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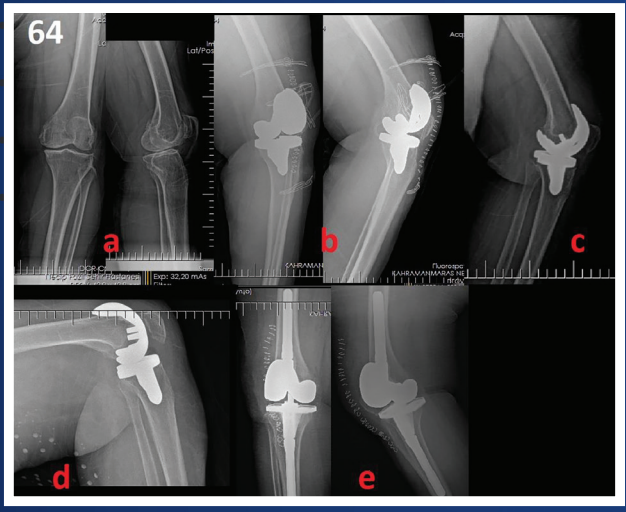

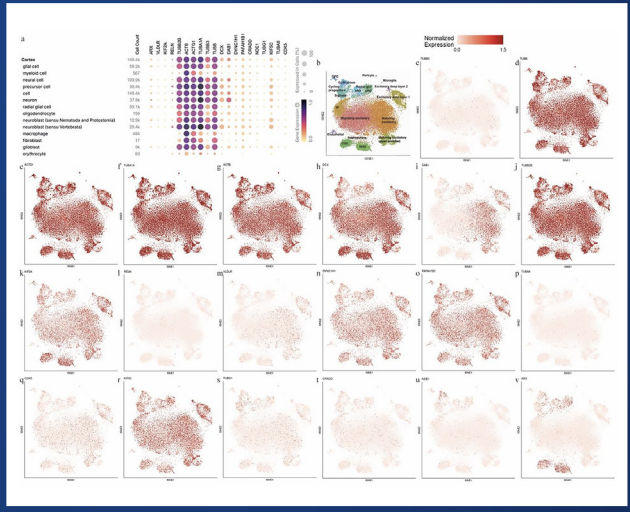

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Chylous Leak Management in Gastric Cancer Patients After D2 Dissection

Mide Kanserli Hastalarda D2 Diseksiyon Sonrası Şilöz Kaçak Yönetimi

Mehmet Güray Duman, Ali Alemdar

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Abstract

Objective: Gastric cancer is the fifth most prevalent cancer and the third leading cause of cancer-related deaths. After gastric cancer surgery, 1.99% of patients developed chylous leaks after dissections of D1 and D2 and 6.3% after dissections of D3 and D4. The milky discharge from the abdominal drains following enteral feeding indicates chylous leak. After cancer surgery, diagnosis and treatment of chylous leaks are crucial. This study aimed to guide the treatment of chylous leaks.

Methods: A total of 213 patients (147 men, 66 women) underwent D2 lymph node dissection after total or subtotal gastric resection. Age, gender, tumor location, type of surgery, number of resected lymph nodes, metastatic lymph nodes, day of lymphatic discharge, diagnosis of chylous leak, treatment, morbidity, mortality, fistula closure, and length of hospital stay were evaluated.

Results: The mean number of lymph nodes removed during surgery was 39 (16-87). Thirteen patients developed chylous leaks, with an average detection time of 5 days (3-7). At the outset of the study, total parenteral nutrition was administered to patients with chylous leaks. The patients were then given a low-fat diet with medium-chain triglycerides (MCT).

Conclusion: The Tg was 230-3497 mg/dL in our study. The chylous leak group had more lymph nodes dissected than the non-chylous leak group, but the difference was not statistically significant. Chylous leaks are associated with preoperative anemia, hypoalbuminemia, and lymph node resection. After drain output dropped below 300 cc/day, a middle-chain triglyceride diet was administered. None of our patients underwent surgery due to chylous leaks, and we can confidently state that patients with chylous leaks can be followed up with the MCT diet.

Keywords: Gastric cancer, surgery, D2 dissection, chylous leak

Öz

Amaç: Mide kanseri en sık görülen beşinci kanser olup, kanserden ölümlerin üçüncü ana nedenidir. Mide kanseri ameliyatı sonrası hastaların %1,99'unda D1 ve D2 diseksiyon sonrası, %6,3'ünde D3 ve D4 diseksiyon sonrası şilöz kaçak görülmektedir. Enteral beslenmeyi takiben abdominal drenlerden gelen süt benzeri sıvı şilöz sızıntıyı oluşturur. Kanser ameliyatından sonra şilöz kaçakların teşhisi ve tedavisi çok önemlidir. Bu çalışma şilöz kaçakların tedavisine rehberlik etmeyi amaçlamaktadır.

Yöntem: Total veya subtotal mide rezeksiyonu sonrası 207 hastaya (142 erkek, 65 kadın) D2 lenf nodu diseksiyonu uygulandı. Yaş, cinsiyet, tümörün yerleşim yeri, ameliyat tipi, çıkarılan lenf nodu sayısı, metastatik lenf nodu, lenfatik kaçağın günü, şilöz kaçağı tanısı, tedavi, morbidite, mortalite, fistül kapanması ve hastanede kalış süresi değerlendirildi.

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Öz

Bulgular: Ameliyat sırasında çıkarılan ortalama lenf nodu sayısı 39 (16-87) idi. On üç hastada ortalama tespit süresi 5 gün (3-7) olan şilöz kaçak mevcuttu. Çalışmanın başında şilöz kaçağı hastalarına total parenteral beslenme verildi. Daha sonra hastalara orta zincirli trigliserit (MCT) içeren düşük yağlı bir diyet verildi.

Sonuç: Çalışmamızda Tg 230-3497 mg/dL idi. Şilöz kaçak olan grupta istatistiksel anlamlılık olmaksızın normalden daha fazla lenf nodu disseke edildi. Şilöz kaçaklar preoperatif anemi, hipoalbüminemi ve lenf nodu rezeksiyonu ile ilişkilidir. Dren çıkışı 300 cc/gün'ün altına düştükten sonra orta zincirli trigliserit diyeti uygulandı. Hiçbir hastamız şilöz kaçağı nedeniyle ameliyat edilmedi ve şilöz kaçağı olan hastaların MCT diyeti ile takip edilebileceğini rahatlıkla söyleyebiliriz.

Anahtar Kelimeler: Mide kanseri, cerrahi, D2 diseksiyon, şilöz kaçak

Introduction

Gastric cancer is the fifth most commonly diagnosed malignancy and the third leading cause of cancer-related deaths worldwide[1]. Gastric resection with D2 lymphadenectomy is a standard surgical procedure for gastric cancer patients[2,3].

Developing surgical techniques and more aggressive dissections improved the survival of patients with gastric cancer. In addition to this improvement in survival, complications related to these interventions have increased over the past 20 years[4].

After gastric cancer surgery, chylous leaks can be seen in 1.99% of patients after D1 and D2 dissection and 6.3% after D3 and D4 dissection[5,6]. The cytoskeleton is lymphatic fluid and is rich in triglyceride (Tg) and lymphocytes. A chylous leak is usually encountered after enteral feeding as a milky discharge from the abdominal drains, which is sterile and rich in Tg. Tg levels are set as ≥110 mg/dL by some authors and ≥200 mg/dL by others, to name it chylous fluid[7,8]. Diagnosis and management of chylous leaks after cancer surgery are essential[9,10].

Lymphatic damage and lymph fluid pressure > abdominal pressure are prerequisites for chylous leakage. Cisterna chyli, which drains intestinal and celiac lymph nodes, is located on the right side of the aorta at the level of L1-L2. Variations in the anatomy may be a reason for the injury, with normal anatomy found only in 50% of patients[11]. After abdominal cancer surgery, it is observed in approximately 1.1% of cases and can also be observed after donor nephrectomy, abdominal aortic surgery, and trauma other than cancer patients[12-14].

Materials and Methods

Ethical approval was obtained from University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethical Committee (number: 2022/30, date: 14.02.2022). All interventions were performed by surgeons experienced in gastric cancer surgery. A total of 213 patients (147 men, 66 women) underwent D2 lymph node dissection after total or subtotal gastric resection. Energy devices are used for the ligation of small vessels and lymphatic vessels. When a large lymph vessel is encountered, it is either ligated with a suture or hemoclip. Patients were analyzed according to age, sex, body mass index (BMI), tumor location, type of surgery, number of resected lymph nodes, metastatic lymph nodes, day of lymphatic discharge, diagnosis of the chylous leak, type of treatment, morbidity, mortality, day of fistula closure, and duration of hospital stay. Data of patients who underwent surgery between January 2011 and September 2021 at University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital in the Gastrointestinal Surgery Department were retrospectively analyzed. Detailed consent was not obtained from the patients because it was a retrospective study and no interventional procedure was performed. A total of 207 patients were enrolled in the study. One hundred and forty-two 142 were male (68.6%), and 65 were (31.4%) female. The mean age of the patients was 60.9 (29-94). All patients underwent D2 lymph node dissection after either total or subtotal gastric resection. A total of 137 patients (66.2%) underwent total gastrectomy, and 70 (33.8%) underwent subtotal gastrectomy with D2 dissection. The mean BMI of the patients was 26.09 kg/m^2 (18-43). Tumor localization was in the cardia in 58 (28%), in the corpus in 72 (34.8%), in the antrum in 73 (35.3%), and diffuse in 4 (1.9%). The mean number of lymph nodes harvested during surgery was 39 (16-87). Among all patients, 76 had no lymph node metastasis and 131 had lymph node metastasis (Table 1).

Statistical Analysis

Descriptive statistics of continuous variables were reported as mean ± standard deviation or median (min-max) depending on the data distribution. The normality

Table 1. Comparison of patient characteristics		
	n	**%**
Age	60.9 (29-94)	
Gender		
Male	142	68.6
Female	65	31.4
Tumor location		
Cardia	58	28
Corpus	72	34.8
Antrum	73	35.3
Diffuse	4	1.9
Operation type		
Subtotal	70	33.8
Total	137	66.2
T stage		
T1	43	20.8
T2	29	14
T3	90	43.5
T4	45	21.7
N stage		
N0	76	36.7
N1	29	14
N2	43	20.8
N3	59	28.5
Tumor differentiation		
Well-differentiated	34	16.4
Moderate differentiated	79	38.2
Poor differentiated	94	45.4
Lymphatic invasion		
Present	124	59.9
Absent	83	40.1

distribution of the data was evaluated using the Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare non-normally distributed data. Relationships or proportion comparisons between categorical variables were performed using the chi-square test or Fisher's exact test. The statistical significance level was set as $p<0.05$.

Results

Total gastrectomy was performed in 140 patients and subtotal gastrectomy in 73 patients. Of the total gastrectomy group, 11 (7.9%) patients, and of the subtotal gastrectomy group, 2 (6.1%) patients had a chylous leak without statistical significance (p=0.22). Patients were given a liquid diet on postoperative day 1. We have 13 patients with chylous leaks. Of the leak group, four were in the N0 group, three in the N1, one in the N2, and 5 in the N3 group. The mean time to leak detection was the 5th (3-7) postoperative day. Routine drain amylase and Tg tests were not performed. When milky white discharge from abdominal drains was detected with high Tg levels, chylous leaks were considered. Biochemical analysis of drain fluid revealed Tg levels between 230 and 3.497 (mean: 843.5). We did not use lymphoscintigraphy for either the diagnosis or treatment of chylous leaks. After detecting chylous leaks, total parenteral nutrition (TPN) was introduced at the beginning of the study; with increasing experience, patients were started on a low-fat diet with medium-chain Tg (MCT). Six patients received TPN and seven received an MCT diet. None of the patients underwent surgery due to chylous leak. All patients recovered with TPN and MCT diet treatment. None of the patients in the MCT arm switched to TPN. Complications related to chylous leak were evaluated according to Clavien-Dindo (CD) classification[15]. Nine patients had CD 2 complications, and four patients had CD 1 complications (Table 2).

Discussion

The number of patients with gastric cancer who undergo radical surgery with aggressive lymph node dissection is increasing. As the number of harvested lymph node increases, the chylous leak also increases with more aggressive surgery, presenting a challenging clinical entity[5]. The standard method of tumor surgery is to remove the tumor with adequate margins and extend lymphadenectomy. For gastric cancers, subtotal or total gastrectomy with D2 resection is the preferred surgical intervention for potentially curable cT2-T4 and cT1N+ tumors. D2 lymphadenectomy should be performed whenever the possibility of nodal involvement can not be dismissed. In addition to the positive effects of extended lymph node dissection, it is associated with an increased risk of complications. The incidence of chylous leaks after major abdominal surgeries varies between 0.17% and 1.1%[16,17]. It is as high as 7.4% after retroperitoneal and esophageal cytoreductive surgeries[12,17]. Chylous fluid, chyliform or pseudochylous fluid, and lymphorrhea explain the nature of fluid from abdominal drains. Lymphorrhea is yellow in color, isosmotic to interstitial fluid, and has nearly equal Tg levels with serum due to injury to prenodal ducts. It occurs in approximately 7.4% of patients after abdominal oncologic surgery. The criteria to name it a chylous leak are a milky appearance, a sterile and odorless character with increased Tg level 2≥ two times of serum Tg level or

Table 2. Characteristics of patients with chylous leak

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Mean
Age	66	41	57	63	61	36	72	65	60	61	54	59	67	58.6 (36-72)
Gender	M	F	M	F	M	F	M	M	M	M	F	M	M	
BMI	24	24	26	28	25	25	23	18	20	25	25	26	24	24.07
Albumin	2.8	2.5	2.9	3.05	3.6	3.2	3.1	3.8	3.1	4.3	2.4	2.6	2.28	3.04 (2.2-4.3
Hemoglobin	11.6	10.9	10.1	10.9	16	12.3	11.5	9.4	15.2	14.4	11.2	16	13.1	12.5 (9.4-16)
Localization	Antrum	Corpus	Cardia	Corpus	Corpus	Diffuse	Cardia	Corpus	Cardia	Corpus	Corpus	Antrum	Cardia	
Surgery type	STG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	TG+D2 LND	STG+D2 LND	TG+D2 LND	
Resected lymph node no	28	35	51	51	31	52	17	27	57	36	78	41	20	40.3 (17-78)
Metastatic lymph node no	1	22	1	8	0	20	5	0	7	0	1	15	0	6.15 (0-22)
Start time of LL (day)	7	7	7	7	4	5	3	4	7	5	3	4	4	5 (3-7)
Diet with MCT	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	
TPN	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	
Fistula closure day	15	10	8	35	5	5	8	5	5	3	30	23	13	12.6 (3-35)

BMI: Body mass index, STG: Subtotal gastrectomy, TG: Total gastrectomy, LND: Lymph node dissection, LL: Lymph leakage, MCT: Middle chain triglycerides, TPN: Total parenteral nutrition

Tg >200 mg/dL. The risk of chylous leaks increases in proximally located tumors. In our study, there were four tumors in the cardia, six in the corpus, two in the antrum, and one diffuse tumor in the chylous leak group. The lowest Tg level was 230 mg/dL, and the highest was 3.497 mg/dL. We obtained a chylous leak ratio of 6.1%, which is compatible with the literature.

Assumpcao et al.[18] determined that after pancreatic surgery of 3.532 patients, postoperative chylous ascites were associated with the number of resected lymph nodes after pancreatic surgery in 3.532 patients. The number of dissected lymph nodes was higher than average (>39) in the chylous leak group, without statistical significance.

All complications were less than CD 3 in our study. No mortality was observed. Most patients recovered after MCT diet intake. The shortest hospitalization period after the detection of the chylous leak was 2 days, whereas the longest was 30 days (mean: 10.3 days). After a decrease in drain discharge below 300 cc/day, if the patient had no symptoms, the drain was withdrawn, and the patient was discharged with the recommendation of a middle-chain Tg diet. Regardless of whether the patients had complaints, they were called for control on the post-op 14th day. If not diagnosed earlier and managed properly, morbidity and mortality can occur.

Preoperative anemia, hypoalbuminemia, and the number and extent of resected lymph nodes are associated with a chylous leak[19]. Patients' BMI with the chylous leak was lower than the mean BMI of all patients (24.07 vs. 26.09). This result was statistically significant (p=0.03). The mean Hgb level was 12.5 (9.4-16) and the albumin level was 3.04 (2.2-4.3) in the chylous leak group. The relationship between preoperative hemoglobin and albumin levels and chylous leakage was not significant. Manipulation of

the para-aortic area and early enteral feeding were identified as independent risk factors for chylous leaks, as described by Kuboki et al.[11] before. Patients were started on a liquid diet on postoperative day 1. Previously, after cessation of oral intake, we were administering TPN with somatostatin. TPN administration has its own vascular and infectious complications. We began administering the MCT diet to these patients after they gained more experience. Our study found no complications following MCT feeding in patients with chylous leaks.

Study Limitations

The patient number in our study is not high enough to make thorough suggestions. This is a limitation of our study.

Conclusion

Surgery may be considered in cases of a chylous leak volume of more than 1000 mL/day for 5 days and a persistent leak for two weeks, but none of our patients were operated on due to a chylous leak. After all, we can confidently state that patients with chylous leaks can be followed up with the MCT diet.

The number of patients in our study was not high enough to prompt thorough suggestions. This is a limitation of our study.

Ethics

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethical Committee (number: 2022/30, date: 14.02.2022).

Informed Consent: Detailed consent was not obtained from the patients because it was a retrospective study and no interventional procedure was performed.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Vision Total Knee Replacement System Mid-term Survival and Radiological Results

Vision Diz Protezi Orta Dönem Sağkalımı ve Radyolojik Sonuçları

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Abstract

Objective: To evaluate and assess radiographic findings, revision causes, and survival rate of a total knee replacement system.

Methods: We retrospectively evaluated 359 total knee arthroplasties performed by the same surgeon at a single center between January 2016 and December 2023. Revisions, reoperations, complications, radiographic, and patient data were thoroughly evaluated to address any problems with patients, surgical procedures, and implants.

Results: Three revisions were made for two deep infections and one patient with arthrofibrosis. Two periprosthetic fractures occurred, which were treated without revision surgery. Five-year survival rate was 99.2% for any reason. Radiolucent lines that were found in 2.8% patients did not progress to loosening. The total number of patients identified with abnormal findings for both femoral and tibial components was 44 (12.2%). There was no aseptic loosening or implant-related complication.

Conclusion: Vision total knee system has a 99.2% survival rate for any reason at 5 years. When complications and revisions are evaluated, it is a safe option for total knee arthroplasty.

Keywords: Total knee, radiologic, survival, mid-term, aseptic, septic

Öz

Amaç: Total diz protezi sisteminin radyografik bulgularını ve revizyon nedenlerini değerlendirmek ve sağkalım oranını belirlemek amaçlanmıştır.

Yöntem: Ocak 2016 ile Aralık 2023 arasında tek bir merkezde aynı cerrah tarafından gerçekleştirilen 359 total diz artroplastisi geriye dönük olarak değerlendirildi. Revizyonlar, yeniden operasyonlar, komplikasyonlar, radyografik veriler ve hasta verileri kapsamlı bir şekilde değerlendirilerek; hastalar, ameliyatlar ve implantlarla ilgili problemler değerlendirilmiştir.

Bulgular: Üç revizyon ameliyatının ikisi derin enfeksiyon için ve biri artrofibrozis için yapılmıştı. İki periprostetik kırık meydana geldi ve revizyon cerrahisi olmadan tedavi edildi. Tüm nedenler için beş yıllık sağkalım oranı %99,2 idi. Radyolüsen hatlar hastaların %2,8'sinde görüldü ve implant gevşemesine ilerlemedi. Femoral ve tibial bileşenler için anormal bulgularla tespit edilen toplam hasta sayısı 44'tür (%12,2). Aseptik gevşeme veya implantla ilgili komplikasyon izlenmedi.

Sonuç: Vision total diz sistemi, 5 yıl boyunca herhangi bir neden için %99,2 sağkalım oranına sahiptir. Komplikasyonlar ve revizyonlar değerlendirildiğinde, total diz artroplastisi için güvenli bir seçenektir.

Anahtar Kelimeler: Total diz, radyolojik, sağkalım, orta dönem, aseptik, septik

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Introduction

Total knee replacement has become the standard method for relieving pain and disability in patients with advanced knee arthritis. Aging populations need an increasing number of total replacement surgeries each year. The success of a total knee replacement procedure depends on relieving pain and reducing disability. However, time is a multiplying factor, and knee implants must last for many years. The survival rate of total knee arthroplasty for all causes is 90-95% for 10 years and 80-90% for 15 years[1,2]. The most frequent revision causes are septic loosening for 36-58% and aseptic loosening (mechanical or bone implant interface problems) for 22-42%[2,3]. Apart from these frequent reasons, polyethylene wear, knee instability, periprosthetic fracture, osteolysis, and malalignment are other factors that play a role in revisions[2-4]. Long-term follow-up studies have shown that reduced survival rates and polyethylene wear or osteolysis dominate the causes of revision surgeries after 10 years[5]. Postoperative follow-up controls are important to address instability, osteolysis, loosening, and infection at an early stage. The purpose of this study is to assess mid-term outcomes of primary knee replacement procedures performed at a single center by the same surgeon using the same replacement system.

Materials and Methods

The earliest recorded patients whose digital medical records could be accessed at the Kahramanmaraş Necip Fazıl City Hospital (January 2016) had been scanned until December 2023. Approval for the study was obtained from Kahramanmaraş Sütçü İmam University Clinical Research Ethics Committee (decision no: 04, date: 18.06.2021). Only patients who had undergone surgery with a single brand of knee prosthesis (Vision Total Knee System, Zimed, Gaziantep, Türkiye) were included in the study, and no other exclusion criteria were applied. Two hundred ninety-eight consecutive patients with 359 total knee replacements were retrospectively included in the study. The patients' medical records were examined to analyze: demographic data, American Society of Anesthesiologists (ASA) surgical risk score, type of prosthesis used, follow-up duration, degree of knee arthrosis, alignment of the prosthesis, complications observed during and after surgery, whether revision was necessary, causes for revision surgery, radiolucent areas indicating bone osteolysis, and prosthesis subsidence.

The follow-up period for patients was recorded as the time until the last images obtained post-surgery. Postoperative complications included deep infections, deep vein thrombosis, pulmonary embolism, iatrogenic fracture, tibiofemoral dislocation, neural deficit, wound complications, periprosthetic fracture, ligament damage, (around the knee tendons), patellar instability, polyethylene fracture, and bleeding complications. The medical records of the patients were examined for side effects such as metal allergy and residual risks. The degree of knee arthrosis was assessed according to the Kellgren-Lawrence classification (Figure 1). Standard criteria accepted in the literature and a scoring system [The Knee Society Roentgenographic Evaluation and Scoring System, (KSRESS)] were used when evaluating knee radiographs[6,7].

The alignment of the coronal plane of the prosthesis was performed according to 5 degrees of valgus in men and 7 degrees of valgus in women. The sagittal plane evaluation was conducted with the knee flexed at 90 degrees and with a tibial slope angle of 5 degrees. Deviations of 3 degrees and above in these angles were considered abnormal. The position of the femoral component in the sagittal plane was evaluated according to the method suggested by Gujarathi et al.[8] regarding femoral notching (excessive femoral resection), accepted in the literature. A cement thickness of less than two millimeters in the femoral and tibial components, as well as an overflow of the prosthetic components under two millimeters (large size or decentralized fixation), were considered normal. Due to the limited number of patients who had knee computed tomography imaging, rotational measurements were not included in the study. When assessing prosthesis subsidence and polyethylene wear, patients with a follow-up of at least 48 months had these aspects examined, and subsidence greater than two millimeters in the femoral or tibial components or more than one millimeter of polyethylene wear was considered significant.

Statistical Analysis

Data were analyzed with the IBM SPSS version 25 program and $p<0.05$ was accepted as the significance level (IBM SPSS Inc., NY/USA). Paired t-tests were compared to previous literature results to detect radiological and clinical outcomes, complications, and safety profiles. Kaplan-Meier survivorship analysis was used for the endpoint of septic loosening, aseptic loosening, or revision for any cause.

Results

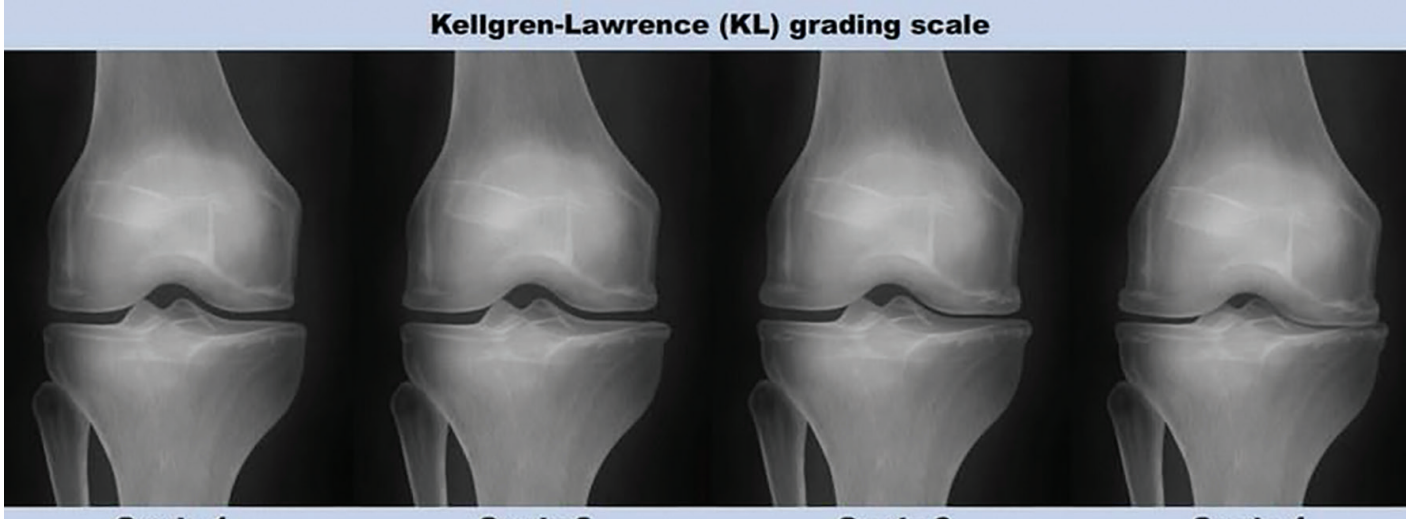
The average age of the 359 patients forming the study group was 66.1 (min: 46 to max: 90). Demographic data of

the patients, arthritis grade, follow-up time, and prosthesis type are presented in Table 1. When evaluating the follow-up durations, the average period for 48 knee prostheses was observed to be 6.2 months. In this group with a short follow-up period, no complications, metal allergies, or need for revision surgery were observed. The average follow-up period for the remaining 311 knee prostheses was 65.2 months (min: 24 to max: 112 months).

In the evaluation of the tibial component alignment, there were 25 patients (6.9%) identified with a varus of 3 degrees or more, while 14 patients (3.9%) were observed with excessive tibial slope. None of the patients had a tibial cement thickness greater than 2 mm or a tibial component eccentricity greater than 2 mm. The number of patients identified outside normal limits specifically for the tibial component was 39 (10.8%). In the evaluation of the femoral component alignment in the coronal plane, two patients had abnormal findings, whereas in the sagittal plane assessment, two patients with grade 2 femoral notching, and one patient with minimal notching were identified. Cumulatively, the total number of patients identified with abnormal findings for both femoral and tibial components was 44 (12.2%). These findings are summarized in Table 2.

A total of 269 patients with a follow-up period of 4 years or longer were examined for polyethylene wear and subsidence. No polyethylene wear or subsidence was detected in measurements made with plain radiographs. In the evaluation of radiolucent areas, non-progressive radiolucent areas were observed in the medial tibial component in six patients and in the anterior femoral component in four patients (in 10 patients, representing 2.8%). No progression or loosening was observed during the follow-up of these patients.

When evaluating complications, it was observed that two patients developed traumatic periprosthetic fractures during follow-up, but there was no need for prosthesis revision (Figure 2). Late-stage prosthetic infection was observed in both patients, and revision was performed due to infection in the fourth year (Figure 3). One patient underwent the revision knee prosthesis in the fourth month because of an inability to achieve knee extension caused by arthrofibrosis (Figure 4). While 5 patients (1.4%) had complications, 3 patients (0.8%) underwent revision surgery. There were no cases of tibiofemoral dislocation, patellar instability, tendon rupture, polyethylene fracture, or secondary surgeries due to vascular or nerve damage. Deep vein thrombosis was



CLASSIFICATION	Normal	Doubtful	Mild	Moderate	Severe
DESCRIPTION	No features of OA	Minute osteophyte: doubtful significance	Definite osteophyte: normal joint space	Moderate joint space reduction	Joint space greatly reduced: subchondral sclerosis

Figure 1. Kellgren-Lawrence arthritis grading scale

observed in 12 patients (3.3%), and deep vein thrombosis with pulmonary embolism was observed in 4 patients (1.2%). Complications are summarized in Table 3.

Survival rate for all-cause at 5-year follow-up is 99.2%. The survival rate for septic failure at 5-year follow-up is 99.5%. The Kaplan-Meier survivorship analysis results are shown in Table 4.

Discussion

After total knee replacement, asymptomatic patients should undergo an X-ray once every year; yet there are no guidelines for follow-up radiographs. This lack of standardization in follow-up care might lead to missed opportunities for early detection of complications, such as instability or joint deterioration. The KSRESS can be a useful tool for monitoring patient progression[7]. Although radiolucent lines are not directly associated with implant loosening[9], progressive radiolucent lines are commonly a sign of aseptic loosening[10]. Compared with neutral alignment, malalignment is also a contributing factor to shorter survival rates[11]. A review of twelve studies showed that when a manual surgical technique is applied and 3 degrees of deviation from the mechanical axis is targeted, 26% of patients could be in the outlier group[12]. Another study comparing robotic surgery to conventional surgery showed 10.9% mechanical axis outliers in conventional surgery group[13]. Our 12.2% malalignment finding is comparable to the literature. In our series, we did not find any progressive radiolucent lines, and malalignment was not associated with any revisions.

The most common reasons for knee replacement revision and re-revision are aseptic loosening, infection, and instability[2]. The 10-year survival rate of total knee arthroplasty for any reason is more than 90%[1]. Also, high crosslinked polyethylene liners have better wear properties, and when used they have shown better survival rates for any reason for revision[14]. Over the past years, the percentage of revision surgeries due to polyethylene wear has declined, and the aseptic loosening percentage has become second after infection, the most common cause, likely due to improved polyethylene materials and surgical techniques[4]. Periprosthetic fractures are minor causes for revision (1.1%) and are associated with implant-related, patient-related, and surgery-related factors[15]. We had two periprosthetic fractures caused by a fall at home, and a revision procedure was not necessary. We found a 99.2% survival rate at 5 years with three revisions: one for arthrofibrosis and two for deep infection. Our result is comparable to mid-term 92.9-99.3% survival rates of cemented knee arthroplasty[16-18].

Table 1. Demographic data and various findings of study group

Age (mean)	**66.1 years**		
Sex	Male 29.6%		Female 70.4%
Side	Left 32.2%	Right 50.8%	Bilateral 17%
ASA score	ASA 1 - ASA 2 42% ASA 3 57% ASA 4 1%		
Kellgren-Lawrence grading	Normal - Grade 1 - Grade 2 13% Grade 3 34% Grade 4 53%		
Prosthesis type	P/S 81.6%		C/R 18.4%
Follow-up months	<24 13.4%	>48 48.8%	>96 12.1%

ASA: American Society of Anesthesiologists

Table 2. Alignment and positional complications

n=359	Tibial component	Femoral component
Sagittal	3.9% slope	None
Coronal	6.9% varus	0.5%
Axial	Not identified	Not identified
Translation, femoral notching	None	0.8% notching
Cement thickness	<2 mm	<2 mm
Cumulative	10.8%	1.3%

Table 3. Complications

n=359	
Prostetic infection*	2 (0.5%)
Periprostetic fracture	2 (0.5%)
Arthrofibrosis*	1 (0.3%)
Deep vein thrombosis	12 (3.3%)
DVT with pulmonary embolism	4 (1.2%)
Cumulative	17 (4.6%)

DVT: Deep vein thrombosis, *: Three patients had revision arthoplasty

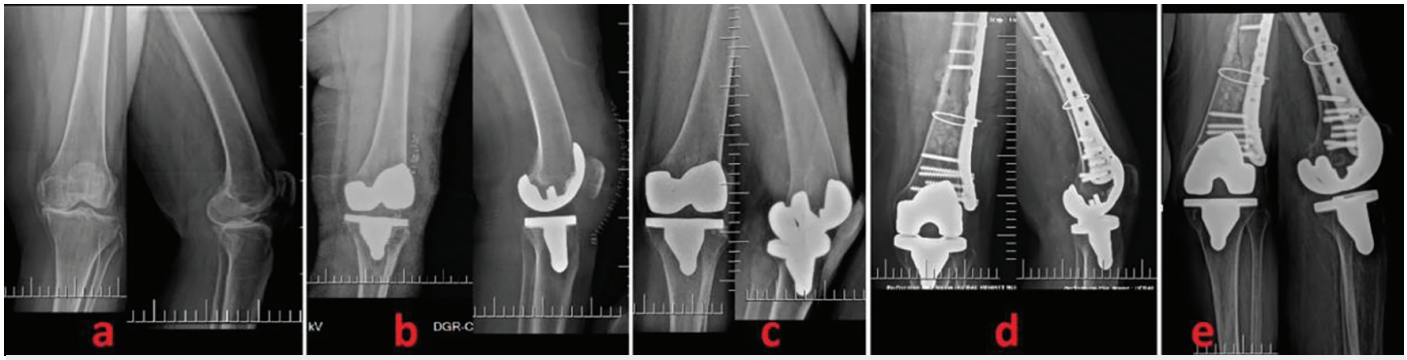


Figure 2. a) Eighty year old women with grade 4 arthritis b) Postoperative X-rays c) 46 months follow-up d) At 56 month periprosthetic fracture occurred and treated accordingly e) 89 month follow-up

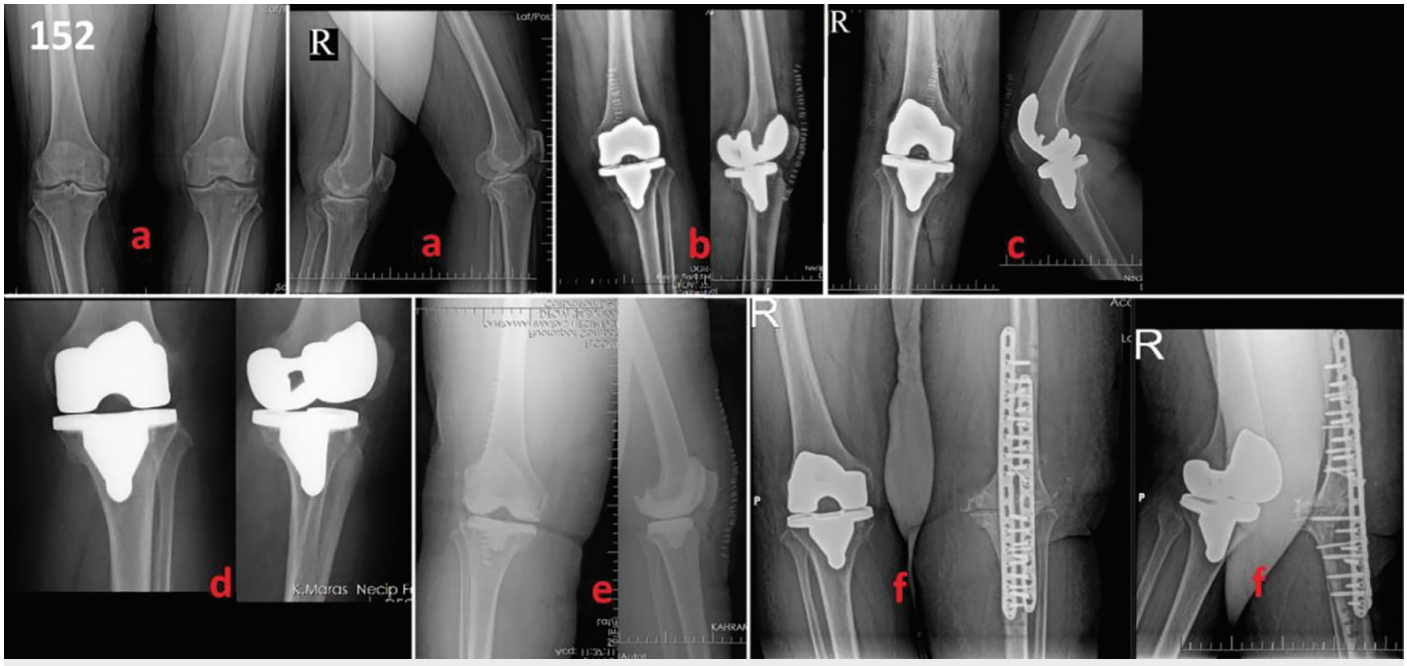


Figure 3. a) Seventy year old women with grade 3 arthritis b,c) One stage bilateral arthroplasty has been made d) At 52 months postoperatively septic loosening occurred e) Two staged treatment started f) Arthrodesis surgery with two plates has been made at 63 month

Table 4. Five year survivorship analysis of vision total knee system

Time period (year)	At risk	Lost to follow-up	Revised or failed	Survival probability estimate	95% confidence interval	
					Lower limit	Upper limit
First	359	19	1	1.000	0.971	0.999
Second	353	29	0	0.995	0.954	0.998
Third	311	43	0	0.995	0.942	0.996
Fourth	269	75	2	0.981	0.927	0.995
Fifth	194	46	0	0.981	0.911	0.995
The number of knees included at the beginning of the study=359						

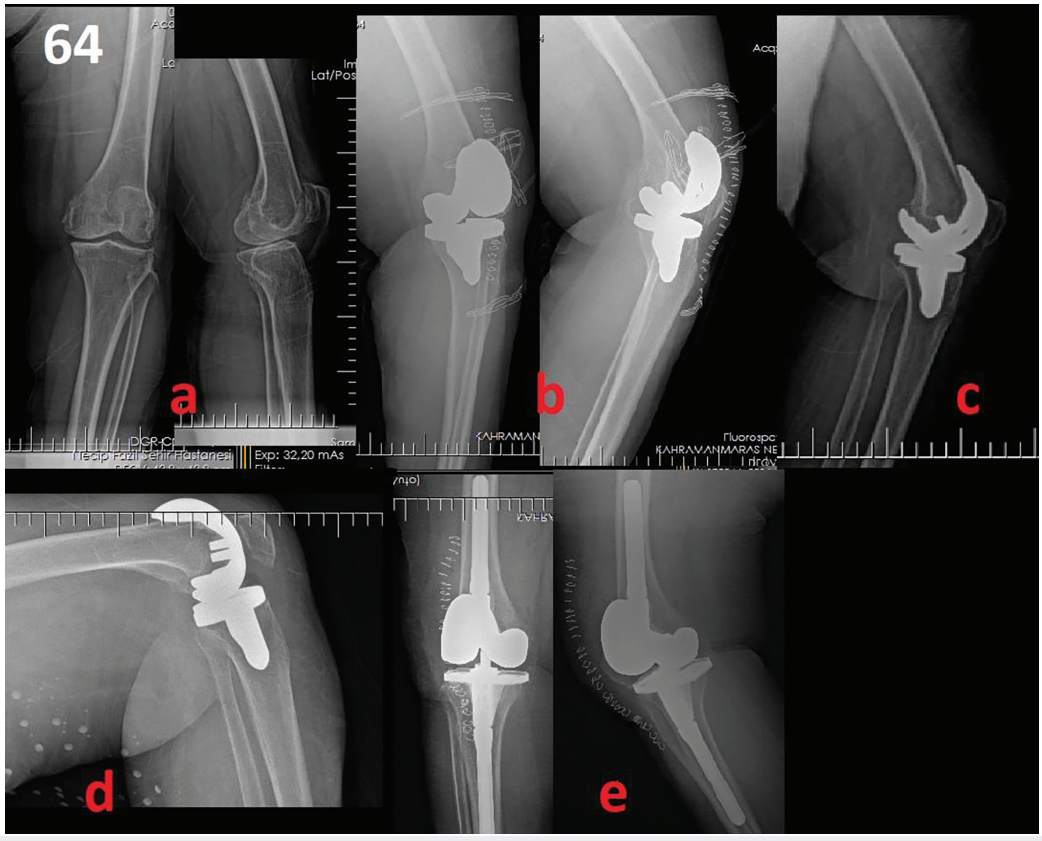


Figure 4. a) Fifty-five year old man with grade 2 arthritis b) Postoperative X-rays c) Extension loss of 40 degrees d) Flexion deformity can be seen at fifth month e) One stage revision has been made

Study Limitations

Although a thorough investigation of the patients' medical data has been conducted, the retrospective nature of our study, which lacks clinical scores and randomization, may limit the strength of our conclusions.

Conclusion

Mid-term results of a particular total knee replacement system showed satisfactory radiological outcomes, no implant-related complications, and a low revision rate. In light of these positive outcomes, it is evident that the Vision Total Knee Replacement System is a safe and effective treatment option for patients suffering from degenerative joint diseases.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Kahramanmaraş Sütçü İmam University Clinical Research Ethics Committee (decision no: 04, date: 18.06.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.N.Ü., Concept: H.T.U., M.N.Ü., Design: H.T.U., M.N.Ü., Data Collection or Processing: H.T.U., Analysis or Interpretation: H.T.U., M.N.Ü., Literature Search: H.T.U., M.N.Ü., Writing: H.T.U., M.N.Ü.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Investigation of the Correlation Between Sleep Quality and Physical Activity Level in Dialysis Patients: A Descriptive Study

Diyaliz Hastalarında Fiziksel Aktivite Düzeyi ile Uyku Kalitesi Arasındaki İlişkinin Belirlenmesi: Tanımlayıcı Bir Çalışma

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Abstract

Objective: The objective of the current research study was to evaluate the influence of physical activity levels on the quality of sleep in dialysis patients.

Methods: The study involved 70 dialysis patients, with an average age of 54.74±17.12 years on average. The Turkish version of the international physical activity questionnaire (IPAQ) was employed to measure levels of physical activity. Sleep quality was evaluated using the Pittsburgh sleep quality index (PSQI).

Results: It was determined that 64.3% of the patients slept well. The average total physical activity score was 1627.66 metabolic equivalents, indicating that patients' physical activity levels were poor. In terms of physical activity levels, no statistically significant distinction was seen between the individuals with a PSQI score of 5 or less and patients, with a score greater than 5 ($p>0.05$). However, a weak negative correlation was discovered between the average walking and total physical activity scores on the IPAQ subscales and the subjective sleep quality subscale of the PSQI. The correlation values were $r=-0.238$, $p=0.047$ for average walking, and $r=-0.241$, $p=0.045$ for total physical activity.

Conclusion: The discovery is that dialysis patients had low levels of exercise but high-quality sleep. There was no significant association between physical activity levels and the quality of sleep. More thorough and intervention-oriented studies in the future are expected to contribute to a better understanding of this link.

Keywords: Dialysis patient, physical activity, sleep quality, Pittsburgh sleep quality index, international physical activity questionnaire

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Öz

Amaç: Bu araştırma çalışmasının amacı, diyaliz hastalarında fiziksel aktivite düzeylerinin uyku kalitesi üzerindeki etkisini değerlendirmektir.

Yöntem: Çalışmaya yaş ortalaması 54,74±17,12 olan 70 diyaliz hastası dahil edilmiştir. Fiziksel aktivite düzeylerini değerlendirmek için uluslararası fiziksel aktivite anketinin (UFAA) Türkçe versiyonu kullanılmıştır. Uyku kalitesi ise Pittsburgh uyku kalitesi indeksi (PUKİ) ile değerlendirilmiştir.

Bulgular: Hastaların %64,3'ünün iyi uyuduğu belirlenmiştir. Ortalama toplam fiziksel aktivite skoru 1627,66 metabolik eşdeğer olup, hastaların fiziksel aktivite düzeylerinin düşük olduğu gösterilmiştir. Fiziksel aktivite düzeyleri açısından, PUKİ skoru 5 veya daha düşük olan hastalar ile 5'ten büyük olan hastalar arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p>0,05). Ancak, UFAA alt ölçeklerinden ortalama yürüme ve toplam fiziksel aktivite skorları ile PUKİ'nin subjektif uyku kalitesi alt ölçeği arasında zayıf negatif bir korelasyon keşfedilmiştir (r=-0,238, p=0,047; r=-0,241, p=0,045).

Sonuç: Diyaliz hastalarının düşük fiziksel aktivite düzeylerine sahip olduğu, ancak uyku kalitelerinin yüksek olduğu tespit edilmiştir. Fiziksel aktivite düzeyleri ile uyku kalitesi arasında anlamlı bir ilişki bulunamamıştır. Gelecekte yapılacak daha kapsamlı ve müdahale odaklı çalışmaların bu ilişkinin daha iyi anlaşılmasına katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: Diyaliz hastası, fiziksel aktivite, uyku kalitesi, Pittsburgh uyku kalitesi indeksi, uluslararası fiziksel aktivite anketi

Introduction

End-stage renal disease is a serious health condition defined by a glomerular filtration rate of less than 15 mL/min, severe uremic symptoms, and organ involvement[1]. In this stage, renal replacement therapy is required, with the primary goal of treatment being to extend life and maintain an ideal quality of life[2]. Despite technological breakthroughs in dialysis treatment, a variety of illness and treatment-related issues exist[3]. Sleep disorders are among the most frequent of these problems. Dialysis patients typically have sleep issues, such as sleep apnea syndrome, daytime drowsiness, insomnia, and restless leg syndrome[4].

The study found that between 50% and 80% of dialysis patients had subjective sleep disturbances, and 71% of them reported having inadequate quality of sleep[5]. Prolonged persistence of these illnesses causes daytime sleepiness and impairments in physical and mental functions in patients, lowering quality of life[6]. Furthermore, sleep disturbances might damage patients' overall health by decreasing their self-care abilities[6,7]. As a result, understanding the variables that contribute to sleep disorders, addressing them, and increasing sleep quality are critical[5].

It is commonly known that stress reduction, physical exercise, healthy eating, and health-conscious behavior all contribute to better quality of sleep[8,9]. It is commonly emphasized that physical activity makes it easier to fall asleep, and that people who exercise regularly enjoy better quality sleep[10]. Physical activity has been shown to enhance one's emotional and physical well-being[11-12]. However, research on the influence of physical activity on sleep in dialysis patients is sparse. Even while research indicates that exercise enhances the quality of sleep, it has primarily been examined as a sub-dimension of healthy living behaviors[13-17]. In the current studies, patients' physical activity levels have not been objectively measured, which precludes fully revealing the real influence of physical exercise on sleep. The current research study sought to accurately calculate dialysis patients' physical activity levels and determine how these levels affected sleep quality. Given the beneficial association between physical exercise and sleep quality, it is anticipated that this study will make an important contribution to health professionals and to the literature.

Materials and Methods

Ethical approval was given by the Aydın Adnan Menderes University Non-Interventional Clinical Research Ethics Committee (approval date: 06.05.2022; protocol number: 2022/010).

The Study Sample

The current research study group includes 104 dialysis patients who were monitored at Aydın Adnan Menderes University Faculty of Medicine, Research and Application Hospital, Department of Nephrology, Dialysis Unit, between May and November of 2022. Being at least 18, a history of hemodialysis for 6 months or more, undergoing dialysis 2 to 3 times per week, being able to communicate verbally, and not having severe mental problems (such as anxiety and depression), were the inclusion criteria of the study. The exclusion criteria were unwillingness to participate. The study enrolled 70 patients who met the inclusion criteria and agreed to participate.

Data Collection Tools

The data were collected using the patient information form, international physical activity questionnaire (IPAQ), and Pittsburgh sleep quality index (PSQI).

Patient information form: The questionnaire has two parts that were prepared by the researcher. The first section contains patients' socio-demographic information, whereas the second section contains variables connected to their disorders.

International physical activity questionnaire short form: Craig et al. (2003) designed the questionnaire, and Saglam et al.[18] investigated the validity and reliability of the Turkish versions of both the long and short forms of the questionnaire. In our study, we employed the questionnaire's short form. The short version, which consists of seven questions, collects data on the amount of time spent walking and engaging in moderate to strenuous physical activity. Individual physical activity levels were determined using metabolic equivalent (MET) values along with day and duration information for each activity. Accordingly, MET values below 600 (<600) are considered to be physically inactive, those between 600-3.000 are seen as having little physical activity, and those above 3.000 (>3.000) are considered to have a high (sufficient) level of physical activity[18].

Pittsburgh sleep quality index: This index was created by Buysse et al. (1989) and translated into Turkish by Ağargün et al.[19]. The quality of sleep was evaluated using the PSQI during the previous month. The index is divided into seven subscales: subjective quality of sleep, sleep latency, length of sleep, habitual efficiency of sleep, disruption of sleep, use of sleeping pills, and daytime sleepiness. A subscale's rating ranges from 0 to 3, and the overall score can be anywhere from 0 to 21. A cumulative score beyond five indicates inadequate quality of sleep[19]. Data were gathered through face-to-face interviews at a time convenient for the patients. Participation in the study lasted an average of 10 minutes.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics 25 (Armonk, NY: IBM Corp.). Descriptive statistics were given as mean ± standard deviation for continuous variables and frequency, and % for categorical variables. The Kolmogorov-Smirnov test was employed to assess the data's compliance with a normal distribution. The independent samples t-test was employed to examine differences between independent groups when the assumptions for parametric testing were fulfilled; if not, the Mann-Whitney U test was utilized. To examine the relationship between numerical variables, the Spearman correlation coefficient was utilized. The threshold for statistical significance was set at $p<0.05$ for every assessment.

Results

The current study investigated the effect of dialysis patients' physical activity levels, on sleep quality, and the results are shown below.

Socio-demographic and Clinical Characteristics

The patients who took part in the trial were 54.74±17.12 years old on average, 55.7% of the patients were male, 70% were primary/secondary school graduates, 71.4% were married, 70% were not employed, and 87.1% lived with their families. Ninety percent of the patients rated their socio-economic status as "moderate". In addition, 50% of the patients stated that they did not know the cause of their kidney disease, while 64.3% stated that they had comorbidities. When renal replacement therapy methods were analyzed, it was found that 21.4% of the patients received hemodialysis, 17.1% received home hemodialysis, 35.7% received hemodiafiltration, and 25.7% received peritoneal dialysis. The average duration of dialysis treatment was 3.67±2.96 years (Table 1).

Sleep Quality and Physical Activity Levels

The average PSQI total score of the patients who participated in the study was calculated as 5.2±3.32. Sixty-four point three percent of the patients had a PSQI score of 5 and below, indicating good sleep quality (Table 2).

Regarding physical activity levels, the average scores were: vigorous physical activity, 464.57±1513.48; moderate physical activity, 634.86±1287.64; walking, 528.24±779.61; and total physical activity, 1627.66±2671.12 (Table 3).

The Relationship Between Sleep Quality and Physical Activity Levels

There were no statistically significant differences in walking, moderate, or vigorous activity, according to an examination of the patients' physical activity levels in connection to their PSQI ratings ($p>0.05$). The statistical analysis indicated that there was no significant difference between (509.33±1728.99) between patients with a PSQI score of 5 or less and the average vigorous physical activity score (384±1046.14)

of patients with a PSQI score greater than 5 (p=0.793). Similarly, no statistical significance was found for moderate physical activity (p=0.621) and walking scores (p=0.852). The cumulative physical activity scores of the PSQI groups did not exhibit any significant difference (p=0.721) (Table 4).

Table 1. Socio-demographic and clinical characteristics

Variable	n	%
Age (mean ± SD, years)	54.74±17.12 (20-88)	
Gender		
Female	31	44.3
Male	39	55.7
Education level		
Primary/secondary	49	70
High school and above	21	30.0
Marital status		
Single	20	28.6
Married	50	71.4
Employment status		
Employed	21	30
Unemployed	49	70
Living situation		
Alone	9	12.9
Living with family	61	87.1
Socio-economic status		
Low	6	8.6
Medium	63	90.0
High	1	1.4
Primary kidney disease		
Unknown	35	50.0
Hypertensive nephropathy	9	12.9
Diabetic nephropathy	14	20.0
Other	12	17.1
Presence of other diseases		
Yes	45	64.3
No	25	35.7
Type of dialysis		
Hemodialysis	15	21.4
Home hemodialysis	12	17.1
Hemodiafiltration	25	35.7
Peritoneal dialysis	18	25.7
Duration of dialysis (mean ± SD, years)	3.67±2.96 (0.5-13)	

SD: Standard deviation

The Relationship Between Sleep Quality Subscales and Physical Activity

The PSQI was not significantly correlated with physical activity levels in the following subscales: subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disruption, use of sleeping medication, and daytime sleep dysfunction (p>0.05). The subjective sleep quality subscale (subscale 1) of the PSQI, however, showed a weakly significant negative correlation with walking (r=-0.238; p=0.047) and overall physical activity (r=-0.241; p=0.045) (Table 5). This finding implies that an increase in walking and overall physical activity levels leads to an enhancement in, so does the subjective perception of sleep quality.

Discussion

The goal of this research was to assess how the levels of physical exercise in dialysis patients levels of physical exercise affected their quality of sleep. Our findings are in line with previous research, but they also diverge slightly from it.

The age range of the patients involved in our study was 20 to 88 years, with an mean age of 54.74±17.12 years. Studies have demonstrated that older individuals undergoing hemodialysis often report poor sleep quality due to these factors. For example, Sert et al.[20] observed that sleep quality declines with age and is further exacerbated by comorbidities and reduced physical activity, contributing to impaired quality of life and higher mortality rates. Similarly, Sabet et al.[21] reported a high prevalence of poor sleep quality among

Table 2. Distribution of Pittsburgh sleep quality index (PSQI) scores

Variable	n	%
Good sleep quality (total PSQI ≤5)	45	64.3
Poor sleep quality (total PSQI >5)	25	35.7
Total PSQI (mean ± SD)	5.2±3.32	

PSQI: Pittsburgh sleep quality index, SD: Standard deviation

Table 3. Distribution of international physical activity questionnaire (IPAQ) scores

Variable	Mean ± SD
Vigorous physical activity	464.57±1513.48
Moderate physical activity	634.86±1287.64
Walking	528.24±779.61
Total physical activity	1627.66±2671.12

IPAQ: International physical activity questionnaire, SD: Standard deviation

Table 4. Comparison of PSQI classification and IPAQ mean scores in dialysis patients

Variable	Good sleep quality (total PSQI ≤5)	Poor sleep quality (total PSQI >5)	p
	Mean ± SD	Mean ± SD	
Vigorous physical activity	509.33±1728.99	384±1046.14	0.793 (z=-0.262)
Moderate physical activity	586.67±1141.9	721.6±1537.55	0.621 (z=-0.494)
Walking	483.27±687.23	609.18±933.22	0.852 (z=-0.186)
Total physical activity	1579.27±2830.58	1714.78±2410.68	0.721 (z=-0.357)

PSQI: Pittsburgh sleep quality index, SD: Standard deviation

Table 5. Comparison of PSQI and IPAQ mean scores in dialysis patients

Variable		PSQI subscales							
		Subjective sleep quality	Sleep latency (delay)	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleep medications	Daytime dysfunction	Total PSQI
Vigorous physical activity	r	-0.179	-0.102	0.008	0.014	0.019	-0.113	-0.061	-0.068
	p	0.138	0.401	0.948	0.910	0.879	0.353	0.616	0.578
Moderate physical activity	r	-0.148	0.006	0.004	-0.154	0.113	-0.006	-0.168	-0.059
	p	0.223	0.960	0.976	0.203	0.350	0.960	0.166	0.627
Walking	r	-0.238*	-0.117	0.023	0.052	-0.037	-0.184	-0.033	-0.126
	p	0.047	0.333	0.849	0.668	0.764	0.127	0.786	0.297
Total physical activity	r	-0.241*	-0.091	-0.036	-0.085	0.103	-0.134	-0.134	-0.132
	p	0.045	0.453	0.768	0.485	0.396	0.269	0.268	0.275

*p<0.05 indicates a statistically significant relationship; r: Spearman correlation coefficient
PSQI: Pittsburgh sleep quality index, IPAQ: International physical activity questionnaire, SD: Standard deviation

hemodialysis patients, with advanced age and associated factors as major contributors.

In contrast, the younger age of participants in our study (mean age 54.74±17.12 years) may account for their relatively better reported sleep quality. Younger individuals are often in better physical and psychological health, which could positively influence their sleep quality. This observation aligns with the findings of Parvan et al.[22], who noted that younger hemodialysis patients [average age of 58.03 (range 20-87)] tended to report better sleep quality and an improved quality of life compared to older patients.

Individuals in the younger age bracket might be in better physical and psychological health, which could have a favorable impact on the quality of their sleep.

The PSQI was employed to evaluate the participants' quality of sleep. The mean PSQI score was 5.2±3.32 (Table 2). Sixty-four point three percent of the participants obtained a PSQI score of five or lower, indicating that their sleep quality was good. Contrary to the findings of our study, a number of reports in the literature indicate that sleep issues are common among dialysis patients[4,20]. For instance, Sabet et al.[21] discovered that 73.8% of hemodialysis patients slept poorly, with a mean PSQI score of 8.39±4.04. Comparably, this rate was reported as 83.3% by Parvan et al.[22]. Eighty-one point five percent of the patients, according to Sert et al.,[20] reported poor sleep quality. We ascribe the lower rates in our study to the younger age group and lower rates of comorbidity among the participants.

The average total physical activity score was 1627.66 metabolic equivalents (METs), which suggests that the patients did not engage in high levels of physical activity (Table 3). These findings support earlier research in the literature that has shown dialysis patients typically engage in little physical exercise[11]. Cupisti et al.[23] came to the conclusion that even dialysis patients without significant physical or neurological disability or acute sickness frequently engaged in low levels of physical activity. Li et al.[24] discovered that dialysis patients were less physically active than healthy people, with notable restricted possibilities seen most noticeably in walking activities related to home chores and transportation. In a

study of hemodialysis patients, Fiaccadori et al.[25] came to realize that only 19% of patients were physically active, while 52% were not active at all.

Comparing the results of our study to those published in the literature, we also discovered decreased levels of physical activity. According to Oskay et al.[26], peritoneal dialysis patients scored 377±870 for walking, 200±217 for moderate physical activity, and 0 for strenuous physical activity. Five hundred ninety-six ± one thousand thirteen was determined to be the average overall physical activity score. Additionally, Wu et al.[27] observed that physical activity levels ≤599 MET were present in 55% of hemodialysis patients. Turkish dialysis patients showed considerably lower levels of physical activity than the healthy group, according to Daskapan et al.[28]. It was shown that just 1.4% of the dialysis patients taking part in the trial were active, while 78.12% were inactive and 20.84% were insufficient. Some of the individuals in our study engaged in more physical activity than those in earlier trials, which might be explained by the fact that the patient group was younger and in general healthier. Furthermore, we think that because the IPAQ is a memory-based evaluation instrument, it might result in different computations. Therefore, it is advised to increase the accuracy of physical activity level by utilizing more dependable instruments, such as accelerometers[29].

According to an examination of the connection between physical activity and sleep quality (Table 4), there was no discernible difference in physical activity levels between the group with a PSQI score of five or less and the group with a score above five ($p>0.05$). This suggests that low physical activity does not have a significant effect on sleep quality. Walking and total physical activity scores showed a significant, albeit weak, negative correlation with the PSQI's subscale 1 (subjective sleep quality) ($r=-0.238$, $p=0.047$; $r=-0.241$, $p=0.045$) (Table 5). This suggests that people who walk more may perceive their sleep quality better. Studies have also shown that low-intensity activities, like walking, have a positive impact on sleep quality[15]. The poor link between physical activity and sleep quality, however, raises the possibility that other biological or psychological variables may be significant sleep determinants.

Studies examining the effects of exercise on sleep in dialysis patients are scarce in the literature. Research has shown that when patients' levels of physical activity rose, so did the quality of their sleep[13-17]. Nonetheless, physical activity has been evaluated as a subscale of healthy living practices in the research that is currently accessible[9,13,17]. The patients' levels of physical activity have not been computed. We believe that these evaluations are inadequate to ascertain the real-world impact of exercise on dialysis patients' sleep quality.

Rezaie and Naji's[30] study on hemodialysis patients reported no significant link between physical exercise and the quality of sleep, which is consistent with our study results. The lack of a significant correlation between low physical activity levels and sleep quality in our study might be explained by the individuals' generally modest activity levels.

Study Limitations

Only dialysis patients treated between May and November 2022 in the Nephrology Department, Dialysis Unit, Research and Application Hospital, Faculty of Medicine, Aydın Adnan Menderes University, were included in the study. As a result, the findings are limited to this particular patient population and might not directly apply to dialysis patients in other regions or with other demographic traits.

The study aimed to provide a general perspective on the relationship between physical activity levels and sleep quality rather than controlling for all factors influencing sleep quality. Therefore, group homogeneity was not ensured, and factors such as comorbidities, smoking, and alcohol use were not assessed in detail. Additionally, although it is well-known that post-dialysis fatigue can directly impact sleep quality, this study did not perform a detailed evaluation of general fatigue levels. Future studies should comprehensively address such factors to gain a better understanding of the biological and psychosocial variables influencing sleep quality.

Conclusion

The current study found that dialysis patients frequently had low levels of physical activity and poor sleep quality. Because of the low comorbidity rates and the young average age of the patient group, the results differed from those of previous studies in the literature. It has been noted that increasing the amount of exercise performed can improve the quality of sleep, but the effect must be substantial.

Furthermore, the study's cross-sectional design makes it more difficult to establish a clear link between increased physical activity and better sleep. Therefore, longer-term, intervention-based studies are needed to provide a deeper knowledge of the relationship between physical activity and

quality of sleep in dialysis patients. Such further study will help shape to improve the quality of life for dialysis patients. It is expected that this research will open doors for greater sample sizes and more in-depth studies.

Ethics

Ethics Committee Approval: This randomized controlled trial was conducted in accordance with the principles outlined in the Declaration of Helsinki. Study presentation followed the guidelines set by the Consolidation Standards of Reporting Trials (CONSORT). Ethical approval was given by the Aydın Adnan Menderes University Non-Interventional Clinical Research Ethics Committee (approval date: 06.05.2022; protocol number: 2022/010).

Informed Consent: Since the study was conducted retrospectively, no formal written informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Concept: A.K., N.Ö., Z.G.Z., Design: A.K., N.Ö., Z.G.Z., Data Collection or Processing: A.K., N.Ö., Z.G.Z., Analysis or Interpretation: A.K., N.Ö., Z.G.Z., Literature Search: A.K., N.Ö., Z.G.Z., Writing: A.K., N.Ö., Z.G.Z.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Comparison of Onset Times and Hemodynamic Changes of Bupivacaine and Levobupivacaine Used in Spinal Anesthesia

Spinal Anestezide Kullanılan Bupivakain ve Levobupivakainin Başlangıç Süreleri ve Hemodinamik Değişikliklerinin Karşılaştırılması

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Abstract

Objective: The present study compared the motor and sensory onset times and hemodynamic effects of bupivacaine and levobupivacaine used in spinal anesthesia. The aim was to assess whether levobupivacaine is a safer alternative.

Methods: The study included 50 patients who were classified as American Society of Anesthesiologists I-II and scheduled for inguinal hernia surgery. The patients were divided into two groups as bupivacaine (0.5%) and levobupivacaine (0.5%). In both groups, motor and sensory block onset times and hemodynamic parameters were evaluated following the administration of spinal anesthesia.

Results: In the levobupivacaine group, the motor block onset time was found as 8.99 minutes and the sensory block onset time as 8.47 minutes. In the bupivacaine group, these times were recorded as 3.54 minutes and 3.26 minutes, respectively ($p<0.001$). No significant difference was found between the groups in terms of hemodynamic parameters. Despite having longer motor and sensory block onset times compared to bupivacaine, levobupivacaine achieved adequate anesthesia, with no difference between the two groups in terms of hemodynamic changes.

Conclusion: Levobupivacaine has been shown to be an effective and safe alternative in spinal anesthesia. However, there is a need for larger-scale studies to generalize these findings.

Keywords: Bupivacaine, levobupivacaine, spinal anesthesia

Öz

Amaç: Bu çalışmada spinal anestezide kullanılan levobupivakain ve bupivakainin motor ve duysal blok başlangıç süreleri ile hemodinamik etkileri karşılaştırılmıştır. Amaç, levobupivakainin daha güvenli bir alternatif olup olmadığını değerlendirmektir.

Yöntem: Çalışmaya inguinal herni operasyonu planlanan, Amerikan Anestezistler Derneği I-II sınıflandırmasındaki 50 hasta dahil edilmiştir. Hastalar bupivakain (%0,5) ve levobupivakain (%0,5) olmak üzere iki gruba ayrılmıştır. Her iki grupta da spinal anestezi uygulandıktan sonra motor ve duysal blok başlangıç süreleri ile hemodinamik parametreler değerlendirilmiştir.

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Öz

Bulgular: Levobupivakain grubunda motor blok başlangıç süresi 8,99 dakika, duysal blok başlangıç süresi ise 8,47 dakika olarak tespit edilmiştir. Bupivakain grubunda bu süreler sırasıyla 3,54 ve 3,26 dakikadır (p<0,001). Gruplar arasında hemodinamik parametrelerde ise anlamlı bir fark bulunmamıştır. Levobupivakainin motor ve duysal blok başlangıç sürelerinin bupivakainin sürelerine göre daha uzun olmasına rağmen anestezi yeterliliği sağlamış, hemodinamik değişiklikler açısından her iki grup arasında fark gözlenmemiştir.

Sonuç: Levobupivakain, spinal anestezide etkili ve güvenli bir alternatif olarak değerlendirilmektedir. Ancak, bu bulguların genellenebilirliği için daha geniş ölçekli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Bupivakain, levobupivakain, spinal anestezi

Introduction

Spinal anesthesia is a reliable regional anesthesia technique commonly preferred for lower abdominal and lower extremity surgeries, providing effective neural blockade and minimizing side effects when local anesthetics are administered in appropriate doses[1]. Bupivacaine is widely utilized in spinal anesthesia due to its prolonged duration of action and effectiveness as a local anesthetic. Levobupivacaine, the S(-) enantiomer of bupivacaine, exhibits similar pharmacokinetic and pharmacodynamic characteristics, but is suggested to offer a more favorable safety profile regarding adverse effects[2-4]. Despite all these advantages, it is not commonly used in routine spinal anesthesia practice[5]. This study aimed to evaluate the motor and sensory block onset times and hemodynamic effects of bupivacaine and levobupivacaine following intrathecal administration in order to determine the reliability of levobupivacaine as a potential alternative. In addition, we aimed to provide guidance for clinical practice by contributing to the limited number of comparative studies in the literature.

Materials and Methods

This study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital and was carried out in compliance with the principles outlined in the Declaration of Helsinki (decision no: 12/07, date: 12.11.2007). All the patients were informed about the procedures to be performed and their written consent was obtained according to ethical standards. A total of 50 patients aged between 18 and 65 years, classified as American Society of Anesthesiologists (ASA) physical status I-II and scheduled for elective inguinal hernia repair without any contraindications to spinal anesthesia, were enrolled in the study. Patients who required intraoperative conversion to general anesthesia were excluded.

All the patients underwent preoperative anesthesia assessment one day before the surgery. Each patient was given 10 mL/kg of crystalloid solution over 30 minutes, one hour before being taken to the operating room. Once at the operating table, the patients were administered 0.03 mg/kg of midazolam intravenously for premedication.

Standard monitoring in general anesthesia (electrocardiogram, non-invasive blood pressure and pulse oximetry) was performed while demographic data [gender, age, height, weight, body mass index (BMI)] were recorded at the operating table. Prior to spinal anesthesia, patients' systolic, diastolic, and mean arterial pressures, as well as pulse rates, were measured and recorded using Petaş® KMA 800 monitors, which the company calibrates monthly. All preparations for a potential conversion to general anesthesia were prepared before initiating spinal anesthesia.

Spinal anesthesia was performed with the patient in the sitting position. While in this position on the operating table, the lumbar region was prepared using an antiseptic solution and then covered with a sterile drape. Later, a 22-gauge Quincke-Babcock type spinal needle (Spinocan®, Braun, Melsungen, Germany) was inserted at the L3-L4 interspace using the median approach, and cerebrospinal fluid flow was monitored. Following this, 3 mL (15 mg) of isobaric 0.5% bupivacaine (Marcaine®) was administered to the 25 patients in Group A and 3 mL (15 mg) of 0.5% levobupivacaine (Chirocaine®) was injected into the other 25 patients in Group B. Spinal anesthesia administration was performed on all patients by a single senior assistant.

Once the procedure was completed, patients were placed on the operating table in the supine position with a 30-degree tilt. Patients' sensory block levels were checked every 30 seconds using the pinprick test. The time from the intrathecal injection to the moment when pain sensation was completely lost was recorded as the sensory block onset time.

Similarly, patients' motor blocks were assessed every 30 seconds using the modified Bromage score. The time when they reached Bromage level 2-3, was defined as the motor block onset time (Table 1).

Postoperative systolic, diastolic, and mean arterial pressures, along with heart rates, were monitored and recorded at 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, and 120 minutes. In cases where hypotension developed during the operation (defined as a reduction in systolic arterial pressure exceeding 30% relative to baseline values), patients were immediately administered 200 mL of isotonic solution in 10 minutes. If the intervention failed to correct the condition, 5 mg of ephedrine was administered intravenously. Bradycardia (a condition where the heart rate is below 45 bpm) was treated with 0.5 mg of intravenous atropine administration.

Statistical Analysis

The analyses were conducted using the SPSS IBM Statistics 25 software. Statistical analyses were performed using the Student's t-test, paired t-test, Fisher's exact test, and chi-square test, where appropriate. A p-value less than 0.05 was considered indicative of statistical significance.

Results

Demographic data of the patients show that 38 of them were male (20 in the bupivacaine group, 18 in the levobupivacaine group), while 12 were female (5 in the bupivacaine group and 7 in the levobupivacaine group). The mean age of patients was 47.68±15.92 in the bupivacaine group and 38.76±15.65 in the levobupivacaine group. According to the ASA classification, in the bupivacaine group, 21 patients were classified as ASA I, 4 patients as ASA II; while 22 patients were classified as ASA I and 3 patients as ASA II in the levobupivacaine group. The distribution of the two groups was comparable with respect to age, sex, height, weight, BMI, and ASA classification (Table 2). Following the intrathecal administration, the mean motor block onset time in the levobupivacaine group was 8.99 minutes, and the mean sensory block onset time was 8.47 minutes. In the bupivacaine group, on the other hand, the mean motor block onset time was found to be 3.54 minutes, and the mean sensory block onset time was found to be 3.26 minutes. These results indicate that the mean onset times for both motor and sensory blocks were significantly longer in the levobupivacaine group compared to the bupivacaine group (p<0.001) (Table 3). At the 10th minute, 12% of the patients in the levobupivacaine group had a modified Bromage score of 3, while 76% of the patients in the bupivacaine group had a modified Bromage score of 3. At the end of 120 minutes, the modified Bromage score was still 2 in 20% of the patients in the levobupivacaine group, while 100% of the patients had a modified Bromage score of 3 in the bupivacaine group (Table 4). When the hemodynamic parameters were compared between the groups, no significant difference was found in their systolic, diastolic, mean arterial pressure, and heart rate values at any point (p>0.05) (Figures 1, 2). In the levobupivacaine group, a significant decrease in hemodynamic values compared to the pre-intrathecal application values was observed; systolic pressure, and mean arterial pressure decreased from the first minute onward and diastolic pressure decreased from the fifth minute onward. Heart rate showed a significant decrease during the first 5 minutes, but no significant difference was observed in the following time intervals.

A significant decrease in systolic pressure was observed throughout all time intervals after intrathecal administration in the bupivacaine group, compared to the pre-intrathecal application hemodynamic values. The mean arterial pressure and diastolic pressure showed a significant decrease from the first minute onward. A significant decrease was detected in the heart rate from the 10th minute onwards. There was no statistically significant difference between the groups

Table 1. Modified Bromage score

0	No paralysis, the patient can fully flex the knees and feet.
1	Can move only knees and feet, cannot lift the leg straight.
2	Cannot flex the knee, can only move the foot.
3	Cannot move the ankle or the big toe, complete paralysis.

Table 2. Patients' demographic characteristics

	Bupivacaine group	Levobupivacaine group	p
	Mean ± SD	Mean ± SD	
Age	47.68±15.92	38.76±15.65	0.051
Height	169.32±9.40	171.44±8.39	0.404
Weight	72.28±12.36	74.08±11.69	0.599
BMI	25.24±4.02	25.26±4.13	0.983

SD: Standard deviation, BMI: Body mass index

Table 3. Motor and sensory block onset times

	Bupivacaine group	Levobupivacaine group	p
	Mean ± SD	Mean ± SD	
Motor block onset time (min)	3.54±1.86	8.99±5.41	0.000
Sensory block onset time (min)	3.26±1.78	8.47±5.25	0.000

SD: Standard deviation, min: Minute

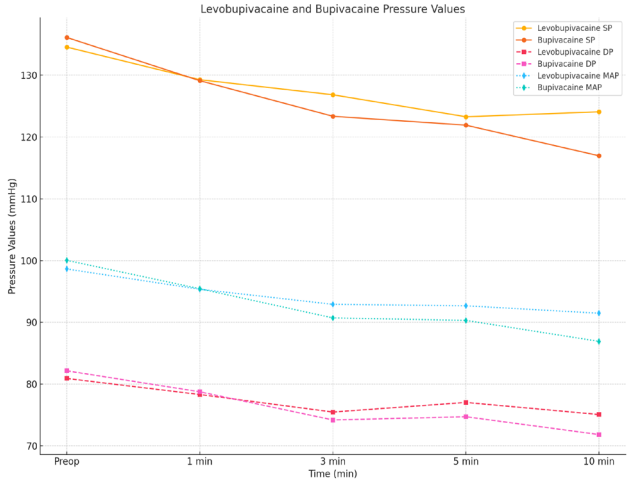

Figure 1: Levobupivacaine and bupivacaine pressure values

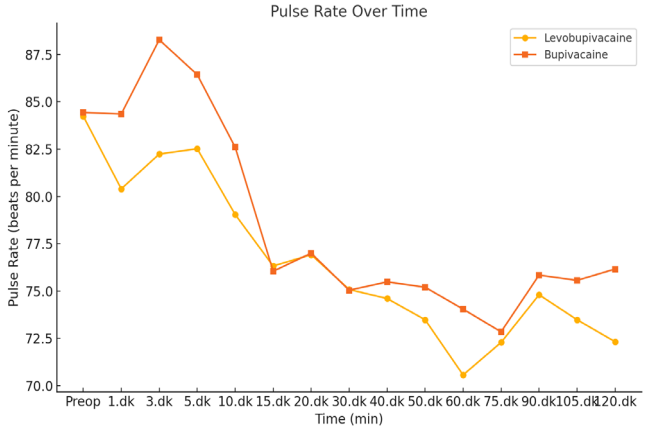

Figure 2: Pulse rate comparison between groups

regarding the requirement for additional medication (ephedrine hydrochloride) (p>0.05) (Table 5).

Discussion

Local anesthetics used for blockade in spinal anesthesia typically exhibit a low side-effect profile when administered in appropriate doses and with proper attention[6,7]. Bupivacaine local anesthetics, is one of the most preferred agents due to its ability to provide sufficient anesthesia and analgesia for medium to long-duration surgical procedures. Levobupivacaine, on the other hand, is the S(-) enantiomer of bupivacaine and shares similar pharmacokinetic properties with racemic bupivacaine. Nonetheless, evidence from *in vitro* studies, animal experiments, and clinical research suggests that levobupivacaine is associated with a reduced risk of cardiotoxicity and central nervous system toxicity when compared to bupivacaine[2-4,8,9]. Additionally, the median lethal dose of levobupivacaine (LD50) has been found to be approximately 50% higher than that of bupivacaine, and hemodynamic changes have been reported to be similar between the two agents after spinal anesthesia[4,5,10-13]. The results indicate that levobupivacaine may serve as a viable alternative, particularly in patients with elevated perioperative risk profiles.

Several randomized controlled trials have investigated the onset and duration of sensory and motor blockade, as well as the adequacy of anesthesia, with levobupivacaine and racemic bupivacaine[14-23]. Some of these studies have indicated that there is no statistically significant difference between levobupivacaine and bupivacaine regarding the onset times of sensory and motor block following intrathecal administration[14]. However, in our study, it was found

Table 4. Motor block status at the 10th and 120th minutes

		Bupivacaine group		Levobupivacaine group		p
		n	%	n	%	
Motor block at the 10th minute	Bromage 2	6	24	22	88	0.000
	Bromage 3	19	76	3	12	
Motor block at the 120th minute	Bromage 2	0	0	5	20	0.050
	Bromage 3	25	100	20	80	

Table 5. Additional medication needs

Vasopressor need	Bupivacaine group		Levobupivacaine group		p
	n	%	n	%	
Yes	20	84	21	80	0.050
No	5	16	4	20	

that the onset times of motor and sensory blockade for levobupivacaine were approximately twice as long as those for bupivacaine. This finding suggests that levobupivacaine could have different pharmacodynamic properties. The S(-) enantiomer configuration of levobupivacaine may alter receptor binding kinetics and agent efficacy, potentially explaining the difference in onset times. Since levobupivacaine provided sufficient anesthesia despite its longer onset time, we did not consider it to be a clinically significant issue.

Studies have indicated that both the initiation and resolution of spinal anesthesia are influenced by the administered dose of local anesthetics. While certain randomized controlled trials have found comparable durations of sensory and motor blockade, as well as overall anesthetic efficacy, between levobupivacaine and racemic bupivacaine, other investigations have reported that levobupivacaine may produce a more prolonged sensory block alongside a relatively shorter motor block[23-27]. In our study, there were no meaningful differences observed between the groups regarding the effectiveness of anesthesia or the length of sensory and motor blockade at 120 minutes. Although statistical significance was not reached, 88% of individuals receiving levobupivacaine exhibited a modified Bromage score of 2 at 10 minutes post-injection, and 20% maintained the score at 120 minutes. On the other hand, all patients in the bupivacaine group were observed to have a Bromage score of 3 at the 120th minute. While this does not affect anesthesia adequacy, it may suggest that levobupivacaine could offer an advantage for patients requiring early postoperative mobilization.

With respect to the hemodynamic impact of levobupivacaine, our results were consistent with existing literature, showing a comparable profile to that of racemic bupivacaine. In both groups, slight decreases in mean arterial pressure and heart rate were recorded following intrathecal administration, yet these fluctuations did not reach statistical significance regarding cardiovascular stability[17,18,21]. According to prior studies, the most frequently encountered adverse effects associated with spinal anesthesia include hypotension, bradycardia, shivering, nausea, and vomiting. However, the incidence rates of these effects did not differ meaningfully between patients receiving levobupivacaine and those administered bupivacaine. Particularly, hypotension has been reported to occur frequently in spinal anesthesia, and a randomized controlled study found that it developed in approximately 80% of the cases[28]. Thus, international guidelines recommend prophylactic use of intravenous fluid loading and vasopressors (ephedrine hydrochloride)[29]. In the present study, the requirement for vasopressor support was found to be comparable between the two groups.

Study Limitations

The research was conducted at a single institution and involved a relatively small number of participants. It covered only certain types of surgeries (elective surgeries) and excluded patients in the higher-risk group (e.g., ASA III and IV). Moreover, the potential effects of preoperative adjunct agents such as midazolam on the efficacy of local anesthetics were not investigated in the present study, which can be considered a significant limitation limiting the generalizability of the study findings.

Conclusion

Levobupivacaine and racemic bupivacaine are local anesthetics that can be used effectively and safely in spinal anesthesia. In our study, levobupivacaine was found to have a longer onset time for motor and sensory blockade compared to bupivacaine. However, this difference did not compromise anesthesia adequacy. Levobupivacaine may offer advantages for early postoperative mobilization. No meaningful statistical variation was observed between the groups in terms of cardiovascular response. Owing to its lower likelihood of inducing cardiac or central nervous system-related toxicity, levobupivacaine emerges as a promising option, especially for individuals with elevated perioperative risk. These findings support the effective and safe use of levobupivacaine in spinal anesthesia; however, there is a need for larger-scale studies involving various surgical indications.

Ethics

Ethics Committee Approval: It can be obtained from the relevant author upon request. This study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital and was carried out in compliance with the principles outlined in the Declaration of Helsinki (decision no: 12/07, date: 12.11.2007).

Informed Consent: All the patients were informed about the procedures to be performed and their written consent was obtained according to ethical standards.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Analysis of Adult Trauma Patients Carried by Helicopter Ambulance According to GAP Score

Helikopter Ambulansıyla Taşınan Yetişkin Travma Hastalarının GAP Skoruna Göre Analizi

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Abstract

Objective: The aim of the scoring systems used in prehospital triage of trauma patients is to determine the patients with treatment priority. The Glasgow Coma scale/age/systolic blood pressure (GAP) score is a physiological scoring system used for this purpose. In this study, the usability of the GAP score in determining the patients with treatment priority in trauma patients transported by helicopter ambulance was examined.

Methods: This study was conducted retrospectively with 151 trauma patients transported from the scene by helicopter ambulance between 01.10.2021-01.10.2023. The patients' age, gender, type of trauma and injury, blood pressure, Glasgow Coma scale, injury site, and time of death of dead patients were recorded. The patients' GAP scores were calculated and their severity was examined. The usability of the GAP score in helicopter ambulance assignments was evaluated.

Results: One hundred and fifty one patients were included in the study. The mean age of the patients was 51.8. 68.9% of the patients were male. 5.2% (n=8) of the patients died within 30 days. It was determined that the GAP score was determinative in mortality prediction with 98% sensitivity and 83.9% specificity when the cut-off value was 2 and below (p<0.001).

Conclusion: The GAP score, based on physiological parameters and quickly calculable, can be utilized in helicopter ambulance services. By using the GAP score, unnecessary helicopter ambulance transfers can be prevented. Additionally, it can minimize time lost in identifying severely injured trauma patients, thereby preventing treatment delays.

Keywords: Glasgow coma scale/age/pressure score, helicopter ambulance, trauma, transfer

Öz

Amaç: Travma hastalarının hastane öncesi triyajında kullanılan puanlama sistemlerinin amacı, tedavi önceliği olan hastaları belirlemektir. Glasgow Koma skalası/yaş/basınç (GAP) skoru bu amaçla kullanılan fizyolojik bir puanlama sistemidir. Bu çalışmada, helikopter ambulansla taşınan travma hastalarında tedavi önceliği olan hastaları belirlemede GAP skorunun kullanılabilirliği incelenmiştir.

Yöntem: Bu çalışma, 01.10.2021-01.10.2023 tarihleri arasında helikopter ambulansla olay yerinden taşınan 151 travma hastası ile retrospektif olarak yürütülmüştür. Hastaların yaşı, cinsiyeti, travma ve yaralanma türü, kan basıncı, Glasgow Koma skalası, yaralanma yeri ve ölen hastaların ölüm zamanı kaydedilmiştir. Hastaların GAP skorları hesaplanmış ve şiddetleri incelenmiştir. GAP skorunun helikopter ambulans görevlendirmelerinde kullanılabilirliği değerlendirilmiştir.

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Öz

Bulgular: Çalışmaya 151 hasta dahil edilmiştir. Hastaların ortalama yaşı 51,8'dir. Hastaların %68,9'u erkektir. Hastaların %5,2'si (n=8) 30 gün içinde öldü. Kesme değeri 2 ve altında olduğunda GAP skorunun %98 duyarlılık ve %83,9 özgüllükle mortalite tahmininde belirleyici olduğu belirlendi (p<0,001).

Sonuç: Fizyolojik parametrelere dayalı ve hızlı bir şekilde hesaplanabilen GAP skoru, helikopter ambulans hizmetlerinde kullanılabilir. GAP skoru kullanılarak gereksiz helikopter ambulans nakilleri önlenebilir. Ayrıca, ağır yaralı travma hastalarının belirlenmesinde kaybedilen zamanı en aza indirebilir ve böylece tedavi gecikmelerinin önüne geçilebilir.

Anahtar Kelimeler: Glasgow koma skalası/yaş/basınç skoru, helikopter ambulans, travma, transfer

Introduction

Trauma ranks as the third leading cause of death across all age groups, following cardiovascular diseases and cancer, and is the leading cause of death among individuals aged 1-44 years[1]. Trauma predominantly affects young individuals and results in significant loss of workforce productivity[2]. Advances in healthcare suggest that trauma will remain one of the most prevalent causes of morbidity in the coming years[3].

Severe traumatic injuries primarily result from traffic accidents, firearm injuries, penetrating and sharp object injuries, falls, and assaults. According to the World Health Organization (WHO), the global annual death toll from road traffic accidents reached approximately 1.35 million in 2016, marking a record high[4]. This represents a significant increase compared to the estimated 1.15 million annual deaths reported by WHO in 2000[4].

Studies have shown that delays in hospital admission or definitive treatment for patients with severe traumatic injuries exacerbate potentially preventable outcomes[5]. Notably, 55.1% of preventable or potentially preventable deaths in prehospital settings have been attributed to hemorrhage[6]. In acute care settings, the majority of preventable deaths are associated with hemorrhage (28.4%), multiple organ dysfunction syndrome or sepsis (23.6%), and traumatic brain injury (21.2%), collectively accounting for 73.2% of preventable deaths[6].

To assess mortality risk in trauma patients, various trauma scoring systems have been developed[7]. These systems are typically based on anatomical and physiological parameters or a combination of both. Physiological scoring systems offer the advantage of being quick and easy to calculate.

The Glasgow Coma score (GCS), one of the most commonly used physiological scoring systems, evaluates the patient's ocular, verbal and motor responses[8]. Advanced age increases the risk of mortality in patients with similar trauma severity, whereas systolic blood pressure serves as an early indicator of shock. Due to the rapid variability of these three parameters, the GCS/age/systolic blood pressure (GAP) score has been reported as an effective tool for early prognosis[9,10]. The GAP score, derived from the initials of GAP, was introduced by Kondo et al.[8] in a multicenter study conducted in 114 centers in Japan.

Time lost during the transportation of trauma patients remains a critical issue. To minimize delays, helicopter ambulances are utilized in addition to ground ambulances[11]. The high costs of helicopter ambulance services impose a substantial economic burden on healthcare systems; therefore, their utilization must be carefully planned[12].

This study aims to investigate the relationship between the GAP score and patient prognosis among adult trauma patients transported via helicopter ambulance. Additionally, it seeks to evaluate the utility of the GAP score in minimizing time lost during the hospital transfer of critically injured trauma patients, thereby optimizing the use of helicopter ambulance services.

Materials and Methods

This retrospective study focused on adult trauma patients transported from the scene of injury by helicopter ambulance between October 1, 2021, and October 1, 2023. Patients with missing data and those under 18 years of age were excluded.

Ethical approval for the study was obtained from University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval number: AEŞH-EK1-2023-649, date: 01.11.2023). The study adhered to the ethical principles outlined in the Helsinki Declaration.

Patients included in the study were identified using the Ministry of Health's Emergency Health Automation System. The recorded data included patients' age, sex, type of trauma, trauma mechanisms, affected body regions, GAP, whether the patient had multiple traumas, and the location

and timing of death for deceased patients. The GAP scores were calculated, and mortality within 30 days was assessed. Information regarding interventions and 30-day mortality status was obtained via the Ministry of Health's e-Nabız system.

All adult trauma patients transported by helicopter ambulance from the scene to the hospital were included. In cases where the helicopter could not land directly at the scene, patients were first transported by ground ambulance to a suitable landing site. No exclusion criteria were set based on flight time or distance. GAP scores were calculated and categorized, and their predictive accuracy for patient prognosis was analyzed. Additionally, the study evaluated whether the GAP score could guide helicopter ambulance services to improve cost-efficiency and reduce delays in treating critically injured trauma patients.

The GAP score is determined by scoring GAP (Table 1). Based on this scoring system, patients are categorized into three groups: low risk of mortality (19-24 points), medium risk (11-18 points), and high risk (3-10 points).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 27 (IBM Inc., Chicago, IL, USA). Non-parametric tests were applied to variables that did not follow a normal distribution. Descriptive statistics were presented as the mean and standard deviation for normally distributed numerical data, median and minimum-maximum values for non-normally distributed numerical data, and numbers and percentages for categorical data.

For non-normally distributed numerical variables, the Mann-Whitney U test was used for two-group comparisons, and the Kruskal-Wallis test was used for three-group comparisons. Categorical data were analyzed using the Pearson chi-square test or Fisher's exact test for two-group comparisons.

To evaluate the suitability of the GAP score in predicting mortality among trauma patients transported by helicopter ambulance, a receiver operating characteristic (ROC) analysis was performed, and the area under the curve (AUC) was calculated. Statistical significance was defined as a p-value of <0.05.

Results

A total of 151 patients were included in the study. The mean age of the patients was 51.8±18.4 years. Of the patients, 68.9% were male. The patients' injuries were classified into 84.2% (n=127) blunt and 15.8% (n=24) penetrating categories. Falling was the most common reason for admission, accounting for 43% (n=65) of the cases. Other trauma causes included traffic accidents outside vehicles (motorcycle, bicycle, pedestrian, etc.) at 23.2%, in-vehicle traffic accidents at 14.6%, gunshot wounds at 4.6%, stab wounds at 11.3%, and assault at 3.3%.

The most frequently injured region was the extremities in 71.5% (n=108) of the patients. Head-neck injuries were the second most frequent at 38.4%, and thoracic injuries ranked third at 22.5%. Multiple trauma was present in 35.1% (n=53) of the patients. Eight patients (5.2%) died within 30 days of follow-up. Of these, 5 patients (3.3%) died in the emergency department. Upon examining the vital signs of the patients included in the study, the average systolic blood pressure was 118±19 mmHg, and the average diastolic blood pressure was 74±12 mmHg. The mean GCS score of the patients was 14 (min: 3-max: 15) (Table 2).

The GAP scores of the patients included in the study were evaluated. Four patients were in Group 1, 27 patients in Group 2, and 120 patients in Group 3. All patients in Group 1 and four patients in Group 2 died within 30 days of follow-up (p<0.001) (Table 3).

When mortality rates were compared based on trauma mechanisms, gunshot wounds ranked first with a mortality rate of 14.3%. Stab wounds ranked second with a mortality rate of 5.9%.

When mortality was evaluated according to the injury region, abdominal injuries were the leading cause with a mortality rate of 31.6% (p<0.001). Pelvic injuries were the second most common cause of mortality, with a rate of 28.6% (p=0.005) (Table 3).

When the relationship between trauma and mortality was further examined, six of the patients who died had multiple trauma. Mortality was significantly higher in patients with

Table 1. GAP score

Glasgow Coma scale	3-15	3-15 points
Age	<60 years	3 points
	>60 years	0 points
Systolic blood pressure	>120 mmHg	6 points
	60-120 mmHg	4 points
	<60 mmHg	0 points

GAP: Glasgow Coma scale/age/systolic blood pressure

multiple trauma (p<0.001). The ROC curve for the GAP score in predicting mortality, along with its sensitivity and specificity findings, is shown below (Figure 1), as well as being presented in Table 4.

Discussion

The findings of our study reveal the relationships between trauma mechanisms, injury regions, and mortality outcomes. In the cohort analysis, the predominance of blunt trauma reflects the impact of falls and traffic accidents. However, penetrating injuries, particularly firearm-related injuries, were associated with significantly higher mortality rates. This underscores the critical need for tailored management strategies and rapid response protocols for high-risk injuries. Abdominal and pelvic injuries emerged as the most significant predictors of mortality, with rates of 31.6% and 28.6%, respectively. This finding highlights the vulnerability of these regions due to the presence of vital organs and major blood vessels. Early diagnosis and timely surgical interventions for abdominal and pelvic trauma are crucial in improving survival rates. Mortality rates were found to be significantly higher in patients with multiple traumas. The complexity of managing injuries involving multiple anatomical regions emphasizes the importance of establishing a comprehensive trauma system and utilizing advanced resuscitation techniques. The GAP score demonstrated exceptional accuracy in predicting mortality. Integrating this score into emergency care protocols could enable clinicians to allocate resources more effectively and prioritize interventions. We believe that such integration would provide a substantial contribution, particularly in the early identification of high-risk patients and the delivery of optimal care. Trauma continues to be one of the leading causes of premature death and disability worldwide[13], largely due to its potential to result in severe and fatal conditions. In our study, the evaluation of patients' mortality status revealed that abdominal and pelvic injuries emerged as the most significant predictors of mortality, with rates of 31.6% and 28.6%, respectively.

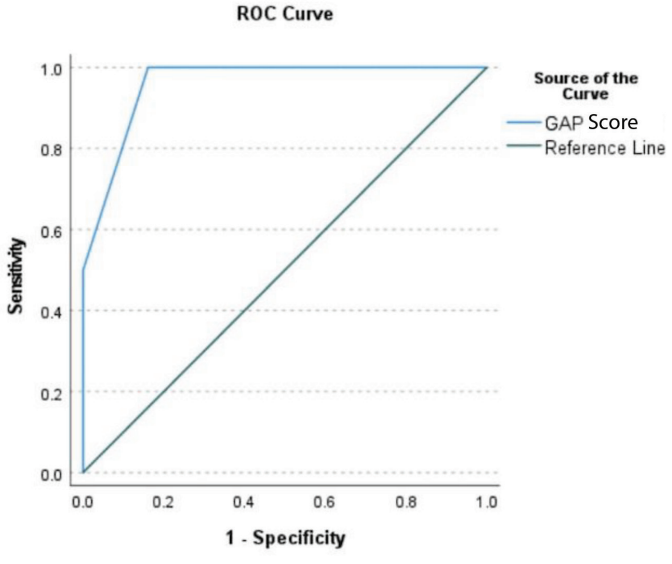

Figure 1. ROC analysis graph of GAP score according to mortality status

GAP: Glasgow Coma scale/age/systolic blood pressure, ROC: Receiver operating characteristic

One-third of trauma-related deaths occur immediately after the injury[14]. To address this critical time frame, helicopter ambulances are utilized for the rapid transportation of patients[15]. However, the use of helicopter ambulances incurs significant costs[16,17]. Proper planning for the allocation of patients and ambulances is essential to ensure the efficient use of resources. Studies have shown that the majority of trauma patients transported from the scene by helicopter ambulances are stable and do not require urgent care[18]. These findings highlight the need for a scoring system capable of accurately predicting patient prognosis in the field to optimize the cost-effective utilization of helicopter ambulances.

In our study, the role of the GAP score in predicting mortality was demonstrated. Incorporating the GAP score into practice for helicopter ambulance transportation could serve as a guide for future multicenter studies involving a larger patient population to further validate its utility and effectiveness.

Studies examining the relationship between gender and trauma have shown that adults, particularly males, are more frequently exposed to trauma[19]. This may be attributed to the higher likelihood of males engaging in high-risk activities, making them more susceptible to accidents resulting in trauma. Similarly, in our study, the majority of trauma patients transported by helicopter ambulance were male. This finding aligns with the existing literature suggesting that males are more prone to trauma. Previous studies have reported that the average age of trauma patients is generally below 40 years[20]. However, in our study, the mean age of trauma patients was found to be 51.8 years. This discrepancy may be explained by the exclusion of patients under the age of 18 in our study. This observation likely reflects differences

Table 2. Demographic characteristics of the patients		
		All patients (n=151) **Mean ± SD**
Age		51.8±18.4
Gender	Male	68.9% (104)
	Female	31.1% (47)
Vitals	Systolic blood pressure	118±19 mmHg*
	Diastolic blood pressure	74±12 mmHg
Glasgow Coma scale		14 (min: 3-max: 15)
Mortality		8 (5.2%)
Type of trauma	Blunt	84.2% (127)
	Penetrating	15.8% (24)
Trauma mechanism	Fall	43% (65)
	Non-vehicle traffic accidents	23.2% (35)
	In-vehicle traffic accidents	14.6% (22)
	Gunshot wounds	4.6% (7)
	Stab wounds	11.3% (17)
	Assault	3.3% (5)
Multitrauma		35.1% (53)
Injury site	Head-neck	38.4% (58)
	Thoracic	22.5% (34)
	Abdominal	12.6% (19)
	Pelvis	4.6% (7)
	Extremities	71.5% (108)

*mmHg (milimeter of mercury), SD: Standard deviation

Table 3. Comparison of surviving and dead patients				
		Surviving patients 94.7% (n=143)	**Dead patients 5.3% (n=8)**	**p-value**
Trauma mechanism	Gunshot wounds	85.7% (n=6)	14.3% (n=1)	0.279
	Non-vehicle traffic accidents	94.1% (n=16)	5.9% (n=1)	0.909
Injury site	Abdominal	68.4% (n=13)	31.6% (n=6)	**<0.001**
	Pelvis	71.4% (n=5)	28.6% (n=2)	**0.005**
Multitrauma		88.7% (n=47)	11.3% (n=6)	**0.015**
Vitals	Systolic blood pressure (mmHg)**	120±16	74±22	**<0.001**
	Diastolic blood pressure (mmHg)	76±9	44±19	
GCS		14.5±0.5	6.2±2.6	**0.001**
Type of trauma	Blunt	95.3% (n=121)	4.7% (n=6)	0.471
	Penetrating	91.7% (n=22)	8.3% (n=2)	
GAP score	1	0	100% (n=4)	**<0.001**
	2	85.2% (n=23)	14.8% (n=4)	
	3	100% (n=120)	0	

*The p-values were analyzed using the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis-H test for three-group comparisons, **mmHg (milimeter of mercury), GCS: Glasgow Coma scale, GAP: Glasgow Coma scale/age/systolic blood pressure

Table 4. ROC analysis results for GAP score in mortality prediction

	AUC	95% CI	Sensitivity	Spesificity	Cut-off	PPV	NPV	LR+	LR-	p-value
GAP score	0.960	91.9-99.8	98	83.9	2	25.8	98.5	6.22	0.02	<0.001

PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, CI: Confidence interval, AUC: Area under the curve, GAP: Glasgow Coma scale/age/systolic blood pressure, ROC: Receiver operating characteristic

in the age range of the patient population analyzed and the specific limitations inherent to the study design.

Blunt trauma constitutes a significant portion of trauma cases worldwide, making it a critical public health concern. Typically resulting from high-energy mechanisms such as motor vehicle collisions, falls, and other accidents, blunt trauma often leads to internal organ damage and life-threatening complications. A study by Lee et al.[21] identified blunt trauma as the most common mechanism of injury, emphasizing its predominant role in trauma cases. Consistent with these findings, our study revealed that blunt trauma was the leading cause of injury, accounting for 84.2% of all cases. This highlights the global prevalence of blunt trauma, often linked to high-energy mechanisms such as motor vehicle collisions and falls, which underscores the need for targeted prevention strategies and optimized treatment protocols.

Multiple trauma continues to represent a significant public health challenge, being responsible for approximately 10% of global mortality and contributing to long-term morbidity in over 50 million individuals annually[22]. The considerable burden associated with multiple trauma extends beyond immediate fatalities to include profound physical and psychological disabilities, often imposing lifelong consequences on survivors and healthcare systems. A study by Zhang et al.[23] highlighted that preventable deaths in multiple trauma cases frequently result from delays in diagnosis and/or treatment, underscoring the critical importance of rapid assessment and intervention. In our study, 35.1% of patients presented with multiple trauma, and among the deceased patients, six had sustained multiple injuries. These findings emphasize the severity and complexity of multiple trauma cases and highlight the necessity of prompt, advanced medical care. In such situations, air transportation may play a pivotal role by minimizing delays in transferring patients to specialized trauma centers. The ability of air medical services to rapidly transport critically injured patients to facilities equipped with advanced diagnostic and therapeutic capabilities can be life-saving and should be considered an essential component of trauma care systems.

The GAP score is a practical scoring system used to assess the prognosis of trauma patients and predict mortality risk. This system combines three parameters-GAP-into a simple, rapid, and effective evaluation tool. In addition to facilitating the classification of trauma patients, the GAP score also serves as a guide in clinical decision-making processes. Studies on the GAP score have demonstrated its utility as an effective tool for predicting the prognosis of trauma patients[24]. In our study, the evaluation of GAP scores in relation to mortality revealed that lower GAP scores were significantly associated with higher mortality rates. Specifically, the AUC value for the GAP score in predicting mortality was 0.96, with a sensitivity of 98% and a specificity of 83.9%. These findings align with those reported in previous studies. For instance, Zeindler et al.[25] identified an AUC value of 0.93 in their analysis; while Mohammed et al.[26] reported an AUC value of 0.89, with a sensitivity of 81% and a specificity of 78%, closely mirroring our results. Similarly, other studies have documented high sensitivity and specificity for the GAP score in trauma patients[7,27]. In a study involving 2007 trauma patients, the specificity was found to be 80.1%, consistent with our findings[28]. Based on the results of our study, the GAP score can be considered a reliable and practical parameter for identifying high-risk patients who may benefit from transportation via helicopter ambulance. The score is straightforward to apply, even in resource-limited field settings, enabling healthcare personnel to effectively triage and manage trauma patients.

The strengths of the study lie in its ability to highlight the general conditions of trauma patients transported by helicopter ambulance and its contribution to cost-effectiveness by identifying patients who genuinely require air transport. However, the study also has notable limitations. Patients who could not be transported by helicopter ambulance due to meteorological conditions were excluded, potentially affecting the completeness of the analysis. In addition, some patients in relatively stable general condition, who were transported by air ambulance due to geographical constraints rather than medical necessity, were included, which may have influenced the overall findings.

Study Limitations

Furthermore, this study has inherent limitations. As the data were collected only between 2021 and 2023, the findings may not be generalizable to a broader time frame. The inclusion of only patients aged 18 years and older excluded the pediatric population, who may exhibit different trauma mechanisms and outcomes. Data were obtained from a specific region or center, limiting the generalizability of the results to other regions or healthcare systems. Meteorological conditions may have prevented the operation of helicopter ambulances in some cases, affecting the representativeness of the analyzed cases. Additionally, the preference for using helicopter ambulances for more critical cases could introduce selection bias, restricting the applicability of the GAP score to the general population. These limitations should be carefully considered when interpreting the findings of this study.

Conclusion

Based on the results of our study, the GAP score can be considered a reliable parameter for the transport of high-risk patients by helicopter ambulance. Healthcare personnel can easily apply this score in the field, where resources are limited, to manage trauma patients effectively.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval number: AEŞH-EK1-2023-649, date: 01.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.A., E.U., Design: E.A., E.U., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., Literature Search: E.U., Writing: E.A., E.U.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Does the Coexistence of Prostate Cancer and Chronic Prostatitis Affect Multiparametric Magnetic Resonance Imaging? Single-center Retrospective Study

Prostat Kanseri ve Kronik Prostatitin Birlikteliği Multiparametrik Manyetik Rezonans Görüntülemeyi Etkiler mi? Tek Merkezli Retrospektif Çalışma

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Abstract

Objective: In this study, we aimed to evaluate whether the presence of concomitant chronic prostatitis leads to a change in multiparametric magnetic resonance imaging (mpMRI) interpretation in patients with histopathological diagnosis of prostate cancer.

Methods: The data of patients who underwent transrectal ultrasound-guided prostate biopsy (TRUS-Bx) with a preliminary diagnosis of prostate cancer were retrospectively analyzed. Patients were divided into two groups according to TRUS-Bx results: those with prostate cancer and chronic prostatitis (Group 1) and those with prostate cancer only (Group 2).

Results: According to TRUS-Bx results, there were 97 patients in the group with prostate cancer + chronic prostatitis (Group 1) and 91 patients in the group with prostate cancer alone (Group 2). There was no significant difference between the two groups in terms of TRUS-Bx Gleason score and mpMRI findings [prostate imaging reporting and data system (PI-RADS) score, extraprostatic extension, and seminal vesicle invasion]. When TRUS-Bx Gleason scores were compared according to PI-RADS scores, similar results were observed and no significant difference was found between both groups.

Conclusion: The coexistence of prostate cancer and chronic prostatitis does not affect mpMRI findings. In addition to TRUS-Bx results, prospective studies with large patient series validated against radical prostatectomy specimens are needed to confirm the accuracy of the findings.

Keywords: Prostate cancer, chronic prostatitis, multiparametric magnetic resonance imaging

Öz

Amaç: Bu çalışmada, prostat kanseri histopatolojik tanısı almış hastalarda eşlik eden kronik prostatitin multiparametrik manyetik rezonans görüntüleme (mpMRI) yorumlamasında değişikliğe yol açıp açmadığını değerlendirmeyi amaçladık.

Yöntem: Prostat kanseri ön tanısıyla transrektal ultrasonografi rehberliğinde prostat biyopsisi (TRUS-Bx) yapılan hastaların verileri retrospektif olarak incelendi. Hastalar TRUS-Bx sonuçlarına göre prostat kanseri + kronik prostatit (Grup 1) ve sadece prostat kanseri (Grup 2) olmak üzere iki gruba ayrıldı.

Bulgular: TRUS-Bx sonuçlarına göre prostat kanseri + kronik prostatit (Grup 1) grubunda 97 hasta, sadece prostat kanseri (Grup 2) grubunda 91 hasta vardı. İki grup arasında TRUS-Bx Gleason skoru ve mpMRI bulguları [prostat görüntüleme raporlama ve veri sistemi (PI-RADS) skoru, ekstraprostatik yayılım

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Öz

ve seminal vezikül invazyonu] açısından anlamlı fark bulunmadı. TRUS-Bx Gleason skorları PI-RADS skorlarına göre karşılaştırıldığında, benzer sonuçlar gözlendi ve her iki grup arasında anlamlı bir fark bulunmadı.

Sonuç: Prostat kanseri ve kronik prostatitin birlikteliği mpMRI bulgularını etkilememektedir. TRUS-Bx sonuçlarına ek olarak, radikal prostatektomi örnekleriyle doğrulanmış geniş hasta serileri içeren prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Prostat kanseri, kronik prostatit, multiparametrik manyetik rezonans görüntüleme

Introduction

Prostate cancer is the second most common cancer in men and the fifth most common cause of cancer death in the world[1]. Multiparametric prostate magnetic resonance imaging (mpMRI) has an important role in the diagnosis and local staging of clinically significant prostate cancer[2]. To standardize mpMRI interpretation, the prostate imaging reporting and data system (PI-RADS) scoring system was published by the European Society of Urogenital Radiology (ESUR) in 2012 and subsequently updated to PI-RADSv2.1 in 2019[3,4].

Although mpMRI has advantages in detecting clinically significant prostate cancer, some benign lesions can also mimic prostate cancer. Benign conditions such as some normal anatomical structures, post-biopsy haemorrhages, necrosis, calcification, prostatitis may be interpreted as prostate cancer, and may cause confusion during interpretation[5-9]. In addition, the effect of the coexistence of prostate cancer and chronic prostatitis on mpMRI interpretation is not known. In this study, we aimed to evaluate whether the presence of concomitant chronic prostatitis leads to a change in mpMRI interpretation in patients with a histopathological diagnosis of prostate cancer.

Materials and Methods

Patient Selection

Atatürk University Non-Interventional Clinical Research Ethics Committee approval was obtained (decision no: 62, date: 27.12.2024). Then, the data of patients who underwent transrectal ultrasound-guided prostate biopsy (TRUS-Bx) with a preliminary diagnosis of prostate cancer at University of Health Sciences Türkiye, Erzurum City Hospital between June 2020 and December 2024 were retrospectively analyzed. Individuals with a history of previous TRUS-Bx, those who had not undergone mpMRI before TRUS-Bx, those who had more than 6 months between TRUS-Bx and mpMRI, and those with missing data were excluded from the study. Patients were divided into two groups according to TRUS-Bx results as patients with prostate cancer + chronic prostatitis (Group 1) and patients with prostate cancer only (Group 2). The parameters analyzed were age, prostate-specific antigen (PSA), prostate size on mpMRI, PSA density, mpMRI findings (PI-RADS score, extraprostatic extension and seminal vesical invasion) and TRUS-Bx pathology results.

TRUS-Bx Protocol

All patients administered an enema at home for intestinal cleansing on the morning of the procedure. Sterile urine culture was obtained for all patients before TRUS-Bx and prophylactic 1 g ceftriaxone was administered. In the left lateral decubitus position, rectal preparation was performed with povidone-iodine, and 4 mL of lidocaine was used bilaterally for peri-prostatic nerve block. Systematic biopsies of 12 cores were obtained from all patients. All mpMRIs performed in our clinic are interpreted by a single radiologist (D.Ö.K.) before TRUS-Bx. In patients with PI-RADS 3 or higher lesions on mpMRI, 3 cores of cognitive fusion biopsy are performed in addition to systematic biopsy.

mpMRI Protocol

All mpMRIs were performed on a 1.5 Tesla MR device (General Electric Signa Explorer, GE Medical Systems, USA) using a pelvic coil. The bladder was emptied in all patients before the procedure. Evaluations were performed with T2-weighted sagittal-axial-coronal, T1-weighted axial, diffusion-weighted, and T1-weighted fat-suppressed dynamic contrast-enhanced images.

In T2-weighted images, time to echo (TE) is 124 msec, time to repeat (TR) is 5095 msec, and slice thickness is 3.5 mm. In diffusion-weighted images, TE is 73 msec, TR is 2000 msec, slice thickness is 3.5 mm, and b-values are 50, 800, 1500. In dynamic contrast-enhanced T1-weighted images, TE is 1.4 msec, TR is 3 msec, and slice thickness is 4.4 mm. For dynamic contrast-enhanced images, 0.2 mL/kg contrast medium (gadoteric acid) was administered intravenously.

Statistical Analysis

All statistical analyses were performed using SPSS, version 22 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as number (percentage). Normal distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. In the comparison of continuous variables the independent t-test was used for those with normal distribution, and the Mann-Whitney U test was used for those without normal distribution. Pearson chi-square or Fisher's exact tests were used to compare categorical variables. A p-value less than 0.05 was considered significant.

Results

According to TRUS-Bx results, there were 97 patients in the group with prostate cancer + chronic prostatitis (Group 1) and 91 patients in the group with prostate cancer alone (Group 2). The mean age of the patients was 63.8±6.9 years, the mean PSA value was 9.9±6.3 ng/mL, the mean prostate volume was 51.7±18.6 mL, and the mean PSA density was 0.21±0.16. Patient characteristics, mpMRI findings and TRUS-Bx results are shown in Table 1.

There was no significant difference between the two groups in terms of age, prostate volume, and PSA density, but PSA value was significantly higher in Group 1 (p=0.028). There was no significant difference between the two groups in terms of TRUS-Bx Gleason score and number of positive cores. Again, no significant difference was observed between the two groups in terms of PI-RADS score, extraprostatic extension, and seminal vesicle invasion determined by mpMRI (Table 2). When TRUS-Bx Gleason scores were compared according to PI-RADS scores, no significant difference were found between the groups (Table 3).

Discussion

T2-weighted images reveal the anatomical features of prostate cancer. Prostate cancer presents in a focal and lower-density form against a background of high-density gland tissue[3,9]. However, it has been reported that the use of anatomical T2-weighted images alone may cause false positive findings[9]. So, in addition to T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging have been added, and prostate imaging with a multiparametric approach has been developed[10,11]. Diffusion-weighted imaging reflects the movement of fluid in tissues, which is related to properties such as cell density, intercellular space and membrane permeability. Prostate

Table 1. Patient characteristics, mpMRI findings and TRUS-Bx results

Variables	n=188
Age (years), mean ± SD	63.8±6.9
Prostate-specific antigen (ng/mL), median (min-max)	8 (3.4-37)
Prostate volume on mpMRI (mL), median (min-max)	46 (26-133)
PSA density, median (min-max)	0.16 (0.05-1.06)
Biopsy Gleason score (%)	
3+3	136 (72.3%)
3+4	31 (16.5%)
4+3	13 (6.9%)
8-10	8 (4.3%)
Number of positive cores, median (min-max)	3 (1-11)
mpMRI, PI-RADS score (%)	
≤2	33 (17.6%)
3	35 (18.6%)
4	112 (59.6%)
5	8 (4.3%)
Presence of EPE on mpMRI (%)	45 (23.9%)
Presence of SVI on mpMRI (%)	16 (8.5%)

SD: Standard deviation, mpMRI: Multiparametric magnetic resonance imaging, EPE: Extraprostatic extension, SVI: Seminal vesicle invasion, PSA: Prostate-specific antigen, PI-RADS: Prostate imaging reporting and data system, TRUS-Bx: transrectal ultrasound-guided prostate biopsy

Table 2. Comparison of patient characteristics, mpMRI findings and TRUS-Bx results between groups			
Variables [mean ± SD/n (%)]	**Bx result**		
	Group 1 (n=97)	**Group 2 (n=91)**	**p-value**
Age (years)	63.4±5.8	64.1±6	0.403
Prostate-specific antigen (ng/mL)	10.8±6.9	9±5.4	0.028
Prostate volume on mpMRI (mL)	51.9±17.9	51.4±19.4	0.724
PSA density	0.24±0.19	0.19±0.12	0.125
Biopsy Gleason score			0.115
3+3	65 (67%)	71 (78%)	
3+4	19 (19.6%)	12 (13.2%)	
4+3	10 (10.3%)	3 (3.3%)	
>8	3 (3.1%)	5 (5.5%)	
Number of positive cores	3.8±2.4	3.7+2.2	0.962
mpMRI, PI-RADS score (%)			0.886
2	18 (18.6%)	15 (16.5%)	
3	17 (17.5%)	18 (19.8%)	
4	57 (58.8%)	55 (60.4%)	
5	5 (5.2%)	3 (3.3%)	
EPE on mpMRI (%)	23 (23.7%)	22 (24.2%)	0.941
SVI on mpMRI (%)	9 (9.3%)	7 (7.7%)	0.697

SD: Standard deviation, mpMRI: Multiparametric magnetic resonance imaging, EPE: Extraprostatic extension, SVI: Seminal vesicle invasion, PSA: Prostate-specific antigen, PI-RADS: Prostate imaging reporting and data system, TRUS-Bx: transrectal ultrasound-guided prostate biopsy

Table 3. Comparison of TRUS-Bx Gleason scores according to PI-RADS scores between groups			
Variables [n (%)]	**Bx result**		
	Group 1	**Group 2**	**p-value**
PI-RADS*			
2			0.530
3+3	17 (94.4%)	13 (86.7%)	
3+4	1 (5.6%)	1 (6.7%)	
4+3	0	1 (6.7%)	
≥8	0	0	
3			0.982
3+3	13 (76.5%)	13 (72.2%)	
3+4	2 (11.8%)	3 (16.7%)	
4+3	1 (5.9%)	1 (5.6%)	
≥8	1 (5.9%)	1 (5.6%)	
4			0.161
3+3	34 (59.6%)	43 (78.2%)	
3+4	15 (26.3%)	8 (14.5%)	
4+3	6 (10.5%)	2 (3.6%)	
≥8	2 (3.5%)	2 (3.6%)	

*PI-RADS 5 was not included in the analysis due to an insufficient number of cases

cancer appears bright on diffusion-weighted imaging and dark on apparent diffusion coefficient (ADC) maps, indicating diffusion restriction[12]. Dynamic contrast-enhanced imaging includes T1-weighted axial images obtained after intravenous contrast material is administered. In prostate cancer, early rapid contrast enhancement followed by washout or plateau is observed[9,13].

In mpMRI of prostatitis, low T2 signal intensity and mild or moderate diffusion restriction can be expected. Diffusion restriction is expected to be less than it is in prostate cancer. Dynamic contrast-enhanced imaging shows early and increased contrast uptake similar to prostate cancer[9,14,15]. Chronic prostatitis and prostate cancer can often be confused because they have similar mpMRI findings. The distinction between prostate cancer and chronic prostatitis has not been clearly demonstrated on mpMRI[5], and clarifying this distinction may lead to a significant reduction in transrectal ultrasound-guided biopsy rates.

Quantitative parameters of mpMRI were investigated to distinguish between prostate cancer and chronic prostatitis. Uysal et al.[5] determined that quantitative ADC values, quantitative pharmacokinetic parameters (Ktrans, kep, Ve, and Vp), and time to peak were significant in the differentiation of prostate cancer and chronic prostatitis, and found that the logistic regression model including all parameters had a diagnostic accuracy of 92.7%. Peker et al.[7] found that ADC had the highest sensitivity and specificity compared to other criteria. However, the combination of normalized T2-signal intensity, ADC values, and washing percentage provided the highest sensitivity (77.7%) and specificity (85.7%) among all combinations. Although quantitative measures of mpMRI, especially ADC, are promising, the role of the PI-RADS scoring system in differentiating prostate cancer from chronic prostatitis is still limited. Further studies may lead to the inclusion of quantitative measurements in new versions of PI-RADS.

In histopathological preparations obtained by TRUS-Bx, the coexistence of prostate cancer and chronic prostatitis can be seen frequently; and it is not known whether this affects mpMRI. Although there are studies in the literature investigating the effect of chronic prostatitis on mpMRI, our study is unique in that it investigates whether chronic prostatitis accompanying prostate cancer affects mpMRI interpretation, and whether there is a discordance between the PI-RADS score and the TRUS-Bx Gleason score. According to our study, there was no significant difference in mpMRI results (PI-RADS score, extraprostatic extension and seminal vesicle invasion) and Gleason scores between patients with only prostate cancer and patients with prostate cancer + chronic prostatitis. In addition, when TRUS-Bx Gleason scores were compared according to PI-RADS scores, no significant difference was observed in both groups.

Study Limitations

The strength of our study is that it is the first to examine whether chronic prostatitis accompanying prostate cancer has an effect on mpMRI interpretation. On the other hand, the retrospective nature of the study and its lack of confirmation with radical prostatectomy material, but only evaluation with TRUS-Bx, are limitations. Another limitation is the absence of a third group of patients with mpMRI findings who did not have prostate cancer but had only chronic prostatitis on TRUS-Bx. Additionally, the 1.5 T MRI device can be considered as one of the limitations.

Conclusion

The coexistence of prostate cancer and chronic prostatitis does not affect mpMRI findings. In future studies, various differences can be identified with new versions of PI-RADS. In addition to TRUS-Bx results, prospective studies with large patient series validated with radical prostatectomy specimens are needed.

Ethics

Ethics Committee Approval: Atatürk University Non-Interventional Clinical Research Ethics Committee approval was obtained (decision no: 62, date: 27.12.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.Ş., D.Ö.K., Design: E.Ş., D.Ö.K., Data Collection or Processing: E.Ş., Analysis or Interpretation: E.Ş., D.Ö.K., Literature Search: E.Ş., D.Ö.K., Writing: E.Ş., D.Ö.K.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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The Learning Curve of Urological Surgeries: A PRISMA-compliant Bibliometric Analysis

Ürolojik Ameliyatların Öğrenme Eğrisi: PRISMA Uyumlu Bibliyometrik Bir Analiz

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Abstract

Objective: With the expanding scope of urological surgery, all surgeons are adapting to new techniques. This situation entails the learning curve of many surgical methods. Therefore, we conducted a bibliometric analysis of these publications, hoping to show current research hotspots and future research trends.

Methods: Web of Science Core Collection (WoS index SCI-Exp, ESCI) articles were retrieved using a specified advanced query: [TS=("urology resident")] OR [TS=("learning curve")], and filtered by document type (article), Open Access, and WoS categories (Urology and Nephrology). A total of 422 articles were included in the study. Four hundred and eight were in English, 11 in Spanish and 3 in French. Two hundred and ninety two are in SCI Exp, 130 in ESCI index.

Results: The United States of America (USA) published 97 (23%) of all articles on the learning curve of urological surgery. After the USA, the highest number of articles were published in Korea with 36 (8.5%) and Italy with 29 (6.5%). International Brazilian Joural of Urology was the journal that published the most articles on this subject with 34 articles, followed by British Journal of Urology International (n=31) and Canadian Urological Association Journal (n=30). Among the articles analyzed, the keyword "learning curve" was the most common. This was followed by "outcomes", "complications", and "experience".

Conclusion: Considering the current upward trend in the number of publications related to the learning curve due to technological advances, the amount of quantitative data available for analysis is expected to increase in the future. This bibliometric analysis may contribute to the advancement of urological surgical practice and the improvement of patient care for those undergoing urological procedures.

Keywords: Learning curve, complications, urological surgeries

Öz

Amaç: Ürolojik cerrahi çeşitliliğinin artmasıyla beraber yeni yöntemlere her cerrah uyum sağlamaya çalışmaktadır. Bu durum birçok cerrahi yöntemin öğrenme eğrisini de beraberinde getirmektedir. Bu nedenle, mevcut araştırma noktalarını ve gelecekteki araştırma eğilimlerini göstermeyi umarak bu yayınların bibliyometrik bir analizini yaptık.

Yöntem: Web of Science Core Collection (WoS index SCI-Exp, ESCI) makaleleri belirtilen gelişmiş sorgu [TS=("üroloji asistanı")] olarak alınmıştır OR [TS=("öğrenme eğrisi")] ve belge türü makale, Açık Erişim, WoS kategorileri Üroloji Nefroloji ve toplam 422 makale çalışmaya dahil edildi. Dört yüz sekizi İngilizce, 11'i İspanyolca ve 3'ü Fransızca'dır. İki yüz doksan ikisi SCI Exp, 130'u ESCI indeksinde yer almaktadır.

Bulgular: Ürolojik cerrahilerin öğrenme eğrisi ile ilgili olarak Amerika Birleşik Devletleri (ABD) tüm makalelerin 97'sini (%23) yayınlamıştır. ABD'den sonra en fazla makaleler 36 (%8,5) ile Kore ve 29 (%6,5) ile İtalya'dan yayınlanmıştır. Bu konu ile ilgili Uluslararası Brezilya Üroloji Dergisi 34 makele ile en çok yayın

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Öz

yapan dergi olurken bunu ise sırasıyla İngiliz Üroloji Dergisi Uluslararası (n=31) ve Kanada Üroloji Derneği Dergisi (n=30) izlemiştir. Analiz edilen makaleler arasında en sık "learning curve" anahtar kelimesi yer almıştır. Bunu ise "outcomes", "complications" ve "experience" takip etmiştir.

Sonuç: Teknolojik ilerlemelere bağlı öğrenme eğrisi ile ilgili yayınlarının sayısındaki mevcut artış eğilimi göz önüne alındığında, bu analizle sağlanan nicel sonuçlar ilerleyen dönemde artış gösterecektir. Bu bibliyometrik analiz ürolojik cerrahi uygulamaların ilerlemesine ve ürolojik prosedürler geçiren hastaların bakım kalitesinin iyileştirilmesine katkıda bulunabilir.

Anahtar Kelimeler: Öğrenme eğrisi, komplikasyon, ürolojik cerrahiler

Introduction

Bibliometric analysis is an analytical method to understand the development of research and knowledge in specific fields, including urologic surgery. This analysis involves the quantitative evaluation of published literature to identify effective studies on the subject[1].

The learning curve in urologic surgery represents a surgeon's skill over time. Initially, a junior surgeon may encounter significant difficulties during procedures. However, as surgeons gain experience, their effectiveness increases with repeated practice, leading to improved patient outcomes[2]. Bibliometric analysis can illuminate this progression by assessing publication patterns of surgical outcomes, the frequency of specific urological procedures, and the impact of educational programs[3]. Key metrics to analyze include the number of publications over time, citation rates, authorship trends, and geographical distribution of research. Techniques such as co-citation analysis and keyword co-occurrence can help identify landmark articles and emerging topics in urologic surgery[4]. Furthermore, bibliometric analysis can reveal the link between research productivity and clinical outcomes[5]. A better description of the learning curve in the context of the literature is associated with the reduction in complication rates in urologic surgery[6]. Optimally defining the learning curve of any surgical procedure helps not only to improve surgical training but also to support further research efforts aimed at optimizing surgical procedures[7].

This study aims to show the development status and structure of the learning curve in urological surgical operations, and the development boundary and evolution path in the form of an information map. On this basis, it provides new insights into the learning curve in urological surgeries through comprehensive analysis and review.

Materials and Methods

Ethics committee approval was received for this study from the Non-Interventional Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no: 2024/07-25, date: 19.08.2024). Web of Science Core Collection WoS indexes SCI-Exp and ESCI articles were taken using specified advanced query parameters: [TS=("urology resident")] OR [TS=("learning curve")], in addition to applying the criteria of document type: article, Open Access status, and WoS categories: Urology and Nephrology. A total of 422 articles met these criteria and were included in the study. Four hundred and eight were in English, 11 in Spanish and 3 in French. 292 are in SCI Exp, 130 in ESCI index. Our analysis included systematic reviews, meta-analyses, level 1-4 research articles, and review articles. WoS's analysis tools were used to record the range of countries, authors, and journals identified. The number of research articles published was used to measure research productivity. The number of citations was used as a criterion to measure the impact of the article. Among the results of articles on the learning curve of urological surgeries, the year, country, journal, institution, and author distribution of the article and the number of citations attributed to each article were evaluated. As a result of these analyses, the top 10 articles, journals, institutions, and authors were summarized graphically.

Statistical Analysis

The data were analyzed using VOSviewer (Leiden University, Netherlands; version 1.6.11) for visualizing research trends and collaboration networks. The analysis focused on: analysis of articles by year, analysis of articles by journal, most cited articles: authors, article titles, journals, publication years, and citation counts, keyword analysis, institutions associated with authors, analysis of inter-institutional publications, analysis of author collaboration, citation distribution by country.

Results

Number of Annual Publications

The first articles on the learning curve of urological surgeries were published in 2003, and the number of such

articles has steadily increased over the years. Currently, the highest number of publications occurred in 2023; 41 articles were written in this year. Between 2003 and 2024, it was determined that there were a total of 422 articles in SCI-E and ESCI on this subject (Figure 1).

Contribution Trends of Countries and Affliations

When the articles on the learning curve in urological surgery, were categorised by country, the United States of America (USA) published 97 (23%) of all articles. After the USA, the most articles were published in Korea with 36 (8.5%) and Italy with 29 (6.5%). When we analyse the published articles, in terms of the cooperation tendencies of the countries, Italy was the country that published the most articles with 16 (55.2%) of the 29 articles on this subject, followed by the USA with 13 (13.4%) articles and the United Kingdom with 9 (56.3%) articles. In the studies carried out by the countries, when the multiple country publication (MCP) is considered proportionally, the United Kingdom was the highest with a rate of 56.3%. This was followed by Italy with 55.2% and Germany with 41.2% (Figure 2). In terms of institutional

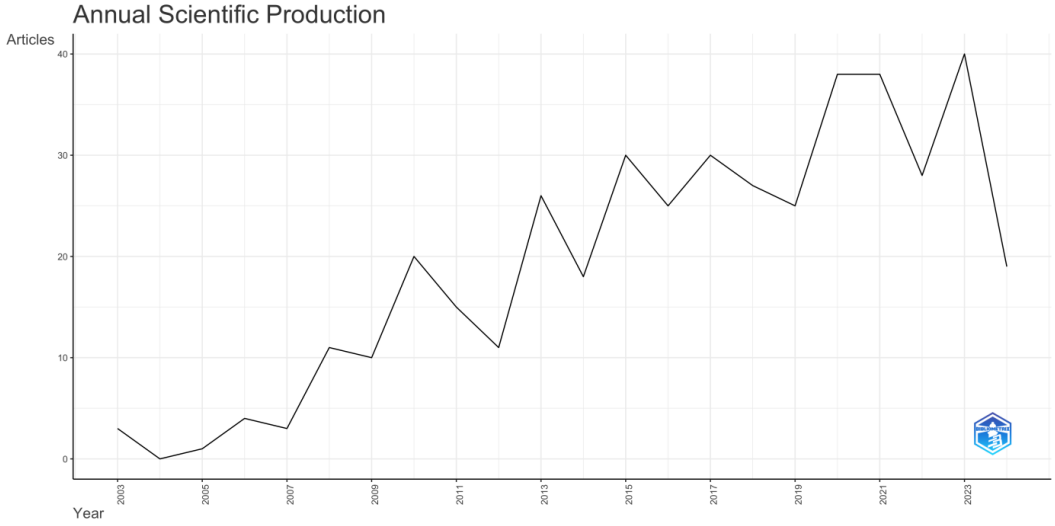

Figure 1. Publications related to learning curve according to years

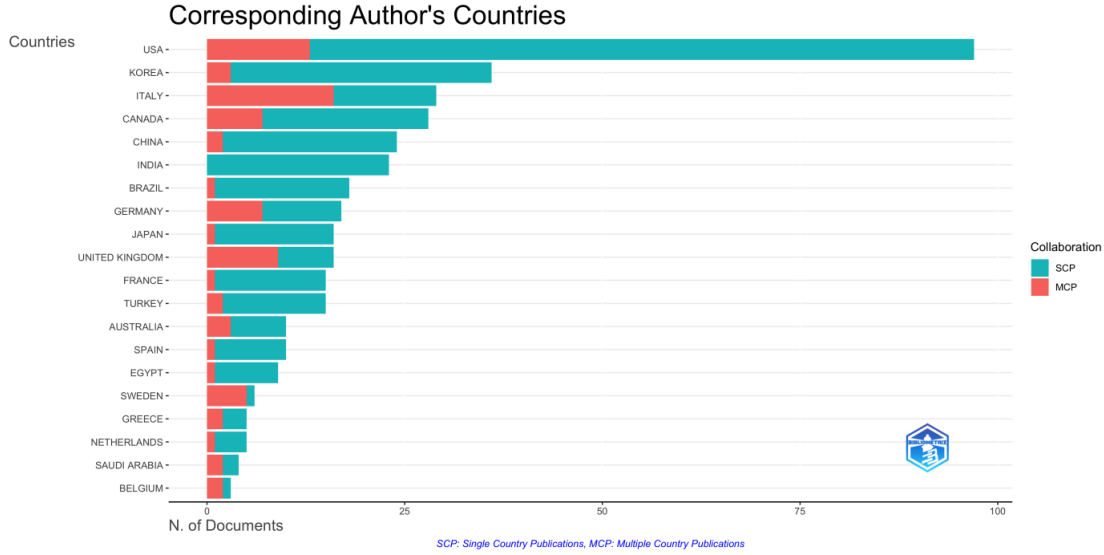

Figure 2. Number and distribution of single-centre and multicentre studies on the learning curve of urological surgeries by country

impact on this subject's literature, Memorial Sloan Kettering Cancer Centre ranked first with 48 publications, followed by the University of Toronto with 17 articles, and Gothenburg University with 14 articles (Figure 3).

Journal and Citation Trends

The top 10 journals on the learning curve in urologic surgery are listed in Figure 4. The International Brazilian Journal of Urology was the journal that published the most articles on this topic with 34 articles, followed by the British Journal of Urology (BJU) International (n=31) and the Canadian Urological Association Journal (n=30). As for the most frequently cited journals, the Journal of Urology ranked first with 1545 citations, despite publishing 17 articles. European Urology was the journal with the highest impact factor, and published seven articles in this field, but it was the 2nd most frequently cited journal (n=1196). The most cited articles and those with the most publications are shown in Figure 5.

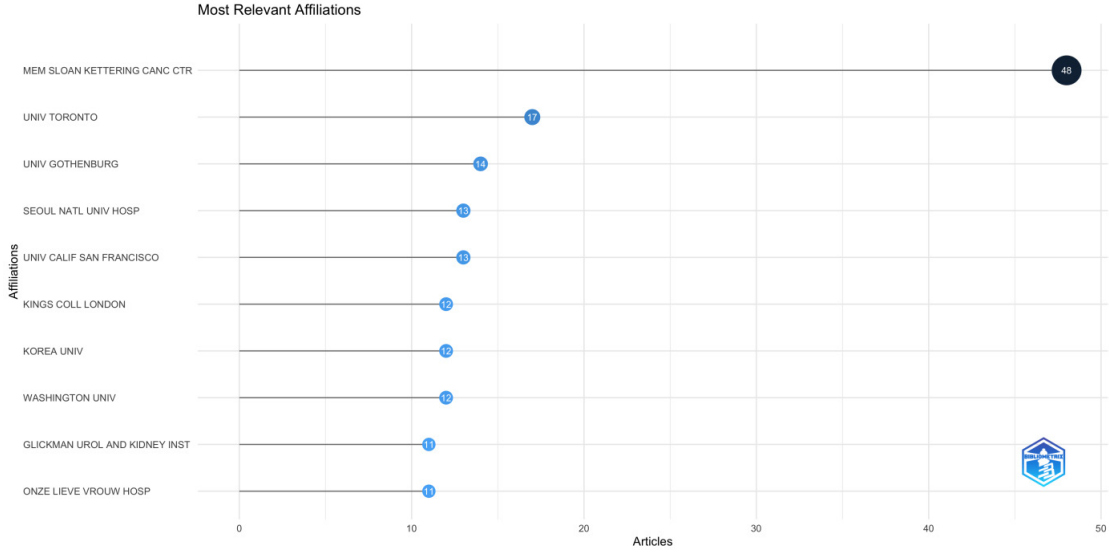

Figure 3. Affliations that publish the most articles with the learning curve of urological surgeries

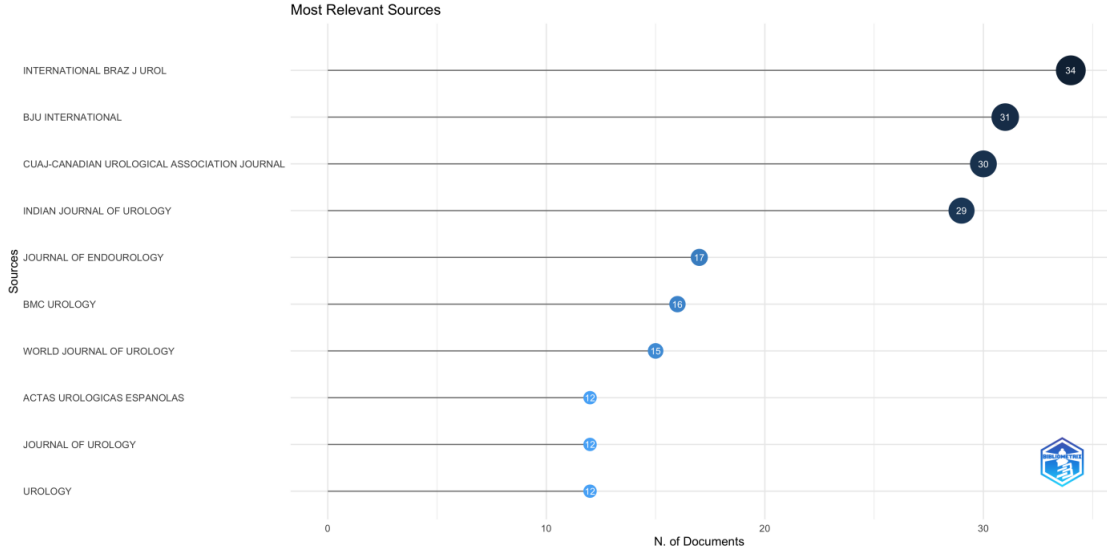

Figure 4. Top 10 journals on the learning curve in urologic surgery

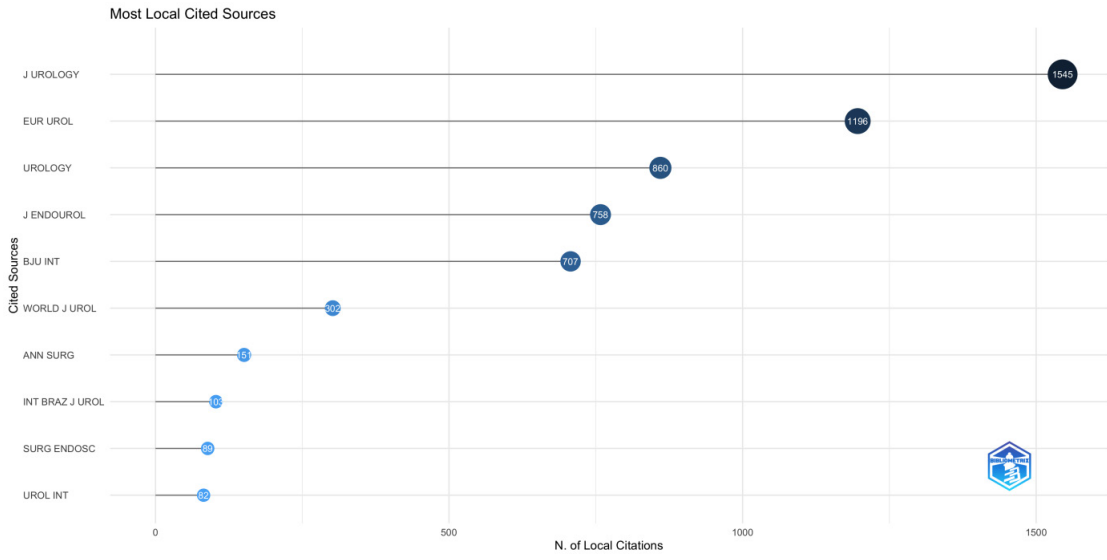

Figure 5. Top 10 most cited journals on the learning curve in urologic surgery

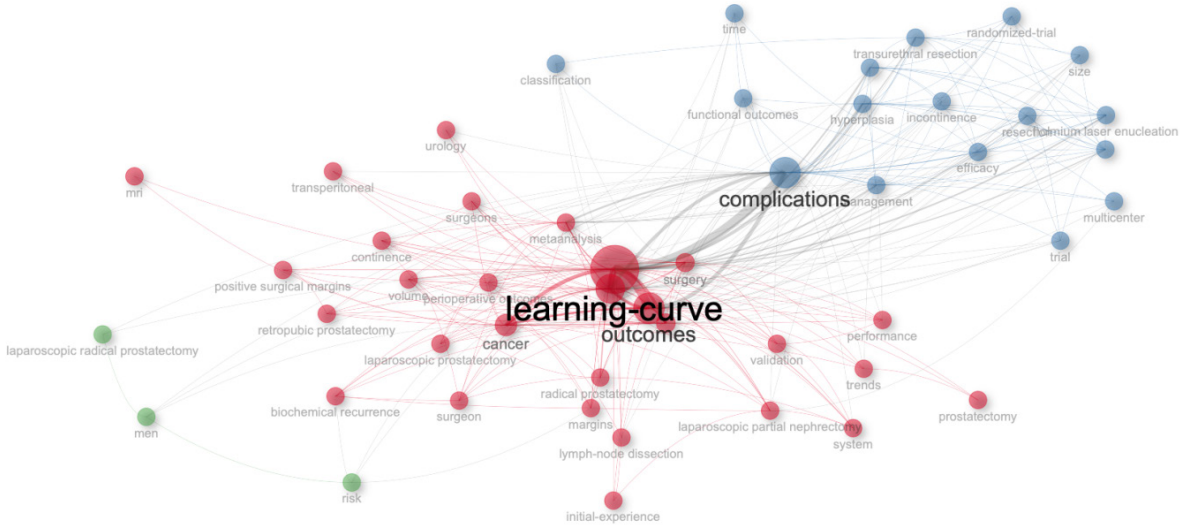

Figure 6. Most searched keywords related to learning curve in urologic surgery

Trends of Learning Curve-Related Keywords

The most common keywords are listed in Figure 6. Among the articles analyzed, the keyword "learning curve" was the most common. This was followed by "outcomes", "complications" and "experience". It is seen that the most frequently used keywords are related to prostate diseases. This indicates that learning curve studies are mostly performed on prostate surgery.

Trend Topics in Learning Curve

When trending topics related to learning curves are examined, it is seen that more endoscopic procedures are the subject of research rather than open surgeries. The most common research topic pertains to prostate surgeries. Trend topics related to the learning curve of urological surgeries are shown in Figure 7.

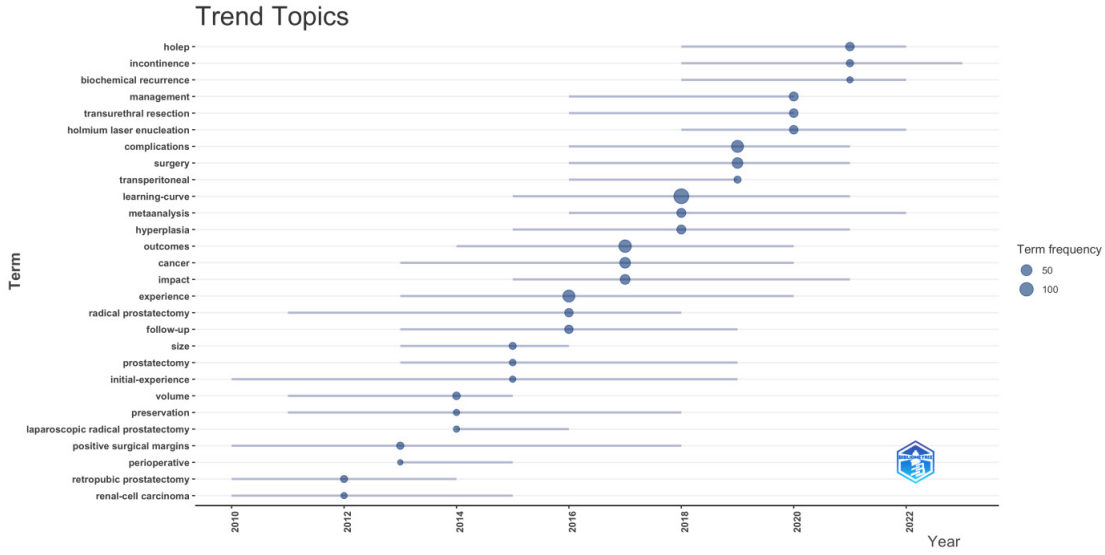

Figure 7. Trend topics related to the learning curve of urologic surgeries

Discussion

Urologic surgeries encompass a wide range of procedures aimed at treating conditions affecting the urinary tract and male reproductive system[8]. As medical science has advanced, the complexity and variety of these surgeries have increased significantly, leading to a greater need for competent surgical skills and knowledge[9]. Understanding the learning curve associated with urologic surgeries is crucial not only for surgical residents but also for experienced surgeons seeking to refine their techniques and improve patient outcomes. The concept of the learning curve in this context refers to the progression of a surgeon's skill and effectiveness in performing urologic procedures over time. This progression is influenced by various factors such as the complexity of the surgery, faculty mentorship, simulation training, and accumulation of procedural experience[10]. Each surgical technique, whether simple or difficult, presents its own unique challenges and subtleties that contribute to the surgeon's learning curve[11]. When assessing somewhat crude outcomes such as safety, efficacy, and operative time, it has been recognized that 15 to 40 cases are probably required to learn procedures to reach basic competence[12-15]. However, technical difficulties will be overcome with more cases to improve surgical success. For this, it is important to follow the learning curve and current knowledge[7].

When we examined the literature on the learning curve over the years, we found that while there were only 41 articles on the learning curve until 2003, there were 422 articles on the learning curve between 2003 and 2024. We attribute this to the variability of surgical operation methods, which are influenced by technological advances, performed on a specific organ. Especially in the 2000s, endoscopic advances and the use of new technology in clinical practice have brought many scientific articles. Considering all these factors, publications on the learning curve of each procedure have increased over time. The countries where the literature is published reveal that research centers in this field are mainly located in developed countries and developing countries with higher economic levels. The United States has published the most on the learning curve, but in terms of collaboration, Italy has contributed the most to the literature, followed by the United Kingdom. MSP rates are highest in the United Kingdom, Italy, and Germany, and European countries show closer cooperation in collaborating on the learning curve of urological procedures.

The most frequently searched keywords in the literature with learning curve were learning curve, outcomes, complications, and experience. The most common articles about the learning curve in medical literature are related to prostate cancer and prostate surgery. Vickers Andrew J is the author who published the highest number of articles on the learning curve, and all of these articles are related to prostate cancer surgery[16-20]. Dell'Oglio P is the author with the second highest number of articles on this subject after Vickers Andrew J[21,22].

This bibliometric analysis was performed using the WoS database. The search strategy was as comprehensive as possible and the data were analyzed thoroughly. However,

results may differ from other databases (e.g., Scopus) or due to the inclusion of different search terms. Given the importance of the topic and the current upward trend in the number of publications on the learning curve due to technological advances, the significance of the quantitative results provided by this analysis will increase in the future.

Study Limitations

This study acknowledges that the search was limited to the WoS database and articles published in English, which may have resulted in the exclusion of relevant studies published in other databases or languages. Additionally, while efforts were made to expand the search terms, some relevant articles may still have been missed due to the specificity of keywords.

Conclusion

Our study provides insights into the learning curve of urological surgeries, the evolution of surgical skills over time, the importance of ongoing research, and the need for effective training mechanisms in this field. Such analyses may ultimately contribute to advancing surgical practice and improving the quality of care for patients undergoing urological procedures.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Non-Interventional Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no.: 2024/07-25, date: 19.08.2024).

Informed Consent: Informed consent was not required.

Footnotes

Authorship Contributions

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

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

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Long-term Neurodevelopmental Outcomes of Very Low Birth Weight Infants

Çok Düşük Doğum Ağırlıklı Bebeklerin Uzun Dönem Nörogelişimsel Sonuçları

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Abstract

Objective: The aim of this study was to examine the long-term neurodevelopmental outcomes of very low birth weight (VLBW) infants and identify factors influencing these outcomes.

Methods: A cohort consists of 66 VLBW infants, aged 2 years and older (2-10 years). They were evaluated through neurological examinations, neurodevelopmental screening [using the Denver developmental screening test-II (DDST) and the Wechsler intelligence scale for children-revised (WISC-R)], and cranial magnetic resonance imaging (MRI).

Results: Cerebral palsy was diagnosed in 13.6% of cases. Meanwhile, 29.6% had significant neurological sequelae such as sensorineural hearing loss, hydrocephalus, and epilepsy. The other health problems, including attention-deficit hyperactivity disorder, strabismus, and refractive errors (myopia, hypermetropia), were observed in 34.8% of the subjects. Developmental delay affected 73.7% of children assessed with DDST; although, all nine children evaluated with WISC-R had normal cognitive function. Cranial MRI abnormalities were observed in 28.8% of cases. Risk factors, such as polyhydramnios, placenta previa, placental abruption, chorioamnionitis, passive smoking, assisted reproductive technologies, and severe neonatal complications [intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP)], were linked to poorer outcomes. PVL, IVH, and ROP increased poor prognosis odds by factors of 33, 10, and 5.8, respectively.

Conclusion: Although the incidence of major neurological disorders, such as cerebral palsy, has decreased with advances in neonatal intensive care, minor neurodevelopmental issues continue to affect the quality of life in VLBW infants. Prevention strategies should focus on addressing both major and minor neurodevelopmental challenges, with an emphasis on reintegrating VLBW individuals into society as healthier members.

Keywords: Very low birth weight infants, long-term neurodevelopmental outcomes, cerebral palsy, cranial magnetic resonance imaging, developmental screening tests

Öz

Amaç: Bu çalışmada çok düşük doğum ağırlıklı (ÇDDA) bebeklerin uzun dönemdeki nörogelişimsel sorunları ve bu sorunları etkileyen faktörlerin araştırılması amaçlanmaktadır.

Yöntem: Yaşları 2 yaş ve üzeri olan 66 ÇDDA olguya nörolojik muayene, nörogelişimsel tarama testleri [Denver gelişimsel tarama testi-II (DGTT), Wechsler çocuklar için zeka ölçeği-revize (WISC-R)], kraniyal manyetik rezonans görüntüleme (MRG) uygulandı.

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Öz

Bulgular: Olguların %13,6'sında serebral palsi tespit edilirken, %29,6'sında sensörinöral işitme kaybı, hidrosefali ve epilepsi gibi majör nörolojik sekeller saptandı. Olguların %34,8'inde dikkat eksikliği hiperaktivite bozukluğu, şaşılık, miyopi, hipermetropi gibi minör nörolojik problemler tespit edildi. DGTT ile değerlendirilen olguların %73,7'sinde gelişimsel gecikme gözlenirken, WISC-R testi ile değerlendirilen 9 olgunun tamamı normal zeka gösterdi. Kraniyal MRG ile hastaların %28,8'inde anormallikler saptandı. Polihidramnios, plasenta previa, plasenta dekolmanı, koryoamniyonit, pasif sigara içimi, yardımcı üreme teknikleri ve bazı neonatal durumlar [intraventriküler kanama (IVK), periventriküler lökomalazi (PVL) ve prematüre retinopatisi (ROP)] gibi risk faktörleri, daha kötü nörolojik prognozla ilişkilendirilmiştir. PVL, IVK ve ROP'un kötü nörolojik prognozu sırasıyla 33, 10 ve 5,8 kat artırdığı görülmüştür.

Sonuç: Yenidoğan yoğun bakım üniteleri bakımındaki gelişmelerle birlikte serebral palsi gibi majör nörolojik bozukluklar azalmış olsa da, minör nörolojik sorunlar hala yaşam kalitesini etkilemektedir. Önleme stratejileri ve programları ile majör ve minör nörogelişimsel problemlerin ele alınması, ÇDDA'lı bebeklerin sağlıklı bireyler olarak topluma yeniden kazandırılması hedeflenmelidir.

Anahtar Kelimeler: Çok düşük doğum ağırlıklı bebekler, uzun dönem nörogelişimsel prognoz, serebral palsi, kraniyal manyetik rezonans görüntüleme, gelişimsel tarama testi

Introduction

Preterm birth is defined as delivery before 37 completed weeks of gestation. However, this study specifically focuses on a high-risk subgroup-infants born before 32 weeks of gestation with a birth weight of less than 1,500 grams, commonly referred to as very low birth weight (VLBW) infants. These infants are at increased risk for neonatal morbidity and long-term neurodevelopmental impairments. Advances in neonatal intensive care have significantly improved the survival rates of VLBW infants. However, these gains have also been accompanied by increased rates of neurodevelopmental challenges[1-3]. The rise in major morbidities such as cerebral palsy (CP), epilepsy, mental retardation, vision and hearing problems and some minor morbidities (learning disabilities, speech delay, communication difficulties, attention deficit hyperactivity coordination and balance disorders, behavioral problems, myopia, strabismus and mild hearing loss) is remarkable and has long-term implications for the quality of life of these infants[2,4,5]. CP is a major neurological condition defined as a group of permanent disorders of movement and posture resulting from static damage to the developing brain. Although CP is not progressive, its clinical manifestations can develop with age and lead to varying degrees of motor limitations[6]. Prematurity is one of the most important risk factors for CP. VLBW preterm infants born before 32 weeks of gestation and weighing less than 1500 grams have a significantly increased risk for CP[1,7]. Motor disorders in CP are frequently accompanied by sensory, perceptual, cognitive, communication, and behavioral disorders, epilepsy, and musculoskeletal problems. These represent a major public health concern. Although many neurological early diagnosic methods have been proposed, there is no standard method accepted internationally. Diagnosis in CP is usually made at the age of two with a detailed history, determination of clinical risk factors, complete neurological examination, developmental tests and supportive brain magnetic resonance imaging (MRI). Diagnosing CP as early and correctly as possible is important for the premature infant to be integrated into society as a useful individual. In addition, early initiation of special education, physiotherapy and other treatment methods, prevention of possible accompanying complications or reduction of their effects and early psychological support to the parent are necessary, and a multidisciplinary approach should be adopted in treatment[7,8]. There are many prenatal and neonatal risk factors that negatively affect neurodevelopmental prognosis in the development of CP[1,3,7,8]. As a result of upper motor neuron damage in the cortex caused by antenatal and prenatal risk factors, motor control is impaired and leading to spasticity. This occurs due to a reduction in signals to the reticulospinal and corticospinal tracts, which affects on the motor units[9]. The risk of brain damage (white matter damage, intraventricular hemorrhage (IVH), and cortical and deep gray matter damage) increases with decreasing gestational age and birth weight. Therefore, optimizing prenatal neonatal and newborn care, identifying risk factors in advance and taking precautions are crucial to ensure optimal neuromotor development[3,8]. Comprehensive monitoring starting from the prenatal period, continuous surveillance during the neonatal intensive care unit (NICU) stay, systematic identification of risk factors, and the implementation of targeted preventive strategies are fundamental for the accurate diagnosis of CP and the anticipation of associated complications. Detailed neurological evaluations, developmental assessments, and MRI, recognized as the gold standard for identifying neuroanatomical abnormalities, are indispensable components of this approach[10]. Thus, neurodevelopmental sequelae will be minimized with early diagnosis and appropriate treatment approaches.

In this study, we aimed to investigate both major and minor issues, particularly CP, in premature infants born with VLBW (≤1500 g) and ≤32 weeks gestational age, who were treated in the NICU of Aydın Adnan Menderes University Faculty of Medicine between January 2000 and December 2010. At age 2 and older, these infants underwent neurological examinations, developmental assessments, and cranial MRI. We also investigated the prenatal and neonatal risk factors that influence long-term neurodevelopmental outcomes and identified the most significant risk factors associated with adverse outcomes.

Materials and Methods

These patients were part of a cohort of 169 preterm infants (≤32 weeks gestation) with (VLBW, birth weight ≤1500 g) who were hospitalized and followed up in the NICU of the Department of Pediatrics at Aydın Adnan Menderes University between January 2000 and December 2010. This retrospective and cross-sectional study included 66 patients aged 2 years and older, who underwent neurological examination, developmental assesments, and cranial MRI, and whose families provided written consent.

Neurological examinations were performed by pediatric neurologists at our center. Perinatal risk factors, including unmonitored pregnancy, maternal smoking during pregnancy, passive smoking, premature rupture of membranes, maternal urinary tract infection, oligohydramnios, polyhydramnios, preeclampsia, placenta previa, abruptio placenta were obtained from medical records. Neonatal risk factors, including mechanical ventilatory support, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity (ROP), apnea, sepsis, IVH, periventricular leukomalacia (PVL), were also collected from the files. CP and accompanying major and minor sequelae were determined. Major neurodevelopmental sequelae were recorded as CP, epilepsy, hydrocephalus and hearing loss[1]. Minor neurodevelopmental sequelae included attention deficit hyperactivity disorder (ADHD), strabismus, refractive errors (myopia/hypermetropia)[5]. The patients diagnosed with functional motor disorders were classified into 5 levels using the gross motor function classification system (GMFCS)[11]. Level 1 was classified as the least dependency in motor functions, while level 5 was classified as the most dependency. The Denver developmental screening test-II (DDST) was administered to children aged six and under, and children at risk who were apparently normal and had age- appropriate skills were assessed in four areas: gross and fine motor, cognitive, personal, and language. In the DDST, if there were no delays or delays in a category and at most one warning, that section was interpreted as "normal" in itself. Two or more delays in a category were interpreted as "abnormal" cases[12]. For verbal and performance assessments in children over 6 years of age, the Wechsler intelligence scale for children-revised (WISC-R) was used[13]. Cranial MRI scans were performed on all participants included in the study. Cranial MRI findings were classified into 6 categories: structural disorders of the central nervous system, white matter lesions, cortical/subcortical lesions, basal ganglia/thalamus lesions, other anomalies (asymmetric ventricle, cystic lesion, hydrocephalus) and normal findings[14]. Ethics committee approval for our study was received from Aydın Adnan Menderes University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval no: 2012/36, date: 26.03.2012). The study was part of a pediatric specialty thesis.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 21 was used in the analysis of data. Pearson chi-square, Linear-by-Linear Association, and Fisher's exact tests were used to compare categorical data. The odds ratio was used to determine the most important risk factor among significant categorical risk factors. Quantitative data were expressed as mean ± standard deviation values, while categorical data were expressed as n (number) and percentages (%). Data were examined at a 95% confidence level and p-values less than 0.05 were considered significant.

Results

A total of 66 cases between 2-10 years of age, 34 (51.5%) of whom were girls, were included in the study. The mean gestational age was 29.5±1.77 (25-31.6) weeks and mean birth weight was 1255±254.2 g. The general characteristics of the cases are summarized in Table 1, while their distribution based on birth weight and gestational age is detailed in Table 2.

Neurological Examination Results

Neurological examination findings were normal in 49 patients (74.2%), while 17 patients (25.8%) exhibited abnormal findings. Among these, nine patients (13.5%) were diagnosed with CP. Six of these patients were already under follow-up in our pediatric neurology clinic with a confirmed diagnosis of CP, while three additional patients were newly diagnosed

with CP as a result of this study and were subsequently referred to physical therapy and special education treatment programs for follow-up. According to the GMFCS of the cases with CP; one was stage 5, one was stage 4, and 7 were stage 2. As a major neurological sequela, 1.5% of the cases had bilateral sensorineural hearing loss, and 1.5% required a shunt for hydrocephalus. Antiepileptic treatment was ongoing in 9.1% of the cases due to epilepsy. Regarding minor neurological findings, 12.1% had strabismus, and 10.6% were using corrective glasses for refractive errors. Additionally, 12.1% were under child psychiatry follow-up for ADHD. The detailed data on major and minor neurological sequelae are presented in Table 3. The relationship between the prenatal risk factor polyhydramnios and neurological examination abnormalities was found to be statistically significant (p=0.015). Additionally, significant associations were observed between neonatal risk factors, including IVH, PVL and ROP, and neurological examination abnormalities (p=0.001, <0.001, 0.008, respectively). The ORs for these factors were 10, 33 and 5, respectively.

Table 1. General characteristics of the study group

Number of cases	66
Birth weight (gr)	1255.3±254.2
Gestational age (weeks)	29.52±1.77
Gender (M/F)	32/34
1st min Apgar ≤6	14 (21.2%)
5th min Apgar ≤6	4 (6.1%)
Normal spontaneous vaginal delivery	16 (24.2%)
Caesarean section	50 (75.8%)
Singleton pregnancy	47 (71.2%)
Twin pregnancy	16 (24.2%)
Triplet pregnancy	3 (4.5%)

Table 2. Distribution of cases by birth weight and gestational age (n=66)

Gestational age (weeks)	**n**	**%**
25-27	11	16.6
28-30	36	54.4
31-32	19	29.0
Birth weight (g)	**n**	**%**
700-750	2	3.0
751-1000	9	13.7
1001-1250	22	33.7
1251-1500	35	49.6

Developmental Test Results

Of the 66 cases, 57 (86.4%) were in their first six years of age and underwent the DDST. Of these, 24 (36.4%) were found to be normal for their age, while 42 (63.6%) showed abnormalities. WISC-R was administered to 9 (13.6%) cases over the age of six, and the mental functioning levels and general functionality of all these cases were found to be normal or above average (Table 4). A statistically significant relationship was observed between prenatal risk factors, including passive smoking, assisted reproductive technology, polyhydramnios, maternal urinary tract infections,

Table 3. Associated minor/major neurological sequelae

Number of cases	**n**	**%**
*ADHD	8	12.1
*Strabismus	8	12.1
*Myopia	5	7.6
**Hypermetropia	2	3
**Deafness (bilateral sensorineural hearing loss)	1	1.5
**Hydrocephalus	3	4.6
**Epilepsy	6	9.1
**Cerebral palsy	9	13.6

*: Minor sequelaes, **: Major sequelaes
ADHD: Attention deficit hyperactivity disorder

Table 4. Developmental screening test results

		Normal n (%)	**Abnormal n (%)**
	Language	24 (42.1)	33 (57.9)
Denver DST (n=57)	Fine motor	35 (61.4)	2 (38.6)
	Gross motor	31 (54.4)	26 (45.6)
	Personal-social	30 (52.6)	27 (47.4)
WISC-R (n=9)		9 (100)	0 (0)
Total		24 (36.4)	42 (63.6)

DST: Developmental screening test, WISC-R: Wechsler intelligence scale for children-revised

chorioamnionitis, placenta previa, and abruptio placenta, and abnormal findings in developmental tests (p=0.047, 0.021, 0.046, 0.042, 0.047, 0.023). Similarly, the relationship between neonatal risk factors, such as IVH and PVL, and abnormalities in developmental tests was statistically significant (p=0.049, 0.043).

MRI Results

MRI findings were normal in 47 cases (71.2%). PVL was detected in 12 cases (18.2%). The distribution of cranial MRI findings is shown in Table 5. The relationship between the prenatal risk factor of polyhydramnios and MRI abnormalities was found to be statistically significant (p=0.006; OR=10.39). Additionally, the relationship between neonatal risk factors, including gender, IVH, PVL, and ROP, and MRI abnormalities was also statistically significant (p=0.001, 0.001, <0.001, 0.002; OR=6.1, 9.4, 13.2, 3.8, respectively). The prenatal and neonatal risk factors associated with adverse neurodevelopmental outcomes are summarized in Table 6.

Table 5. Cranial MRI findings of the cases

Number of cases	**n**	**%**
Normal	47	71.2
PVL	12	18.2
Cortical/subcortical lesion	1	1.5
Basal ganglia/thalamus lesion	1	1.5
Other abnormalities		
-Asymmetric ventricle	1	1.5
-Cystic lesion	1	1.5
-Hydrocephalus	3	4.6
Total	66	100

MRI: Magnetic resonance imaging, PVL: Periventricular leukomalacia

Discussion

CP is a condition that significantly impacts motor development, cognitive abilities, and overall quality of life, particularly in premature infants. The risk of CP in VLBW infants is 50-70 times higher than in term infants. However, with technological advancements in NICUs, the global the rate of CP and neurological pathologies was between 8-37%[1-3,8,15]. Improved survival rates and better care in NICUs have contributed to a decline in CP prevalence; however, minor sequelae in these infants may be overlooked in clinical practice. In response, our study emphasized the importance of closely monitoring minor neurological abnormalities, which, despite their subtlety, can significantly impact long-term outcomes. The frequency of CP and other neurodevelopmental morbidities varies across studies, with global and national differences observed in VLBW populations. Erdem et al.[16] reported a neurological abnormality rate of 24.2% in 62 VLBW infants, with 14.5% developing CP. Similarly, Valcamonico et al.[17] observed a CP prevalence of 20.6% among severe cases and 18.7% among mild cases in their cohort. Aslan and Çalkavur[1] detected neurological examination pathologies as CP in 8% of 107

Table 6. Prenatal and neonatal risk factors with negative effects on neurodevelopment

		Neurological examination		**Developmental test**		**Cranial MRI**	
		p	**Odss ratio (95% CI)**	**p**	**Odss ratio (95% CI)**	**p**	**Odss ratio (95% CI)**
	Polyhydramnios	ns	-	0.046	7.19 (0.859-60.1381)	ns	-
	Passive smoking	ns	-	0.047	3 (0.994-9.051)	ns	-
	ART	ns	-	ns	-	ns	-
	Maternal UTI	ns	-	ns	-	ns	-
Prenatal	Chorioamnionitis	ns	-	ns	-	ns	-
	Placenta previa	ns	-	ns	-	0.006	10.39 (1.869-57.714)
	Placental abruption	ns	-	ns	-	ns	-
Neonatal	Male gender	ns	-	ns	-	<0.001	6.133 (2.111-17.824)
	IVH	0.001	10 (2.472-40.447)	ns	-	0.001	9.462 (2.224-40.252)
	PVL	<0.001	33.571 (6.052-186.228)	ns		<0.001	13.2 (3.017-57.759)
	ROP	0.008	5.766 (1.707-19.469)	ns	-	0.002	3.8 (1.195-12.087)

ns: Not significant, ART: Assisted reproductive technology, UTI: Urinary tract infection, MRI: Magnetic resonance imaging, CI: Confidence interval, IVH: Intraventricular hemorrhage, PVL: Periventricular leukomalacia, ROP: Retinopathy of prematurity

premature babies. In studies conducted in our country on preterms at 34 weeks and below, the prevalence of CP was found to be 8.5% and 11.1%, respectively[2,8]. Evensen et al.[18] evaluated infants with VLBW at the age of 5 years and found the rate of CP and neurological pathologies was between 8-37%. In a study conducted in Australia between 1980-2017, in which data were collected from 6 different centres, CP was found to be 7.1%, minor neurological sequelae 1.6% and severe neurological sequelae 16.9%[7]. In our study, CP was identified in 13.5% of VLBW infants, major neurological sequelae in 25.8%, and minor abnormalities in 34.8%. These findings are consistent with the results reported in previous studies[2,7,8,16]. These results highlight the need for structured follow-up programs to track both major and minor neurodevelopmental outcomes in VLBW infants, ensuring comprehensive care and timely interventions to mitigate long-term complications.

CP risk is significantly higher in VLBW infants (<1500 g, <32 weeks), with risk increasing as gestational age and birth weight decrease, consistent with Aslan and Çalkavur[1], Bulbul et al.[2], and Göçer et al.[8] findings. In our study of high -risk infants treated in NICUs, birth weight showed no significant impact on neurological examinations, developmental test outcomes, or cranial MRI findings. These results are consistent with those of Thompson et al.[19], who reported similar findings in a comparable cohort, highlighting the challenges of establishing clear associations in smaller sample sizes. These discrepancies underline the importance of larger, more homogeneous cohorts to better define the relationship between prematurity and neurodevelopmental outcomes.

Several prenatal and neonatal risk factors, including passive smoking (p=0.047), placenta previa (p=0.047), abruptio placenta (p=0.023), polyhydramnios (p=0.046), male gender (p=0.001), IVH (p=0.001), PVL (p≤0.001) and ROP (p=0.002), were identified as significant contributors to adverse neurodevelopmental outcomes in our study, in line with previous literature[1,3,8]. Moreover, the risk of brain injury, including white matter damage and IVH, increases with lower gestational age and birth weight. Early identification and optimization of prenatal and neonatal care are essential for improving neuromotor development.

There are studies in the literature showing that all risk factors in the antenatal and neonatal periods may cause spasticity, mostly spastic diplegia. In the study conducted by Ahlin et al.[20], it was shown that all factors in the antenatal, perinatal and postnatal periods increase the risk of spastic diplegia and quadriplegia. In the study conducted by Himmelmann et al.[21], it was determined that perinatal or postnatal etiologies played a role in 80% of the patients with dyskinetic CP. In our study, 7 of all cases diagnosed with CP were diplegic and 2 were tetraplegic. Similar to the literature, spastic diparesis was found more.

Studies on premature infants with CP have consistently shown a higher prevalence of male predominance. Metz et al.[22] reported a male-to-female ratio of 1.72 in 384 cases and Ekici et al.[23] found a ratio of 1.5 in a Turkish population. The increased vulnerability of males to CP and other neurodevelopmental disorders has been attributed to differences in brain organization, genetic predispositions, and the neuroprotective effects of female sex hormones. Importantly, our findings revealed that the association between male sex and MRI abnormalities was six times higher compared to females, further emphasizing the role of gender in the neurodevelopmental prognosis of this population.

The importance of developmental tests has long been recognized, with screening highlighting the risk of neurological and developmental delays in VLBW infants, even in the absence of major morbidities. Studies have consistently shown significant delays across all areas of the DDST in this population compared to term infants. Göçer et al.[8] reported abnormal DDST results in 27.4% of 117 high-risk preterm infants, while Bulbul et al.[2] identified delays in personal-social (4.2%), fine motor (6.3%), language (5.2%), and gross motor (9.4%) skills in preterm infants assessed at a corrected age of 12-18 months. In our study, 63.6% of patients evaluated with the DDST exhibited abnormal findings, with delays in gross motor skills (45.6%), fine motor skills (38.6%), language (57.9%), and personal-social (47.4%) areas. Prenatal and neonatal risk factors have been shown to negatively impact long-term WISC-R scores. Kucur et al.[24] found that PVL reduced WISC-R scores in their study of 11-12 year old late/early preterm children. However, in our study, all 9 cases tested with WISC-R had normal or above-average verbal and performance scores. This discrepancy may be due to the small sample size and suggests that the NICU care at our institution was well-developed during that period. Developmental tests are essential for tracking neurodevelopmental prognosis, premature with CP, where motor impairments frequently coexist with sensory, cognitive, and behavioral disorders, epilepsy, and musculoskeletal issues. Although CP diagnosis often occurs around two

years of age using clinical risk assessment, neurological examination, developmental tests, and MRI findings, there is no universally accepted early diagnostic standard. To bridge this gap, comprehensive developmental evaluations are essential to detect cognitive and behavioral disorders that may not be evident through neurological examination alone[10]. Our study utilized DDST and WISC-R developmental tests. This methodology underscores the critical role of comprehensive developmental evaluations in the long-term monitoring of premature infants, providing valuable contributions to the literature on neurodevelopmental care.

Cranial MRI is a crucial tool for assessing the neurodevelopmental prognosis of premature infants with VLBW. MRI plays a key role in identifying neonatal factors, such as IVH and PVL, which contribute to white and grey matter damage and are involved in the etiology of CP. It also helps detect major and minor morbidities observed in infants with VLBW by the age of 2 and beyond[15,17]. Several studies in the literature have highlighted the significance of MRI in detecting abnormalities in VLBW infants. Erdem et al.[16] identified radiological abnormalities in 40% of CP cases, including 6.5% with PVL. Woodward et al.[25] reported 17% moderate and 4% severe white matter abnormalities in premature infants, while Boswinkel et al.[26] found white matter abnormalities in 23.5% and cerebellar hemorrhage in 12.6% of cases[25,26]. Aslan and Çalkavur[1] observed cranial MRI abnormalities in 29% of infants under 34 weeks. Katušić et al.[27] found abnormal MRI in LBW infants and noted a correlation with motor performance deficits. Martini et al.[28] found significant associations between developmental delays and abnormal cranial MRI findings, particularly with white matter lesions, which were linked to poorer motor and cognitive outcomes. In our study, 28.8% of cranial MRI findings were abnormal, with PVL identified in 18.2% of the cases. Our research underscores the crucial role of MRI in assessing the neurodevelopmental prognosis of preterm infants, making a significant contribution to the literature.

Study Limitations

The limitations of our study include the small sample size, with only nine cases out of 169 participants being over the age of six.

Conclusion

Our study emphasizes the critical role of comprehensive developmental evaluations, such as the DDST and WISC-R, in the long-term monitoring of premature infants, highlighting the importance of early interventions for improving neuromotor outcomes. Moreover, it underscores the value of MRI as an indispensable tool for assessing the neurodevelopmental prognosis of preterm infants, contributing significantly to the existing literature on neurodevelopmental care. The findings also stress the importance of minimizing predictable and preventable prenatal and neonatal risks associated with CP and its sequelae. Through neurological examination, developmental testing, and cranial MRI in VLBW infants, particularly at two years of age and beyond, we highlight the ongoing need for continued surveillance in monitoring CP and its often-overlooked minor sequelae. This calls for more frequent follow-up assessments to improve early detection and outcomes. Finally, our study advocates for more comprehensive, nationally representative research to better understand and address the risks associated with CP, underscoring the need for targeted public health strategies to support this issue at risky population.

Ethics

Ethics Committee Approval: Ethics committee approval for our study was received from Aydın Adnan Menderes University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval no: 2012/36, date: 26.03.2012).

Informed Consent: This retrospective and cross-sectional study included 66 patients aged 2 years and older, who underwent neurological examination, developmental assesments, and cranial MRI, and whose families provided written consent.

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of Measles, Mumps, Hepatitis A and Hepatitis B Seroprevalence in Health Care Providers of a Training and Research Hospital

Bir Eğitim ve Araştırma Hastanesi Çalışanlarında Kızamık, Kabakulak, Hepatit A ve Hepatit B Seroprevalansının Değerlendirilmesi

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Abstract

Objective: The study aims to evaluate the antibody levels in the blood of hospital employees against vaccine-preventable diseases and determine the immunity rates for measles, mumps, and hepatitis A and B among hospital staff.

Methods: This cross-sectional, retrospective study included hospital employees with available measles antibody data. Antibody levels for measles, mumps, hepatitis A and B were examined.

Results: Six hundred and two employees' data were obtained as part of the periodic health screening. Of the employees, 29.4% (n=177) were male and 70.6% (n=425) were female. Measles antibodies were found to be positive in 53.5% (n=322), negative in 38.2% (n=230), and in the gray zone in 8.3% (n=50) of the employees. Mumps antibodies were positive in 81% (n=265), in the gray zone in 16.2% (n=53) and 2.8% (n=9) were in the gray zone. Hepatitis B antibodies were positive in 75.6% (n=455), while hepatitis A antibody levels were positive in 72% (n=431) of the employees. Hepatitis B positivity was significantly higher in physicians. Measles and hepatitis A positivity increased with age, while hepatitis B positivity decreased with age ($p<0.05$). Employees in intensive care units had a notably lower measles positivity rate (35.8%), and pediatric department staff showed lower hepatitis B positivity than the hospital average.

Conclusion: Healthcare workers, who are at a higher risk compared to the general population, must have immunity to these diseases. Ongoing screening and vaccination are essential, as antibody levels may change. Large-scale, multicenter seroprevalence studies will help refine national immunity strategies.

Keywords: Health surveillance, occupational health and safety, health care providers, measles antibody

Öz

Amaç: Çalışmanın amacı; hastane çalışanlarının aşıyla önlenebilir hastalıklara karşı kandaki antikor düzeylerinin değerlendirilmesi ve hastane çalışanlarının kızamık, kabakulak, hepatit A ve hepatit B'ye karşı bağışıklık düzeylerinin belirlenmesidir.

Yöntem: Retrospektif kesitsel tipteki bu çalışmaya kızamık antikor verilerine sahip hastane çalışanları dahil edildi. Kızamık, kabakulak, hepatit A ve B için antikor düzeyleri incelendi.

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Öz

Bulgular: Periyodik sağlık taramaları kapsamında 602 çalışanın verisi elde edildi. Çalışanların %29,4'ü (n=177) erkek ve %70,6'sı (n=425) kadındı. Kızamık antikorlarının çalışanların %53,5'inde (n=322) pozitif, %38,2'sinde (n=230) negatif ve %8,3'ünde (n=50) gri bölgede olduğu bulundu. Kabakulak antikorları %81'inde (n=265) pozitif, %16,2'sinde (n=53) gri bölgede ve %2,8'inde (n=9) gri bölgedeydi. Hepatit B antikorları çalışanların %7,6'sında (n=455) pozitifken, hepatit A antikor seviyeleri çalışanların %72'sinde (n=431) pozitifti. Hepatit B pozitifliği hekimlerde anlamlı olarak daha yüksekti. Kızamık ve hepatit A pozitifliği yaşla birlikte artarken, hepatit B pozitifliği yaşla birlikte azaldı (p<0,05). Yoğun bakım ünitelerindeki çalışanların kızamık pozitiflik oranı belirgin şekilde daha düşüktü (%35,8) ve pediatri bölümünde çalışanların hepatit B pozitifliği hastane ortalamasından düşük bulundu.

Sonuç: Bulaşıcı hastalıklar açısından topluma kıyasla daha yüksek risk altında olan sağlık çalışanlarının bu hastalıklara karşı bağışık olmaları gerekmektedir. Zaman içerisinde antikor düzeylerinde değişim de olabileceğinden sürekli tarama ve aşılama esastır. Büyük ölçekli, çok merkezli seroprevalans çalışmaları ulusal bağışıklık stratejilerini iyileştirmeye yardımcı olacaktır.

Anahtar Kelimeler: Sağlık gözetimi, iş sağlığı ve güvenliği, sağlık hizmeti sağlayıcıları, kızamık antikoru

Introduction

Healthcare workers are at higher risk of infection than the general population because they come into contact with patients' body fluids, blood, and respiratory particles. When infected, they carry the risk of spreading the disease to other healthcare workers, patients, and the community. Therefore, being immune to diseases that can be prevented through vaccination is very important for both personal and public health[1]. One of the viruses that is increasing in frequency globally and that threatens society is the measles virus. According to the data published by the World Health Organization, 2.367 measles cases were reported in Türkiye between September 2023 and August 2024. The total number of cases reported in the European region during this period is 138.740[2].

Measles is a contagious and fatal disease that can spread through airborne particles and cause serious complications and death. It can affect individuals of all ages, especially children. When the virus is transmitted, it first infects the respiratory tract and then spreads throughout the body. Symptoms include high fever, runny nose, cough, and widespread rash on the body. The disease develops on average 10-12 days after contact with a person with measles. People with measles are considered contagious for 4 days before after the rash begins[3]. The most effective way to prevent the transmission and spread of measles is vaccination[4]. Adults without a record of vaccinated against measles or rubella, who have had the disease, or who have serologically negative antibodies, should receive at least 1 dose. Individuals working in healthcare facilities should receive two doses of the measles-mumps-rubella vaccine at least 28 days apart[5].

Mumps is a contagious disease caused by the mumps virus, which belongs to the paramyxovirus family. The disease begins with mild symptoms such as headache, fatigue, and fever. However, parotitis develops later, typically causing tenderness and swelling of the cheeks and jaw. The incubation period is 7-25 days on average. The virus is transmitted through direct contact with infected saliva or respiratory droplets from an infected person. Mumps is preventable due to the vaccine's effectiveness[6].

Viral hepatitis continues to be a major health problem worldwide as it is one of the infectious diseases with high mortality. The global hepatitis report 2024 published by the World Health Organization reported that an estimated 254 million people are living with the hepatitis B virus (HBV)[7]. Hepatitis A is a disease that can be transmitted through the fecal-oral route. Hepatitis B is a vaccine-preventable disease caused by HBV and can be transmitted to an uninfected person through the blood, semen, or body fluids of an infected person. Vaccination programs in our country are planned and implemented to protect both the community and healthcare professionals.

Our study was conducted at Buca Seyfi Demirsoy Training and Research Hospital. Our hospital was opened in 2002 as a Social Insurance Institution (SSK) Hospital, and gained the status of training and research hospital in 2020 with the joint use protocol signed between İzmir Democracy University and the Ministry of Health. It has a bed capacity of 318; 152 of which are intensive care.

According to article 15 of the Occupational Health and Safety Law No. 6331, employers take into account the health and safety risks that workers will be exposed to in the workplace and ensure that they are subject to health surveillance. Within this scope, pre-employment examinations are carried out. Serological examinations are carried out in our hospital for healthcare workers who are deemed at risk.

Our aim in the study is to determine the healthcare workers' immunity rate for measles, mumps, hepatitis A, and B by evaluating the antibody levels in the blood of hospital workers against vaccine-preventable diseases.

Materials and Methods

This study was designed as a retrospective cross-sectional study. The sample of the study consisted of all healthcare workers in Buca Seyfi Demirsoy Training and Research Hospital whose measles antibodies were checked during the annual health screening.

Ethics committee approval for the study was received from the Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee with the decision number: 2024/363 dated: 27.11.2024.

Measles, mumps, hepatitis A, and hepatitis B antibody Immunoglobulin G levels determined by enzyme-linked immunosorbent assay were evaluated. It was evaluated whether there was a difference in these values according to the age, gender, profession and unit of employment of the individuals.

Statistical Analysis

Statistical analysis of the obtained data was performed using the SPSS-29 software package. Descriptive distribution analysis was used in the evaluation of the data, and the chi-square test was used in statistical analysis. A p-value of less than $p<0.05$ was considered statistically significant.

Results

Within the scope of periodic health screening, antibody values for measles, mumps, hepatitis B, and hepatitis A were retrospectively scanned, and data from a total of 602 employees were obtained. 29.4% (n=177) of the employees were male and 70.6% (n=425) were female (Table 1).

Measles antibodies were found to be positive in 53.5% (n=322) of the workers, negative in 38.2% (n=230), and in the gray zone in 8.3% (n=50). Mumps antibodies were found to be positive in 81% (n=265), gray-zone in 16.2% (n=53), and negative in 2.8% (n=9). Hepatitis B antibodies were found to be positive in 75.6% (n=455) and negative in 24.4% (n=147); hepatitis A antibody values were reported as positive in 72% (n=431) and negative in 28% (n=168). No significant difference was found in antibody values between the gender groups. When the employees were examined according to their professions, 23.6% (n=142) were physicians, 34.1% (n=205) were nurses and midwives, 26.2% (n=158) were workers, 7.6% (n=46) were technicians, and 8.5% (n=51) were other hospital employees. Although no statistically significant difference was found, the measles antibody seropositivity rate was observed to be the lowest in physicians (43.7%) and the highest in technicians (60.9%). Hepatitis B antibody positivity was found to be significantly higher in physicians ($p<0.05$) (Table 2). It was observed that measles and hepatitis A antibody positivity of employees examined according to age groups, increased significantly with age. While the positive measles and hepatitis A antibody rates in employees aged 50 and over were 87.5-95%, these values were found to be 36.3-65% in the 19-30 age group. The hepatitis B antibody positivity rate was negatively correlated with age ($p<0.05$). The rate of mumps antibodies was found to be significantly high in the 31-49 age group (87.8%). When examined based on the departments in which they worked, measles antibody positivity among intensive care unit workers was well below average at 35.8%. No significant difference was found between units in terms of mumps and hepatitis A antibodies. Among pediatric patients, the hepatitis B antibody positivity rate was found to be below the hospital average (Table 3).

Table 1. Sociodemographic characteristics of participants

Variable	Category	n	%
Gender	Male	177	29.4
	Female	425	70.6
Age group	19-30 years	281	46.7
	31-49 years	281	46.7
	50 years and above	40	6.6
Profession	Nurse	205	34.1
	Physician	142	23.6
	Worker	158	26.2
	Technician	46	7.6
	Other staff	51	8.5
Department	Emergency service	71	11.8
	Surgical clinics	64	10.6
	Pediatrics	48	8
	Internal clinics	122	20.3
	Administrative department	103	17.1
	Gynecology	29	4.8
	Laboratory	13	2.2
	Cleaning services	71	11.8
	ICU	81	13.4

ICU: Intensive care unit

Table 2. Antibody values according to profession

Profession		Measles antibody				Mumps antibody				Hepatitis A antibody			Hepatitis B antibody		
		Negative	GZ	Positive	Total	Negative	GZ	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
Nurse	n	73	13	119	205	23	3	116	142	48	155	203	46	159	205
	%	35.6%	6.3%	58.0%	100.0%	16.2%	2.1%	81.7%	100.0%	23.6%	76.4%	100.0%	22.4%	77.6%	100.0%
Physician	n	65	15	62	142	11	1	53	65	48	94	142	25	117	142
	%	45.8%	10.6%	**43.7%**	100.0%	16.9%	1.5%	81.5%	100.0%	33.8%	66.2%	100.0%	17.6%	82.4%	100.0%
Worker	n	53	16	89	158	9	1	51	61	42	116	158	52	106	158
	%	33.5%	10.1%	56.3%	100.0%	14.8%	1.6%	83.6%	100.0%	26.6%	73.4%	100.0%	32.9%	**67.1%**	100.0%
Technician	n	14	4	28	46	3	2	25	30	11	35	46	15	31	46
	%	30.4%	8.7%	60.9%	100.0%	10.0%	6.7%	83.3%	100.0%	23.9%	76.1%	100.0%	32.6%	**67.4%**	100.0%
Other staff	n	25	2	24	51	7	2	20	29	19	31	50	9	42	51
	%	49.0%	3.9%	**47.1%**	100.0%	24.1%	6.9%	69.0%	100.0%	38.0%	62.0%	100.0%	17.6%	82.4%	100.0%
Total	n	230	50	322	602	53	9	265	327	168	431	599	147	455	602
	%	38.2%	8.3%	**53.5%**	100.0%	16.2%	2.8%	**81.0%**	100.0%	28.0%	**72.0%**	100.0%	24.4%	**75.6%**	100.0%
p-value		p>0.05				p>0.05				p>0.05			**p=0.01***		

*: p<0.05, GZ: Gray zone

Discussion

The results of this study showed that the highest seropositivity rate among our hospital staff was for mumps (81%), while the lowest seropositivity rate was for measles (53.5%). Hepatitis B antibody positivity was 75.6%, and hepatitis A positivity was 72%. Many seroprevalence studies have been conducted among healthcare workers in our country and around the world, and seropositivity rates have varied from region to region.

In some studies conducted in our country, the anti-HBs positivity rate was found to be between 56.5% and 88%, similar to our study[8-14]. In a study conducted among healthcare workers in an oncology hospital, 95.7% were found to be seropositive for measles and 82.3% for mumps[15]. In a study conducted by Cılız et al. [16] in a university hospital close to our region, seropositivity was observed as 84.1% seropositivity for hepatitis B, 99.7% for measles, and 99.7% for mumps in healthcare workers. In a study conducted in Eskişehir, the seropositivity rate for hepatitis B was found to be high in nurses and doctors, and hepatitis A seropositivity was also 71.7%, similar to our study[9]. In a study conducted on 384 volunteer healthcare workers at Zonguldak Bülent Ecevit Hospital in 2019, the antibody positivity rate against measles was found to be 92.2%[17]. In a cross-sectional study conducted by Altın et al.[13] the positivity rate was reported as 74.17% for hepatitis B, 31.48% for hepatitis A, 64.36% for measles, and 72.2% for mumps; the average age of those with positive hepatitis A, measles, and mumps antibodies was found to be higher. In our study, the measles and hepatitis A antibody positivity rates were found to be similarly high, and hepatitis B antibody positivity was found to be lower in those with an older average age. We believe that the viral load an individual has been exposed to throughout life may contribute to the increasing measles antibody positivity rate with age. In another multicenter study conducted in our country, measles seropositivity was reported as 77.6% and mumps seropositivity as 81.6%[18]. In a study conducted in Korea to compare measles seroprevalence among healthcare workers in two hospitals, the general measles seropositivity rate was 93.1%. It was found that the antibody positivity rate increased as the average age increased[19]. In another study conducted in Korea, the general measles seropositivity rate was found to be 73%, and, when the workers were examined according to their birth years, the seropositivity rate of those born in earlier years was found to be higher, similar to the findings of our study. It was thought that this situation might have been due to vaccination failure, insufficient immune

Table 3. Antibody values according to department

Department		Measles antibody				Mumps antibody				Hepatitis A antibody			Hepatitis B antibody		
		Negative	GZ**	Positive	Total	Negative	GZ**	Positive	Total	Negative	Positive	Total	Negative	Positive	Total
Emergency service	n	30	7	34	71	3	0	27	30	24	45	69	13	58	71
	%	42.3%	9.9%	**47.9%**	100.0%	10%	0.0%	90.0%	100.0%	34.8%	65.2%	100.0%	18.3%	81.7%	100.0%
Surgical clinics	n	20	7	37	64	6	1	38	45	20	44	64	7	57	64
	%	31.3%	10.9%	57.8%	100.0%	13.3%	2.2%	84.4%	100.0%	31.3%	68.8%	100.0%	10.9%	89.1%	100.0%
Pediatrics	n	16	5	27	48	7	0	40	47	12	36	48	14	34	48
	%	33.3%	10.4%	56.3%	100.0%	14.9%	0.0%	85.1%	100.0%	25.0%	75.0%	100.0%	29.2%	**70.8%**	100.0%
Internal medicine	n	53	9	60	122	17	4	51	72	38	83	121	29	93	122
	%	43.4%	7.4%	**49.2%**	100.0%	23.6%	5.6%	**70.8%**	100.0%	31.4%	68.6%	100.0%	23.8%	76.2%	100.0%
Administrative department	n	35	6	62	103	5	2	34	41	34	69	103	36	67	103
	%	34.0%	5.8%	60.2%	100.0%	12.2%	4.9%	82.9%	100.0%	33.0%	67.0%	100.0%	35.0%	**65.0%**	100.0%
Gynecology	n	9	0	20	29	3	1	18	22	7	22	29	8	21	29
	%	31.0%	0.0%	69.0%	100.0%	13.6%	4.5%	81.8%	100.0%	24.1%	75.9%	100.0%	27.6%	**72.4%**	100.0%
Laboratory	n	2	1	10	13	0	0	9	9	2	11	13	2	11	13
	%	15.4%	7.7%	76.9%	100.0%	0.0%	0.0%	100.0%	100.0%	15.4%	84.6%	100.0%	15.4%	84.6%	100.0%
Cleaning service	n	19	9	43	71	5	0	24	29	12	59	71	22	49	71
	%	26.8%	12.7%	60.6%	100.0%	17.2%	0.0%	82.8%	100.0%	16.9%	83.1%	100.0%	31.0%	**69.0%**	100.0%
ICU	n	46	6	29	81	7	1	24	32	19	62	81	16	65	81
	%	56.8%	7.4%	**35.8%**	100.0%	21.9%	3.1%	**75.0%**	100.0%	23.5%	76.5%	100.0%	19.8%	80.2%	100.0%
Total	n	230	50	322	602	53	9	265	327	168	431	599	147	455	602
	%	38.2%	8.3%	**53.5%**	100.0%	16.2%	2.8%	**81.0%**	100.0%	28.0%	**72.0%**	100.0%	24.4%	**75.6%**	100.0%
p-value		**p=0.015***				p>0.05				p>0.05			**p=0.022***		

*: p<0.05, **: GZ: Gray zone, ICU: Intensive care unit

response to the vaccine, or exposure to infection during the nationwide epidemic in 2000-2001[20]. In a study conducted in Spain in 2013, measles seropositivity was found to be 98%, and in a study conducted in 2023, it 89%[21,22]. Again, in a study conducted in Spain to screen for hepatitis B seroprevalence in healthcare workers, hepatitis B antibody positivity was found to be 64.4%, and a higher positive antibody rate was reported in workers under the age of 25, similar to our results[23].

As we found in our study and the existing literature, the level of immunity against infectious diseases can vary from region to region and over the years. In recent years, there has been an increase in infectious diseases, especially measles, due to the entry of people with unknown immunity. It is thought that the interruption of vaccination during the pandemic period may also have an impact on this situation.

Study Limitations

The limitations of our study can be listed as its retrospective and single-center nature, the lack of screening for the antibody values of all employees in the hospital, and the inability to access the vaccination status of the employees.

Conclusion

Healthcare workers, who are at higher risk of infectious diseases compared to the general public, need to be immunized against these diseases. The low seropositivity rates we have detected in departments that are particularly risky, such as intensive care units and pediatrics, are of great importance.

Since antibody levels may change over time, screening and vaccination programs should be continued without slowing down as recommended by the Ministry of Health. Protecting healthcare workers from infectious diseases will also be significantly effective in protecting public health. We believe that conducting multicenter, comprehensive seroprevalence studies will contribute to the development of health strategies by determining the current immunity status in our country.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was received from the Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee with the decision number: 2024/363 dated: 27.11.2024.

Informed Consent: This study was designed as a retrospective cross-sectional study.

Footnotes

Authorship Contributions

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

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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An Investigation of Patient Experiences from Outpatient to Inpatient Services in an Integrated Health Campus: The Case of Ankara Etlik City Hospital

Entegre Bir Sağlık Kampüsünde Poliklinikten Kliniğe Hasta Deneyimlerinin İncelenmesi: Ankara Etlik Şehir Hastanesi Örneği

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Abstract

Objective: The aim of this study is to examine the experiences of outpatients and inpatients at University of Health Sciences Türkiye, Ankara Etlik City Hospital and to investigate the factors influencing patient satisfaction in the integrated healthcare campus environment.

Methods: A cross-sectional research design was employed, and a patient experience survey was administered to both outpatient and inpatient groups. The survey assessed various dimensions of patient experience, including communication with healthcare providers, hospital environment, medication information, discharge information, and overall satisfaction. The collected data were then subjected to analysis using both descriptive and comparative statistical methods to identifying significant differences based on the demographic characteristics of the participants.

Results: The results indicate that patients generally express high satisfaction with the healthcare services provided, particularly in terms of communication with healthcare providers and the hospital environment. However, experiences were reported as average regarding appointment scheduling, waiting times, and accessibility of transportation. The analysis revealed significant disparities in patient experience based on demographic characteristics such as age, educational attainment, and general health status. Patients aged 65 and above, those with lower education levels, and those reporting better health status generally scored higher satisfaction levels.

Conclusion: The study suggests that while patient experiences at University of Health Sciences Türkiye, Ankara Etlik City Hospital are generally positive, improvements are needed in appointment systems, transportation infrastructure, and waiting area comfort. The findings of this study offer valuable insights that can inform the enhancement of healthcare quality within the context of integrated health campuses.

Keywords: Integrated healthcare campus, city hospital, patient experience, healthcare service quality, outpatient and inpatient services

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Öz

Amaç: Bu çalışma, Sağlık Bilimleri Üniversitesi, Ankara Etlik Şehir Hastanesi'nde ayaktan ve yatarak hizmet alan hastaların deneyimlerini incelemeyi ve entegre sağlık kampüsü ortamında hasta memnuniyetini etkileyen faktörleri araştırmayı amaçlamaktadır.

Yöntem: Kesitsel bir araştırma deseni kullanılarak, hem ayaktan hem de yatarak tedavi gören hastalara bir hasta deneyimi anketi uygulanmıştır. Anket, sağlık çalışanlarıyla iletişim, hastane ortamı, ilaç bilgisi, taburculuk bilgisi ve genel memnuniyet gibi farklı hasta deneyimi boyutlarını değerlendirmiştir. Veriler, demografik özelliklere göre anlamlı farkları belirlemek amacıyla betimsel ve karşılaştırmalı istatistiksel yöntemlerle analiz edilmiştir.

Bulgular: Sonuçlar, hastaların genel olarak sunulan sağlık hizmetlerinden yüksek memnuniyet duyduklarını, özellikle sağlık çalışanlarıyla iletişim ve hastane ortamından memnuniyetin yüksek olduğunu göstermektedir. Ancak, randevu planlama, bekleme süreleri ve ulaşım erişilebilirliği gibi alanlarda ortalama deneyimler söz konusu olmuştur. Yaş, eğitim durumu ve genel sağlık durumu gibi demografik özelliklere göre hasta deneyiminde anlamlı farklılıklar tespit edilmiştir. Altmış beş yaş ve üzeri hastalar, düşük eğitim seviyesindeki hastalar ve daha iyi sağlık durumu bildiren hastalar genel olarak daha yüksek memnuniyet puanları almışlardır.

Sonuç: Araştırma, Sağlık Bilimleri Üniversitesi, Ankara Etlik Şehir Hastanesi'nde hasta deneyimlerinin genel olarak olumlu olduğunu, ancak randevu sistemleri, ulaşım altyapısı ve bekleme alanı konforu gibi faktörlerde iyileştirmeler yapılması gerektiğini önermektedir. Bu bulgular, entegre sağlık kampüslerinde sağlık hizmetleri kalitesinin artırılması için önemli ipuçları sunmaktadır.

Anahtar Kelimeler: Entegre sağlık kampüsü, şehir hastanesi, hasta deneyimi, sağlık hizmet kalitesi, ayaktan ve yatan hasta hizmetleri

Introduction

The primary objective of healthcare services is to improve the health status of individuals receiving care, ensure a positive experience, and to facilitate their discharge from the hospital with satisfaction. Patient experiences, recognised as a pivotal quality indicator in the monitoring and evaluation of health systems, are instrumental in addressing patients' needs, enhancing their satisfaction, and implementing improvements[1]. Consequently, the measurement of patient satisfaction and experience is frequently favoured. These measurements provide valuable insights for the improvement of healthcare services[2]. Furthermore, they serve as pivotal instruments from a patient policy standpoint, aiding in the support of healthcare delivery, the formulation and management of health policies, the fulfilment of legal obligations, and the protection of patients' rights[3]. The adequacy of the service provided is determined by the patient's perceived level of service quality, which is developed over time in relation to the institution. This perception is also influenced by the institution's actual performance in delivering a specific service[4].

In the contemporary healthcare sector, the implementation of strategies aimed at enhancing patient satisfaction, ensuring reliability, and fostering patient loyalty has become imperative for organisations in the market. To implement these strategies effectively, it is crucial to heed the voices of patients who directly experience the service. In the context of intensifying competition within the healthcare sector, providers are moving beyond the provision of medical treatment and care to include the delivery of a superior standard of comfort. Consequently, patient feedback, derived from their experiences, emerges as a valuable source of information for enhancing the quality of healthcare services. This information should be actively utilised as a fundamental quality indicator in the planning and management of healthcare delivery. Positive patient experiences have been shown to engender memorable impressions, thereby strengthening satisfaction and loyalty[5].

It is evident that patients who have positive experiences and are satisfied with the care they receive provide long-term benefits to healthcare providers. Their favourable behaviours, such as praising or recommending the institution, contribute significantly to enhancing the competitive advantage of healthcare organisations[6]. Given that the cost of retaining existing patients is considerably lower than that of acquiring new ones, patient loyalty plays a critical role in ensuring the sustainability of healthcare institutions within the sector[6]. In the context of escalating costs associated with attracting new patients and intensifying market competition, healthcare providers are progressively orienting their strategic focus towards fostering customer loyalty[7]. In this context, while customer loyalty is regarded as the currency of the 21st century for businesses, patient loyalty is considered one of the most important competitive advantages for healthcare organizations[8].

Patient experience is a critical indicator of the effectiveness and efficiency of a healthcare system. Consequently, enhancing patient experience within healthcare organisations has emerged as a pivotal concern for administrators, clinical leaders, and policymakers. Patients utilising healthcare

services have expectations of receiving the highest quality of care, accompanied by commensurate service standards. In this regard, the patient is the only actor who experiences the entire journey by connecting every step of the healthcare process. Consequently, hospitals can enhance the quality of services provided by discovering and understanding the individual patient journey[9]. Patients who report negative experiences often exhibit delayed responses to treatment and have lower levels of adherence. The repercussions of substandard patient experiences are manifold, encompassing not only diminished patient health outcomes and treatment effectiveness but also the escalating costs of healthcare[10].

In response to the need for qualified hospitals and hospital beds in Türkiye, integrated health campuses -commonly referred to as city hospitals- have been established through the public-private partnership model. The objective of these hospitals is to integrate geographically dispersed and hierarchically diverse healthcare institutions within a centralized system, harmonize fragmented administrative structures, and transfer financial responsibilities to private sector investors in order to share financial risks[11,12]. Furthermore, the intention is to enhance the delivery of healthcare services by utilising advanced technology and a highly qualified workforce, while also aiming to improve patient safety and satisfaction. The hospitals have been designed to provide a wide range of healthcare services under one roof and are structured as major regional medical centres. Türkiye's strategic restructuring and modernisation of these large-scale healthcare facilities is driven by two key objectives: the enhancement of healthcare service quality and the attainment of a more prominent global healthcare market position[13].

The primary focus of this study is to assess the evaluations of patients who have received services from city hospitals, which were established within the framework of this objective. In this context, the study aims to evaluate the experiences of patients who received care at University of Health Sciences Türkiye, Ankara Etlik City Hospital. Specifically, the study seeks to compare the experiences of outpatients and inpatients based on their individual characteristics and reasons for admission, focusing on their general perceptions of outpatient clinics and their propensity to recommend the hospital. Another objective of the study is to examine the relationship between outpatient experience, general perception of outpatient clinics, and recommendation scores, as well as the relationship between inpatient experience and recommendation score. The evaluation of patient experiences across the continuum of care, from outpatient clinics to inpatient wards within an integrated health campus such as University of Health Sciences Türkiye, Ankara Etlik City Hospital, is of paramount importance in identifying both the strengths and areas in need of improvement at different stages of service delivery. Furthermore, the comparative analysis of experiences between outpatients and inpatients may reveal how service differences are perceived by patients and thus contribute to the development of a more equitable, effective, and sustainable healthcare delivery model.

Materials and Methods

Patients and the Study Design

The study population comprised patients who received services from University of Health Sciences Türkiye, Ankara Etlik City Hospital (decision no: 09/231, date: 22.11.2023. According to data obtained from the official website of the Ministry of Health, a total of 5.016.501 outpatient visits and 118.032 inpatient admissions were recorded at the hospital between September 28, 2022, and September 28, 2023. The minimum sample size was calculated to be 385 for outpatient surveys and 383 for inpatient surveys, based on a 95% confidence level, a 5% margin of error, and 80% power.

Patients who received services from the clinics and outpatient departments of the general hospital, neurology and orthopaedics hospital, chest and cardiovascular hospital, oncology hospital, obstetrics and gynaecology hospital, and physical therapy and rehabilitation hospital were included in the sample. however, patients from the paediatric hospital, psychiatric hospital, emergency departments, and intensive care units were excluded from the study.

A stratified sampling method was employed to ensure representativeness across the institutions within the health campus. The allocation of strata was proportional, with hospital-specific patient volumes (both outpatient and inpatient) being utilized as the basis for this calculation. Participants were selected through random sampling, with participation being a voluntary basis. The final sample comprised 421 outpatients and 406 inpatients who completed the questionnaires in their entirety. Data were collected between January and February 2024.

This descriptive cross-sectional study employed structured face-to-face questionnaires. The assessment of outpatient experiences was facilitated by items adapted from the care quality commission questionnaire, while the measurement of inpatient experiences was conducted using the hospital

consumer assessment of healthcare providers and systems survey. The net promoter score (NPS) was utilised to assess the likelihood of recommending the hospital at the conclusion of each questionnaire. The collection of inpatient data occurred after discharge decisions had been made but prior to patients' physical departure from the hospital, whereas the collection of outpatient data was undertaken immediately following clinical consultations.

The reliability of the questions used to assess the experiences of the patients who participated in the study was evaluated using the internal consistency coefficient (Cronbach's Alpha, α).

The overall reliability level of the outpatient experience questionnaire was found to be 0.920. This indicates that the set of questions developed to evaluate patients' outpatient experiences is internally consistent and therefore reliable.

The overall reliability level of the inpatient experience questionnaire was determined to be 0.764. This suggests that the set of questions designed to assess the inpatient experience also demonstrates internal consistency and can be considered reliable.

Statistical Analysis

The data were summarised using descriptive statistics, including frequency, percentage, mean, and standard deviation. The normality of the experience scores was assessed using histogram plots, Kolmogorov-Smirnov/Shapiro-Wilk tests, and Skewness-Kurtosis coefficients. Following the confirmation of normal distribution, independent samples t-tests, were employed for comparisons between two groups, and analysis of variance (ANOVA) was used for comparisons across more than two groups. Tukey's honestly significant difference test was conducted for post-hoc analyses following significant ANOVA results. Pearson correlation analysis was used to evaluate relationships between variables. All statistical analyses were performed using SPSS version 23, with the level of statistical significance set at $p<0.05$.

Results

Results of Outpatient

Table 1 shows that the 421 outpatients participating in the study were predominantly female (60.1%) and aged between 30 and 44 (36.3%). The majority of participants had a high school diploma (38.7%) or an associate/bachelor's degree (40.9%), with only 1.9% holding a master's or doctoral degree. The majority of the participants were covered by SGK (98.0%), while a small proportion had private health insurance, and another small proportion used contracted institutions (1.0% each).

A perusal of Table 2 reveals that outpatients have a favourable perception at a "good" level of the hospital's diagnostic and treatment processes, accessibility, and outpatient services.

As demonstrated in Table 3, a statistically significant discrepancy was identified in the "diagnosis and treatment processes" subdimension based on age ($f=3.140$, $p=0.025$). The 18-29 age group exhibited higher scores (4.00±0.67) compared to those aged 65 and above (3.58±0.71). Furthermore, a statistically significant discrepancy was identified in the "accessibility" subdimension based on the rationale for hospital attendance ($f=2.557$, $p=0.014$), with patients attending for postoperative follow-up (4.60±0.23) demonstrating higher accessibility scores compared to those visiting for test results (3.72±0.57).

As demonstrated in Table 4, the subdimensions "diagnosis and treatment processes" and "accessibility" of outpatient

Table 1. Demographic characteristics of outpatient patient

Demographic characteristics	Frequency (n)	Percentage (%)
Gender		
Female	253	60.1
Male	168	39.9
Age		
18-29	102	24.2
30-44	153	36.3
45-64	139	33.0
65 and above	27	6.4
Education level		
Primary school	78	18.5
High school	163	38.7
Associate/bachelor's degree	172	40.9
Master's/doctorate degree	8	1.9
Social security		
SGK	413	98.0
Private health insurance	4	1.0
Contracted institutions	4	1.0
Total	**421**	**100**

SGK: Social insurance

experience exhibited a strong correlation both with each other and with the "general perception of the polyclinic" variable. The relationship between these variables and NPS was found to be moderate.

Results of Inpatients

Table 5 presents the results related to the individual characteristics of inpatients. The majority of the participants were female (n=244), aged between 45 and 64 years (n=141), had received a primary school education (n=164), and had SGK social security (n=181). With regard to general health status, the majority of participants perceived their health as good (n=251).

As demonstrated in Table 6, the analysis indicates that inpatients have a favourable perception of communication with nurses and doctors, communication regarding medications, and the hospital environment. Given that the response options for discharge information were "yes" and "no," further analysis is needed to determine if the perception of discharge information is at the desired level.

Table 7 analysis shows significant differences in hospital environment scores by age (f=2.805, p=0.040), with those aged 65 and above scoring higher than the 30-44 and 45-64 age groups. Both medication communication scores (f=2.727, p=0.044) and discharge information scores (f=2.556, p=0.048) were higher for primary school graduates compared

Table 2. Descriptive statistics of outpatient experience survey questions and dimensions

Questions	Mean ($\bar{x}$)	Standard deviation (±)
How would you evaluate the process of being informed by your consultants and other staff members?	3.95	0.81
Did your doctor explain your illness and treatment process in a way that you could understand?	3.87	0.96
How would you evaluate your doctor's examination time related to your health or medical condition?	3.87	0.92
How would you evaluate the importance given to your privacy during your examination or while discussing your condition/treatment?	4.00	0.88
How would you evaluate your participation in decisions related to your care and treatment?	3.84	0.80
How would you evaluate the adequacy of the information provided during and after the tests?	3.85	0.88
How would you evaluate your participation in decisions about your medication and the information you received regarding your medications?	3.76	0.88
How would you evaluate the resolution of the reason for your visit to the outpatient clinic, according to your expectations?	3.81	0.83
Diagnosis and treatment processes	**3.86**	**0.68**
How would you evaluate your ability to schedule an appointment?	3.69	0.98
Was your appointment rescheduled by the hospital to a later date?	4.70	0.61
How would you evaluate the waiting time for your appointment at the hospital?	3.55	0.92
How would you evaluate the hospital's accessibility?	3.50	1.02
How would you evaluate the behavior of the reception and consultation staff toward you?	4.02	0.85
How would you evaluate the waiting area? (seating, temperature, cleanliness)	3.79	0.94
How would you evaluate your access to the necessary departments (radiology, laboratory, etc.) for the tests requested by your doctor?	3.70	0.91
Ease of access	**3.84**	**0.57**
General perception level of outpatient services	**3.93**	**0.87**

Table 3. Comparison of outpatient experience survey subdimensions and NPS by demographic characteristics

Demographic characteristics	Diagnosis and treatment processes		Ease of access		General perception of polyclinic		NPS	
	Mean ± SD	t/F p	Mean ± SD	t/F p	Mean ± SD	t/F p	Mean ± SD	t/F p
Gender								
Female	3.83±0.68	t=-1.246	3.81±0.55	t=-1.342	3.92±0.87	t=-0.224	7.59±2.47	t=0.325
Male	3.92±0.69	p=0.214	3.89±0.59	p=0.180	3.94±0.89	p=0.823	7.67±2.45	p=0.745
Age								
18-29	4.00±0.67[a]		3.87±0.63		4.08±0.81		7.82±2.34	
30-44	3.86±0.67[ab]	F=3.140	3.85±0.58	F=0.127	3.92±0.85	F=1.975	7.65±2.41	F=0.543
45-64	3.82±0.68[ab]	p=0.025	3.83±0.62	p=0.944	3.88±0.92	p=0.117	7.53±2.62	p=0.653
65 and above	3.58±0.71[b]		3.79±0.60		3.67±0.87		7.22±2.41	
Education level								
Primary school	3.98±0.70		4.01±0.60		4.09±0.84		7.62±2.93	
High school	3.86±0.68	F=1.083	3.80±0.60	F=2.409	3.87±0.86	F=1.169	7.65±2.12	F=0.486
Associate/bachelor's degree	3.81±0.67	p=0.356	3.81±0.61	p=0.067	3.91±0.89	p=0.321	7.56±2.57	p=0.692
Master's/doctoral degree	3.93±0.82		3.92±0.65		4.00±1.07		8.63±1.60	
Social security								
SGK	3.87±0.68	F=0.754	3.85±0.60	F=1.577	3.94±0.87	F=1.306	7.65±2.46	F=1.144
Private health insurance	3.62±0.72	p=0.471	3.32±0.45	p=0.208	3.75±0.95	p=0.272	6.00±2.44	p=0.320
Contracted institutions	3.53±0.99		3.75±0.88		3.25±1.25		6.75±2.06	
Hospital visit-related questions								
Frequency of visit								
Once	4.06±0.70		4.00±0.63		4.13±0.87		7.90±2.58	
2-3 times	3.81±0.66		3.87±0.56		3.91±0.85		7.62±2.39	
4-8 times		F=2.337		F=2.003		F=2.574		F=0.686
8-10 times	3.83±0.69	p=0.055	3.75±0.63	p=0.093	3.80±0.86	p=0.051	7.65±2.29	p=0.602
More than 10 times	3.73±0.69		3.72±064		3.73±0.94		7.03±2.85	
Once	3.98±0.67		3.83±0.62		4.17±0.88		7.64±2.64	
Reasons for hospital visit								
To undergo tests	3.85±0.69		3.91±0.61[ab]		3.84±0.85		7.56±2.49	
To show test results	3.88±0.65		3.72±0.57[a]		3.99±0.81		7.42±2.49	
To receive medical diagnosis and treatment	3.84±0.71		3.82±0.60[ab]		3.92±0.92		7.80±2.35	
To undergo regular check-ups	3.80±0.42	F=0.762	4.11±0.49[ab]	F=2.557	3.80±0.83	F=1.188	7.60±3.13	F=0.959
Pre-surgical examination	3.58±0.59	p=0.619	3.33±0.92[ab]	p=0.014	3.00±1.00	p=0.308	5.33±2.08	p=0.461
Post-treatment follow-up	3.95±0.58		3.91±0.65[ab]		4.04±0.75		7.33±2.92	
Post-surgical follow-up	4.47±0.32		4.60±0.23[b]		4.40±0.89		9.20±1.30	
Other	3.95±0.67		4.07±0.62[ab]		4.23±0.72		7.38±2.72	

Note: Groups with the same letters ([a], [b]) in the same row do not show significant differences.
NPS: Net promoter score, SGK: Social insurance, SD: Standard deviation

Table 4. Correlation values between the sub-dimensions of the outpatient experience survey and NPS

	Diagnosis and treatment processes	Accessibility	General polyclinic perception	NPS
Diagnosis and treatment processes	1			
Accessibility	0.767**	1		
General polyclinic perception	0.765**	0.635**	1	
NPS	0.588**	0.543**	0.563**	1

NPS: Net promoter score, **: p<0.01

to associate/bachelor's graduates; NPS scores were higher for associate/bachelor's graduates, compared to high school graduates (f=2.574, p=0.043). Furthermore, individuals who self-reported "very good" health status demonstrated significantly elevated scores across all subdimensions and the NPS.

Table 8 provides an overview of the correlation values between the sub-dimensions of the inpatient experience survey and NPS. In this context, statistically significant relationships were identified between all sub-dimensions and NPS, with the exception of the relationship between the sub-dimensions of discharge information and hospital environment. The strength of the relationship indicates a moderate correlation between "nurse and physician communication" "hospital environment", and NPS. Conversely, the relationships between the remaining sub-dimensions and NPS were found to be weak.

Discussion

The objective of the study is to assess individuals' experiences receiving medical care in city hospitals. Although patient satisfaction surveys have been conducted for many years in Türkiye, the measurement of patient experience is a relatively new concept. In the context of large and complex healthcare delivery environments, such as integrated health campuses, studies that evaluate patient experiences across different service levels, including outpatient and inpatient services, in a holistic manner, are quite limited. Nevertheless, such structures provide a significant foundation for exploring the impact of different departmental operations on patient perceptions.

The study examines seven dimensions of patient experience as outcome measures: diagnostic and treatment processes, ease of access, overall outpatient clinic perception, communication with nurses and physicians, communication about medications, discharge information, and hospital environment. The study also explores the potential influences on the hospital experience, including factors such as appointment and waiting times, geographical location, physical size, staff-to-patient ratio, communication, and hospitality services.

Table 5. Demographic characteristics of inpatient patient

Demographic characteristics	Frequency (n)	Percentage (%)
Gender		
Female	162	39.9
Male	244	60.1
Age		
18-29	82	20.2
30-44	114	28.1
45-64	141	34.7
65 and above	69	17.0
Education level		
Primary school	164	40.4
High school	156	38.4
Associate/bachelor's degree	80	19.7
Master's/doctoral degree	6	1.5
Social security		
SGK	397	97.8
Private health insurance	6	1.5
Contracted institutions	3	0.7
General health status		
Very good	74	18.2
Good	251	61.8
Average	55	13.5
Poor	22	5.4
Very poor	4	1.0
Total	**406**	**100**

The majority of outpatients are female and belong to the middle to older age groups. A subsequent examination of their educational attainment revealed that the proportion of high school and university/graduate school graduates was comparable. These findings are consistent with those

reported by Erdem and Pirinçci[14], although it is hypothesised that this congruence is attributable to the predominance of female patients and older age groups within the hospital population, and the absence of stratification by gender and education level during the sample selection process. With respect to the frequency of hospital visits, a significant proportion of patients had visited the hospital 2-8 times in the past year, which is below the national average in Türkiye[15].

Patients receiving outpatient care report satisfaction with both the quality of communication with their healthcare providers and the duration of their medical examinations. The impact of effective doctor-patient communication on the quality of care has been well-documented[16]. Furthermore, patients with higher health literacy report a more positive treatment experience[17]. Participants expressed high satisfaction with privacy during examination, which is consistent with findings from a study in Konya[18].

With regard to accessibility, patients expressed satisfaction with appointment scheduling, and the frequency of appointment date changes initiated by the hospital was low. The percentage of patients whose symptoms worsened while waiting was lower than a UK study[19]. Nepal et al.[20] found that clear expectations reduced patients' concerns and positively impacted their treatment experience.

Statistically significant differences were identified in outpatient diagnosis and treatment scores according to age. In contrast to the findings of this study, McFarland et al.[21] reported that younger and more educated patients exhibited lower levels of satisfaction. The overall perception of outpatient clinic services was 78.6% (3.93), a figure comparable to data from the UK[22].

Research on nurse-patient communication highlights that inpatient dissatisfaction is attributable to communication deficiencies[23]. The present study yielded favourable outcomes in the communication subdimensions related to

Table 6. Descriptive statistics of inpatient experience survey questions and dimension

Questions	Mean ($\bar{x}$)	Standard deviation (±)
During your stay at the hospital, how often did nurses treat you with courtesy and respect?	4.78	0.52
During your stay at the hospital, how often did nurses listen to you carefully?	4.74	0.52
During your stay at the hospital, how often did nurses provide explanations and information about your treatment and care?	4.67	0.61
During your stay at the hospital, how often did doctors treat you with courtesy and respect?	4.52	0.76
During your stay at the hospital, how often did doctors listen to you carefully?	4.39	0.94
During your stay at the hospital, how often did doctors provide explanations about your treatment and care in a way you could understand?	4.41	0.80
Communication with nurses and doctors	**4.58**	**0.48**
How often were you given information about the medication by nurses before being given a new medication?	4.60	0.70
Did the nurses explain the potential side effects of a new medication before administering it?	4.07	1.25
Communication about medicines	**4.33**	**0.87**
During your stay at the hospital, did you receive written information about which symptoms or health problems to watch for after leaving the hospital?	1.85	0.35
During your stay, did doctors, nurses, or other hospital staff discuss with you whether you would receive the necessary help after leaving the hospital?	1.82	0.38
Discharge information	**1.83**	**0.32**
During your stay at the hospital, how often was your room environment quiet?	4.55	0.68
During your stay at the hospital, how often was your room and bathroom cleaned?	4.17	0.90
Hospital environment	**4.35**	**0.65**

interactions with nurses and doctors. Concurrently, studies by Hitawala et al.[24] have demonstrated the efficacy of visual brochures in enhancing doctor-patient communication. Chen et al.[25] emphasized that satisfaction with healthcare staff is a significant factor influencing inpatient satisfaction.

In the context of the medication subdimension, participants expressed satisfaction with the information provided by nurses regarding their treatments. Wilkes et al.[26] found that inpatients preferred to be informed about the side effects and benefits of medications, and this knowledge positively contributed to treatment.

In the discharge information subdimension, the majority of participants expressed positive sentiments regarding discharge and subsequent care. The importance of written discharge instructions in enhancing patient satisfaction is underscored by the findings of[27]. Patel and Bechmann[28] also found that patient education improves not only satisfaction but also the quality of follow-up care.

Table 7. Comparison of inpatient experience survey subdimensions and NPS by demographic characteristics

Demographic characteristics	Nurse and doctor communication		Medication communication		Discharge information		Hospital environment		NPS	
	Mean ± SD	t/F p	Mean ± SD	t/F p	Mean ± SD	t/F p	Mean ± SD	t/F p	Mean ± SD	t/F p
Gender										
Female	4.57±0.47	t=0.401	4.31±0.88	t=0.608	1.82±0.33	t=0.288	4.32±0.66	t=1.149	8.50±2.11	t=0.321
Male	4.59±0.51	p=0.689	4.36±0.85	p=0.544	1.83±0.32	p=0.773	4.40±0.64	p=0.251	8.43±2.03	p=0.748
Age										
18-29	4.63±0.42		4.23±0.88		1.79±0.37		4.32±0.61^{ab}		8.81±1.67	
30-44	4.55±0.51	F=1.802	4.32±0.82	F=0.846	1.87±0.27	F=1.719	4.30±066^{b}	**F=2.805**	8.42±2.10	F=2.811
45-64	4.52±0.50	p=0.146	4.33±0.89	p=0.469	1.80±0.34	p=0.162	4.31±0.70^{b}	**p=0.040**	8.12±2.30	p=0.079
65 and above	4.67±0.46		4.46±0.88		1.86±0.29		4.56±0.54^{a}		8.84±1.90	
Education level										
Primary school	4.56±0.51		4.42±0.78^{a}		1.88±0.28^{a}		4.44±0.66		8.49±2.10^{ab}	
High school	4.59±0.46		4.29±0.92^{ab}		1.81±0.34^{ab}		4.26±0.67		8.19±2.28^{a}	
Associate/ bachelor's degree	4.59±0.47	F=0.190 p=0.903	4.28±0.87^{ab}	**F=2.727 p=0.044**	1.76±0.36^{b}	**F=2.556 p=0.048**	4.39±0.58	F=2.764 p=0.062	8.94±1.53^{b}	**F=2.574 p=0.043**
Master's/ doctoral degree	4.66±0.31		3.50±1.30^{b}		1.83±0.25^{ab}		4.00±0.77		9.17±0.75^{ab}	
Social security										
SGK	4.58±0.48		4.34±0.86		1.83±0.32		4.35±0.65		8.46±2.09	
Private health insurance	4.47±0.67	F=0.741 p=0.478	3.75±1.40	F=1.855 p=0.158	1.83±0.40	F=0.387 p=0.679	4.25±0.68	F=1.523 p=0.219	8.50±1.76	F=0.497 p=0.609
Contracted institutions	4.88±0.19		4.83±0.28		2.00±0.00		5.00±0.00		9.67±0.57	
General health status										
Very good	4.79±0.34^{a}		4.49±0.93^{a}		1.92±0.22^{a}		4.67±046^{a}		9.28±1.60^{a}	
Good	4.58±0.47^{b}	**F=7.733**	4.35±0.78^{ab}	**F=2.225**	1.83±0.32^{a}	**F=5.693**	4.32±0.63^{b}	**F=7.836**	8.51±1.89^{b}	**F=7.323**
Average	4.40±0.52^{bc}	**p=0.001**	4.04±1.03^{b}	**p=0.032**	1.79±0.34^{a}	**p=0.001**	4.21±0.79^{b}	**p=0.001**	7.62±2.52^{c}	**p=0.001**
Poor	4.29±0.67^{c}		4.29±1.06^{ab}		1.72±0.42^{ab}		3.97±0.76^{b}		7.95±2.55^{bc}	
Very poor	4.41±056^{abc}		4.50±0.57^{ab}		1.25±0.50^{b}		4.75±0.28^{ab}		6.00±4.89^{bc}	

Note: Same letters (^{a}, ^{b}, ^{c}) in the same row indicate no significant difference between groups.
NPS: Net promoter score, SGK: Social insurance, SD: Standard deviation

Table 8. Correlation values between the sub-dimensions of the inpatient experience survey and NPS

	Nurse and doctor communication	Medication communication	Discharge information	Hospital environment	NPS
Nurse and doctor communication	1				
Medication communication	0.272**	1			
Discharge information	0.150**	0.290**	1		
Hospital environment	0.426**	0.222**	0.080	1	
NPS	0.525**	0.108**	0.134**	0.297**	1

**: p<0.01, NPS: Net promoter score

In the hospital environment subdimension, participants reported positive experiences regarding noise levels and cleanliness. Taylor et al.[29] identified noise as the predominant sleep disruptor among hospitalized patients. Pyrke et al.[30] further corroborated the efficacy of single rooms in mitigating noise disturbances and enhancing sleep quality.

Statistical analysis revealed significant variations in hospital environment scores based on age, with patients aged 65 and above demonstrating higher scores compared to younger age groups (f=2.805, p=0.040). These findings are consistent with those of[31].

A further analysis compared educational levels, with primary school graduates demonstrating higher scores in the medication communication and discharge information subdimensions. These findings are consistent with those reported by Jalil et al.[32] who found that lower levels of education were associated with poorer outcomes.

Study Limitations

The present study was subject to several limitations. The dearth of analogous studies within Türkiye and internationally impeded the establishment of direct comparisons. The research focused on a single hospital campus, so the findings may not be generalizable to other healthcare settings. The potential for selection bias arises if patients who declined participation differ significantly from those who accepted. Furthermore, the exclusion of patients who did not speak Turkish may have influenced the results. Despite the study's objective to establish a comprehensive framework, further research is necessary to investigate potential variations related to language, ethnicity, and cultural factors. Furthermore, because patient interviews were conducted immediately prior to discharge, the accuracy of reported experiences may have been compromised since patients had not yet undergone the post-discharge process.

Conclusion

This study, which examined the experiences of patients receiving outpatient and inpatient care at University of Health Sciences Türkiye, Ankara Etlik City Hospital, found that patients were generally satisfied with the services provided and reported positive experiences. Nevertheless, issues such as average experiences in appointment scheduling, waiting times, and suboptimal accessibility in transportation suggest that improvements in appointment systems, transportation infrastructure, and waiting area comfort could enhance the overall patient experience.

Ethics

Ethics Committee Approval: This study received Ankara Yıldırım Beyazıt University of Social and Human Sciences approval (decision no: 09/231, date: 22.11.2023) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Our study was conducted using a survey method with patients, and information was provided before the survey and their approval was obtained. Patients who agreed to participate completed the survey.

Footnotes

This study is based on the first author's master thesis.

Authorship Contributions

Surgical and Medical Practises: S.C.Ö., K.A., Concept: S.C.Ö., K.A., Design: S.C.Ö., K.A., Data Collection or Processing: S.C.Ö., Analysis or Interpretation: S.C.Ö., K.A., Literature Search: S.C.Ö., K.A., Writing: S.C.Ö., K.A.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Utilizing of the Lymphocyte/CRP Ratio as a Predictor of Ischemia in Acute Incarcerated Hernias

Akut İnkarsere Hernilerde Lenfosit/CRP Oranının İskemi Öngörücüsü Olarak Kullanılması

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Abstract

Objective: This study aimed to evaluate the lymphocyte-to-[C-reactive protein (CRP)] (LCR) ratio as a potential biomarker for predicting ischemia in patients with acute incarcerated hernias (AIH) and its role in determining the need for bowel resection.

Methods: A retrospective analysis was conducted on 132 patients with AIH who presented to the Ege University Department of Emergency between January 2020 and January 2022. Clinical data, laboratory values (including leukocyte and lymphocyte counts, CRP, and LCR), and imaging results were collected. Patients were divided into two groups: those who underwent bowel resection (n=37) and those who did not (n=95). Relevant parameters were compared between the groups, and receiver operating characteristic (ROC) analysis was performed to assess the predictive value of LCR for ischemia.

Results: The study found that LCR was significantly lower in patients who required bowel resection ($p<0.001$). The ROC curve analysis showed that LCR had an area under the curve of 70.1%, with a sensitivity of 91.6% and specificity of 78.4%. A cut-off value of 0.0409 was identified, with patients above this threshold showing a lower likelihood of requiring resection ($p<0.001$). Mortality was also higher in the low LCR group ($p<0.001$).

Conclusion: The LCR was found to be a significant and reliable predictor of ischemia in AIH. LCR can be used as a simple, cost-effective biomarker to assist in clinical decision-making, particularly in predicting the need for resection and improving patient outcomes. Further studies are recommended to validate these findings.

Keywords: Incarcerated hernia, lymphocyte, C-reactive protein

Öz

Amaç: Bu çalışmada; akut inkarsere herni (AİH) hastalarında iskemiyi öngörmede potansiyel bir biyobelirteç olarak lenfosit/[C-reaktif protein (CRP)] (LCO) oranını değerlendirmek ve barsak rezeksiyonu ihtiyacını belirlemedeki rolü amaçlanmıştır.

Yöntem: Ocak 2020 ile Ocak 2022 tarihleri arasında Ege Üniversitesi Acil Servisi'ne başvuran 132 AİH hastası üzerinde retrospektif bir analiz gerçekleştirilmiştir. Klinik veriler, laboratuvar değerleri (lökosit ve lenfosit sayıları, CRP ve LCO dahil) ve görüntüleme sonuçları değerlendirildi. Hastalar, barsak rezeksiyonu yapılan (n=37) ve yapılmayan (n=95) olmak üzere iki gruba ayrıldı. Gruplar arasında ilgili parametreler karşılaştırıldı ve LCO'nun iskemi için prediktif değerini değerlendirmek için alıcı çalışma karakteristiği (ROC) analizi yapıldı.

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Öz

Bulgular: Çalışma, barsak rezeksiyonu gerektiren hastalarda LCO'nun anlamlı olarak daha düşük olduğunu buldu (p<0,001). ROC eğrisi analizi, LCO'nun eğri altındaki alanın %70,1 olduğunu, duyarlılığının %91,6 ve özgüllüğünün %78,4 olduğunu gösterdi. 0,0409 kesme değeri belirlendi ve bu eşiğin üzerindeki hastaların rezeksiyon gerekliliği olasılığı daha düşük bulundu (p<0,001). Mortalite de LCO düşük olan grupta daha yüksekti (p<0,001).

Sonuç: LCO, AİH'lerde iskeminin önemli ve güvenilir bir belirleyicisi olarak bulunmuştur. LCO, özellikle rezeksiyon ihtiyacını tahmin etmek ve hasta sonuçlarını iyileştirmek için klinik karar verme sürecine yardımcı olacak basit ve uygulanabilir bir biyomarker olarak kullanılabilir. Bu bulguları doğrulamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: İnkarsere herni, lenfosit, C-reaktif protein

Introduction

An acute incarcerated hernia (AIH) occurs when the contents of the hernia sac cannot be reduced back into the abdominal cavity. In contrast, a strangulated hernia involves compromised blood flow to the herniated intestinal segment due to incarceration, representing a serious complication associated with high morbidity and mortality that often necessitates emergency surgery[1]. It is well established that in the emergency repair of incarcerated and strangulated hernias, postoperative mortality, the need for reoperation, and the rate of readmission can increase by up to 15-fold compared to elective hernia surgery[2].

Although emergency surgery plays a critical role in the treatment of AIH, it may not always be immediately feasible due to associated risks and limited surgical availability[3]. In such cases, manual reduction by gently repositioning the herniated tissues back into the abdominal cavity can serve as a temporary solution, potentially delaying the need for surgery from days to even months[4]. Following successful reduction, patients can be monitored for signs of recurrence or ischemia and subsequently scheduled for elective surgery, thereby reducing the risk of high morbidity and mortality.

It is known that postoperative complications are also more common in patients who develop strangulation and need resection[5,6]. Therefore, development of ischemia is of critical importance in terms of complications both in patients scheduled for elective surgery following reduction and in patients who will undergo emergency surgery.

With the widespread use of laboratory tests, proportional parameters have recently become popular in the diagnosis of diseases and prediction of prognosis[7]. Many studies and meta-analyses have been published showing that biomarkers such as neutrophil/lymphocyte ratio (NLR), neutrophil/C-reactive protein (CRP) ratio (NCR), lymphocyte/CRP ratio (LCR) -which are obtained from parameters including leukocytes, neutrophils, lymphocytes, platelets, CRP, and albumin for the evaluation of inflammation- can be used in the diagnosis and follow-up of acute and chronic inflammatory pathologies, sepsis, and malignancies[8,9].

In our study, we aimed to examine the patient's clinical and laboratory parameters in order to evaluate and predict the presence of ischemia, which plays a critical role in the decision-making process in the treatment of AIH.

Materials and Methods

Study Design

Patients presenting to the Ege University Department of Emergency with AIH and evaluated by our team were retrospectively analyzed. Demographic data, blood counts, and computed tomography findings were reviewed. Patients were categorized into two groups: those who underwent bowel resection and those who did not. Bowel ischemia was evaluated intraoperatively and confirmed by histopathological examination in the resection group. Relevant parameters were compared between the groups, and factors associated with the need for resection were identified. The aim was to determine potential predictive markers of ischemia.

Patient Selection

Patients who presented to the emergency department with AIH between January 2020 and January 2022, and were evaluated by our team, were included in the study. Inclusion criteria were: age over 18 years, diagnosis of AIH (including incisional, umbilical, inguinal, or femoral hernias), availability of complete clinical and laboratory data, and acceptance of hospital admission from the emergency department to our surgical clinic. Patients who underwent successful reduction in the emergency department and were not admitted for hospitalization were excluded from the study.

Data Collection

Demographic data, blood counts, and imaging methods of the patients were collected retrospectively through the electronic patient file. Demographic data, complete blood counts, presence of resection (if any), known history of hernia, lactate, lactate dehydrogenase (LDH), CRP values, duration of admission to the emergency department and evaluation in the emergency department, duration of hospitalization, and mortality were collected electronically. Statistical analyses were performed. The value of LCR was calculated as [1.000*lymphocyte count ($\times 10^9$ cells/L)]/[CRP (mg/L)].

Statistical Analysis

SPSS v29.0 (IBM-Chicago, USA) was used to analyze the data, and the normality of continuous data was evaluated by Shapiro-Wilk and Kolmogorov-Smirnov tests. Student's t-test was used for univariate pairwise group analysis of continuous data showing normal distribution, and Mann-Whitney U test was used for univariate pairwise group analysis of continuous data not showing normal distribution. In the analysis of categorical variables, chi-square and Pearson chi-square tests were used according to the table width, and Fisher's exact test was applied when necessary. The ROC curve was utilized as a predictive test, and the Youden index was used to determine the cut-off value.

Ethics

Our study was evaluated by Ege University Medical Research Ethics Committee and approved (decision no: 24-8T/41, date: 22.08.2024).

Results

A total of 132 patients fulfilling the specified criteria were included in our study. Age was not normally distributed, and the median age was 69 years (interquartile range: 64.87-69.87 years). Seventy (53.0%) of the patients were male and 62 (47.0%) were female. Incisional hernia was present in 47 patients (35.6%), umbilical hernia in 19 patients (14.4%), inguinal hernia in 56 patients (42.4%), and femoral hernia in 10 patients (7.6%). Six patients (4.5%) were followed up after reduction and referred to elective surgery, while 126 patients (95.4%) underwent emergency surgery.

Among the patients who underwent emergency surgery, 37 (29.3%) required bowel resection, while 89 (70.7%) did not. Of those who underwent resection, 29 patients (78.4%) had small bowel resection, and 8 patients (21.6%) underwent colon resection. Relevant parameters are summarized in Table 1 and Figure 1.

Six patients who were managed conservatively after successful reduction were included in the non-resection group, as they did not require surgical resection during their hospitalization. Thus, patients were divided into two groups: resection (n=37) and non-resection (n=95). The following variables were compared between the groups: age, sex, presence of a known hernia, recurrent hernia status, time from symptom onset to emergency department presentation, time to surgical evaluation, hernia type at presentation, imaging modalities used, the American Society of Anesthesiology (ASA) scores, leukocyte and lymphocyte counts, lactate, LDH, CRP, LCR, length of hospital stay, and mortality. (Related parameters and p-values are summarized in Table 2).
The female-to-male ratio differed significantly between the non-resection (40/60%) and resection (35.5/64.5%) groups (p=0.010).

The ASA 1 rate was 32.6% in the non-resection group, compared to 16.2% in the resection group. ASA scores were significantly higher in the resection group, with the difference reaching statistical significance (p=0.020).

Table 1. Demographic data of the patients

Parameters	Median/number	95% CI/percent
Age (years)	69	[64.87-69.87]
Gender		
Male	70	53.0%
Woman	62	47.0%
Hernia type		
Incisional	47	35.0%
Umblical	19	14.0%
Inguinal	56	42.2%
Femoral	10	7.6%
Known presence of hernia	36	27.3%
Presence of recurrent hernia	22	16.7%
USG	35	26.5%
CT	60	45.5%
CT+ USG	37	28.0%
ASA score		
1	37	28.0%
2	65	49.2%
3	30	22.7%

ASA: American Society of Anesthesiology, CI: Confidence interval, USG: Ultrasonography, CT: Computed tomography

When the lymphocyte count was evaluated, the median value was 1.45×10³/μL in the non-resection group, compared to 1.07×10³/μL in the resection group. The difference was statistically significant (p=0.001).

CRP levels were compared between the two groups; the median value was 10.32 U/L in the non-resection group and 26.59 U/L in the resection group, with a statistically significant difference (p=0.006). The median LCR value was 0.130 in the non-resection group, compared to 0.027 in the resection group, a difference that was statistically significant (p<0.001). Regarding the duration of hospitalization, a significant difference was observed between the groups (p=0.005), with a median stay of 2.0 days in the non-resection group and 4.0 days in the resection group.

During hospitalization, mortality occurred in 8 patients (8.4%) in the non-resection group and in 9 patients (24.8%) in the resection group, with the difference being statistically significant (p=0.014).

There was no statistically significant difference between the groups in the other available parameters and the relevant values are summarized in Table 2.

LCR was found to be a significant parameter for predicting ischemia, prompting the use of a receiver operating characteristic (ROC) curve to evaluate its predictive value, given its simplicity, effectiveness, and low cost. The area under the curve was 70.1%, which was statistically significant (p<0.001, 95% confidence interval: 0.59-0.79) (Figure 2).

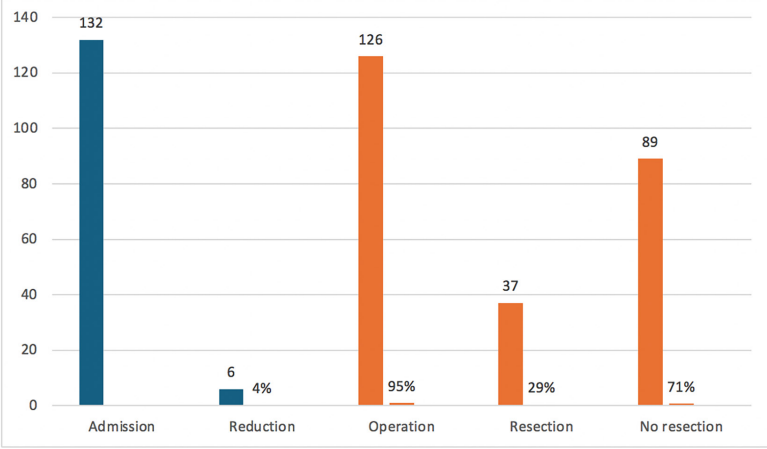

Figure 1. Distribution of operations and resections

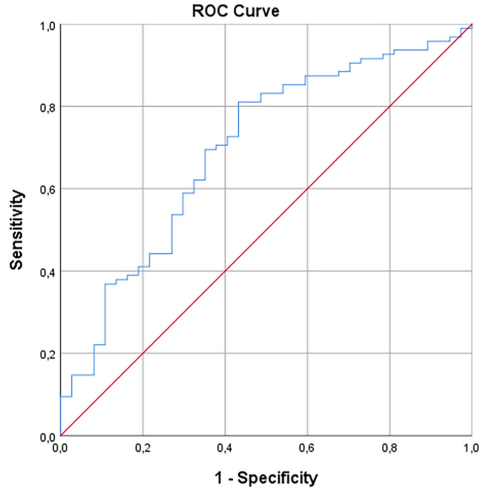

Figure 2. ROC curve for LCR

ROC: Receiver operating characteristic, LCR: Lymphocyte/C-reactive protein ratio

The test demonstrated a sensitivity of 91.6%, specificity of 78.4%, positive predictive value of 91.6%, and negative predictive value of 78.4%.

After obtaining statistical significance in the ROC analysis, the Youden index was used to determine the cut-off value, which was found to be 0.0409. Based on this threshold, patients were divided into two groups: those with LCR higher than 0.0409 and those with LCR lower than 0.0409. A total of 39 patients (29.5%) were in the low LCR group, and 93 patients (70.5%) were in the high LCR group. Among the low LCR group, 46.2% did not require resection, whereas 82.8% of the high LCR group also avoided it, with the difference being statistically significant (p<0.001). Mortality was 28.2% in the low LCR group and 6.5% in the high LCR group, being with the difference with the difference also being statistically significant (p<0.001). Relevant parameters are summarized in Table 3 and Figure 3.

Discussion

In our study, we demonstrated that laboratory parameters can be used simply and effectively to predict the need for

Table 2. Comparation of parameters between groups

Parameter	No resection	Resection	p
Age (years)	69 (63.75-69.74)	71 (64.25-73.69)	0.383
Gender			
Male Female	57 (60%) 38 (40%)	13 (35.1%) 24 (64.9%)	**0.010**
Known presence of hernia	26 (27.4%)	10 (27.0%)	0.968
Presence of recurrent hernia	17 (17.9%)	5 (13.5%)	0.544
Hernia type Incisional Umbilical Inguinal femoral	34 (35.8%) 13 (13.7%) 42 (44.2%) 6 (6.3%)	14 (37.8%) 5 (13.5%) 14 (37.8%) 4 (10.8%)	0.603
Time between symptom and emergency department admission (days)	2.00 (2.52-4.11)	2.00 (2.15-3.79)	0.948
Duration of evaluation in the emergency department (hours)	7.00 (7.21-9.53)	7.00 (5.49-11.27)	0.322
Imaging			
USG CT CT+USG	24 (25.3%) 45 (47.5%) 26 (27.3%)	11 (29.7%) 15 (40.6%) 11 (29.7%)	0.769
ASA score			
1 2 3	31 (32.6%) 48 (50.6%) 16 (16.8%)	6 (16.2%) 17 (45.9%) 14 (37.9%)	0.020
Leukocyte count (10^3/µL)	11.99 (10.97-12.94)	10.18 (10.22-15.37)	0.669
Lymphocyte count (10^3/µL)	1.45 (1.46-2.12)	1.07 (0.85-1.30)	**0.001**
Lactate (mmol/L)	3.60 (4.56-7.38)	5.00 (5.70-10.09)	0.063
LDH (U/L)	211.0 (213.17-243.99)	234.0 (225.00-279.59)	0.104
CRP (mg/L)	10.32 (20.62-48.79)	26.59 (51.72-130.53)	**0.006**
Lymphocyte/CRP ratio	0.130 (0.68-2.18)	0.027 (0.07-0.54)	**<0.001**
Hospitalization	2.0 (2.54-4.24)	4.0 (3.18-5.52)	**0.005**
Mortality	8 (8.4%)	9 (24.8%)	**0.014**

ASA: American Society of Anesthesiology, CRP: C-reactive protein, LDH: Lactate dehydrogenase, USG: Ultrasonography, CT: Computed tomography

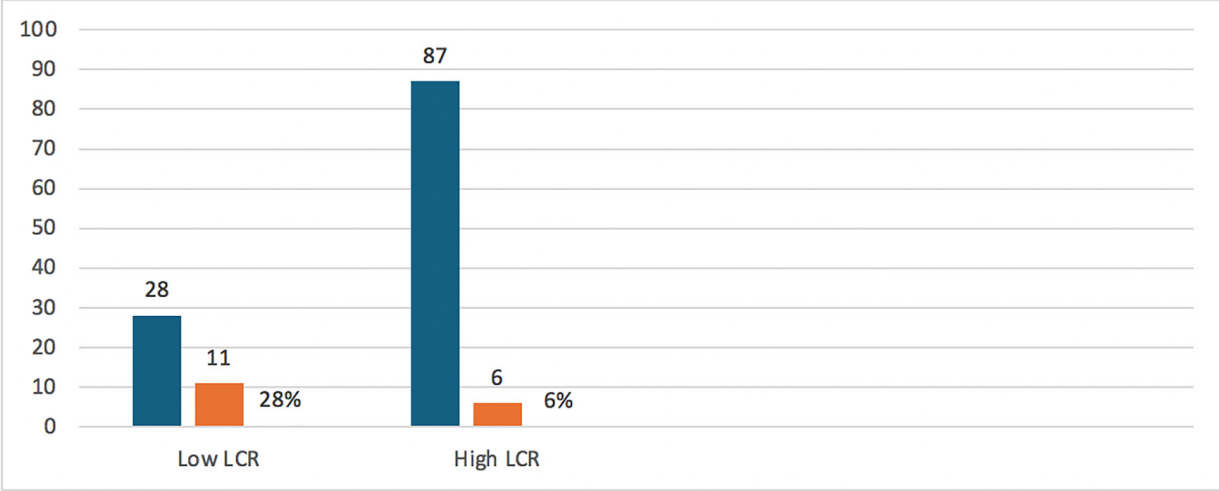

Figure 3. LCR groups and mortality

LCR: Lymphocyte/C-reactive protein ratio

Table 3. LCR groups and ischemia rates

Parameter	Ischemia negative	Ischemia positive
Low LCR	18 (46.2%)	21 (53.8%)
High LCR	77 (82.8%)	16 (17.2%)

LCR: Lymphocyte/C-reactive protein ratio

resection to manage AIH, in line with existing literature. Specifically, the LCR was shown to be a valuable predictive marker, which is clinically helpful for diagnosis. Eyvaz et al.[10] evaluated 129 patients who underwent surgery for acute incarcerated inguinal hernia. They divided the patients into two groups -resection and non-resection- based on the presence of intestinal necrosis, and compared biochemical markers for diagnosing necrosis. In their study, cut-off values for NLR, LCR, and NCR were determined, and all were found to be significant in indicating ischemia. Their results showed that patients with NCR <0.45 (sensitivity: 93.3%, specificity: 87.8%) and LCR <0.1 (sensitivity: 90%, specificity: 78.8%) had an increased risk of ischemia and a higher likelihood of requiring resection, consistent with our findings[10].

In our study, female sex was found to be statistically significant in the resection group in relation to (specific outcome). A meta-analysis by Chen et al.[11], which examined risk factors for bowel resection in incarcerated inguinal hernias, reported that female sex and age (>65) were significant risk factors for resection, in addition to inflammatory parameters. Our findings align with the literature in this regard, although no statistically significant difference was observed between the two groups in terms of age.

Similarly, a study by Kulah et al.[12] evaluating 385 patients who underwent surgery for AIH found that the risk of strangulation was significantly higher in female patients, those with femoral and umbilical hernias, and elderly patients. The study highlighted these factors as important risk indicators for strangulation[12]. A similar study conducted by Alvarez-Pérez et al. [13] in Spain observed strangulation in 43.5% of 230 patients, with bowel resection performed in 13.5% of these cases. The study also found that the resection rate was higher among patients with comorbidities, patients over 60 years old, women, and those with femoral hernias.

In a prospective study by Sneiders et al.[14], which included 4472 patients, risk factors for incarcerated primary and incisional ventral hernias were evaluated. The study found that female sex and the presence of severe comorbidities (ASA 3-4) were associated with an increased risk of incarceration, with the most significant risk factor being the width of the defect (3-4 cm)[14]. In our study, there was a statistically significant difference in ASA scores between the resection and non-resection groups, and our results are consistent with the literature in this regard. However, hernia size data were not available in our study, which represents a limitation.

In the meta-analysis conducted by Emile et al.[15] on biochemical parameters used to identify intestinal necrosis in acute mesenteric ischemia, several studies indicated

that predictors such as white blood cell, NLR, and platelet-lymphocyte ratio were useful in detecting ischemia and necrosis. Although the LCR value was not included in the studies reviewed in this meta-analysis, the findings support the use of biochemical parameters for detecting ischemia.

The presence of ischemia in incarcerated hernias is the most significant factor contributing to increased mortality and morbidity. Early detection or prediction of ischemia plays a crucial role in reducing these risks. In their study on incarcerated inguinal hernias, Zhou et al.[16] highlighted the relationship between ischemia and mortality. They also developed a predictive model and emphasized the importance of identifying key predictive factors. In our study, although hernia type varied, factors such as gender, ASA score, lymphocyte count, CRP level, and the LCR showed statistically significant differences between the resection and non-resection groups. LCR was evaluated as a predictive parameter.

In their study, Yildirim et al.[17] evaluated patients who underwent surgery for strangulated anterior abdominal wall hernias and compared outcomes of patients with and without bowel resection. The study identified neutrophilia, lymphopenia, and elevated CRP as significant biochemical parameters in the resection group. Subsequently, the LCR and NLR were assessed. The study found that an LCR<0.0204 was a significant biomarker for diagnosing strangulation, with 80% sensitivity and 80.2% specificity[17].

Although various parameters are used as markers of ischemia in the literature, the LCR has been found to be a significant marker in the studies by Yildirim et al.[17] and Eyvaz et al.[10]. While Yildirim et al.[17] evaluated incarcerated inguinal hernias, Eyvaz et al.[10] focused on incarcerated incisional hernias. In our study, we evaluated all types of hernias- incisional, umbilical, inguinal, and femoral -and found that LCR was a valuable predictive marker, clinically helpful, and supportive of the diagnosis. Our results are consistent with the existing literature in this regard.

Alhambra-Rodriguez de Guzmán et al.[18] reported that early hospital admission, rapid preoperative evaluation, and timely emergency surgery led to a significant reduction in morbidity and mortality. Therefore, the early detection or prediction of ischemia is crucial for minimizing complications.

Study Limitations

This study has several limitations. First, it is a retrospective design, which inherently carries the risk of bias due to reliance on existing medical records, potentially overlooking unrecorded variables. The sample size of 132 patients may be too small to generalize the results to a broader population, and the single-center nature of the study limits its external applicability. Additionally, the absence of hernia size data, a key factor influencing incarceration and strangulation risk, hinders the full understanding of its role in predicting resection and ischemia. The exclusion of non-surgical patients who underwent successful reduction may introduce selection bias, while the short follow-up period limits insight into long-term outcomes. Confounding factors, such as comorbidities and medication use, were not fully accounted for, and measurement bias in laboratory parameters could affect the consistency of the findings. These limitations suggest the need for further research to address these gaps and confirm the generalizability of the results.

Conclusion

As a conclusion; we demonstrated that the likelihood of resection decreased as the LCR increased in acute incarcerated abdominal wall hernias in our study. LCR can be used alongside other parameters as a simple, effective, and low-cost biomarker to predict ischemia in incarcerated hernias.

Ethics

Ethics Committee Approval: Our study was evaluated by Ege University Medical Research Ethics Committee and approved (decision no: 24-8T/41, date: 22.08.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.G., Y.T., B.G., Concept: T.G., E.K., M.S.E., Design: T.G., E.K., M.S.E., Data Collection or Processing: R.T., S.T., Analysis or Interpretation: R.T., Y.T., Literature Search: E.K., B.G., Writing: T.G., R.T.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Endometrial Pathology in Tamoxifen-treated Breast Cancer Patients: Correlation of Endometrial Thickness on Ultrasound, Preoperative Sampling, and Final Pathology

Tamoksifen Tedavisi Alan Meme Kanseri Hastalarında Endometrial Patoloji: Ultrasonografide Endometrial Kalınlık, Preoperatif Örnekleme ve Nihai Patoloji Arasındaki İlişki

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Abstract

Objective: This study aims to evaluate the relationship between endometrial thickness measured via transvaginal ultrasonography (TVUSG), preoperative endometrial biopsy findings, and final histopathology results, in breast cancer patients receiving tamoxifen therapy who underwent hysterectomy for benign indications.

Methods: A retrospective observational study was conducted on 77 tamoxifen-treated breast cancer patients who underwent hysterectomy between January 1, 2020; and January 1, 2025. Data included patient demographics, tamoxifen usage, TVUSG measurements of endometrial thickness, preoperative biopsy outcomes, and final hysterectomy pathology findings were collected. Statistical analyses included t-tests, Mann-Whitney U, chi-square, receiver operating characteristic (ROC) curve, and Cohen's Kappa tests.

Results: Postoperative endometrial pathology was detected in 36.4% of patients. Those with pathological findings had significantly greater endometrial thickness (11.74±6.20 mm vs. 7.93±4.27 mm; p=0.01) and longer tamoxifen use duration (4.52±2.97 vs. 2.83±2.07 years; p=0.01). ROC curve analysis revealed moderate diagnostic performance of endometrial thickness (area under the curve =0.686; 95% confidence interval: 0.565-0.807; p=0.007), with an optimal cut-off of 7.5 mm, yielding 75.0% sensitivity and 63.3% specificity. A lower threshold of 4.5 mm provided higher sensitivity (96.4%) but poor specificity (24.5%). Preoperative biopsy demonstrated limited diagnostic utility, with 35.7% sensitivity, 73.5% specificity, and a low agreement with final pathology (Cohen's Kappa =0.095; p=0.397).

Conclusion: The diagnostic accuracy of preoperative endometrial biopsy and endometrial thickness measurement was found to be limited in tamoxifen-treated patients. Individualized follow-up strategies are needed, particularly for symptomatic patients with prolonged tamoxifen use or increased endometrial thickness. Larger-scale studies are required to guide clinical management.

Keywords: Tamoxifen, breast cancer, endometrial biopsy

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Öz

Amaç: Bu çalışma, benign nedenlerle histerektomi uygulanan tamoksifen tedavisi alan meme kanseri hastalarında transvajinal ultrasonografi (TVUSG) ile ölçülen endometrial kalınlık, preoperatif endometrial biyopsi bulguları ve nihai histopatoloji sonuçları arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntem: 1 Ocak 2020 ile 1 Ocak 2025 tarihleri arasında histerektomi uygulanan tamoksifen tedavisi altındaki 77 meme kanseri hastası üzerinde retrospektif gözlemsel bir çalışma gerçekleştirildi. Hastaların demografik verileri, tamoksifen kullanım süresi, TVUSG ile ölçülen endometrial kalınlık, preoperatif biyopsi sonuçları ve nihai histerektomi patoloji bulguları değerlendirildi. İstatistiksel analizlerde t-testi, Mann-Whitney U, ki-kare, alıcı çalışma karakteristiği (ROC) eğrisi ve Cohen's Kappa testleri kullanıldı.

Bulgular: Hastaların %36,4'ünde postoperatif endometrial patoloji saptandı. Patolojik bulgusu olan hastalarda endometrial kalınlık (11,74±6,20 mm'ye karşı 7,93±4,27 mm; p=0,01) ve tamoksifen kullanım süresi (4,52±2,97 yıla karşı 2,83±2,07 yıl; p=0,01) anlamlı olarak daha yüksekti. ROC analizine göre endometrial kalınlığın tanısal gücü orta düzeydeydi (eğri altında kalan alan =0,686; %95 güven aralığı: 0,565-0,807; p=0,007). 7,5 mm'lik eşik değeri %75,0 duyarlılık ve %63,3 özgüllük sağladı. 4,5 mm'lik daha düşük eşik değeri daha yüksek duyarlılık (%96,4) ancak düşük özgüllük (%24,5) ile ilişkiliydi. Preoperatif biyopsinin tanısal değeri sınırlı olup duyarlılığı %35,7, özgüllüğü %73,5 ve nihai patoloji ile uyumu düşüktü (Cohen's Kappa =0,095; p=0,397).

Sonuç: Tamoksifen tedavisi alan hastalarda preoperatif endometrial biyopsi ve endometrial kalınlık ölçümünün tanısal doğruluğu sınırlı bulunmuştur. Özellikle semptomatik, uzun süre tamoksifen kullanan veya artmış endometrial kalınlığa sahip hastalarda bireyselleştirilmiş takip stratejilerine ihtiyaç vardır. Klinik yönetimi yönlendirebilmek adına daha geniş ölçekli çalışmalara gereksinim duyulmaktadır.

Anahtar Kelimeler: Tamoksifen, meme kanseri, endometrial biyopsi

Introduction

Breast cancer is one of the most common malignancies among women, with the majority of cases being estrogen receptor-positive. Tamoxifen, used as adjuvant therapy in these patients, acts as an estrogen antagonist in breast tissue, thereby reducing the risk of recurrence and improving survival[1,2]. Recent studies suggest that extending tamoxifen treatment up to 10 years can further enhance its therapeutic efficacy[3]. However, unlike its antagonistic effect on breast tissue, tamoxifen exhibits estrogen agonist activity in the endometrium, leading to endometrial thickening and various pathologies[4]. Studies have demonstrated that women taking tamoxifen have an increased risk of developing endometrial hyperplasia, polyps, and cancer, with the risk increasing in a dose- and duration-dependent manner[5]. Given that breast cancer and endometrial cancer share several epidemiological and genetic risk factors, the impact of tamoxifen on the endometrium warrants close attention[6]. Despite the widespread use of tamoxifen, there is still no clear consensus on the most effective strategy for endometrial surveillance in these patients. While routine screening for endometrial pathology is not recommended in asymptomatic postmenopausal women receiving tamoxifen therapy, research indicates that sonohysterography may enhance the diagnostic accuracy of ultrasonography by better detecting or ruling out anatomical abnormalities when clinically indicated[7]. Identifying factors associated with the development of endometrial pathologies in women taking tamoxifen is essential for designing individualized surveillance strategies. This is particularly relevant, as the clinical significance of these factors increases with prolonged tamoxifen use.

Most studies in this area have examined the overall risk for endometrial pathologies associated with tamoxifen use, with limited research focusing on the specific factors contributing to these pathologies[8]. Furthermore, in cases of abnormal vaginal bleeding, diagnostic modalities such as ultrasonography, hysteroscopy, and pathological examination play a vital role. The primary aim of this study is to investigate the relationship between endometrial thickness measured by transvaginal ultrasonography (TVUSG) and preoperative biopsy results, and final hysterectomy pathology in breast cancer patients receiving tamoxifen therapy. In addition, a key objective of the study is to evaluate the reliability of these two diagnostic methods in predicting endometrial pathologies and their contribution to the clinical diagnostic process.

Materials and Methods

This retrospective observational study evaluated the relationship between endometrial thickness, preoperative endometrial biopsy results, and final pathology findings in breast cancer patients who underwent hysterectomy for benign indications between January 1, 2020; and January 1, 2025. This retrospective study was conducted by reviewing the medical records of patients who underwent surgery in the gynecology clinics of our tertiary referral center during the specified period.

Female breast cancer patients who underwent hysterectomy for benign indications during the specified period were using tamoxifen, had their endometrial thickness measured by TVUSG prior to hysterectomy, underwent preoperative

endometrial biopsy with available histopathological results, and had accessible final hysterectomy pathology reports were included in the study. Decrease in hemoglobin (Hb) was defined as the reduction in Hb levels measured by comparing preoperative Hb values with those obtained at the sixth postoperative hour. The study was approved by the Local Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no: 2025:03-17, date: 10.04.2025).

Patients diagnosed with endometrial or cervical malignancy, patients with a history of previous endometrial ablation, radiotherapy, or chemotherapy, patients with incomplete clinical data, and cases with missing or unavailable pathological assessment at the time of hysterectomy were excluded. The patients' demographic characteristics, clinical history, tamoxifen use status, and duration, endometrial thickness measured by transvaginal ultrasonography, perioperative data, preoperative endometrial biopsy results, and final hysterectomy pathology findings were retrospectively collected from the electronic medical record system.

Statistical Analysis

All statistical analyses were carried out using the SPSS software package (version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median (interquartile range), depending on the distribution of the data. Categorical variables were presented as counts and percentages. The distribution of continuous variables was assessed with the Shapiro-Wilk test. For comparisons between two groups, the independent samples t-test was applied for normally distributed data, whereas the Mann-Whitney U test was used when normality assumptions were not met. Relationships between categorical variables were examined using the chi-square test or Fisher's exact test, as appropriate, based on expected frequencies. The ability of transvaginal ultrasonographic endometrial thickness measurements to predict the presence of histopathological abnormalities was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated to determine overall diagnostic performance, and the optimal cut-off point was established using the Youden Index. Agreement between preoperative endometrial biopsy results and final pathology findings from hysterectomy specimens was analyzed using Cohen's Kappa statistic. A p-value less than 0.05 was considered statistically significant in all tests.

Results

A total of 77 patients were included in the study. The mean age of the participants was 49.05±7.88 years, and the mean parity was 2.03±1.03. The mean decrease in Hb (g/dL) was 1.58±0.84, and the mean body mass index (BMI) was 27.12±3.80 kg/m^2. The mean preoperative endometrial thickness was 8.81±5.14 mm regarding menopausal status, 68.8% (n=53) of the patients were premenopausal and 31.2% (n=24) were postmenopausal. Preoperative endometrial evaluation revealed pathological findings in 23 patients (29.8%), while 54 patients (70.1%) had normal results. Final hysterectomy pathology revealed pathological findings in 28 patients (36.4%) while 49 patients (63.6%) were classified as normal (Table 1).

Preoperative endometrial histopathology results were available for all 77 patients. The most common finding was the insufficient samples in 28 patients (36.4%). Endometrial polyps were observed in 15 patients (19.5%), endometrial hyperplasia without atypia in 5 patients (6.5%), and hyperplasia with atypia in 3 patients (3.9%). Functional endometrial phases included the secretory phase in 9 patients (11.7%) and the proliferative phase in 9 patients (11.7%). Additionally, 8 patients (10.4%) had atrophic endometrium (Table 2). Postoperative endometrial histopathology was available for all patients. The most common postoperative finding was atrophic endometrium (18 patients, 23.4%), followed by endometrial polyps (15 patients, 19.48%), endometrial hyperplasia without atypia (10 patients, 12.99%), and hyperplasia with atypia (3 patients, 3.9%). The secretory phase was identified in 16 patients (20.8%), and the proliferative phase in 13 patients (16.9%). These results indicate a wide distribution of endometrial conditions in the study population (Table 3).

Analysis of patient characteristics according to final histopathology revealed that both the duration of tamoxifen use and endometrial thickness were significantly higher in patients with endometrial pathology. Specifically, mean tamoxifen use was 4.52±2.97 years in the pathologic group compared to 2.83±2.07 years in the normal group (p=0.01). Similarly, the mean endometrial thickness measured by TVUSG was significantly greater in patients with pathologic findings (11.74±6.20 mm vs. 7.93±4.27 mm; p=0.01). No statistically significant differences were observed between the groups in terms of age, parity, BMI, menopausal status, or postoperative Hb drop (all p>0.05) (Table 4).

The diagnostic concordance between preoperative endometrial biopsy and final hysterectomy pathology in tamoxifen-treated breast cancer patients was suboptimal. Among 28 patients with pathological findings in the final hysterectomy specimens, only 10 were correctly identified by preoperative biopsy, yielding a sensitivity of 35.7%. Specificity was higher at 73.5%, with 36 out of 49 normal cases accurately detected. The overall diagnostic accuracy of the biopsy was calculated as 59.7%. Positive and negative predictive values were 43.5% and 66.7%, respectively, suggesting limited predictive performance. Cohen's Kappa coefficient was 0.095 [standard error (SE): 0.113; p=0.397], indicating poor agreement between biopsy and final pathology results, with no statistically significant concordance beyond chance. These findings highlight the limited diagnostic reliability of preoperative endometrial biopsy in this patient population (Table 5).

ROC curve analysis was performed to assess the diagnostic utility of endometrial thickness in predicting endometrial pathology. AUC was calculated as 0.686 (SE: 0.062; 95% confidence interval: 0.565-0.807; p=0.007), indicating a moderate level of diagnostic accuracy. According to the Youden index, the optimal cut-off value was identified as 7.5 mm, which yielded a sensitivity of 75.0% and a specificity of 63.3%. Additionally, a lower threshold of 4.5

Table 1. Characteristics of tamoxifen-treated breast cancer patients undergoing hysterectomy

Variables	n=77
Age (year) ± SD	49.05±7.88
Parity (n) ± SD	2.03±1.03
Decrease in Hb* (g/dL) ± SD	1.58±0.84
BMI* (kg/m²) ± SD	27.12±3.80
Endometrial thickness (mm) ± SD	9.06±5.19
Premenopausal n (%) Postmenopausal n (%)	53 (68.8%) 24 (31.2%)
Preoperative endometrium evaluation Pathological n (%) Normal n (%)	 23 (29.8%) 54 (70.1%)
Final pathology Pathological n (%) Normal n (%)	 28 (36.4%) 49 (63.6%)

Hb: Hemoglobin, BMI: Body mass index, SD: Standard deviation, *: Statistically significant

Table 2. Preoperative endometrial histopathology results

Endometrial polyp n (%)	15 (19.5%)
Endometrial hyperplasia without atypia n (%)	5 (6.5%)
Endometrial hyperplasia with atypia n (%)	3 (3.9%)
Secretory endometrium n (%)	9 (11.7%)
Proliferative endometrium n (%)	9 (11.7%)
Atrophic endometrium n (%)	8 (10.4%)
Insufficient sample n (%)	28 (36.4%)
Total	77 (100.0%)

Table 3. Postoperative endometrial histopathology results

Endometrial polyp n (%)	15 (19.48%)
Endometrial hyperplasia without atypia n (%)	10 (12.99%)
Endometrial hyperplasia with atypia n (%)	3 (3.9%)
Secretory endometrium n (%)	16 (20.8%)
Proliferative endometrium n (%)	13 (16.88%)
Atrophic endometrium n (%)	20 (25.97%)
Total n (%)	77 (100.0%)

Table 4. Comparison of clinical, demographic, and sonographic characteristics according to final endometrial pathology

	Normal n=49	Pathologic n=28	p
Age ± SD	49.49±8.451	48.29±6.847	0.6
Parite ± SD	1.9796±1.14546	2.1071±0.78595	0.3
BMI (kg/m²) ± SD	27.43±4.082	26.57±3.259	0.5
Tamoxifen use duration (years) ± SD	2.83±2.07	4.52±2.97	<0.05*
Premenopausal n (%) Postmenopausal n (%)	34 (69.4%) 15 (30.6%)	19 (67.9%) 9 (32.1%)	0.5
Endometrial thickness (mm) ± SD	7.93±4.27	11.74±6.20	<0.05*
Decrease in Hb (g/dL) ± SD	1.5±0.81	1.6±0.89	0.7

SD: Standard deviation, BMI: Body mass index, Hb: Hemoglobin, *: Statistically significant

Table 5. Diagnostic concordance between preoperative endometrial biopsy and final hysterectomy pathology in tamoxifen-treated breast cancer patients

	Final pathology: pathologic	Final pathology: normal	Total
Preoperative pathologic	10	13	23
Preoperative normal	18	36	54
Total	28	49	77

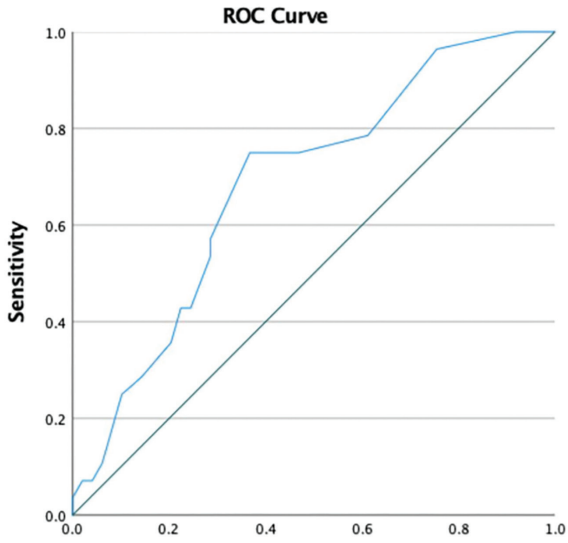

Figure 1. ROC curve demonstrating the diagnostic performance of endometrial thickness in predicting final histopathological outcomes in tamoxifen-treated breast cancer patients. AUC was 0.686 (SE: 0.062; 95% CI: 0.565-0.807; p=0.007), indicating moderate diagnostic accuracy. The optimal cut-off value determined by the Youden index was 7.5 mm, with 75.0% sensitivity and 63.3% specificity. A lower threshold of 4.5 mm yielded higher sensitivity (96.4%) but lower specificity (24.5%)

ROC: Receiver operating characteristic, AUC: Area under the curve, SE: Standard error, CI: Confidence interval

mm demonstrated higher sensitivity (96.4%) but markedly reduced specificity (24.5%), indicating an increased rate of false positives when using this more conservative cut-off (Figure 1).

Discussion

The primary aim of this study was to evaluate the relationship between endometrial thickness measured by TVUSG, preoperative endometrial biopsy results, and final hysterectomy pathology in breast cancer patients receiving tamoxifen therapy. Given tamoxifen's known estrogen agonist effect on endometrial tissue, there is growing concern regarding its potential to induce various endometrial pathologies, including hyperplasia and malignancy[9]. Understanding whether non-invasive imaging findings and biopsy results correlate with definitive surgical pathology is crucial for optimizing follow-up strategies and minimizing unnecessary interventions in this patient population. This study contributes to the existing body of literature by providing data from a surgically confirmed cohort, offering insights into the diagnostic reliability of TVUSG and endometrial biopsy in tamoxifen-treated breast cancer patients.

Preoperative endometrial biopsy demonstrated a moderate diagnostic performance, with a sensitivity of 53.6% and specificity of 71.4% in predicting pathological outcomes. The Cohen's Kappa coefficient was calculated as 0.248, indicating a low level of agreement between the preoperative biopsy and final hysterectomy pathology. While TVUSG provides moderate diagnostic discrimination, as evidenced by AUC values, biopsy is limited by sampling limitations that compromise reproducibility and concordance with final histopathological results, as reflected by the low kappa coefficient. This discordance may be explained by the heterogeneous or focal nature of endometrial lesions, insufficient tissue sampling, or pathology residing in areas not captured during biopsy[10]. A single biopsy sample may not accurately represent the entire endometrium; thus, relying solely on biopsy results may be insufficient for clinical decision-making in asymptomatic tamoxifen users. Therefore, a comprehensive assessment incorporating ultrasonographic findings, clinical symptoms, and-when indicated-surgical intervention is recommended to ensure accurate diagnosis and appropriate management.

Researchers found a statistically significant difference in tamoxifen usage duration between patients with and without endometrial pathology, indicating that longer exposure may be a contributing factor to endometrial abnormalities (4.52±2.97 years for patients with vs. 2.83±2.07 years for patients without, p=0.01). Extended tamoxifen use has been reported to increase the risk of conditions such as hyperplasia, polyps, and carcinoma due to its partial estrogen agonist effect on endometrial tissue[11]. These findings highlight the importance of implementing individualized monitoring protocols in long-term tamoxifen users, even in the absence of symptoms.

In asymptomatic patients, tamoxifen-associated subepithelial stromal hypertrophy may lead to thickened endometrium that does not accurately reflect histological pathology; it may also be affected by operator dependency and interobserver variability[12]. Consequently, standard screening tools such as TVUSG and blind endometrial biopsy have shown limited diagnostic value in detecting focal intrauterine lesions[13]. In contrast, when used selectively based on clinical indications, sonohysterography has demonstrated superior accuracy in identifying or excluding structural anomalies[14]. Although

tracking endometrial thickness may assist in risk stratification, interpretation must be approached cautiously in light of these limitations. The comparison of endometrial thickness between groups revealed a statistically significant difference, with higher measurements observed in patients with pathological outcomes. While ROC analysis demonstrated only moderate diagnostic capability (AUC: 0.686), certain threshold values showed clinical potential. A cut-off of 7.5 mm offered a balanced sensitivity and specificity, whereas lowering the threshold to 4.5 mm markedly increased sensitivity at the expense of specificity. These results underline that although thickened endometrium in asymptomatic tamoxifen users may raise suspicion, it should not be used in isolation for diagnostic decision-making due to its limited discriminative power. This interpretation is consistent with previous literature indicating that thresholds between 4 and 8 mm may hold clinical relevance in identifying endometrial pathology in tamoxifen users[15]. Moreover, reliance on endometrial thickness alone in asymptomatic individuals has been linked to unnecessary intervention[16]. Therefore, clinical symptoms-particularly postmenopausal vaginal bleeding-should remain the principal indication for further endometrial evaluation. This approach aligns with current guidelines from the American College of Obstetricians and Gynecologists, which recommend limiting endometrial assessment to symptomatic tamoxifen users[17].

This study has several strengths, including the integrated evaluation of endometrial thickness, preoperative biopsy findings, and final histopathological outcomes in a defined cohort of tamoxifen-treated breast cancer patients. The use of both TVUSG and histopathological confirmation strengthens diagnostic reliability, while ROC analysis adds clinical relevance by identifying practical threshold values. Additionally, systematic data collection enhances internal validity.

Study Limitations

However, limitations include the retrospective design, which may introduce selection bias due to the inclusion of only those patients undergoing hysterectomy for benign indications. The modest sample size restricts generalizability, and factors such as cumulative tamoxifen dose, hormonal milieu, and other endometrial risk factors were not evaluated. Moreover, the low sensitivity of preoperative endometrial biopsy observed in this study highlights its limited utility in predicting final pathology. Prospective, multicenter studies with larger populations are warranted to confirm and expand upon these findings.

Conclusion

In conclusion, the agreement between preoperative endometrial biopsy and final hysterectomy pathology was found to be low, highlighting the limited diagnostic reliability of biopsy in tamoxifen-treated patients. Likewise, endometrial thickness measured by TVUSG alone demonstrated limited predictive value for detecting pathology in asymptomatic individuals. In the presence of vaginal bleeding, endometrial biopsy should be performed even if TVUSG shows a normal endometrial thickness. Nevertheless, when endometrial thickness exceeds specific thresholds—particularly in patients with prolonged tamoxifen use—more vigilant clinical follow-up may be warranted. These findings emphasize the need for individualized surveillance strategies that strike a balance between early detection and the risk of overdiagnosis and overtreatment. To optimize endometrial monitoring and inform future clinical guidelines, further prospective, large-scale studies are required in this patient population.

Ethics

Ethics Committee Approval: The study complied with the Declaration of Helsinki, and approval was obtained from the Scientific and Ethical Committee for Medical Research at University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital before starting the system search (approval number: 2025:3-17, date: 10.04.2025).

Informed Consent: A retrospective observational study was conducted on 77 tamoxifen-treated breast cancer patients who underwent hysterectomy between January 1, 2020; and January 1, 2025.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., A.H.İ., Concept: S.K., A.K., A.H.İ., Design: İ.U., Data Collection or Processing: A.K., S.K., U.D., Analysis or Interpretation: S.K., U.D., Literature Search: A.K., S.K., U.D., Writing: S.K.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Association Between C-reactive Protein to Albumin Ratio and Mortality in Geriatric Hip Fracture Patients

Geriatrik Kalça Kırığı Hastalarında C-reaktif Protein/Albümin Oranı ile Mortalite Arasındaki İlişki

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Abstract

Objective: The objective of this study was to evaluate the relationship between admission C-reactive protein (CRP) to albumin ratio (CAR) and 30-day mortality in older adults undergoing surgical treatment for hip fractures.

Methods: This retrospective study included patients aged ≥65 years who presented to the emergency department of a tertiary care hospital with a diagnosis of hip fracture and subsequently underwent surgical treatment between January 2023 and January 2025. Demographic, clinical, and laboratory data were extracted from electronic records. The CAR was determined by dividing the serum CRP level (mg/L) by the serum albumin level (g/L), based on laboratory values obtained upon hospital admission. The primary outcome was 30-day all-cause mortality. Multivariable logistic regression was used to identify independent predictors. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUROC), and calibration was evaluated using the Hosmer-Lemeshow test. The optimal CAR cut-off was determined via Youden's index.

Results: Among the 411 patients, 43 (10.5%) died within 30 days. Non-survivors were older, predominantly male, and had higher American Society of Anesthesiologists scores, lower serum albumin and hemoglobin levels, and higher CRP levels. Median CAR was significantly higher in deceased patients (14.8 vs. 3.5, p<0.001). In multivariate analysis, CAR remained an independent predictor of 30-day mortality [adjusted odds ratio: 2.77; 95% confidence interval (CI): 2.14-3.76]. The AUROC for CAR was 0.930 (95% CI: 0.860-0.988), and the optimal cut-off value of 6.5 yielded 88.4% sensitivity and 96.2% specificity.

Conclusion: CAR at admission was independently associated with short-term mortality in geriatric patients undergoing hip fracture surgery. As a readily obtainable marker reflecting systemic inflammation and nutritional status, CAR may serve as a valuable tool for early risk stratification in emergency orthopedic care.

Keywords: C-reactive protein, albumin, hip fracture, mortality, elderly

Öz

Amaç: Bu çalışmanın amacı, kalça kırığı nedeniyle cerrahi uygulanan yaşlı hastalarda, başvuru anındaki C-reaktif protein (CRP)/albümin oranının (CAR) 30 günlük mortalite ile ilişkisini araştırmaktır.

Yöntem: Bu retrospektif çalışmaya, Ocak 2023 ile Ocak 2025 tarihleri arasında bir üçüncü basamak hastanesinin acil servisine kalça kırığı tanısıyla başvuran ve cerrahi tedavi uygulanan ≥65 yaş hastalar dahil edildi. Demografik, klinik ve laboratuvar verileri elektronik kayıtlardan elde edildi. CAR, başvuru sırasında

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Öz

ölçülen serum CRP (mg/L) değerinin serum albümin (g/L) değerine bölünmesiyle hesaplandı. Birincil sonlanım 30 günlük tüm nedenlere bağlı mortaliteydi. Bağımsız prediktörleri belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı. Modelin ayırt ediciliği alıcı çalışma karakteristik eğrisinin altındaki alan (AUROC) ile, kalibrasyonu ise Hosmer-Lemeshow testi ile değerlendirildi. En uygun CAR kesim noktası Youden indeksi ile belirlendi.

Bulgular: Toplam 411 hastanın 43'ü (%10,5) 30 gün içinde hayatını kaybetti. Hayatını kaybeden hastalar daha yaşlı, çoğunlukla erkekti; Amerikan Anesteziyoloji Derneği skorları daha yüksek, serum albümin ve hemoglobin düzeyleri daha düşük, CRP düzeyleri ise daha yüksekti. Ortanca CAR değeri ölen hastalarda anlamlı olarak daha yüksekti (14,8 vs. 3,5; p<0,001). Çok değişkenli analizde CAR, 30 günlük mortalitenin bağımsız bir prediktörü olarak kaldı [düzeltilmiş olasılık oranı: 2,77; %95 güven aralığı (GA): 2,14-3,76]. CAR için AUROC 0,930 (%95 GA: 0,860-0,988) olarak bulundu ve 6,5'lik eşik değeri %88,4 duyarlılık ve %96,2 özgüllük sağladı.

Sonuç: Kalça kırığı nedeniyle cerrahi uygulanan yaşlı hastalarda başvuru anındaki CAR değeri, kısa vadeli mortalite ile bağımsız olarak ilişkilidir. Sistemik enflamasyonu ve beslenme durumunu yansıtan kolay elde edilebilen bir belirteç olarak CAR, acil ortopedi bakımında erken risk sınıflandırması için değerli bir araç olabilir.

Anahtar Kelimeler: C-reaktif protein, albümin, kalça kırığı, mortalite, yaşlı

Introduction

Hip fractures in older adults represent a major public health concern due to their high incidence, associated comorbidities, and significant postoperative morbidity and mortality. Globally, the number of hip fractures is projected to exceed 6 million by 2050, with mortality rates 19% at 30 days and up to 30% at one year following surgery[1-3]. Given the vulnerability of this population, early identification of patients at high risk of adverse outcomes remains a clinical priority.

Among various prognostic markers, inflammation and nutritional status have emerged as critical determinants of postoperative survival in geriatric patients. C-reactive protein (CRP), an acute-phase reactant produced by hepatocytes in response to interleukin-6 and other pro-inflammatory cytokines, is widely used to reflect systemic inflammation[4,5]. On the other hand, serum albumin serves as an indicator of both nutritional status and chronic disease burden and has been shown to inversely correlate with frailty and postoperative complications[6,7].

The CRP-to-albumin ratio (CAR) combines these two markers into a single index, capturing both inflammatory and nutritional dimensions of physiological stress. CAR has been proposed as a prognostic marker in various clinical settings, including sepsis, cardiovascular disease, malignancy, and postoperative complications[8-10]. Recent studies have suggested that elevated CAR may be independently associated with higher mortality in patients undergoing orthopedic surgeries, including hip fracture repair[11,12]. However, despite these findings, data specific to the geriatric hip fracture population remain limited. Few studies have systematically evaluated the association between CAR measured at admission and short-term mortality outcomes in this high-risk group.

Moreover, the integration of CAR into routine preoperative assessment remains controversial due to variability in study designs, thresholds, and confounding factors.

Accordingly, this study investigates the prognostic value of the admission CAR in predicting 30-day mortality among elderly patients undergoing surgical treatment for hip fractures.

Materials and Methods

This retrospective observational study included patients presenting to the emergency departments of two tertiary care hospitals-Memorial Bahçelievler Hospital and Beykent University Faculty of Medicine Hospital-with a diagnosis of hip fracture. The study includes patients aged 65 years and older who were admitted with a diagnosis of hip fracture and underwent surgical treatment between January 1, 2023, and January 1, 2025. All patients were managed according to standardized institutional protocols for perioperative care and rehabilitation. Ethical approval was obtained from the Local Research Ethics Committee of Memorial Bahçelievler Hospital (approval no: 147, date: 27.03.2025). Inclusion criteria were: patients aged ≥65 years with low-energy, fragility hip fractures (including femoral neck, intertrochanteric, and subtrochanteric fractures), who underwent surgical treatment within 72 hours of hospital admission, and had complete preoperative laboratory data, including serum CRP and albumin levels. Patients were excluded if they had pathological or periprosthetic fractures, high-energy trauma, recent surgery (within the last 6 months), chronic liver disease, immunosuppressive therapy, active malignancy, or if they were discharged against medical advice. Patients with missing key laboratory data (CRP or albumin) were also excluded.

Demographic characteristics (age, sex), comorbidities (e.g., diabetes, cardiovascular, pulmonary diseases), American Society of Anesthesiologists scores (ASA) classification, time to surgery, type of anesthesia, and laboratory results (including CRP, albumin, hemoglobin, creatinine, and sodium) were recorded at admission. CAR, calculated as the ratio of serum CRP (mg/L) to albumin (g/L), serves as a composite marker of systemic inflammation and nutritional condition[13]. Postoperative complications were classified as minor or major. Minor complications included urinary tract infections, superficial wound infections, and delayed wound healing. Major complications included pulmonary embolism, myocardial infarction, cardiac arrest, sepsis, and unplanned intubations. Complications were identified within 30 days postoperatively, based on clinical and laboratory documentation in patient records.

The primary outcome was 30-day all-cause mortality, defined as death occurring within 30 days of surgery. Mortality status was verified through hospital records and national electronic death notification systems.

Statistical Analysis

All statistical analyses were conducted using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize baseline characteristics, and comparisons between survivors and non-survivors were performed using independent samples t-tests or Mann-Whitney U tests for continuous variables, depending on normality, assessed via the Kolmogorov-Smirnov test and visual inspection of histograms. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. A multivariable logistic regression model was constructed to identify independent predictors of 30-day mortality. Variables with $p<0.20$ in univariate analysis were considered for inclusion, and it was ensured that CAR remained in the model regardless of statistical significance. Multicollinearity was assessed using the variance inflation factor (VIF), with variables exhibiting VIF >5 removed to improve model stability. Model performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test, Nagelkerke's R^2, and area under the receiver operating characteristic curve (AUROC). The AUROC was internally validated using 5-fold cross-validation. The diagnostic accuracy of CAR was further assessed using receiver operating characteristic (ROC) analysis. The optimal cut-off value for predicting 30-day mortality was determined using Youden's index, and corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value with 95% confidence intervals (CIs), were computed using the Wilson score interval method. The ROC curve was plotted with a 95% confidence band, and model discrimination was evaluated via DeLong's test for area under the curve comparison. All statistical tests were two-tailed, with $p<0.05$ considered statistically significant.

Results

A total of 411 patients were included in the analysis, of whom 43 (10.5%) died within 30 days. The mean age was significantly higher in the deceased group (87.3±6.9 years) compared to the survivor group (82.2±6.2 years, $p<0.001$) (Table 1). The proportion of male patients was higher among deceased patients (51.2% vs. 30.2%, $p=0.009$). The Parker Mobility score was significantly lower in the deceased group (4.3±2.0 vs. 5.8±1.9, $p<0.001$), and cognitive impairment was more prevalent (48.8% vs. 28.3%, $p=0.009$).

Among comorbidities, diabetes mellitus (37.2% vs. 19.3%, $p=0.012$), chronic heart disease (60.5% vs. 32.9%, $p=0.001$), and chronic lung disease (41.9% vs. 19.6%, $p=0.002$) were significantly more common in deceased patients. No significant differences were observed for hypertension, chronic kidney disease, or malignancy.

Table 1. Baseline characteristics of hip fracture patients stratified by 30-day mortality

Variable	Survivors (n=368)	Deceased (n=43)	p
Demographics & baseline			
Age (years)	82.2±6.2	87.3±6.9	<0.001
Male sex	111 (30.2)	22 (51.2)	0.009
Parker mobility score	5.8±1.9	4.3±2.0	<0.001
Cognitive impairment	104 (28.3)	21 (48.8)	0.009
Comorbidities			
Hypertension	225 (61.1)	25 (58.1)	0.829
Diabetes mellitus	71 (19.3)	16 (37.2)	0.012

Table 1. Continued

Variable	Survivors (n=368)	Deceased (n=43)	p
Chronic heart disease	121 (32.9)	26 (60.5)	0.001
Chronic lung disease	72 (19.6)	18 (41.9)	0.002
Chronic kidney disease	58 (15.8)	9 (20.9)	0.516
Malignancy	46 (12.5)	9 (20.9)	0.194
Surgical & perioperative factors			
Time to surgery (hours)	24.5±5.3	30.6±5.2	<0.001
ASA score	3.0±0.7	3.9±0.4	<0.001
Laboratory markers			
Hemoglobin (g/dL)	12.5±1.8	10.8±2.4	<0.001
Serum albumin (g/dL)	3.9±0.5	3.2±0.6	<0.001
CRP (mg/L)	11.9 (6.5-18.9)	28.6 (15.4-38.4)	<0.001
CAR	3.5 (1.8-6.2)	14.8 (7.5-24.3)	<0.001
Creatinine (mg/dL)	0.9±0.3	1.5±0.5	<0.001
eGFR (mL/min/1.73 m^2)	68.5±15.4	48.9±18.1	<0.001
BMI (kg/m^2)	24.7±4.2	22.2±3.9	<0.001
Postoperative & metabolic indicators			
Minor complications	112 (30.4)	13 (30.2)	1.000
Major complications	40 (10.9)	17 (39.5)	<0.001
Lactate (mmol/L)	1.9±0.5	3.7±1.3	<0.001

CRP: C-reactive protein, CAR: C-reactive protein to albumin ratio, ASA: American Society of Anesthesiologists, eGFR: Estimated glomerular filtration rate, BMI: Body mass index

Deceased patients had significantly longer time until surgery (30.6±5.2 hours vs. 24.5±5.3 hours, p<0.001) and a higher ASA score (3.9±0.4 vs. 3.0±0.7, p<0.001). Regarding laboratory markers, deceased patients had lower hemoglobin (10.8±2.4 g/dL vs. 12.5±1.8 g/dL, p<0.001) and had lower serum albumin (3.2±0.6 g/dL vs. 3.9±0.5 g/dL, p<0.001). Conversely, they exhibited significantly higher CRP levels [28.6 (15.4-38.4) mg/L vs. 11.9 (6.5-18.9) mg/L, p<0.001] and CAR [14.8 (7.5-24.3) vs. 3.5 (1.8-6.2), p<0.001]. Postoperative complications were more frequent in the deceased group, with major complications occurring in 39.5% of deceased patients compared to 10.9% of survivors (p<0.001). Lactate levels were also significantly higher among deceased patients (3.7±1.3 mmol/L vs. 1.9±0.5 mmol/L, p<0.001).

In the multivariable model, CAR remained a significant predictor of 30-day mortality (adjusted odds ratio: 2.77, 95% CI: 2.14-3.76) (Table 2). Other independent predictors included ASA score (1.89, 95% CI: 1.57-2.24), hemoglobin (0.78, 95% CI: 0.62-0.99), CRP (2.12, 95% CI: 1.64-2.70), creatinine (2.23, 95% CI: 1.77-2.78), and major complications (1.39, 95% CI: 1.10-1.73). The AUROC of the multivariable model was 0.889 (95% CI: 0.833-0.941), the Hosmer-Lemeshow goodness-of-fit test was p=0.41, and Nagelkerke's R^2 was 0.78.

The AUROC for CAR in predicting 30-day mortality was 0.930 (95% CI: 0.860-0.988) (Table 3, Figure 1). The optimal cut-off, determined by Youden's index, was 6.5, yielding a sensitivity of 88.4% (95% CI: 75.5-94.9) and specificity of 96.2% (95% CI: 93.7-97.7). At lower thresholds (3.5 and 5.0), sensitivity remained high (93.0%), but specificity improved significantly at 5.0 (81.0%). A cut-off of 7.5 provided a balanced trade-off with a specificity of 98.6% and a PPV of 87.5%. At higher cut-offs (10.0 and 14.0), specificity reached 100%, but sensitivity declined to 72.1% and 46.5%, respectively.

Discussion

In this retrospective cohort of elderly patients undergoing hip fracture surgery, the CAR measured at admission was significantly associated with 30-day mortality. The ratio remained an independent predictor even after adjusting for clinical and laboratory confounders, demonstrating strong discriminative power for early mortality risk. These findings suggest that CAR may serve as a practical and biologically plausible marker for early risk stratification in this high-risk population.

Table 2. Multivariable logistic regression analysis for 30-day mortality in hip fracture patients

Variable	Adjusted OR (95% CI)
ASA score	1.89 (1.57-2.24)
Hemoglobin	0.78 (0.62-0.99)
CRP	2.12 (1.64-2.70)
Creatinine	2.23 (1.77-2.78)
Major complications	1.39 (1.10-1.73)
CAR	2.77 (2.14-3.76)

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, CAR: C-reactive protein to albumin ratio, ASA: American Society of Anesthesiologists

Table 3. Diagnostic performance of CAR for 30-day mortality

CAR	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	PLR (95% CI)	NLR (95% CI)
3.5	93.0 (81.4-97.6)	50.0 (44.9-55.1)	17.9 (13.4-23.4)	98.4 (95.4-99.5)	1.86 (1.50-2.31)	0.14 (0.05-0.34)
5.0	93.0 (81.4-97.6)	81.0 (76.7-84.7)	36.4 (28.0-45.7)	99.0 (97.1-99.7)	4.89 (3.72-6.33)	0.09 (0.03-0.24)
7.5	81.4 (67.4-90.3)	98.6 (96.9-99.4)	87.5 (73.9-94.5)	97.8 (95.8-98.9)	59.91 (28.85-124.41)	0.19 (0.09-0.37)
10.0	72.1 (57.3-83.3)	100.0 (99.0-100)	100.0 (89.0-100)	96.8 (94.6-98.2)	Inf (NA)	0.28 (0.16-0.49)
14.0	46.5 (32.5-61.1)	100.0 (99.0-100)	100.0 (83.9-100)	94.1 (91.3-96.0)	Inf (NA)	0.53 (0.37-0.77)

CAR: C-reactive protein to albumin ratio, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, NA: Not available

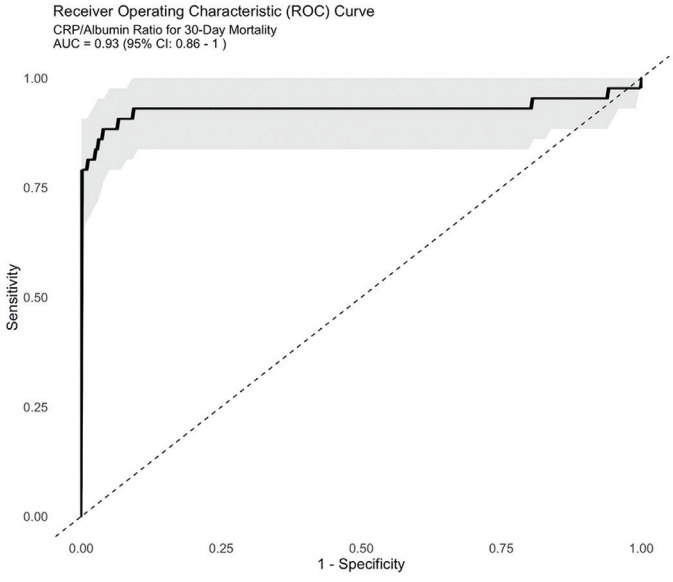

Figure 1. ROC curve of C-reactive protein (CRP)/albumin ratio for predicting 30-day mortality in hip fracture patients

CI: Confidence interval, AUC: Area under the curve

The CAR represents the dynamic interaction between systemic inflammation and nutritional status-two interdependent pathways influencing outcomes in elderly patients with hip fractures. Elevated CRP levels are a hallmark of the acute-phase response, triggered by cytokines such as interleukin-6 during tissue injury and trauma[14]. In hip fracture patients, a pronounced inflammatory response has been associated with increased risks of postoperative complications including delirium, pneumonia, and cardiovascular events[15]. Conversely, serum albumin, a negative acute-phase reactant and marker of visceral protein stores, reflects both baseline nutritional reserve and the body's ability to counteract catabolic stress[16]. Hypoalbuminemia is frequently observed in frail older adults and has been linked to impaired wound healing, immune dysfunction, and higher infection rates[17,18]. As such, CAR integrates two biologically relevant dimensions-proinflammatory activation and protein depletion-into a single composite index. In geriatric trauma patients, who often exhibit diminished physiological reserve and multimorbidity, this ratio may serve as a more sensitive indicator of vulnerability and mortality risk than either marker alone[19].

In the present study, the CAR was identified as an independent predictor of 30-day mortality in elderly patients undergoing surgery for hip fracture. This finding aligns with prior evidence that supports the role of CAR as a robust biomarker

combining inflammatory and nutritional status in predicting short-term postoperative outcomes. In the study by Aydın and Kaçmaz[19] CAR was evaluated in a cohort of elderly patients undergoing hemiarthroplasty and was found to be independently associated with both intensive care unit admission and 1-year mortality. The authors reported a CAR cut-off value of 1.03, with a high specificity (92.7%) and significant discriminative ability in ROC analysis[19]. Balta et al.[20] investigated preoperative inflammatory biomarkers, including CAR, in patients with intertrochanteric femur fractures and demonstrated that CAR had the highest predictive value among the studied ratios. A cut-off value of 12.42 yielded a sensitivity of 81.8% and specificity of 69.4%. CAR remained statistically significant in both univariate and multivariate models for 30-day mortality. In a more recent study, Kaya and Efendioglu[21] reported that a CAR threshold of 0.15 was significantly associated with early mortality, though with more modest sensitivity and specificity (74% and 53%, respectively). They concluded that CAR was superior to CRP or albumin alone and recommended its use as part of routine risk stratification for elderly hip fracture patients[21]. Collectively, these findings reinforce the clinical utility of CAR as a non-invasive, cost-effective, and biologically meaningful tool to identify elderly patients at increased risk of early postoperative mortality following hip fracture surgery. Despite variability in methodological design and cut-off values across studies, the consistent independent association between CAR and mortality across different clinical settings highlights its translational relevance.

Study Limitations

This study has several limitations that merit consideration. As a single-center, retrospective analysis, the findings may be subject to selection bias and may not be generalizable to other healthcare settings with different perioperative protocols or patient demographics. Although multivariate modeling was used to adjust for potential confounders, the presence of residual confounding cannot be entirely excluded, particularly with respect to unmeasured variables such as frailty scales or detailed nutritional assessments. Furthermore, CRP and albumin levels were assessed only at the time of admission, without accounting for perioperative changes that may influence outcomes. Finally, although mortality data were obtained through national registries and hospital records, other important outcomes such as functional recovery, or long-term complications were not evaluated.

Conclusion

This study demonstrates that the CAR at hospital admission is significantly associated with short-term mortality in elderly patients undergoing surgery for hip fracture. As a combined marker of systemic inflammation and nutritional status, the ratio showed strong independent predictive value and diagnostic accuracy. These findings support its potential utility as an accessible and cost-effective tool for early risk stratification in the emergency care of geriatric trauma patients. Future prospective studies are warranted to validate these results and explore whether targeted interventions based on CRP/albumin levels could improve clinical outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Memorial Bahçelievler Hospital (approval no: 147, date: 27.03.2025).

Informed Consent: Given the retrospective nature of the study, the institutional review board approved a waiver of informed consent.

Footnotes

Authorship Contributions

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Poor Prognostic Indicators Associated with Increased Mortality in Deep Neck Abscesses

Derin Boyun Apselerinde Mortalitenin Artmasıyla İlişkili Kötü Prognostik Faktörler

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Abstract

Objective: We aimed to identify the poor prognostic factors contributing to increased mortality and morbidity in patients with deep neck abscesses and to develop a clinical guide to assist physicians in optimizing patient management.

Methods: A total of 295 patients who underwent surgical intervention for deep neck abscess formation were included in this retrospective analysis. The laboratory tests of all patients were analyzed. Contrast-enhanced neck and thoracic computed tomography were performed to assess the localization of the abscess within cervical spaces and to identify complications such as mediastinitis and laryngeal edema. In this study, we investigated the association between mortality and mediastinitis, tracheotomy status, with laboratory parameter elevations, microbiological cultures from abscess specimens, and the specific anatomical neck spaces involved.

Results: Among patients who developed mortality, statistically significant increases were observed in age (p=0.01), C-reactive protein (p<0.001), neutrophil count (p<0.001), neutrophil-to-lymphocyte ratio, (p<0.001), white blood cell count (p<0.001), and hospital stay (p=0.001). Conversely, lymphocyte levels were significantly lower (p<0.001). The highest incidence was observed in cases with infections affecting the submandibular, carotid, and parapharyngeal spaces (66.7%). In cases of mediastinitis with fatal outcomes, the most frequently isolated microorganism was *Bacteroides fragilis* (41.7%).

Conclusion: Elevated serologic findings, diabetes mellitus, involvement of multiple cervical anatomical spaces (particularly submandibular, carotid, and parapharyngeal regions), and the isolation of pathogens such as *Streptococcus constellatus* and *Bacteroides fragilis* from abscess cultures are significant negative prognostic factors associated with increased morbidity and mortality.

Keywords: Deep neck abscess, mortality, mediastinitis, tracheotomy

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Öz

Amaç: Bu çalışmada derin boyun apselerinde mortalite ve morbidite artışına katkıda bulunan kötü prognostik faktörleri belirlemeyi ve klinisyene yardımcı olacak klinik bir rehber geliştirmeyi amaçladık.

Yöntem: Derin boyun apsesi nedeniyle cerrahi müdahale geçiren toplam 295 hasta bu retrospektif çalışmaya dahil edildi. Tüm hastaların laboratuvar testleri analiz edildi. Kontrastlı boyun ve torasik bilgisayarlı tomografi, apsenin servikal boşluklardaki lokalizasyonunu değerlendirmek ve mediastinit ve laringeal ödem gibi komplikasyonları belirlemek için istendi. Bu çalışmada, enflamatuvar laboratuvar parametrelerinin yüksekliği, apse örneklerinden alınan mikrobiyolojik kültürler ve etkilenen spesifik anatomik boyun boşlukları ile mediastinit, trakeotomi ve mortalite arasındaki ilişki araştırıldı.

Bulgular: Mortalite ile sonuçlanan hastalarda yaş (p=0,01), C-reaktif protein (p<0,001), nötrofil sayısı (p<0,001), nötrofil-lenfosit oranı (p<0,001), beyaz kan hücre sayısı (p < 0,001) ve hastanede kalış süresinde (p=0,001) istatistiksel olarak anlamlı bir yükseklik gözlendi. Buna karşılık lenfosit düzeyleri bu hastalarda anlamlı şekilde düşüktü (p<0,001). En yüksek mortalite oranı, multipl submandibular, karotis ve parafaringeal boşlukların etkilendiği enfeksiyonlarda (%66,7) gözlendi. Mortalite ile sonuçlanan mediastinit hastalarında en sık izole edilen mikroorganizma *Bacteroides fragilis* (%41,7) idi.

Sonuç: Serolojik bulgulardaki yükseklik, diabetes mellitus, birden fazla servikal anatomik boşluğun (özellikle submandibular, karotis ve parafaringeal bölgeler) tutulumu, apse kültürlerinden *Streptococcus constellatus* ve *Bacteroides fragilis* gibi patojenlerin izole edilmesi artmış morbidite ve mortalite ile ilişkili önemli olumsuz prognostik faktörlerdir.

Anahtar Kelimeler: Derin boyun enfeksiyonu, mortalite, mediastinit, trakeotomi

Introduction

Deep neck infection (DNI) is a prevalent inflammatory pathology characterized by the rapid progression of cellulitis or abscess formation, involving the fascial planes of the neck and deep cervical spaces[1]. The anatomy of the neck is highly complex, with deep cervical spaces interconnected[2]. Most DNIs originate from pharyngeal sources (36-47%) or odontogenic infections (33-45%)[3]. These initially localized infections can rapidly spread to the parapharyngeal, carotid, prevertebral, and pretracheal spaces, due to the anatomical communication between cervical spaces. In severe cases, the infection may further extend into the mediastinum, leading to life-threatening complications[3]. Consequently, DNI can result in significant morbidity and mortality due to complications such as laryngeal edema and airway obstruction, mediastinitis, septic thrombophlebitis, pericarditis, pneumonia, pleural effusion, jugular vein thrombosis, septic shock, carotid artery rupture, causing massive hemorrhage, and disseminated intravascular coagulation[4].

The source of these infections, their patterns of spread, and the microbiological agents involved vary among patients. Therefore, effective treatment requires a comprehensive understanding of deep neck spaces, the microbiology of the infection, potential complications, and additional factors that may exacerbate DNI[5,6]. A complete blood count (CBC) is an essential and widely utilized laboratory test for patients presenting with DNI. It also serves as a cost-effective diagnostic tool. The serological biomarkers assessed in CBC provide significant insights into inflammatory activity during acute infections. in addition to these serological markers, the neutrophil-to-lymphocyte ratio (NLR), which can be derived from CBC results, is recognized as a reliable indicator of systemic inflammation[7]. During an infection, the body increases neutrophil and leukocyte production to combat pathogens while reducing lymphocyte production due to redistribution or suppression. Consequently, an elevated NLR may serve as a significant indicator of severe or serious infections, particularly in cases of deep neck abscesses[7,8]. C-reactive protein (CRP) is an acute-phase protein present in plasma and synthesized by hepatocytes. Due to its rapid increase and decrease in response to the inflammatory process, CRP serves as a more sensitive marker of inflammation compared to the white blood cell (WBC) count[9]. In this study, a retrospective analysis was conducted on 295 patients treated for deep neck abscesses in our clinic over the past fifteen years, categorized based on abscess location. Laboratory findings at the time of initial hospital admission were recorded. Various factors, including gender, age, mediastinitis, tracheotomy status due to laryngeal and neck edema, concomitant diabetes mellitus, mortality, and bacterial growth, were analyzed to identify key indicators in the management of DNI. In this study, we examined the relationship between mortality and morbidities, such as mediastinitis and tracheotomy status, and laboratory parameter elevations, bacterial cultures from abscess samples, and the anatomical neck spaces affected. Consequently, this study aimed to identify the poor prognostic factors contributing to increased mortality and morbidity in patients with deep neck abscesses and to develop a clinical guide to assist physicians in optimizing patient management.

Materials and Methods

A total of 295 patients who underwent surgical intervention for deep neck abscess formation at Dicle University Otorhinolaryngology Clinic between January 2020 and January 2025 were included in this retrospective analysis. The study was approved by the Local Institutional Ethics Committee of Dicle University (date: 15.05.2024, number: 94). The demographic data of all patients, including age, gender, address, detailed clinical history, general examination, otorhinolaryngology examination, systemic evaluation, and duration of hospitalization, were recorded. Laboratory tests, including WBC count, neutrophil count, lymphocyte count, NLR, platelet count, and CRP levels, measured at the time of initial hospital admission, were analyzed. Contrast-enhanced neck and thoracic computed tomography (CT) and/or ultrasonography scans were performed to assess the localization of the abscess within cervical spaces, and to identify complications such as mediastinitis and laryngeal edema. These patients underwent abscess drainage in the operating room using a transcervical and transoral approach. After abscess drainage, the abscess content was sent to microbiology for culture, and the microorganisms identified according to the microbiology results were recorded. Tracheotomy surgery was performed on patients with severe respiratory distress and laryngeal edema. Drainage was also performed in collaboration with the chest surgery clinic on patients who developed mediastinitis. The patients were then admitted to the clinic or intensive care unit. They were monitored in the intensive care unit by an anesthesiologist. Intravenous 1 g ceftriaxone twice daily and clindamycin 500 mg twice daily were started as antibiotic treatment at the time of admission. During the patient follow-up, antibiotic treatment was adjusted according to the abscess culture results and the response. Patients who underwent tracheotomy due to laryngeal edema during abscess drainage and those who experienced mortality during the postoperative follow-up period were documented. Patients diagnosed with tuberculosis, those with abscesses resulting from foreign bodies, trauma, or malignancies, patients with cellulitis leading to deep neck infection, or those whose abscesses were drained using fine-needle aspiration, were excluded from the study. In conclusion, this study investigated the association of mortality and morbidity, including mediastinitis and tracheotomy status, with laboratory parameter elevations, microbiological cultures from abscess specimens, and the specific anatomical neck spaces involved. Our objective is to provide clinicians with valuable prognostic markers to assess mortality and morbidity in patients presenting with DNI.

Statistical Analysis

Quantitative variables were expressed using measures of central tendency and dispersion: mean ± standard deviation. The chi-square test was employed to assess differences between proportions and relationships between categorical variables. To evaluate differences in group means, the Mann-Whitney U test was applied in cases where the assumptions of normality and homogeneity of variance were not met. The correlation between two numerical variables was analyzed using Spearman's rank correlation test, a non-parametric method, as the data did not follow a normal distribution. Statistical significance was set at p=0.05 for all analyses. Statistical computations were performed using IBM SPSS (Statistical Package for the Social Sciences for Windows, version 21.0, Armonk, NY, IBM Corp.).

Results

The study population comprised 148 males (50.2%) and 147 females (49.8%). The age range for male patients was 0 to 77 years, with a mean age of 31.13±19.0 years, while the age range for female patients was 0 to 86 years, with a mean age of 29.09±18.82 years. Mediastinitis developed in 24 patients (8.1%), while tracheotomy was performed in 46 patients (15.6%) due to laryngeal edema and respiratory distress. Mortality occurred in 12 patients (4.1%) with mediastinitis during postoperative follow-up, primarily due to septic shock, electrolyte imbalances, and cardiovascular or cerebrovascular complications. Diabetes mellitus was present in 13 patients (4.4%), whereas it was absent in the remaining 282 patients (95.6%) (Table 1).

Table 1. Mortality and morbidity rates in deep neck infections

Parameter	Group	n (%)
Gender	Female	147 (49.8%)
	Male	148 (50.2%)
Mediastinitis	Present	24 (8.1%)
	Absent	271 (91.9%)
Mortality	Present	12 (4.1%)
	Absent	283 (95.9%)
Tracheotomy	Performed	46 (15.6%)
	Not performed	249 (84.4%)
Diabetes mellitus	Present	13 (4.4%)
	Absent	282 (95.6%)

Among patients who developed mediastinitis, the mean neutrophil count was 17.4±6.53×10^9/L, the mean lymphocyte count was 1.39±0.94×10^9/L, and the mean NLR was 19.13±10.05. The mean CRP level was 287.92±69.3 mg/L, the mean platelet count was 305.63±114.76×10^9/L, and the mean WBC count was 20.34±6.72×10^9/L. The average duration of hospitalization was 18.58±8.8 days. Statistically significant increases were observed in age (p=0.006), CRP (p<0.001), neutrophil count (p<0.001), NLR (p<0.001), and WBC count (p<0.001), with a mean patient age of 40.88±19.57 years. The length of hospital stay was also significantly longer (p<0.001). Conversely, lymphocyte levels were significantly lower (p<0.001). However, no significant difference was found in platelet counts (p=0.438) (Table 2).

Among patients who died, the mean neutrophil count was 19.98±8.02×10^9/L, the mean lymphocyte count was 1.04±0.52×10^9/L, and the mean NLR was 23.78±8.55. The mean CRP level was 294.25±86.03 mg/L, the mean platelet count was 267.0±130.29×10^9/L, and the mean WBC count was 22.83±8.54×10^9/L. The mean age of these patients was 44.92±20.64 years, and the mean duration of hospitalization was 18.33±12.15 days. Statistically significant increases were observed in age (p=0.01), CRP (p<0.001), neutrophil count (p<0.001), NLR (p<0.001), WBC count (p<0.001), and hospital stay (p=0.001). Conversely, lymphocyte levels were significantly lower (p<0.001). However, no significant difference was found in platelet counts (p=0.092) (Table 2).

In patients who underwent tracheotomy, the mean neutrophil count was 15.94±5.84×10^9/L, the mean lymphocyte count was 1.42±0.83×10^9/L, and the mean NLR was 15.92±9.21. The mean CRP level was 257.41±78.11 mg/L, the mean platelet count was 292.39±98.45×10^9/L, and the mean WBC count was 18.82±6.07×10^9/L. The mean age of this patient group was 39.52±18.51 years, and the mean duration of hospitalization was 16.09±7.23 days. Statistical analysis revealed significantly higher values for age (p<0.001), CRP (p<0.001), neutrophil count (p<0.001), NLR (p<0.001), WBC count (p<0.001), and hospital stay (p<0.001). In contrast, lymphocyte (p<0.001) and platelet (p=0.029) levels were significantly lower (Table 2). The association of inflammatory parameters with mortality, mediastinitis, and tracheotomy is shown in Figure 1. Mediastinitis developed in 6 out of 13 patients with diabetes mellitus (25%), tracheotomy was performed in 8 patients (17%), and 4 patients (33%) succumbed to the disease (Table 2).

The distribution of infection across various cervical spaces, as assessed following contrast-enhanced neck and thoracic CT, is presented in Table 3. The most commonly affected region was the submandibular space (24.1%), followed by the peritonsillar (14.6%) and parotid (8.1%) regions. Additionally, multiple space involvement, including the submandibular, carotid, and parapharyngeal spaces (6.8%), as well as isolated parapharyngeal involvement (5.4%), was observed.

Table 2. The association of inflammatory parameters and hospital stay with mortality, mediastinitis, and tracheotomy

	Mediastinitis			Tracheotomy			Mortality		
	Present (n=24)	Absent (n=271)	p-value	Present (n=46)	Absent (n=249)	p-value	Present (n=12)	Absent (n=283)	p-value
CRP	292	103	**<0.001**	256.5	92	**<0.001**	307.5	107	**<0.001**
Lymphocyte	1.25	2	**<0.001**	1.3	2	**<0.001**	0.9	2	**<0.001**
Neutrophil	16.1	10.9	**<0.001**	15.1	10.6	**<0.001**	17.75	11	**<0.001**
NLR	17.25	5.3	**<0.001**	14	5.1	**<0.001**	25.15	5.5	**<0.001**
Platelet	294	312	0.438	294	318	**0.029**	259	312	0.092
WBC	18.9	14.6	**<0.001**	17.75	14.5	**<0.001**	19.75	14.8	**<0.001**
Age	37.5	28	**0.006**	34	27	**<0.001**	45.5	28	**0.01**
Duration of hospitalization	17.5	7	**<0.001**	15	7	**<0.001**	15.5	7	**0.001**
Diabetes mellitus	6 (25%)	7 (3%)	**<0.001**	8 (17%)	5 (2%)	**<0.001**	4 (33%)	9 (3%)	**<0.001**

Mann-Whitney U test, n (%) – Fisher's exact test, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell

Among the 24 patients who developed mediastinitis, the infection commonly involved multiple anatomical regions. The highest incidence was observed in cases with infections affecting the submandibular, carotid, and parapharyngeal spaces (66.7%). The second most frequent pattern of involvement included infections spanning the submandibular, submental, and carotid spaces (12.5%), while the third most common presentation was associated with infections localized in the retropharyngeal space (8.3%) (Table 4).

During the follow-up period, 10 patients who developed mediastinitis died. Among these patients, abscess formation was most frequently identified in multiple submandibular, carotid, and parapharyngeal regions, with an incidence of 83.3%. The second most common site of abscess formation among mortal cases was the retropharyngeal region, accounting for 16.7% of cases (Table 4).

Among the 46 patients who underwent tracheotomy, the most frequently observed infection involved the submandibular, carotid, and parapharyngeal regions, occurring in 43.5%

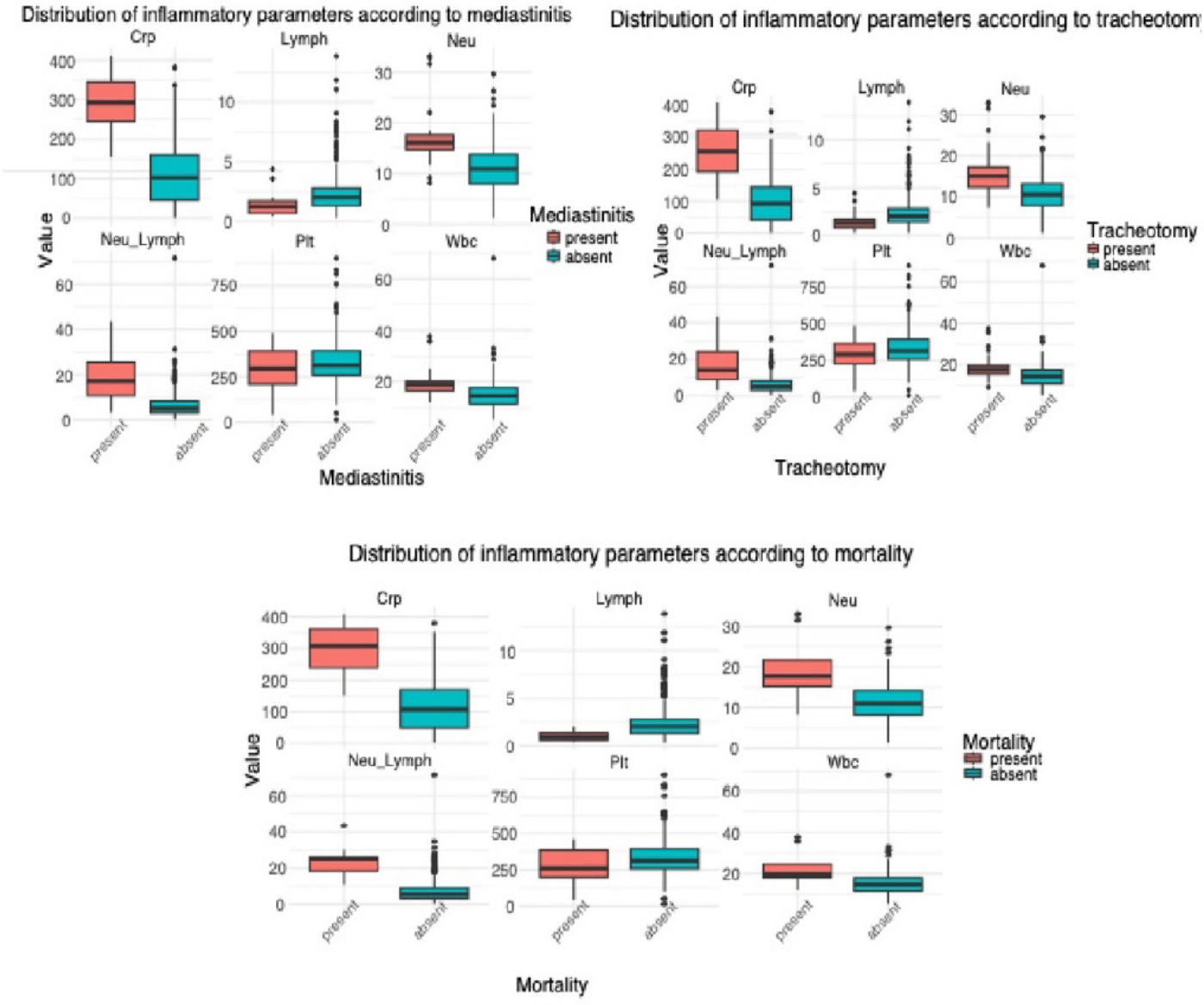

Figure 1. Association of inflammatory parameters with mortality, mediastinitis, and tracheotomy

of cases. The second most common infection pattern was identified in the multiple submandibular, submental, and parapharyngeal regions, with an incidence of 17.4%. The distribution of infections across other cervical spaces in patients with tracheotomy is detailed in Table 4.

Bacterial analysis was conducted on abscess samples aspirated from 295 patients during surgery, followed by culture and sensitivity testing for all specimens. After a 48-hour incubation period, microbial growth was observed in all cases. The most frequently identified microorganism was *Streptococcus constellatus* (27.1%), followed by *Streptococcus anginosus* (21.4%) and *Staphylococcus aureus* (13.6%). Other isolated organisms included Gram-positive cocci (6.1%), *Streptococcus pyogenes* (5.1%), *Fusobacterium nucleatum* (4.4%), *Streptococcus viridans* (3.1%), and *Bacteroides fragilis* (2.4%). Additional microorganisms, as detailed in Table 5, were detected in smaller proportions.

Table 3. Cervical spaces affected in deep neck infections

Affected cervical spaces	n (%)
Submandibular	71 (24.1%)
Peritonsillar	43 (14.6%)
Parotid	24 (8.1%)
Submandibular, carotid, parapharyngeal	20 (6.8%)
Parapharyngeal	16 (5.4%)
Retromandibular	12 (4.1%)
Submandibular, submental	10 (3.4%)
Retromandibular, masticator	9 (3.1%)
Submandibular, parapharyngeal	9 (3.1%)
Submental	9 (3.1%)
Submandibular, submental, parapharyngeal	8 (2.7%)
Masticator	7 (2.4%)
Paratracheal	7 (2.4%)
Retropharyngeal	6 (2.0%)
Posterior cervical	5 (1.7%)
Submandibular, submental, carotid	5 (1.7%)
Submandibular, parotid	4 (1.4%)
Submandibular, retromandibular	4 (1.4%)
Peritonsillar, parapharyngeal	3 (1.0%)
Submandibular, submental, paratracheal	3 (1.0%)
Submental, sublingual	3 (1.0%)
Buccal	2 (0.7%)
Parapharyngeal, masticator	2 (0.7%)
Submandibular, buccal	2 (0.7%)
Submandibular, masticator	2 (0.7%)
Submandibular, submental, parapharyngeal, paratracheal	2 (0.7%)
Carotid, parapharyngeal	2 (0.7%)
Parotid, parapharyngeal	1 (0.3%)
Peritonsillar, submandibular, parapharyngeal	1 (0.3%)
Peritonsillar, submandibular, submental, parapharyngeal	1 (0.3%)
Retromandibular, buccal	1 (0.3%)
Submandibular, carotid	1 (0.3%)
Submandibular, submental, sublingual	1 (0.3%)

In abscess cultures obtained from patients who developed mediastinitis, the most frequently isolated microorganism was *Streptococcus constellatus*, accounting for 45.8% of cases. This was followed, in descending order of prevalence, by *Bacteroides fragilis* (20.8%), *Streptococcus anginosus* (12.5%), *Staphylococcus aureus* (12.5%), *Fusobacterium necrophorum* (4.2%), and *Peptostreptococcus* (4.2%). In cases of mediastinitis with fatal outcomes, the most frequently isolated microorganism was *Bacteroides fragilis* (41.7%), followed by *Streptococcus constellatus* (33.3%), *Streptococcus anginosus* (16.7%), and *Staphylococcus aureus* (8.3%) (Table 6).

In patients who underwent tracheotomy, the most frequently isolated microorganism from abscess cultures was *Streptococcus constellatus* (32.6%), followed by *Streptococcus anginosus* (17.4%). *Bacteroides fragilis* (15.2%) and *Staphylococcus aureus* (15.2%) ranked third in frequency, with other microorganisms listed in descending order of prevalence in Table 6.

Affected cervical spaces and bacterial analysis in patients with tracheotomy status, mediastinitis, and mortality are shown in Figures 2-4.

Discussion

DNI represent a significant cause of morbidity and mortality, particularly in developing countries. Despite advancements in early antibiotic intervention and contemporary preventive and therapeutic strategies for dental diseases, these infections—which commonly originate from odontogenic or pharyngeal sources—remain prevalent worldwide[6]. In this study, a retrospective analysis was conducted on 295 patients, diagnosed with deep neck abscesses to evaluate the inflammatory serological biomarkers, including WBC count, neutrophil count, lymphocyte count, NLR, platelet count, and CRP levels, in relation to mortality, mediastinitis, and tracheotomy. The findings revealed that CRP, neutrophil

Table 4. The relationship between multiple neck space involvement and mortality, mediastinitis, and tracheotomy

Mediastinitis		**Tracheotomy**		**Mortality**	
Multiple neck space	(n=24)	Multiple neck space	(n=46)	Multiple neck space	(n=12)
Submandibular, carotid, parapharyngeal	16 (66.7%)	Submandibular, carotid, parapharyngeal	20 (43.5%)	Submandibular, carotid, parapharyngeal	10 (83.3%)
Submandibular, submental, carotid	3 (12.5%)	Submandibular, submental, parapharyngeal	8 (17.4%)	Retropharyngeal	2 (16.7%)
Retropharyngeal	2 (8.3%)	Submandibular, submental, carotid	5 (10.8%)		
Submandibular, submental, Parapharyngeal, paratracheal	2 (8.3%)	Submandibular, submental, paratracheal	3 (6.5%)		
Carotid, parapharyngeal	1 (4.2%)	Retropharyngeal	2 (4.3%)		
		Submandibular, submental, parapharyngeal, paratracheal	2 (4.3%)		
		Carotid, parapharyngeal	1 (2.2%)		
		Peritonsillar, submandibular, parapharyngeal	1 (2.2%)		
		Peritonsillar, submandibular, submental, parapharyngeal	1 (2.2%)		
		Submandibular, retromandibular	1 (2.2%)		
		Submandibular, submental, sublingual	1 (2.2%)		
		Submental, sublingual	1 (2.2%)		

count, WBC count, and NLR values were significantly elevated in patients who experienced mortality or morbidity, such as mediastinitis and tracheotomy, whereas the lymphocyte ratio was significantly reduced. A review of the literature indicates the presence of numerous studies investigating inflammatory parameters in DNI[6,10,11]. In their study, Koç et al.[12] reported that in patients with a hospitalization period exceeding 7 days, neutrophil count, CRP levels, NLR, and WBC count were elevated, while lymphocyte levels were decreased. Consequently, they identified age, CRP levels, and NLR as significant factors influencing morbidity. Similarly, Dogruel et al.[13] examined the relationship between NLR and hospitalization duration, concluding that patients with an NLR value greater than 5.6 experienced prolonged hospitalization and increased antibiotic requirements. Ghasemi et al.[14] identified a positive correlation between the NLR and hospitalization duration in their study. Gallagher et al.[15] reported that patients with elevated CRP and NLR levels had prolonged hospital stays and suggested that the NLR could serve as a prognostic marker for DNI. Conversely, Mirochnik et al.[9] concluded that CRP concentration was not a prognostic factor for the spread of DNI in their study. Our

Table 5. Bacterial microorganisms identified in cultures from all patients

Bacterial analiysis	n=295
Streptococcus constellatus	80 (27.1%)
Streptococcus anginosus	63 (21.4%)
Staphylococcus aureus	40 (13.6%)
Gram positive cocci	18 (6.1%)
Streptococcus pyogenes	15 (5.1%)
Fusobacterium nucleatum	13 (4.4%)
Streptococcus viridans	9 (3.1%)
Bacteroides fragilis	7 (2.4%)
Parvimonas micra	6 (2%)
Streptococcus oralis	5 (1.7%)
Streptococcus pneumoniae	5 (1.7%)
Actinomyces odontolyticus	3 (1.0%)
Fusobacterium necrophorum	3 (1.0%)
Prevotella denticola	3 (1.0%)
Prevotella intermedia	3 (1.0%)
Peptostreptococcus	2 (0.7%)
Streptococcus intermedius	2 (0.7%
Atopobium parvulum	1 (0.3%)
Bacillus licheniformis	1 (0.3%)
Eggerthia catenaformis	1 (0.3%)
Enterobacter aerogenes	1 (0.3%)
Finegoldia magna	1 (0.3%)
Fusobacterium nucleatus	1 (0.3%)
Gemella morbillorum	1 (0.3%)
Gram-negative cocci	1 (0.3%)
Haemophilus aphrophilus	1 (0.3%)
Klebsiella pneumoniae	1 (0.3%)
Prevotella buccae	1 (0.3%)
Prevotella loescheii	1 (0.3%)
Proteus mirabilis	1 (0.3%)
Serratia marcescens	1 (0.3%)
Staphylococcus carnosus	1 (0.3%)
Streptococcus agalactiae	1 (0.3%)
Streptococcus parasanguinis	1 (0.3%)
Veilonella atypica	1 (0.3%)

analysis revealed that CRP, NLR, neutrophil count, and WBC levels were significantly elevated, while the lymphocyte ratio was lower in patients with deep neck abscesses; consistent with findings reported in the majority of the literature. These alterations were associated with increased mortality and morbidity. Furthermore, we observed that patients with these elevated inflammatory markers experienced prolonged hospital stays. Based on these findings, we suggest that these serological biomarkers may serve as important prognostic indicators in patients presenting with deep neck abscesses.

O'Brien et al.[16] reported that age and diabetes are significant factors influencing morbidity and mortality in patients with DNI. Similarly, Gehrke et al.[3] concluded that diabetes contributes to increased morbidity and mortality in these infections. Consistent with these findings, our study also identified advanced age and diabetes as key predisposing factors, particularly for mortality and morbidity.

Numerous studies have reported that the submandibular region is the most frequently affected site in deep neck abscesses[17,18]. Similarly, Das et al.[19] identified the submandibular region as the most commonly involved site, followed by the sublingual region, while the carotid space was among the least frequently affected areas. Furthermore, Suehara et al.[10] reported that the submandibular region is the most commonly involved site, with multiple submandibular and parapharyngeal regions being the second most frequently affected areas. Gehrke et al.[3] reported that abscess formation most frequently occurred in the carotid space, followed by the submandibular space. In our study, we found that abscess formation was most commonly observed in the submandibular region, followed by the peritonsillar region. However, mortality, mediastinitis, and the need for tracheotomy were most frequently observed in patients with multiple submandibular, parapharyngeal, and carotid region involvements. Additionally, while the retropharyngeal space was the second most common site associated with mortality, multiple submandibular, submental, and carotid region involvement were the second most frequent sites associated with mediastinitis.

The microbiology of deep neck abscesses is generally similar, as these infections typically originate from oropharyngeal, (peritonsillar and parapharyngeal) or nasopharyngeal flora[20]. A diverse range of aerobic, microaerophilic, and anaerobic pathogens contribute to the infection, with microbiological patterns varying based on geographical differences[21]. In deep neck abscesses, *α-hemolytic Streptococcus*, *Enterococcus*, and *Klebsiella* species are commonly identified as aerobic pathogens, while *Peptostreptococcus* and *Bacteroides* species are frequently observed as anaerobic bacteria[22]. Singhal et al.[23] reported that *Staphylococcus aureus* was the most frequently isolated organism in both pediatric and

Table 6. Bacterial analysis in patients with mortality and morbidity					
Mediastinitis		**Tracheotomy**		**Mortality**	
Bacterial analysis	**(n=24)**	**Bacterial analysis**	**(n=46)**	**Bacterial analysis**	**(n=12)**
Streptococcus constellatus	11 (45.8%)	*Streptococcus constellatus*	15 (32.6%)	*Bacteroides fragilis*	5 (41.7%)
Bacteroides fragilis	5 (20.8%)	*Streptococcus anginosus*	8 (17.4%)	*Streptococcus constellatus*	4 (33.3%)
Streptococcus anginosus	3 (12.5%)	*Bacteroides fragilis*	7 (15.2%)	*Streptococcus anginosus*	2 (16.7%)
Staphylococcus aureus	3 (12.5%)	*Staphylococcus aureus*	7 (15.2%)	*Staphylococcus aureus*	1 (8.3%)
Fusobacterium necrophorum	1 (4.2%)	*Gram positive cocci*	2 (4.3%)		
Peptostreptococcus	1 (4.2%)	*Actinomyces odontolyticus*	1 (2.2%)		
		Eggerthia catenaformis	1 (2.2%)		
		Fusobacterium necrophorum	1 (2.2%)		
		Parvimonas micra	1 (2.2%)		
		Peptostreptococcus	1 (2.2%)		
		Streptococcus pyogenes	1 (2.2%)		
		Streptococcus viridans	1 (2.2%)		

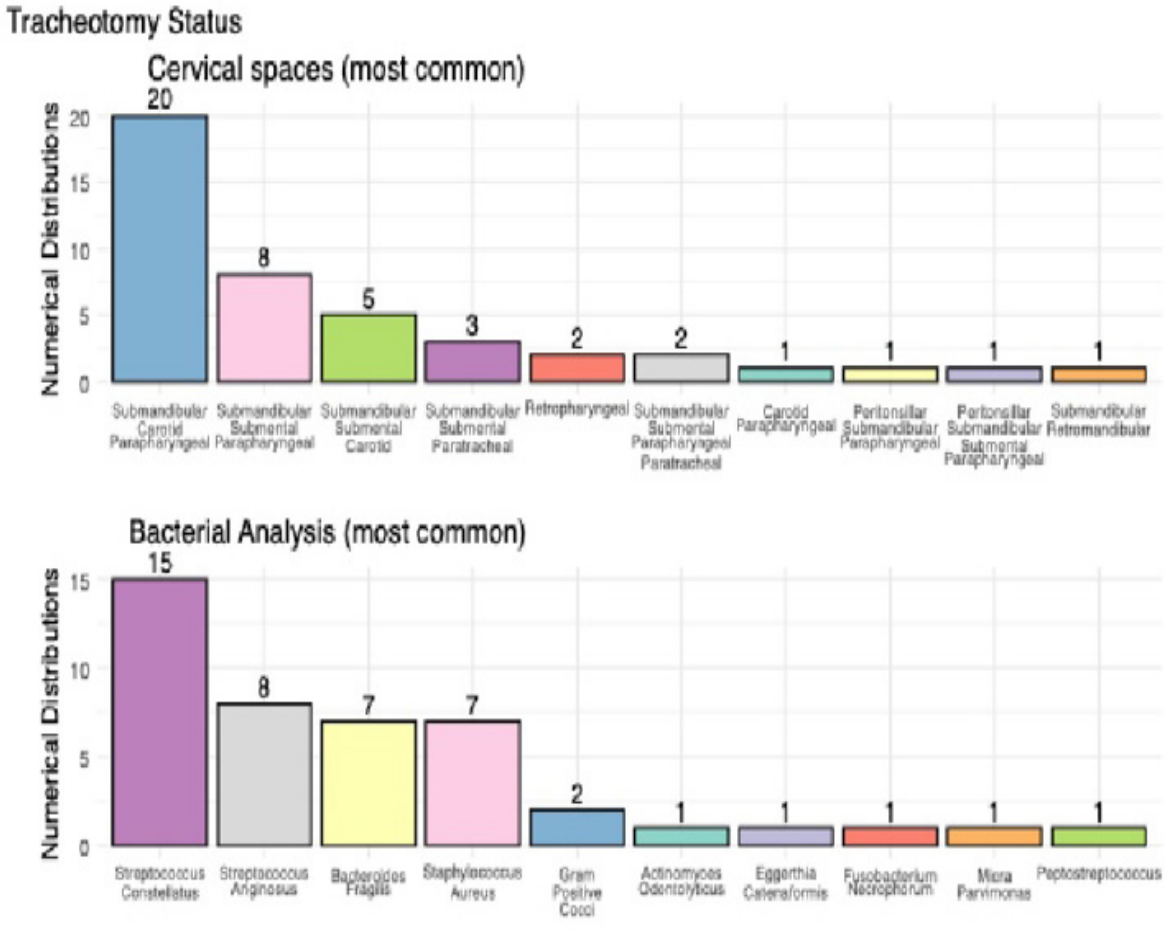

Figure 2. Affected cervical spaces and bacterial asnalysis in patients with tracheotomy status

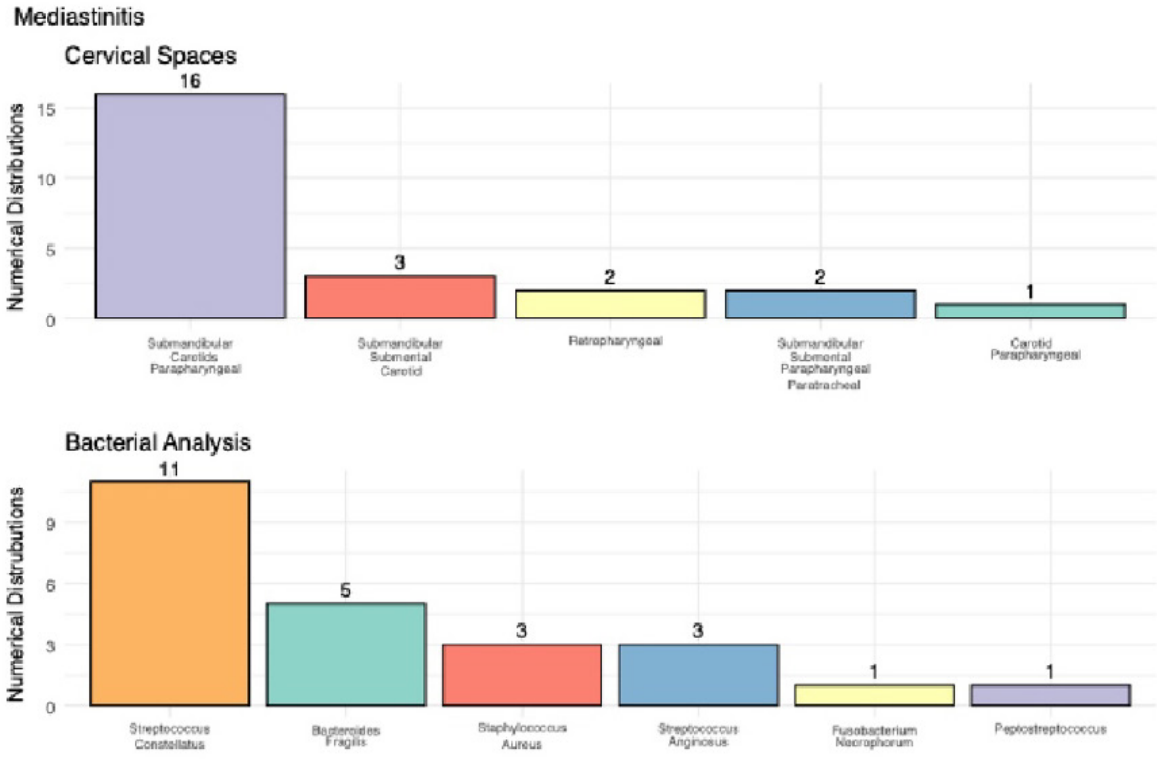

Figure 3. Affected cervical spaces and bacterial analysis in patients with mediastinitis

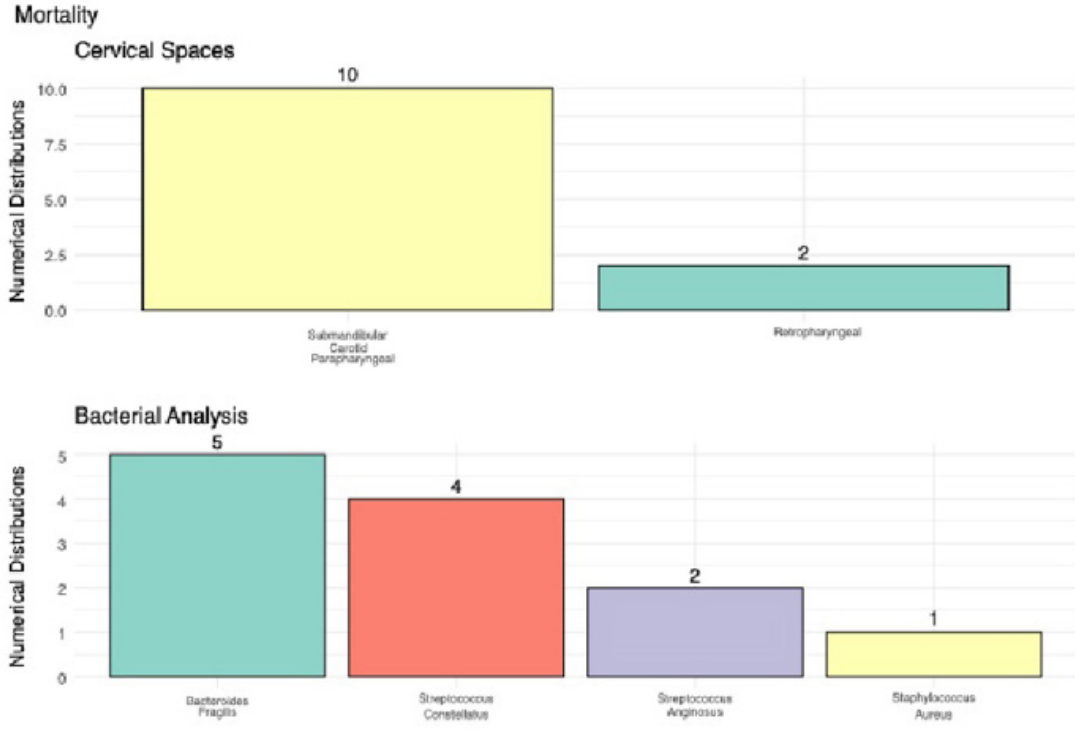

Figure 4. Affected cervical spaces and bacterial analysis in patients with mortality

adult populations. In contrast, Mathew et al.[24] found that *Streptococcus pyogenes* was the predominant pathogen, followed in frequency by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Rijal et al. reported that *Klebsiella pneumoniae* was the most frequently isolated organism, followed by *Streptococcus anginosus*, *Staphylococcus aureus*, and *Streptococcus constellatus* in decreasing order of frequency. In our study, *Streptococcus constellatus* was identified as the predominant pathogen, with *Streptococcus anginosus*, *Staphylococcus aureus*, and Gram-positive cocci following in order of frequency. Similarly, Hu et al.[25] observed frequent isolation of *Streptococcus constellatus*, *Streptococcus anginosus*, *Peptostreptococcus micros*, and *Prevotella buccae* in patients diagnosed with mediastinitis. In our study, the most frequently isolated pathogens in patients who developed mediastinitis were *Streptococcus constellatus*, *Bacteroides fragilis*, and *Streptococcus anginosus*. Among patients who died, however, *Bacteroides fragilis* was the predominant organism, followed by *Streptococcus constellatus* and *Streptococcus anginosus*. Additionally, in patients who experienced respiratory distress and required tracheotomy, the organisms isolated most frequently were *Streptococcus constellatus*, *Streptococcus anginosus*, *Bacteroides fragilis*, and *Staphylococcus aureus*, in descending order of frequency.

Based on the findings of our study, we emphasize that elevated serological markers—including WBC count, NLR, CRP levels, and neutrophil percentage, coupled with reduced lymphocyte percentage—as well as the presence of diabetes mellitus, involvement of multiple cervical anatomical spaces (particularly submandibular, carotid, and parapharyngeal regions), and isolation of pathogens such as *Streptococcus constellatus* and *Bacteroides fragilis* from abscess cultures, are associated with higher rates of mortality and mediastinitis. Additionally, these patients may require tracheotomy more frequently due to respiratory distress.

Study Limitations

The limitations of this study should be acknowledged. Firstly, the study was retrospective in design and conducted at a single center, potentially limiting the generalizability of the findings. Future research should aim to validate these results through prospective studies involving larger, multicenter cohorts.

Conclusion

The management of deep neck abscesses requires a multidisciplinary approach. Our findings indicate that elevated WBC counts, NLR, CRP levels, increased neutrophil percentages, decreased lymphocyte percentages, comorbidities such as diabetes mellitus, involvement of multiple cervical anatomical spaces (particularly submandibular, carotid, and parapharyngeal regions), and the isolation of pathogens such as *Streptococcus constellatus* and *Bacteroides fragilis* from abscess cultures, are significant negative prognostic factors associated with increased morbidity and mortality. We suggest that clinicians and surgeons who recognize these prognostic indicators and initiate timely and comprehensive medical treatment may substantially reduce patient mortality rates.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Ethics Committee of Dicle University (date: 15.05.2024, number: 94).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.C., M.A., Concept: S.C., G.K., Design: S.C., M.E.E., Data Collection or Processing: S.C., S.B., Analysis or Interpretation: S.C., M.Ak., Literature Search: S.C., M.E.E., Writing: S.C., M.A.

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Distribution of Ovarian Neoplasms in Young Females Aged 15-24: A Single-center Retrospective Observational Study

15-24 Yaş Arası Gençlerde Over Neoplazmlarının Dağılımı: Tek Merkezli Retrospektif Gözlemsel Bir Çalışma

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Abstract

Objective: Ovarian neoplasms are relatively uncommon in young females; however, they require a multidisciplinary approach to ensure early diagnosis, appropriate treatment planning, consideration of long-term psychosocial effects, and preservation of future reproductive potential. In this study, we aim to evaluate the types and distribution of ovarian tumors in females aged 15 to 24 years who underwent surgery at our institution. We will also review the clinical presentations and treatment strategies employed at the time of diagnosis.

Methods: A retrospective analysis was conducted on 196 patients aged 15 to 24 years who were admitted to the Pediatric Surgery and Obstetrics and Gynecology Departments for gynecological tumors between 2020 and 2025 at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital. Patient data, including age, obstetric and medical history, and current medications, were reviewed. Ultrasound findings at the time of diagnosis, abdominal magnetic resonance imaging results (if available), tumor marker levels, preoperative and postoperative hemogram values, surgical interventions, and histopathological outcomes were recorded. Statistical analyses were performed to evaluate the distribution of ovarian cyst types in relation to patient age.

Results: The mean age of the patients included in the study was 16.44 years (±1.76). The distribution of ovarian cyst types in the 196 patients was analyzed. The most common type was corpus luteum cyst (n=97), accounting for 49.5% of cases. This was followed by dermoid cysts (n=20, 10.2%), serous cystadenomas (n=15, 7.7%), and mucinous cystadenomas and endometriomas (n=5 each, 2.6%).

Conclusion: Our study contributes to the existing literature on ovarian masses in females aged 15 to 24 years, confirming that the majority of adnexal masses in this age group are benign, with functional cysts and dermoid cysts being the most common.

Keywords: Ovarian neoplasm, young females, cyst types

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Öz

Amaç: Over neoplazmları gençlerde daha az görülür, ancak erken tanı ve tedavi yönetimlerinin belirlenmesi, uzun vadeli psikososyal etki ve gelecekteki üreme sağlığı için multidisipliner bir yaklaşım gerektirir. Bu çalışmada, kurumumuzda opere edilen 15-24 yaş arası genç kadınlarda over tümörlerinin tipleri ve dağılımı incelenecek ve tanı anındaki klinik bulgular ve tedavi yaklaşımları gözden geçirilecektir.

Yöntem: Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi'nde 2020-2025 yılları arasında over neoplazmı nedeniyle Çocuk Cerrahisi Kliniği ile Kadın Hastalıkları ve Doğum Anabilim Dalı'na başvuran 15-24 yaş arası 196 hastanın retrospektif analizi yapıldı. Hastaların yaşı, obstetrik öyküsü, tıbbi öyküsü ve kullandığı ilaçlar gözden geçirildi. Tanı anındaki ultrason bulguları, varsa abdominal manyetik rezonans görüntüleme bulguları, tümör belirteçlerinin seviyeleri, preoperatif ve postoperatif hemogram değerleri, cerrahi prosedürler ve patoloji sonuçları kaydedildi. Over kist türlerinin yaşla ilişkili dağılımını değerlendirmek amacıyla istatistiksel analizler gerçekleştirildi.

Bulgular: Çalışmaya katılan hastaların yaş ortalaması 16,44 (±1,76) idi. Toplam 196 hastada saptanan over kistlerinin dağılımı analiz edildi. En sık görülen kist tipi %49,5 oranıyla korpus luteum kistiydi (n=97) Bunu %10,2 ile dermoid kist (n=20), %7,7 ile seröz kistadenom (n=15) ve %2,6'şar (n=5) oranla müsinöz kistadenom ve endometrioma izledi.

Sonuç: Çalışmamız 15-24 yaş arası kadınlarda over neoplasmları ile ilgili literatüre katkıda bulunmakta ve bu gruptaki adneksiyal kitlelerin çoğunun, özellikle fonksiyonel ve dermoid kist gibi benign özellikte olduğunu doğrulamaktadır.

Anahtar Kelimeler: Over neoplazmı, genç kadınlar, kist tipleri

Introduction

Although the exact incidence of ovarian neoplasms in young girls remains unknown, it is estimated to be approximately 2.6 cases per 100,000 girls annually, with malignant ovarian tumors accounting for about 1% of all childhood malignancies[1,2]. Ovarian neoplasms are histologically classified into three main groups: Germ cell tumors, sex cord-stromal tumors, and epithelial tumors. Among these, surface epithelial tumors are less common during childhood and adolescence, while metastatic tumors are extremely rare. Germ cell and sex cord-stromal tumors are more frequently observed in this age group[3]. The majority of ovarian tumors in girls are of non-epithelial origin and can be diagnosed from birth through 9 years of age. Benign functional cysts such as follicular cysts, corpus luteum cysts, and theca lutein cysts are the most commonly encountered ovarian lesions in childhood[4]. Malignancy is present in only 3-8% of adnexal masses, with its incidence increasing with age[5,6].

Ovarian tumors present unique diagnostic challenges during adolescence and young adulthood, as benign neoplasms are significantly more common than malignant ones, and clinical signs, and symptoms are often non-specific. Presenting symptoms may range from acute abdominal pain to a palpable pelvic or abdominal mass, often raising suspicion of malignancy. Assessing the risk of malignancy is a critical step in the diagnostic process. Therefore, early detection and differentiation between benign and malignant masses are essential, requiring a thorough evaluation, including clinical examination, imaging, laboratory tests, and serum tumor markers.

Preoperative evaluation in young women scheduled for ovarian surgery should include a pelvic examination, gynecologic ultrasonography, assessment of hormonal status, and measurement of serum tumor markers. Advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) may also be utilized to further characterize the mass and determine its origin. Surgical intervention in this age group must be carefully considered due to potential implications for future fertility. Ovarian tissue may be inadvertently removed during surgery, and postoperative adhesions may impair reproductive function. While minimally invasive laparoscopic approaches are preferred for the evaluation and excision of benign ovarian tumors, oophorectomy may be necessary in cases with a high likelihood of malignancy, ovarian tissue destruction, or torsion-related necrosis[7-9].

This retrospective study was conducted to review the clinical features and operative management of ovarian tumors in young women aged 15 to 24 years treated at our institution over the past five years.

Materials and Methods

Study Design and Setting

This retrospective observational study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital. Data from patients operated on between January 2020 and January 2025 were reviewed.

Inclusion Criteria

- Female patients aged 15 to 24 years,

- Underwent surgical intervention for an adnexal mass,

- Complete clinical, imaging, and pathology records available.

Exclusion Criteria

- Conservative management without surgery,

- Incomplete or missing diagnostic or histopathologic records.

Surgical Indications

Patients were selected for surgery based on the following clinical criteria:

- Cyst size >5 cm,

- Persistence of cyst beyond two menstrual cycles,

- Acute abdomen symptoms suggestive of torsion, rupture, or hemorrhage,

- Imaging findings suggestive of malignancy (solid components, papillary projections),

- Elevated tumor markers such as CA-125, CA 19-9, alpha-fetoprotein (AFP).

Preoperative Evaluation and Perioperative Management

All patients underwent preoperative pelvic ultrasonography, and MRI was used in cases with inconclusive findings. Tumor markers (CA-125, CA 19-9, AFP, CA 15-3) were routinely assessed. Surgical interventions included laparoscopic or open cystectomy, or oophorectomy, depending on intraoperative findings. Postoperative management included routine follow-up at 1 week and 1 month.

Follow-up

Postoperative follow-up focused on short-term complications, histopathological correlation, and readmission within 30 days. Long-term fertility preservation or recurrence monitoring was not routinely documented.

Ethics

The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no: E-96317027-514.10-269244759, date: 26.02.2025).

Statistical Analysis

Descriptive statistics were used to summarize the distribution of ovarian cyst types and the associated age characteristics. The number and percentage of each cyst type were reported, along with mean ± standard deviation and median (minimum-maximum) age values. Statistical analyses were performed using the open-source software Jamovi (version 2.3.21).

Results

The mean age of the 196 patients was 16.44±1.76 years. The distribution and age characteristics of the ovarian cysts are presented in Table 1. The most common cyst type was corpus luteum cyst (n=97, 49.5%), followed by dermoid cyst (n=20, 10.2%), serous cystadenoma (n=15, 7.7%), and unspecified serous cyst (n=15, 7.7%). Simple/follicular cyst was observed in 14 patients (7.1%), serous cystadenofibroma in 7 patients (3.6%), and mucinous cystadenoma and endometrioma in 5 patients (2.6%) each. Rare tumors included dysgerminoma (n=3, 1.5%) endometrioid adenocarcinoma (n=3, 1.5%), sex cord-stromal tumors (n=2, 1.0%), lymphoma (n=2, 1.0%), and mixed germ cell tumors (n=2, 1.0%). Fibroma, leiomyoma, juvenile-type granulosa cell tumor, low-grade serous carcinoma, and serous carcinoma were observed in 1 patient each (0.5%). No ovarian neoplasm was detected in 15 patients (7.7%), who underwent surgery upon clinical and radiological suspicion.

The mean ages for simple/follicular cyst and corpus luteum cyst were 16.14±0.66 years and 16.12±0.88 years, respectively. The mean ages for dermoid cyst, serous cystadenoma, and mucinous cystadenoma were 16.20±0.95, 15.80±0.68, and 16.20±1.10 years, respectively. The ages for sex cord-stromal tumors, mixed germ cell tumors, and lymphoma ranged from 16.00 to 19.50 years. The mean and median ages for endometrioid adenocarcinoma and serous carcinoma were 24.00 years.

Of the 196 patients, 2 had an obstetric history and 2 had a prior appendectomy. Paratubal cysts were observed in 27 patients (13%), and ovarian torsion was identified in 24 patients (12%), with pathology of the identified cases confirming mainly serous cystadenoma and simple follicular cyst. In acute abdomen cases, 22 patients (11%) underwent appendectomy in the same session as the ovarian cyst excision, and pathology revealed a corpus luteum or a simple follicular cyst. Two patients presented with both ovarian torsion and acute appendicitis.

All patients had normal carcinoembryonic antigen levels. CA-125 was elevated in 15 patients, primarily in those with mucinous cystadenoma, endometrioma, serous carcinoma, and endometrioid adenocarcinoma. CA 19-9 was elevated in 12 patients with mucinous cystadenoma, dermoid cyst, serous cystadenoma, and endometrioid adenocarcinoma. CA-125 and CA 19-9 values were higher in patients with malignancies, and minimally elevated in a few patients with benign conditions such as simple follicular or corpus luteum cysts. CA 15-3 was elevated in one patient with serous carcinoma; and AFP was highly elevated in two patients with mixed germ cell tumors. Preoperative ultrasonography and MRI findings were consistent with intraoperative and histopathological results.

Table 1. Distribution of ovarian cyst types and age characteristics

Cyst type	N (%)	Age (years), Mean ± SD	Age (years), Median (min-max)
Non-ovarian mass	15 (7.7)	17.33±3.09	16 (15-24)
Simple/follicular cyst	14 (7.1)	16.14±0.66	16 (15-17)
Sex cord-stromal tumor	2 (1.0)	19.50±6.36	19.50 (15-24)
Dysgerminoma	3 (1.5)	17.33±3.21	16 (15-21)
Dermoid cyst	20 (10.2)	16.20±0.95	16 (15-18)
Serous cystadenoma	15 (7.7)	15.80±0.68	16 (15-17)
Mucinous cystadenoma	5 (2.6)	16.20±1.10	17 (15-17)
Serous cystadenofibroma	7 (3.6)	16.00±0.58	16 (15-17)
Lymphoma	2 (1.0)	16.00±1.41	16 (15-17)
Endometrioma	5 (2.6)	16.40±0.55	16 (16-17)
Mixed germ cell tumor	2 (1.0)	17.50±2.12	17.50 (16-19)
Endometrioid adenocarcinoma	3 (1.5)	24.00±0.00	24 (24-24)
Corpus luteum	97 (49.5)	16.12±0.88	16 (15-19)
Fibroma	1 (0.5)	15.00	15 (15-15)
Leiomyoma	1 (0.5)	16.00	16 (16-16)
Sex cord-stromal tumor (other)	1 (0.5)	17.00	17 (17-17)
Juvenile-type granulosa cell tumor	1 (0.5)	17.00	17 (17-17)
Serous carcinoma (low grade)	1 (0.5)	18.00	18 (18-18)
Serous carcinoma	1 (0.5)	24.00	24 (24-24)
Total	196 (100)	16.44±1.76	-

SD: Standard deviation

Benign cysts, such as corpus luteum and follicular cysts, were predominantly observed during mid-adolescence, whereas malignant and epithelial tumors tended to occur in later adolescence or adulthood within the studied group (Figure 1).

Discussion

Ovarian tumors are generally reported to be rare in teens and adolescents[10-13]. The present study is one of the first

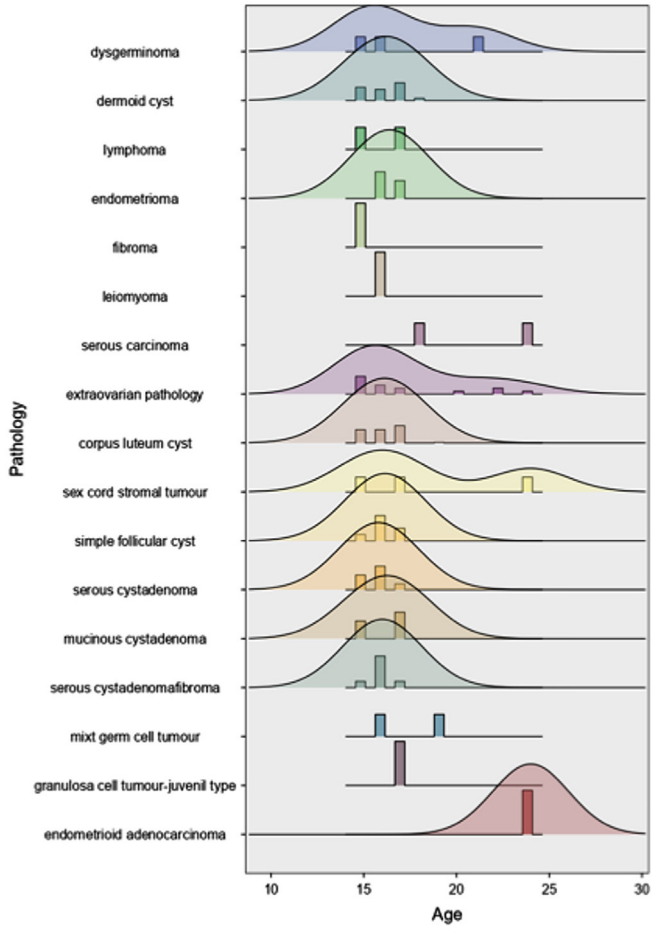

Figure 1. Plot curves showing tumor distributions according to age. This plot shows the distribution of various types of ovarian cysts in different age groups. Benign cysts, such as corpus luteum and follicular cysts, are usually seen in mid-puberty, while malignant and epithelial tumors tend to occur at an older age

studies to focus on young females aged 15-24 years, and our findings support the idea that benign pathologies such as corpus luteum cyst, simple follicular cyst, and dermoid cyst are more common in this age group. Recent studies revealed that most ovarian masses observed in children and adolescents are not neoplastic. Templeman et al.[14] found that 57.9% of girls and young women under 21 who underwent surgery for non-inflammatory ovarian masses had simple, non-neoplastic ovarian cysts. In a study by Deligeoroglou et al.[15], 49.0% of cases were benign neoplasms, 2.1% were malignant neoplasms, and 48.9% were non-neoplastic ovarian cysts. The results of our study support the low rate of gynecologic malignancy in this age group, with only eight patients diagnosed with malignant ovarian tumors. This may be due to the relatively young mean age (16 years), which may partially explain the low malignancy rates observed in our cohort. It may also result from the predominantly benign pathology of adnexal masses in emergent gynecologic operations. One of the drawbacks of our study is the more emergent operations compared to elective procedures.

Many studies have reported that functional cysts account for a significant percentage of non-neoplastic lesions. Functional ovarian cysts include follicular, corpus luteum, and theca lutein cysts. Although most of these cysts regress spontaneously, a few are treated surgically because of persistence or an urgent clinical scenario. In our study, corpus luteum cysts ranked first among benign lesions with 49%, followed by dermoid cysts with 20%. In a study in which functional ovarian cysts were excluded, mature teratoma was reported as the most common benign tumor (73%)[16]. The fact that dermoid cysts were the most common (10.2%) lesion after functional ovarian cysts in our study is consistent with the results of other studies[14,15,17]. Epithelial ovarian tumors are rare in teens and adolescents, and their incidence increases with age[17]. In the present study, 7.7% serous cystadenomas and 2.6% mucinous cystadenomas were found, supporting the fact, that epithelial ovarian cancers are more common in the older age group. Endometrioid cysts represented 2.6% of all ovarian lesions in our study. In contrast to common endometriosis, they are rarely seen in adolescents. Also, the mean age of rare tumors, such as lymphoma, sex cord stromal tumors, and mixed germ cell tumors was slightly higher (16.00-19.50 years). Notably, endometrioid adenocarcinoma and serous carcinoma were observed in significantly younger women with a median age of 24 years, in line with recent reports.

Ovarian pathologies can have a variety of symptoms. These symptoms are often non-specific. The non-specificity of these symptoms makes accurate preoperative diagnosis more difficult. As an initial symptom, abdominal pain is one of the most common. It is difficult to suspect ovarian masses in this age group. This is because acute symptoms are often attributed to more common conditions, such as appendicitis. In our study, 22 patients (11%) who presented with acute abdominal pain underwent appendectomy with ovarian cyst excision in the same surgical session. The presence of an ovarian cyst on preoperative imaging increased clinical suspicion and created diagnostic uncertainty. Therefore, both appendiceal and ovarian pathologies were treated during the same operation. Another condition that clinically presents with acute abdominal symptoms is ovarian torsion. The frequency of ovarian torsion has varied between 10% and 42% in studies[18,19]. This may be due to differences in the patient group included in the study. In our study, this rate was 12%.

In our study, ultrasonography was 100% accurate in diagnosing ovarian pathology. However, it was impossible to differentiate between benign and malignant tumors in the patients included in the study. The use of ultrasonography in the first-line evaluation is reliable. If ultrasonography detects a suspicious adnexal mass, CT and/or MRI might confirm the diagnosis. These imaging modalities provide thorough information about a suspicious mass, its location, and exclusion of other pathologies. Color Doppler sonography is essential in the diagnosis of emergencies such as ovarian torsion and can also help in differentiating ovarian malignancies.

Tumor markers can be used as a follow-up parameter in cancer patients. Biomarkers may increase in malignant germ cell tumors, endometriomas, and epithelial tumors, and are used for follow-up in these patients[20]. For the screening and early diagnosis of epithelial ovarian cancer, serum CA-125 levels are commonly used[21]. Shan et al.[22] showed that the detection of combined tumor markers, including CA-125, in serum in epithelial ovarian cancer has higher sensitivity and specificity. In our study, CA-125 was elevated in 15 patients, who were diagnosed with mucinous cystadenoma, endometrioma, serous carcinoma, and endometrioid adenocarcinoma. Twelve patients had elevated CA 19-9 levels and were classified as having mucinous cystadenoma, dermoid cyst, serous cystadenoma, and endometrioid adenocarcinoma. This supports combined elevation of CA-

125 and CA 19-9 in epithelial ovarian tumors, endometriosis, and malignancy. In a review by Matonóg and Drosdzol-Cop[23], the importance of serum AFP measurement in children in the early diagnosis and treatment of ovarian masses was mentioned, and it was reported that it was high, especially in germ cell tumors. In our study, only two cases of germ cell tumors were identified; however, both were associated with markedly elevated AFP levels. Elevated tumor markers in these patients contributed to both the preoperative suspicion of malignancy and the postoperative confirmation of the diagnosis of adnexal masses in the young population.

Study Limitations

Our study has some important strengths. We used a relatively large sample covering a variety of ovarian diseases with a specific focus on histopathological subgroups and the distribution of adnexal masses by age. Our study also has some limitations. First, the study had the inherent limitations of any retrospective study. Secondly, the inclusion of urgent ovarian pathologies may have increased the proportion of benign lesions observed, potentially influencing the overall malignancy rate. Future research should focus on collecting data in a prospective manner from multiple centers. In addition, exclusion criteria could be established for benign ovarian cysts, which may resolve spontaneously without the need for surgery but are nevertheless operated on due to acute clinical presentations.

Conclusion

This study adds valuable insight to the existing literature on ovarian masses in young females aged 15 to 24 years. Consistent with previous research, the majority of adnexal masses in this age group were benign, with functional cysts and dermoid cysts being the most commonly identified lesions. These findings highlight the importance of a comprehensive diagnostic approach that includes clinical assessment, imaging techniques, and tumor marker evaluation to ensure accurate diagnosis and appropriate management of adnexal masses in this population.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital (approval no: E-96317027-514.10-269244759, date: 26.02.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Assessing Physicians' Readiness for Medical Artificial Intelligence

Hekimlerde Tıbbi Yapay Zeka Hazırbulunuşluğunun Değerlendirilmesi

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Abstract

Objective: This study aims to assess the level of readiness among physicians at University of Health Sciences Türkiye, İzmir City Hospital for the adoption of medical artificial intelligence (AI) technologies.

Methods: Participants' readiness levels were assessed with the medical artificial-intelligence readiness scale devised by Karaca et al. University of Health Sciences Türkiye, İzmir City Hospital employs 1.867 physicians. Using Baş's (2006) sample-size formula with a ±0.05 margin of error and a 95% confidence level, the minimum required sample was calculated as 319, and 320 physicians ultimately completed the questionnaire. The 22-item scale was subjected to exploratory and confirmatory factor analysis (EFA). The initial solution explained 85.432% of the total variance, with excellent sampling adequacy (Kaiser-Meyer-Olkin=0.964) and a highly significant Bartlett's test of sphericity (χ^2=9.376.445, p<0.001). Inspection of the pattern matrix revealed substantial cross-loadings on three items; these items were removed, and the EFA was rerun on the refined item set.

Results: Statistical analyses showed no significant variation in physicians' medical-AI readiness (MAIR) across age, sex, or marital status, either for the composite score or for any of the sub-dimensions (p>0.05). Years in practice influenced only the third factor, Foresight, with a significant difference emerging there (p<0.05) but not on the remaining dimensions. Departmental affiliation, by contrast, proved important: except for the ethics sub-scale, all dimensions -and the overall MAIR score- differed significantly among departments (p<0.05). The grand-mean MAIR score was 3.11 on a five-point scale. Thus, physicians' readiness levels lie slightly above the midpoint, reflecting a generally positive yet essentially ambivalent attitude toward medical AI. The same "marginally above neutral" pattern applies to each individual sub-dimension.

Conclusion: The analysis reveals that physicians adopt a moderately positive stance toward AI, yet they exhibit a pronounced shortfall in the technical knowledge and practical competence required for its effective implementation.

Keywords: Artificial intelligence, readiness, management, health technologies

Öz

Amaç: Bu çalışmanın amacı, Sağlık Bilimleri Üniversitesi, İzmir Şehir Hastanesi'nde çalışan hekimlerin tıbbi yapay zeka (YZ) teknolojilerine yönelik hazırbulunuşluk düzeylerini değerlendirmektir.

Yöntem: Katılımcıların hazırbulunuşluk düzeylerini değerlendirmek amacıyla, Karaca ve ark. tarafından geliştirilen "tıbbi yapay zeka hazırbulunuşluk ölçeği" kullanılmıştır. Sağlık Bilimleri Üniversitesi, İzmir Şehir Hastanesi'nde toplam 1,867 hekim görev yapmaktadır. Örneklem yeter sayısını belirlemek için Baş'ın (2006) belirttiği formül kullanılarak örneklem sayısı ±0,05 hata toleransı ve %95 güven aralığında 319 hesaplanmış 320 kişiye ulaşılmıştır. Yirmi iki ifadeden oluşan ölçeğe açıklayıcı faktör analizi (AFA)-doğrulayıcı faktör analizi uygulanmış ve toplam açıklanan varyans=85,432, Kaiser-Meyer-Olkin=0.964, Bartlett'ın küresellik testi (χ^2=9,376.445, p<0,001) olarak bulunmuştur. Ancak yapılan incelemede ölçekte yer alan üç ifadede binişiklik olduğu saptanarak bu üç ifade analizden çıkarılarak tekrar AFA yapılmıştır.

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Öz

Bulgular: Analizlerde yaşa, cinsiyete ve medeni duruma göre hekimlerin tıbbi YZ hazırbulunuşluk (TYZH) durumunun tüm alt boyutlar da dahil olmak üzere istatistiksel olarak anlamlı biçimde farklılaşmadığı (p>0,05) saptanmıştır. Meslekteki çalışma süresine göre hekimlerin üçüncü faktörde farklılaştığı (p<0,05) ancak diğer boyutlarda bir farklılık olmadığı saptanmıştır. Bölümlere göre etik faktör dışında tüm faktörler ve ölçek genelinde farklılaştığı (p<0,05) saptanmıştır. Ölçeğin tamamının ortalaması 3,11'dir. Genel olarak katılımcıların TYZH düzeyleri, ortalamanın biraz üzerinde olmakla birlikte durumları kararsız olarak değerlendirilmektedir. Aynı durum tüm alt boyutlar için de geçerlidir.

Sonuç: Analiz sonucunda elde edilen bulgular, hekimlerin yapay zekaya kısmen olumlu bir tutum sergilediğini ancak teknik bilgi açısından ve uygulama yeterliliği konusunda belirgin bir eksiklik yaşadığını ortaya koymuştur.

Anahtar Kelimeler: Yapay zeka, hazırbulunuşluk, yönetim, sağlık teknolojileri

Introduction

In recent years, health-care systems have been among the domains most profoundly affected by technological integration. Rapid population growth, the escalating prevalence of chronic diseases, shortages of health professionals, and persistent concerns over patient safety now necessitate the delivery of care that is more effective, efficient, and universally accessible. One of the principal drivers of this ongoing transformation is, unquestionably, artificial intelligence (AI) technology[1].

AI applications are currently spearheading an extensive process of change and transformation within health and medical domains[2]. This technological evolution promises numerous benefits-chief among them greater sector-wide efficiency, improved patient-care services, and a reduction in clinicians' workload[2,3]. Far from simply easing that workload, AI systems actively support professional judgment across a broad spectrum of functions, ranging from clinical decision-support systems and patient-monitoring tools to image-processing technologies and digital triage platforms[4]. Yet the ultimate success of these innovations hinges on whether the health-care personnel who will use them are cognitively, affectively, and ethically prepared for such sweeping change.

Because physicians occupy a central position in the provision of health-care services, it is crucial that they interact directly with emerging technologies and be fully prepared to employ them in their decision-making processes[5]. Accordingly, the present study has been undertaken to evaluate physicians' readiness for AI. Its specific objective is to measure the level of readiness among hospital-based physicians with respect to the adoption of AI technologies in clinical practice.

AI: Conceptual and Clinical Perspectives

AI is a set of cognitive algorithms that enables machines to develop human-like capacities for thinking, learning, decision-making, and problem-solving[6]. Broadly speaking, AI is defined as the technologies that allow computers to emulate human intelligence. In other words, it describes the reasoning and learning processes of information-technology systems that behave as if endowed with human intellect[7]. Yet another formulation defines AI as a system's ability to interpret data accurately, draw inferences from those data, and-through flexible adaptation-use those inferences to achieve specified goals and execute designated tasks[8]. Recent definitions go further, positing the complete transfer of the knowledge stored in the human brain to machines. It is now claimed that a machine can perform cognitive functions traditionally associated with the human mind-perception, inference, learning, environmental interaction, problem-solving, and decision-making-and can even display creativity beyond these capabilities[9].

In the health sector, AI-most notably through machine learning, deep learning, and radiological image-analysis techniques-helps orchestrate the entire treatment pathway by supporting tasks such as disease diagnosis, radiography, pathology, electronic record keeping, risk prediction, patient monitoring, and personalised therapy[6,10]. Beyond these capabilities, AI technologies confer additional advantages, including higher diagnostic accuracy, more practical and effective treatment planning, and easier patient access to care. By harnessing information on patients' medical histories and drug reactions, AI algorithms allow physicians to design treatment plans more efficiently and to deliver the required interventions in a timely manner[11].

The coronavirus disease-2019 pandemic has made the role of AI in health-care systems even more conspicuous, particularly through its capacity to lighten patient loads, generate data-driven predictions, and supply robust decision-support tools[12]. At the same time, the expanding use of AI in the health sector has prompted fresh debates over system explainability, legal liability, ethical limits, and the distribution of professional responsibilities[13,14].

Today, significant strides are being made toward the integration of routine medical practice with AI technologies[15]. Physicians are expected to become adept users who can employ these tools on a broad scale, critically analyse their outputs, and develop a deeper grasp of the underlying algorithms[1]. By devising solutions to a wide range of clinical problems and simplifying workflows, medical AI applications hold revolutionary potential in health care-potential that will likely accelerate their incorporation into everyday clinical practice.

Readiness: Conceptual Framework

The concept of readiness refers to the extent to which individuals are mentally, cognitively, emotionally, and socially equipped before undertaking a task. It has also been framed as "the cognitive-emotional disposition to consciously accept, embrace, or reject a specific plan intended to alter the status quo"[16]. Although the term has long been used in educational research, it is now widely examined in the contexts of digital transformation and organisational alignment. For health-care professionals, readiness involves far more than possessing relevant knowledge; it also includes an openness to change, the ability to operate new systems, and the capacity to evaluate those systems within ethical and legal frameworks[17].

Successful adoption and implementation of any technology demand a high degree of user acceptance that is calibrated to the specific needs of those who will operate the system[18]. In the context of technologies such as AI, readiness should be construed not merely as cognitive awareness but equally as professional competence and digital literacy. The requisite level of technological readiness in an individual provides the essential foundation for learning about-and meaningfully engaging with-the technology[19].

Materials and Methods

Aim and Significance

Given physicians' pivotal role in health-care delivery, it is essential that they engage directly with emerging technologies and be adequately prepared to employ them in their decision-making processes[5]. The present research, entitled "assessment of physicians' readiness for AI," seeks to determine whether hospital-based physicians possess a sufficient level of readiness for AI technologies in clinical care. Beyond this overarching aim, the study also examines whether AI readiness varies according to physicians' age, gender, marital status, department, and years of professional experience.

A review of the domestic literature shows that prior investigations have focused on emergency medical personnel as well as medical-school and nursing students. Notable examples include Boillat et al.'s[20] survey study, "Readiness to Adopt AI among Medical Doctors and Students", and AlZaabi et al.'s[21] work, "Are Physicians and Medical Students Ready for AI Applications in Health Care?", both of which compared doctors with students. By contrast, the present study is the first to concentrate exclusively on physicians' medical-AI readiness.

Research Hypotheses

Drawing on the findings reported in the literature, the study tests the following main and subsidiary hypotheses:

$\mathbf{H_1}$ Physicians' total medical AI-readiness (MAIR) differs significantly by age.

- $\mathbf{H_{1a}}$ The cognitive factor differs by age.
- $\mathbf{H_{1b}}$ The skill factor differs by age.
- $\mathbf{H_{1c}}$ The foresight factor differs by age.
- $\mathbf{H_{1d}}$ The ethics factor differs by age.

$\mathbf{H_2}$ Physicians' total AI-readiness differs significantly by sex.

- $\mathbf{H_{2a}}$ The cognitive factor differs by sex.
- $\mathbf{H_{2b}}$ The skill factor differs by sex.
- $\mathbf{H_{2c}}$ The foresight factor differs by sex.
- $\mathbf{H_{2d}}$ The ethics factor differs by sex.

$\mathbf{H_3}$ Physicians' total AI-readiness differs significantly by marital status.

- $\mathbf{H_{3a}}$ The cognitive factor differs by marital status.
- $\mathbf{H_{3b}}$ The skill factor differs by marital status.
- $\mathbf{H_{3c}}$ The foresight factor differs by marital status.
- $\mathbf{H_{3d}}$ The ethics factor differs by marital status.

$\mathbf{H_4}$ Physicians' total AI-readiness differs significantly by years of professional experience.

- $\mathbf{H_{4a}}$ The cognitive factor differs by years of experience.
- $\mathbf{H_{4b}}$ The skill factor differs by years of experience.

- H_{4c} The foresight factor differs by years of experience.
- H_{4d} The ethics factor differs by years of experience.

H_5 Physicians' total AI-readiness differs significantly by department.

- H_{5a} The cognitive factor differs by department.
- H_{5b} The skill factor differs by department.
- H_{5c} The foresight factor differs by department.
- H_{5d} The ethics factor differs by department.

Population and Sample

The study was deliberately situated within the health sector-an arena of paramount importance to human well-being-and focused on physicians, whose contributions are pivotal to disease diagnosis and treatment. The target population therefore consisted of all physicians employed at University of Health Sciences Türkiye, İzmir City Hospital, where 1.867 doctors are currently on staff. Applying Baş's[22] formula, the minimum required sample size was calculated as 319, assuming a ±0.05 margin of error and a 95% confidence level. During the online data-collection phase, 320 physicians completed the survey, thereby surpassing the threshold for adequacy.

Ethical Approval

Ethical approval for the study was granted by the University of Health Sciences Türkiye, İzmir City Hospital Social Research Ethics Committee (decision no: 2025/193, dated: 18 April 2025), and data collection commenced only after this clearance had been obtained.

Statistical Analysis

The survey instrument comprised two sections. The first contained seven items eliciting participants' demographic characteristics. The second employed the medical AI readiness scale developed by Karaca et al.[1] which consists of 22 items grouped into four sub-dimensions-cognitive, skills, foresight, and ethical factors. Data were therefore gathered with a 22-item questionnaire formatted on a five-point Likert scale.

The questionnaire was created online (see link) and circulated to all potential respondents via WhatsApp messaging groups. Alongside demographic information, participants rated every statement on a scale from 1 ("strongly disagree") to 5 ("strongly agree") and submitted their responses electronically. Because the entire physician workforce at University of Health Sciences Türkiye, İzmir City Hospital was targeted and the population size was substantial, web-based data collection was deemed most practical.

All data were analysed with appropriate statistical software. Demographic variables were summarised by frequency and cross-tabulation analyses, and overall reliability was assessed by Cronbach's (1951) alpha. Construct validity and dimensionality were investigated through principal-components analysis with Varimax rotation-initially via exploratory factor analysis (EFA) and subsequently via confirmatory factor analysis (CFA). Hypotheses involving two groups were tested with independent-samples t-tests, whereas comparisons across more than two groups were conducted using One-Way Analysis of Variance (ANOVA). When ANOVA indicated a statistically significant difference, post-hoc multiple comparisons were performed with Tukey's test to pinpoint specific group differences.

Statistical Thresholds and Study Design

All analyses were performed at the 95% confidence level, and results were deemed statistically significant when $p<0.05$. The five-point Likert means were interpreted as follows:

Mean range	Interpretation
1.00-1.79	Strongly disagree
1.80-2.59	Disagree
2.60-3.39	Undecided
3.40-4.19	Agree
4.20-5.00	Strongly agree

This cross-sectional, descriptive field study was conducted online between May and June 2025 and reached 320 physicians.

Results

Demographic Characteristics

A summary of participants' descriptive statistics is presented in Table 1.

Of the physicians surveyed, 39.7% (n=127) were aged 20-30 years, 22.2% (n=71) were 31-40 years, 23.8% (n=76) were 41-50 years, 10.3% (n=33) were 51-60 years and 4.1% (n=13) were over 61 years. Women accounted for 51.9% (n=166) of respondents, men for 48.1% (n=154). With respect to marital status, 54.1% (n=173) of participants were married, while 45.9% (n=147) were single. In terms of academic rank,

49.4% (n=158) were resident physicians, 34.1% (n=109) were specialists, and 16.6% (n=53) held associate- or full-professor titles. Departmental distribution showed that 57.5% (n=184) worked in internal-medicine disciplines, 38.4% (n=123) in surgical disciplines, 2.5% (n=8) in basic medical sciences and 1.6% (n=5) in health-sciences units. Regarding professional seniority, 53.8% (n=172) had 1-10 years of service, 19.7% (n=63) had 11-20 years and 26.6% (n=85) had 21 years or more. Finally, 90.6% (n=290) reported having at least one social-media account, whereas 9.4% (n=30) did not.

Findings from the Factor-structure and Reliability Analyses

Scale reliability was assessed with Cronbach's (1951) alpha, while the factor structure and construct validity were evaluated first by EFA and subsequently by CFA. Physicians' overall MAIR scores were then calculated via descriptive (mean) statistics.

An initial EFA on the 22-item instrument yielded excellent sampling adequacy (KMO=0.964) and a highly significant Bartlett's test of sphericity (χ^2=9.376.445, sig.=0.000). Close inspection revealed cross-loadings on three items; after removing those items, the EFA was repeated. The consolidated outcomes of the final EFA, the CFA fit indices, the sub-scale means and the reliability coefficients are summarised in Table 2.

As Table 2 shows, the scale and all four sub-dimensions display very high internal consistency EFA revealed a four-factor solution, and the subsequent CFA demonstrated that this structure provides the best overall fit: every fit index lies within acceptable limits[19,23-28], and the CFA factor loadings are uniformly strong. Hence, all further analyses were conducted on the basis of these four factors: Cognitive-6 items, Skill-5 items, Foresight-6 items, Ethics-2 items. The grand-mean score for the scale was 3.11, indicating that, on average, physicians were undecided about their readiness for medical AI-a pattern that held across each sub-dimension as well.

Hypothesis Tests

Age

An ANOVA was performed to determine whether physicians' total MAIR differs significantly across age groups. The results are summarised in Table 3.

Gender

A series of independent-samples t-tests compared female and male respondents on each readiness dimension and on the overall MAIR score. Descriptive statistics and test results are presented in Table 4.

Independent-samples t-tests showed no statistically significant differences between female and male physicians on the total MAIR score or on any of the four sub-dimensions (p>0.05 for every comparison). Consequently, H_2 was rejected.

Table 1. Descriptive profile of the physician sample (n=320)

		n	%			n	%
Age (years)	20-30	127	39.7	**Gender**	Female	166	51.9
	31-40	71	22.2		Male	154	48.1
	41-50	76	23.8	**Marital status**	Married	173	54.1
	51-60	33	10.3		Single	147	45.9
	61+	13	4.1	**Academic rank**	Assistant	158	49.4
Department	Internal medical sciences	184	57.5		Specialist	109	34.1
	Surgical medical sciences	123	38.4		Associate Professor-Professor	53	16.6
	Basic medical sciences	8	2.5	**Social-media account**	Yes	290	90.6
	Health	5	1.6		No	30	9.4
Years in practice	1-10	172	53.8				
	11-20	63	19.7				
	21+	85	26.6				

Table 2. Summary of the EFA and CFA, scale means and internal-consistency coefficients

ITEM	Exploratory-factor loadings				CFA factor loading
	Cognitive factor	Skill factor	Foresight factor	Ethics factor	
A12	**0.773**	0.268	0.350	0.267	0.886
A10	**0.753**	0.411	0.357	0.162	0.937
A11	**0.750**	0.406	0.373	0.163	0.943
A9	**0.735**	0.413	0.386	0.190	0.943
A14	**0.721**	0.118	0.430	0.317	0.806
A13	**0.627**	0.511	0.431	0.140	0.909
A4	0.229	**0.830**	0.254	0.240	0.834
A3	0.156	**0.825**	0.238	0.259	0.775
A6	0.408	**0.723**	0.280	0.238	0.917
A5	0.447	**0.692**	0.311	0.244	0.927
A7	0.503	**0.671**	0.299	0.177	0.900
A22	0.240	0.217	**0.801**	0.276	0.801
A21	0.484	0.210	**0.734**	0.236	0.864
A19	0.388	0.413	**0.730**	0.158	0.939
A20	0.429	0.241	**0.728**	0.307	0.866
A18	0.400	0.459	**0.681**	0.113	0.922
A17	0.390	0.454	**0.659**	0.126	0.900
A2	0.297	0.325	0.287	**0.770**	0.846
A1	0.237	0.474	0.285	**0.713**	0.908
	KMO=0.958 Bartlett's test of sph.=7894.421 Sig.=0.000 Total variance explained=85.432				
	α=0.977				
	$\bar{x}$=3.11				
	α=0.965	α=0.946	α=0.958	α=0.868	
	$\bar{x}$=3.32	$\bar{x}$=2.78	$\bar{x}$=3.18	$\bar{x}$=3.10	
	χ^2= 551.580; DF=143; p=0.000; χ^2/DF=3.857				
	RMR=0.056; GFI=0.841; AGFI=0.788; PGFI=0.633; NFI=0.932; CFI=0.948; RFI=0.918; IFI=0.948; TLI=0.938; PNFI=0.779; RMSEA=0.095				

EFA: Exploratory factor analysis, CFA: Confirmatory factor analyses, SD: Standard deviation, KMO: Kaiser-Meyer-Olkin, DF: Degrees of freedom, RMR: Root mean square residual, TLI: Tucker–lewis index, AGFI: Adjusted goodness-of-fit index, NFI: Normed fit index, IFI: Incremental fit index, PGFI: Parsimonious goodness-of-fit index, RMSEA: Root mean square error of approximation, PNFI: Parsimonious normed fit index

Table 3. MAIR by age group (n=320)

Dimension	Age group (years)	n	x̄	SD	F	p
Cognitive factor	20-30	127	3.4016	1.15572	0.592	0.669
	31-40	71	3.3380	1.24944		
	41-50	76	3.2193	1.14219		
	51-60	33	3.3636	1.27778		
	61 and over	13	2.9615	1.31964		
Skill factor	20-30	127	2.8882	1.09360	1.394	0.236
	31-40	71	2.7634	0.98811		
	41-50	76	2.6816	0.97334		
	51-60	33	2.8485	1.20523		
	61 and over	13	2.2462	0.82119		
Forsight factor	20-30	127	3.2874	1.12681	0.746	0.561
	31-40	71	3.0775	1.16252		
	41-50	76	3.1075	1.09535		
	51-60	33	3.2424	1.20768		
	61 and over	13	2.8846	1.20451		
Ethics factor	20-30	127	3.0866	1.14970	1.202	0.310
	31-40	71	3.0563	1.11339		
	41-50	76	3.1250	1.14346		
	51-60	33	3.3788	1.15265		
	61 and over	13	2.5769	1.30458		
Total scale	20-30	127	3.2874	1.03264	0.881	0.475
	31-40	71	3.0749	1.07288		
	41-50	76	3.0325	1.00334		
	51-60	33	3.1914	1.09050		
	61 and over	13	2.7085	1.04969		

MAIR: Medical-AI readiness, SD: Standard deviation

Table 4. MAIR by gender

Dimension	Gender	n	x̄	SD	t	DF	p
Cognitive factor	Female	166	3.3665	1.15590	0.687	318	0.493
	Male	154	3.2749	1.22823			
Skill factor	Female	166	2.7783	1.00569	-0.052	318	0.959
	Male	154	2.7844	1.09629			
Forsight factor	Female	166	3.2048	1.12391	0.452	318	0.651
	Male	154	3.1472	1.15422			
Ethics factor	Female	166	3.1175	1.13073	0.307	318	0.759
	Male	154	3.0779	1.17034			
Total scale	Female	166	3.1344	1.00494	0.426	318	0.670
	Male	154	3.0848	1.08074			

MAIR: Medical-AI Readiness, SD: Standard deviation, DF: Degrees of freedom

Marital Status

Whether readiness varies by marital status was examined with another independent-samples t-test. The descriptive statistics and test results are displayed in Table 5.

Physicians' overall AI-readiness does not differ by marital status in any dimension ($p>0.05$), so H_3 is rejected.

Years in Practice

A One-Way ANOVA tested whether readiness varies across three seniority bands (1-10 y, 11-20 y, ≥21 y). Descriptive statistics and results appear in Table 6.

Only the foresight dimension shows a significant tenure-related difference: physicians with 1-10 years in practice are more optimistic than those with 11-20 years ($p<0.05$). No significant contrasts appear in the cognitive, skill, ethics, or composite MAIR scores, so H_4 is supported solely for the foresight factor.

Department

Whether physicians' levels of Medical AI Readiness (MAIR) differ according to their department of employment was examined using One-Way Analysis of Variance (ANOVA), and the findings are presented in Table 7.

Table 5. MAIR by marital status (n=320)

Dimension	Marital status	n	x̄	SD	t	DF	p
Cognitive factor	Married	173	3.2832	1.20831	-0.638	318	0.524
	Single	147	3.3685	1.17110			
Skill factor	Married	173	2.7699	1.05567	-0.209	318	0.835
	Single	147	2.7946	1.04369			
Forsight factor	Married	173	3.1233	1.15842	-0.917	318	0.360
	Single	147	3.2404	1.11226			
Ethics factor	Married	173	3.1358	1.18875	0.631	318	0.528
	Single	147	3.0544	1.10126			
Total scale	Married	173	3.0821	1.06568	-0.529	318	0.597
	Single	147	3.1439	1.01326			

MAIR: Medical-AI readiness, SD: Standard deviation, DF: Degrees of freedom

Table 6. MAIR by years of professional experience (n=320)

Dimension	Time (years)	n	x̄	SD	F	p	Pairwise comparison (mean difference)*
Cognitive factor	1-10 (a)	172	3.4012	1.19327	1.133	0.323	
	11-20 (b)	63	3.1402	1.20230			
	21+(c)	85	3.2980	1.17319			
Skill factor	1-10 (a)	172	2.8453	1.07738	1.336	0.264	
	11-20 (b)	63	2.5937	0.96317			
	21+(c)	85	2.7906	1.04558			
Forsight factor	1-10 (a)	172	3.2636	1.13425	3.059	0.048	a-b (0.40113)
	11-20 (b)	63	2.8624	1.13416			
	21+(c)	85	3.2353	1.11783			
Ethics factor	1-10 (a)	172	3.0610	1.13454	0.943	0.390	
	11-20 (b)	63	3.0079	1.09799			
	21+(c)	85	3.2412	1.21158			
Total scale	1-10 (a)	172	3.1756	1.04944	1.730	0.179	
	11-20 (b)	63	2.8947	1.02349			
	21+(c)	85	3.1387	1.02662			

MAIR: Medical-AI readiness, SD: Standard deviation

To test H_5, we ran a ANOVA on total MAIR and each sub-dimension across the hospital's four departmental clusters (internal medicine, surgical sciences, basic medical sciences, health sciences).

Post-hoc Analysis (Tukey)

Homogeneous subsets are indicated by letter codes, with the mean difference between significantly different pairs shown in parentheses within the same column. The ANOVA revealed that-with the exception of the ethics factor-all sub-dimensions and the overall MAIR score varied significantly across departments ($p<0.05$). Accordingly, H_5 is partially supported. Follow-up comparisons showed that: Physicians working in basic medical sciences achieved higher scores than their colleagues in internal medicine and surgical sciences on the total scale and on both the cognitive and skill factors. They also outperformed physicians in surgical sciences on the foresight factor. No departmental differences emerged for the ethics factor.

Table 7. MAIR levels by department

Dimension	Department	N	x̄	SD	F	p	Pairwise comparison (mean difference)
Cognitive factor	Internal medical sciences (a)	184	3.4067	1.15110	3.668	0.013	c-b (1.26846) c-a (0.98913)
	Surgical medical sciences (b)	123	3.1274	1.23568			
	Basic medical sciences (c)	8	4.3958	0.73968			
	Health sciences (d)	5	3.3000	1.01653			
Skill factor	Internal medical sciences (a)	184	2.8293	1.01066	3.632	0.013	c-a (0.97065) c-b (1.13659)
	Surgical medical sciences (b)	123	2.6634	1.07347			
	Basic medical sciences (c)	8	3.8000	1.20949			
	Health sciences (d)	5	2.2800	0.57619			
Forsight factor	Internal medical sciences (a)	184	3.2183	1.07472	3.041	0.029	c-b (1.19715)
	Surgical medical sciences (b)	123	3.0528	1.22815			
	Basic medical sciences (c)	8	4.2500	0.59761			
	Health sciences (d)	5	3.0000	0.87401			
Ethics factor	Internal medical sciences (a)	184	3.1196	1.13770	1.065	0.364	
	Surgical medical sciences (b)	123	3.0325	1.15719			
	Basic medical sciences (c)	8	3.7500	1.25357			
	Health sciences (d)	5	2.9000	1.14018			
Total scale	Internal medical sciences (a)	184	3.1650	1.00120	3.588	0.014	c-a (0.95995) c-b (1.15324)
	Surgical medical sciences (b)	123	2.9718	1.08742			
	Basic medical sciences (c)	8	4.1250	0.72925			
	Health sciences (d)	5	2.8947	0.82633			

MAIR: Medical-AI readiness, SD: Standard deviation

Discussion

Identifying physicians' MAIR via a web-based survey-and examining how that readiness varies across demographic strata-helps forecast both the likely pace of technology adoption and its eventual impact on diagnostic and therapeutic workflows. Because AI systems now permeate virtually every stage of health-care delivery, such insight is indispensable. The present analyses revealed no statistically significant differences ($p>0.05$) in overall readiness or any sub-dimension with respect to age, sex or marital status. These findings echo those of Çankaya[29], who likewise observed no demographic variation in either total MAIR scores or their sub-scales among emergency-service personnel. By contrast, AlZaabi et al.[21] reported significant discrepancies when comparing physicians with medical students-suggesting that mixed or trainee-inclusive samples may yield patterns that do not apply to practising doctors alone.

Length of professional experience influenced only the foresight dimension of readiness ($p<0.05$); no differences emerged for the other sub-scales. Hence, H_4 was partially supported. Post-hoc analysis showed that physicians with 1-10 years of service were significantly more optimistic than those with 11-20 years. Çankaya's[29], study of emergency-service staff found no tenure-related differences in either the overall scale or its sub-dimensions, whereas AlZaabi et al.[21] did report significant experience effects.

Analyses showed that, with the sole exception of the ethics sub-scale, every readiness dimension-and the total MAIR score-varied significantly by physicians' departmental affiliation ($p<0.05$); thus, H_5 is partially supported. Post-hoc Tukey comparisons reveal that physicians based in basic medical sciences score more favourably than their ınternal medicine and surgical sciences colleagues on the overall scale as well as on the cognitive and skill factors. They also outperform surgical-sciences physicians on the foresight factor. No departmental differences emerged for ethics. By contrast, Çankaya's[29], study of emergency-service staff detected no department-related variation in either the composite scale or its sub-dimensions.

The overall mean score for the scale was 3.11, indicating that participants' readiness for medical AI hovers just above the midpoint and can best be characterised as ambivalent. The same ambivalence holds across all four sub-dimensions. These findings align with several international studies[6,12], which likewise report mildly positive-yet still uncertain-attitudes among physicians. Although clinicians view AI favourably, gaps in conceptual understanding and hands-on technical training appear to hinder seamless adoption. Accordingly, we recommend embedding core content on AI, machine learning and ethical data use into both undergraduate and residency curricula. In parallel, national guidance that clarifies the legal framework surrounding medical AI is essential to ensure that technological advances proceed in harmony with health-policy objectives.

Study Limitations

Several constraints should be acknowledged. First, the investigation was limited to physicians working at University of Health Sciences Türkiye, İzmir City Hospital; future studies could widen the sample to encompass all hospitals in İzmir and include other health-care professionals in addition to physicians. Second, the demographic section of the questionnaire was restricted to a narrow set of variables-sex, age, marital status, department, years in practice, academic title, and social-media use-thereby excluding potentially relevant factors. Finally, owing to the large target population and the heavy workload within the hospital, data were collected online rather than through face-to-face administration.

Conclusion

This study offered a multidimensional assessment of physicians' readiness for medical-AI technologies at University of Health Sciences Türkiye, İzmir City Hospital in Türkiye. The analyses show that clinicians hold a moderately positive attitude toward AI, yet they exhibit clear deficits in technical knowledge and hands-on competence. Although their awareness of ethical and legal issues is slightly higher than in other domains, that knowledge remains largely theoretical and has not yet translated into the practical skills needed to evaluate, select or integrate AI systems effectively. In broad terms, the present results are consistent with much of the international literature, even if a few discrepancies emerge across individual studies.

This shortfall can undermine both the effective use of management- and clinical-decision-support systems and the quality of physician–patient–technology communication. A lack of familiarity with algorithmic logic, data types, model-training workflows and system limitations may also erode clinicians' trust in AI-based tools. In this light, technological adaptation must be treated not merely as the installation of new devices but as a broader cognitive and

cultural transformation. To raise physicians' AI readiness, we recommend the following:

1. Curricular integration – embed core content on algorithm design, machine learning and data ethics in undergraduate and specialty-training syllabi.

2. Continuous professional development – offer regular digital-literacy workshops that focus on hands-on use of AI platforms.

3. Specialty-specific guidance – develop branch-tailored clinical AI guidelines to help physicians select and evaluate tools relevant to their fields.

4. Legal and ethical frameworks – establish national regulations that clarify accountability, data governance and malpractice boundaries for medical AI.

5. Collaborative decision-support models – integrate AI modules into existing clinical-decision workflows so that algorithms and physicians function as partners rather than substitutes.

6. Digital health-communication training – equip clinicians with strategies for explaining AI-assisted care to patients in clear, accessible language.

Treating AI adoption as a composite of technical proficiency, ethical competence and cultural change will position health professionals-and the systems they serve-to realise the full potential of AI in clinical practice.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the University of Health Sciences Türkiye, İzmir City Hospital Social Research Ethics Committee (decision no: 2025/193, dated: 18 April 2025), and data collection commenced only after this clearance had been obtained.

Informed Consent: Physicians who agreed to participate in the study were informed about the study and their consent was obtained.

Footnotes

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

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Comparison of Short-term Outcomes in Anticoagulated Patients with GI Bleeding: Warfarin versus NOACs

Antikoagülan Tedavi Gören Gastrointestinal Kanamalı Hastalarda Kısa Vadeli Sonuçların Karşılaştırılması: Warfarin ve NOAC'lar

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Abstract

Objective: Gastrointestinal (GI) bleeding is a major complication of oral anticoagulant therapy. While non-vitamin K oral anticoagulants (NOACs) offer advantages over warfarin, limited real-world data exist comparing short-term clinical outcomes following GI bleeding events in anticoagulated patients. This study aims to compare clinical characteristics, intervention requirements, hospitalization outcomes, and mortality in patients presenting with GI bleeding while receiving warfarin or NOAC therapy, and to explore differences among individual NOAC agents.

Methods: We conducted a single-center, retrospective, cross-sectional study including 299 adult patients who presented to the emergency department with GI bleeding while on oral anticoagulants. Data collected included demographics, laboratory values, interventions, and clinical outcomes. Subgroup analysis was performed among NOAC agents. Statistical comparisons used appropriate univariate tests; multivariable analysis was not feasible due to limited event counts.

Results: Of 299 patients (mean age 75.8±10.4 years, 52.2% male), 30.1% were receiving warfarin and 69.9% NOACs. Emergency department mortality (2.0%) and in-hospital mortality (7.4%) were similar among the groups (p>0.05). Endoscopic interventions (75.3%) and erythrocyte transfusion needs (56.8%) did not differ significantly by anticoagulant type. Elevated creatinine was independently associated with in-hospital mortality (p=0.016). No significant differences in outcomes were found among individual NOAC agents.

Conclusion: GI bleeding remains a serious but generally manageable event in patients on oral anticoagulants, with comparable short-term outcomes between warfarin and NOAC users. Renal dysfunction is an important predictor of mortality. Larger prospective studies are needed to refine risk stratification and optimize management in this population.

Keywords: Gastrointestinal bleeding, warfarin, NOAC, emergency department

Öz

Amaç: Gastrointestinal (GI) kanama, oral antikoagülan tedavisinin önemli bir komplikasyonudur. Vitamin K içermeyen oral antikoagülanlar (NOAC) warfarine göre avantajlar sunsa da antikoagülan tedavisi gören hastalarda GI kanama olaylarını takiben kısa vadeli klinik sonuçları karşılaştıran sınırlı sayıda gerçek dünya verisi bulunmaktadır. Warfarin veya NOAC tedavisi gören ve GI kanaması geçiren hastaların klinik özelliklerini, müdahale gereksinimlerini, hastaneye yatış sonuçlarını ve mortaliteyi karşılaştırmak ve bireysel NOAC ajanları arasındaki farkları araştırmaktır.

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Öz

Yöntem: Oral antikoagülan tedavisi gören ve GI kanaması ile acil servise başvuran 299 yetişkin hastayı içeren tek merkezli, retrospektif, kesitsel bir çalışma yürüttük. Toplanan veriler demografik bilgiler, laboratuvar değerleri, müdahaleler ve klinik sonuçları içeriyordu. NOAC ajanları arasında alt grup analizi yapıldı. İstatistiksel karşılaştırmalarda uygun tek değişkenli testler kullanıldı; olay sayısının sınırlı olması nedeniyle çok değişkenli analiz yapılamadı.

Bulgular: İki yüz doksan dokuz hastanın (ortalama yaş 75,8±10,4 yıl, %52,2'si erkek) %30,1'i warfarin, %69,9'u NOAC alıyordu. Acil servis mortalitesi (%2,0) ve hastane içi mortalite (%7,4) gruplar arasında benzerdi (p>0,05). Endoskopik müdahaleler (%75,3) ve eritrosit transfüzyonu ihtiyacı (%56,8) antikoagülan türüne göre önemli ölçüde farklılık göstermedi. Yükselmiş kreatinin, hastane içi mortalite ile bağımsız olarak ilişkiliydi (p=0,016). Bireysel NOAC ajanları arasında sonuçlarda önemli bir fark bulunmamıştır.

Sonuç: GI kanaması, oral antikoagülan kullanan hastalarda ciddi ancak genellikle yönetilebilir bir olay olmaya devam etmektedir ve warfarin ve NOAC kullanıcıları arasında kısa vadeli sonuçlar benzerdir. Böbrek fonksiyon bozukluğu, mortalitenin önemli bir belirleyicisidir. Bu popülasyonda risk sınıflandırmasını iyileştirmek ve yönetimi optimize etmek için daha büyük prospektif çalışmalar gereklidir.

Anahtar Kelimeler: Gastrointestinal kanama, warfarin, NOAC, acil servis

Introduction

The use of oral anticoagulant therapy has dramatically increased over recent decades due to the growing prevalence of cardiovascular and thromboembolic disorders, particularly in aging populations. Conditions such as atrial fibrillation (AF), mechanical heart valve replacement, venous thromboembolism, and coronary artery disease (CAD) often necessitate long-term anticoagulation to prevent thromboembolic complications, which can result in significant morbidity and mortality if untreated[1,2].

Historically, vitamin K antagonists (VKAs), primarily warfarin, have served as the cornerstone of oral anticoagulation therapy. However, warfarin's narrow therapeutic window, numerous drug and food interactions, and requirement for frequent monitoring of the international normalized ratio (INR) have posed substantial clinical management challenges. In response to these limitations, non-vitamin K oral anticoagulants (NOACs) have been introduced and increasingly adopted due to their more predictable pharmacokinetic profiles, fewer dietary restrictions, and lack of routine coagulation monitoring requirements[3-5].

Despite these advantages, bleeding complications remain the most feared adverse effect of all oral anticoagulants, with gastrointestinal (GI) bleeding being among the most frequent and clinically significant events[6]. Although large randomized controlled trials have demonstrated lower rates of intracranial hemorrhage with NOACs compared to VKAs, data on GI bleeding have shown conflicting results, with some studies suggesting comparable or even slightly increased rates of GI bleeding in NOAC users, particularly with certain agents[7-9].

GI bleeding in anticoagulated patients presents complex management dilemmas for clinicians. These include decisions on temporary or permanent discontinuation of anticoagulation, timing of endoscopic evaluation, reversal strategies, transfusion thresholds, and balancing the competing risks of thrombosis and rebleeding. Furthermore, patient-specific factors such as age, comorbidities, renal function, and polypharmacy contribute additional layers of complexity to clinical decision-making[10-12].

Although numerous studies have evaluated the overall bleeding risks associated with anticoagulant use, data comparing short-term clinical outcomes specifically among patients presenting with GI bleeding while on either warfarin or NOACs remain relatively limited[13]. Most prior investigations have focused on bleeding incidence rates, with less emphasis on the real-world outcomes following acute GI bleeding episodes requiring emergency care and hospitalization[14].

The primary objective of this study was to compare the clinical characteristics, intervention requirements, hospitalization courses, and mortality outcomes of patients presenting to the emergency department with GI bleeding while receiving either warfarin or NOAC therapy. Additionally, we aimed to assess potential differences in outcomes among individual NOAC agents. By addressing these questions in a real-world, emergency care setting, this study seeks to provide valuable insights into the acute management and prognostic implications of GI bleeding in anticoagulated patients.

Materials and Methods

Study Design and Population

This single-center, retrospective, cross-sectional study was conducted in the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Department of Emergency between January 2020 and December 2023. A

total of 299 adult patients (≥18 years old) who presented to the emergency department with GI bleeding while receiving oral anticoagulant therapy were included in the study. The anticoagulants evaluated included VKA (warfarin) and NOACs, specifically apixaban, rivaroxaban, dabigatran, and edoxaban (Table 1).

Patients who were using oral anticoagulant therapy and presented with either upper or lower GI bleeding were eligible for inclusion. Exclusion criteria comprised patients under 18 years of age, those with traumatic bleeding, and individuals with incomplete medical records regarding their anticoagulant use or bleeding diagnosis.

Data Collection

Data were retrospectively extracted from electronic medical records and included the following parameters: additionally, data regarding concomitant antiplatelet therapy, non-steroidal anti-inflammatory drug usage, proton pump inhibitor co-medication, and detailed endoscopic bleeding lesion characteristics were not available, which may act as unmeasured confounding variables impacting outcomes.

- Demographic data (age, sex),
- Type and indication of anticoagulant therapy,
- Laboratory parameters at admission [white blood cell count (WBC), hemoglobin, platelet count, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, INR, activated partial thromboplastin time, and prothrombin time],
- Consultations performed (gastroenterology, anesthesiology, surgery, cardiology, internal medicine),
- Interventional procedures [endoscopy, colonoscopy, erythrocyte transfusion (ERT)],
- Emergency department outcomes (discharge, hospitalization, intensive care unit admission, death, transfer, and treatment refusal),
- In-hospital mortality and length of stay.

The primary clinical indications for anticoagulation included AF, mechanical valve replacement, CAD, ischemic stroke, pulmonary embolism, and deep vein thrombosis. Final clinical diagnoses were categorized into upper GI bleeding, lower GI bleeding, anemia-related causes, malignancy-related causes, and other rare etiologies (Tables 1-3).

Outcome Measures

The primary outcomes of interest were emergency department mortality, in-hospital mortality, duration of stay in the emergency department, total hospital length of stay, and the requirement for endoscopic or transfusion interventions. Subgroup analyses were performed based on the type of anticoagulant used (warfarin vs. NOACs, and among the individual NOAC agents) (Tables 4, 5).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 26, IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, median, minimum, and maximum values. Categorical variables were expressed as numbers and percentages. Comparisons between groups were conducted using the Pearson's chi-square test or Fisher's exact test for categorical variables, depending on the expected frequencies. For continuous variables, normality was assessed, and appropriate tests were applied: Mann-Whitney U test for two-group comparisons and Kruskal-Wallis test for multiple group comparisons. A two-tailed p-value of <0.05 was considered statistically significant.

Due to the limited number of mortality events, multivariate regression analyses could not be performed to adjust for potential confounders such as age, renal function,

Table 1. Baseline characteristics of study population (n=299)

Characteristic	n (%) or mean ± SD
Age (years)	75.8±10.4
Male sex	156 (52.2%)
Female sex	143 (47.8%)
Warfarin	90 (30.1%)
NOACs total	209 (69.9%)
- Apixaban	67 (22.4%)
- Rivaroxaban	90 (30.1%)
- Edoxaban	30 (10.0%)
- Dabigatran	22 (7.4%)
AF	94 (31.4%)
Valve replacement	63 (21.1%)
Coronary artery disease	47 (15.7%)
AF + CAD	36 (12.0%)
SVO	12 (4.0%)
Others	Remaining 15.8%

SD: Standard deviation, NOACs: Non-vitamin K oral anticoagulants, AF: Atrial fibrillation, CAD: Coronary artery disease, SVO: Cerebrovascular disease

comorbidities, and medication co-use. Future studies incorporating larger sample sizes are necessary to allow for robust multivariate modeling.

Ethical Considerations

The study was approved by the Institutional Review Board of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Ethics Committee approval no: 2023/12-22, 10.01.2024 and was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Patient Characteristics

A total of 299 patients were included in the study, with a mean age of 75.8±10.4 years (range 40-95 years). Of these, 52.2% were male (n=156), and 47.8% were female (n=143). Warfarin was used in 30.1% of patients (n=90), while 69.9% (n=209) were receiving NOACs: apixaban (22.4%), rivaroxaban (30.1%), edoxaban (10.0%), and dabigatran (7.4%).

Table 2. Emergency department interventions and outcomes

Intervention	Warfarin (n=90)	NOAC (n=209)	Total (n=299)	p-value
ED mortality (%)	2 (2.2%)	4 (1.9%)	6 (2.0%)	1.000
Gastroenterology consult	88 (97.8%)	205 (98.1%)	293 (98.0%)	-
Endoscopy performed	62 (68.9%)	163 (78.0%)	225 (75.3%)	0.175
Colonoscopy performed	0	1	1 (0.3%)	-
ERT performed	57 (63.3%)	112 (53.6%)	169 (56.8%)	0.119
Median ED stay (minutes)	668	612	-	0.329

ED: Emergency department, ERT: Erythocyte replacement transfusion

Table 3. In-hospital mortality and outcomes

Outcome	Warfarin (n=90)	NOAC (n=209)	Total (n=299)	p-value
In-hospital mortality (%)	7 (7.8%)	15 (7.2%)	22 (7.4%)	0.855
Median hospital stay (days)	5	5	-	0.931
Discharged	48 (53.3%)	107 (51.2%)	155 (51.8%)	0.543
ICU admission	19 (21.1%)	34 (16.3%)	53 (17.7%)	-

NOAC: Non-vitamin K oral anticoagulant, ICU: Intensive care unit

Table 4. Laboratory parameters associated with mortality

Parameter	Mortality (+) (n=22)	Mortality (-) (n=277)	p-value
WBC (×10³/µL)	12.67±6.51	10.20±5.04	0.055
Creatinine (mg/dL)	2.19±1.54	1.51±0.97	0.016
Hemoglobin (g/dL)	7.58±2.59	8.18±2.52	0.216
Platelets (×10³/µL)	271±105.73	248±96.05	0.291

WBC: White blood count

Table 5. NOAC subgroup outcomes (n=209)

NOAC agent	ED mortality (%)	In-hospital mortality (%)	Endoscopy performed (%)	ERT (%)	Median hospital stay (days)
Apixaban	0	9.0%	83.6%	50.7%	5
Rivaroxaban	1.1%	8.9%	71.1%	52.2%	5
Dabigatran	0	4.5%	81.8%	54.5%	5
Edoxaban	3.3%	6.7%	83.3%	63.3%	4

NOAC: Non-vitamin K oral anticoagulant, ED: Emergency department, ERT: Erythocyte replacement transfusion

Emergency Department Outcomes

The overall mortality rate in the emergency department was 2.0% (6/299), with no significant difference between warfarin (2.2%) and NOAC users (1.9%) (p=1.000). Most patients (97.3%) required consultation, with gastroenterology being the most frequent specialty involved (98.0%). Endoscopic evaluation was performed in 75.3% of patients. Colonoscopy was rarely utilized (0.3%). ERT was administered in 56.8% of patients; however, there was no statistically significant difference observed in the comparative outcomes (Table 2).

In-hospital Outcomes

In-hospital mortality occurred in 22 patients (7.4%). Mortality rates were similar between warfarin (7.8%) and NOAC users (7.2%) (p=0.855). Median hospitalization duration was 5 days in both groups, with no significant difference (p=0.931) (Table 3).

Laboratory Parameters and Mortality

Deceased patients had significantly higher creatinine levels (2.19±1.54 mg/dL vs. 1.51±0.97 mg/dL; p=0.016). Elevated WBC was marginally significant (p=0.055). Other laboratory values showed no significant differences (Tables 4, 5).

NOAC Subgroup Analysis

No statistically significant differences were found among individual NOAC agents regarding emergency department mortality, in-hospital mortality, endoscopic intervention rates, transfusion needs, or discharge outcomes (all p>0.05) (Table 5).

Discussion

In this study, we analyzed the clinical characteristics, intervention needs, and short-term outcomes of patients presenting to the emergency department with GI bleeding while receiving oral anticoagulant therapy. Our findings demonstrated that both warfarin and NOAC users experienced comparable rates of emergency department mortality, in-hospital mortality, endoscopic interventions, transfusion requirements, and hospitalization duration.

The rising prevalence of anticoagulation use, particularly NOACs, has brought increasing attention to their associated bleeding risks. Several randomized trials have shown that while NOACs are generally associated with lower rates of intracranial hemorrhage than warfarin, GI bleeding remains a common and clinically significant complication for both drug classes[15-17]. Our study reinforces this observation by demonstrating that GI bleeding continues to be a frequent cause of emergency admission among anticoagulated patients, irrespective of the anticoagulant type used. However, the lack of data on timing of endoscopic intervention, antiplatelet therapy, or ulcer characteristics limits deeper mechanistic interpretation.

Consistent with previous research, AF was the predominant indication for anticoagulation in our cohort[18]. The clinical spectrum of bleeding sources was also in line with existing data, with upper GI bleeding being the most frequent presentation, followed by lower GI bleeding and anemia-related presentations. This distribution reflects the well-established vulnerability of the upper GI tract to anticoagulation-associated mucosal injury[19].

Importantly, both emergency department and in-hospital mortality rates were relatively low in our population (2.0% and 7.4%, respectively). These findings are consistent with prior studies suggesting that most anticoagulation-related GI bleeding events, when appropriately managed, do not result in fatal outcomes[20,21]. Furthermore, the absence of significant differences in mortality between warfarin and NOAC users supports the accumulating evidence that NOACs do not substantially increase the severity of GI bleeding compared to warfarin[22,23].

Endoscopic intervention rates were high (75.3%) in our study, reflecting current best practice guidelines that recommend early endoscopic evaluation for most cases of GI bleeding in anticoagulated patients[24]. Similarly, ERT was frequently required, but again with no significant differences between warfarin and NOAC users, suggesting comparable clinical severity of bleeding episodes across drug classes.

One of the notable findings in our study was the association between elevated creatinine levels and in-hospital mortality. Renal dysfunction has previously been identified as a significant predictor of adverse outcomes in patients with both GI bleeding and anticoagulation use[25,26].

This may be attributed to impaired drug clearance, accumulation of active drug levels, and overall increased frailty in patients with renal impairment. In addition, renal dysfunction may indirectly reflect overall frailty, sarcopenia, or impaired drug metabolism capacity, all of which have been linked to poor outcomes in elderly anticoagulated patients experiencing GI bleeding.

Our subgroup analysis among different NOAC agents revealed no statistically significant differences in clinical outcomes, including mortality, endoscopy rates, transfusion requirements, or hospitalization duration. Although certain observational studies have suggested differential GI bleeding risk profiles between individual NOAC agents (with dabigatran and rivaroxaban potentially having higher GI bleeding rates than apixaban)[27,28], our real-world data indicate that once GI bleeding occurs and leads to emergency care, the clinical course may be similar across NOAC agents. This finding aligns with several recent meta-analyses that question the clinical relevance of minor variations in bleeding risk between NOAC agents, particularly regarding major bleeding occurrences[29].

Furthermore, our data suggest that individualized bleeding risk stratification incorporating renal function, polypharmacy, and possibly frailty indices may improve patient selection and early intervention planning.

Our findings emphasize the need for vigilant monitoring and prompt management of GI bleeding in all anticoagulated patients, regardless of the anticoagulant agent. Early gastroenterology consultation and endoscopic intervention remain cornerstone approaches in minimizing morbidity and mortality. Additionally, careful assessment of renal function may help identify patients at higher risk for adverse outcomes and guide individualized treatment strategies.

Study Limitations

The strengths of this study include its real-world, emergency department-based design and inclusion of both warfarin and multiple NOAC agents in a single cohort, allowing direct comparison of short-term clinical outcomes. However, several limitations warrant consideration. First, the retrospective nature of the study may have introduced selection or documentation biases. Second, the relatively small number of mortality events limited the statistical power for subgroup analyses, particularly for NOAC agents. Third, unmeasured variables such as concomitant antiplatelet use, endoscopic timing, or specific bleeding lesion characteristics were not captured and may have influenced outcomes. Another limitation is that we did not assess the timing of anticoagulation interruption or resumption post-bleeding, which can influence both thromboembolic risk and rebleeding events. Finally, the single-center design may limit generalizability to broader populations.

Conclusion

In conclusion, our study demonstrates that GI bleeding in anticoagulated patients represents a serious but generally manageable clinical challenge, with comparable outcomes between warfarin and NOAC users. Renal dysfunction remains a relevant prognostic factor for mortality. Future prospective, multicenter studies with larger sample sizes are warranted to further refine risk stratification and optimize management strategies for this complex patient population.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Ethics Committee approval no: 2023/12-22, 10.01.2024 and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: This study is single-center, retrospective, and cross-sectional study.

Footnotes

Authorship Contributions

Concept: O.S., Design: O.S., N.Y.O., Data Collection or Processing: N.Y.O., Analysis or Interpretation: O.S., Literature Search: O.S., N.Y.O., Writing: O.S.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Transcriptomic Comparison of Lissencephaly-related Genes: From Correlation to Clinical Relevance

Lizensefali ile İlişkili Genlerin Transkriptomik Karşılaştırması: Korelasyondan Klinik Öneme

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Abstract

Objective: Lissencephaly is a neurodevelopmental disorder resulting from genetic and cellular defects in neuronal migration processes. In this study, correlation-based gene networks were analyzed to understand the functional and cellular relationships of lissencephaly-associated genes.

Methods: Hierarchical clustering and genetic network analyses based on Jaccard indices and Spearman's rank correlation were performed using fetal brain gene expression data from Allen Brain Atlas. These analyses identified functional similarities between gene pairs and suggested potential shared roles in cortical developmental processes.

Results: Hierarchical clustering analysis confirmed known associations, such as those between tubulins and microtubule-associated genes involved in migration and layering processes. Genes that relay extracellular signals to the migrating cells, such as Reelin and very low-density lipoprotein receptor, were observed to form a separate group. Using t-distributed stochastic neighbor embedding analyses of single-cell RNA sequencing data, specific expression patterns of these genes in brain cellular subpopulations were compared. Correlation network graphs showed that genes such as *PAFAH1B1* and *TUBG1* play central roles in cortical development, whereas genes such as *CRADD* and *ARX* have more specific functions.

Conclusion: These findings explain the relationships of lissencephaly-related genes with each other and their functional connections in neuronal migration processes. This study provides new perspectives for understanding the mechanisms of cortical development and points to previously unknown associations.

Keywords: Cortical development, neuronal migration, brain development, transcriptome, gene expression networks

Öz

Amaç: Lizensefali, nöronların göç süreçlerindeki genetik ve hücresel kusurlardan kaynaklanan bir nörogelişimsel bozukluktur. Bu çalışmada, lizensefaliyle ilişkili genlerin fonksiyonel ve hücresel ilişkilerini anlamak amacıyla korelasyon temelli gen ağları analiz edilmiştir.

Yöntem: Allen Beyin Atlası'ndan elde edilen fetal beyin gen ekspresyon verileri kullanılarak, Jaccard indeksleri ve Spearman sıralama korelasyonuna dayanan hiyerarşik kümeleme ve genetik ağ analizleri gerçekleştirilmiştir. Bu analizler, gen çiftleri arasında fonksiyonel benzerlikleri belirlemiş ve kortikal gelişim süreçlerinde olası ortak roller olduğuna işaret etmiştir.

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Öz

Bulgular: Hiyerarşik kümeleme analizi, göç ve tabakalaşma süreçlerinde rol oynayan tübülinler ile mikrotübül ilişkili genler arasındaki bilinen ilişkileri doğrulamıştır. Reelin ve çok düşük yoğunluklu lipoprotein reseptörü gibi dış sinyalleri göç etmekte olan hücrelere ileten genlerin ise ayrı bir grup oluşturduğu gözlenmiştir. Tek hücreli RNA dizileme verilerinin t-dağılımlı stokastik komşu gömme analizleri kullanılarak, bu genlerin beyin hücresel alt popülasyonlarındaki spesifik ekspresyon paternleri karşılaştırılmıştır. Korelasyon ağı grafiklerinde, *PAFAH1B1* ve *TUBG1* gibi genlerin kortikal gelişimde merkezi roller oynadığı, *CRADD* ve *ARX* gibi genlerin ise daha spesifik işlevlere sahip olduğu gösterilmiştir.

Sonuç: Bu bulgular, lizensefali ile ilişkili genlerin birbirleriyle olan etkileşimlerini ve nöron göçü süreçlerindeki fonksiyonel bağlantılarını açıklamaktadır. Ayrıca bu çalışma, kortikal gelişim mekanizmalarını anlamaya yönelik yeni bakış açıları sunmakta ve daha önce bilinmeyen ilişkilere işaret etmektedir.

Anahtar Kelimeler: Kortikal gelişim, nöronal migrasyon, beyin gelişimi, transkriptom, gen ifade ağları

Introduction

Neuronal migration is a fundamental process during brain development, crucial for the proper organization and functionality of the cerebral cortex. Disruptions in this process can lead to various developmental brain diseases, including autism spectrum disorders, schizophrenia, and epilepsy. Studies have shown that aberrant neuronal migration contributes to the pathogenesis of these disorders, characterized by mislocalized neurons and disrupted cortical lamination[1-4]. The mechanisms underlying these migration defects often involve genetic and molecular factors, such as mutations in genes like *PAFAH1B1* and *DCX*, which are essential for cytoskeletal organization and neuronal positioning[5,6]. Furthermore, environmental factors, including in utero exposure to infections or trauma, can also influence neuronal migration, leading to malformations of cortical development[7,8]. Understanding the intricate signalling pathways and cellular interactions that govern neuronal migration is critical for elucidating the etiology of neurodevelopmental disorders and developing potential therapeutic strategies[9,10].

The discovery of genes associated with lissencephaly has significantly advanced our understanding of the molecular pathways involved in neuronal migration and cortical development. Lissencephaly, characterized by an abnormally smooth cerebral cortex due to impaired neuronal migration, has been linked to several critical genes, including *PAFAH1B1*, *DCX*, and *TUBA1A*, which encode proteins essential for cytoskeletal organization and neuronal positioning during embryogenesis[11-13]. For instance, mutations in the *PAFAH1B1* gene, located on chromosome 17p13, have been shown to disrupt microtubule dynamics, leading to severe forms of lissencephaly[14,15]. Similarly, the identification of *DCX* as a key player in X-linked lissencephaly has highlighted the role of microtubule-associated proteins in guiding neuronal migration[16,17]. Recent studies have also uncovered additional genes, such as *CEP85L*, which further elucidate the genetic landscape of lissencephaly and its phenotypic variability[18,19]. These genetic insights have not only improved diagnostic capabilities but have also provided a framework for understanding the complex signalling pathways that regulate neuronal migration, thereby paving the way for potential therapeutic interventions in related neurodevelopmental disorders[19,20].

TUBG1, *PAFAH1B1*, and *DAB1* genes play critical roles in different stages of neuronal migration. *TUBG1* regulates cell polarity by participating in microtubule organization and plays an important role in the initial stages of migration. *PAFAH1B1* supports nuclear movements by interacting with microtubule motor proteins and functions in the intermediate stages of migration. *DAB1* ensures correct placement of neurons by participating in the RELN signalling pathway and is effective in the final stages of migration. It is known that these genes are important in understanding the mechanisms of neuronal migration and in elucidating the genetic basis of neurodevelopmental diseases such as lissencephaly.

The expression weighted cell type enrichment (EWCE) method is a computational approach designed to analyse gene expression data by identifying the specific cell types that contribute to the expression of a given gene list. This method leverages single-cell transcriptomic data to provide insights into the cellular composition underlying various biological conditions and diseases. By applying the EWCE method, researchers can interrogate gene lists derived from diverse sources, such as mouse phenotyping studies, to uncover the cell types associated with specific phenotypes or disorders, including major brain disorders like schizophrenia and Alzheimer's disease[21].

Gene-correlation analyses, which can be performed using various statistical methods, play a crucial role in generating

hypotheses about gene function and interactions. For instance, methods like gene set net correlation analysis allow researchers to assess changes in the correlation structure of gene sets across different conditions, thereby revealing potential regulatory relationships among genes[22]. Additionally, the identification of co-expression networks through correlation-based methods provides a framework for understanding how genes may work together in biological processes, facilitating the generation of hypotheses regarding their functional roles[23,24]. These analyses can lead to the identification of gene modules that are significantly associated with specific traits or diseases, thus guiding further experimental validation and exploration of underlying mechanisms[25,26].

In an effort to develop a consensus on the genetic networks associated with lissencephaly, Di Donato et al.[27] examined the expression profiles and functional pathways of genes using gene-correlation analyses, providing important insights into how genetic networks are organized at the cellular level[27]. In this study, we sought to carry these efforts further by utilizing various computational tools, as well as incorporating single-cell transcriptomic data, to better understand cell types, biological processes, and their relationship with clinical outcomes. Networks created through correlations in gene expressions allowed us to elucidate the associations of genes with specific cellular environments and biological processes. We reveal the hierarchical organization and functional distinctions of genes involved in brain development, and show that microtubule-related genes play a central role in regulating the cytoskeleton, while genes involved in extracellular signaling constitute a separate functional group. Single-cell RNA sequencing analyses show that these genes exhibit differential expression patterns in specific cell subpopulations, indicating their dynamic roles in development. Correlation network analyses confirm that some genes are essential components of cortical development, while others have more specific functions. Thus, we demonstrate that the genetic mechanisms driving neuronal migration and cortical stratification processes should be addressed from a holistic perspective.

Materials and Methods

Databases

In this study, 15 lissencephaly-associated gene sets (*TUBB*, *TUBB3*, *ACTB*, *ACTG1*, *TUBA1A*, *DCX*, *TUBB2B*, *KIF2A*, *VLDLR*, *Reelin (RELN)*, *DYNC1H1*, *ARX*, *KIF5C*, *CRADD*, and *TUBA8*) identified by Di Donato et al.[27] were analysed. Correlation data were obtained from the Allen Brain Atlas and used to evaluate the distribution of gene expressions according to cell types[28,29]. Venn diagrams were created with the PSB Bioinformatics Venn Tool (https://bioinformatics.psb.ugent.be/webtools/Venn/) to visualize the intersections of gene sets. t-distributed stochastic neighbor embedding (t-SNE) analyses were performed using CoDeX Viewer to visualize the high-dimensional distributions of cell types and gene expressions[30]. For single-cell transcriptome analyses, the CellxGene platform was utilized, and gene expression patterns, associated with different cellular environments, were examined[31]. All data were evaluated with an integrated analysis strategy aimed at understanding the roles of genes in biological processes and clinical contexts.

Expression Weighted Cell Type Enrichment Analysis

EWCE analysis is a robust computational method utilized to evaluate the enrichment of gene or gene set expression across distinct cell types. In this approach, gene expression data are first normalized and subsequently compared against a reference cellular atlas. For each gene, the mean expression level across various cell types is calculated and assessed against randomly generated gene lists derived from the reference atlas. This comparison determines whether a given gene is preferentially expressed in specific cell types. The distribution of enrichment scores generated from these random gene lists serves as the null model for statistical evaluation.

The method employs weighted expression profiles of genes within the gene set, coupled with permutation testing, to statistically ascertain the significance of observed enrichments. The results not only identify cell types in which the target genes are significantly enriched but also provide insights into the biological relevance of these expression patterns, highlighting their potential functional roles within specific cellular contexts.

Jaccard Index Calculation

Jaccard indices are a metric used to measure the similarity between two gene sets by expressing the ratio of common genes to total genes. In our analysis, the Jaccard index was calculated for each gene set pair. The Jaccard index between two gene sets is calculated by the following formula:

$$J(A, B)=|A\cap B|/|A\cup B|$$

Where $|A\cap B|$ is the number of genes shared by both sets and $|A\cup B|$ is the total number of genes found in the union

of both sets. For calculation, correlated gene lists were used for each gene set, and intersection and union sizes were carefully evaluated to provide a meaningful gene set match within a biological context. The results numerically represent the similarity level of each gene set pair and allow interpretation of commonalities in genetic function or biological processes. This analysis has been used as an important tool to evaluate the connection of genes through common functional pathways and biological processes[32].

Spearman's Rank Correlation Analysis

Spearman's rank correlation analysis was performed to evaluate the monotonic relationship between the gene expressions associated with lissencephaly. The analysis was used to reveal the interdependence and common patterns of gene expression. First, gene expressions were normalized and made suitable for analysis. Then, correlation coefficients between genes were calculated and a correlation matrix was created using these coefficients. The obtained matrix was represented with a heatmap to visualize the relationships between genes and determine clustering patterns. Hierarchical clustering was performed to group genes with similar correlation patterns[32]. The Python programming language was used during correlation analysis, and the spearmanr function in the scipy library was used preferably for calculations. Strong positive and negative relationships were observed between gene expressions. The observed relationships were used to evaluate the possible commonalities or contrasts of genes in biological processes.

Enrichment Analysis

CellxGene and CoDEx Viewer tools were utilized to support gene expression and functional enrichment analyses. First, CellxGene was used to examine the cell types in which our genes were expressed using single-cell RNA-seq data. This tool was used to visualize the expression levels of selected genes in different cell populations and to explore their potential functions in a cellular context. Then spatial gene expression data were evaluated using CoDEx Viewer to analyse the spatial expression patterns of the genes. This analysis allowed us to understand the localization of cell types within the tissue, cell-cell interactions, and spatial features of gene expression.

Statistical Analysis

We adopted a multi-step approach to statistically evaluate the correlation and enrichment results. The Spearman's rank correlation coefficient was used to calculate the correlations between gene sets. This method allowed us to evaluate the monotonic relationships between the expression levels of genes. For statistical significance assessment, p-values were calculated, and multiple testing correction was performed using the Benjamini-Hochberg method. The corrected p-values (q-values) obtained were evaluated at a threshold of $q<0.05$ to determine significant correlations.

For enrichment analyses, a hypergeometric test was applied for each gene set. To determine significant results, p-values of each test were calculated, and multiple testing correction was performed again using the Benjamini-Hochberg method. After correction, enriched biological pathways, functional categories, and phenotypes were selected using a threshold of $q<0.05$.

Additionally, random permutation tests were applied to increase the reliability of the correlation and enrichment results in a biological context. Background distributions obtained with random permutations were compared to assess the significance of the observed enrichment scores or correlation coefficients. This statistical framework allowed us to interpret the findings of our study in a robust and reliable way.

Results

Jaccard indices obtained from the correlation data of genes associated with lissencephaly enabled an analysis of the functional relationship between lissencephaly genes by evaluating the common gene sets. Network analysis based on Jaccard indices of lissencephaly-associated genes allowed the visualization of functional relationships between genes. *TUBA1A*, *TUBG1*, and *PAFAH1B1* genes stand out as central nodes and form dense connections with other genes (Figure 1a). This suggests that these genes have close functional connections with other genes, especially in processes such as neuronal migration and cortical layering. The central location of genes related to microtubule organization and motor proteins, such as *CDK5* and *KIF5C*, supports their key role in these processes (Figure 1a).

On the other hand, *ARX* and *CRADD* genes are located in a more peripheral position, indicating that these genes have more specific functional relationships with other genes (Figure 1a). *ARX*, in particular, is located further away from the other genes, indicating that it may have a more independent role in cortical development.

This network analysis allows us to understand not only the pairwise relationships between genes, but also their positions and importance within the collective functional network.

To further investigate the relations between lissencephaly genes, we compared the findings of network analysis to those of hierarchical clustering-based analysis. There is a high level of similarity between certain groups of genes. In particular, it was determined that *PAFAH1B1* (w/*ACTB* cor: 0.04; *ACTG1* cor: 0.03; *DCX* cor: 0.03; *DYNC1H1* cor: 0.30; *KIF2A* cor: 0.23; *KIF5C* cor: 0.03; *TUBA1A* cor: 0.04; *TUBA8* cor: 0.03; *TUBB2B* cor: 0.001; *TUBB3* cor: 0.06; *TUBB* cor: 0.05; *TUBG1* cor: 0.04) , *TUBA1A* (w/*ACTB* cor: 0.68; *ACTG1* cor: 0.74; *DCX* cor: 0.61; *DYNC1H1* cor: 0.03; *KIF2A* cor: 0.27; *PAFAH1B1* cor: 0.04; *TUBB2B* cor: 0.50; *TUBB3* cor: 0.71; *TUBB* cor: 0.75), and *DAB1* (w/*ACTB* cor: 0.44; *ACTG1* cor: 0.54; *DCX* cor: 0.66; *DYNC1H1* cor: 0.06; *KIF2A* cor: 0.36; *PAFAH1B1* cor: 0.04; *TUBA1A* cor: 0.50; *TUBB2B* cor: 0.40; *TUBB3* cor: 0.71; *TUBB* cor: 0.60) genes exhibited a strong correlation with other microtubule-related genes involved in cortical neuronal migration processes. These genes were located in the same clusters in the dendrogram, indicating that they are in a common network based on shared gene co-expression (Figure 1b). On the other hand, genes related to the extracellular matrix-associated processes, such as RELN (w/*ACTB* cor: 0.31; *ACTG1* cor: 0.35; *DCX* cor: 0.40; *DYNC1H1* cor: 0.14; *KIF2A* cor: 0.60; *PAFAH1B1* cor: 0.14; *TUBA1A* cor: 0.33; *TUBB2B* cor: 0.18; *TUBB3* cor: 0.35; *TUBB* cor: 0.40; *VLDLR* cor: 0.50; *DAB1* cor: 0.46) and *VLDLR* (w/*ACTB* cor: 0.23; *ACTG1* cor: 0.24; *DCX* cor: 0.33; *DYNC1H1* cor: 0.26; *KIF2A* cor: 0.51; *PAFAH1B1* cor: 0.20; *RELN* cor: 0.50; *TUBA1A* cor: 0.25; *TUBB2B* cor: 0.13; *TUBB3* cor: 0.30; *TUBB* cor: 0.32; *DAB1* cor: 0.37), were grouped separately from other genes, suggesting that these genes regulate cortical layering processes in distinct ways. These results demonstrate the potential of co-expression-based transcriptomic approaches in improving our understanding of the genetic basis of neuronal migration processes and the pathophysiology of lissencephaly.

To further confirm these findings, we compared the gene sets using the Spearman's rank correlation test. The genes were grouped into five groups: Genes including *ACTG1*, *ACTB* and *TUBB* (*ACTG1-ACTB* cor: 0.74; *ACTG1-TUBB3* cor:

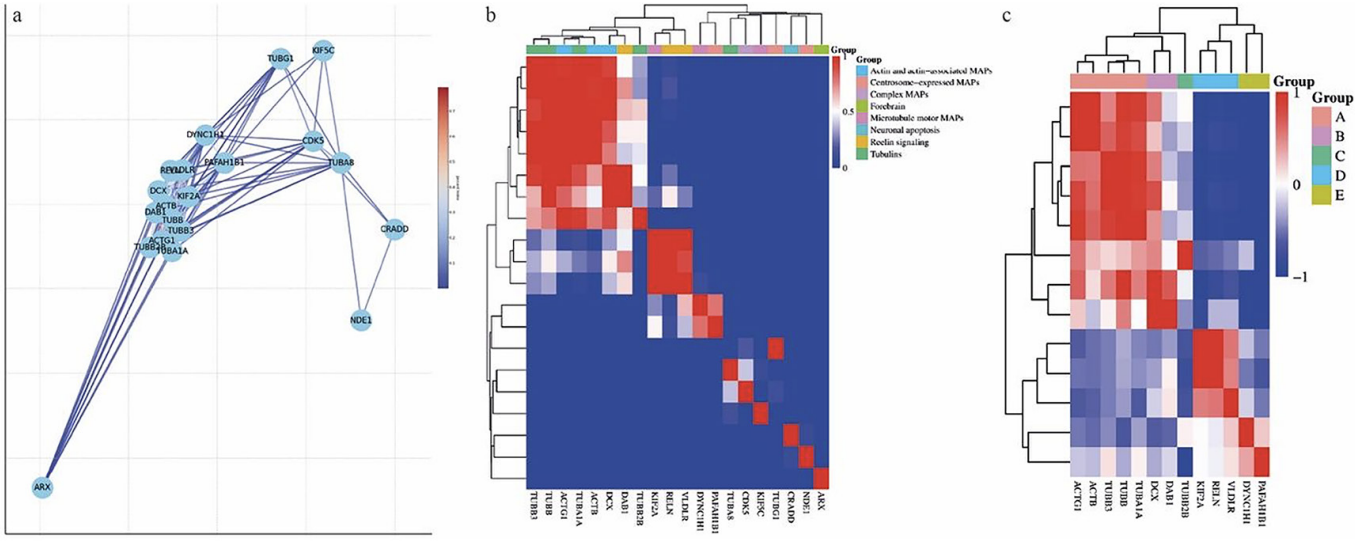

Figure 1. Visualization of lissencephaly-associated genes based on Jaccard index and Spearman's rank correlation analysis. (a) Weighted gene network visualizing the common biological pathways and processes among genes based on Jaccard index scores is represented. Genes are connected according to the proportion of traits they share with each other, and the thickness of the connections represents the magnitude of Jaccard scores. (b) Hierarchical clustering heatmap constructed based on Jaccard index scores shows the grouping of genes based on their biological traits. The color intensity represents the magnitude of Jaccard scores among genes (red: high similarity, blue: low similarity). The upper colored bands reflect the classification of genes according to their biological functions (e.g., actin-associated proteins, microtubule motor proteins, etc.). (c) Hierarchical clustering heatmap based on Spearman rank correlation analysis shows the grouping of genes based on the monotonic relationships between gene expressions. The correlation coefficients are indicated by colors (red: positive correlation, blue: negative correlation). The clustering of genes was determined based on the correlation patterns in their expressions

0.53; *ACTG1-TUBB* cor: 0.73; *ACTG1-TUBA1A* cor: 0.70; *ACTB-TUBB3* cor: 0.53; *ACTB-TUBB* cor: 0.62; *ACTB-TUBA1A* cor: 0.59; *TUBB3-TUBB* cor: 0.83; *TUBB3-TUBA1A* cor: 0.68; *TUBB-TUBA1A* cor: 0.76) in Group A show strong positive correlations (Figure 1c). It is highly likely that these genes are co-regulated, participate in similar functional pathways, or are expressed in similar cellular subtypes or states during neuronal migration. In addition, the *PAFAH1B1* and *DYNC1H1* genes [*PAFAH1B1-ACTG1* cor: -0.21; *PAFAH1B1-ACTB* cor: -0.23; *PAFAH1B1-TUBB3* cor: -0.07; *PAFAH1B1-TUBB* cor: -0.25; *PAFAH1B1-TUBA1A* cor: -0.09; *DYNC1H1-ACTG1* cor: -0.21; *DYNC1H1-ACTB* cor: -0.23; *DYNC1H1-TUBB3* cor: -0.18; *DYNC1H1-TUBB* cor: -0.26; *DYNC1H1-TUBA1A* cor: -0.16] in Group E show negative correlations with most of the genes in Group A, indicating that the expression profiles or activities of these genes may be inversely related (Figure 1c). The fact that genes such as *TUBA1A*, *TUBB2B*, and *DCX* show strong positive correlations with each other indicates that they are critical in microtubule dynamics and neuronal migration. Their clustering indicates their common roles in similar biological processes. The negative correlations of the *RELN*, *VLDLR*, and *KIF2A* genes in Group D with genes in Groups A and B, as evidenced by their correlation scores (*RELN-ACTG1* cor: -0.08; *RELN-ACTB* cor: -0.08; *RELN-TUBB3* cor: -0.06; *RELN-TUBB* cor: -0.02; *RELN-TUBA1A* cor: -0.05; *VLDLR-ACTG1* cor: -0.12; *VLDLR-ACTB* cor: -0.10; *VLDLR-TUBB3* cor: -0.06; *VLDLR-TUBB* cor: -0.03; *VLDLR-TUBA1A* cor: -0.11; *KIF2A-ACTG1* cor: -0.16; *KIF2A-ACTB* cor: -0.14; *KIF2A-TUBB3* cor: -0.11; *KIF2A-TUBB* cor: -0.06; *KIF2A-TUBA1A* cor: -0.11), may reflect that they play a separate role in extracellular matrix interactions and signal transduction, unlike cytoskeletal organization. The negative correlation of the *PAFAH1B1* gene with microtubule polymerization-related genes (Group A and B) may indicate that the pathways regulated by these genes are functionally separated at different stages of neuronal migration (Figure 1c). Spearman's rank correlation measures the monotonic relationship between the expression levels of genes. This relationship may indicate that they follow a similar pattern in the regulation of gene expression.

To further gain insight into the gene-gene associations at a more cellular level, single-cell RNA sequencing data from the human brain cortex were analysed. Microtubule-related genes such as *TUBA1A*, *TUBB*, and *DCX* were found to be highly expressed, especially in neurons (0.79, 0.56, 0.15), neural precursor cells (0.77, 0.53, 0.16), and radial glial cells (0.55, 0.48, 0.08) (Figure 2a). This supports the critical roles of these genes in neuronal migration and cortical development. In addition, cell-membrane and extracellular matrix-related genes such as *RELN* and *VLDLR* were found to be significantly expressed in glial cells (0.07, 0.07) and radial glial cells, with expression levels of 0.07 for both in each cell type (0.07, 0.07) (Figure 2a). This finding confirms that these genes regulate neuronal migration via extracellular signalling.

On the other hand, the expression of genes such as *CRADD* and *KIF5C* was found to be limited to more specific cell types. In particular, the *CRADD* gene showed low but significant expression in cell types such as macrophages (0.09) and glioblasts (0.08), indicating potential interactions of this gene with the immune system and glial differentiation during cortical development (Figure 2a). This analysis sheds light on the possible mechanisms in the pathophysiology of lissencephaly by revealing the cell type-specific expression patterns of the genes.

t-SNE analysis reveals the clustering of cellular groups and the cell type-specific distribution of genes by reducing high-dimensional gene expression data to a two-dimensional plane. The general t-SNE plot of developing human cortex, according to the Codex Viewer [30], shows the cell populations present during cortical development in Figure 2b on the upper left. Among these cell populations, different cell types were identified: radial glial cells, migrating excitatory neurons, maturing excitatory neurons, interneurons, and microglia. In the other panels (c-v), the normalized expression density of each gene is shown in different cellular subgroups. High expression of the *ARX* gene is visible, especially in migrating excitatory neurons and interneurons (Figure 2v). This supports the critical role of the *ARX* gene in neuronal migration and differentiation processes. *VLDLR* showed low to moderate expression in radial glial cells and excitatory neurons, suggesting its role in extracellular matrix signaling (Figure 2m). *KIF2A*, which showed a broad distribution among all cell groups, suggests a universal role in regulating intracellular microtubule dynamics (Figure 2k). The *RELN* gene showed a localized expression profile in radial glial cells and upper layer enriched regions of excitatory neurons, confirming the regulatory function of *RELN* in stratification processes (Figure 2l).

These observations suggest that genes that play critical roles in microtubule dynamics and neuronal migration, such as *TUBB2B*, *ACTB*, *TUBA1A*, *TUBB*, and *DCX*, are widely expressed, especially in migrating excitatory neurons and

radial glial cells (Figure 2d-h). The *DAB1* gene was observed to have high expression levels, especially in migrating neurons (Figure 2i), supporting its critical role in neuronal migration processes in the *RELN* signalling pathway. The expression patterns among all genes, were arranged in accordance with their biological roles associated with cell types. The results reveal the contributions of the analysed genes in different stages of neuronal migration and their cell type-specific functions. These findings provide an important basis for better understanding the functions and cellular effects of lissencephaly-associated genes.

DYNC1H1 and *PAFAH1B1* have a broad expression pattern in most cell types (Figure 2n-o), supporting their role in universal functions such as microtubule dynamics and intracellular transport. *CRADD* and *NDE1* show a more restricted expression profile (Figure 2t-u) suggesting more specific roles in certain cellular subpopulations

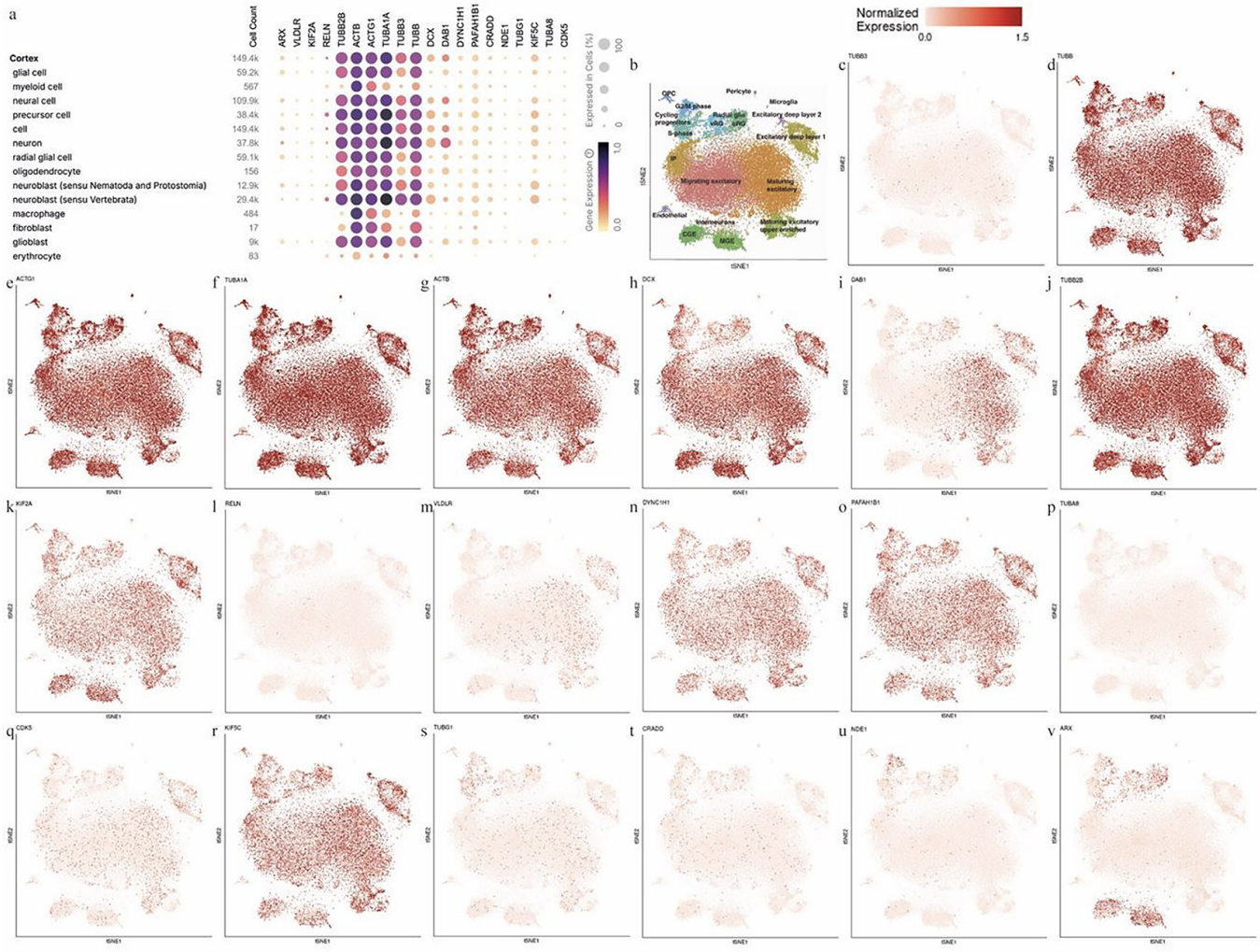

Figure 2. Expression patterns of lissencephaly-associated genes in cortical cell types and cortical cell population. (a) Single-cell RNA sequencing analysis. Each bubble represents the percentage of cells in a given cell type in which the gene is expressed (bubble size) and the intensity of gene expression (color scale). The size of the bubbles reflects the width of the cell population in which the gene is expressed, while the colour scale represents the intensity of gene expression level (0: low, 1: high). The genes studied are shown on the horizontal axis and the cell types on the vertical axis. (b-v) Expression patterns of lissencephaly-associated genes in cortical cell populations by t-SNE analysis. (b) This panel shows cell populations identified during cortical development by t-SNE analysis. Each dot represents a cell, and colors represent different cell types. In the other panels, normalized expression intensities of specific genes [(c) *TUBB3*, (d) *TUBB*, (e) *ACTG*, (f) *TUBA1A*, (g) *ACTB*, (h) *DCX*, (i) *DAB1*, (j) *TUBB2B*, (k) *KIF2A*, (l) *RELN*, (m) *VLDLR*, (n) *DYNC1H1*, (o) *PAFAH1B1*, (p) *TUBA8*, (q) *CDK5*, (r) *KIF5C*, (s) *TUBG1*, (t) *CRADD*, (u) *NDE1* and (v) *ARX*] are visualized on cellular groups. Red tones indicate high levels of gene expression, light tones indicate low levels

(e.g., neuronal precursor cells and interneurons). *TUBG1* and *TUBA8*, involved in microtubule organization, are prominently expressed in populations associated with neuronal migration and cytoskeletal organization (Figure 2p and 2s). *KIF5C*, which is directly associated with neurons, is particularly highly expressed in excitatory neurons (Figure 2r), suggesting an important role in neuronal transport. *CDK5* showed widespread expression across various cellular groups (Figure 2q), suggesting that it may play a regulatory role in cortical developmental processes.

Discussion

A better understanding of the genetic factors leading to lissencephaly and neuronal migration disorders is critical for the elucidation of the mechanisms of the disease and the identification of potential therapeutic targets. In this study, we focused on lissencephaly-related genes and analysed the gene expression correlations of these genes in the developmental brain using the EWCE approach. We determined the common correlations between the expression patterns of 20 genes associated with lissencephaly (*TUBB*, *TUBB3*, *ACTB*, *ACTG1*, *TUBA1A*, *DCX*, *TUBB2B*, *KIF2A*, *VLDLR*, *RELN*, *DYNC1H1*, *ARX*, *KIF5C*, *CRADD*, and *TUBA8*) and performed Jaccard index and Spearman's rank correlation analyses. The data obtained provide important findings on the ways in which these genes may interact at the cellular and functional levels. Our study provides a broader perspective on the mechanisms leading to lissencephaly and contributes to the identification of potential biomarkers that may provide new insights from a clinical perspective.

In lissencephaly and related neurodevelopmental disorders, interactions between *VLDLR*, *KIF2A*, and *RELN* genes are of great importance. *RELN* encodes the Reelin protein, which plays a critical role in the regulation of neuronal migration and cellular organization during brain development. *VLDLR* is one of the main receptors that transmit the Reelin signal[33]. *KIF2A* is a motor protein that regulates microtubule dynamics and is known to be particularly effective in cilium destruction, synaptic function, and neuronal localization processes[34]. The interactions of these genes with each other play important roles in ensuring neuronal positioning and synaptic stability. Mutations in *VLDLR* or *RELN* can lead to impaired cortical layering and serious neurodevelopmental diseases, while mutations in *KIF2A* have been associated with diseases such as epilepsy and autism[35,36].

TUBB2B, which is involved in the organization of microtubules, is distinctly different from other tubulin family members such as *TUBA1A*, *TUBB3* and *TUBB*. *TUBB2B*, which is particularly associated with cortical malformations such as asymmetric polymicrogyria, plays a specific role in neuronal migration and axonal guidance processes[37]. Epigenetic regulations are thought to shape the expression patterns of *TUBB2B* in the brain and cause it to diverge from other tubulin genes. This provides an understanding of the specific functions of *TUBB2B* in neurodevelopmental processes and more clearly demonstrates its relationship with cortical developmental disorders[38].

The *PAFAH1B1* gene, one of the most common causes of lissencephaly, is a key component in the regulation of neuronal migration. Studies show that 87% of classic lissencephaly cases have *PAFAH1B1* mutations. This high prevalence may cause the effects of other lissencephaly-associated genes to become relatively less obvious. While other lissencephaly-associated genes such as *TUBA1A* are associated with additional phenotypes such as cerebellar hypoplasia, *PAFAH1B1* mutations are usually identified by an isolated lissencephaly sequence[39]. This explains the central role of *PAFAH1B1* in cortical development and its differentiation from other genes.

TUBA8 and *TUBG1*, which are involved in the regulation of microtubule dynamics, have functional properties distinct from other tubulin genes. *TUBA8* is more highly expressed in tissues outside the brain, especially in megakaryocytes[40], while *TUBG1* plays an important role in microtubule nucleation and neuronal migration processes[41]. *TUBA8* mutations are associated with phenotypes other than classic lissencephaly, such as polymicrogyria and optic nerve hypoplasia, while *TUBG1* mutations have been observed to cause mild cortical abnormalities. The fact that *TUBG1* does not cause a migration defect as pronounced as *TUBA1A* reveals the different position of this gene in the lissencephaly spectrum.

Our study comprehensively analyzed the positive and negative correlations among genes involved in cortical development and neuronal migration. It was observed that while genes showing positive correlations regulate common biological processes and signaling pathways, negative correlations should not be considered antagonistic interactions regardless of the context. In particular, it was determined that negative correlations sometimes reflect developmental timing differences and expression patterns specific to different cellular subpopulations. For example, genes such as *PAFAH1B1* and *TUBG1* were found to play

central roles in cortical development, whereas genes such as *CRADD* and *ARX* were found to be associated with more specific processes. Hierarchical clustering and correlation network analyses confirmed the expected clustering of tubulin and microtubule-related genes, while genes involved in extracellular signaling such as *RELN* and *VLDLR* formed a different cluster. t-SNE analyses of single-cell RNA sequencing data revealed that these genes exhibit differential expression in specific cellular subpopulations, suggesting that negative correlations may not reflect functional antagonism but rather cell type-specific regulation or differential timing of developmental processes. In this context, the functional significance of negative correlations should be assessed according to the specific roles of the genes in cortical development and the cellular context in which they are located.

Barkovich et al.[42] classified brain malformations into three main groups based on their genetic etiology and developmental stages: atypical proliferation/apoptosis, atypical neuronal migration, and atypical post-migratory development. Clinically, these patients present with a wide spectrum of phenotypes, including neuromotor developmental delay, cognitive impairment, and epilepsy. Although cranial imaging plays a critical role in the diagnosis of the disease, establishing phenotype-genotype correlations is challenging because variable patterns such as agyria-pachygyria, dysgyria, heterotopia, and polymicrogyria can be seen. It is important to carefully evaluate these imaging findings to identify cases that may be candidates for epilepsy surgery.

The spectrum of tubulinopathy can vary widely, including dysgyria, lissencephaly, basal ganglia anomalies, and cerebellar anomalies. Kinesin-related diseases should be considered in the differential diagnosis. The lissencephaly spectrum includes subcortical band heterotopia (SBH), pachygyria, and classic lissencephaly; it is known to be associated with more than 20 genes in this group. Mutations in tubulin genes are not only limited to developmental disorders but have also been linked to degenerative diseases. *TUBB3* and *TUBB2B* mutations can be distinguished by additional clinical findings such as facial dysmorphism, extraocular muscle fibrosis, and peripheral neuropathy[43,44].

From an imaging perspective, three basic patterns of tubulinopathies have been identified: classic lissencephaly, microlissencephaly, dysgyria[44]. Asymmetry due to instability in the tubulin skeleton is common in cases of tubulinopathy and helps distinguish it from other causes. Classical lissencephaly can be classified as posterior dominant types and central dominant types, while microlissencephaly is considered the most severe form and is often seen with corpus callosum agenesis and cerebellar hypoplasia. Pathognomonic findings specific to tubulinopathy include basal ganglia hypoplasia, internal capsule anomalies, and frontal ventricular deformities[45].

In terms of genetic analyses, approximately 150 different variants have been identified in the *TUBA1A*, *TUBB2B*, and *TUBB3* genes. *TUBA1A* mutations are responsible for 4-5% of lissencephaly. Since the changes in the p.Arg402 residue of this gene are located in an area that interact with kinesin and dynein, they can lead to malformations related to motor proteins[45]. *TUBB2B* predominantly affects polymicrogyria, while *TUBB3* mutations have been associated with extraocular muscle fibrosis and peripheral neuropathy. *TUBA8* mutations are less commonly associated with cortical malformations and are thought to play a role in the post-migratory phase and axon maintenance. The fact that *TUBA1A* and *TUBA8* have similar structures but exhibit different electrostatic properties may explain the functional differences in microfilament interactions[45-48].

The lissencephaly spectrum covers a wide range from lissencephaly characterized by thickened cortex and sulcal-gyral anomalies to conditions such as SBH, in which abnormal neuronal clusters form beneath the normal cortex. Involvement within this spectrum can be widespread or regional, anteriorly or posteriorly, dominant. The most common pattern is the presence of pachygyria in the frontal region and agyria in the posterior cortex. Cerebellar hypoplasia is among the most common non-cortical findings in this spectrum. In tubulinopathies, an intermediate form is observed, characterized by dysgyria (such as blurring of the gray-white transition line and the presence of large and small gyria together) is observed[32,43,47].

The genes most commonly associated with lissencephaly are *PAFAH1B1* and *TUBA1A*, although *TUBG1* mutations can also cause posteriorly dominant pachygyria (Table 1). However, TUBG1 mutations do not affect the basal ganglia, cerebellum, and corpus callosum, which would cause a different phenotype compared to *TUBA1A* mutations[49]. *PAFAH1B1* and *NDE1* are proteins that play a role in regulating the cytosolic dynein motor complex and enable the movement of the cell nucleus during neuronal migration. While *PAFAH1B1* mutations are generally associated with more severe phenotypes, *NDE1* mutations may cause milder forms of dysgyria (Table 1)[50,51].

Table 1. Phenotypic effects of genes associated with lissencephaly and other neurodevelopmental disorders

Genes	Diffuse	Partial	P>A gradient	A>P gradient	Temporal> A and P	MicroLIS	Diffuse agyria	Agyria - Pachgyria (P>A)	Pachygyria (P>A)	Agyria - Pachygyria (A>P)	Pachygyria (A>P)	ScBH	PMG	Dysgyria	Diff ScBH thick	Diff ScBH thin	Par ScBH P	Par ScBH A	Pachygyria A/thin CB	Pachygyria A/thin normal CB	CB	CC	BG	Lat vent	Other
TUBA1A	+	+	+			+	+[c]	+[c]	+		+[a]	+	+	+							+	+	+	+	
TUBB3		+	+			+[a]			+					+							+/-	+/-	+/-		
TUBB3		+	+			+[a]			+					+							+/-	+/-	+/-		
ACTG1		+									+[d]	+													
ACTB		+									+[d]	+													
DCX	+	+[a]					+			+[a]	+	+			+	+		+[a]			+/-				
DAB1											+										+	+/-		+/-	
TUBB2B	+[a]	+				+	+[a]		+				+[g]	+							+	+	+	+	
KIF2A		+							+			+[e]										+/-			
RELN		+									+								+		+				
VLDLR		+									+								+		+				
DYNC1H1		+							+	+	+		+[e]	+[a]							+[*]	+/-	+/-		
PAFAH1B1	+	+[a]					+	+	+			+					+	+							
TUBA8		+											+	+[a]								+			**Optic nerve hypoplasia**
CDK5	+[a]	+					+[a]																		
KIF5C									+		+[a]		+[e]	+[h]								+/-			
TUBG1		+	+						+			+[f]										+/-			
CRADD											+								-	+	**N**				
NDE1						+[b]																			
ARX					+																	+	+		**White matter changes**

The symbol "+" indicates a positive association with the phenotype. The symbol "+/-" indicates a limited or variable association. P: Posterior, A: Anterior, ScBH: Subcortical band heterotopia, PMG: Polymicrogyria, CB: Cerebellum, CC: Corpus callosum, BG: Basal ganglia, (a): Rare, (b): Intermediate, (c): R402 variant, (d): With or without band, (e): Frontal, (f): Posterior, (g): Asymmetric, (h): A>P, [*]: Vermis colours indicate similar radiological findings

The interaction between microtubule dynamics and actin filaments plays a critical role in neuronal polarity and migration[52]. *ACTG1* and *ACTB* mutations are usually characterized by anterior dominant lissencephaly and short SBH (Table 1). The doublecortin (*DCX*) gene codes for one of the basic proteins, DCX, that regulate the interaction between microtubules and actin filaments, and studies have shown that *DCX* strongly correlates actin isoforms. *PAFAH1B1* and *DCX* are the major proteins involved in the regulation of microtubule homeostasis, and mutations in these genes are among the most common causes of diffuse agyria[53].

The microtubule-dependent motor proteins kinesin and dynein are the only gene families associated with anterior and posterior dominant lissencephaly. *KIF2A*, *KIF5C* and *DYNC1H1* are involved in many processes from mitotic division to the migration of post-mitotic neurons[54], causing a variety of clinical presentations such as pachygyria, SBH or polymicrogyria (Table 1). *RELN*, *VLDLR*, and *DAB1*, which are involved in the Reelin signalling pathway, are critical for the regulation of cortical layering and cerebellar development[43,52]. Pathogenic variants in these genes can cause anterior dominant mild pachygyria and cerebellar involvement (Table 1).

Study Limitations

This study is based entirely on in silico analyses, and this approach brings with it some limitations. Gene similarity analyses were performed on correlation data, overlap assessments performed with the Jaccard index, cell type level expression abundance analyses performed with the EWCE method, and functional enrichment studies based on Enrichr-KG provide strong predictions based on the literature, however, the biological validity of these findings remains limited without experimental verification. Since the transcriptomic data used may vary depending on parameters such as tissue, developmental stage, and cell type, the biological context of the relationships between genes should be interpreted with caution. In addition, the relevance and scope of the databases used may also affect the accuracy of the results. Therefore, although we believe that the predictions put forward in this study provide an important basis for developing hypotheses, they should be supported by molecular and cellular experiments to definitively reveal the functional roles of the relevant genes.

Conclusion

In conclusion, the lissencephaly spectrum is a group of neurodevelopmental disorders, which are genetically heterogeneous and occur through different mechanisms. Dynamic interactions between tubulin, actin, and motor proteins regulate different stages of cortical development, allowing certain genetic variants to cause specific phenotypes. A better understanding of these genetic interactions may enable new approaches to the diagnosis and treatment of lissencephaly and related disorders.

Future studies may include advanced experimental systems such as patient-derived induced pluripotent stem cells (iPSCs), brain organoids, and animal models to further investigate the biological validity of our findings. iPSC-derived neuronal models may allow us to examine the cellular functions of identified genes and their roles in developmental processes in a patient-specific context. Brain organoids may provide a valuable platform to understand how these genes are organized within the three-dimensional tissue architecture and contribute to cortical layering processes. In addition, *in vivo* validation can be performed using animal models, and the effects of genetic manipulations on neuronal migration and cortical development can be assessed. In addition to elucidating the mechanisms underlying the correlations between genes, these approaches may contribute to a better understanding of neuronal migration disorders and the identification of therapeutic targets.

Ethics

Ethics Committee Approval: As only publicly available data were used, there was no need to obtain ethics approval.

Informed Consent: Not applicable, as no ethics committee approval was needed.

Footnotes

Authorship Contributions

Concept: Y.O., Design: Y.O., Data Collection or Processing: A.K., Y.O., Analysis or Interpretation: A.K., İ.P., Y.O., Literature Search: A.K., İ.P., Y.O., Writing: A.K., İ.P., Y.O.

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

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CASE REPORT / OLGU SUNUMU

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From Benign to Malignant: A Rare Case Report on the Journey of Misdiagnosis to Porocarcinoma

Benignden Maligne: Yanlış Tanıdan Porokarsinoma Yolculuğuna İlişkin Nadir Bir Olgu Sunumu

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Abstract

Eccrine porocarcinoma (EPC) is a rare epithelial cutaneous tumor that includes a wide range of entities in the differential diagnosis. It is observed in older people and is most commonly observed in the lower extremities. Due to its various pathological features, it is often confused with other malignant cutaneous tumors. We presented a case of a very rare skin appendage tumor with deceptive features on incisional biopsy. A 62-year-old male patient presented to the hospital due to a mass on his back that had been present for a long-time but has recently shown rapid growth. The initial diagnosis of the lesion from the incisional biopsy indicated clonal seborrheic keratosis; however, subsequent analysis of the excisional biopsy revealed the presence of EPC. EPC is a rare malignant skin appendage tumor. Due to its rarity, its risk factors and pathogenesis have not been fully elucidated. Differential diagnosis is challenging because the clinical characteristics of this tumor are similar to those of other tumors. Incisional biopsies of the mass can result in false-negative results due to heterogeneous histomorphology. Clinicopathological correlation is of vital importance for the patient to reach the correct treatment in such cases.

Keywords: Porocarcinoma, eccrine poroma, seborrheic keratosis, rare cutaneous tumor

Öz

Ekrin porokarsinom (EPC) nadir bir epitelyal kutanöz tümör olup ayırıcı tanıda çok çeşitli antiteler yer almaktadır. İleri yaşta ve sıklıkla alt ekstremitelerde görülürler. Çeşitli patolojik özellikleri nedeniyle sıklıkla diğer malign kutanöz tümörlerle karıştırılır. İnsizyonel biyopside yanıltıcı görünüme sahip olan oldukça nadir görülen bir deri eki tümör olgusu sunduk. Altmış iki yaşında erkek hasta sırtında uzun süredir var olan ancak son zamanlarda hızlı büyüme gösteren kitle nedeni ile hastaneye başvurdu. Biyopsiden alınan insizyonel biyopsi klonal seboreik keratozis lehine yorumlandı ancak gönderilen eksizyonel biyopsi sonucu EPC olarak sonuçlandı. EPC oldukça nadir görülen malign deri eki tümörüdür. Nadir görülmesi nedeniyle tümörün patogenezisi ve risk faktörleri henüz net olarak ortaya konulamamıştır. Klinik görüntüsü diğer tümörlere benzediği için ayırıcı tanısı zorlayıcıdır. Heterojen histomorfolojisinden dolayı kitleden alınan insizyonel biyopsilerde yanlış negatif sonuçlar ortaya çıkabilmektedir. Bu tip olgularda klinikopatolojik korelasyon doğru tanı ve tedavi için hayati önem taşımaktadır.

Anahtar Kelimeler: Porokarsinoma, ekrin poroma, seboreik keratozis, nadir kutanöz tümör

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Introduction

Eccrine porocarcinoma (EPC) is the malignant form of eccrine poroma and is frequently observed in the lower extremities of older people[1]. The prevalence of this condition is less than 0.01% of all epithelial cutaneous tumors. Although cases can be observed in all age groups, they are most commonly diagnosed in the 6th and 7th decades[2,3]. There is no significant difference in the incidence rate between both genders[4,5]. Long-term exposure to sunlight, radiation, advanced age, immunosuppression, and history of dermatological neoplasia are the known risk factors[2-4]. They are most frequently located in the head and neck region (39.9%), lower extremities (33.9%), upper extremities (8.8%), and trunk (9.7%)[2]. Although EPC can be seen *de novo*, they may also result from malignant transformation of a benign poroma, which has existed for a long-time[5-9]. Although the pathogenesis of porocarcinoma has not been fully elucidated, signaling pathways and cell cycle irregularities are involved in porocarcinoma formation[2]. Molecular analyses performed in recent years have revealed that the *YAP1* and *WWTR1* fusion genes play a role in the tumorigenic transformation of poromas. In this publication, we present a case of invasive EPC based on intraepidermal eccrine poroma.

Case Report

A 62-year-old male patient with a known diagnosis of hypertension and diabetes mellitus was admitted to the hospital because of a mass lesion on the right upper skin of his back. In the anamnesis, it was learned that the lesion had existed for 3-4 years but had grew rapidly in the last 2-3 months. In cases in which incisional biopsy was performed with preliminary diagnoses of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma, the pathological diagnosis was evaluated in favor of clonal seborrheic keratosis (Figure 1). Then, total excision of the lesion was completely excised. On the material brought to the pathology laboratory, there was a mass of 4.8x4.6x1.1 cm in size, with an irregular appearance and occasionally ulcerated and nodular areas. Microscopically, on the samples taken from the flat areas of the lesion, intraepidermal sharply demarcated nodular cellular communities similar to the previous biopsy were observed. However, on the samples taken from the ulcerated and nodular area in the center, there was tumoral infiltration extending from the epidermis to the dermis, bridging each other, and cystic spaces were observed in focal areas (Figure 2). Neoplastic cells have a monotonous appearance without atypia in most areas. However, atypical cell populations with stromal infiltrative extension into the dermis were also noted in some areas of the lesion. An increase in mitosis occurs in these areas (Figure 3). Immunohistochemically, xytokeratin 7, CK5/6, p40, and GATA-3 neoplastic cells were diffusely positive, and focal ductular staining was detected with carcinoembryonic antigen and epithelial membrane antigen (Figure 4). Although Ki-67 was low in the intraepidermal

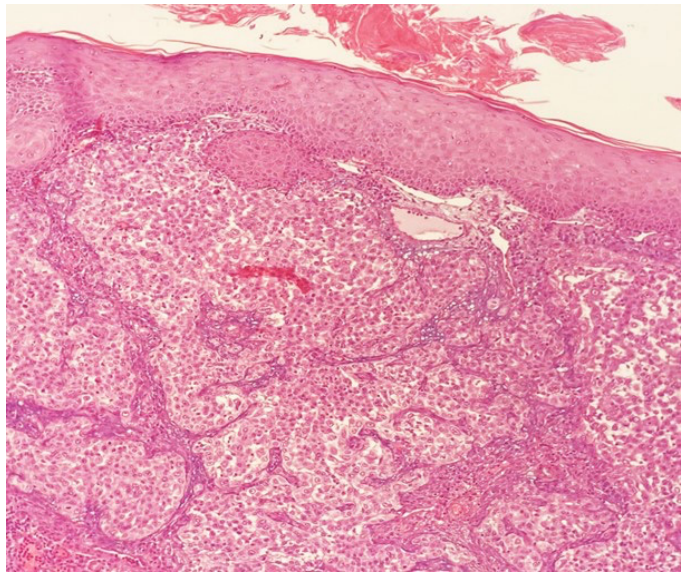

Figure 1. Anastomosis of tumor islands showing continuity with the epidermis, (H&E, X200)

H&E: Hematoxylin and eosin

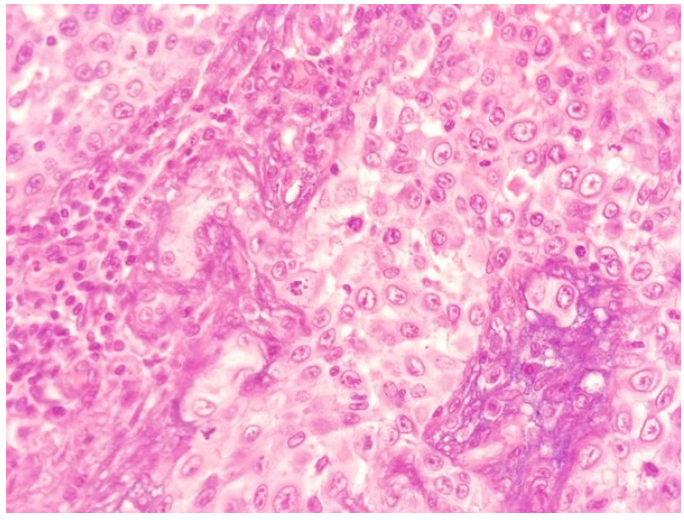

Figure 2. Tumor cells showing cytological atypia, mitosis,necrosis, and pleomorphism, (H&E, X400)

H&E: Hematoxylin and eosin

benign component, it was around 40% on average in areas showing malignant transformation. Periodic acid-Schiff was performed histochemically, and luminal positivity was observed in duct-like areas. Cells, though resembling eosinophilic keratinocytes with large cytoplasm, had more monotonous nuclei and were strictly separated from epidermocytes,compared to keratinocytes. When the immunohistochemical and histopathological findings were evaluated together, the patient was diagnosed with EPC based on hydroacanthoma simplex. Lymphovascular and perineural invasion was not detected. No additional surgical procedures or medical treatment was provided to patients whose surgical margins were determined to be intact.

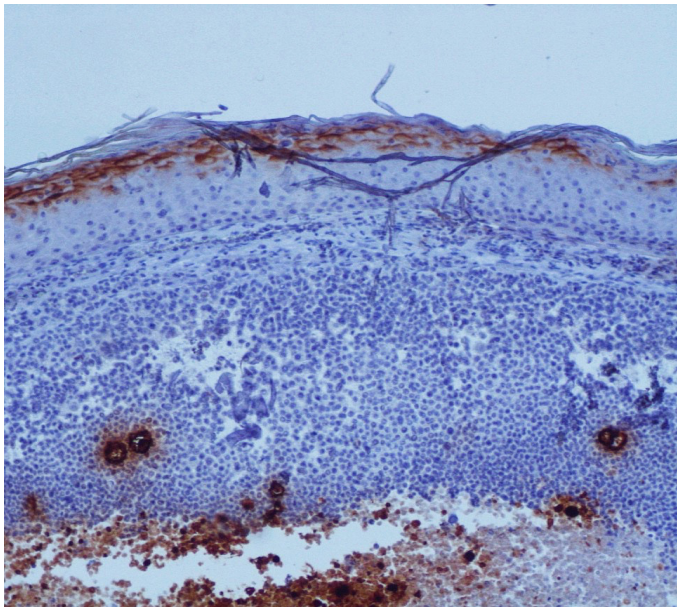

Figure 3. Positive staining with CEA in ductal-differentiation cells (immunohistochemistry, X200)

CEA: Carcinoembryonic antigen

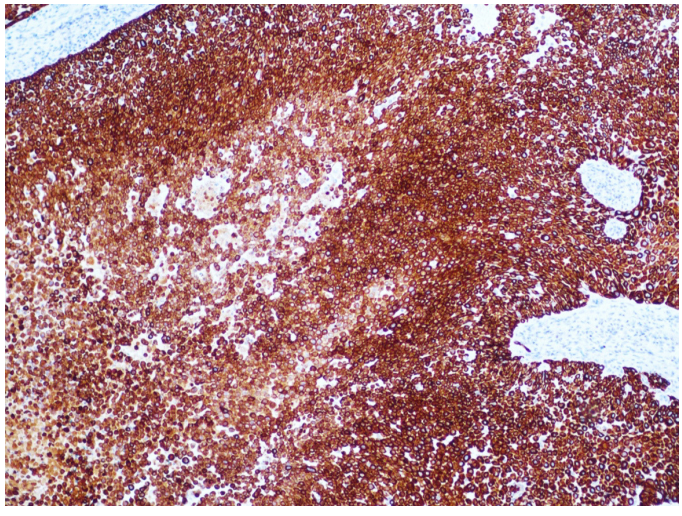

Figure 4. Positive staining with CK7 in tumor cells (immunohistochemistry, X200)

CK7: Cytokeratin 7

Discussion

EPC, first described in 1963, is a rare malignant skin appendage tumor. Due to its rarity, risk factors and pathogenesis have not been fully elucidated[5]. Although the cases range from 6 months to 97 years of age, the incidence increases in the advancing decades. It is commonly seen in the head, the neck and the extremities; however, breast and penis skin cases were also reported in the literature. Tumor; varying from 1 to 10 cm, and they may be red and brown in color and may be nodular, infiltrative, ulcerated, and polypoid in appearance[1,2]. It has an aggressive behavior, and lymphovascular invasion, local recurrence, and distant metastases are very common[1,5]. Multinodularity, ulceration, and rapid growth; it may indicate local recurrence or distant metastasis[4].

Porocarcinoma is a dermal-based malignant tumor characterized by ill-defined margins and a tendency to connect with the epidermis at multiple points. It is often accompanied by ulceration. The tumor may exhibit either pushing or diffuse infiltrative growth patterns and can extend into subcutaneous tissue and deeper layers. In approximately 11% of cases, it arises from a preexisting benign poroma. Histologically, it consists of irregularly shaped, interconnected strands and clusters of polygonal epithelioid cells, showing varying levels of nuclear pleomorphism and cytological atypia. Ductal differentiation is essential for diagnosis. Additional features may include necrosis, invasion of lymphovascular structures, and perineural spread. Rarely, a tumor may display squamous or clear cell changes, as well as sarcomatoid transformation[6]. Porocarcinoma is frequently mistaken for squamous cell carcinoma. Due to its rarity, unclear etiology, and limited amount of research available, there are no established protocols for its diagnosis or treatment. Most of the information on this tumor is from individual case reports and a small number of case series. According to Belin et al.[7], 37% of cases of EPC were initially misidentified as SCC. One study noted a benign component in almost 43.2% of PC cases, with poroma being the most frequently identified. This finding supports the hypothesis that some PCs develop from pre-existing poroma[8].

Approximately 20% of patients have regional lymph node metastases. The most common sites of distant metastasis are the lungs, liver, and brain[4,9]. Although excision is the first and most effective treatment option, chemotherapeutic agents and radiotherapy are also used in metastatic cases[2-4].

Differential diagnosis is challenging because its clinical appearance is similar to that of other tumors, and it is extremely rare. Entities include a wide range of tumors, including seborrheic keratosis, nevus, pyogenic granuloma, squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and metastatic carcinoma. Definitive diagnosis is made by tissue diagnosis[1].

As in our case, incisional biopsy may have led to incorrect results. The biopsy area, which represents the specifically ulcerated or nodular area, may be helpful in obtaining a correct diagnosis. In our case, the biggest reason for the incorrect diagnosis from the incisional biopsy was that the biopsy location was chosen from a flatter area at the nodule's periphery rather than the nodular and hemorrhagic area at the center where the lesion was showing rapid growth. However, given the clinician's preliminary diagnosis of malignancy, even though the incisional biopsy pointed toward a benign lesion, the present findings could belong to an area that does not represent the lesion. In cases with high clinical suspicion of malignancy, total lesion removal was recommended.

In cases of rapid growth of the lesion that has existed for a long-time, the presence of ulceration, bleeding, irregular borders, and a nodular appearance should be considered as indicators of malignant transformation[10]. Due to its rarity, data are limited for accurate diagnosis, treatment method, and prognosis, but surgical excision with intact surgical margins is the first treatment option due to its aggressive course[5]. Additionally, cases should be closely followed with the possibility of metastasis.

Ethics

Informed Consent: Informed consent was obtained.

Footnotes

Authorship Contributions

Concept: E.Y., H.T., E.Yı., Design: E.Y., H.T., E.Yı., Data Collection or Processing: E.Y., H.T., Analysis or Interpretation: E.Y., H.T., Literature Search: E.Y., H.T., Writing: E.Y., H.T.

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