vancomycin is a glycopeptide antibiotic that blocks the formation of the bacterial cell wall and is particularly active against resistant gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA). It is frequently administered in management of serious gram-positive infections. Its half-life is around 6 hours in patients with normal renal functions, but it can be as long as 7.5 days in anuric cases. After IV administration, 70-90% of the drug is extracted unchanged through glomerular filtration. It cannot be extracted through haemodialysis or peritoneal dialysis.[1]

By therapeutic drug monitoring, it is aimed to keep the blood drug level between therapeutical range, thus having optimal outcome while reducing the risk of drug toxicity. By monitoring the patient during the treatment, it helps us to determine the optimal dosage for the patient regarding their age, weight, renal functions and other variables. Blood drug level monitoring helps us to determine optimal dosage from the drug while having minimal risk of side effects by regarding administration time, desired clinical levels and attainment of a stable state.[1-3]

Sampling time may vary depending on the purpose of the sample, some examples of which may be blood drug levels coherence, toxicity or dose suitability monitorization. Generally, monitorization is based on trough levels instead of peak levels. Trough level is the level right before ad-

ministration of the next those and it shows the lowest concentration of the administered therapeutic dose, while peak level shows the highest concentration after dispersion of the drug after administration. There are many factors affecting peak dose. The route of administration for the drug, formulation of the drug (slow or fast release), additional maladies which may affect gastric motility and pharmacokinetic properties of the drug.[1,4,5]

In routine practice, it is not required to measure serum concentrations for vancomycin. Therapeutic peak level range is 20-40 µg/mL, and trough level range is 5-10 µg/mL. Since irreversible autotoxicity is seen in blood levels above 80 µg/mL, it is more convenient to measure trough levels instead of peak levels. When trough levels are kept in desired range, peak levels cannot be above 40 µg/mL and considering that there is not enough evidence backing peak level toxicity, trough level monitorization is the widely recommended choice. Best time to monitor peak levels is about 1 hour after end of administering IV infusion. Vancomycin trough level monitorization helps dose adjustment in a way that keeps the concentration above minimum inhibitor concentration (MIC) value while preventing accumulation of drug in the body. The most optimal time for trough level measurement is right before administration of third dose. If the trough level is suitable (5-10 µg/mL), renal functions are stable and clinical response is favourable, there is no need for a second trough level measurement. For patients with renal failure, regarding the stage of renal failure, vancomycin through level should be seen 2-5 days after the administered dose, and the next dose should be applied after getting blood concentration in the target range.[1,5-8]

Pediatric Intensive Care Unit (PICU) patients are complicated ones. Managing dosage of antibiotics regarding accompanying organ failures decreases complications, thus reducing mortality and morbidity rates. In our study, we have aimed to examine the serum levels of vancomycin among the patients we have used the drug on.

MATERIALS AND METHODS

This study was conducted following the ethical guidelines outlined in the Helsinki Declaration. Ethical approval was obtained from the Ethical Committee of Marmara University Clinical Research (Date: 12/06/2020, No: 09.2020.649).

In this study, we have retrospectively assessed the files of PICU patients who were treated with vancomycin and had blood level monitorization between 01.01.2015-01.01.2019. Their demographic features, vancomycin treatment dosages and serum drug levels were assessed. Blood samples were obtained from the patients with 2.5 mL tubes (Vacutainer SST II, Becton Dickinson, USA) then centrifuged for 10 minutes at 2500 G at our hospital laboratory. Serum vancomycin levels were assessed by automated device (Cobas Integra 400, Roche Diagnostics, USA) by using fluorescent polarization immunoassay (FPIA) method. As per producer data, coefficient of variation values (CV%) for 8.68-26.3-54.6 mg/L serum vancomycin levels are stated as 2.2%-1.6%-3.1%; and between studies they are shown as 3.0%-2.2%-3.3%. Categorical data is shown as n and % while continuous variables were shown as median (IQR) values.

RESULTS

The data of patients who were treated by vancomycin and had blood level measurement during their stay at our PICU between 2015-2019 were analysed. Of 14 patients with a median age 45.4 (IQR), 42.9% were male (n:6). The most common indication for vancomycin was sepsis (50%) and pneumonia (21.4%). The median duration of vancomycin treatment was 7 days (2-10), and the dose was 50 (40-60) mg/kg/day. During treatment, a total of 30 serum vancomycin levels were sent from 14 patients (once from 6 patients, twice from 4 patients, four times from 2 patients, three times from 1 patient and five times from one patient), and the median level was 18.4 (11.6-31.0, min-max; 5.5-49.0) mg/L. Treatment doses and associated serum vancomycin levels are shown in Table 1. Trough

Table 1. Vancomycin serum concentration levels and administered doses

Vancomycin dose	Serum vancomycin levels (mg/L), Median (IQR)*	
10 mg/kg/day	12.0 (n:1) **	
40 mg/kg/day	15.0 (8.6-29.5) (n:9) **	
60 mg/kg/day	14.6 (9.6-25.8) (n:9) **	
Vancomycin serum readings	First reading	All readings
Median, IR (mg/L)	15.0, 9.1-29.5	18.4, 11.6-31.0
Minimum-maximum	5.5-40.4	5.5-49.0
Trough level		
Median, CAA (mg/L)	10.7, 7.2-35.5	10.9, 7.0-40.0
Minimum-maximum	7.0-40.0	7.0-40.0

Trough level is the level right before the next dose. IQR: Inter quartile range. *p: 0.9, Kruskal Wallis test. **n shows the reading amount, not the patient count.

level was measured in 47.6% of patients and peak level was measured in 52.4% of patients. Serum vancomycin levels were normal in 44.4%, low in 44.4% and high in 11.1%. In 18 patients with normal renal function, vancomycin levels were found to be low in 8(44.4%) patients and normal in 10(55.6%).

DISCUSSION

The studies among adults have shown that increasing MRSA resistance is directly related to the need to increase the vancomycin dose. It has been proven that the clinical effect is correlated with trough levels.[9] Latest pediatric research has shown that the target trough concentration should be 15-20 mg/L and vancomycin overdose is highly correlated with increase in toxicity risk.[10,11] The increase in vancomycin resistance among MRSA has resulted in higher empirical dose usage to reach the target 15-20 mg/L starter trough levels. In pediatric patients, even though the data is limited, the findings are significantly similar. Treatment strategies should be planned in accordance with pediatric data and bacterial resistance tendencies.

Vancomycin is a drug that is known to be nephrotoxic, especially with long term usage. Hidayat et. al. has shown among adults that have MRSA infection who take vancomycin treatment, when they get other nephrotoxic agents with a trough level of 15-20 mg/L, have vancomycin related nephrotoxicity incidence.[12] A study from 2011 has shown adults with MRSA infection have higher renal injury risk with vancomycin trough level ≥15 mg/L (OR, 3.6; 95% CI, 1.75-7.59).[13] Likewise, it was shown in adults with MRSA pneumonia that there is three to five times higher risk of acute kidney injury with a trough level of 15 mg/L or higher.[14,15]

Maloni et al.[16] has shown similar results to our study, as they had reached therapeutic level of 7-14 mg/L at 44.7% of their cases, which is similar to our results of 44.4%. In our unit, we are using vancomycin for treatment of many multidrug-resistant gram-positive infections with a starter dose of 40 mg/kg/day unless there is a suspicion of serious meningitis infection. We are not studying serum levels for every patient who undergoes vancomycin treatment routinely. The serum levels were studied for patients who have partial or no response to therapy, who have organ failure or are at risk of it. The treatment dose is increased up to 60 mg/kg/day if deemed necessary. Due to factors such as the current conditions in the hospital and the availability of test kits, the number of patients studied is not optimal for now.

Conclusion

Our study has importance as a guidance for other studies which contain more patients with additional contributing centres. Critically ill children may require different dosage to reach desired trough concentration for each patient. Vancomycin levels should be monitored closely especially when there is a need to avoid toxicity while reaching treatment serum trough levels.

Ethics Committee Approval

The study was approved by the Ethical Committee of Marmara University Clinical Research (Date: 12.06.2020, Decision No: 09.2020.649).

Informed Consent

Retrospective study.

Peer-review

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Authorship Contributions

Concept: F.I.G., M.N.Y.; Design: F.I.G., M.N.Y.; Supervision: F.I.G., M.N.Y., O.S., T.S.; Materials: F.I.G.; Data collection &/or processing: F.I.G., T.S.; Analysis and/or interpretation: F.I.G., T.S.; Literature search: F.I.G., O.S.; Writing: F.I.G., O.S., T.S.; Critical review: F.I.G., O.S., T.S., M.N.Y.

Conflict of Interest

None declared.

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Kritik Durumdaki Pediatrik Hastalarda Vankomisin İlaç Düzeyleri ve Klinik Korelasyonlar

Amaç: Vankomisin, dirençli gram-pozitif enfeksiyonların tedavisinde sıklıkla kullanılan bir antibiyotiktir. Pediatrik hastalarda etkinliği ve güvenliği ile ilgili veriler sınırlı olmasına rağmen, klinik uygulamada yaygın olarak kullanılmaktadır. Önerilen serum trough (çukur) düzeyleri 15-20 mg/L, peak (zirve) düzeyleri ise 20-40 mg/L'dir. Bu hedef değerlere ulaşmak için genellikle enfeksiyon tipine göre 40-60 mg/kg/gün dozunda uygulanır. Pediatrik yoğun bakım ünitesi (PYBÜ) hastaları genellikle karmaşık klinik özellikler taşır. Bu çalışmada, ünitemizde tedavi edilen hastalarda vankomisin serum düzeylerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, 2015-2019 yılları arasında PYBÜ'de yatan, vankomisin tedavisi alan ve serum vankomisin düzeyi ölçülen hastalar dahil edilmiştir.

Bulgular: Toplam 14 hastanın (median yaş: 45.4 ay; %42.9 erkek) verileri değerlendirildi. En sık tedavi endikasyonları sepsis (%50) ve pnömoni (%21.4) idi. Median vankomisin dozu 50 mg/kg/gün (40-60) ve tedavi süresi 7 gün (2-10) olarak saptandı. Toplam 30 serum vankomisin düzeyi analiz edildi; bunların %47.6'sı çukur ve %52.4'ü tepe düzeyleriydi. Düzeylerin %44.4'ü hedef aralıkta, %44.4'ü hedefin altında ve %11,'i hedefin üzerindeydi.

Sonuç: Kritik durumdaki pediatrik hastalarda optimal vankomisin düzeylerine ulaşmak genellikle bireyselleştirilmiş doz ayarlamaları gerektirir. Hem etkinliği hem de güvenliği sağlamak için yakın terapötik izlem esastır.

Anahtar Sözcükler: Pediatri; terapötik ilaç izlemi; vankomisin.

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Original Article

Impact of Urinary Incontinence on Sleep and Quality of Life in Non-obese Premenopausal Women

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Keywords: Quality of life urinary; sleep quality; incontinence.

ABSTRACT

Objective: Urinary incontinence refers to the involuntary leakage of urine in individuals of any age but is more common in women. Identifying urinary incontinence in premenopausal women and developing effective prevention and management strategies are crucial to improve quality of life and sleep by reducing patients' physical complaints. This study aimed to determine the quality of life and sleep of patients with and without urinary incontinence in a premenopausal, nonobese population.

Methods: This prospective study, included 110 patients (55 study group, 55 control group). The study group consisted of premenopausal women aged 35–50 with urinary incontinence complaints. ICIQ-SF assessed urinary incontinence's impact on quality of life, and the PSQI evaluated sleep quality. Statistical analysis followed data collection.

Results: The study evaluated 110 non-obese premenopausal patients. No statistically significant difference was found between the study and control groups in terms of demographic characteristics. The ICIQ-SF score was 1.58±2.01 in the control group and 12.23±4.90 in the study group, with a statistically significant difference ($p<0.0001$). The PSQI score was 3.58±1.64 in the control group and 6.45±2.89 in the urinary incontinence group, with a significant difference ($p<0.001$)

Conclusion: This study found that urinary incontinence significantly impaired quality of life and sleep in premenopausal women, both obese and nonobese. Raising awareness, informing patients, promoting lifestyle changes, and initiating treatment can improve overall health, quality of life, and sleep in affected individuals.

INTRODUCTION

Urinary incontinence refers to the involuntary leakage of urine in individuals of any age but is more common in women. It is of five types: stress, urge, mixed, overflow, and functional. Women are reluctant to report urinary incontinence, making it difficult to determine the prevalence of this condition. Studies have reported that 12.4% of young women and 45% of middle-aged and postmenopausal women experience urinary incontinence.[1,2] High parity, obesity, smoking, constipation, macrosomic delivery, and caffeine consumption are among the best-known causes of urinary incontinence.[3] Urinary incontinence decreases women's general quality of life by limiting social relations, self-confidence, and daily activities besides its physical effects. An increase in incontinence severity increases the negative impact.[4] Sleep quality is another important condition affected by urinary incontinence. Frequent nocturia and anxiety associated with incontinence attacks disrupt sleep patterns, leading to a decrease in sleep quality. The physical effects of this condition increase the psychological burden and create a vicious cycle of insomnia and persistent poor sleep quality.[5] Studies comparing samples with the general population have reported poor sleep quality.[6] Assessing patients with this condition and determining their quality of life and sleep are vital for correct diagnosis. The International Incontinence Society recommends that quality-of-life measurements be included in clinical practice and that improvement practices be established accordingly.[7] The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) is a tool to measure the quality of life of patients with urinary incontinence. The Pittsburgh Sleep Quality Index (PSQI), which comprehensively examines various demographic characteristics of

participants, is another tool used to assess sleep quality.

Identifying urinary incontinence in premenopausal women and developing effective prevention and management strategies are crucial to improve quality of life and sleep by reducing patients' physical complaints. The effects of obesity on urinary incontinence are well known. This study aimed to determine the quality of life and sleep of patients with and without urinary incontinence in a premenopausal, nonobese population.

MATERIALS AND METHODS

This prospective study was conducted between September 01, 2023, and September 01, 2024. It was approved by the Biruni University Clinical Research Ethics Committee (Date: 29/03/2023, No: 2023/79-09) and conducted following the principles of the Declaration of Helsinki.

The study was performed with 110 patients, of which 55 were control and the other 55 were study patients. The study group comprised premenopausal women aged 35–50 years and patients with urinary incontinence. The control group consisted of patients without urinary incontinence. Participants were excluded if they were menopausal, had a body mass index (BMI) of 30 or higher, had undergone surgery for urinary incontinence, had pelvic organ prolapse, had comorbid conditions that affected their quality of sleep, or had a history of taking sleep aids. All individuals were provided with detailed verbal and written explanations of the study, and their written informed consent was secured before participation.

The demographic and obstetric data, including age, BMI (calculated by dividing weight in kilograms by the square of height in meters), gravida, and parity, were obtained from the information forms filled out in the clinic. Two sets of questionnaires were used in the study. First, the Turkish version of ICIQ-SF was used to examine the effect of urinary incontinence on life quality. The Turkish validation study of ICIQ-SF was performed by Çetinel et al.[8] The questionnaire includes six questions. The first five questions are scored based on the answers given by the patient. Question 6 inquiries about the patient's subjective complaint. The answers are scored on a numerical scale of 0–10. The total score varies between 0 and 21, with 0 indicating that urinary incontinence affects the person's daily life very little and 10 indicating that it affects it very much. Second, the PSQI questionnaire was used to assess sleep quality. This index was developed by Buysse et al.[9] The reliability study in Turkey was conducted by Ağargün et al.[10] The PSQI includes 24 questions; of these, 19 are answered by the individual themselves and 5 by the individual's spouse or a person with whom the individual lives. Each question is scored between 0 and 3, and the total score varies between 0 and 21. A total score of less than 5 indicates a good sleep quality, while a score of 5 or more indicates a poor sleep quality. Statistical analysis was performed after collecting all study data.

Statistical analyses

To check the distribution of the data, the Shapiro–Wilk test was performed, and homogeneity of variances was verified by Levene's test. Data were reported as mean (standard deviation), median (25th–75th percentile), or number with percentage. Between-group comparisons for categorical data were made using Pearson's chi-square or Fisher's exact test, while continuous variables were assessed with the Student's t test or Z test. In cases where normality assumptions were not met, the Mann–Whitney U test was used. The association between the PSQI and ICIQ-SF scores was evaluated by data analysis. They employed the Spearman correlation test. The p-value, 95% CIs, and correlation coefficient (r) were presented.

All analyses were carried out with SPSS version 18 (http://www.spss.com.hk/statistics/).

RESULTS

The study evaluated 110 non-obese patients with menstrual irregularities and vasomotor symptoms of menopause who were near the end of their reproductive period.

The study group had a mean participant age 46.04±4.09 years, whereas the control group's mean age 45.73±3.33. The mean numbers of gravida were 2.71±1.05 and 2.60±0.93 in the study and control groups, respectively. The study group had a mean BMI of 26.77±3.79, while the control group had a mean BMI of 26.26±2.15. The study and control groups were comparable in terms of demographic characteristics (age, gravida, parity, BMI), with no statistically significant differences. (p=0.665, p=0.566, p=0.547, and p=0.382, respectively) (Table 1).

Table 1. Comparison of Demographic Characteristics and Survey Results between Groups

	Study group (n=55)	Control group (n=55)	p
Age	46.04±4.09	45.73±3.33	0.665
Gravida	2.71±1.05	2.60±0.93	0.566
Parity	2.53±0.88	2.44±0.69	0.547
BMI	26.77±3.79	26.26±2.15	0.382
ICIQ-SF score	12.24±4.91	1.58±2.02	<0.001
PSQI score	6.45±2.89	3.58±1.64	<0.001

BMI: Body mass index; ICIQ-SF: International Consultation on Incontinence. Questionnaire Short Form; PSQI: Pittsburgh Sleep Quality Index.

The ICIQ-SF score was 1.58±2.01 in the control group and 12.23±4.90 in the study group, with a statistically significant difference (p<0.0001). The PSQI score was 3.58±1.64 in the control group and 6.45±2.89 in the urinary incontinence group, with a significant difference (p<0.001) (Table 1).

ICIQ-SF and PSQI scores showed a strong positive connection (r=0.52, p<0.001) when all subjects were assessed. Women without incontinence showed no correlation (r=-0.02, p=0.876), but those with incontinence showed a slight but statistically non-significant link (r=0.17, p=0.215). These results imply that worsening urine incontinence may have an adverse effect on the quality of sleep.

DISCUSSION

Women who experience urinary incontinence prior to menopause suffer from physical and emotional health issues. Identifying these premenopausal patients and developing effective prevention and management strategies are crucial to reduce their physical complaints and improve their quality of life and sleep. Obesity has an impact on urinary incontinence and has been less examined in nonobese patients. Therefore, this study investigated the quality of life and sleep of patients with and without urinary incontinence in a premenopausal, nonobese population. Using the ICIQ-SF is recommended because it is an easily applicable and comprehensible questionnaire form for evaluating urinary incontinence and its effect on life quality, with proven reliability and validity.[11] The PSQI has a sensitivity of 89.6% and a specificity of 86.5% in detecting sleep disorders.[12] In this study, the results obtained using the ICIQ-SF were statistically significant while comparing the control and study groups (p<0.0001). A statistically significant difference was also observed in the PSQI score between the control and study groups (p<0.001). The quality of life and sleep quality were significantly decreased in the study group compared to the control group. Urinary incontinence may affect sleep quality through emotional and behavioral impacts in addition to physical symptoms, as indicated by the high association seen in the entire group. The subgroup analyses' lack of significance suggests that other factors, like age, BMI, and comorbidities, may potentially have an impact on sleep quality in addition to the occurrence of incontinence.

The prevalence of urinary incontinence demonstrates an age-related increase, with earlier studies reporting rates of 7% among women aged 20–39 years, 17% in the 40–59 age group, and 23% among women aged 60–79 years.[13] The most comprehensive epidemiologic study conducted in Norway involving 27,936 women reported that 54% of the patients were in the premenopausal period.[14] The risk factors include increased BMI, multiparity, excessive caffeine consumption, constipation, and sedentary lifestyle.[15,16] Although urinary incontinence is not a lethal disease, it affects the individual in every aspect. Premenopausal patients are actively involved in life; however, the complaints of urinary incontinence can lead to emotional problems such as loss of self-esteem, feelings of inadequacy, and depression.[17,18] A decrease in quality of life is observed in patients, including obsession with bladder emptying, a feeling of restriction when leaving the house, severe restriction of fluid intake, and avoidance of activities that may pose a risk of urinary incontinence.[19,20] In a study conducted among women aged 20-64 years with urinary incontinence, it was found that health related quality of life decreased remarkably in the group with urinary incontinence. Another study revealed that the physical and social activities of patients with urinary incontinence were negatively affected, and these negative effects increased significantly with increasing severity of incontinence.[21] Yorgancı et al.[22] found that women in the reproductive period with incontinence complaints without pelvic organ prolapse had substantially lower quality of life and sexual life. In the literature, studies have shown that menopause is associated with decline in quality of life and an increase in social anxiety among women with inconitenence.[23-25] In this study, ICIQ-SF score was found to be statistically significantly higher in the study group. The ICIQ-SF scoring system has shown a decrease in the wellbeing of patients as the severity of incontinence increases. The data we have revealed in this study support other similar studies in the literature. The study results showed that urinary incontinence affected not only physical health but also psychosocial health. This indicated that patients should be approached holistically by providing psychological support and symptomatic treatment while treating them.

A study conducted on pregnant women with urinary incontinence observed lower sleep quality.[26] In a multicenter, double-blind, randomized controlled study, antimuscarinic treatment was initiated for 12 weeks in patients with incontinence, and a decrease in incontinence complaints and an increase in sleep quality were observed after treatment.[27] Another study conducted on patients with type 2 diabetes mellitus and urinary incontinence reported that women with increased severity of urinary incontinence had lower sleep quality.[28] Ge et al.[29] demonstrated a significant correlation between age, sex, and frequency of going to the restroom at night and sleep quality in middle-aged adults with overactive bladder.[29] Similarly, Winkelman et al.[30] found a significant correlation between poor sleep quality and the severity of urinary incontinence. The present study revealed lower sleep quality in premenopausal women with urinary incontinence, as reported by relatively fewer studies conducted on women in the premenopausal period compared with the postmenopausal period. The negative effect of urinary incontinence on sleep quality could be explained by the need to urinate at night, interruption of sleep due to fear of urinary incontinence, and difficulty transitioning to rapid eye movement sleep. Longitudinal studies show a two-way relationship: nocturia can lead to new-onset sleep problems, and poor sleep can increase the risk of developing nocturia, especially in women and younger adults.[31,32] The results of this study suggested that the decrease

in sleep quality reinforced the decrease in quality of life.

Limitations

This study had some limitations. First, it had a small sample size, which might have influenced the results, and we did not perform a power analysis for this study. Second, socioeconomic factors and psychological variables affecting quality of life were not addressed comprehensively in this study. Instead of using questionnaires to measure sleep quality, objective sleep measurement (e.g., polysomnography, actigraphy) may help in obtaining more objective results.

Conclusion

This research indicated that, in premenopausal women, urinary incontinence was associated with a marked deterioration in both sleep quality and overall quality of life, independent of obesity. Promoting awareness about the risk factors of this disease negatively affecting the quality of life outcomes and sleep of people with its physical, social, economic, and psychological effects, informing patients, encouraging changes in lifestyles, and initiating treatment, when necessary, can increase the general health levels, quality of life, and sleep of these individuals.

Ethics Committee Approval

This study was conducted between September 01, 2023, and September 01, 2024. It was approved by the Biruni University Clinical Research Ethics Committee (Date: 29.03.2023, Decision No: 2023/79-09).

Informed Consent

Retrospective study.

Peer-review

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Authorship Contributions

Concept: B.N.A.H.; Design: B.N.A.H.; Materials: B.N.A.H.; Analysis and/or interpretation: M.M.K., B.N.A.H.; Literature search: B.N.A.H., H.S.T., M.M.K.; Writing: B.N.A.H., M.M.K.; Critical review: B.N.A.H.

Conflict of Interest

None declared.

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Obez Olmayan Premenopozal Hastalarda Üriner İnkontinansın Uyku ve Yaşam Kalitesi Üzerine Etkisinin Değerlendirilmesi

Amaç: Üriner inkontinans, her yaştan bireyde görülebilen istemsiz idrar kaçırma durumudur, ancak kadınlarda daha yaygındır. Premenopozal kadınlarda üriner inkontinansın tespiti ve etkili önleme ve yönetim stratejilerinin geliştirilmesi, hastaların fiziksel şikayetlerini azaltarak yaşam kalitesini ve uyku düzenini iyileştirmek açısından büyük önem taşır. Bu çalışma, premenopozal ve obez olmayan bir popülasyonda üriner inkontinans varlığına göre hastaların yaşam kalitesi ve uyku durumunu değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Bu prospektif çalışmaya 110 hasta dahil edilmiştir (55 çalışma grubu, 55 kontrol grubu). Çalışma grubunu, 35–50 yaş arası, üriner inkontinans şikayeti olan premenopozal kadınlar oluşturmuştur. Üriner inkontinansın yaşam kalitesi üzerindeki etkisi ICIQ-SF ile, uyku kalitesi ise PSQI ile değerlendirilmiştir.

Bulgular: Çalışmada, obez olmayan 110 premenopozal hasta değerlendirilmiştir. Çalışma ve kontrol grupları arasında demografik özellikler açısından istatistiksel olarak anlamlı bir fark bulunmamıştır. ICIQ-SF skoru kontrol grubunda 1.58±2.01, çalışma grubunda ise 12.23±4.90 olarak bulunmuş ve bu fark istatistiksel olarak anlamlıdır ($p<0.0001$). PSQI skoru kontrol grubunda 3.58±1.64, üriner inkontinans grubunda ise 6.45±2.89 olarak saptanmış olup aradaki fark anlamlıdır ($p<0.001$).

Sonuç: Bu çalışma, üriner inkontinansın premenopozal kadınlarda –obez olsun ya da olmasın– yaşam kalitesi ve uyku üzerinde önemli ölçüde olumsuz etkiler yarattığını ortaya koymuştur. Farkındalık yaratmak, hastaları bilgilendirmek, yaşam tarzı değişikliklerini teşvik etmek ve tedaviye başlamak, etkilenen bireylerin genel sağlık durumunu, yaşam kalitesini ve uyku düzenini iyileştirebilir.

Anahtar Sözcükler: Uyku kalitesi; üriner inkontinans; yaşam kalitesi.

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Original Article

The Relationship Between Perceived Social Support and Functional Status, Life Quality and Depression in Stroke Patients

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Keywords: Depression; functional status; life quality; perceived social support; stroke.

ABSTRACT

Objective: We aimed to examine the relationship of perceived social support with functional status, life quality and depression in stroke patients.

Methods: This study was carried out on 50 stroke patients who were diagnosed with stroke for the first time, who had a stroke for at least 6 months. Perceived social support with multidimensional perceived social support scale, functional status with Barthel index, life quality with stroke specific quality of life scale, and depression with Beck depression inventory were evaluated.

Results: The mean age of the patients (34 males, 16 females) was 56.70±10.78 years. The mean disease duration was 25.9±31.46 months. Mean multidimensional perceived social support scale score of the patients was 51.42±14. The multidimensional perceived social support scale scores were found significantly lower in stroke patients with fully/highly dependent than those of the other groups (p=0.02). There was no significant relationship between family support and functional status, but there was a significant correlation between functional status and friends support, private individual support (p=0.477, p=0.022, p=0.021, respectively). There was a significant positive correlation between life quality and all subscales of multidimensional perceived social support scale (p<0.05). Beck depression inventory score was significantly high in patients with low social support (p=0.001).

Conclusion: The perceived social support has a significant impact on functional status, quality of life and depression in stroke patients. The development of new intervention programs for perceived social support may significantly contribute to the rehabilitation treatment of stroke patients.

INTRODUCTION

Stroke has been the first place of terms of frequency and importance in the neurological diseases of adult life.[1] It is the first cause of disability and labor loss.[2] The aim of stroke rehabilitation is to maximize functional independence, to minimize the level of disability, to ensure successful reintegration into the home, family, and society, to regain a meaningful and satisfying life.[3] It is a known fact that problems after stroke cause serious deficits in physical, psychological, and social dimensions of life and cause a significant decrease in the life quality.[4] In recent years, factors related to the life quality after stroke and studies to improve the life quality has gained importance.[5,6] Stroke is a disease with a heavy social burden. One year after stroke, the rate of dependence on daily activities due to physical or cognitive deficits varies by 20-30%. Motor, cognitive, sensory, and emotional disorders after stroke prevent people's social participation by limiting their skills in some or all of basic, auxiliary daily living activities, edu-

cation, work, and leisure activities.[7] Social support is defined as the material and moral assistance provided to the stressed or troubled individuals by the people (wife, family, friends) around them.[8] Social support is an important factor to consider in the relationship between depression and functional disability. The theory of social support shows that social support has a direct and indirect impact on a variety of life aspects, including health indexes such as morbidity and mortality.[9]

Social relationships and social support are increasingly recognized as closely linked to individuals' overall health status, the progression of diseases, and the rehabilitation process. In individuals who have experienced a stroke, social support is considered to have a positive impact on patient care and treatment outcomes, particularly in terms of physical recovery and psychosocial well-being.[10]

After stroke, functional impairment, major depression, and social disintegration often adversely affect the life quality. Stroke patients who have physical or emotional impairment suffer from social disintegration and therefore they need intensive social support. Researches define potentially more effective patterns in providing rehabilitative care and suggest that an appropriate plan for rehabilitation of patients should aim to improve functional status, depressive disorder, and social participation.[11,12] The aim of this study was to investigate the relationship between perceived social support and functional status, life quality, and depression in stroke patients.

MATERIALS AND METHODS

This study was carried out on 50 stroke patients who were admitted to our outpatient. Stroke patients who were diagnosed with stroke for the first time, who had a stroke for at least 6 months, and who could communicate well enough to understand simple orders were included in the study. Patients with musculoskeletal and nervous system diseases (developmental hip dysplasia, severe osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, amputation, myasthenia gravis, Parkinson's disease, dementia, Alzheimer's disease) that could cause physical disability, communication, significant cognitive and emotional problems, and ataxia-dystonia-dyskinesia were excluded from the study.

The age, gender, marital status, occupational-educational status, disease duration, etiology of stroke (ischemic-hemorrhagic), body side affected by the stroke, additional concomitant diseases, and proximity to the caregiver were questioned in the patients. This study was approved by the University's Ethics in Research Committee and conducted according tothe Helsinki Declaration. The study procedure was told to the patients and before participating the study, written consent form was signed by all patients. Perceived social support with multidimensional perceived social support scale (MSPSS), functional status with Barthel index, life quality with stroke specific quality of life scale (SS-QOL), and depression with Beck depression inventory (BDI) were evaluated.

The multidimensional scale of perceived social support; the Turkish version of MSPSS was used in our study. The scale subjectively evaluates the adequacy of social support provided in three different areas and consists of 12 items. There are three sub-groups (family, friends and special person support) in the support areas of the scale, and each group consists of 4 items. The total score is obtained by adding the scores obtained from the subscales and the lowest score is 12, and the highest score is 84.[13,14]

Barthel index; Barthel index which is a dependable and validated index for use in Turkish patients were used to measure for changes in functional status. Barthel index evaluates performance in daily living activities. The total score ranges from 0 to 100. 0-20 points are fully dependent, 21-61 points are highly dependent, 62-90 are moderately dependent, 91-99 points are slightly dependent, and 100 are fully independent.[15,16]

Stroke specific quality of life scale; the SS-QOL consists of 49 items including 12 domains: Mobility, energy, upper limb function, work / productivity, mood, self-care, social roles, family role, seeing, language, thinking, and personality characteristics. The reliability and validity of the scale for the Turkish population were assessed by Hakverdioglu Yont.[17,18]

Beck depression inventory; the validity of the scale for the Turkish population were assessed by Hisli and the cut-off point of the scale was accepted as 17 points or higher. BDI consists of 21 questions and the score is 0-3 for each question. The highest score is 63. The high total score indicates the severity of depression.[19,20]

Statistical Analysis

The data obtained from the study were evaluated by using SPSS 21.0 software package. Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. T test / Mann Whitney U and One Way Anova / Kruskal Wallis tests were used to evaluate mean scores of the subscales of social support and the differences between the groups. Bonferroni Correction was used to determine which group was of significance. Pearson / Spearman correlation coefficients were calculated to evaluate the relationship between the outcomes in patients with stroke. P values less than 0.05 were considered statistically significant.

RESULTS

The mean age of the patients (34 males, 16 females) was 56.70±10.78 years. The mean disease duration was 25.92±31.46 months. The sociodemographic characteristics of the patients were shown in Table 1. Mean MSPSS score of the patients was 51.42±14. Among subgroups of social support, family support was 21.80±4.85, friend support was 15.22±5.95, and private individual support was 14.52±5.40. BDI score was 14.24±7.54, mean Barthel index score was 74.40±21.42 and mean SS-QOL scale was 3.07±0.60.

MSPSS score was higher in patients with disease duration longer than 1 year, but this difference was not statistically significant (t=-1.03, p=0.30). When education level increased in patients, the MSPSS score increased. MSPSS score in illiterate patients was 45.5±20.09, MSPSS score was 51.23±13.10 for the primary school graduates, MSPSS score was 57.21±11.01 for the secondary school and others graduates, but this difference is not statistically significant (f=1.59, p=0.21). The relationship between MSPSS scores and demographic characteristics is shown in Table 1. Patients with lower MSPSS scores than other groups had much worse functional status. The perceived social support was significantly lower in those with fully / highly dependent patients than other groups (f=3.90, p=0.02) (Table 2).

According to the Barthel index, 28 patients (56%) were moderately dependent, 10 patients (20%) were highly dependent, 6 patients (12%) were fully independent, 5 patients (10%) were mild dependent and 1 patient (2%) were fully dependent. According to cut-off score of BDI, 34% of the patients had depressive symptoms at the syndromic level, and 66% of the patients had lower scores than the cut-off score. There was a significant relationship between depressive status and perceived social support. The MSPSS score was significantly low in the group with scores above 17 points according to BDI (t=3.73, p=0.001). There was a significantly association between BDI scores and MSPSS scores (Table 3). There was a positive correlation between total MSPSS sore and the life quality (r=0.55, p=0.000). As the perceived social support increased, the life quality of the patients increased. Based on the analysis of perceived social support subscales data, there was a moderate positive correlation between the life quality and family support whereas the the life quality demonstrated a strong positive correlation with friend and private individual supports (r=0.42, p=0.002; r=0.51, p=0.000; r=0.52, p=0.000, respectively).

Table 1. Comparison of different socio-demographic characteristics with perceived social support levels in stroke patients

	Number (%)	Mean±SD	Perceived social support score, mean±SD	
Gender				
Female	16 (32)		46.25±16.41	T:-1.81
Male	34 (68)		53.85±12.44	P:0.07
Age (years)	56.7±10.78	51.42±14.12		R:-0.08
				P:0.56
Stroke etiology				
Hemorrhagic	13 (26)	50.62±12.65		T:-0.236
Ischemic	37 (74)	51.70±14.76		P:0.81
Marital status				
Married	36 (72)	52.00±13.60		T:-0.46
Single/ widowed	14 (28)	49.93±15.83		P:0.64
Affected side				
Right	15 (30)	53.93±13.18		T:0.82
Left	35 (70)	50.34±14.56		P:0.41
Additional disease				
No	7 (14)	52.86±16.24		T:0.28
Yes	43 (86)	51.19±13.95		P:0.80
Caregiver				
Caregiver	4 (8)	52±17.83		
Spouse	24 (48)	51.92±12.70		F:0.01
Spouse and child	12 (24)	52.17±15.84		P:0.95
Child	10 (20)	49.10±15.92		
Duration of the stroke				
≤1 year	29 (58)	49.66±14.26		T:-1.03
>1 year	21 (42)	53.86±13.90		P:0.30
Education status				
Illiterate	4 (8)	45.5±20.09		F:1.59
Primary school	30 (60)	51.23±13.10		P :021
Secondary school and others	14 (28)	57.21±11.01		

SD: Standart deviation.

Table 2. The relationship between perceived social support and functional status in stroke patients

	Fully/ highly dependent (N=11)	Moderately dependent (N=28)	Slightly/fully independent (N=11)	
Total perceived social support				
Mean±SD	41.55±13.50	53.79±13.17	55.27±13.69	F:3.90 P:0.02
Family support				
Mean±SD	20.27±5.64	21.93±4.65	23.00±4.56	KW:1.48 P:0.47
Friends support				
Mean±SD	10.91±5.35	16.36±5.65	16.64±5.67	KW:7.61 P:0.02
Special person support				
Mean±SD	10.55±4.48	15.64±5.25	15.64±5.12	KW:7.75 P:0.02

SD: Standart deviation; N: Number.

Table 3. The relationship between perceived social support and depression in stroke patients

	BDI<17 (N=33)	BDI≥17 (N=17)	
Total perceived social support	56.18±12.92	2.18±11.81	T:3.73,
Mean±SD			P:0.001
Family support	23.09±3.88	19.29±5.64	Z:-2.53
Mean±SD			P:0.011
Friends support	17.09±5.80	11.59±4.45	T:3.41
Mean±SD			P:0.001
Special person support	16.09±5.12	11.47±4.67	Z:-3.00
Mean±SD			P:0.003

SD: Standart deviation; N: Number; BDI: Beck depression inventory.

DISCUSSION

Life quality decreases significantly in patients with stroke due to functional deficiencies and medical, social, and psychological problems. Multidisciplinary comprehensive rehabilitation programs are needed to make easy patients' life and to improve their existing functions. The importance of the concept of social support has been demonstrated on individuals with chronic diseases and physical disabilities in studies in recent years. There are considerable evidence that social support positively affects mental and physical health.[21] It was stated that social support can prevent the occurrence of stress by changing the perception of events in stressful situations and by supporting the individual in situations where he is forced by affecting the ways of coping with stres.[22] In our study, there was relationship between perceived social support and the life quality, functional status, and depression in patients with stroke for the first time. As the perceived social support level increased, functional status and life quality level increased and depressive symptoms decreased in patients.

In the literature, there were no studies showing the relationship between age and social support in stroke patients. Molu et al.[23] showed that social support decreased, as patients get age in the psychiatric clinic. The decrease in the number of people around patients, due to the death of patient' peers due to aging, and retirement status of the patient is thought to be effective in this result. In our study, no significant relationship was found between perceived social support and age. In literature, there was no statistically significant difference between gender and social support in the study on social support in physically disabled individuals; however, level of social support was found to be higher in men than in women.[8] Dayapoglu et al.[12] showed that the level of social support in women was statistically lower than in men. Most of patients were male in our study. Perceived social support score was lower in women than in men, but no statistically significant difference was found. Dayapoglu et al.[12] found that a relationship between social support and education in stroke patients and social support score was found to be higher in highly educated people than other groups. In addition, they also found that married people had higher social support than other groups, but this was not statistically significant. In our study, it was found that perceived social support increased as education level increased and social perceived support was higher in married patients than un-

married patients, but this was not statistically significant. Procidano et al.[24] found that family support score was higher than social support sub-groups. Külcü et al.[25] reported that almost all inpatient stroke patients had family support. Furthermore, Bursa et al.[8] found that family support was higher in disabled individuals compared to subgroups of social support In our study, family support score was statistically significant compared to the sub-groups of social support. Most stroke patients require care because of functional losses and difficulties in self-expression. This situation may get the stroke patient dependent on another person. Since stroke patients who have a broader social network, friends, and relatives before stroke are dependent on home and bed after stroke, their social networks gradually decrease over time, and patients become more lonely. We think that the high family support score in our study is related to above reasons.

In our study, a significant relationship was found between perceived social support and functional status of the patients. Patients with lower perceived social support scores had worse functional status than other groups. In the subgroups of patients who are fully / advanced dependent, the level of subgroups of friend and private individual support was significantly lower than the other groups. The family support rate was similar across all groups, unaffected by the disease's functional status. The mean family support is statistically significantly lower in individuals with higher Beck Depression Index scores. This highlights the significance of family support. However, there was no significant relationship between family support and functional status compared to other groups. Glass et al.[26] found that patients with low social support were unable to maintain functional recovery and decreased functional status over time.

Morris et al.[27] reported that the amount of post-stroke social contact may reduce the risk of depression in later times. In a prospective study by Volz et al.[28] it is stated that the beneficial effects of perceived social support had a protective effect in terms of not developing depression after stroke. Lewin et al.[29] stated that taking into account self-efficacy and perceived social support in rehabilitation treatment may help prevent depression after stroke. In our study, a significant relationship was found between depression and sub-groups of social support (family-friend-special person). The level of social support was significantly lower in the patient group with high depressive symptoms than groups. These findings were consistent with the literature.

Stroke is a disease that causes severe loss of physical activity in the person and has a significant impact on health-related life quality.[5] Huang et al.[30] showed that social support fully mediated the prediction of the life quality and they recommended that social support be included for effective rehabilitation treatment.[30] When the relationship between life quality and perceive social support was investigated, we found that as the perceived social support of the patients increased, the life quality also increased in our study. We found a moderately positive relationship between family support and life quality, and a strong positive relationship between life quality and support of friends and private individuals. Strong social support given to post-stroke patients can significantly reduce the negative impact of stroke on patients' life quality.[31]

We recognize that the present study has some limitations. At first, The sample size in our study may be to small to make a definitive decision. Further studies with larger patient populations are needed to confirm our results. Second, the number of male patients was higher than female patients in our study. This may create certain restrictions in evaluating the relationship between perceived social support and gender.

In conclusions, results of this study showed that a relationship was between perceived social support and functional status, life quality, and depression in stroke patients. Although the results of the study were predictable, it may be useful to consider the importance of the concept of perceived social support in stroke rehabilitation and to develop strategies aimed at enhancing existing social support in the treatment management of stroke patients.

Ethics Committee Approval

The study was approved by the Recep Tayyip Erdoğan University Hospital Ethics Committee (Date: 16.03.2018, Decision No: 2018/56).

Informed Consent

Retrospective study.

Peer-review

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Authorship Contributions

Concept: E.O., G.D.; Design: E.O., G.D.; Supervision: E.O., G.D., M.S.B.; Fundings: E.O., M.Y., G.D.; Materials: E.O., G.D., M.Y.; Data collection &/or processing: E.O., G.D., M.Y., M.S.B.; Analysis and/or interpretation: E.O., G.D.; Literature search: E.O.,G.D., M.Y.; Writing: E.O., G.D.; Critical review: E.O., G.D., M.Y., M.S.B.

Conflict of Interest

The authors declare that they have no conflict of interest.

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İnmeli Hastalarda Algılanan Sosyal Destek ile Fonksiyonel Durum, Yaşam Kalitesi ve Depresyon Arasındaki İlişki

Amaç: İnme hastalarında algılanan sosyal desteğin fonksiyonel durum, yaşam kalitesi ve depresyonla ilişkisini incelemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, ilk kez inme tanısı almış, en az 6 aydır inme tanısı olan 50 inmeli hastada gerçekleştirildi. Algılanan sosyal destek çok boyutlu algılanan sosyal destek ölçeği ile, fonksiyonel durum Barthel indeksi ile, yaşam kalitesi inmeye özgü yaşam kalitesi ölçeği ile ve depresyon Beck depresyon envanteri ile değerlendirildi.

Bulgular: Hastaların (34 erkek, 16 kadın) yaş ortalaması 56.70±10.78 yıl idi. Hastalık süresi ortalaması 25.9±31.46 aydı. Hastaların çok boyutlu algılanan sosyal destek ölçeği puanı ortalaması 51.42±14 idi. Tam/yüksek derecede bağımlı inme hastalarında çok boyutlu algılanan sosyal destek ölçeği puanları diğer gruplara göre anlamlı derecede düşük bulundu (p=0.02). Aile desteği ile fonksiyonel durum arasında anlamlı bir ilişki bulunmazken, arkadaş desteği, özel bireysel destek ile fonksiyonel durum arasında anlamlı bir korelasyon vardı (sırasıyla p=0.477, p=0.022, p=0.021). Yaşam kalitesi ile çok boyutlu algılanan sosyal destek ölçeğinin tüm alt ölçekleri arasında anlamlı ve pozitif bir korelasyon vardı (p<0.05). Beck depresyon ölçeği puanı, düşük sosyal desteği olan hastalarda anlamlı derecede yüksekti (p=0.001).

Sonuç: Algılanan sosyal destek, felçli hastalarda fonksiyonel durum, yaşam kalitesi ve depresyon üzerinde önemli bir etkiye sahiptir. Algılanan sosyal destek için yeni müdahale programlarının geliştirilmesi, inmeli hastaların rehabilitasyon tedavisine önemli ölçüde katkıda bulunabilir.

Anahtar Sözcükler: Algılanan sosyal destek; depresyon; fonksiyonel durum; inme; yaşam kalitesi.

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Original Article

Fracture Type, Radiological Alignment, and Motion: Predictors of Functional Recovery After ORIF in Distal Radius Fractures

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Keywords: Correlation analysis; distal radius fractures; factors affecting outcome; locking plate fixation; trauma.

ABSTRACT

Objective: Distal radius fractures are among the most common fractures in adults. Open reduction and internal fixation (ORIF) using locking plates represents the standard surgical approach. However, factors influencing functional outcomes after surgery remain controversial. This study assessed how patient characteristics, fracture type, and radiological factors influence functional recovery after distal radius fractures treated with locking plates.

Methods: Eighty-one patients (55 males, 26 females; mean age: 43.7 years) who underwent ORIF with locking plates between 2007 and 2013 were retrospectively analyzed. Functional outcomes were assessed using the QuickDASH, PRWE, and Modified Green and O'Brien scoring systems. Radiological evaluations included the Stewart and Knirk & Jupiter classifications. Spearman correlation and group comparison analyses were performed to identify factors associated with functional outcomes.

Results: Fracture classification significantly affected functional outcomes, with AO type B fractures demonstrating superior QuickDASH and Modified Green and O'Brien scores compared to type C fractures ($p<0.05$). Ulnar styloid nonunion did not affect functional outcomes but was associated with higher arthritis grades ($p=0.039$). PRWE scores were significantly correlated with arthritis severity, radiological reduction quality, patient age, and most wrist range of motion parameters (excluding pronation). Additionally, PRWE scores were negatively correlated with radial inclination and radial height, and positively correlated with ulnar variance.

Conclusion: Functional recovery following distal radius fracture surgery is influenced by fracture type, reduction quality, age, arthritis, and wrist mobility. Anatomical reduction and near-complete wrist mobility are key to optimal outcomes.

INTRODUCTION

Distal radius fractures are among the most common traumatic injuries, accounting for about 17.5% of all adult fractures presenting to emergency departments.[1] The primary objective of treatment is to restore joint anatomy, maintain alignment, and achieve optimal functional outcomes.

Open reduction and internal fixation (ORIF) with locking plates is widely utilized in managing distal radius fractures.[2] Locking plates provide biomechanical advantages by maintaining fracture reduction, preserving radial height, and resisting forces across the fracture site.[2,3] Identifying the factors that influence functional outcomes helps predict prognosis, guide treatment, and plan follow-up.

While many studies confirm the effectiveness of fixation using locking plates,[2,3] others have examined factors affecting recovery.[4] However, no clear consensus exists on which factors are most critical.[4,5]

This retrospective study analyzed patients treated with locking plates for distal radius fractures to identify factors linked to functional outcomes. We hypothesized that patient characteristics, fracture type, radiological parameters, and wrist range of motion (ROM) would influence recovery. The primary outcome measure was the Patient-Rated Wrist Evaluation (PRWE) score, a validated and reliable instrument for assessing wrist pain and function.[6]

MATERIALS AND METHODS

This retrospective study analyzed patients who underwent ORIF with locking plates for distal radius fractures at Kartal Dr. Lütfi Kirdar Training and Research Hospital between 2007 and 2013. All patients had at least 12 months of follow-up. The study was approved by the Ethics Committee of the Kartal Dr. Lütfi Kırdar Hospital (Date: 19/12/2013, No: 89513307/1009/231) and the study was conducted according to Helsinki Declaration.

Of 158 surgically treated patients, 23 were excluded due to treatment with closed reduction with percutaneous pinning or external fixation. Another 22 were excluded for having concomitant fractures in the ipsilateral upper extremity, contralateral wrist, or hand, 15 lacked adequate radiographs, and 17 were lost to follow-up. The final analysis included 81 patients.

At presentation, patient histories were obtained, and anteroposterior (AP), lateral, and true lateral radiographs were taken. Closed reduction and short-arm casting were performed without anesthesia. Computed tomography (CT) was performed in cases of suspected intra-articular fractures. Surgery was indicated for patients presenting with more than 5 mm of radial shortening, radial inclination less than 15 degrees (AP view), dorsal tilt greater than 15 degrees or volar tilt greater than 20 degrees (lateral view), more than 2 mm of articular step-off or gap, a change in ulnar variance greater than 2 mm, or dorsal comminution.[7]

Of the 81 patients, 60 underwent volar plating, 14 underwent dorsal plating, and seven received combined volar and dorsal plating through dual incisions.

Postoperative rehabilitation included early finger mobilization, splint removal at approximately one month, initiation of active wrist motion, and strengthening exercises after six weeks. Patients were permitted to return to work after radiographic union was confirmed.

Outcome Evaluations

All patients were evaluated based on radiological and clinical parameters. Radiographs were obtained at presentation, after reduction, postoperatively, and at approximately 45 days, 3 months, 6 months, and final follow-up, including the uninjured side.

At the final follow-up, patient records and clinical findings were reviewed to assess and document age, sex, operated side, hand dominance, surgical indication, injury mechanism, AO/OTA fracture type, grip strength, complications, and the presence of ulnar styloid nonunion. Open fractures and associated neurovascular injuries were evaluated according to the Gustilo-Anderson classification.

Volar tilt, radial inclination, radial height, and ulnar variance were measured and compared with the uninjured side. Radiological outcomes were graded using Stewart's system,[8]

Table 1. Patient characteristics

Variable	Min–Max	Mean±SD
Age (years)	17-73	43.73±12.12
Follow-up period (months)	12-63	29.35±13.96
	n	%
Sex		
Male	55	67.9
Female	26	32.1
Affected side		
Dominant	31	38.3
Non-dominant	50	61.7
Surgical approach		
Volar plating	60	74.1
Dorsal plating	14	17.3
Double plating	7	8.6
Trauma mechanism		
Low-energy	42	51.9
High-energy	39	48.1
Grip strength		
Operated side (kg)	6-61	28.88±11.12
Healthy side (kg)	14-63	38.79±11.86
Grip strength (%)	26-100	72.07±19.26
Ulnar Styloid Nonunion		
Absent	50	61.7
Present	31	38.3
Fracture classification (AO/OTA)		
A2	1	1.2
A3	12	14.8
B1	2	2.5
B2	3	3.7
B3	9	11.1
C1	24	29.6
C2	5	6.2
C3	25	30.9

Table 2. Range of motion values of both sides

Movement (°)	Operated Side Mean±SD (Min–Max)	Healthy Side Mean±SD (Min–Max)	Loss* Mean±SD (Min–Max)	Recovery % * Mean±SD (Min–Max)
Palmar Flexion	51.5±13.9 (15-80)	70.7±5.7 (60-80)	19.1±14.1 (0-50)	73.1±19.3 (23-100)
Dorsiflexion (Extension)	55.6±14.5 (10-80)	70.1±6.0 (60-80)	14.9±13.3 (0-60)	78.8±18.5 (14-100)
Supination	75.8±9.4 (30-90)	83.4±4.0 (75-90)	7.7±9.3 (0-50)	90.8±11.0 (38-100)
Pronation	74.1±12.0 (20-90)	84.1±5.4 (65-90)	9.9±11.8 (0-65)	88.3±14.0 (23-100)
Radial Deviation	8.5±5.2 (0-20)	17.3±3.7 (10-30)	9.0±5.2 (0-20)	50.6±29.2 (0-100)
Ulnar Deviation	18.4±10.1 (0-35)	32.9±4.6 (25-45)	14.6±9.8 (0-40)	55.7±29.3 (0-100)

* 'Loss' indicates the difference in degrees compared with the contralateral (healthy) wrist. 'Recovery %' represents the percentage of motion regained relative to the healthy side.

Table 3. Distribution of radiological measurements

Measurement	Preoperative (Before Reduction) Mean±SD (Min–Max)	Preoperative (After Reduction) Mean±SD (Min–Max)	Postoperative (Early Phase) Mean±SD (Min–Max)	Postoperative (Final Follow-up) Mean±SD (Min–Max)	Healthy Side Mean±SD (Min–Max)
Volar Tilt (°) *	-11.29±23.64 (-60.0-45.0)	3.12±11.23 (-25.7-45.0)	5.86±5.98 (-10.0-16.0)	4.30±6.37 (-11.2-20.0)	9.06±3.55 (0.0-20.0)
Radial Inclination (°)	11.80±10.06 (-5.0-50.1)	19.39±6.86 (5.0-41.8)	20.89±4.67 (7.0-30.4)	19.39±4.95 (5.0-28.9)	23.22±2.35 (18.0-28.9)
Radial Height (mm)	3.34±6.24 (-15.0-16.9)	8.75±3.88 (-2.0-18.4)	10.09±2.92 (2.0-17.1)	9.00±3.37 (0.0-17.0)	12.07±1.97 (7.0-16.8)
Ulnar Variance (mm)	2.33±2.67 (-3.3-12.0)	0.29±1.97 (-3.0-8.4)	-0.64±1.44 (-3.1-5.0)	0.08±1.80 (-4.3-5.8)	-1.16±0.67 (-2.6-1.9)

*Negative volar tilt values indicate dorsal tilt.

scoring dorsal tilt, radial inclination loss, and radial height loss. According to this scoring system, a score of 0 is considered an excellent result, 1–3 a good result, 4–6 a fair result, and 7–12 a poor result.

Post-traumatic arthritis (PTA) was graded using the Knirk and Jupiter classification,[9] based on joint space narrowing and structural changes, from stage 0 (normal) to stage 3 (severe arthritis).

Grip strength was measured using a Jamar dynamometer (Asimow Engineering, Co., Los Angeles, CA, USA). Patients were seated with the shoulder relaxed, the elbow flexed at 90 degrees, and the forearm in a neutral position with slight wrist extension. Each side was tested three times, and the mean was recorded.

Table 4. Distribution of functional scores

	Min–Max	Mean±SD
QuickDASH	0-47.70	17.33±15.17
PRWE	0-52.50	17.55±15.07
Modified Green and O'Brien	50-100	79.01±13.95
	n	%
Modified Green and O'Brien *		
Excellent	28	34.6
Good	17	21.0
Fair	26	32.1
Poor	10	12.3

* Modified Green & O'Brien categories were defined as follows — Excellent: 90–100, Good: 80–89, Fair: 65–79, Poor: <65.

Table 5. Radiological outcomes and arthritis scores

Final Follow-up	Min–Max	Mean±SD
Stewart	0-6	1.46±1.59
	n	%
Stewart		
Excellent	33	40.7
Good	39	48.1
Fair	9	11.1
Knirk & Jupiter		
0	37	45.7
1	27	33.3
2	14	17.3
3	3	3.7

Range of motion for both wrists was measured in three planes (flexion-extension, radioulnar deviation, and pronation-supination) using a standard goniometer positioned at the joint's center of rotation.

Functional outcomes were assessed using the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH)[10] and PRWE[11] scores, both validated patient-reported measures. In addition, the Modified Green and O'Brien clinical scoring system[12] was used to evaluate pain, functional status, ROM, and grip strength.

Statistical Analysis

Statistical analyses were performed using NCSS 2007 and PASS (Power Analysis and Sample Size) 2008 software (NCSS, LLC, Kaysville, UT, USA). Descriptive statistics (mean, SD, frequency, ratio, min, max) were reported. For non-normally distributed quantitative variables, the Mann-Whitney U test was used for two-group comparisons, and the Kruskal-Wallis test for three or more groups. The Mann-Whitney U test identified the group responsible for the difference. Within-group comparisons of non-normally distributed parameters were performed using the Wilcoxon signed-rank test. Categorical variables were compared using the Fisher-Freeman-Halton exact test. Spearman correlation analysis assessed relationships between parameters. Statistical significance was considered at $p<0.01$ and $p<0.05$ levels. Correlation coefficients were classified as low (Rs=0.10–0.29), moderate (Rs=0.30–0.49), or high (Rs=0.50–1.00).[13]

RESULTS

Eighty-one patients (55 males and 26 females; age range: 17 to 73 years, mean age: 43.7 years) were included in this study. Patient characteristics are presented in Table 1.

According to the Gustilo-Anderson classification, seven fractures were classified as Type I and three as Type II open fractures. Of the open fractures, nine resulted from high-energy trauma, and one from low-energy trauma. The low-energy trauma fracture was classified as Type I.

Complications occurred in 12 patients (eight treated with volar plates, four with dorsal plates). Among those treated with dorsal plates, one patient developed an extensor tendon rupture one year postoperatively, requiring implant removal and tendon reconstruction. One patient experienced ulnar nerve paresthesia, which was managed conservatively; another had intra-articular screw penetration, treated with implant removal at eight months; and a third patient with screw penetration and collapse declined further surgery. In the volar plate cases, four patients developed carpal tunnel syndrome (three treated surgically, one conservatively), two experienced flexor pollicis longus tendon ruptures (requiring implant removal and tendon repair), and two had intra-articular screw-related complications (with or without lunate collapse) managed by implant removal.

An ulnar styloid fracture was detected in 40 patients. Of these, nine achieved union, while 31 resulted in nonunion.

At the final follow-up, palmar flexion, dorsiflexion, supination, pronation, radial and ulnar deviation of both wrists were recorded, along with ROM loss and recovery percentages, as shown in Table 2.

Preoperative (before and after reduction), early postoperative, final postoperative, and healthy-side measurements of volar tilt, radial inclination, radial height, and ulnar variance are presented in Table 3.

Functional evaluations using the QuickDASH, PRWE, and Modified Green and O'Brien scores are presented in Table 4, with radiological and arthritis assessment results based on the Stewart and Knirk & Jupiter scores in Table 5.

Differences in QuickDASH ($p=0.047$) and Modified Green and O'Brien scores ($p=0.036$) according to fracture classification were statistically significant, favoring type B fractures. Although PRWE scores showed a trend toward better outcomes in type B fractures, the difference was not statistically significant. Patients with type B fractures had significantly better QuickDASH and PRWE scores compared to those with type C fractures ($p<0.05$), whereas no significant differences were observed between type A and type C fractures. No significant differences in functional outcomes were found based on trauma mechanism (low- vs. high-energy) or the presence of ulnar styloid nonunion ($p>0.05$). However, ulnar styloid nonunion was associated with a significantly higher Knirk & Jupiter arthritis grade ($p=0.039$). Detailed results are presented in Table 6.

Spearman correlation analysis demonstrated significant associations between PRWE scores and arthritis severity (Knirk & Jupiter scores), radiological reduction quality (Stewart scores), patient age, and most ROM parameters, except pronation ($p>0.05$). Additionally, PRWE scores showed significant correlations with radiological parameters: They were negatively correlated with radial inclination and radial height, positively correlated with ulnar variance, and not significantly correlated with volar tilt. The detailed correlation coefficients are presented in Table 7.

Table 6. Relationship between surgical indication, trauma type, ulnar styloid nonunion, fracture classification, and patient outcomes

	n	%	QuickDASH (Mean±SD)	PRWE (Mean±SD)	Modified Green and O'Brien (Mean±SD)	Knirk & Jupiter
Trauma Type						
Low-energy	42	51.9	19.22±15.17	19.26±15.06	79.17±14.5	
High-energy	39	48.1	15.30±15.1	15.71±15.0	78.85±13.4	
p			0.200	0.212	0.966	
Ulnar Styloid Nonunion						
Absent	50	61.7	16.13±15.79	16.50±15.27	81.20±14.31	Grade 0: 26 Grade 1: 18 Grade 2: 6 Grade 3: 0
Present	31	38.3	19.27±14.17	19.24±14.82	75.48±12.80	Grade 0: 11 Grade 1: 9 Grade 2: 8 Grade 3: 3
p			0.306	0.293	0.068	**0.039**
Fracture Classification						
A[1]	13	16.0	19.21±15.66	19.23±15.19	82.69±12.52	Grade 0: 10 Grade 1: 2 Grade 2: 1
B[2]	14	17.3	8.88±11.85	9.71±10.87	86.07±10.77	Grade 0: 7 Grade 1: 4 Grade 2: 3
C[3]	54	66.7	19.07±15.33	19.18±15.55	76.30±14.55	Grade 0: 20 Grade 1: 21 Grade 2: 10 Grade 3: 3
p			**0.047**	0.092	**0.036**	0.318
Post-hoc			*2<1,3*	*2<3*	*2>3*	

Significant p values are written in bold.

Table 7. Correlation between Stewart score, Knirk& Jupiter score, age, ROM, radiological measurements, and PRWE scores

	PRWE	
	r	p
Stewart score	0.447	0.001†
Knirk & Jupiter score	0.441	0.001†
Age	0.243	0.030*
Flexion	0.406	0.001†
Extension	0.443	0.001†
Supination	0.328	0.003†
Pronation	0.188	0.093
Radial deviation	0.581	0.001†
Ulnar deviation	0.822	0.001†
Volar tilt	0.014	0.900
Radial inclination	-0.461	0.001†
Radial height	-0.504	0.001†
Ulnar variance	0.441	0.001†

r: Spearman's rank correlation coefficient. *p<0.05, †p<0.01. Significant p values are written in bold.

DISCUSSION

This study examined several factors influencing the functional outcomes of distal radius fractures treated with locking plates. The key finding was that recovery was most strongly determined by wrist range of motion, particularly ulnar and radial deviation, which showed the highest correlation with PRWE scores. In addition, significant correlations were observed between functional outcomes and radiological reduction quality, severity of posttraumatic arthritis, and patient age. Although AO type B fractures showed better short-term results than types A and C, preserving wrist motion and accurate reduction emerged as the most critical determinants of functional recovery.

AO type B fractures demonstrated better functional outcomes compared to type A and C fractures, as reflected by significantly lower QuickDASH (p=0.047) and higher Modified Green and O'Brien scores (p=0.036). Although PRWE scores also favored type B fractures, the difference was not significant (p=0.092). These results align partially with the findings of Souer et al.,[14] who reported no sig-

nificant functional differences between type B and type C fractures at 24 months postoperatively, although type C fractures were associated with more early pain. In another study, Souer et al.[15] observed no significant differences in wrist function between intra-articular and extra-articular fractures treated with volar plating but noted a higher incidence of osteoarthritis in intra-articular fractures, consistent with our higher arthritis rate in type C fractures. Bolmers et al.[16] also found comparable long-term outcomes between partial (type B) and complete (type C) articular fractures. The inclusion of patients treated with volar, dorsal, and combined plating in our study may explain discrepancies with prior research that focused solely on volar plating. Additionally, the relatively small sample size within each fracture type group may have limited the detection of certain differences. Overall, while type B fractures tend to show early functional advantages, different fracture types may converge toward similar outcomes over time.

We found no significant difference in functional scores between high- and low-energy trauma groups ($p>0.05$), consistent with Lee et al.,[5] who reported no impact of injury mechanism at 12 months. Roh et al.[17] noted lower scores after high-energy trauma in the early months, but no difference at one year. Overall, these results suggest that while trauma mechanisms may affect early recovery, it has a limited influence on long-term functional outcomes.

Ulnar styloid fractures frequently accompany distal radius fractures.[18] In our study, ulnar styloid fractures occurred in 40 patients, none of whom underwent fixation. At follow-up, union was achieved in nine cases, whereas 31 cases (38.3%) resulted in nonunion. Previous studies have demonstrated that the presence of an ulnar styloid fracture or subsequent nonunion does not significantly affect functional outcomes.[4,19-21] Consistent with these findings, we found no statistically significant difference in functional outcomes between patients with and without ulnar styloid nonunion ($p>0.05$). However, patients with nonunion had a higher incidence of PTA, according to the Knirk & Jupiter classification ($p<0.05$). Moreover, correlation analysis revealed a significant association between arthritis severity and PRWE scores ($r=0.441$, $p<0.01$). Although its impact on function seems limited, ulnar styloid nonunion may contribute to PTA and warrants long-term study.

In our study, a weak but statistically significant positive correlation was found between age and PRWE scores ($r=0.243$, $p=0.03$), suggesting that functional outcomes decline with age. Similarly, Chung et al.[4] reported a 0.29-point decrease in Michigan Hand Questionnaire (MHQ) scores per year of age, Aggarwal et al.[22] found better outcomes in patients younger than 60 years, and Amorosa et al.[23] observed a significant negative correlation between age and QuickDASH scores ($r=0.27$, $p<0.05$). These findings consistently highlight age as a predictor of poorer recovery after distal radius fractures.

Aggarwal et al.[22] reported that loss of radial height and radioulnar inclination worsened functional outcomes, while changes in volar tilt and ulnar variance had no significant effect. Our findings for radial height, radioulnar inclination, and volar tilt were consistent, but unlike Aggarwal et al.,[22] we observed a strong correlation between ulnar variance and PRWE scores. Similar to our results, other studies have also highlighted the impact of ulnar variance on functional outcomes.[5,13] This discrepancy may be due to differences in patient populations or variations in assessment methods. We also found a significant and moderate correlation between the Stewart score, reflecting radiological reduction quality, and PRWE scores ($r=0.447$, $p=0.001$), emphasizing the importance of good reduction for optimal functional recovery.

Many studies in the literature suggest that PTA has a limited impact on functional outcomes and is not directly associated with patient-reported outcomes (PROs).[16,24] In a systematic review, Lameijer et al.[25] found that while PTA affects clinician-reported outcomes, there is insufficient evidence regarding its relationship with PROs. However, Lameijer et al.[26] later reported that patients with PTA had significantly lower total MHQ and SF-36 physical function scores. In our study, a significant correlation was observed between the Knirk & Jupiter arthritis classification and PRWE scores ($r=0.441$, $p=0.001$), suggesting that PTA may indeed be associated with PROs. Nevertheless, the relationship between radiographic evidence of PTA and clinical outcomes remains inconclusive. These findings highlight the need for future research involving larger patient cohorts and longer follow-up periods to better understand the long-term functional impact of PTA.

Maintaining wrist ROM is essential for sustaining daily functional activities. However, studies examining the relationship between wrist movements and functional outcomes following distal radius fractures remain limited. Yang et al.[27] found that wrist flexion/extension, supination, ulnar deviation, thumb opposition, and grip strength significantly affected QuickDASH scores, whereas radial deviation and forearm pronation did not. In our study, losses in wrist flexion, extension, radioulnar deviation, and supination were significantly associated with poorer PRWE scores, while pronation did not have a notable impact. Correlation analysis revealed that PRWE scores had the strongest association with ulnar deviation, followed by radial deviation. While Yang et al.[27] identified wrist extension as the most influential movement, we found a moderate but significant correlation between wrist extension and PRWE scores. These differences may reflect population and treatment variations, as our cohort was surgically treated (81 patients), while Yang et al.[27] analyzed 138 conservatively treated patients using QuickDASH. Thus, further studies are necessary to clarify these discrepancies and better understand the relationship between wrist motion and functional recovery.

Our study is one of the few investigations to comprehensively evaluate multiple factors influencing functional outcomes after distal radius fractures, incorporating detailed correlation analyses. However, several limitations

should be acknowledged. First, the retrospective design introduces inherent biases. Second, variability in follow-up durations among patients limited standardization and may have reduced the homogeneity of outcomes. Additionally, the heterogeneity of surgical techniques employed represents a potential source of bias when interpreting treatment outcomes. Although we found significant associations between ROM and functional outcomes, we did not evaluate postoperative rehabilitation protocols, potentially overlooking an important confounding variable. Finally, the sample size was relatively small compared to some reports in the literature. Future studies with larger cohorts and standardized follow-up protocols are required to provide more generalizable conclusions.

Conclusion

In conclusion, our study demonstrated that factors such as fracture type, ulnar styloid nonunion, patient age, radiological scores and parameters, arthritis grading, and wrist ROM significantly influence functional outcomes following the surgical treatment of distal radius fractures with locking plates. Achieving good functional results requires not only an adequate reduction but also the restoration of near-complete wrist ROM.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar Training and Research Hospital Ethics Committee (Date: 19.12.2013, Decision No: 89513307/1009/231).

Informed Consent

Informed consent was obtained from all patients.

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Conflict of Interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions

Concept: G.P., T.O., E.E.; Design: G.P., T.O., E.E., H.I.B.; Supervision: G.P., T.O., E.E., H.I.B.; Materials: G.P., H.G.; Data collection &/or processing: G.P., T.O., E.E., H.G.; Analysis and/or interpretation: G.P., E.E., H.G., H.I.B.; Literature search: G.P., T.O., H.G., E.E.; Writing: G.P., T.O., H.I.B.; Critical review: G.P., T.O., E.E., H.I.B.

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Kırık Tipi, Radyolojik Dizilim ve Hareket Açıklığı: Distal Radius Kırıklarında ARİF Sonrası Fonksiyonel İyileşmenin Belirleyicileri

Amaç: Distal radius kırıkları, erişkinlerde en sık görülen kırıklar arasındadır. Kilitli plaklarla yapılan açık redüksiyon ve internal fiksasyon (ARİF), standart cerrahi yaklaşımı temsil etmektedir. Ancak cerrahi sonrası fonksiyonel sonuçları etkileyen faktörler hâlâ tartışmalıdır. Bu çalışmada, kilitli plaklarla tedavi edilen distal radius kırıklarında hasta özellikleri, kırık tipi ve radyolojik faktörlerin fonksiyonel iyileşme üzerine etkisi araştırıldı.

Gereç ve Yöntem: 2007-2013 yılları arasında kilitli plaklarla ARİF uygulanan 81 hasta (55 erkek, 26 kadın; ortalama yaş: 43.7 yıl) retrospektif olarak incelendi. Fonksiyonel sonuçlar QuickDASH, PRWE ve Modifiye Green & O'Brien skorları ile değerlendirildi. Radyolojik değerlendirmelerde Stewart ve Knirk & Jupiter sınıflamaları kullanıldı. Fonksiyonel sonuçlarla ilişkili faktörleri belirlemek için Spearman korelasyon ve grup karşılaştırma analizleri yapıldı.

Bulgular: Kırık sınıflaması fonksiyonel sonuçları anlamlı şekilde etkiledi. AO tip B kırıkları, tip C kırıklarına kıyasla daha iyi QuickDASH ve Modifiye Green & O'Brien skorları gösterdi ($p<0.05$). Ulnar stiloid kaynamaması fonksiyonel sonuçları etkilemedi, ancak daha yüksek artrit dereceleri ile ilişkili bulundu ($p=0.039$). PRWE skorları; artrit şiddeti, radyolojik redüksiyon kalitesi, hasta yaşı ve pronasyon hariç çoğu el bileği eklem hareket açıklığı parametresi ile anlamlı korelasyon gösterdi. Ayrıca PRWE skorları, radial inklinasyon ve radial yükseklik ile negatif ulnar varyans ile pozitif korelasyon gösterdi.

Sonuç: Distal radius kırığı cerrahisi sonrası fonksiyonel iyileşme; kırık tipi, redüksiyon kalitesi, hasta yaşı, artrit varlığı ve el bileği hareketliliğinden etkilenmektedir. Anatomik redüksiyon ve el bileğinin neredeyse tam hareket açıklığının sağlanması, optimal sonuçlar için kritik öneme sahiptir.

Anahtar Sözcükler: Distal radius kırıkları; kilitli plak fiksasyonu; korelasyon analizi; sonuçları etkileyen faktörler; travma.

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Original Article

The Effect of Midurethral Sling Operations on Sexual Function in Premenopausal Sexually Active Women: A Comparative Prospective Study

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Keywords: FSFI; midurethral sling; sexual function; stress urinary incontinence; TOT; TVT-O.

ABSTRACT

Objective: The aim of this study was to evaluate the effects of transobturator tape (TOT) and transvaginal tape-obturator (TVT-O) midurethral sling surgeries on sexual function, in addition to their efficacy in the treatment of stress urinary incontinence (SUI), in premenopausal sexually active women.

Methods: This prospective, comparative, and observational study was conducted between 2020 and 2022 at the Department of Obstetrics and Gynecology, Kartal Dr. Lütfi Kırdar City Hospital. A total of 290 premenopausal, sexually active women diagnosed with SUI and treated with TOT or TVT-O surgery were included. The Female Sexual Function Index (FSFI) was administered preoperatively and at the 6th and 12th postoperative months. The results were compared with a control group consisting of 70 healthy women without urinary incontinence.

Results: Following TOT and TVT-O surgeries, significant increases were observed in FSFI total scores and all subdomains ($p<0.0001$). The most prominent improvements were noted in the satisfaction, orgasm, and pain domains. At the 12-month follow-up, the mean FSFI score of the intervention group was statistically comparable to that of the control group ($p=0.34$). Additionally, 91.4% of the patients reported an improvement in sexual function. Dyspareunia was observed in only 5.8% of the participants and was mostly attributed to physical or psychological factors.

Conclusion: Midurethral sling surgeries (TOT and TVT-O) not only effectively resolve urinary incontinence complaints but also contribute to the improvement of sexual function in premenopausal sexually active women. The observed positive outcomes are influenced by a combination of physiological, psychological, and relational factors. Therefore, a comprehensive and multidimensional approach should be adopted in the evaluation and follow-up of patients.

INTRODUCTION

Stress urinary incontinence (SUI) is one of the most common pelvic floor disorders among women of reproductive age and negatively affects quality of life by causing involuntary urine leakage during daily activities.[1] In addition to its physical manifestations, SUI can lead to psychosocial consequences such as embarrassment, social isolation, and sexual dysfunction, thereby reducing overall life satisfaction.[2]

Conservative treatment modalities, including pelvic floor muscle training, lifestyle modifications, bladder training, and pessary use, are generally recommended as first-line therapeutic options.[3] However, in patients who do not respond adequately to these approaches, minimally invasive surgical techniques—particularly midurethral sling (MUS) procedures—are considered the gold standard due to their high success rates and low complication profiles.[4]

Among these surgical techniques, transobturator tape (TOT) and transvaginal tape–obturator (TVT-O) procedures are widely performed. Both aim to restore urethral support and improve continence by positioning a synthetic mesh beneath the mid-urethra. Nevertheless, anatomical variations in the surgical approach may influence postoperative outcomes, including sexual function.[5,6]

Female sexual function is a complex process influenced by anatomical, hormonal, psychological, and relational factors. The Female Sexual Function Index (FSFI) is a validated, multidimensional self-report questionnaire that evaluates six domains—desire, arousal, lubrication, orgasm, satisfaction, and pain.[7] In recent years, interest in assessing the effects of MUS procedures on sexual function has increased. While some studies have reported significant improvements in sexual satisfaction and orgasm scores following surgery,[8] others have highlighted potential adverse outcomes such as dyspareunia or mesh-related discomfort.[9]

Given these conflicting results, there remains a need for prospective and comparative studies to elucidate the true impact of MUS techniques on female sexual health.

Therefore, the present study aimed to evaluate the effects of TOT and TVT-O midurethral sling procedures on sexual function in premenopausal, sexually active women using FSFI scores as an objective and standardized measurement tool.

MATERIALS AND METHODS

Study Design and Ethical Approval

This comparative and observational study was conducted between January 2020 and December 2022 at the Department of Obstetrics and Gynecology of a tertiary care center. The study protocol was reviewed and approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 15/11/2023, No: 2023/514/261/18). Written informed consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki.

Participants

A total of 290 premenopausal, sexually active women aged 30–55 years with a clinical and urodynamic diagnosis of anatomical stress urinary incontinence were included. All participants underwent either TOT or TVT-O midurethral sling surgery.

Exclusion criteria included postmenopausal status, absence of a sexual partner, previous pelvic surgery, psychiatric or neurological disorders, and evident vaginal atrophy. Women with pelvic organ prolapse (POP-Q stage ≥2) were excluded because pelvic floor descent may independently influence sexual function and FSFI scores.

Surgical Techniques

All procedures were performed under regional anesthesia by the same experienced surgeon using standardized techniques.

• TOT procedure: A polypropylene mesh tape was inserted through an outside-in route via the obturator foramen and positioned under the mid-urethra without tension.

• TVT-O procedure: The same mesh material was placed using an inside-out approach through the obturator membrane.

Prophylactic antibiotics were administered perioperatively, and patients were instructed to abstain from sexual intercourse for six weeks postoperatively.

Control Group

For comparison, a control group consisting of 70 healthy premenopausal women aged 30–55 years without urinary incontinence or pelvic floor dysfunction was included. These participants were selected from individuals attending routine gynecological examinations at outpatient clinics. Although randomization was not performed, the groups were comparable in terms of mean age, parity, and sexual activity level.

Assessment of Sexual Function

Sexual function was evaluated using the Female Sexual Function Index (FSFI), which measures six domains: Desire, arousal, lubrication, orgasm, satisfaction, and pain.[5] All participants completed the FSFI questionnaire preoperatively and at the 6th and 12th postoperative months. Total FSFI scores range from 2 to 36, with scores below 23 indicating sexual dysfunction.

Statistical Analysis

Statistical analyses were performed using SPSS software (version XX; IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean±standard deviation (SD). Pre- and postoperative FSFI scores were compared using paired t-tests, while changes at 6 and 12 months were analyzed using repeated-measures ANOVA with Bonferroni correction. A p-value <0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 290 premenopausal, sexually active women underwent midurethral sling (MUS) surgery for stress urinary incontinence (SUI). The mean age of the participants was 42.0±6.0 years. According to the surgical technique, 145 women (50%) underwent the transobturator tape (TOT) procedure and 145 (50%) the transvaginal tape–obturator (TVT-O) procedure.

The control group consisted of 70 healthy women with a mean age of 41.8±5.9 years. There was no significant difference in mean age between the intervention and control groups ($p>0.05$).

FSFI Total Scores

The mean preoperative FSFI total score in the intervention group was 20.96±3.1, which increased to 25.94±3.2 at six months and 26.2±3.1 at twelve months postoperatively, representing an overall 25% improvement from baseline.

This change was highly statistically significant (t=20.02; p<0.001).

When the two surgical subgroups were compared, postoperative improvement was observed in both TOT and TVT-O groups, with no significant difference between the techniques (p>0.05).

Comparison with the Control Group

The mean FSFI score in the control group was 26.4±2.8. At twelve months, the postoperative FSFI score in the intervention group (26.2±3.1) showed no statistically significant difference compared with the control group (p=0.34).

This finding indicates that MUS surgeries restored sexual function to levels comparable to those of healthy women without urinary incontinence.

FSFI Subdomain Analysis

Analysis of the six FSFI domains-desire, arousal, lubrication, orgasm, satisfaction, and pain-revealed significant improvements between baseline and twelve-month follow-up (p<0.001 for all).

The most prominent improvements were observed in satisfaction, pain, lubrication, and orgasm domains, suggesting that the benefits of MUS surgery extend beyond continence restoration to include physical and psychosexual dimensions.

A summary of pre- and postoperative FSFI domain scores is presented in Table 1.

Patient-Reported Outcomes

At twelve months postoperatively, subjective feedback from participants revealed the following:

• 91.4% (n=265) reported a noticeable improvement in sexual function, including enhanced libido, arousal, lubrication, and orgasm frequency.

• 3.4% (n=10) experienced mild superficial dyspareunia related to limited mesh exposure.

• 2.4% (n=7) reported deep dyspareunia attributed to vaginal scarring and narrowing.

• 2.8% (n=8) reported no notable change in sexual function.

In cases of dyspareunia, both anatomical (mesh exposure, scarring, tissue rigidity) and psychological factors (body image concerns, performance anxiety) were considered contributing elements.

General Evaluation

Overall, the results demonstrated that midurethral sling procedures, including both TOT and TVT-O, are not only effective for managing stress urinary incontinence but also significantly enhance female sexual function.

Postoperative normalization of FSFI scores highlights the positive impact of MUS surgery on both physical and emotional aspects of women's health.

Minor complications such as mesh erosion, vaginal scarring, and dyspareunia in a small subset of patients underline the importance of thorough preoperative counseling and careful postoperative monitoring.

Although postoperative continence and coital incontinence rates were not systematically recorded, this limitation was acknowledged. Future multicenter, long-term studies are warranted to further clarify sexual outcomes following MUS surgery.

DISCUSSION

This prospective comparative study demonstrated that midurethral sling (MUS) surgeries-specifically the transobturator tape (TOT) and transvaginal tape–obturator (TVT-O) techniques-performed in premenopausal, sexually active women significantly improved both total Female Sexual Function Index (FSFI) scores and subdomain values. These results indicate that MUS procedures provide not only anatomical correction of stress urinary incontinence (SUI) but also substantial recovery in sexual function through physiological and psychosocial mechanisms.[1]

The observed improvement in sexual function following MUS surgery is likely multifactorial. Restoration of continence reduces coital anxiety and embarrassment,

Table 1. Comparison of preoperative and postoperative FSFI scores in the study group

FSFI Domain	Preoperative (Mean±SD)	6th Month (Mean±SD)	12th Month (Mean±SD)	p Value*
Desire	3.1±0.7	3.8±0.6	3.9±0.5	<0.001
Arousal	3.2±0.8	4.0±0.7	4.1±0.6	<0.001
Lubrication	3.3±0.9	4.2±0.8	4.3±0.7	<0.001
Orgasm	3.2±0.8	4.1±0.7	4.2±0.6	<0.001
Satisfaction	3.1±0.8	4.3±0.6	4.4±0.5	<0.001
Pain	3.0±0.9	4.2±0.8	4.3±0.7	<0.001
Total FSFI	20.96±3.1	25.94±3.2	26.2±3.1	<0.001

*Paired t-test; statistically significant at p<0.05. FSFI: Female Sexual Function Index; SD: Standard Deviation.

while improved pelvic floor support and enhanced self-confidence contribute to greater sexual satisfaction and arousal.[2] Particularly, the marked postoperative increases observed in the satisfaction, lubrication, and orgasm domains suggest that these effects extend beyond urinary control and positively influence both physical and emotional aspects of female sexuality.[3]

Our findings are consistent with previous reports in the literature. Pace et al.[4] observed more than 90% improvement in FSFI scores after TOT and retropubic sling procedures, highlighting the beneficial impact of midurethral support on sexual function. Similarly, Wadie et al.[5] and Liang et al.[6] reported significant postoperative improvements in sexual satisfaction and orgasmic function following MUS surgery, although the latter found a slightly higher incidence of dyspareunia with the TOT technique, likely due to differences in the surgical route and periurethral dissection.

In the present study, both TOT and TVT-O techniques resulted in comparable FSFI improvements at 12 months, with no significant intergroup difference. This supports the notion that, when properly performed, both approaches yield equally favorable outcomes for sexual function recovery.

Although the majority of patients reported improvement, a small proportion (approximately 5–6%) experienced postoperative dyspareunia. These cases were primarily attributed to mesh exposure, vaginal scarring, or tissue retraction. Psychological factors, such as altered body image, fear of pain, or relationship anxiety, may also contribute to persistent discomfort.[7] Therefore, postoperative follow-up should not be limited to anatomical success but should also include psychosexual evaluation and counseling when necessary.

A systematic review and meta-analysis by Jha et al.[8] reported that approximately one-third of women experienced improvement in sexual function after incontinence surgery, whereas around 12% reported deterioration. These findings highlight the variability of outcomes and underscore the importance of adopting a patient-centered and multidisciplinary approach that integrates both physical and psychological aspects of recovery.

In the current study, postoperative FSFI scores at 12 months were comparable to those of healthy control women, suggesting that MUS procedures can restore sexual function to levels similar to those in women without urinary incontinence. This normalization of sexual health not only reflects continence restoration but also an enhancement in overall quality of life.[9]

Recent Literature and Clinical Implications

Recent studies have continued to support the positive effects of MUS surgeries on female sexual function. Yildiz et al.[9] demonstrated significant improvements in arousal and satisfaction scores following MUS, emphasizing the psychological benefit of regained continence. Moreover, it's been found no significant long-term differences between TOT and TVT-O techniques, although transient dyspareunia was slightly more frequent in the TOT group. These findings strengthen the notion that postoperative sexual improvement after MUS is the result of both functional recovery and psychosexual adaptation. Similarly, Bağlar et al.[10] reported that the mode of delivery influences sexual function through anatomical mechanisms, supporting the idea that the improvement in sexual function following MUS procedures may occur via similar anatomical and psychosexual pathways.

Strengths and Limitations

The main strengths of this study include its large sample size (n=290), prospective design, use of a validated tool (FSFI), and incorporation of subjective patient-reported outcomes, all of which enhance the reliability of the findings.

However, several limitations should be acknowledged. This was a single-center, non-randomized study, which may introduce selection bias. Additionally, psychological variables such as anxiety and depression were not evaluated. The absence of systematic documentation of coital incontinence rates represents a limitation of this study. Moreover, the one-year follow-up period, although adequate for short-term evaluation, may not capture long-term outcomes. Future multicenter randomized studies with extended follow-up and inclusion of psychosexual parameters would provide a more comprehensive understanding of postoperative sexual recovery after MUS procedures.

Conclusion

This study demonstrated that midurethral sling (MUS) surgeries, including transobturator tape (TOT) and transvaginal tape-obturator (TVT-O) techniques, are not only highly effective in the treatment of stress urinary incontinence (SUI) but also lead to significant and sustained improvements in female sexual function.

The postoperative increase observed in both total Female Sexual Function Index (FSFI) scores and its subdomains reflects substantial improvements across physical, emotional, and relational dimensions. The finding that FSFI scores at the one-year follow-up were comparable to those of healthy women without urinary incontinence suggests that MUS procedures are effective in restoring sexual function to normal levels.

MUS surgeries not only achieve continence but also reduce sexual dysfunctions commonly associated with SUI, such as decreased sexual desire, difficulty in achieving orgasm, and loss of self-confidence caused by coital urinary leakage. This underscores the multidimensional nature of female sexual health and emphasizes the importance of considering psychosocial as well as anatomical factors in patient assessment and counseling.

Minor complications such as dyspareunia, mesh exposure, or scar formation were observed in a small number of pa-

tients; however, these were manageable and did not significantly affect overall patient satisfaction.

In conclusion, TOT and TVT-O midurethral sling procedures can be considered safe, effective, and patient-satisfying surgical options that not only restore continence but also enhance female sexual health and overall quality of life.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 15.11.2023, Decision No: 2023/514/261/18).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: T.T., C.O.K.; Design: T.T., C.O.K.; Supervision: T.T., C.O.K., M.A.; Fundings: T.T.; Materials: T.T., C.O.K.; Data collection &/ or processing: T.T., C.O.K.; Analysis and/or interpretation: T.T., C.O.K., M.A.; Literature search: T.T.; Writing: T.T.; Critical review: T.T., M.A.

Conflict of Interest

None declared.

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Premenopozal Seksüel Aktif Kadınlarda Midüretral Sling Operasyonlarının Cinsel Fonksiyon Üzerine Etkisi: Karşılaştırmalı Prospektif Bir Çalışma

Amaç: Bu çalışmanın amacı, premenopozal ve seksüel olarak aktif kadınlarda uygulanan transobturator tape (TOT) ve transvaginal tape-obturator (TVT-O) midüretral sling cerrahilerinin, stres tipi üriner inkontinans (SÜİ) tedavisindeki etkinliğinin yanı sıra cinsel işlev üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Çalışma, 2020–2022 yılları arasında Kartal Dr. Lütfi Kırdar Şehir Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde prospektif, karşılaştırmalı ve gözlemsel olarak yürütülmüştür. SÜİ tanısı almış ve TOT veya TVT-O cerrahisi uygulanmış, premenopozal ve cinsel olarak aktif 290 kadın çalışmaya dahil edilmiştir. Tüm katılımcılara cerrahi öncesinde ve postoperatif 6. ile 12. aylarda Kadın Cinsel İşlev İndeksi (FSFI) uygulanmıştır. Bulgular, üriner inkontinansı olmayan 70 sağlıklı kadından oluşan kontrol grubuyla karşılaştırılmıştır.

Bulgular: TOT ve TVT-O operasyonlarını takiben FSFI toplam skorlarında ve tüm alt boyutlarda istatistiksel olarak anlamlı düzeyde artış gözlenmiştir ($p<0.0001$). En belirgin iyileşme tatmin, orgazm ve ağrı alt başlıklarında saptanmıştır. Müdahale grubunun 12. ayda ulaştığı ortalama FSFI skoru, kontrol grubuyla istatistiksel olarak benzer bulunmuştur ($p=0.34$). Ayrıca, hastaların %91.4'ü cinsel fonksiyonda iyileşme bildirmiştir. Disparoni yalnızca %5.8 oranında görülmüş ve bu durum çoğunlukla fiziksel veya psikolojik faktörlerle ilişkilendirilmiştir.

Sonuç: Midüretral sling cerrahileri (TOT ve TVT-O), yalnızca idrar kaçırma şikayetlerini gidermekle kalmayıp, premenopozal dönemdeki seksüel aktif kadınlarda cinsel işlevin iyileştirilmesine de katkı sağlamaktadır. Bu olumlu etkinin fizyolojik, psikolojik ve ilişkisel bileşenleri birlikte etkilediği göz önünde bulundurulmalı; hasta değerlendirmeleri bu çok yönlü çerçevede ele alınmalıdır.

Anahtar Sözcükler: Cinsel fonksiyon; FSFI; midüretral sling; stres üriner inkontinans; TOT; TVT-O.

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Original Article

Assessment of Radiation Dose Levels Associated with C-Arm Fluoroscopy in Orthopedics and Traumatology Operating Rooms: A Technical Study on Radiation Area Monitoring

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Keywords: Fluoroscopy; operating room; orthopedics and traumatology; radiation dose levels.

ABSTRACT

Objective: One of the surgical teams that uses fluoroscopy most frequently during operations is the orthopedics and traumatology team. This study aims to indicate that the radiation dose decreases with distance and to stimulate awareness of radiation protection of the team through real-time measurements during fluoroscopy.

Methods: The study was carried out in the operating rooms of orthopedics and traumatology clinic between 1.08.2025 and 31.08.2025. The radiation dose emitted from the fluoroscopy during imaging in both AP and LAT positions of the X-ray tube for each case was measured with a Geiger-Müller detector at defined distances inside the room, and recorded in the data form.

Results: Real-time measurements were performed during 62 operations. Of these 62 operations, 15 were upper extremity, 39 were lower extremity and 8 were pelvis/acetabulum surgeries. A total of 3062 imaging were recorded in 62 cases, with a mean of 49 per case, and a total of 2051.54 seconds of imaging time, with a mean of 33.09 seconds per case. The measurements taken at A1, A5 and L1, L5 points which are closer to the primary source, were statistically significantly higher than the measurements taken at further distances, $p<0.05$.

Conclusion: In addition to annual and periodic radiation area monitoring of operating rooms at our institution, this study has increased awareness of the orthopedics and traumatology team through detailed, real-time measurements. The results underlined once again the importance and effectiveness of applying the distance rule as well as the use of personal shielding equipment for radiation protection.

INTRODUCTION

Shortly after Roentgen's discovery in 1895, X-rays began to be used in medical imaging. Conventional fluoroscopy and angiography were the first imaging modalities used intraoperatively.[1] Over time, the use of intraoperative fluoroscopy has enabled a significant change in surgical techniques and postoperative patient outcomes.[2]

Mobile image intensifier system (C-arm) is widely used in surgical operations, especially in orthopedic surgery, and it provides real-time imaging and accurate guidance throughout the surgical process and shortens the operation time.[3] Especially in cases conducted under the guidance of C-arm systems, it offers early recovery advantages by minimizing postoperative wounds and pain.[4] However, these devices produce artificial ionizing radiation (X-rays) and their widespread use in the diagnosis or treatment exposes healthcare workers and patients to a certain amount of radiation.[5]

Ionizing radiation has adverse biological effects on living organisms that may vary depending on the amount of exposure dose and the duration of exposure.[6,7] The biological effects of ionizing radiation depend on the type and amount of energy. To define the amount or type of radiation dose exposure due to any medical intervention we use dose units. The unit of absorbed radiation dose on biologic material is the Gray (Gy). The equivalent dose unit obtained by multiplying the absorbed dose by the biological effective quality factor of the radiation type and is used in radiation protection. The unit of equivalent dose (H) is Sievert (Sv). Effective Dose (E) defines the total risk throughout the body and for individual critical organs in Sv. Ionization in air unit is roentgen (R). It is a dosimetric concept based on the ionization ability of radiation in the air. Since we are working with X-ray, we can use the conversion for roentgen and Sievert, 100 mR/h=1 mSv/h.

The cumulative radiation dose (total exposure over time) is expressed in mSv or mSv/year. The instantaneous radiation intensity is expressed as μSv/h. Based on the measured intensity, a rough estimate of cumulative dose can be made: 1 μSv/h × 24 hours × 365 days ≈ 8.76 mSv/year. This value corresponds to continuous exposure for 24 hours a day, 365 days a year.

We are exposed to different amounts of radiation with different imaging techniques. While a normal Lung Anterior-Posterior (AP) radiograph is 0.02 mSv,[8] dose values ranging from 5.1 mSv,[9] to 10-40 mSv[10] have been reported for Lung Computerized Tomography (CT) in different studies.[11]

The National Council for Radiation Protection (NCRP) and the International Council for Radiation Protection (ICRP) announces with regular reports annual cumulative dose radiation exposure limits. Based on stocastic events effective dose limit 50 mSv at any year / 20 mSv average for five consecutive years for radiation workers and 1mSv for public.[12,13] The ICRP Limits for eye lens are reduced 150 mSv to 20 mSv by increased knowledge about the biologic hazards of the radiation.[14,15]

The use of intraoperative fluoroscopy has increased with the development of minimally invasive procedures and technology, resulting in increased radiation exposure of surgeons and operating room (OR) team.[16,17] And fluoroscopy plays an important role especially in orthopedics and spine surgery.[18]

Chou et al.[19] investigated the prevalence of cancer among female orthopedic, urological, and plastic surgeons in the United States. The study found that female orthopedic surgeons had a higher than expected prevalence of cancers that may or may not be caused by occupational exposure to ionizing radiation. Specifically, breast cancer was reported to be 2.5 times more common among female orthopedic surgeons who used fluoroscopy.

Following the intraoperative fluoroscopy-induced radiation exposure, orthopedic surgeons do not experience serious organ damage from radiation exceeding threshold values. However, ionizing radiation accumulates over a long period of time and has the effect of causing genetic mutations or various cancers.[20,21] These effects, defined as stochastic effects, are not related to the amount of radiation dose exposed.

This situation underlines the importance of radiation protection awareness and performing the operation with the least possible radiation exposure. Three basic elements defined as radiation protection principles by the ICRP-Justification, Optimization (AsLowAsReasonablyAchievable-ALARA), and Dose Limitations-must be taken into consideration in clinical management and during surgery by the surgeons and the OR team.[22]

Studies have highlighted the influence of optimizing imaging technique and working within a reasonably achievable dose, aka the ALARA principle, while using fluoroscopy during a case.[23] We can categorize the principles of fluoroscopy protection for the OR team under four headings: Distance and position (distance 'D'), duration (exposure 'E'), use of barrier (barrier 'B'), and technical features of the device (technique 'T').[24]

In the OR, the distance rule is the easiest to comply with and on of the most effective method for radiation protection, radiation decreases inversely proportional to the square of the distance. To minimize the number of scattered photons, the fluoroscopy device should be positioned appropriately and the OR team should stand on the correct side of the fluoroscopy. The X-ray tube must be under the table. When taking a lateral (LAT) image, the team should be positioned on the opposite side of the X-ray tube. With this technique, radiation scattered from the patient cannot reach us. If it is not possible to apply the distance rule during imaging, taking a position opposite the X-ray tube reduces the radiation dose we will be exposed to by up to 10 times. By increasing the distance between the X-ray tube and the patient, both the patient's dose and the team's exposure dose will decrease.[24]

The duration of radiation exposure is directly proportional to the amount of radiation to be received. Therefore, in preoperative planning, determining the location of fluoroscopy inside the OR, marking the area to be imaged on the patient's body if possible, and being familiar with the other medical images of the patient. And also keeping the last image on the screen or recording the previous images by using the technological features of the fluoroscopic device will prevent the repetition of imaging during the case.[24]

Additionally, all shielding equipment and barriers must be available in the OR and must be worn whenever fluoroscopy is used. These equipment prevent radiation exposure at different rates depending on the regions where they are used. Lead-coated (0.15 mm) glasses reduce the amount of radiation reaching the eye by 70%. It was found that exposure was reduced by 2.5 times after thyroid shielding was used. A lead apron increases protection by 16 times in the AP plane and 4 times in the LAT plane.

Lead alloy-coated gloves are difficult to use but can reduce exposure by up to 35%.[25] The question 'Did everyone wear protective clothing?' should be asked out loud before each shooting, or should be warned with a loud voice during the shooting scopy.[26]

An article titled 'Radiation Exposure in Orthopedics' published in 2020 analyzed the historical processes and research data of the use of orthopedists in the United States. The report highlighted that orthopedic surgeons should embrace the ALARA principle: To lead by taking all available precautions to protect all members of the OR from radiation exposure while performing the most appropriate procedure for patients whenever possible. Furthermore, the study suggested that orthopedic surgeons and assistants need to receive adequate training on proposed security precautions to help reduce these potential risks, the emphasis on radiation safety and protection in this context be universally included in graduate medical education.[21]

Another study conducted in the UK with orthopedics and traumatology teams highlight the lack of knowledge and awareness of radiation protection guidelines and the resulting insufficient use of personal protective equipment in procedures involving fluoroscopy. The study recommends mandatory training for all OR team. Additional suggestions for methods to increase radiation protection awareness include the use of posters in the OR, regular inspections to monitor the use of personal protective equipment, and discussion of the results in clinical management meetings. [27] Also annual periodic measurements of all OR that uses fluoroscopy is necessary for the team to observe real-time measurements during a case and be aware of the ionizing radiation.

The main purpose of the study is to record the radiation measurements taken with the Geiger Muller (GM) radiation area detector during the intraoperative fluoroscopy imaging at defined distances with different X-ray tube positions (AP / LAT) in the OR of orthopedics and traumatology clinic. Analysis of recorded radiation doses within the scope of case subgroups and fluoroscopy tube positions, determination of radiation dose levels and observation of the reduction in the dose with the distance.

The second purpose of the study is to stimulate radiation protection awareness in surgeons and OR team via real-time measurements with a GM radiation monitoring detector and to increase awareness of the existence of radiation as an invisible type of energy. As a result, to increase the implementation of radiation protection principles and radiation protection precautions during fluoroscopic imaging.

MATERIALS AND METHODS

Our study was conducted in the OR of our hospital's orthopedics and traumatology clinic using a GM radiation area monitoring detector obtained from the radiation oncology clinic. The study was carried out during workdays between 1.08.2025 and 31.08.2025; during this period, cases using fluoroscopy were observed.

The amount of radiation dose measured with GM during fluoroscopic imaging was recorded on a data collection form for each case. The Geiger Muller dose rate meter used in the measurements is NEB brand 211 model, calibration date was 2 December 2024. Doses were measured at defined distances inside the room and at different positions of fluoroscopy (AP / LAT) and recorded on the data collection form. No extra fluoroscopic imaging was performed for this study.

C-arm fluoroscopy devices used in OR are technologically advanced devices with automatic exposure control mode. With this mode, the device automatically sets the kVp and mAs values, the parameters that affect the exposure dose during imaging, taking into account patient thickness and the imaing position. High-quality images are achieved with the least possible dose exposure. This mode is used actively in all shootings. The technician also sets the child / adult mode on the device before shooting.

To obtain more analytical observation and to guide the radiation physicist performing the measurements, the defined distances were numbered and schematized on the data collection form. (Fig. 1) A data recording form has been designed for two different fluoroscopy X-ray tube positions, AP/LAT. In each case, the radiation dose measured at the defined distances and directions, and recorded on the relevant line on the dose table, Figure 1A. For AP position defined distances; A 1-3, A 2-4, A 5-8, A 6-7 were 50 cm, A9 and A10 were 100 cm from the operating table. For AP position defined distances; L 1-3, L 2-4, L 5-8, L 6-7 were 50 cm, L 9 and L 10 100 cm were from the operating table.

Parameters to be recorded: Total number of fluoroscopy imaging, total imaging time, dose values measured with GM at positions 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 on AP position of the fluoroscopy Figure 1B, dose values read with GM at positions 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 on LAT position of the fluoroscopy Figure 1C.

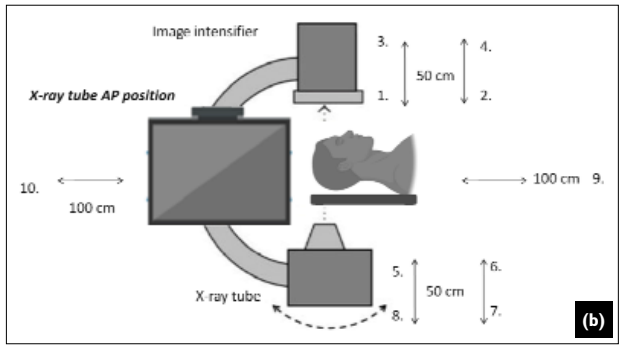
The data forms, were divided into case subgroups at the end of the observation and each case subgroup was reported individually. (Table 1) The closest distances to the primary sourse (X-ray tube), may change according to the operation side of the case, were A1-L1(represents the same point at different positions) or A5-L5 points.

Descriptive analysis was performed for mean, minimum (min) and maximum (max) values of measured dose values and recorded time data. Mean dose values at different distances of case subgroups compared via paired-sample t-test for parametric and Wilcoxon 2-related samples test for nonparametric in SPSS 27.0. The p value for statistical significance was determined as $p<0.05$.

Ethical approval for this study was obtained from Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee, taken on 25.06.2025 (No: 2025/010.99/17/26), and this study was conducted in accordance with the Declaration of Helsinki.

Case No					Case Procedure					
Total Imaging Number					Total Imaging Time					
Dose at defined distances for AP position	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Dose at defined distances for LAT position	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.

(a)



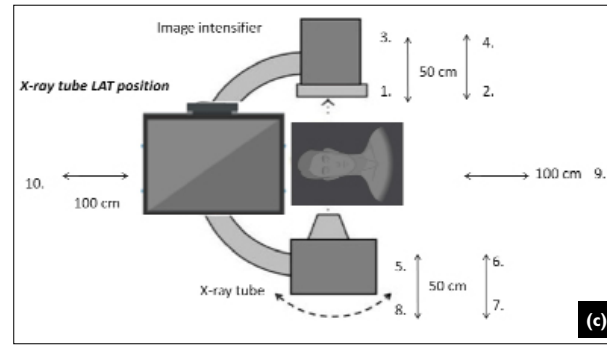


Figure 1. Data form for a single case **(a)** Table of measured radiation dose at defined points. **(b)** Defined dose distances for AP X-ray tube position. **(c)** Defined dose distances for LAT X-ray tube position.

RESULTS

Real-time measurements were performed during 62 operations in our hospital's orthopedics and traumatology OR's for 16 working days between 01.08.2025 and 30.08.2025. Of these 62 operations, 15 were upper extremity, 39 were lower extremity and 8 were pelvis/acetabulum surgeries. A total of 3062 imaging were recorded in 62 cases, with a mean of 49 imaging per case, and a total of 2051.54sec of imaging time, with a mean of 33.09sec per case. The measured dose unit with the GM detector was µR/h. We created our tables based on µSv/h for easier comparison with international annual dose limitations represented as mSv. As an example of unit conversion, 100µR/h = 1µSv/h. Background readings in operating rooms were between 4 - 12 µR/h ≈ 0,04-0,12 µSv/h.

Of the 15 upper extremity surgeries, 6 were closed reduction and pinning for pediatric supracondylar humerus fracture and 9 were open reduction and osteosynthesis with plate for distal radius fractures. In 15 upper extremity surgery cases, a total of 800 imaging were taken, with a mean of 53 imaging. The total imaging time for these 15 cases was 536.35sec, and the mean was 36.13sec. (Table 1)

Of the 39 lower extremity surgeries, 26 were in the hip region (proximal femoral nailing in 21 and dynamic hip nailing in 5), 5 were femoral nailing or biological plating, and 8 were nailing or minimally invasive plating. In 39 upper extremity surgery cases, a total of 1816 imaging were taken, with a mean of 47 imaging. The total imaging time for these 39 cases was 1217.12sec, and the mean was 31.19sec. (Table 1)

In 8 pelvis / acetabulum surgery cases, a total of 446 imaging were taken, with a mean of 56 imaging. The total imaging time for these 8 cases was 299.22sec, and the mean was 37.40sec. (Table 1)

During upper extremity surgery, fluoroscopic imaging was performed only in the AP position in 14 of 15 cases. This

Table 1. Total / mean imaging number and total / mean imaging time for case subgroups

	Upper Extremity	Lower Extermity	Pelvic Area
Number of cases	15	39	8
Total imaging	800	1816	446
Mean imaging per case	53	47	56
Min imaging / Max imaging	12 / 223	10 / 212	12 / 203
Total imaging time (sec.)	536.35	1217.12	299.22
Mean total imaging time per case (sec.)	36.13	31.19	37.40

Table 2. Mean dose values at defined distances at the AP imaging position and statistical analysis of the measurements at different distances in upper extremity cases

Defined distances for AP position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose μSv/h	0.935	0.592	0.339	0.317	0.622	0.553	0.362	0.482	0.196	0.201
p value (comparison by distance)	A1-A3 p=0.002		A2-A4 p=0.041		A5-A8 p=0.029		A6-A7 p=0.002		A9-A10 p=0.495	
	A1-A2 p=0.047		A3-A4 p=0.198		A5-A6 p=0.078		A7-A8 p=0.910			

Table 3. Mean dose values at defined distances at the AP and ALT imaging positions and statistical analysis of the measurements at different distances in lower extremity cases

Defined distances for for AP position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose μSv/h	0.904	0.745	0.398	0.394	0.958	0.812	0.331	0.349	0.251	0.239
p value (comparison by distance)	A1-A3 p=0.000		A2-A4 p=0.000		A5-A8 p=0.000		A6-A7 p=0.000		A9-A10 p=0.907	
	A1-A2 p=0.0367		A3-A4 p=0.070		A5-A6 p=0.049		A7-A8 p=0.260			
Defined distances for LAT position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose μSv/h	0.929	0.733	0.386	0.400	1.184	0.902	0.429	0.909	0.239	0.235
p value (comparison by distance)	L1-L3 p=0.000		L2-L 4 p=0.000		L 5-L 8 p=0.000		L 6- L 7 p=0.000		L 9- L 10 p=0.795	
	L 1-L2 p=0.000		L 3-L 4 p=0.818		L 5-L 6 p=0.000		L 7- L 8 p=0.544			

was related to the upper extremity anatomy and surgical techniques. Dose values recorded were compared statistically, with the Wilcoxon 2-related samples test.

Measurements taken at distances close to the primary source are statistically significantly higher than measurements taken further back (50 cm) from the same point, p<0.005, except at points A9 and A10 (100 cm). Since A9-A10 are at a sufficient distance, they did not establish a statistically significant superiority over each other, p=0.495. The measurement taken at position A1 is significantly higher compared to both the more posterior position (50cm) A3 (p=0.002) and the relatively distal position (50cm) A2 (p=0.047). (Table 2)

In lower extremity surgery, both AP and LAT positioned fluoroscopy images were taken. This was related to the lower extremity anatomy and surgical techniques. Dose values recorded were compared statistically with paired-sample t-test.

Measurements taken at distances close to the primary source are statistically significantly higher than measurements taken further back from the same point in both AP and LAT fluoroscopy positions, p<0.005, except for points A9-A10 and L9-L10. Since A9-A10 and L9-L10 are at a sufficient distance, p=0.907 for AP and p=0.795 for LAT positions. (Table 3)

Also the measurement taken at position A1 is significantly higher compared to both the more posterior position A3(p=0.000) and the relatively distal position A2 (p=0.0367). The same statistical significance was observed for A5, L1 and L5 points. The A5 compared to both A8 (p=0.000) and A6 (p=0.049). The L1 compared to both L3(p=0.000) and L2 (p=0.000). The L5 compared to both L8 (p=0.000) and L6 (p=0.000). (Table 3)

In pelvis / acetabulum surgery, fluoroscopy images were taken both AP and LAT positions. This was related to the pelvic anatomy and surgical techniques. Dose values were compared statistically, with Wilcoxon 2-related samples test.

Measurements taken at distances close to the primary source are statistically significantly higher than measurements taken further back from the same point in both AP and LAT fluoroscopy positions, p<0.005, except for points A9-A10 and L9-L10. Since A9-A10 and L9-L10 at a sufficient distance, they did not establish a statistically significant superiority over each other, p=0.703 for AP and p=0.055 for LAT positions. (Table 4)

Table 4. Mean dose values at defined distances at the AP and ALT imaging positions and statistical analysis of the measurements at different distances in pelvis /acetabulum cases

Defined distances for for AP position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose µSv/h	2.559	1.883	0.679	0.671	2.467	1.935	0.635	0.749	0.274	0.275
p value (comparison by distance)	A1-A3 p=0.012		A2-A4 p=0.012		A5-A8 p=0.012		A6-A7 p=0.012		A9-A10 p=0.703	
	A1-A2 p=0.047		A3-A4 p=0.674		A5-A6 p=0.049		A7-A8 p=0.183			
Defined distances for LAT position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose µSv/h	5.224	3.384	2.759	1.594	2.504	2.105	1.238	1.145	0.398	0.367
p value (comparison by distance)	L1-L3 p=0.046		L2-L 4 p=0.028		L 5-L 8 p=0.028		L 6- L 7 p=0.046		L 9- L 10 p=0.055	
	L 1-L2 p=0.046		L 3-L 4 p=0.596		L 5-L 6 p=0.028		L 7- L 8 p=0.753			

Table 5. Estimated mean dose values and corresponding daily mean dose values measured at AP position distances and LAT position distances in the sum of subgroups

Defined distances for for AP position	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
Mean dose µSv/h	1.466	1.074	0.472	0.461	1.349	1.099	0.443	0.527	0.240	0.238
	0.092	0.067	0.029	0.029	0.084	0.069	0.028	0.033	0.015	0.015
Defined distances for	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
LAT position Mean	3.077	2.058	1.573	0.997	1.844	1.504	0.833	1.027	0.319	0.301
dose µSv/h	0.192	0.129	0.098	0.062	0.115	0.094	0.052	0.064	0.019	0.018

Also the measurement taken at position A1 is significantly higher compared to both the more posterior position A3 (p=0.012) and the relatively distal position A2 (p=0.047). The same statistical significance was observed for A5, L1 and L5 points. The A5 compared to both A8 (p=0.012) and A6 (p=0.049). The L1 compared to both L3 (p=0.046) and L2 (p=0.046). The L5 compared to both L8 (p=0.028) and L6 (p=0.028). (Table 4)

The results provide evidence for the principle of distance for all case subgroups.

Mean dose values from all AP position distances and LAT position distances and corresponding daily dose values for 16 working days were estimated from the sum of all case subgroup measurements. The highest mean dose measurement per day for fluoroscopy-AP position were A1=0.092 µSv/h and A5=0.084 µSv/h. The highest mean dose measurement per day for fluoroscopy-LAT position were L1=0.192 µSv/h and L2=0.129 µSv/h. (Table 5)

For mean dose and daily mean dose values in the LAT position were higher than those in the AP position. The LAT imaging position was most commonly used in lower extremity and pelvic surgery cases, and dose data collected from these two groups were high. Because these anatomical regions are thicker thus in the LAT position, tube generates X-rays with higher penetration and energy for appropriate image quality. With this result, the relationship between the anatomical area to be imaged the exposure dose and the X-ray tube position was observed.

Another conclusion from our study results is dose reduction rate. The measurement taken at one distance and the measurement at a relatively posterior distance (50 cm) were compared and dose reduction ratios were calculated for both AP and LAT positions. The mean doses taken from Table 5, which presents the analysis of total cases. Measurements at A1, A2, A5 and A6 were 1.466 µSv/h, 1.074 µSv/h, 1.349 µSv/h and 1.099 µSv/h, respectively. And the dose reduction rates were estimated for the corresponding distances; for A1-A3 32.20%, A2-A4 42.99%, A5-A8 38.81% and A6-A7 40.37% dose reduction in 50cm. For LAT position; L1, L2, L5 and L6 were 3.077 µSv/h, 2.058 µSv/h, 1.844 µSv/h and 1.504 µSv/h, respectively. The dose reduction rates were estimated for the corresponding distances; for L1-L3 30.70%, L2-L4 48.20%, L5-L8 55.43% and L6-L7 55.33% dose reduction in 50 cm. When the distance increased by 50cm, a dose decrease between 30% and 55% was observed.

The effect of variables such as imaging technique, anatomical area, position of the X-ray tube and distance to the primary source on the radiation dose exposure is obvious with these results. Furthermore, it is crucial the apply the distance rule while using personal shielding equipment.

DISCUSSION

The biological effects of ionizing radiation are well understood; to minimize these effects and ensure a safe working environment, for the OR team, being trained in radiation protection principles and having awareness of radiation safety are a essential. While using fluoroscopy during a case, studies have emphasized the influence of optimizing imaging technique and working within a reasonably achievable dose, aka ALARA principle.[22,23]

In a study monitoring radiation emitted during C-arm fluoroscopy imaging, doses measured across a 60 cm radius from the beam center (X-ray tube) were reduced by an average of 66.3%, and doses measured at distances greater than 60 cm were less than 0.1 mSv/h in both scenarios.[5]

In our study, the average dose reduction rate was 38.60% for AP fluoroscopy position and 47.42% for LAT fluoroscopy position. Since we have compared the measurements from a 50cm distance difference, the decrease rate is lower. While the dose decreases with the square of the distance, a little distance makes a big difference. Still, our results are parallel to both the previous study and the processing principle of the distance rule. Also in our study, we observed a dose lower than 2 µSv/h at all points 50 cm away. With developing tecnology and for the better surgery / patient outcomes the use of fluoroscopy is a standart; where the focus should be on working under minimal exposure techniques and using personal protective equipment.

Besides personal awareness, institutional awareness and support on radiation protection is very important. An other study conducted in our hospital focused on determining radiation dose levels in the orthopedics and traumatology OR a decade ago. In this study 4 optically stimulated luminescence (OSL) dosimeters were used. Dosimeter-1 was placed below the foot-end of the operating table, dosimeter-2 was placed below the head-end, dosimeter-3 was placed on the wall at a height of 60 cm (200 cm from the foot end), and dosimeter-4 was placed on the wall at a height of 60cm (200 cm from the head end). Estimated daily dose values were 8.70 µSv, 6.55 µSv, 0.72 µSv and 0.50 µSv in dosimeters 1-4, respectively.[28]

According our data, highest daily mean dose at AP imaging position was 0.092 µSv/h (A1) and lowest 0.015µSv/h (A10). And highest daily mean dose at LAT imaging position was 0.192 µSv/h(L1) and lowest 0.018 µSv/h (L10). (Table 5) Relatively lower doses were observed in our measurement results.

The reason for the lower daily dose measurements in our study is the GM detector and the difference between the OSL. We would like to emphasize that the data from the GM detector, measured at defined distances, are instantaneous dose readings in µR/h. They provide a relative overview and do not represent the individual absorbed dose. Reports of personal dosimeters provide more accurate data on individual dose exposure and dose unit will be represented in mSv. Another possible explanation for the dose difference is the increased awareness of radiation protection in recent years, which may have resulted in fewer exposures, as well as the impact of technological advances in imaging.

In a radiation protection awareness study conducted with surgeons at our institution, more than half of the survey questions were answered correctly (≥50%), indicating a high level of radiation protection awareness and knowledge among our surgeons.[29] Ultimately, the orthopedics and traumatology team and the operating room staff in our hospital demonstrate a high level of radiation safety awareness, and our institution actively supports and prioritizes radiation protection and safety.

Conclusion

The use of imaging and technology is important for better surgical outcomes. The use of ionizing radiation requires the implementation of radiation protection principles and actions for a safe working environment. To provide these requirements, the theatre team needs to be educated up to date and aware of radiation safety. In addition, the dose reduction modes of the device used must be well known. Together with annual and periodic monitoring of dose levels at our institution's OR, radiation protection education is repeated systematically for work groups.

This study clearly demonstrated that radiation dose exposure decreases with distance. And the theatre team was able to observe this during real-time measurements performed, which is a strength of our study and improved radiation safety awareness. And the results underlined once again the importance of applying the distance rule as well as the use of personal shielding equipment for radiation protection.

Ethics Committee Approval

Ethical approval for this study was obtained from Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 25.06.2025, Decision No: 2025/010.99/17/26).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: N.C., M.S.A., S.K.G.; Design: N.C., S.K.G.; Supervision: E.E., S.K.G., R.D.; Data collection &/or processing: N.C., M.S.A., E.E.; Analysis and/or interpretation: N.C., S.K.G.; Literature search: N.C., M.S.A.; Writing: N.C.; Critical review: E.E., S.K.G., R.D.

Conflict of Interest

None declared.

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Ortopedi ve Travmatoloji Ameliyathanelerinde C-Kollu Floroskopi ile İlişkili Radyasyon Doz Düzeylerinin Değerlendirilmesi: Radyasyon Alanı İzleme Üzerine Teknik Bir Çalışma

Amaç: Ameliyatlar sırasında floroskopiyi en sık kullanan cerrahi ekiplerden biri ortopedi ve travmatoloji ekibidir. Bu çalışma, floroskopi kaynaklı radyasyon dozunun mesafeyle azaldığını göstermeyi ve floroskopi çekim sırasında gerçek zamanlı ölçümler yoluyla ekibin radyasyon korunma konusunda farkındalığını artırmayı amaçlamaktadır.

Gereç ve Yöntem: Çalışma, 01.08.2025-31.08.2025 tarihleri arasında ortopedi ve travmatoloji kliniği ameliyathanelerinde gerçekleştirildi. Her olgu için X-ray tüpünün hem AP hem de LAT pozisyonlarında görüntüleme sırasında floroskopiden yayılan radyasyon dozu, oda içerisinde belirlenen mesafelerde Geiger-Müller dedektörü ile ölçülerek veri formuna kaydedildi.

Bulgular: Gerçek zamanlı ölçümler 62 operasyon sırasında gerçekleştirildi. Bu 62 operasyonun 15'i üst ekstremite, 39'u alt ekstremite ve 8'i pelvis/asetabulum cerrahisiydi. 62 vakada toplam 3062 görüntüleme alındı, vaka başına ortalama 49 görüntüleme ve toplam 2051.54 saniye görüntüleme süresi, vaka başına ortalama 33.09 saniye olarak raporlandı. Birincil kaynağa daha yakın olan A1, A5 ve L1, L5 mesafelerinden alınan ölçümler, daha uzak mesafelerde alınan ölçümlerden istatistiksel olarak anlamlı derecede yüksektir ($p<0.05$).

Sonuç: Kurumumuzdaki ameliyathanelerin yıllık ve periyodik radyasyon alanı izlemelerine ek olarak, bu çalışma sırasında ortopedi ve travmatoloji ekibinin detaylı ve gerçek zamanlı ölçümler yoluyla farkındalığı artırmıştır. Sonuçlar, radyasyondan korunmada mesafe kuralının uygulanmasının kişisel koruyucu ekipman kullanımı kadar önemli ve etkin olduğunu bir kez daha vurgulamıştır.

Anahtar Sözcükler: Ameliyathane; floroskopi; ortopedi ve travmatoloji; radyasyon doz düzeyleri.

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Review

Bibliometric Analysis: Mapping the Global Research Landscape of Inflammation in Bipolar Disorder

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ABSTRACT

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression. Emerging evidence suggests that inflammation plays a critical role in the pathophysiology of BD, with elevated levels of pro-inflammatory cytokines and systemic immune dysregulation implicated. Despite growing interest, there is no comprehensive bibliometric analysis focusing on bipolar disorder and inflammation. A bibliometric analysis was performed using the Web of Science Core Collection (WOSCC) database, encompassing publications from inception to 2024. VOSviewer was utilized to analyze key trends, including publication dynamics, influential authors, citation patterns, keyword co-occurrences, and co-authorship networks. A total of 2,530 publications were identified, including 1,812 original articles and 718 reviews, demonstrating exponential growth since 2015. The United States, Brazil, and Canada emerged as the leading contributors, with significant output from institutions such as the University of Toronto and Deakin University. Influential authors included Michael Berk, Roger McIntyre, and Michael Maes. Research focused on keywords such as "cytokines", "neuroinflammation", and "oxidative stress", while emerging topics like "gut microbiota" and "neuroprogression" indicate evolving research priorities. Citation burst analysis highlighted significant advancements in inflammatory biomarkers and novel therapeutic approaches. However, global collaboration networks remain limited, particularly in underrepresented regions. This bibliometric analysis highlights the increasing interest in inflammation's role in BD and identifies key contributors, research trends, and emerging directions. Future research should prioritize international collaboration, systemic and molecular mechanisms, and translational efforts to improve diagnostics and treatment. These findings provide a roadmap for advancing research on bipolar disorder and inflammation.

INTRODUCTION

Bipolar disorder (BD) is a chronic and severe mental health condition characterized by alternating episodes of mania, hypomania, and depression, significantly impairing psychosocial functioning and reducing life expectancy.[1,2] Affecting approximately 1-2% of the global population, BD contributes substantially to the global burden of mental health disorders.[3] In recent years, inflammation has emerged as a critical focus in the study of BD's pathophysiology. Inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP), are frequently elevated in individuals with BD.[4] These findings underscore the role of systemic inflammation in disease progression and highlight its potential as a therapeutic target.

The relationship between inflammation and psychiatric disorders, including BD, has garnered increasing attention. Immune-inflammatory pathways are now recognized as central to the pathophysiology of mood disorders and other psychiatric conditions. Elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-alpha, have been documented not only in BD but also in major depressive disorder (MDD) and schizophrenia, suggesting shared underlying mechanisms.[5-7] Additionally, studies suggest that neuroinflammation, microglial activation, and altered cytokine networks modulate neuronal-glial plasticity and mood regulation, further elucidating inflammation's role in psychiatric conditions.[8] Beyond biological mechanisms, environmental and stress-related factors, including childhood maltreatment, play significant roles in BD pathophysiology. Early-life adversity has been linked to heightened inflammatory responses and an increased risk for severe psychiatric outcomes, underscoring the complex interplay between environmental and biological factors. Advances in molecular and epigenetic research further highlight these

processes, paving the way for novel therapeutic strategies. Interventions such as anti-inflammatory agents and rapid-acting treatments, including ketamine, show promise in addressing treatment-resistant cases of mood disorders.[9]

Inflammation's role in the pathophysiology of BD underscores the importance of identifying and synthesizing key research findings in this evolving field. With the increasing volume of studies exploring immune-inflammatory pathways, bibliometric analysis offers a systematic approach to uncover patterns, trends, and gaps in the literature, providing valuable insights for advancing research and clinical applications. While several bibliometric analyses have examined "bipolar disorder" and "inflammation" independently, none have comprehensively explored their intersection.[10-12]

A bibliometric analysis provides a quantitative and qualitative overview of the research landscape, identifying key authors, countries, institutions, journals, and trends. This study aims to address this gap by conducting a comprehensive bibliometric analysis of publications on bipolar disorder and inflammation, offering a roadmap to advance the field and identify emerging research priorities.

MATERIALS AND METHODS

Data Acquisition and Search Strategy

Bibliometric analysis requires comprehensive and reliable data sources. For this study, the Web of Science Core Collection (WOSCC) database was exclusively selected. This methodological decision was based on WOSCC's status as a gold standard for bibliometric research, which provides highly structured, clean, and consistent metadata essential for the accurate construction of co-authorship, co-occurrence, and citation networks in VOSviewer.[13,14]

While other databases like Scopus offer broader coverage and PubMed provides deep clinical focus, WOSCC is renowned for its rigorous journal selection process and detailed citation data, making it the optimal choice for analyzing the structure and impact of an established research field.

The bibliometric data for this study were retrieved from WOSCC on November 29, 2024. Relevant literature was identified using the search strategy: (TS = ("bipolar disorder") AND TS = ("inflammation" OR "inflammatory")). This query was designed to be specific yet comprehensive, targeting the direct intersection of the two core concepts. The 'TS' (Topic) tag searches the Title, Abstract, and Keywords fields, providing a balance between specificity and sensitivity, and capturing papers that explicitly link the two fields. We opted not to include terms for specific biomarkers (e.g., 'IL-6', 'CRP') in the primary search to avoid excluding broader conceptual or review articles.

The search was conducted without any restrictions on publication type to capture the complete landscape, including both original research articles and reviews. All relevant data were exported in plain text format, including full records and cited references, for further analysis. It is important to note that all analyses were conducted on this exported bibliographic metadata (titles, abstracts, keywords, author information, etc.). Full-text content analysis of the articles was not performed, as is standard for bibliometric mapping.

Data Analysis

Bibliometric analysis was performed using VOSviewer, a widely adopted tool for mapping and visualizing bibliometric networks.[15] It enables the identification of clusters and relationships among authors, institutions, and keywords through color-coded node mapping.[16] In this study, VOSviewer was used to generate co-authorship networks to examine collaboration patterns, and keyword co-occurrence networks to identify thematic trends and emerging topics. Additionally, the overlay visualization feature illustrated the temporal evolution of research focus by displaying keyword and author distributions across time.[17]

RESULTS

Publication Trends

A total of 2,530 publications on bipolar disorder and inflammation were identified, comprising 1,812 research articles and 718 review articles. The number of publications has shown an exponential growth rate over the past two decades, with a significant surge in articles between 2015 and 2023. The annual growth rate was calculated at 12.8%, indicating increasing attention to the role of inflammation in bipolar disorder. This was determined using the Compound Annual Growth Rate (CAGR) formula, a standard metric for assessing growth over time.

The formula was applied to the study period as follows: CAGR = [((End Value / Start Value) ^ (1 / n)) – 1]*100. ('Start Value' and 'End Value' are the publication counts in the first and last year of the analysis period, and 'n' is the number of years.)

Most Productive Countries

The United States emerged as the most prolific country, contributing 691 articles (27.3% of total publications), followed by Brazil (282 articles), Canada (273 articles), and China (244 articles). International collaborations were most frequent between the USA and Canada, as well as between the USA and the United Kingdom (Fig. 1).

Most Active Institutions

The University of Toronto led institutional output with 159 publications, followed by Deakin University (134) and the University of Melbourne (119). Other major contributors included the University of London (110), University of Texas System (101), and Florey Institute of Neuroscience and Mental Health (98). South American and European centers such as Universidade Federal do Rio Grande do Sul (95) and INSERM (90) also featured prominently.Institutions with a focus on youth mental health,

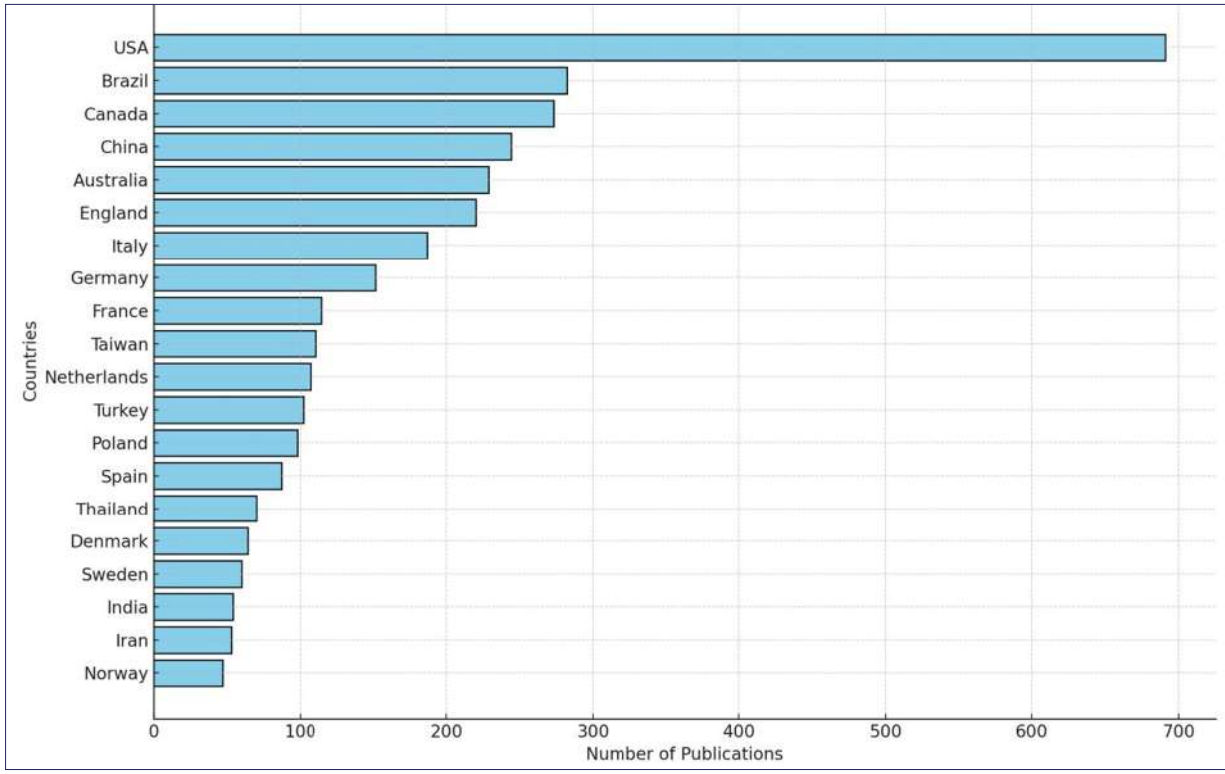

Figure 1. Top 20 countries by number of publications on bipolar disorder and inflammation.

like Orygen (90), and large academic hospitals such as King's College London (80), AP-HP (79), and Johns Hopkins University (75), reflected a diverse research base. Additional contributors included the University of Texas Health Science Center Houston (75), University Health Network Toronto (72), Baylor College of Medicine (71), and University of California System (66). European institutions such as Université Paris-Est Créteil (63), Centre for Addiction and Mental Health (61), and Université Paris Cité (61) completed the top 20. These institutions act as key research hubs, fostering regional and international collaborations that drive the interdisciplinary evolution of this field.

Key Journals

The top 10 journals publishing research on bipolar disorder and inflammation included Journal of Affective Disorders (133 articles), Brain Behavior and Immunity (82 articles), and Frontiers in Psychiatry (94 articles). Most of these journals are classified as Q1 in the Journal Citation Reports (JCR), indicating their high impact in the field (Table 1).

Table 1. Top 10 journals in bipolar disorder and ınflammation research: Articles, Impact Factor (IF), and JCR classification

Ranking	Sources	Articles	Country	IF	JCR-c
1	Journal of affective disorders	133	Netherlands	5.4	Q1
2	Frontiers ın psychiatry	94	Swıtzerland	3.9	Q2
3	Brain behavıor and immunıty	82	USA	9.8	Q1
4	Journal of psychiatric research	68	UK	4.3	Q1
5	Progress in neuro psychopharmacology Biologıcal psychıatry	58	UK	4.9	Q1
6	Translational psychiatry	58	UK	6.3	Q1
7	Psychiatry research	55	Netherlands	5.3	Q1
8	Molecular psychiatry	47	UK	11.1	Q1
9	Bipolar disorders	45	Denmark	5.9	Q1
10	International journal of molecular sciences	38	Switzerland	5.6	Q2

Table 2. Top 10 authors in psychiatric research on bipolar disorder and ınflammation: Articles and h-index rankings

Ranking	Authors	Articles	h-index
1	Berk, Michael	98	123
2	McIntyre, Roger	70	98
3	Maes, Michael	69	116
4	Kapczinski, Flavio	59	86
5	Teixeira, Antonio	49	68
6	Leboyer, Marion	45	105
7	Yolken, Robert	41	100
8	Brietzke, Elisa	41	54
9	Mansur, Rodrigo	38	47
10	Dean, Olivia	38	47

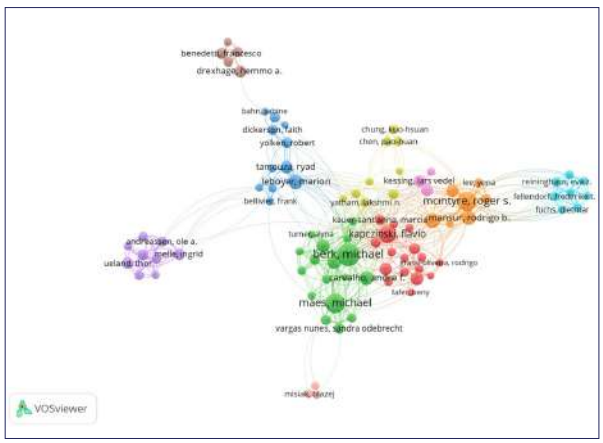

Figure 2. Co-authorship network in bipolar disorder and inflammation research.

Influential Authors

Michael Berk, Roger McIntyre, and Michael Maes were identified as the most prolific authors, contributing 98, 70, and 69 articles, respectively (Table 2).

The co-authorship analysis revealed distinct clusters of researchers actively contributing to the field of bipolar disorder and inflammation. Using VOSviewer, we identified prominent authors such as Michael Berk, Roger McIntyre, and Michael Maes as central figures within highly interconnected networks. These clusters underscore strong collaborative relationships among leading researchers and their teams. For example, Michael Berk's cluster (green) demonstrated extensive collaboration with researchers such as Flavio Kapczinski and Sandra Odebrecht Vargas Nunes, reflecting their shared focus on neurobiological and therapeutic studies. Similarly, Roger McIntyre's cluster (orange) highlighted partnerships with Rodrigo Mansur and Lars Vedel Kessing, emphasizing clinical and translational aspects of bipolar disorder research. Additionally, smaller yet significant clusters emerged, such as the blue

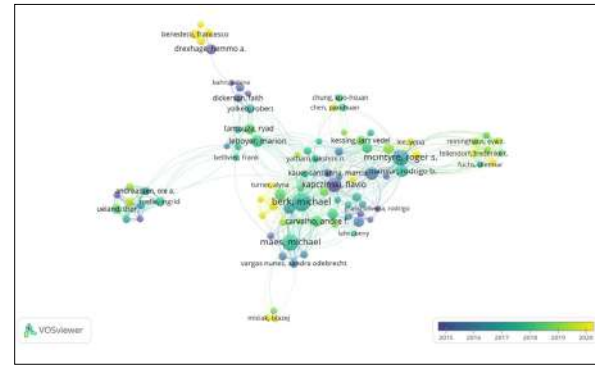

Figure 3. Temporal co-authorship network in bipolar disorder and inflammation research.

group led by Marion Leboyer, focusing on immune dysregulation, and the purple group led by Ole Andreassen, which delved into genetic associations (Fig. 2).

The co-authorship overlay visualization further highlights the evolving collaborative trends within the field. This map depicts clusters of active researchers, with Michael Berk (green cluster) and Roger McIntyre (yellow-green cluster) being central contributors. The color gradient from blue (earlier publications) to yellow (recent activity) illustrates the progression of research contributions over time. For instance, authors like Francesco Benedetti (yellow cluster) show increased recent activity, pointing to emerging focus areas. In contrast, Marion Leboyer and Ole Andreassen (blue-green clusters) represent foundational work that continues to shape the field through ongoing collaborations (Fig. 3).

Research Hotspots and Keyword Burst Detection

The keyword co-occurrence network offers valuable insights into the thematic structure and evolving research trends in the intersection of bipolar disorder and inflammation. Central terms such as bipolar disorder, depression, and cytokines emerged as pivotal nodes, connecting diverse research areas and highlighting their foundational role in this field. Distinct clusters reflect specific thematic focuses as follows: The green cluster emphasized inflammation and immune activation, featuring terms such as CRP, microglia, and maternal immune activation. The red cluster centered on systemic and metabolic perspectives, with keywords like cytokines, psychiatric disorders, and metabolic syndrome. The blue cluster focused on clinical and therapeutic aspects, including bipolar depression, antidepressants, and gut microbiota. The purple cluster encompassed methodologies and tools, with keywords like clinical trial and machine learning (Fig. 4).

Emerging trends were evident in terms such as COVID-19, epigenetics, and gut-brain axis, underscoring the growing interest in systemic and integrative approaches to understanding bipolar disorder. The overlay visualization revealed a temporal progression in research themes. Earlier topics, including oxidative stress and serotonin (2017–

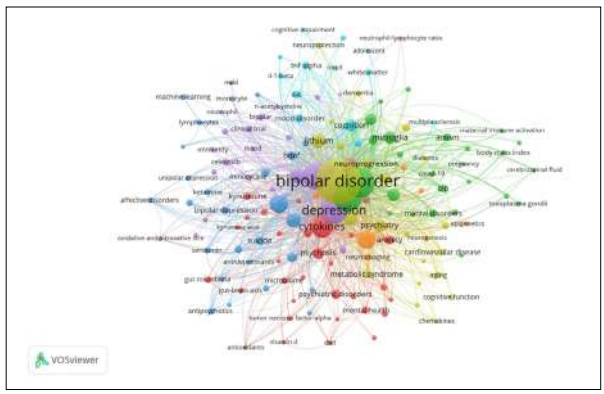

Figure 4. Keyword co-occurrence network in bipolar disorder and inflammation research.

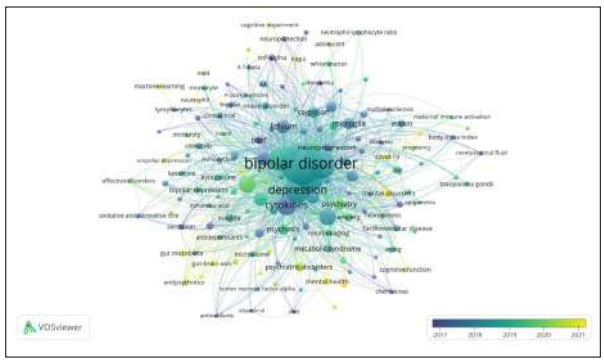

Figure 5. Temporal dynamics of keyword co-occurrence in bipolar disorder and inflammation research.

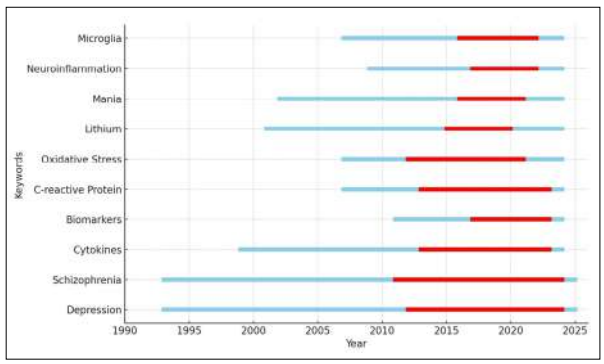

Figure 6. Keyword trends with burst periods.

2018, depicted in purple and blue), transitioned to newer themes such as neutrophil-lymphocyte ratio and maternal immune activation (2020–2021, depicted in yellow and green) (Fig. 5).

To quantitatively identify which research topics have experienced a rapid surge in scholarly attention, we performed a 'burst detection' analysis on keywords. This algorithm, integrated within VOSviewer, identifies keywords whose frequency increases sharply compared to other keywords, signaling a new or re-emerging research hotspot.

The results of this burst detection are visualized in Figure 6.

The analysis reveals significant temporal dynamics, with core terms such as "Depression", "Schizophrenia", and "Cytokines" maintaining prolonged activity since the early 1990s, as evidenced by their extensive blue spans. Notably, periods of heightened attention (indicated by red bursts) highlight the evolving focus of research, with "C-reactive Protein", "Oxidative Stress", and "Neuroinflammation" showing distinct bursts of activity from 2012 to 2023. Emerging terms like "Microglia" and "Neuroinflammation" demonstrate more recent research interest, reflecting the expanding exploration of systemic and molecular mechanisms underlying psychiatric conditions (Fig. 6).

The red lines represent the burst periods, indicating heightened attention to the respective keywords, while the blue bars denote the total time span of activity for each keyword.

DISCUSSION

This bibliometric analysis of bipolar disorder and inflammation provides a detailed overview of the research development in this field over the past several decades. The increasing number of publications, particularly in the last decade, reflects the growing recognition of inflammation as a critical component in the pathophysiology of bipolar disorder. Similar trends have been observed in bibliometric studies focusing on other psychiatric disorders, such as schizophrenia and depression, further emphasizing the importance of inflammation in mental health research.

The findings of this study align with a growing body of literature that underscores the central role of inflammation in the pathophysiology of bipolar disorder and related psychiatric conditions. Consistent with previous meta-analyses, elevated levels of key pro-inflammatory cytokines have been implicated in both acute and chronic phases of illness, highlighting their potential utility as biomarkers for diagnosis and treatment stratification.[4,18] Moreover, the association between persistent inflammation and treatment resistance, as observed in MDD, suggests that targeting inflammatory pathways may offer a promising avenue for improving therapeutic outcomes.[6]

Recent research underscores the transdiagnostic relevance of inflammatory markers, as similar patterns are observed in bipolar disorder, depression, and schizophrenia. For example, the consistent enrichment of pro-inflammatory bacteria and depletion of anti-inflammatory butyrate-producing genera in the gut microbiota of patients with psychiatric disorders suggests a systemic and integrative perspective on mental health.[19] This is further supported by evidence linking microglial activation and astrocyte dysfunction to neuroinflammatory processes, which may compromise the blood-brain barrier and exacerbate dis-

ease progression.[8] The interplay between environmental stressors and inflammation also warrants further discussion. Studies have shown that childhood maltreatment is associated with heightened inflammatory responses and structural brain changes, contributing to the severity and complexity of psychiatric presentations.[20] These findings underscore the need for preventive strategies targeting early-life adversity to mitigate long-term psychiatric and medical comorbidities.

Advances in treatment modalities, including anti-inflammatory agents and rapid-acting therapeutics targeting glutamate and GABA systems, offer hope for addressing the limitations of conventional pharmacological approaches.[21,22]

Future research should focus on integrating these approaches with psychosocial interventions to develop personalized treatment strategies that account for the heterogeneity of inflammation-related pathways in psychiatric disorders.

Growth in Publications

The number of publications on bipolar disorder and inflammation has grown exponentially, especially since 2015, reflecting a significant increase in research activity in this area. This surge coincides with a qualitative shift towards more mechanistic and integrative research approaches, with growing interest in topics like gut microbiota and neuroprogression, as well as advancements in related fields such as neuroimmunology and psychoneuroimmunology. This trend suggests a broader movement toward exploring systemic mechanisms underlying mental health conditions. The expanding body of evidence linking these inflammatory biomarkers to the clinical presentation and progression of bipolar disorder, coupled with the recognition of inflammation as a potential therapeutic target, has likely driven this increased research output.

Contributions of Countries and Institutions

The United States, Brazil, and Canada led research output on bipolar disorder and inflammation, likely due to strong academic infrastructure and high healthcare investment.[23-26] The U.S., in particular, dominated both publication volume and international collaboration, mirroring trends in related fields such as depression and schizophrenia. In contrast, regions like Africa and Southeast Asia remain underrepresented, highlighting the need for greater funding and collaborative efforts to reduce global disparities in mental health research.

At the institutional level, the University of Toronto (Canada), Deakin University, and the University of Melbourne (both Australia) were top contributors. Their output reflects specialized programs in mental health and inflammation, along with strong clinical integration. These trends are consistent with other bibliometric studies in psychiatric research.[12] Robust institutional collaboration networks across North America, Europe, and Australia underscore the importance of fostering global, interdisciplinary partnerships to advance the field.

Dominant Journals and Authors

Top-tier journals such as Journal of Affective Disorders and Brain, Behavior, and Immunity (both Q1) are primary outlets for research on bipolar disorder and inflammation, underscoring the field's relevance across psychiatry and immunology.

Michael Berk is a leading figure, with a prolific and influential publication record. Our analysis identified him as the most productive author in this field (98 publications), alongside other key contributors like Michael Maes (69 publications) and Roger McIntyre (70 publications).

To contextualize the overall scientific standing of these key contributors, we also identified their h-index as reported by the Web of Science Core Collection. Michael Berk (h-index=130), Michael Maes (h-index=122), and Roger McIntyre (h-index=104) all possess exceptionally high h-index values. This confirms their status as central, high-impact figures in the broader scientific community, reinforcing their dominance in this specific research nexus.

As the most prolific contributor identified in our analysis, Michael Berk's work in particular highlights the field's evolution. His research has notably advanced understanding of the link between immune dysfunction and bipolar disorder, with publication peaks aligning with growing interest in immunopsychiatry (e.g., 2016, 2019, 2020).[27,28] His output rose from ~3 articles per year (2010–2013) to ~9 annually (2014–2020), reflecting increasing engagement.

Despite strong individual contributions, co-authorship analysis reveals limited collaboration among top researchers. This highlights the need for interdisciplinary partnerships, international research programs, and funding strategies to promote data sharing and collective progress. Initiatives such as global workshops and consortium-based projects could enhance knowledge integration and accelerate clinical translation.

Research Hotspots and Emerging Trends

Keyword analysis highlighted "cytokines", "inflammation", and "oxidative stress" as central themes, with emerging topics such as "gut microbiota", "neuroprogression", and "epigenetics" gaining prominence in recent years. These trends reflect a growing interest in understanding the systemic and molecular mechanisms underlying the inflammatory processes in bipolar disorder. The role of the gut-brain axis has particularly captured attention, with studies demonstrating the impact of microbiota dysbiosis on systemic inflammation and mood regulation. The consistent depletion of anti-inflammatory butyrate-producing bacteria and enrichment of pro-inflammatory genera in individuals with bipolar disorder underscores the potential for microbiota-targeted interventions, such as probiotics or dietary modifications. Furthermore, the concept of neuroprogression, characterized by chronic inflammation-induced structural and functional brain changes, has emerged as a critical area of study. Microglial activation, astrocyte dysfunction, and mitochondrial impairments

have been implicated in this process, suggesting that interventions targeting neuroinflammation may hold promise for halting or reversing disease progression. These emerging trends hold significant promise for the development of novel diagnostic and therapeutic strategies, including microbiota-targeted interventions, personalized medicine approaches based on individual inflammatory profiles, and interventions aimed at preventing or mitigating neuroprogression. Such advancements could lead to more effective and personalized treatments for bipolar disorder, ultimately improving patient outcomes.

Global Analysis of Publication Trends

The findings of this bibliometric analysis reveal a significant increase in research output on bipolar disorder and inflammation over the past two decades, underscoring the growing recognition of inflammation as a critical component in psychiatric disorders. The publication trajectory can be categorized into distinct phases: An early growth phase (2000–2010) with sparse publications reflecting the nascent stage of research exploring the link between inflammation and bipolar disorder.[29,30]; an acceleration phase (2011–2020) marked by increased publications, driven by advancements in immunopsychiatry, the identification of key inflammatory biomarkers (e.g., IL-6 and TNF-alpha), and the development of improved methodologies. [31,32]; and a recent surge phase (2021–2024) with continued growth and increasing focus on emerging themes like the gut-brain axis, neuroprogression, and precision medicine.[33-36]

The global distribution of research output reveals notable disparities. The United States leads, contributing 27.3% of all publications, likely due to robust funding, advanced research infrastructure, and a strong emphasis on mental health. Brazil and Canada follow as the second and third most prolific contributors, reflecting strong regional focus on psychiatric and immunological research. Other key contributors include China, Australia, and the United Kingdom. However, research output from underrepresented regions such as Africa and Southeast Asia remains limited, emphasizing the need for increased funding and international collaborations to address global disparities in mental health research.

Emerging research themes align with the increased publication volume, with growing interest in understanding the role of the gut-brain axis, epigenetics, and precision medicine in bipolar disorder. Studies exploring how microbiota dysbiosis contributes to systemic and neuroinflammation, as well as the impact of environmental factors (e.g., stress, early-life adversity) on inflammatory pathways, are driving new avenues of research. Precision medicine, particularly the use of inflammatory biomarkers for targeted therapeutic interventions, represents a promising direction.

Looking ahead, projections suggest continued expansion, with publications on bipolar disorder and inflammation expected to double by 2030. This growth will likely be driven by advancements in technology (e.g., multi-omics approaches, neuroimaging, machine learning) and increasing interdisciplinary and international collaborations. These trends underscore sustained global interest and investment in immunopsychiatry.

Beyond publication metrics, this analysis reveals the qualitative evolution of research on bipolar disorder and inflammation. Early work focused on peripheral cytokines and cross-sectional associations, but the field has shifted toward mechanistic studies exploring microglia, gut microbiota, oxidative stress, and neuroprogression. Methodologies have advanced from correlational designs to longitudinal cohorts, neuroimaging, and clinical trials of anti-inflammatory agents.

Emerging topics such as "gut microbiota", "epigenetics", and "neuroprogression" reflect a broader move toward integrative, systems-level approaches. Despite this progress, causality remains a challenge-most studies demonstrate associations, not mechanisms. Identifying inflammatory endophenotypes that predict treatment response or disease trajectory is a key research priority.

Translation from bench to bedside also lags, with few findings yet informing clinical practice. Future efforts should focus on well-designed trials of targeted therapies and personalized interventions based on inflammatory profiles. Finally, while publication counts reflect activity, they don't capture quality or impact. Integrating citation metrics and alternative indicators of influence—such as translational reach or policy impact—can offer a fuller picture of research significance.

Challenges and Future Directions

Despite significant advances, several challenges persist. A key issue is the heterogeneity of inflammatory biomarkers and their inconsistent relationship with clinical outcomes, hindering their integration into diagnostic and therapeutic frameworks. Future research should prioritize identifying robust biomarkers that reliably stratify patients and predict treatment response. Emerging technologies, such as machine learning, neuroimaging, and multi-omics approaches, offer exciting opportunities to unravel the complex interplay between immune, genetic, and environmental factors in bipolar disorder. This includes investigating the causal relationships between inflammation and BD, moving beyond observed associations. Furthermore, research should focus on translating these findings into clinically useful tools, such as diagnostic assays and personalized treatment strategies.

Implications for Clinical Practice

The findings of this bibliometric analysis have significant implications for clinical practice. Identifying inflammatory subtypes in bipolar disorder could pave the way for personalized treatment approaches, combining mood stabilizers with targeted anti-inflammatory therapies. Interventions aimed at modulating the gut microbiome or mitigating the impact of early-life stressors offer novel avenues for

prevention and management. Ultimately, these research efforts aim to improve diagnostic accuracy, personalize treatment selection, and develop more effective preventative strategies for individuals with bipolar disorder.

Limitations

This study has several limitations. First, and most significantly, our reliance exclusively on the Web of Science Core Collection (WOSCC) introduces a potential selection bias. While WOSCC was chosen for its robust and clean metadata ideal for bibliometric network analysis, this decision omits publications indexed in other major databases. The omission of Scopus, which generally has broader journal coverage (including more conference proceedings and non-English journals), may mean our study underrepresents contributions from certain geographical regions or emerging research groups. The omission of specialized biomedical databases like PubMed and Embase may lead to an underestimation of clinically-focused research, such as specific clinical trials or detailed pharmacological studies that might not be indexed in WOSCC. Consequently, our findings map the research landscape as reflected in the high-impact, WOSCC-indexed literature and may not represent the entire corpus of research on this topic. Furthermore, as noted in our methods, WOSCC predominantly indexes English-language literature. While our search had no language restriction, this database-level bias likely excludes significant research published in other languages, further skewing the geographical distribution of productivity.

Second, while VOSviewer effectively maps networks and trends, it may oversimplify complex relationships among authors, keywords, and institutions. Third, reliance on citation counts may bias results toward older publications, underestimating recent impactful work. Fourth, a significant language bias is a key limitation of this study. While our search query did not include language restrictions, the WOSCC database itself is overwhelmingly English-language based. This is a substantial methodological constraint, as our analysis almost certainly excludes a large body of relevant research published in other languages. This bias directly impacts the perceived productivity and global rankings of non-Anglophone countries and research clusters. Therefore, our findings on international contributions must be interpreted with this strong caveat in mind, as they reflect the landscape of high-impact, English-language publishing rather than the totality of global research. Future analyses should use multiple databases and consider linguistic and cultural diversity. Fifth, this study does not evaluate the methodological rigor or clinical relevance of included publications, limiting practical interpretation. Sixth, while identifying top authors highlights leadership, it may overlook emerging contributors or those publishing in less visible venues. Alternative influence metrics, such as societal or translational impact, should be considered.

The Co-authorship analyses reflect network structure but not the quality of individual contributions. Balanced assessments should integrate established and emerging voices. Journals could help address linguistic disparities by offering language support and promoting open-access publishing to improve global research visibility and inclusivity.

Finally, this analysis reports the authors' general career h-index as a proxy for their overall influence, rather than a dataset-specific h-index. While this contextualizes their standing, it does not measure their specific impact within the niche field of bipolar disorder and inflammation. Future analyses could calculate the dataset-specific h-index for a more granular assessment.

Conclusion

This bibliometric analysis highlights the dynamic and rapidly evolving nature of research on bipolar disorder and inflammation. By identifying key contributors, research hotspots, and emerging trends, this study provides valuable insights into the current state and future directions of the field. Strengthening international collaborations, leveraging advanced methodologies, translating these findings into clinical practice, and engaging patients in research design and dissemination will be critical for addressing the unmet needs of individuals with bipolar disorder and advancing mental health research globally.

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Informed Consent

Not applicable. This study did not involve human participants or patient data.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: I.O.U., T.D.B.; Design: I.O.U., T.D.B.; Supervision: I.O.U., T.D.B; Fundings: I.O.U., T.D.B.; Materials: I.O.U., T.D.B.; Data collection &/or processing: I.O.U., T.D.B.; Analysis and/or interpretation: I.O.U., T.D.B.; Literature search: I.O.U., T.D.B.; Writing: I.O.U., T.D.B.; Critical review: I.O.U., T.D.B.

Conflict of Interest

There is no conflict of interest to declare.

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Bibliyometrik Analiz: Bipolar Bozuklukta İnflamasyon Konulu Küresel Araştırma Alanının Haritalandırılması

Bipolar bozukluk (BB), mani, hipomani ve depresyon ataklarıyla seyreden kronik bir psikiyatrik hastalıktır. Son yıllarda artan kanıtlar, inflamasyonun BB'nin patofizyolojisinde kritik bir rol oynadığını, özellikle pro-inflamatuar sitokin düzeylerinde artış ve sistemik bağışıklık disfonksiyonunun hastalıkla ilişkili olduğunu göstermektedir. Ancak, bipolar bozukluk ve inflamasyon konusunu odak noktasına alan kapsamlı bir bibliyometrik analiz bulunmamaktadır. Bu çalışma kapsamında, 2024 yılına kadar olan dönemi kapsayacak şekilde Web of Science Core Collection (WOSCC) veri tabanı kullanılarak bibliyometrik bir analiz gerçekleştirilmiştir. VOSviewer yazılımı ile yayın dinamikleri, etkili yazarlar, atıf örüntüleri, anahtar kelime eş-oluşumları ve ortak yazarlık ağları analiz edilmiştir. Toplamda 1.812'si özgün makale ve 718'i derleme olmak üzere 2.530 yayın tespit edilmiş ve 2015 yılından itibaren belirgin bir artış gözlemlenmiştir. Amerika Birleşik Devletleri, Brezilya ve Kanada en çok yayın yapan ülkeler olarak öne çıkarken, Toronto Üniversitesi ve Deakin Üniversitesi gibi kurumlar önemli katkılarda bulunmuştur. Etkili yazarlar arasında Michael Berk, Roger McIntyre ve Michael Maes dikkat çekmektedir. Araştırmaların odaklandığı anahtar kelimeler arasında "sitokinler","nöroenflamasyon" ve "oksidatif stres" yer alırken, "bağırsak mikrobiyotası" ve "nöroprogresyon" gibi yeni kavramlar, araştırma eğilimlerinin evrildiğini göstermektedir. Ani atıf artışı analizi, inflamatuvar biyobelirteçler ve yeni tedavi yaklaşımlarındaki önemli gelişmeleri ortaya koymuştur. Bununla birlikte, özellikle az temsil edilen bölgelerde, küresel iş birliği ağlarının sınırlı olduğu görülmektedir. Bu bibliyometrik analiz, inflamasyonun BB'deki rolüne artan ilgiyi ortaya koymakta ve başlıca katkı sağlayıcıları, araştırma eğilimlerini ve gelecekteki yönelimleri tanımlamaktadır. Gelecek çalışmaların uluslararası iş birliklerine, sistemik ve moleküler mekanizmalara ve tanı ve tedaviyi iyileştirmeye yönelik translasyonel çalışmalara öncelik vermesi önerilmektedir. Bu bulgular, bipolar bozukluk ve inflamasyon araştırmalarını ilerletmek için bir yol haritası sunmaktadır.

Anahtar Sözcükler: Bibliyometrik analiz; bipolar bozukluk; inflamasyon; nöroenflamasyon; sitokinler.